CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-436/S-019, S-020, S-022
21-713/S-014, S-015, S-017
21-729/S-006, S-007, S-009
21-866/S-006, S-007, S-009

Trade Name: Abilify

Generic Name: Aripiprazole

Sponsor: Otsuka Pharmaceutical

Approval Date: May 6, 2008

Indications: As oral formulations for the treatment of Schizophrenia in adults and adolescents aged 13 to 17 years. The treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults and pediatric patients aged 10 to 17 years. Adjunctive treatment of Major Depressive Disorder in adults. As an injection for the treatment of adults with agitation associated with Schizophrenia or Bipolar I Disorder, manic or mixed.

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21-729/S-006, S-007, S-009
21-866/S-006, S-007, S-009

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436 S-019, S-020, S-022
NDA 21-713 S-014, S-015, S-017
NDA 21-729 S-006, S-007, S-009
NDA 21-866 S-006, S-007, S-009

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attn: Kusuma Mallikaarjun, Ph.D.
Senior Director, Regulatory Affairs
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your supplemental new drug applications [sNDAs] submitted and received on July 11, 2007 [NDA 21-436 S-019, S-020] under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) Tablets.

Please also refer to your supplemental new drug applications [sNDAs] submitted August 28, 2007 and received on August 29, 2007 [NDA 21-713 S-014, S-015; NDA 21-729 S-006, S-007; and NDA 21-866 S-006, S-007] under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) Oral Solution, Orally Disintegrating Tablet, and Injection for Intramuscular Use, respectively.

Please also refer to your labeling supplements NDA 21-436 S-022, NDA 21-713 S-017, NDA 21-729 S-009, and NDA 21-866 S-009, submitted December 27, 2007 and received December 28, 2007.

Please also refer to your amendments to NDA 21-436 S-019 and S-020, NDA 21-713 S-014 and S-015; NDA 21-729 S-006 and S-007; and NDA 21-866 S-006 and S-007, submitted on September 4, 2007, September 6, 2007, October 18, 2007, January 18, 2008, and March 19, 2008.

Your supplemental NDAs 21-436 S-019, 21-713 S-014, 21-729 S-006, and 21-866 S-006 provide for the use of Abilify as monotherapy in the acute treatment of bipolar disorder, manic or mixed, at a starting dose of 15 mg/day.

Your supplemental NDAs 21-436 S-020, 21-713 S-015, 21-729 S-007, and 21-866 S-007 provide for the use of Abilify as adjunctive therapy added to lithium or valproate in the short-term treatment of bipolar disorder, manic or mixed, again at a starting dose of 15 mg/day.

Your labeling supplements NDA 21-436 S-022, NDA 21-713 S-017, NDA 21-729 S-009, and NDA 21-866 S-009 provide for revision of the "Drug Interactions" section of labeling to state that aripiprazole has no clinically meaningful effect on the pharmacokinetics of lamotrigine.

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

Content of Labeling: Structured Product Labeling [SPL]. the final printed labeling (FPL) must be identical to the enclosed labeling [package insert], and must be formatted in accordance with the requirements of 21 CFR 201.66.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured Product Labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html , that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "SPL for approved NDA labeling under NDA 21-436 S-019, NDA 21-436 S-020, NDA 21-713 S-014, NDA 21-713 S-015, NDA 21-729 S-006, NDA 21-729 S-007, NDA 21-866 S-006, and NDA 21-866 S-007".

Pediatric Research Equity Act (PREA) Requirements: Phase 4 Commitments.
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.

With reference to NDA 21-436 S-019, NDA 21-713 S-014, NDA 21-729 S-006, and NDA 21-866 S-006, we are waiving the requirement for pediatric studies in all age groups, because:

A) necessary studies are impossible or highly impracticable. The pediatric starting dose of aripiprazole is 2 mg/day; this is titrated to 5 mg/day after 2 days and 10 mg/day after 2 more days. The target dose for pediatric patients is 10 mg/day. Therefore, study of a 15 mg starting dose in pediatric patients is not feasible.

With reference to NDA 21-436 S-020, NDA 21-713 S-015, NDA 21-729 S-007, and NDA 21-866 S-007, this product is now appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

There are no other Phase 4 commitments or Phase 4 requirements for any of these submissions.

"Dear Healthcare Professional" Letters.
If you issue a letter communicating important information about this product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to all four NDAs referenced above, with a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Introductory Promotional Materials.
In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-796-1040.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: agreed-upon labeling.

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

/s/

Thomas Laughren
5/6/2008 10:47:15 AM

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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

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDALITY AND ANTIDEPRESSANT DRUGS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ABILIFY is not approved for the treatment of patients with dementia-related psychosis. (5.1)
- Children, adolescents, and young adults taking antidepressants for Major Depressive Disorder (MDD) and other psychiatric disorders are at increased risk of suicidal thinking and behavior. (5.2)

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

Boxed Warning, Suicidality and Antidepressant Drugs	11/2007
Indications and Usage,	
Adolescent (13 to 17 years) Schizophrenia (1.1)	05/2008
Adjunctive Therapy (Lithium or Valproate) in Adult and Pediatric (10 to 17 years) Patients with Bipolar Mania (1 2)	05/2008
Pediatric (10 to 17 years) Bipolar Mania (1.2)	05/2008
Adjunctive Treatment in Adults with MDD (1.3)	11/2007
Dosage and Administration,	
Adolescent Schizophrenia (2.1)	05/2008
15 mg starting dose in Bipolar Mania (2.2)	05/2008
Adjunctive Therapy (Lithium or Valproate) in Adult and Pediatric Patients with Bipolar Mania (2.2)	05/2008
Pediatric Bipolar Mania (2.2)	05/2008
Adjunctive Treatment in Adults with MDD (2.3)	11/2007
Warnings and Precautions, Clinical Worsening of Depression and Suicide Risk (5.2)	11/2007

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

ABILIFY is an atypical antipsychotic indicated

as oral formulations for:

- Treatment of Schizophrenia in adults and adolescents aged 13 to 17 years (1.1)
- Treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy or adjunctive to lithium or valproate in adults and pediatric patients aged 10 to 17 years (1.2)
- Adjunctive treatment of Major Depressive Disorder in adults (1.3)

as an injection for:

- Treatment of adults with agitation associated with Schizophrenia or Bipolar I Disorder, manic or mixed episodes (1.4)

----------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 or as an adjunct to lithium or valproate (2.2)	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 (2.3)	2-5 mg /day	5-10 mg /day	15 mg /day
Agitation associated with Schizophrenia or Bipolar Mania – adults (2.4)	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 (2.4)

----------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----------

- *Elderly Patients with Dementia-Related Psychosis* Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack, including fatalities) (5.1)
- *Suicidality and Antidepressants* Increased risk of suicidality in children, adolescents, and young adults with Major Depressive Disorder (5 2)
- *Neuroleptic Malignant Syndrome* Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia* Discontinue if clinically appropriate (5.4)
- *Hyperglycemia and Diabetes Mellitus* Monitor glucose regularly in patients with and at risk for diabetes (5.5)
- *Orthostatic Hypotension* Use with caution in patients with known cardiovascular or cerebrovascular disease (5.6)
- *Seizures/Convulsions* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.7)
- *Potential for Cognitive and Motor Impairment* Use caution when operating machinery (5.8)
- *Suicide* The possibility of a suicide attempt is inherent in Schizophrenia and Bipolar Disorder. Closely supervise high-risk patients (5.10)

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

Commonly observed adverse reactions (incidence ≥5% and at least twice that for placebo) were (6.2):

- 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, tremor, restlessness, 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
- 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----------

- *Strong CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, fluoxetine) inhibitors will increase* ABILIFY drug concentrations; reduce ABILIFY dose by one-half when used concomitantly (2.5, 7.1), except when used as adjunctive treatment with antidepressants (2.5)
- *CYP3A4 inducers (eg, carbamazepine) will decrease* ABILIFY drug concentrations; double ABILIFY dose when used concomitantly (2.5, 7.1)
-

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescr bing information are not listed

FULL PRESCRIBING INFORMATION

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDALITY AND ANTIDEPRESSANT DRUGS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis *[see WARNINGS AND PRECAUTIONS (5.1)].*

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression *[see WARNINGS AND PRECAUTIONS (5.2)].*

1 INDICATIONS AND USAGE

1.1 Schizophrenia

ABILIFY is indicated for acute and maintenance treatment of Schizophrenia in adults and in adolescents 13 to 17 years of age *[see CLINICAL STUDIES (14.1)]*.

1.2 Bipolar Disorder

Monotherapy

ABILIFY is indicated for acute and maintenance treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults and in pediatric patients 10 to 17 years of age *[see CLINICAL STUDIES (14.2)]*.

Adjunctive Therapy

ABILIFY is indicated as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults and in pediatric patients 10 to 17 years of age [*see CLINICAL STUDIES (14.2)*].

1.3 Adjunctive Treatment of Major Depressive Disorder

ABILIFY is indicated for use as an adjunctive therapy to antidepressants for the acute treatment of Major Depressive Disorder in adults *[see CLINICAL STUDIES (14.3)]*.

1.4 Agitation Associated with Schizophrenia or Bipolar Mania

ABILIFY Injection is indicated for the acute treatment of agitation associated with Schizophrenia or Bipolar Disorder, manic or mixed in adults. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care (eg, threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior), leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation *[see CLINICAL STUDIES (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Usual Dose for Acute Treatment

Adults

The recommended starting and target dose for ABILIFY is 10 mg/day 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 mg/day to 30 mg/day, when administered as the tablet formulation; however, doses higher than 10 mg/day or 15 mg/day were not more effective than 10 mg/day or 15 mg/day. Dosage increases should not be made before 2 weeks, the time needed to achieve steady-state *[see CLINICAL STUDIES (14.1)]*.

Adolescents

The recommended target dose of ABILIFY is 10 mg/day. Aripiprazole was studied in pediatric 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)]*.

Maintenance Therapy

Adults

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, systematic evaluation of patients with Schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks, has demonstrated a benefit of such maintenance treatment *[see CLINICAL STUDIES (14.1)]*. Patients should be periodically reassessed to determine the need for maintenance treatment.

Adolescents

The efficacy of ABILIFY for the maintenance treatment of Schizophrenia in the pediatric population has not been evaluated. While there is no body of evidence available to answer the question of how long the adolescent patient treated with ABILIFY should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. 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 Disorder

Usual Dose for Acute Treatment

Adults

The recommended starting and target dose is 15 mg as monotherapy or as adjunctive therapy with lithium or valproate given once a day, without regard to meals. The dose can 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 *[see CLINICAL STUDIES (14.2)]*.

Pediatric Patients

The efficacy of aripiprazole has been established in the treatment of pediatric patients 10 to 17 years of age with Bipolar I Disorder at doses of 10 mg/day or 30 mg/day. The recommended target dose of ABILIFY is 10 mg/day, as monotherapy or as adjunctive therapy with lithium or valproate. The starting daily dose of the tablet formulation in these patients was 2 mg/day, which was titrated to 5 mg/day after 2 days and to the target dose of 10 mg/day after 2 additional days. Subsequent dose increases should be

administered in 5 mg/day increments. ABILIFY can be administered without regard to meals. *[See CLINICAL STUDIES (14.2).]*

Maintenance Therapy

Adults

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, whether used as monotherapy or as adjunctive therapy, adult patients with Bipolar I Disorder who had been symptomatically stable on ABILIFY Tablets (15 mg/day or 30 mg/day as monotherapy with a starting dose of 30 mg/day) for at least 6 consecutive weeks and then randomized to ABILIFY Tablets (15 mg/day or 30 mg/day) or placebo and monitored for relapse, demonstrated a benefit of such maintenance treatment *[see CLINICAL STUDIES (14.2)]*. While it is generally agreed that pharmacological treatment beyond an acute response in Mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of aripiprazole in such longer-term treatment (beyond 6 weeks). Physicians who elect to use ABILIFY for extended periods, that is, longer than 6 weeks, should periodically re-evaluate the long-term usefulness of the drug for the individual.

Pediatric Patients

The efficacy of ABILIFY for the maintenance treatment of Bipolar I Disorder in the pediatric population has not been evaluated. While there is no body of evidence available to answer the question of how long the pediatric patient treated with ABILIFY should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.3 Adjunctive Treatment of Major Depressive Disorder

Usual Dose for Acute Treatment

Adults

The recommended starting dose for ABILIFY as adjunctive treatment for patients already taking an antidepressant is 2 mg/day to 5 mg/day. The efficacy of ABILIFY as an adjunctive therapy for Major Depressive Disorder was established within a dose range of 2 mg/day to 15 mg/day. Dose adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week *[see CLINICAL STUDIES (14.3)]*.

Pediatric Patients

The efficacy of ABILIFY for the adjunctive treatment of Major Depressive Disorder in the pediatric population has not been evaluated.

Maintenance Therapy

The efficacy of ABILIFY for the adjunctive maintenance treatment of Major Depressive Disorder has not been evaluated. While there is no body of evidence available to answer the question of how long the patient treated with ABILIFY should be maintained, patients should be periodically reassessed to determine the need for maintenance treatment.

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

Usual Dose

Adults

The recommended dose in these patients is 9.75 mg. The effectiveness of aripiprazole injection in controlling agitation in Schizophrenia and Bipolar Mania was demonstrated over a dose range of 5.25 mg 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 aripiprazole 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 (14.4)]*.

If ongoing aripiprazole therapy is clinically indicated, oral aripiprazole in a range of 10 mg/day to 30 mg/day should replace aripiprazole 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.

Pediatric Patients

ABILIFY Intramuscular Injection has not been evaluated in pediatric patients.

2.5 Dosage Adjustment

Dosage adjustments in adults are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status *[see USE IN SPECIFIC POPULATIONS (8.4-8.10)]*.

Dosage adjustment for patients taking aripiprazole concomitantly with strong CYP3A4 inhibitors: When concomitant administration of aripiprazole with strong CYP3A4 inhibitors such as ketoconazole or clarithromycin is indicated, the aripiprazole dose should be reduced to one-half the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should then be increased *[see DRUG INTERACTIONS (7.1)]*.

Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP2D6 inhibitors: When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should then be increased *[see DRUG INTERACTIONS (7.1)]*. 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)*.

Dosage adjustment for patients taking potential CYP3A4 inducers: When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 mg to 15 mg *[see DRUG INTERACTIONS (7.1)]*.

2.6 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)]*.

2.7 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, and 2.3)]*.

3 DOSAGE FORMS AND STRENGTHS

ABILIFY® (aripiprazole) Tablets are available as described in Table 2.

Table 2: 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	"A-008"

Table 2: ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
	modified rectangle	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 3.

Table 3: 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

Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis *[see ADVERSE REACTIONS (6.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Use in Elderly Patients with Dementia-Related Psychosis

Increased Mortality

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

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 (eg, stroke, transient ischemic attack), including fatalities, in aripiprazole-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 aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis *[see also BOXED WARNING]*.

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

In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the treatment-emergent adverse events that were reported at an incidence of ≥3% and aripiprazole incidence at least twice that for placebo were lethargy [placebo 2%, aripiprazole 5%], somnolence (including sedation) [placebo 3%, aripiprazole 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole 5%], excessive salivation [placebo 0%, aripiprazole 4%], and lightheadedness [placebo 1%, aripiprazole 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, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration *[see also BOXED WARNING]*.

5.2 Clinical Worsening of Depression and Suicide Risk

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 Major Depressive Disorder (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 4.

Table 4:

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

Table 4:

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 Major Depressive Disorder 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.

5.3 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 aripiprazole. Rare cases of NMS occurred during aripiprazole 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 (eg, 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.

5.4 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.

5.5 Hyperglycemia and 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 few reports of hyperglycemia in patients treated with ABILIFY *[see ADVERSE REACTIONS (6.2, 6.3)]*. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. 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 which did not include ABILIFY suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. 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 events 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 (eg, 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.

5.6 Orthostatic Hypotension

Aripiprazole 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 (aripiprazole incidence, placebo incidence) orthostatic hypotension (1%, 0.3%), postural

dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%); of pediatric patients 10 to 17 years of age (n=399) on oral ABILIFY included orthostatic hypotension (1%, 0%), postural dizziness (0.5%, 0%), and syncope (0.3%, 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%).

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 when comparing standing to supine values) for aripiprazole was not meaningfully different from placebo (aripiprazole incidence, placebo incidence): in adult oral aripiprazole-treated patients (4%, 2%), in pediatric oral aripiprazole-treated patients aged 10 to 17 years (0%, 0.5%), or in aripiprazole injection-treated patients (3%, 2%).

Aripiprazole 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).

If parenteral benzodiazepine therapy is deemed necessary in addition to aripiprazole injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension *[see DRUG INTERACTIONS (7.3)]*.

5.7 Seizures/Convulsions

In short-term, placebo-controlled trials, seizures/convulsions occurred in 0.1% (3/2467) of adult patients treated with oral aripiprazole, in 0.3% (1/399) of pediatric patients (10 to 17 years), and in 0.2% (1/501) of adult aripiprazole injection-treated patients.

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

5.8 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 (aripiprazole incidence, placebo incidence):

in adult patients (n=2467) treated with oral ABILIFY (11%, 6%), in pediatric patients ages 10 to 17 (21%, 5%), and in adult patients on ABILIFY Injection (9%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients, and 1% (4/399) of pediatric patients (10 to 17 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.

5.9 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 aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) *[see ADVERSE REACTIONS (6.3)]*.

5.10 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 (6.2, 6.3)]*.

In two 6-week placebo-controlled studies of aripiprazole as adjunctive treatment of Major Depressive Disorder, the incidences of suicidal ideation and suicide attempts were 0% (0/371) for aripiprazole and 0.5% (2/366) for placebo.

5.11 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. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk

for aspiration pneumonia *[see WARNINGS AND PRECAUTIONS (5.1) and ADVERSE REACTIONS (6.3)]*.

5.12 Use in Patients with Concomitant Illness

Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses is limited *[see USE IN SPECIFIC POPULATIONS (8.6, 8.7)]*.

ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies *[see WARNINGS AND PRECAUTIONS (5.1, 5.6)]*.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reactions Profile

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

- Use in Elderly Patients with Dementia-Related Psychosis *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*
- Clinical Worsening of Depression and Suicide Risk *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.2)]*
- Neuroleptic Malignant Syndrome (NMS) *[see WARNINGS AND PRECAUTIONS (5.3)]*
- Tardive Dyskinesia *[see WARNINGS AND PRECAUTIONS (5.4)]*
- Hyperglycemia and Diabetes Mellitus *[see WARNINGS AND PRECAUTIONS (5.5)]*
- Orthostatic Hypotension *[see WARNINGS AND PRECAUTIONS (5.6)]*
- Seizures/Convulsions *[see WARNINGS AND PRECAUTIONS (5.7)]*
- Potential for Cognitive and Motor Impairment *[see WARNINGS AND PRECAUTIONS (5.8)]*
- Body Temperature Regulation *[see WARNINGS AND PRECAUTIONS (5.9)]*
- Suicide *[see WARNINGS AND PRECAUTIONS (5.10)]*

- Dysphagia *[see WARNINGS AND PRECAUTIONS (5.11)]*

- Use in Patients with Concomitant Illness *[see WARNINGS AND PRECAUTIONS (5.12)]*

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, extrapyramidal disorder, headache, and nausea.

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

Aripiprazole has been evaluated for safety in 514 patients (10 to 17 years) who participated in multiple-dose, clinical trials in Schizophrenia or Bipolar Mania and who had approximately 205 patient-years of exposure to oral aripiprazole. A total of 278 pediatric patients were treated with oral aripiprazole for at least 180 days.

The conditions and duration of treatment with aripiprazole (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.

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, MedDRA dictionary terminology has been used to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while

receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; ie, all events meeting the defined criteria, regardless of investigator causality are included.

Throughout this section, adverse reactions are reported. These are adverse events that were considered to be reasonably associated with the use of ABILIFY (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for ABILIFY often cannot be reliably established in individual cases.

The figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

6.2 Clinical Studies 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 aripiprazole was administered in doses ranging from 2 mg/day to 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

Overall, there was little difference in the incidence of discontinuation due to adverse reactions between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse reactions that led to discontinuation were similar for the aripiprazole-treated and placebo-treated patients.

Commonly Observed Adverse Reactions

The only commonly observed adverse reaction associated with the use of aripiprazole in patients with Schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 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 aripiprazole was administered at doses of 15 mg/day or 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

Overall, in patients with Bipolar Mania, there was little difference in the incidence of discontinuation due to adverse reactions between aripiprazole-treated (11%) and placebo-treated (10%) patients. The types of adverse reactions that led to discontinuation were similar between the aripiprazole-treated and placebo-treated patients.

Commonly Observed Adverse Reactions

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

Table 5: 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	
	Aripiprazole	Placebo
Preferred Term	**(n=917)**	**(n=753)**
Akathisia	13	4
Sedation	8	3
Restlessness	6	3
Extrapyramidal Disorder	5	2
Tremor	6	3

Less Common Adverse Reactions in Adults

Table 6 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 aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 6: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class	**Aripiprazole**	**Placebo**
Preferred Term	**(n=1843)**	**(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 aripiprazole, 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.

Adults 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 aripiprazole was administered at doses of 15 mg/day 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 aripiprazole compared to 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive aripiprazole-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 aripiprazole 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 7 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 aripiprazole (doses of 15 mg/day 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 7: 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**	**Aripiprazole + 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 aripiprazole, except the 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 aripiprazole was administered in doses ranging from 2 mg/day to 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between aripiprazole-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 aripiprazole in adolescent patients with Schizophrenia (incidence of 5% or greater and aripiprazole 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 aripiprazole was administered in doses of 10 mg/day or 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between aripiprazole-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 aripiprazole in pediatric patients with Bipolar Mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 8.

Table 8: 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	**Aripiprazole (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

Less Common Adverse Reactions in Pediatric Patients (10 to 17 years) with Schizophrenia or Bipolar Mania

Table 9 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 4 weeks in Bipolar Mania), including only those reactions that occurred in 1% or more of pediatric patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo.

Table 9: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (10 to 17 years) Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**Aripiprazole** **(n=399)**	**Placebo** **(n=197)**
Eye Disorders		
Blurred Vision	5	0
Gastrointestinal Disorders		
Nausea	10	5
Salivary Hypersecretion	4	1
Diarrhea	3	0
Stomach Discomfort	2	1
Dry Mouth	2	1
General Disorders and Administration Site Conditions		
Fatigue	7	3
Pyrexia	3	1
Infections and Infestations		
Nasopharyngitis	4	3
Investigations		
Weight Increased	3	1
Metabolism and Nutrition Disorders		
Increased Appetite	4	2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	2	0
Nervous System Disorders		
Somnolence	20	5
Extrapyramidal Disorder	19	4
Headache	16	13
Akathisia	9	4
Dizziness	5	2
Tremor	5	2
Dystonia	2	0
Dyskinesia	1	0

Table 9: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (10 to 17 years) Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class	**Aripiprazole**	**Placebo**
Preferred Term	**(n=399)**	**(n=197)**
Sedation	1	0
Skin and Subcutaneous Disorders		
Rash	2	1
Vascular Disorders		
Orthostatic Hypotension	1	0

[a] Adverse reactions reported by at least 1% of pediatric patients treated with oral aripiprazole, 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 aripiprazole 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 aripiprazole-treated patients and 2% for adjunctive placebo-treated patients.

Commonly Observed Adverse Reactions

The commonly observed adverse reactions associated with the use of adjunctive aripiprazole in patients with Major Depressive Disorder (incidence of 5% or greater and aripiprazole 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 10 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 aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with adjunctive

aripiprazole was greater than the incidence in patients treated with adjunctive placebo in the combined dataset.

Table 10: 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**	**Aripiprazole+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 aripiprazole, 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 aripiprazole injection was administered at doses of 5.25 mg to 15 mg.

Adverse Reactions Associated with Discontinuation of Treatment

Overall, in patients with agitation associated with Schizophrenia or Bipolar Mania, there was little difference in the incidence of discontinuation due to adverse reactions between aripiprazole-treated (0.8%) and placebo-treated (0.5%) patients.

Commonly Observed Adverse Reactions

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

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

Table 11 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 aripiprazole injection (doses ≥5.25 mg/day) and for which the incidence in patients treated with aripiprazole injection was greater than the incidence in patients treated with placebo in the combined dataset.

Table 11: 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**	**Aripiprazole (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

Table 11: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Patients Treated with ABILIFY Injection

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction[a] Aripiprazole (n=501)	 Placebo (n=220)
Dizziness	8	5
Somnolence	7	4
Sedation	3	2
Akathisia	2	0

[a] Adverse reactions reported by at least 2% of patients treated with aripiprazole 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 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, and 30 mg/day) of oral aripiprazole 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%).

Extrapyramidal Symptoms

In short-term, placebo-controlled trials in Schizophrenia in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo. In the short-term, placebo-controlled trial of Schizophrenia in pediatric (13 to 17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 25% vs. 7% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 9% vs. 6% for placebo. 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 aripiprazole-treated patients was 16% vs. 8% for placebo and the incidence of akathisia-related events for monotherapy aripiprazole-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 aripiprazole-treated patients was 15% vs. 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive aripiprazole-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 aripiprazole-treated patients was 26% vs. 5% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 10% vs. 2% for placebo. 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 aripiprazole-treated patients was 8% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive aripiprazole-treated patients was 25% vs. 4% for adjunctive placebo-treated patients.

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 aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the pediatric (13 to 17 years) Schizophrenia trial, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Simpson Angus Rating Scale (aripiprazole, 0.24; placebo, -0.29). In the adult Bipolar Mania trials with monotherapy aripiprazole, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo

(aripiprazole, 0.50; placebo, -0.01 and aripiprazole, 0.21; placebo, -0.05). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups. In the Bipolar Mania trials with aripiprazole as adjunctive therapy with either lithium or valproate, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.73; placebo, 0.07 and aripiprazole, 0.30; placebo, 0.11). Changes in the Assessments of Involuntary Movement Scales were similar for adjunctive aripiprazole 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 aripiprazole and placebo (aripiprazole, 0.90; placebo, -0.05). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups. In the Major Depressive Disorder trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.31; placebo, 0.03 and aripiprazole, 0.22; placebo, 0.02). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive aripiprazole and adjunctive placebo groups.

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 aripiprazole and placebo.

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 aripiprazole-treated patients was 2% vs. 2% for placebo and the incidence of akathisia-related events for aripiprazole-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 aripiprazole and placebo.

Dystonia

Class Effect: 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.

Laboratory Test Abnormalities

A between group comparison for 3-week to 6-week, placebo-controlled trials in adults or 4-week to 6-week, placebo-controlled trials in pediatric patients (10 to 17 years) revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis in adult or pediatric patients.

In the 6-week trials of aripiprazole as adjunctive therapy for Major Depressive Disorder, there were no clinically important differences between the adjunctive aripiprazole-treated and adjunctive placebo-treated patients in the median change from baseline in prolactin, fasting glucose, HDL, LDL, or total cholesterol measurements. The median % change from baseline in triglycerides was 5% for adjunctive aripiprazole-treated patients vs. 0% for adjunctive placebo-treated patients.

In a long-term (26-week), placebo-controlled trial there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, or total cholesterol measurements.

Weight Gain

In 4-week to 6-week trials in adults with Schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively) and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)]. In a 6-week trial in pediatric patients (13 to 17 years) with Schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.13 kg vs. -0.83 kg, respectively) and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (5%) compared to placebo (1%)]. In 3-week trials in adults with Mania with monotherapy aripiprazole, the mean weight gain for aripiprazole and placebo patients was 0.1 kg vs. 0.0 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (2%) compared to placebo (3%). In the 6-week trial in Mania with

aripiprazole as adjunctive therapy with either lithium or valproate, the mean weight gain for aripiprazole and placebo patients was 0.6 kg vs. 0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight with adjunctive aripiprazole was 3% compared to adjunctive placebo 4%.

In the trials adding aripiprazole to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive aripiprazole or placebo in addition to their ongoing antidepressant treatment. The mean weight gain with adjunctive aripiprazole was 1.7 kg vs. 0.4 kg with adjunctive placebo. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was 5% with adjunctive aripiprazole compared to 1% with adjunctive placebo.

Table 12 provides the weight change results from a long-term (26-week), placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline. Although there was no mean weight increase, the aripiprazole group tended to show more patients with a ≥7% weight gain.

Table 12: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample

	BMI <23		BMI 23-27		BMI >27	
	Placebo (n=54)	Aripiprazole (n=59)	Placebo (n=48)	Aripiprazole (n=39)	Placebo (n=49)	Aripiprazole (n=53)
Mean change from baseline (kg)	-0.5	-0.5	-0.6	-1.3	-1.5	-2.1
% with ≥7% increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

Table 13 provides the weight change results from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 13: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample

	BMI <23 (n=314)	BMI 23-27 (n=265)	BMI >27 (n=260)
Mean change from baseline (kg)	2.6	1.4	-1.2
% with ≥7% increase BW	30%	19%	8%

ECG Changes

Between group comparisons for a pooled analysis of placebo-controlled trials in patients with Schizophrenia, Bipolar Mania, or Major Depressive Disorder revealed no significant differences between oral aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. Aripiprazole was associated with a median increase in heart rate of 2 beats per minute compared to no increase among placebo patients.

In the pooled, placebo-controlled trials in patients with agitation associated with Schizophrenia or Bipolar Mania, there were no significant differences between aripiprazole injection and placebo in the proportion of patients experiencing potentially important changes in ECG parameters, as measured by standard 12-lead ECGs.

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 ≤49 days), and were of limited duration (7/12 ≤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 study in Bipolar Disorder.

Other Adverse Reactions Observed During the Premarketing Evaluation of Aripiprazole

Following is a list of MedDRA terms that reflect adverse reactions as defined in *ADVERSE REACTIONS (6.1)* reported by patients treated with oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 13,543 adult patients. All events assessed as possible adverse drug reactions have been included with the exception of more commonly occurring events. In addition, medically/clinically meaningful adverse reactions, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in other parts of *ADVERSE REACTIONS (6)*, or those considered in *WARNINGS*

AND PRECAUTIONS (5) or *OVERDOSAGE (10)* have been excluded. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); those occurring in 1/100 to 1/1000 patients; and those occurring in fewer than 1/1000 patients.

Adults - Oral Administration

Blood and Lymphatic System Disorders:

≥1/1000 patients and <1/100 patients - leukopenia, neutropenia, thrombocytopenia

Cardiac Disorders:

≥1/1000 patients and <1/100 patients - bradycardia, palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, sinus tachycardia, atrial fibrillation, angina pectoris, myocardial ischemia; *<1/1000 patients* - atrial flutter, supraventricular tachycardia, ventricular tachycardia

Eye Disorders:

≥1/1000 patients and <1/100 patients - photophobia, diplopia, eyelid edema, photopsia

Gastrointestinal Disorders:

≥1/1000 patients and <1/100 patients - gastroesophageal reflux disease, swollen tongue, esophagitis; *<1/1000 patients* - pancreatitis

General Disorders and Administration Site Conditions:

≥1/100 patients - asthenia, peripheral edema, irritability, chest pain; *≥1/1000 patients and <1/100 patients* - face edema, thirst, angioedema; *<1/1000 patients* - hypothermia

Hepatobiliary Disorders:

<1/1000 patients - hepatitis, jaundice

Immune System Disorders:

≥1/1000 patients and <1/100 patients - hypersensitivity

Injury, Poisoning, and Procedural Complications:

≥1/100 patients - fall; *≥1/1000 patients and <1/100 patients* - self mutilation; *<1/1000 patients* - heat stroke

Investigations:

≥*1/100 patients* - weight decreased, creatine phosphokinase increased; ≥*1/1000 patients and <1/100 patients* - hepatic enzyme increased, blood glucose increased, blood prolactin increased, blood urea increased, electrocardiogram QT prolonged, blood creatinine increased, blood bilirubin increased; <*1/1000 patients* - blood lactate dehydrogenase increased, glycosylated hemoglobin increased, gamma-glutamyl transferase increased

Metabolism and Nutrition Disorders:

≥*1/100 patients* - decreased appetite; ≥*1/1000 patients and <1/100 patients* - hyperlipidemia, anorexia, diabetes mellitus (including blood insulin increased, carbohydrate tolerance decreased, diabetes mellitus non-insulin-dependent, glucose tolerance impaired, glycosuria, glucose urine, glucose urine present), hyperglycemia, hypokalemia, hyponatremia, hypoglycemia, polydipsia; <*1/1000 patients* - diabetic ketoacidosis

Musculoskeletal and Connective Tissue Disorders:

≥*1/1000 patients and <1/100 patients* - muscle rigidity, muscular weakness, muscle tightness, mobility decreased; <*1/1000 patients* - rhabdomyolysis

Nervous System Disorders:

≥*1/100 patients* - coordination abnormal; ≥*1/1000 patients and <1/100 patients* - speech disorder, parkinsonism, memory impairment, cogwheel rigidity, cerebrovascular accident, hypokinesia, tardive dyskinesia, hypotonia, myoclonus, hypertonia, akinesia, bradykinesia; <*1/1000 patients* - Grand Mal convulsion, choreoathetosis

Psychiatric Disorders:

≥*1/100 patients* - suicidal ideation; ≥*1/1000 patients and <1/100 patients* - aggression, loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation; <*1/1000 patients* - catatonia, sleep walking

Renal and Urinary Disorders:

≥*1/1000 patients and <1/100 patients* - urinary retention, polyuria, nocturia

Reproductive System and Breast Disorders:

≥*1/1000 patients and <1/100 patients* - menstruation irregular, erectile dysfunction, amenorrhea, breast pain; <*1/1000 patients* - gynaecomastia, priapism

Respiratory, Thoracic, and Mediastinal Disorders:

≥*1/100 patients* - nasal congestion, dyspnea, pneumonia aspiration

Skin and Subcutaneous Tissue Disorders:

≥*1/100 patients* - rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis; ≥*1/1000 patients and <1/100 patients* - pruritus, photosensitivity reaction, alopecia, urticaria

Vascular Disorders:

≥*1/100 patients* - hypertension; ≥*1/1000 patients and <1/100 patients* - hypotension

Pediatric Patients - Oral Administration

Most adverse events observed in the pooled database of 514 pediatric patients aged 10 to 17 years were also observed in the adult population. Additional adverse reactions observed in the pediatric population are listed below.

Gastrointestinal Disorders:

≥*1/1000 patients and <1/100 patients* - tongue dry, tongue spasm

Investigations:

≥*1/100 patients* - blood insulin increased

Nervous System Disorders:

≥*1/1000 patients and <1/100 patients* - sleep talking

Skin and Subcutaneous Tissue Disorders:

≥*1/1000 patients and <1/100 patients* - hirsutism

Adults - Intramuscular Injection

All adverse reactions observed in the pooled database of 749 adult patients treated with aripiprazole injection, were also observed in the adult population treated with oral aripiprazole. Additional adverse reactions observed in the aripiprazole 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

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), and blood glucose fluctuation.

7 DRUG INTERACTIONS

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally-acting drugs or alcohol.

Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect ABILIFY

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Ketoconazole and Other CYP3A4 Inhibitors

Coadministration of ketoconazole (200 mg/day for 14 days) with a 15 mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When ketoconazole is given concomitantly with aripiprazole, the aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; moderate inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased.

Quinidine and Other CYP2D6 Inhibitors

Coadministration of a 10 mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when quinidine is given

concomitantly with aripiprazole. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and should lead to similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased. 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)*.

Carbamazepine and Other CYP3A4 Inducers

Coadministration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, with aripiprazole (30 mg/day) resulted in an approximate 70% decrease in Cmax and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced.

7.2 Potential for ABILIFY to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10 mg/day to 30 mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*.

No effect of aripiprazole was seen on the pharmacokinetics of lithium or valproate.

Alcohol

There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

7.3 Drugs Having No Clinically Important Interactions with ABILIFY

Famotidine

Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40 mg single dose of the H_2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the Cmax of aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

Valproate

When valproate (500 mg/day-1500 mg/day) and aripiprazole (30 mg/day) were coadministered, at steady-state the Cmax and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

When aripiprazole (30 mg/day) and valproate (1000 mg/day) were coadministered, at steady-state there were no clinically significant changes in the Cmax or AUC of valproate. No dosage adjustment of valproate is required when administered concomitantly with aripiprazole.

Lithium

A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200 mg/day-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (Cmax and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

Coadministration of aripiprazole (30 mg/day) with lithium (900 mg/day) did not result in clinically significant changes in the pharmacokinetics of lithium. No dosage adjustment of lithium is required when administered concomitantly with aripiprazole.

Lamotrigine

Co-administration of 10 mg/day to 30 mg/day oral doses of aripiprazole for 14 days to patients with Bipolar I Disorder had no effect on the steady-state pharmacokinetics of 100 mg/day to 400 mg/day lamotrigine, a UDP-glucuronosyltransferase 1A4 substrate. No dosage adjustment of lamotrigine is required when aripiprazole is added to lamotrigine.

Dextromethorphan

Aripiprazole at doses of 10 mg/day to 30 mg/day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methoxymorphinan, a pathway dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole.

Warfarin

Aripiprazole 10 mg/day for 14 days had no effect on the pharmacokinetics of R-warfarin and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

Omeprazole

Aripiprazole 10 mg/day for 15 days had no effect on the pharmacokinetics of a single 20 mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with aripiprazole.

Lorazepam

Coadministration of lorazepam injection (2 mg) and aripiprazole injection (15 mg) to healthy subjects (n=40: 35 males and 5 females; ages 19-45 years old) did not result in clinically important changes in the pharmacokinetics of either drug. No dosage adjustment of aripiprazole is required when administered concomitantly with lorazepam. However, the intensity of sedation was greater with the combination as compared to that observed with aripiprazole alone and the orthostatic hypotension observed was greater

with the combination as compared to that observed with lorazepam alone *[see WARNINGS AND PRECAUTIONS (5.6)]*.

Escitalopram

Coadministration of 10 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of 10 mg/day escitalopram, a substrate of CYP2C19 and CYP3A4. No dosage adjustment of escitalopram is required when aripiprazole is added to escitalopram.

Venlafaxine

Coadministration of 10 mg/day to 20 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg/day venlafaxine XR, a CYP2D6 substrate. No dosage adjustment of venlafaxine is required when aripiprazole is added to venlafaxine.

Fluoxetine, Paroxetine, and Sertraline

A population pharmacokinetic analysis in patients with Major Depressive Disorder showed no substantial change in plasma concentrations of fluoxetine (20 mg/day or 40 mg/day), paroxetine CR (37.5 mg/day or 50 mg/day), or sertraline (100 mg/day 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. Aripiprazole dosing was 2 mg/day to 15 mg/day (when given with fluoxetine or paroxetine) or 2 mg/day to 20 mg/day (when given with sertraline).

8 USE IN SPECIFIC POPULATIONS

In general, no dosage adjustment for ABILIFY is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function *[see DOSAGE AND ADMINISTRATION (2.5)]*.

8.1 Pregnancy

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

Pregnant rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, 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. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 mg/kg and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 mg/kg and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 mg/kg and 30 mg/kg 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. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

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

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

In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, 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, which produced 5 times the human exposure at the MRHD based on AUC and is 6 times the MRHD based on mg/m^2.

In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose.

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

There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

8.2 Labor and Delivery

The effect of aripiprazole on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

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.

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 INDICATIONS AND USAGE (1.1), DOSAGE AND ADMINISTRATION (2.1), ADVERSE REACTIONS (6.2), 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.

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 INDICATIONS AND USAGE (1.2), DOSAGE AND ADMINISTRATION (2.2), ADVERSE REACTIONS (6.2), 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.

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 weights.

8.5 Geriatric Use

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in Schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients *[see also BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*.

Of the 13,543 patients treated with oral aripiprazole in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. The majority (81%) of the 1073 patients were diagnosed with Dementia of the Alzheimer's type.

Placebo-controlled studies of oral aripiprazole 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 aripiprazole injection in clinical trials, 99 (13%) were ≥65 years old and 78 (10%) were ≥75 years old. Placebo-controlled studies of aripiprazole 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.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with Schizophrenia *[see also BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*. The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

8.6 Renal Impairment

In patients with severe renal impairment (creatinine clearance <30 mL/min), Cmax of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

8.7 Hepatic Impairment

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

8.8 Gender

Cmax and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30% to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

8.9 Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

8.10 Smoking

Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ABILIFY is not a controlled substance.

9.2 Abuse and Dependence

Aripiprazole 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 (eg, 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

A total of 76 cases of deliberate or accidental overdosage with oral aripiprazole have been reported worldwide. These include overdoses with oral aripiprazole alone and in combination with other substances. No fatality was reported from these cases. Of the 44 cases with known outcome, 33 cases recovered without sequelae and one case recovered with sequelae (mydriasis and feeling abnormal). The largest known case of acute ingestion with a known outcome involved 1080 mg of oral aripiprazole (36 times the maximum recommended daily dose) in a patient who fully recovered. Included in the 76 cases are 10 cases of deliberate or accidental overdosage in children (age 12 and younger) involving oral aripiprazole ingestions up to 195 mg with no fatalities.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole 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 aripiprazole 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

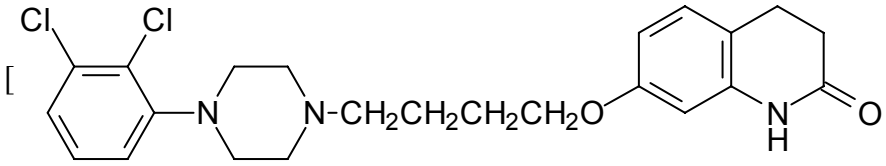
No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, 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 aripiprazole, 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 aripiprazole, 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 $C_{23}H_{27}Cl_2N_3O_2$ 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 150 mg/mL of sulfobutylether β-cyclodextrin (SBECD), tartaric acid, sodium hydroxide, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole, as with other drugs having efficacy in Schizophrenia, Bipolar Disorder, Major Depressive Disorder, and agitation associated with Schizophrenia or Bipolar Disorder, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole (eg, the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic $alpha_1$ 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, $alpha_1$-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 are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

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 mg/day to 30 mg/day aripiprazole for 14 days, there was dose-dependent D_2 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.

Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Coadministration of ABILIFY with known inhibitors of CYP2D6, such as quinidine or fluoxetine in EMs, approximately doubles aripiprazole plasma exposure, and dose adjustment is needed *[see DRUG INTERACTIONS (7.1)]*. The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs, respectively. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Following a single oral dose of [^{14}C]-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.

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 and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1 mg/kg/day, 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day to ICR mice and 1 mg/kg/day, 3 mg/kg/day, and 10 mg/kg/day to F344 rats (0.2 times to 5 times and 0.3 times 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 mg/kg/day, 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day (3 times to 19 times the MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 mg/kg/day to 30 mg/kg/day (0.1 times to 0.9 times human exposure at MRHD based on AUC and 0.5 times 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 mg/kg/day, 6 mg/kg/day, and 20 mg/kg/day (0.6 times, 2 times, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 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 mg/kg and 20 mg/kg and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day (6 times, 13 times, 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 mg/kg 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 mg/kg and 60 mg/kg. The 40 mg/kg and 60 mg/kg doses are 13 times and 19 times the maximum recommended human dose (MRHD) based on mg/m^2 and 7 times 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

14.1 Schizophrenia

Adult

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 aripiprazole 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. The Positive and Negative Syndrome Scale (PANSS) is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in Schizophrenia. The PANSS positive subscale is a subset of items in the PANSS that rates seven positive symptoms of Schizophrenia (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility). The PANSS negative subscale is a subset of items in the PANSS that rates seven negative symptoms of Schizophrenia (blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, stereotyped thinking). 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 mg/day or 30 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, 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 mg/day or 30 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

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

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

In a fifth study, a 4-week trial (n=103) comparing ABILIFY in a range of 5 mg/day to 30 mg/day to placebo, ABILIFY was only significantly different compared to placebo in a responder analysis based on the CGI-severity score, a primary outcome for that trial.

Thus, the efficacy of 10 mg, 15 mg, 20 mg, 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.

Pediatric

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 mg/day 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, 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.

14.2 Bipolar Disorder

Monotherapy

Adults

The efficacy of ABILIFY in the treatment of acute 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 (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) 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 15 mg/day in two studies and 30 mg/day in two studies), ABILIFY was superior to placebo in the reduction of Y-MRS total score 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.

A trial was conducted in 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 mg/day 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. The majority of these relapses were due to manic rather than depressive symptoms. There is insufficient data to know whether ABILIFY is effective in delaying the time to occurrence of depression in patients with Bipolar I Disorder.

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.

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 four-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 mg/day 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. 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.

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 mEq/L to 1.0 mEq/L) or valproate (50 μg/mL 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 YMRS total score) to lithium or valproate were randomized to receive either aripiprazole (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 mEq/L to 1.0 mEq/L or 50 μg/mL to 125 μg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score and CGI-BP Severity of Illness score (mania). Seventy-one percent of the patients co-administered valproate and 62% of the patients co-administered lithium, were on 15 mg/day at 6-week endpoint.

Although 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, such efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

14.3 Adjunctive Treatment of Major Depressive Disorder

The efficacy of ABILIFY in the adjunctive treatment of Major Depressive Disorder was demonstrated in two short-term (6-week), placebo-controlled trials of adult patients meeting DSM-IV criteria for Major Depressive Disorder 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 (apparent sadness, reported sadness, inner

tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts). 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 (work/school, social life, and family life) 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. 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 mg/day, 5 mg/day, 10 mg/day, 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 mg/day 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.

14.4 Agitation Associated with Schizophrenia or Bipolar Mania

The efficacy of intramuscular aripiprazole 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 (ie, 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 aripiprazole 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 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 aripiprazole injection dose of 9.75 mg was evaluated. At 2 hours post-injection, aripiprazole for injection was statistically superior to placebo in the PANSS Excited Component 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 aripiprazole 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.

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

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 14.

Table 14: ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code

Table 14: 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	59148-007-13
			Blister of 100	59148-007-35
10 mg	pink modified rectangle	"A-008" and "10"	Bottle of 30	59148-008-13
			Blister of 100	59148-008-35
15 mg	yellow round	"A-009" and "15"	Bottle of 30	59148-009-13
			Blister of 100	59148-009-35
20 mg	white round	"A-010" and "20"	Bottle of 30	59148-010-13
			Blister of 100	59148-010-35
30 mg	pink round	"A-011" and "30"	Bottle of 30	59148-011-13
			Blister of 100	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 15.

Table 15: 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 25º C (77º F); excursions permitted between 15º C to 30º C (59º F to 86º F) [see USP Controlled Room Temperature].

Oral Solution

Store at 25° C (77° F); excursions permitted between 15º C to 30º C (59º F to 86º 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 25º C (77º F); excursions permitted between 15° C to 30º C (59° F to 86º 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 (17.2)

17.1 Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY:

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. ABILIFY is not approved for elderly patients with dementia-related psychosis *[see WARNINGS AND PRECAUTIONS (5.1)]*.

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 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 aripiprazole 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 aripiprazole therapy does not affect them adversely *[see WARNINGS AND PRECAUTIONS (5.8)]*.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY *[see USE IN SPECIFIC POPULATIONS (8.1)]*.

Nursing

Patients should be advised not to breast-feed an infant if they are taking ABILIFY *[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)]*.

Alcohol

Patients should be advised to avoid alcohol while taking ABILIFY *[see DRUG INTERACTIONS (7.2)]*.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see WARNINGS AND PRECAUTIONS (5.9)]*.

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

Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

US Patent Nos: 5,006,528; 6,977,257; and 7,115,587

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17.2 Medication Guide

MEDICATION GUIDE

ABILIFY® (a BIL ĭ fī)

Generic name: aripiprazole

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

• all risks and benefits of treatment with antidepressant medicines

• all treatment choices for depression or other serious mental illness

What is the most important information I should know about 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.

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

It should be noted that ABILIFY is approved to be added to an antidepressant when the response from the antidepressant alone is not adequate. ABILIFY is not approved for pediatric patients with depression.

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

ABILIFY is a trademark of Otsuka Pharmaceutical Company.

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/s/

Thomas Laughren
5/6/2008 10:47:15 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S-019, S-020, S-022
21-713/S-014, S-015, S-017
21-729/S-006, S-007, S-009
21-866/S-006, S-007, S-009

SUMMARY REVIEW

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: May 6, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval actions for Abilify supplements for a 15 mg/day starting dose in bipolar disorder and for Abilify supplements for adjunctive therapy at a 15 mg/day starting dose in bipolar disorder patients who are "partial non-responders" to either valproate or lithium

TO: -File NDAs 21-436/S-019 (Abilify tabs), 21-713/S-014 (oral solution), 21-729/S-006 (ODT), and 21-866/S-006 (IM)
-File NDAs 21-436/S-020 (Abilify tabs), 21-713/S-015 (oral solution), 21-729/S-007 (ODT), and 21-866/S-007 (IM)
-[Note: This overview should be filed with the 7-11-07 original submission of these supplements.]

1.0 BACKGROUND

Abilify (aripiprazole) is an atypical antipsychotic (5HT2 antagonist and D2 receptor partial agonist) that is approved for both schizophrenia and bipolar disorder in adults (mania and mixed episodes), both acute and maintenance therapy for both, for schizophrenia and bipolar disorder (mania and mixed episodes) in pediatric patients, and as adjunctive treatment in patients with MDD who have had a partial response to available antidepressant therapy. These supplements provide support for:

- The efficacy and safety of a 15 mg/day starting dose in the treatment of bipolar disorder (mania and mixed episodes). [Note: Current labeling recommends a starting dose of 30 mg/day.] The support for this new claim includes the results of 2 short-term (3-week) studies in this population where the starting dose was 15 mg/day, and where the dose could be increased to 30 mg/day as needed.
- The efficacy and safety of a 15 mg/day starting dose as adjunctive therapy in bipolar disorder patients who were "partial non-responders" to either valproate or lithium. The support for this new claim includes the results of a short-term (6-week) study in this population where the starting dose was 15 mg/day, and where the dose could be increased to 30 mg/day as needed.
- We held a preNDA meeting with the sponsor on 2-26-07.

2.0 CHEMISTRY

The only CMC issues requiring review were very minor labeling changes and environmental assessment. The minor labeling issues have been addressed, and the sponsor sought and was granted a categorical exclusion.

3.0 PHARMACOLOGY

There were no pharm/tox review issues for consideration.

4.0 BIOPHARMACEUTICS

The only relevant biopharmaceutics results requiring review came from a drug-drug interaction study involving aripiprazole and lamotrigine. These data were submitted in a separate supplement but were reviewed and will be acted on as part of the review of these supplements. This review revealed no effect of aripiprazole on lamotrigine pharmacokinetics. OCP recommended a slight modification to labeling regarding these findings, and we have reached agreement with the sponsor on these changes.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Efficacy data for a 15 mg/day starting dose in mania

Our efficacy review focused on two nearly identically designed 3-week, multicenter, double-blind, parallel group, randomized, placebo-controlled, flexible-dose monotherapy studies in adult patients with bipolar disorder (mania or mixed episodes) (CN138135 and CN138162). Each study had an active comparator group, lithium for study C-135 and haloperidol for study C-162. Thus, patients were assigned to aripiprazole, an active comparator, or placebo. Patients assigned to aripiprazole had a starting dose of 15 mg/day, and the dose could be increased to 30 mg/day as early as day 4, if needed. The primary endpoint was change from baseline to endpoint in YMRS total score, and the key secondary endpoint was change from baseline to endpoint in the CGI-S-BP (bipolar) score. There was a 9-week active controlled phase following the initial 3 weeks of treatment during which patients who had been receiving placebo were switched to aripiprazole and patients already receiving active drug were simply continued. Data from this phase have not been reviewed from the standpoint of efficacy.

5.1.1.1 Study CN-138135

N=480 patients were randomized to treatment (ITT Sample: 163 to placebo, 155 to lithium, and 154 to aripiprazole). Overall, there was about a 50% dropout rate by week 3. The mean

aripiprazole dose during the 3rd week was approximately 23 mg/day. The outcome for aripiprazole vs placebo was significant for both YMRS (P<0.001) and CGI-S-BP (P=0.002).

5.1.1.2 Study CN-138162

N=485 patients were randomized to treatment (ITT Sample: 152 to placebo, 161 to lithium, and 166 to aripiprazole). Overall, there was about a 25% dropout rate by week 3. The mean aripiprazole dose during the 3rd week was approximately 23 mg/day. The outcome for aripiprazole vs placebo was significant for both YMRS (P=0.039) and CGI-S-BP (P=0.044).

5.1.2 Efficacy data for adjunctive therapy in bipolar disorder patients who were "partial non-responders" to either valproate or lithium t a 15 mg/day starting dose

Our efficacy review focused on a 6-week, multicenter, double-blind, parallel group, randomized, placebo-controlled, flexible-dose, adjunctive therapy study in adult patients with bipolar disorder (mania or mixed episodes, with or without psychotic features) (CN138134) who were partially non-responsive to either lithium or valproate. Thus, patients were assigned to either adjunctive aripiprazole or adjunctive placebo, on a 2:1 ratio. Patients assigned to adjunctive aripiprazole had a starting dose of 15 mg/day, and the dose could be increased to 30 mg/day as early as day 7, if needed. The primary endpoint was change from baseline to endpoint in YMRS total score, and the key secondary endpoint was change from baseline to endpoint in the CGI-S-BP (bipolar) score. N=384 patients were randomized to treatment (ITT Sample: 130 to placebo and 247 to aripiprazole). Overall, about 81% of patients completed the study. The outcome for aripiprazole vs placebo was significant for both YMRS (P=0.002) and CGI-S-BP (P=0.014).

5.1.3 Summary of Efficacy

There was unanimous agreement within the review team on the positive outcomes for the primary and key secondary endpoints in these studies. I agree.

5.2 Safety Data

The safety data for the monotherapy supplements were derived from a total of n=917 bipolar patients exposed to treatment with aripiprazole monotherapy. This was a database that combined aripiprazole exposures from this program and the previous monotherapy studies of aripiprazole in bipolar disorder. Overall, the adverse event profile for aripiprazole when used as monotherapy in bipolar disorder was similar to that seen when it has been used in other disorders.

The safety data for the adjunctive therapy supplements were derived primarily from study 134. Overall, the adverse event profile for aripiprazole when used as adjunctive treatment in bipolar disorder was similar to that seen when it has been used in other disorders. There was a suggestion that the combination of aripiprazole and lithium was associated with a somewhat higher incidence of akathisia than was seen with aripiprazole alone or with the aripiprazole/valproate combination.

5.3 Clinical Sections of Labeling

We made several modifications to the sponsor's proposed labeling, and have now reached agreement on final labeling.

6.0 WORLD LITERATURE

The sponsor warranted that they conducted an extensive literature review and found no relevant papers that would adversely affect conclusions about the safety of aripiprazole for the proposed use.

7.0 DSI INSPECTIONS

Inspections were conducted at 2 sites, i.e., 1 for study 162 from the 15 mg/day starting dose program and 1 for study 134 from the adjunctive therapy program. Data from the study 162 site were deemed to be acceptable. However, data from 6 patients from the study 134 site were deemed to be unreliable. A re-analysis of the data for study 134 was still positive, even without the data from this unreliable site.

8.0 PREA REQUIREMENTS

We decided to waive the requirement for pediatric studies with a starting dose of 15 mg/day, because the recommended pediatric starting dose is 2 mg/day, and the target dose is 10 mg/day. Regarding pediatric studies for adjunctive therapy, it is our judgment that it is reasonable to extrapolate from the adult adjunctive studies to pediatric patients. Thus, we have not requested pediatric adjunctive studies. Given our current views on extrapolation from adult studies, we have also extrapolated from the adult schizophrenia and bipolar studies (i.e., positive acute studies in adults and pediatric patients, and positive maintenance studies in adults) to maintenance therapy in pediatric patients with these conditions, resulting in our judgment that this product is entitled to maintenance claims for both conditions in the pediatric population.

9.0 LABELING AND APPROVAL LETTER

We have included the mutually agreed upon final label with the approval letter.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Otsuka has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe as monotherapy with a starting dose of 15 mg/day in the treatment of patients with bipolar disorder (manic or mixed episodes) and as adjunctive therapy (i.e., added on to either lithium or valproate) with a starting dose of 15 mg/day in the treatment of patients

with bipolar disorder (manic or mixed episodes). We have now reached agreement with the sponsor on final labeling, and we will issue the attached approval letter along with agreed upon final labeling.

cc:
Orig NDAs 21-436/S-019 (Abilify tabs), 21-713/S-014 (oral solution), 21-729/S-006 (ODT), and 21-866/S-006 (IM)
Orig NDAs 21-436/S-020 (Abilify tabs), 21-713/S-015 (oral solution), 21-729/S-007 (ODT), and 21-866/S-007 (IM)
HFD-130/TLaughren/MMathis/GZornberg/KBrugge/DBates

DOC: Aripiprazole_15 mg Start Dose_ Adjunctive Therapy_Bipolar_Laughren_AP_Memo.doc

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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/

Thomas Laughren
5/6/2008 09:00:03 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S-019, S-020, S-022
21-713/S-014, S-015, S-017
21-729/S-006, S-007, S-009
21-866/S-006, S-007, S-009

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review Memorandum

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

Date:	21 April 2008 (originally filed in DFS on April 15, 2008, the document was deleted mistakenly by the document room as documented in an email dated 16 April 2008 at 7:03 am)
From:	Gwen L. Zornberg, M.D., Sc.D. Division of Psychiatry Products HFD-130
Subject:	Cross-discipline team leader review
NDA #:	21-436 (SN 019, 020, 022 tablets); 21-713 (oral solution SN 014, 015, 017); 21-729 (oral dissolving tablets SN 006, 007, 009); 21-866 (injection SN 006, 007, 009)
Proprietary Name:	Abilify® (aripiprazole)
Dosage Forms/ Strengths:	Aripiprazole tablets, oral solution, ODT, IM
Reviewers:	Karen Brugge, M.D., Clinical; Nallaperum Chidambaram Ph.D., CMC; Andre Jackson, Clinical Pharmacology; Philip Dinh, Ph.D., Biometrics.
Recommended:	Approval Action for aripiprazole for the treatment of bipolar disorder, manic or mixed episodes; monotherapy starting at 15 mg (019); adjunctive to lithium or valproate (020); and PA lamotrigine drug-drug interaction supplement contingent upon agreement with BMS/Otsuka on final labeling language.

1.0 BACKGROUND

The purpose of this memorandum is to assist the Division Director in the regulatory processing of three NDA supplements. Aripiprazole is the first approved member of

drugs that mediate antipsychotic effects as partial agonists at dopamine D_2 receptors that are posited to act as agonists in states of dopaminergic hypoactivity and as antagonists in states of dopaminergic hyperactivity. Aripiprazole was first approved for the treatment of schizophrenia on 15 November 2002.

This memorandum reviews three supplements for all 4 formulations. The efficacy supplement to the NDA seeks a claim for the short-term use of aripiprazole as an adjunctive treatment starting with aripiprazole 15 mg daily for patients diagnosed with bipolar I disorder (BP), manic or mixed episodes who have been partial responders to treatment with lithium or valproate as mood stabilizers, following 2 positive trials evaluating aripiprazole 15 mg daily as the starting dose in the treatment of the manic or mixed episodes of bipolar disorder.

Otsuka /BMS also submitted PA labeling supplements (NDA 021-436, SN 022) to pertain also to all 4 aripiprazole formulations regarding a drug-drug interaction study (CN138402) between steady-state aripiprazole and steady-state lamotrigine, which are due 28 June 2008.

2.0 CMC

Dr. Nallaperum Chidambaram, in his review dated 29 February 2007, has provided no objection to the applicants' submissions of categorical exclusion claims pursuant to 21 CFR 25.22 (b) that states, "This bundled efficacy supplement provides for the use of Abilify in the adjunctive treatment of bipolar disorder, manic or mixed. The applicant has not provided any new chemistry, manufacturing and controls (CMC) information other than some minor formatting changes to table numbers in the *How Supplied* section of the labeling. The applicant has submitted a claim for categorical exclusion from filing an environmental assessment document under 21 CFR 25.31 (b); the expected introduction concentration (EIC) of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The applicant's claim is found to be acceptable. In summary, Dr. Chidambaram found the provided information to be adequate. This supplement and others in this bundle are recommended for approval from the standpoint of chemistry, manufacturing and controls."

Consequently, I am not aware of any (CMC) issues at this point that would preclude an approval action for these supplements.

3.0 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

I am not aware of any pharmacology/toxicology issues at this point that would preclude an approval action for these supplements.

4.0 CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

Based on Dr. Andre Jackson's review of the drug-drug interaction study (CN138402) between steady-state aripiprazole and steady-state lamotrigine in the labeling supplements indexed by number 022 (Abilify tablets) complementing these studies of aripiprazole as adjunctive treatment of bipolar disorder, the study was appropriately designed and conducted with a validated assay (first summarized in an email dated 31 March 2008). Dr. Jackson confirmed in his review dated 14 April 2008 that the kinetic results showed a very small decrease in PK parameters of 10-15%. He found that the data showed that "co-administration of 10 mg/day to 30 mg/day oral doses of aripiprazole for 14 days to patients diagnosed with Bipolar I Disorder had no effect on the steady-state pharmacokinetics of 100 mg/day to 400 mg/day lamotrigine, a UDP-glucuronosyltransferase 1A4 substrate. No dosage adjustment of lamotrigine is required when aripiprazole is added to lamotrigine," which supports the applicants' claim of no effect of aripiprazole on steady-state lamotrigine serum levels. Dr. Jackson had no changes to recommend to the sponsors' proposed labeling language.

I am not aware of any biopharmaceutics issues at this point that would preclude an approval action for these 3 supplements.

5.0 CLINICAL/STATISTICAL

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

<u>Aripiprazole Starting Dose of 15 mg Daily Treatment of Bipolar Disorder (manic and mixed episodes)</u>

The first studies in the application NDA 21-436 SE1 N019 were 2 similarly designed 3-week double-blind, multicenter, randomized, parallel group, active and placebo-controlled trials (CN138135 and CN138162) in patients diagnosed with BP I disorder. Following the primary efficacy assessments at week-3, the patients in the placebo group were switched to aripiprazole while in study CN138135, the patients in the lithium group remained on lithium and in study CN138162 the patients in the haloperidol group remained on haloperidol for the remaining 9 weeks of blinded treatment. Those patients who completed the trial were eligible for a 40-week double-blind extension study.

The dose design of adjunctive aripiprazole treatment was flexible in both studies. All patients in the aripiprazole treatment group were started on 15 mg/day. The patients and investigators were allowed the option to increase the dose to 30 mg/day, if needed, over the 12 weeks of blinded treatment. Lithium was initiated at 900 mg/day with an option to increase to 1200 mg/day at day 4 and to 1500 mg/day at Day 7. In trial CN138135, 480 patients between the ages of 18 and 69 years were enrolled in the U.S. In trial CN138162, 485 patients between ages 18 and 76 were randomized from Bulgaria, Croatia, Mexico, Peru, Russia, South Africa, and the U.S.

The primary endpoint analysis for these two 3-week, parallel-group efficacy studies were the standard analysis of mean change from baseline to endpoint on the YMRS total score. The key secondary analysis was the change in the Clinical Global Impression-Bipolar Version (CGI-BP) Severity of Illness (mania) score.

Dr. Dinh confirmed the statistical findings and related sensitivity analyses in his review dated 3 March 2008. In study CN138135, both the primary (<0.001) and the key secondary (0.002) analytic findings were highly significantly superior to treatment with placebo. In trial CN138162, the primary (p=0.04) and the key secondary analyses (0.04) were significant. The subgroup results for the U.S. study sample did not show a significant separation between aripiprazole and placebo. Nonetheless, study took place entirely in the U.S. and was positive. In trial CN138135, the improvement in the aripiprazole treatment groups were also numerically superior to lithium. In trial CN138162, haloperidol held a slight numeric edge versus on both the primary and key secondary analyses that was not material in comparison to aripiprazole.

Treatment of Bipolar disorder Adjunctive to Lithium or Valproate (manic and mixed episodes)

In the application NDA 21-436 SE1 020, the findings from the 6-week double-blind, multicenter, randomized, parallel group, placebo-controlled trial (CN138134) in patients diagnosed with BP I disorder who were demonstrated to be to be partial responders to lithium or valproate therapy. The design consisted of a 3-day to 4-week washout prior to 2 weeks in prospective open-label treatment with lithium or valproate phase. Patients on stable lithium or valproate mood stabilizer therapy with a reduction of $\leq$ 25% and $\geq$ 16 on the YMRS total score were eligible to be randomized (2:1) to 6-weeks double-blind aripiprazole or placebo adjunctive treatment groups. Patients who completed 6-weeks the 6-week double-blind adjunctive treatment phase were eligible to continue on 46 weeks of open-label aripiprazole treatment.

In his Biometrics review dated 3 March 2008, Dr. Dinh confirmed the statistical primary and key secondary analyses, identical to those in the 15 mg starting dose studies. Aripiprazole was superior to placebo on the primary efficacy analysis of LOCF change from baseline to endpoint on the YMRS total score ($p = 0.002$) and on the CGI-BP key secondary analysis ($p < 0.001$). Analyses stratified by U.S vs. non-U.S. groupings suggested similar treatment effects across the geographical groupings.

Aripiprazole Exposure in the 3 Positive Trials

To evaluate data other than the mean dose administered during the trials, the undersigned requested additional data from the sponsors to provide to the Division Director. The following data was sent by BMS/Otsuka on 28 March 2008.

Monotherapy with Aripiprazole starting dose of 15 mg daily:

Percent in 15 mg Compared to 30 mg Aripiprazole Groups at 3-week Endpoint

CN138135 **Monotherapy** Treatment of Bipolar I (manic, mixed)			
3-week endpoint	**Lithium**	**Placebo**	**Aripiprazole**
0 mg			13 (8%)
15 mg			68 (44%)
30 mg			72 (47%)

Percent in 15 mg Compared to 30 mg Dose Aripiprazole Groups at 3-week Endpoint

CN138162 **Monotherapy** Treatment of Bipolar I (manic, mixed)			
3-week endpoint	**Haloperidol**	**Placebo**	**Aripiprazole**
0 mg			8 (4.8%)
15 mg			69 (42%)
30 mg			88 (53%)

Adjunctive Aripiprazole Starting dose 15 mg daily

Percent of Patients in 15 mg Compared to 30 mg Dose Groups at 6-week Endpoint

CN138134 **Adjunctive** Treatment of Bipolar I (manic, mixed)			
6-week endpoint	**LITHIUM**	**Placebo**	**Aripiprazole N=118**
15 mg		50%	**63 (62%)**
30 mg		40%	24 (24%)
	VALPROATE	Placebo	Aripiprazole
15 mg		60%	**84 (71%)**
30 mg		40%	29 (25%)

Weekly Mean Dose - CN138134 Adjunctive Treatment of Bipolar I (manic, mixed)

	Placebo		Aripiprazole			
Days	N	(%)	N	(%)	Mean (mg/day)	Min - Max (mg/day)
1 - 7	130	(100)	253	(100)	15.5	10.7 - 45.0
8 - 14	129	(99.2)	242	(95.7)	17.3	6.0 - 30.0
15 - 21	124	(95.4)	233	(92.1)	18.4	7.5 - 30.0
22 - 28	123	(94.6)	217	(85.8)	18.8	2.1 - 30.0
29 - 35	119	(91.5)	208	(82.2)	18.7	6.4 - 30.0
36 - 42	115	(88.5)	197	(77.9)	19.0	8.6 - 40.7
43 - 49	46	(35.4)	81	(32.0)	18.5	12.0 - 45.0
> 49	6	(4.6)	14	(5.5)	18.6	15.0 - 45.0

Data provided by BMS/Otsuka in an email attachment 28 March 2008

In, summary in the adjunctive treatment of bipolar disorder, patients treated with valproate or lithium were most likely to remain on the 15 mg dose, which is associated with a reduced risk of adverse events such as akathisia offers coupled with satisfactory efficacy in the majority of patients in the aripiprazole treated group. In contrast, in the monotherapy trials, patients who started on aripiprazole 30 mg tended to remain on 30 mg, while patients started on 15 mg are almost equally likely to remain on 15 mg as to increase to the 30 mg aripiprazole dose level.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has in my view, based on the data in the application supporting the conclusions of the reviews of Dr. Brugge and Dr. Dinh, provided sufficient evidence to support the claim of short-term efficacy of aripiprazole with a starting dose of 15 mg as adjunctive treatment in patients diagnosed with bipolar disorder (manic or mixed episodes) who are partial responders to lithium or valproate. In terms of adjunctive treatment of bipolar disorder, the majority of patients that start at 15 mg dose level are more likely to remain at the 15 mg dose over 6-weeks, irrespective of co-administration with lithium or valproate. In contrast, in monotherapy, patients are more likely to be raised to 30 mg than with adjunctive treatment, however, the likelihood o was similar of remaining in the15 mg group or being raised to the 30 mg dose group in study CN138135 (U.S. study) in contrast to the International study in which there was s modestly greater tendency to increase the aripiprazole dose to 30 mg.

5.2 Safety Data

5.2.1 Common Adverse Drug Reaction Profile for Aripiprazole As Monotherepay and Adjunctive Treatment of Bipolar Disorder

The safety and tolerability profile of aripiprazole in these 2 most recent monotherapy trials with the reduced starting dose of 15 mg was similar with no increase in toxicity.

Monotherapy

The profile of aripiprazole continues to include akathisia, tremor, restlessness, and constipation as in monotherapy trials of schizophrenia and bipolar disorder. In the short-term, placebo-controlled of monotherapy the percentage of akathisia-related events for aripiprazole-treated patients was 12% compared to 6% for placebo- treated patients, as presented in Dr. Brugge's addendum signed off 4 March 2008.

Adjunctive Therapy

Akathisia occurrence was greater in the aripiprazole group (18.6%) than the placebo group (5.4%) in the placebo-controlled trials of aripiprazole as adjunctive to lithium or valproate. Tremor was greater also in the placebo-controlled adjunctive trials in the aripiprazole exposed group (9.1%) versus the placebo (6.2%) exposed group. The most commonly observed adverse events (occurrence of 5% or greater and twice that for

adjunctive placebo) in these trials of aripiprazole as adjunctive to lithium or valproate were: akathisia, insomnia, and extrapyramidal disorders. In the 6-week, placebo-controlled trial of aripiprazole in the treatment of bipolar mania for adjunctive therapy with lithium or valproate (CN138134), the incidence of reported EPS-related events, excluding events related to akathisia for adjunctive aripiprazole-treated patients was 15% compared to 8% for adjunctive placebo. The elevated frequencies of these adverse events in adjunctive treatment study are not unexpected from a clinical viewpoint.

Any interpretation is limited of the exploratory subgroup analyses by mood stabilizer, as randomization was not stratified by mood stabilizer and the samples were small and unstable. Nonetheless, given these limitations, Dr. Brugge examined the subgroups for exploratory glimpses of potential trends. Akathisia in particular was noted by Dr. Brugge to more frequent in the subgroup exposed to concomitant lithium compared to valproate in the adjunctive aripiprazole treatment group, which is not unexpected given the adverse event profile of lithium salt.

5.2.2 Adverse Reactions of Particular Interest

There was 1 death in open label phase of CN138134, the adjunctive bipolar disorder database. As Dr. Brugge acknowledged on page 31 of her review (SN 020), "The events are complicated and it is difficult to ascertain the potential role of Arip with these events."

5.2.3 Use in Elderly Patients

As aripiprazole and the mood stabilizer drugs evaluated are approved drugs, the sponsor did not conduct any special population studies. Patients aged greater than 65 years were excluded from the short-term registration trials of the 15 mg starting dose in bipolar disorder as monotherapy and the adjunctive treatment of bipolar disorder, manic and mixed episodes.

5.2.4 Risk: Benefit Evaluation

In view of the known morbidity and mortality of the manic and mixed episodes of such a serious disorder as bipolar I disorder, maintaining treatment of patients with only a partial response to lithium or valproate alone is considered inappropriate in the literature and is no longer the accepted standard of care. To the best of my knowledge, no other antipsychotic drug with partial agonist properties is approved for the indication of adjunctive treatment (b) (4)
As there is little data to suggest greater efficacy at the higher 30 mg dose, these 3 studies demonstrating the benefit of starting and remaining at 15 mg /day. Consequently, these pivotal trials support significant efficacy with the 15 mg dose of aripiprazole, which may offer similar efficacy to the 30 mg dose with fewer adverse reactions.

5.2.5 Conclusions Regarding the Safety of Aripiprazole As Monotherapy (starting at 15 mg daily) and Adjunctive Treatment of Bipolar Disorder Partially Responsive To Therapy with Lithium or Valproate

The adverse drug reaction profile for aripiprazole in the adjunctive treatment of bipolar disorder appears similar qualitatively to that observed with aripiprazole in the treatment of schizophrenia and bipolar for corresponding dosage levels.

5.3 Clinical Sections of Labeling

We have made modifications to the sponsors' proposed Abilify® labeling that had already been converted to PLR format for the first time in the context of the approval of the pediatric schizophrenia and bipolar disorder, as well as the adjunctive treatment of major depressive disorder indications.

(b) (4) recommended by Dr. Brugge in her addendum to SN 019 signed off 4 March 2008.

Dr. Laughren clarified the policy o (b) (4) n an email sent to the sponsors dated 21 April 2008.

6.0 WORLD LITERATURE

The sponsors provided certification that they had reviewed the literature and found no relevant articles that would adversely affect conclusions about the safety of aripiprazole in the adjunctive treatment of partial response to lithium or valproate in patients diagnosed with bipolar I disorder.

7.0 FOREIGN REGULATORY ACTIONS

The applicant provided a listing of approved applications for foreign marketing of Abilify and discusses their foreign marketing experience in Section 6 of Module 2.7.4 of the submission. The sponsor stated that Abilify has not been withdrawn from the market in any country.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC)

It was decided that there was no need to take this application to the PDAC as antipsychotic drugs are commonly used in the treatment of bipolar disorder and no unusual or unexpected safety findings emerged.

9.0 DSI INSPECTIONS

Inspections were conducted at two sites, and data from one of these sites (Adam F. Lowy, M.D. in Washington, D.C.) were found by the Consumer Safety Officer, Diane Tesch, to be acceptable as documented in her review dated 8 April 2008. At the second site (# 122), Richard Weisler, M.D., in Raleigh, N.C., inspection revealed significant discrepancies in drug accountability. There were no limitations in the records inspected for 19 subjects (13 randomized). To evaluate the contributions from this site to the overall outcome, Dr. Philip Dinh reanalyzed the primary and key secondary analyses to compare the findings with and without data from site # 122 in the amendment to his review dated 16 April 2008. The results support that removal of the data from this site did not affect the significance of the findings from the trials and that he would file an addendum to that effect. There were no material differences with respect to the primary efficacy analysis (change from baseline to endpoint on the YMRS score) in the LS means and p-values for the entire study population compared to the study population minus site #122 that were (-13.31, 0.002) and (-13.27, 0.003), respectively. Similarly, with respect to the changes from baseline to endpoint in the CGI-BP scores, the LS means and p-values for the entire study population compared to the study population minus site #122 were (-1.89, 0.01) and (-1.87, 0.02), respectively.

10.0 PHASE 4 COMMITMENTS

Based on the extensive body of exposure data with no serious unexpected adverse events emerging and substantial efficacy data on the treatment of bipolar disorder in adult and pediatric populations, we recommend no Phase 4 commitments.

11.0 LABELING AND APPROVABLE LETTER

We have sent a modified version of the recently revised PLR version of labeling with the approvable letter with revisions to the language proposed by the sponsors for these new changes to the USPI. (b) (4)

Lamotrigine drug-drug interactions language proposed by BMS/Otsuka in the supplement permitted, SN 022, was added.

Dr. Laughren clarifie (b) (4)

12.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that BMS/Otsuka has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe in the treatment of bipolar disorder, manic and mixed episodes as adjunctive treatment to lithium and valproate, as well as in monotherapy. Based on Dr. Jackson's review, I recommend also that we approve the labeling language proposed by BMS/Otsuka regarding the absence of drug-drug interactions between aripiprazole and lamotrigine.

Suggested labeling changes approved by Dr. Mathis for the final decisions on language were sent to Dr. Laughren following the internal labeling meeting. The remaining major question of language that we raised for Dr. Laughren to clarify pertained to the (b) (4)

(b) (4)

The exposure data form the adjunctive treatment trial was informative. (b) (4)

Before we can take an approval action, agreement with the sponsors on labeling needs to be achieved.

Finally, on page 5 of Dr. Brugge's review of the adjunctive therapy trial (CN138134), she highlighted the clinically relevant occurrence of higher frequencies of adverse events such as akathisia and tremor, particularly in the lithium and aripiprazole treated compared to the valproate and aripiprazole-treated patients. The higher frequencies of these adverse events are not entirely unexpected in the clinical setting given the tolerability and safety profiles of lithium and aripiprazole. It would be worthwhile to add in labeling that akathisia, insomnia, and extrapyramidal disorders were commonly observed during treatment of bipolar disorder (mania or mixed episodes) with aripiprazole as adjunct to lithium and valproate. As these adverse events did not manifest as major toxicities in terms of unusually high rates and severity of akathisia associated with adjunctive treatment and given the absence of valid comparisons with other commonly used antipsychotic drugs, in my opinion, I do not think that the data supports the use of scarce resources for an OSE consultation regarding akathisia associated with aripiprazole use as adjunct to lithium at this point in time. Particularly given the available evidence of widespread use of antipsychotic drugs with lithium in clinical practice over the past few decades without the emergence of major toxicities observed. Given the observation of elevated rates of akathisia beyond those found with monotherapy in a small study base, we will continue to monitor the aripiprazole database and annual reports for a potential signals as the extent of exposure to the combination of lithium and aripiprazole (as well

as valproate and aripiprazole) amplifies with increased use in bipolar disorder following an expected approval action.

cc: NDA 21-436 (019, 020, 022)
21-713 (014, 015, 017)
21-729 (006, 007, 009)
21-866 (006, 007, 009)
HFD-130
HFD-130/TLaughren/MMathis/GZornberg/KBrugge/DBates/SHardeman/AJackson/RBaweja/PDinh/PYang

DOC:Aripiprazole_Zornberg_AE_Memo.doc

71 pages immediately following are withheld for b(4), draft labeling.

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

/s/

Gwen Zornberg
4/21/2008 10:11:46 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S-019, S-020, S-022
21-713/S-014, S-015, S-017
21-729/S-006, S-007, S-009
21-866/S-006, S-007, S-009

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21436
Submission Code	SE1 N019
Letter Date	7/11/07
Stamp Date	7/11/07
PDUFA Goal Date	5/11/08
Reviewer Due Date	3/11/08
Reviewer Name	Karen Brugge, MD
Review Completion Date	2/25/08
Established Name	Aripiprazole
Trade Name	Abilify®
Therapeutic Class	atypical antipsychotic
Applicant	Otsuka Pharmaceutical Developmental & Commercialization, Inc
Priority Designation	S
Formulation	2, 5, 10, 15, 20, 30 mg oral tablet
Dosing Regimen	(b) (4) 15 mg/day starting dose
Indication	Lower starting dose of 15 mg/day
Intended Population	Bipolar I Disorder

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

An approvable action is recommended, from a clinical perspective.
From a clinical perspective, the following are considered by the undersigned reviewer as contingencies before the Agency would consider a final decision on approving this NDA:

- Input from the Biometric Team and the Division of Scientific Investigations.
- Negotiation of labeling.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no recommendations for specific risk management activities.

1.2.2 Required Phase 4 Commitments

None are recommended.

1.2.3 Other Phase 4 Requests

None are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Approved labeling recommends a starting dose of 30 mg daily for acute monotherapy of Bipolar I (mixed or manic). Labeling also specifies that approximately 15% of patients had their daily dose reduced to 15 mg for tolerability reasons.

In this N20 application, the sponsor proposes a lower starting dose of15 mg daily of Abilify (aripiprazole oral tablet formulation) for acute monotherapy of Bipolar I (mixed or manic). 2 pivotal trials were conducted to support this proposal.

1.3.2 Efficacy

The sponsor conducted two pivotal Phase III trials (3-week monotherapy) that were positive for efficacy using a starting daily dose level of 15 mg (oral tablets) in which the daily dose of Aripiprazole (Arip) could be increased from 15 mg to 30 mg on Study Visit Days 4 or 7 (corresponding to Days 4 or 7 of Arip treatment during the double-blind phase).

The pivotal trials were CN138135 (C-135) and CN138162 (C-162). These trials involved a multicenter, 3-week, PBO controlled, randomized, multicenter (US and non-US), double-blind (DB), parallel group design using flexible dosing of DB Arip treatment (15- 30 mg). The daily starting dose was 15 mg. The total number of subjects randomized to DB treatment in each study was 480 subjects in Study C-135 and 485 subjects in Study C-162 (over 150 subjects/treatment group in each study). Each study included an active comparator group for assay sensitivity (lithium in Study C-135 and haloperidol in Study C-162).

The primary efficacy and the key secondary variables in each of these studies were the following scales, respectively:

- Young Mania Rating Scale (YMRS)
- Clinical Global Impression-Bipolar (CGI-BP) rating scale.

1.3.3 Safety

The primary focus of the safety review was on results from the 2 new pivotal trials (C-135 and C-162), as provided in an integrated database. The data from these new trials was integrated with the data from Phase III monotherapy Bipolar trials that were previously subject to review. A total of 917 Arip treated and 753 PBO treated subjects were included in this integrated safety dataset.

No new and clinically remarkable safety signal was revealed or was anticipated with the proposed lower starting dose level in patients with Bipolar I (in an acute mixed or manic episode).

1.3.4 Dosing Regimen and Administration

The dosing in Studies C-135 and C-162 involved a lower daily starting dose of 15 mg than the approved daily dose of 30 mg for acute treatment of Bipolar I (manic or mixed). The dose could be increased to 30 mg daily, as early as Day 4 during the DB phase.

1.3.5 Drug-Drug Interactions

No new information was found in the submission that is relevant to the new proposed claim.

1.3.6 Special Populations

Studies in special populations were not conducted as part of the program for this application.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor is seeking approval of a 15 mg starting dose level (daily dose-level) for Abilify in treating an acute episode of mania or mixed Bipolar I disorder as a monotherapy regimen. The sponsor conducted 2 pivotal Phase III trials (CN138135, CN138162 also referred in this review as Study C-135 and C-162).

The sponsor is submitting a parallel supplemental NDA (sNDA) N20 for adjunctive treatment claim (with valproate or lithium) for treatment of acute mania or mixed episode of Bipolar I, using a 15 mg daily as a starting dose level. The sponsor cross-references N19 for safety information to support their N20 submission, as specified in their cover letter of N20.

Abilify is already approved for the monotherapy Bipolar I indication (for acute and maintenance monotherapy claims) but the trials supporting efficacy used a starting daily dose-level of 30 mg using a flexible dose design (15 or 30 mg daily). The sponsor also has safety results from completed and ongoing trials as discussed later in this review.

Abilify (aripiprazole) is an atypical neuroleptic that is approved for Schizophrenia, Bipolar I-acute mania or mixed episode, and other psychiatric indications as described in approved labeling. It is among a drug class of atypical neuroleptics that are also approved for schizophrenia (and in some cases for other psychiatric indications).

2.2 Currently Available Treatment for Indications

Several atypical neuroleptic agents (e.g. quetiapine, risperidone, olanzapine) are approved for the Bipolar I (mania/mixed) indication.

2.3 Availability of Proposed Active Ingredient in the United States

Abilify® has been on the market for a number of years. This drug was first approved in the US on November 15, 2002 for schizophrenia and September 29, 2004 for Bipolar I, mixed or manic. See sections in this review discussing the postmarketing experience with the drug.

The sponsor notes (on page 465 of Module 2.7.4) that Arip has not be withdrawn from the market (from any country).

2.4 Important Issues With Pharmacologically Related Products

Refer to labeling of approved drugs in this drug class that describe important issues relevant to safety. Other safety related sections of this review also discuss safety related issues or potential issues, when applicable.

According to the 1/15/08 DPP DDRE Safety Meeting Agenda.doc the following projects involving atypical neuroleptic agents are listed as current projects in OSE:

- An update (since the last 2004 review) of reported cases of agranulocytosis, neutropenia and leukopenia (regarding quetiapine and other atypical neuroleptic agents).
- Other current projects involving atypical neuroleptic involve other specific agents (not Arip) or involve other patient populations (or non-adult populations).
- Cases of prolactinomas (for the drug class)
- (b) (5)
- NME evaluation of Arip
- Medication errors with Arip (errors with strengths).
    - OSE was notified by the undersigned reviewer that there were subjects with "accidental overdose" found by the undersigned reviewer on a review of selected narratives in this N19 submission (and in the narratives for Study C-134 found in the review of N20).

DARRTS Safety Issues (listed in the DARRTS SAFETY_ISSUE 11-05-07.pdf file) are the following active projects regarding one or more atypical neuroleptic agents:

- Weight gain and hyperglycemia, metabolic effects (lipids and weight), Torsades de pointes, prolactinemia, hepatotoxicity, QT prolongation, (b) (5) medication errors, agranulocytosis,
- Laryngeal dystonia is listed specifically with regards to Abilify

Refer to the above specified documents for more details and for a more complete listing.

The focus of the current review is on safety data relevant to this sNDA and as provided in the submission. To the knowledge of the undersigned reviewer, the safety projects (under review by OSE or in the Safety Group) that include those listed above are either pending or an action has subsequently been taken, if indicated.

2.5 Presubmission Regulatory Activity

The sponsor refers to the following presubmission activities:

- February 26, 2007 pre-sNDA meeting. Based on discussions during this meeting, the sponsor is submitting N19 and N20, as parallel NDA submissions. N20 is being submitted in order to seek approval for an adjunctive treatment Bipolar claim (with lithium or valproate) based on results from Study CN138134. The cover letter of N20 cross-references N19 for the integrated safety and efficacy data and other safety data from Bipolar trials.
- S-002 and S-005 were previously approved for acute monotherapy and maintenance monotherapy Bipolar I (mixed/manic) claims.
- IND73863 is referenced regarding monotherapy Bipolar trials that were conducted in support of the approved acute and maintenance monotherapy claims (S-002 and S-005).

2.6 Other Relevant Background Information

The sponsor provides a listing of approved applications for foreign marketing of Arip and discusses their foreign marketing experience in Section 6 of Module 2.7.4 of the submission.

Abilify® is approved for the indications of schizophrenia and/or bipolar mania in approximately 40 countries (the sponsor lists the countries in Table 6.1.A in Section 6 of Module 2.7.4). Arip was first approved for schizophrenia in Mexico on July 17, 2002 and later in the USA on November 15, 2002.

The sponsor notes (on page 465 of Module 2.7.4) that Arip has not been withdrawn for the market (in any country).

The sponsor also lists a number of marketing applications that are under review in other countries (as of 12/31/06).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Only a categorical exclusion statement is included in the submission (as specified in the guide.pdf file of the submission). Dr. Nallaperum Chidambaram has no issues at the time of this writing.

3.2 Biometrics

The undersigned reviewer is not aware of any key Biometric issues (Dr. Phillip Dinh is the assigned reviewer), at the time of this writing (a final review is pending at this time).

3.3 Division of Scientific Investigations

A final Division of Scientific Investigations (DSI) report remains reviewer Dr. Dianne Tesch is assigned to this NDA and DSI inspections are underway at the time of this writing.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary datasource for efficacy relevant to this application is from the 2 pivotal trials Studies CN138135 and CN138162 (see tables in Section 4.2 of the trials).

Refer to the next section for safety databases and Section 7 of this review for additional non-clinical trial datasources.

4.2 Tables of Clinical Studies

The following table outlines databases described in Module 2.7.4 (Introduction and Appendices IA and IB).

Section 4.3 and Section 7.1 of this review provides the review strategy for each dataset.

Note the following key points regarding the table below:

- All studies below and elsewhere in this review are referred to by the last 3 numbers of the complete protocol number (e.g. Study CN138135 is referred to as Study C-135).
- Note that the Adjunctive Bipolar trial (C-134) was conducted as a pivotal trial to support a proposed adjunctive claim in a parallel supplemental NDA21436 N20 submission.
- The table below of Bipolar trials does not include (b) (4) Study C-037 that that only 24 ITT subject (Ss).

Efficacy Studies*	
Studies C-135 and C-162, Bipolar I (mania/mixed) 3-week monotherapy Trials (using a 15 mg starting dose level)	3-week PBO-controlled, randomized, multicenter (US and non-US), DB, parallel group trials using a flexible dose design (15- 30 mg daily using a 15 mg starting dose level) and an active comparator group (lithium or haloperidol).
ITT Sample sizes in Study C-135	Arip (154 ITT Ss) or PBO (164 ITT Ss) or Lithium (159 ITT Ss 900-150 mg daily)
ITT Sample Sizes Study C-162	Arip (166 ITT Ss) or PBO (153 ITT Ss) or Haloperidol (165 ITT Ss; 5-15 mg daily)
Total completers:	Placebo: 187 subjects Arip: 199 subjects
Total of ITT Efficacy Subjects:	Placebo: 315 subjects Arip: 320 subjects

* Arip=aripiprazole ITT=intent-to-treat sample (randomized subjects who received at least one dose of study drug). OL=open-label DB=double-blind SB=single blind PBO=placebo

Studies for Each Safety Dataset from Phase 2/3/4 MDD and Other Psychiatric Patients*	
Pooled 3-week Short-term Bipolar Trial Dataset	
Study C-135 (see above)	Arip (154 ITT Ss) or PBO (164 ITT Ss) or Lithium (159 ITT Ss)
Study C-162	Arip (166 ITT Ss) or PBO (153 ITT Ss) or

(see above)	Haloperidol (165 ITT Ss)
Studies C-007, C-009, C-062, C-074 & aborted trials -062 and -077; aborted for administrative reasons)	Over approximately 500 Arip Ss and over approximately 300 PBO Ss
Total of ITT Safety Subjects:**	Placebo: 753 subjects Arip: 917 subjects

6-Week Adjunctive Treatment Unpooled Bipolar Dataset (Study C-134)

Study phases: 2-week Mood Stabilizer phase to initiate Lithium (500-1500 mg/day in non-US Ss, 600-1500 mg/day in US subjects; 0.6-1.0 mmol/l lithium levels) or valproate treatment (500=2500 mg/daily; 50-125 ug/ml valproate levels) 6-week DB adjunctive treatment phase of Arip (15-30 mg/day; 15 mg starting dose) or PBO 46-week OL phase that is ongoing and not included in this dataset (specified on page 51 of Module 2.7.4)	
DB phase data was included in this dataset and consisted of: Arip (154 ITT Ss), PBO (164 ITT Ss), and Lithium (159 ITT Ss)	
Total of ITT Safety Subjects:**	Placebo: 130 subjects Arip: 253 subjects

12-week Active Controlled Unpooled Bipolar Dataset (12-weeks of Arip or Active Control in Studies – C-135 and C-162)

Studies -135 and -162 also included DB, active controlled phases that followed the 3-week PBO controlled DB phase. The 3-week phase was followed by 9 weeks of a non-PBO controlled, active comparator phase in which Ss on active drug continued their assigned blinded treatment (PBO Ss were switched to Arip but were not included in this dataset). Table 1.1.A of Module 2.7.4 shows a 40 week Phase 3 treatment phase. The Clinical Study Report (CSR) describes this phase as a DB extension phase from which results will be provided "as a separate report" (see page 48).	
Total of ITT Safety Subjects:**	Haloperidol or Lithium: 169 Arip: 175 subjects

Maintenance Treatment Unpooled Dataset (Study -010)

The results of this study were previously subject to review in previous sNDA submissions and safety update reports, as specified on page 57 of Module 2.7.4. Therefore this dataset was not included in this review.	

Pooled "All Aripiprazole Treated Dataset"
Ongoing or OL Phase II, III and IV Bipolar Trials and Other Trials

Ongoing or OL Bipolar Trials:	
All completed Bipolar Trials (previous listed above)	See above
Ongoing OL Extension Phases of (15-30 mg Arip): • OL adjunctive (lithium or valproate) Study C-134 (46 weeks) • OL monotherapy treatment in Study C-135 (40-weeks)	See above
OL phases of Ongoing Maintenance Studies C-189 and C-392	Maintenance trials involving: • OL acute, active "mood stabilizer" treatment phase (with lithium, valproate in Study -189 or lamotrigine in Study -392), • Stabilization phase of OL Arip added to the treatment

	regimen in Study -189 only (12 weeks) • 52-week, DB, randomized Arip or PBO added to OL "mood stabilizer" treatment (time-to-relapse is the primary endpoint). These data remain blinded (specified on page 54 of Module 2.7.4).
Total of ITT Safety Arip Subjects:**	2626 Total Subjects (74 subjects and 146 subject exposed to ≥360 days and ≥270 days of treatment, respectively, based on results shown in Table 1.2.5.1A of Module 2.7.4)

(b) (4)

Other Studies of Additional Pooled or Unpooled Safety Datasets*	
Pediatric Bipolar I/Schizophrenia Disorder Datasets	Selected safety results from Studies 31-03-240 and 31-03-239 (in Section 5.10 of Module 2.7.4).
Sample Sizes	Could not be found
(b) (4)	The

	(b) (4)
	Arip (N=360), PBP (N=367)
2 Completed Studies (31-02-A01 & OBRI 0002) in Patients with Schizophrenia that were conducted in either Taiwan or China	Selected safety results are summarized in Section 5.11 in Module 2.7.4 (ongoing Asian trial results were not provided). None of these trials involved Bipolar patients.
Sample Sizes (Appendix 5.9 in Module 2.7.4 provides more details)	120 Arip subjects in China and 49 Arip subjects in Taiwan

*Arip=aripiprazole PK=pharmacokinetic properties

Refer to Section 8.4 of this review regarding the above Study 31-03-240 of pediatric patients with Bipolar I mania. The sponsor notes in their cover letter that this study was conducted to fulfill a pediatric postmarketing commitment for S-002, and they plan to submit a separate sNDA that includes the results of this study.

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4.3 Review Strategy

The following table lists the datasources that were reviewed, as described in more detail in subsections that follow.

TABLE 4.3.1: ITEMS THE REVIEWED

Submission Date	Items Reviewed
7/11/07	Efficacy Review: Clinical Study Report (efficacy and other selected sections): Pivotal Studies C…135 and C…162 Some tables and results that were reviewed were obtained from other sources (e.g. in other sections of the submission or in appendices or attachments) as specified in applicable sections of this review. Safety Review: Module 2.7.4: in-text and selected appendices/attachments and selected narratives (narratives were provided in Appendix 2.2B). Selected sections of the Clinical Study reports of the 2 pivotal trials (as specified in sections of this review where applicable). Proposed Labeling (side-by-side version) Financial Disclosure Certification Literature Search Item 8 (litserach.pdf) Selected Case Report Forms
1/18/08	Responses to inquiries (refer to 12/6/07 questions e-mail (Telecon) document under the NDA.

Safety Review:
Comments on Review Strategy: *The primary focus of the safety review was on results from the 2 new pivotal trials (C-135 and C-162), as provided in an integrated database. Data from these new trials was integrated with data from past Phase III monotherapy Bipolar trials that were previously subject to review. A total of 917 Arip treated and 753 PBO treated subjects were included in this safety dataset.*

Safety results from other clinical trials were also provided but the relevance to this sNDA or interpretation of the results were limited, given the nature of these trials or by the patient population under examination (e.g. a number of trial involved other patient populations, trials or safety datasets differed by key aspects of the study design and methods). Selected safety results were reviewed and summarized in this review.

Regarding methods and review strategy of narratives in the submission, only a selected review of narratives was conducted on the 2 new pivotal trials (note that Study C-134 underwent a more comprehensive review for the parallel N20 application with more comprehensive results described in the review of the N20 submission). A more comprehensive review of the narratives was not conducted since these trials used a lower starting dose, while using the same duration of treatment employed in most of the previous monotherapy Bipolar trials. Moreover, approved labeling recommends treatment with 30 mg (as a starting dose). Finally there is extensive experience with Arip treatment at the higher 30 mg dose level.

Refer to Section 7.1 of this review for more details.

4.4 Data Quality and Integrity

DSI has not conveyed any key concerns to the undersigned reviewer at the time of this writing.

All pivotal trials include protocols describing methods for quality assurance (in Section 4.2 of the Clinical Study Report). Appendix 10.1 of this review summarizes protocol deviations in each study. Section 6 notes that the per protocol population analyses on the primary efficacy variable revealed positive efficacy results.

Comparisons between arbitrarily selected Case Report Forms (CRFs) with corresponding narratives revealed adequate accuracy (no inconsistencies were found, as described in detail below).

Methods of the CRF and Narrative Audit
CRF to Narrative comparisons for each arbitrarily selected subject of each pivotal trial revealed no inconsistencies as follows (serious adverse event terms were compared for each subject but other items were also arbitrarily selected for a given subject, as specified below):

- Subject CN138135-28-388: Comparisons were made on: serious adverse event (SAE) terms, the timing of the SAE relative to onset of DB treatment and additional descriptive information regarding the SAE (a quote was provided from the SAE form in the CRF). The information matched.

- Subject CN138162-16-38: Comparisons were made on: SAE terms, the timing of the SAE relative to onset of DB treatment and additional descriptive information regarding the SAE (comments in a supplemental report). The information matched.
- Subject CN138134-49-25: Compared the age, gender, SAE terms and timing relative to DB treatment and AE terms (ongoing at the time and comments quoted from the SAE from). The information matched.

4.5 Compliance with Good Clinical Practices

DSI has not conveyed any key concerns to the undersigned reviewer at the time of this writing (and a final report is pending at this time).

The knowledge of the undersigned reviewer, pivotal studies were conducted in accordance to the Declaration of Helsinki and Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines (this aspect of the pivotal trials is described in Section 4.1 of each CSR).

4.6 Financial Disclosures

The below excerpt from the submission summarizes financial disclosure information.
Reviewer Comment. *The sponsor attempted to contact outstanding cases (only 4 were listed), as described in the submission and included adequate financial information for the purposes of this review.*

(b) (4) Financial Disclosure Letters (b) (4) and Forms (b) (4) (b) (4) were mailed with prepaid return mailers to the following:

CN138-135: 54 investigators and 447 subinvestigators
CN138-162: 70 investigators and 273 subinvestigators

As of May 29, 2007, BMS has received a total of 124 statements of the 124 investigators, and 2 individuals had disclosable information reported. In addition, BMS received a total of 716 statements of the 720 subinvestigators, 3 of which had disclosable information. There are a total of 4 responses that have not been returned as of June 4, 2007.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new information was provided.

5.2 Pharmacodynamics

Studies included in the NDA were not conducted to examine specific pharmacodynamic effects except for the pivotal trials that were designed to examine efficacy as described in Section 6 of this review. Section 7 of this review discusses safety findings (but there were no special safety studies conducted for the proposed adjunctive treatment claim).

5.3 Exposure-Response Relationships

Placebo controlled pivotal trials employed a flexible dose design, as described in Section 6 of this review. Consequently, the studies were not designed to examine the relationship of dose and efficacy.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Studies C-135 and C-162 were conducted to support a proposed new starting dose of monotherapy (from the approved starting dose of 30 mg to 15 mg daily) for treatment of a manic or mixed episode of Bipolar I disorder.

6.1.1 Methods

The studies involved a multicenter, 3-week, PBO controlled, randomized, multicenter (US and non-US), DB, parallel group design using flexible dosing of DB Arip treatment (15- 30 mg) with a daily starting dose of 15 mg (over 150 ITT efficacy subjects were in each DB treatment group of each study). Each study included an active comparator group (lithium in Study C-135 and haloperidol in Study C-162).

6.1.2 General Discussion of Endpoints

Young-Mania Rating Scale (YMRS) total score was the primary efficacy variable
The Clinical Global Impression-Bipolar Version-Severity Illness Score (CGI-PB-S) for mania is specified in the CSR as the key secondary variable.

Reviewer Comment. *The above variables are acceptable primary and key secondary, respectively endpoints for a pivotal Phase III efficacy trial for a Bipolar I-mania/mixed claim and are appropriate for Study C-134 as the pivotal trial for this NDA.*

6.1.3 Study Design

Reviewer comment. *The study design of each pivotal trial C-135 and C-162, as described in the following paragraphs, is similar to the study design of previous pivotal trials that are described in approved labeling, except for one key difference. Past pivotal trials described in approved labeling employed a 30 mg daily starting dose-level rather than a 15 mg daily starting dose-level employed in Studies C-135 and C-162.*

Each study is a multi-center, randomized, DB, PBO controlled, flexible dose study using a parallel group design. Each study also included an active comparator group to serve as an internal control for assay sensitivity. Study C-135 had 46 US study centers (that randomized Ss).

Study Phases and Overall Treatment Methods
Generally healthy adult (≥18 years old) inpatients with Bipolar I (mixed or manic episode) underwent the following study phases:

- Phase 1: 2 to 14-days long to allow for:
  - Screening
  - Medication washout.

- 3-week DB, PBO Controlled, Treatment Phase 2: Subjects were randomized to (1:1:1 ratio):
  - Arip treatment: used a starting dose of 15 mg daily that could be increased to 30 mg after 4 days or at Day 7, as clinically indicated. The daily dose-level could also be adjusted on any study day, thereafter as clinically indicated (flexible daily dose levels were 15 mg or 30 mg).
  - PBO treatment
  - Active comparator drug
    - Lithium in Study C-135: 900 mg as the daily starting dose-level (900-1200 mg flexible dose, adjusted as clinically indicated and according to serum levels and according to a specified)
    - Haloperidol in Study C-162: 5 mg as the daily starting dose-level (5-15 mg daily flexible dose, adjusted as clinically indicated)
  - Other Aspects of treatment:
    - Treatment was given without regard to meals.
    - Refer to Appendix 10.1 of this review for the timing and dose increments for dose adjustments of each DB drug.
    -

Additional Study Phases
The following additional study phases provided safety data (refer to Section 7 of this review):

- 9-week DB, non-PBO controlled (Active Treatment only) Phase 3: Subjects receiving active drug continued their DB treatment and Ss receiving PBO were blindly switched to Arip treatment during this 12-week phase.
- 40-week DB, non-PBO controlled (Active treatment only) Phase 4: Subjects had the option to continue their DB treatment for 40 weeks.

Eligibility criteria: each protocol included eligibility criteria. The following outlines some key criteria:

- Must be at least 18 years old
- Must meet DSM-IV-TR criteria for Bipolar I-mania or mixed that requires hospitalization.
  - Must have a history of at least one prior manic or mixed episode that required hospitalization.
  - In their first manic or mixed episode.
  - Hospitalized for over 3 weeks with their current episode.
  - Considered as treatment refractory.
  - Nonresponsive to previous Arip treatment or to previous treatment with the active comparator drug (lithium in Study C-135 or haloperidol in Study C-162).
- Must meet enrichment criteria:
  - Y-MRS Total Score ≥ 20 at screening and at the baseline and < 25% decrease between these 2 visits
  - MADRS Total Score ≤ 17 at baseline, ≤ 4-point increase between these 2 visits (each of these ratings must occur at least 2 days apart).
- Cannot have specified Axis I disorders.
- Must meet eligibility criteria relevant to being generally healthy and having normal baseline clinical values (as specified).

Concomitant Medications.
Restrictions and prohibition of concomitant medications were specified. Refer to Appendix 10.1 for details on common concomitant medications used during the DB phase of the study.

Study Assessments
See Section 6.1.2 for primary (b) (4) efficacy assessments.
The study flow chart is provided in Section 10.1 of this review and includes efficacy assessments at multiple time-points, as specified.

Statistical Analyses
The following outlines key aspects of the methods (using the LOCF dataset):

- Primary efficacy variable: The mean change from baseline to treatment endpoint of the DB Phase 2 on the total YMRS score.
- Key Secondary variable (specified in the CSR): The mean change from baseline to treatment endpoint of the DB Phase 2 on the CGI-BP-S mania score.
- Statistical Test: The sponsor employed an ANCOVA model with DB treatment (between Arip and PBO) and study center as the main factors, with the baseline score as a covariate.
- Methods of Conducting Subgroup Analyses: Subgroup analyses was conducted to determine the potential influence of a given subgroup on the mean change from baseline to treatment endpoint (Week 6, LOCF) on each efficacy variable (on the primary and on the key secondary efficacy variables) for each of the following subgroups:

- Gender
- Study center
- Psychotic features (present versus absent)
- Type of current episode of Bipolar disorder (manic versus mixed)

The statistical test used for each subgroup analyses was an ANCOVA model with baseline as a covariate and with the given subgroup category and treatment group (PBO versus Arip) as the main effects in the model.

The sponsor also conducted subgroup analyses on the integrated, short-term Phase III dataset (which allows for larger sample size). These studies are almost identical in key aspects with the study design of reach study except that one trial employed a fixed dose design. This sole fixed dose trial was either negative or failed study on efficacy, such that pooling this study with data from the positive flexible dose trials may lead to a dilution effect on revealing significant subgroup interaction effects on efficacy. The sponsor used an ANCOVA model for this integrated analyses to determine treatment, study and subgroup main effects with baseline Y-MRS Total Score as a covariate. From this model the sponsor determined treatment-by-subgroup interaction effects.

6.1.4 Efficacy Findings

Reviewer Comment. *The studies showed positive results for efficacy. The following are summary tables of on the primary and key secondary variables for each study (copied from the submission). See additional tables in Appendix 10.2 (copied from the submission).*

Primary and Key Secondary Results of Study -135 (copied from Table 2D of Module 2.7.3).

	Placebo	Lithium	Aripiprazole
Primary Efficacy Measure			
Y-MRS Total Score	N = 163	N = 155	N = 154
Mean Baseline	28.90	29.22	28.53
Mean Change at Week 3 (LOCF)	-9.01	-12.03**	-12.64**
Key Secondary Efficacy Measure			
CGI-BP Severity of Illness (mania) Score	N = 162	N = 154	N = 153
Mean Baseline	4.60	4.54	4.55
Mean Change at Week 3 (LOCF)	-1.06	-1.34*	-1.48**

Source: CN138135 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

Primary and Key Secondary Results of Study -162 (copied from Table 2E of Module 2.7.3).

	Placebo	Haloperidol	Aripiprazole
Primary Efficacy Measure			
Y-MRS Total Score	N = 152	N = 161	N = 166
Mean Baseline	28.82	28.01	28.35
Mean Change at Week 3 (LOCF)	-9.70	-12.83**	-11.98*
Key Secondary Efficacy Measures			
CGI-BP Severity of Illness (mania) Score	N = 151	N = 161	N = 166
Mean Baseline	4.60	4.46	4.50
Mean Change at Week 3 (LOCF)	-1.17	-1.56**	-1.44*

Source: CN138135 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

Subgroup Analyses Results on Efficacy
Refer to Section 6.1.3, above regarding subgroups analyzed and a brief overview of statistical methods employed. Refer to summary tables in Appendix 10.2 of this review for the results.

The integrated monotherapy Bipolar I dataset failed to show any significant treatment group interactions effects on the basis of age, "race" or gender as shown in Appendix 10.2 of this review.

Results of the OC dataset are shown below for each study.

Study C-135

	Adjusted Mean Changes from Baseline (Mean Actual Score for Baseline) (a)						Pairwise Comparisons (b)				
	Placebo		Lithium		Aripiprazole		Lithium - Placebo		Aripiprazole - Placebo		
Visit	N	Mean	N	Mean	N	Mean	Diff. in Adj. Means (95% CI)	p-value	Diff. in Adj. Means (95% CI)		p-value
Baseline	163	29.00	155	29.26	154	28.51	0.26	(-1.02,1.54)	0.692	-0.49	(-1.77,0.79)	0.450
Day 2	162	-2.53	154	-3.09	153	-4.09	-0.56	(-1.62,0.49)	0.296	-1.56	(-2.62,-0.50)	0.004
Day 4	151	-4.84	144	-6.50	142	-7.95	-1.67	(-3.11,-0.22)	0.024	-3.12	(-4.57,-1.67)	< 0.001
Day 7	141	-6.68	143	-8.29	132	-10.11	-1.61	(-3.43,0.21)	0.082	-3.43	(-5.29,-1.57)	< 0.001
Day 10	122	-8.60	123	-11.86	121	-12.43	-3.26	(-5.27,-1.25)	0.002	-3.83	(-5.85,-1.80)	< 0.001
Week 2	118	-10.88	116	-14.53	113	-14.54	-3.65	(-5.79,-1.51)	< 0.001	-3.65	(-5.81,-1.50)	< 0.001
Week 3	90	-12.81	93	-15.79	94	-14.73	-2.98	(-5.33,-0.63)	0.013	-1.92	(-4.26,0.42)	0.107

(a) Y-MRS Total Score is from 0 to 60.
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment, is used for baseline.
ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline up to and including Week 3.
Means, differences in means, 95% CI for the differences and p-values are based on the ANOVA/ANCOVA model.

Study C-162

	Adjusted Mean Changes from Baseline (Mean Actual Score for Baseline) (a)						Pairwise Comparisons (b)				
	Placebo		Haloperidol		Aripiprazole		Haloperidol - Placebo		Aripiprazole - Placebo		
Visit	N	Mean	N	Mean	N	Mean	Diff. in Adj. Means (95% CI)	p-value	Diff. in Adj. Means (95% CI)		p-value
Baseline	152	28.36	161	27.60	166	28.01	-0.76	(-2.04,0.52)	0.245	-0.35	(-1.62,0.92)	0.589
Day 2	151	-1.21	158	-2.02	165	-1.87	-0.81	(-1.61,-0.01)	0.046	-0.66	(-1.45,0.13)	0.100
Day 4	148	-3.32	152	-4.69	158	-4.03	-1.37	(-2.59,-0.16)	0.027	-0.71	(-1.92,0.49)	0.245
Day 7	137	-5.93	136	-7.94	155	-6.86	-2.01	(-3.62,-0.39)	0.015	-0.93	(-2.49,0.63)	0.243
Day 10	135	-8.06	146	-10.03	151	-9.45	-1.97	(-3.77,-0.17)	0.032	-1.39	(-3.17,0.40)	0.128
Week 2	133	-10.10	142	-12.07	150	-11.64	-1.97	(-3.90,-0.03)	0.047	-1.54	(-3.45,0.37)	0.115
Week 3	117	-12.44	129	-14.34	139	-14.30	-1.91	(-3.95,0.13)	0.067	-1.87	(-3.87,0.14)	0.068

(a) Y-MRS Total Score is from 0 to 60.
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment, is used for baseline.
ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline up to and including Week 3.
Means, differences in means, 95% CI for the differences and p-values are based on the ANOVA/ANCOVA model.

Reviewer Comments on Results of Subgroup Analyses.

<u>Country Subgroups and Study Center Subgroups</u>
Sample sizes of most country subgroups were generally small in Study C-162 (based on a review of Table S.5.7 in the CSR). The US site did not show numerically greater improvement in Arip compared to PBO Ss in Study C-162 (N=50 and 47 in each group, respectively). However the active control (Haloperidol) group in this study also failed to show greater numerical improvement in the Arip compared to PBO groups.

Study C-135 was exclusively done in the US and showed significantly greater improvement in Arip compared to PBO groups on the primary and key secondary variables.

Samples sizes by study center were small. Results are difficult to interpret.

Gender Subgroups

Gender subgroup analyses were generally consistent with no interaction effect and with efficacy for each subgroup (sample sizes of these subgroups were not significantly skewed in which the incidence of each subgroup for each study is provided in Appendix 10.2).

Age-Subgroups

Results for each pivotal trial could not be found. However, results of all 3-week Bipolar Phase III trials, combined, were found in the sum-clin-efficacy.pdf file in the submission. See Appendix 10.2 of this review for these results.

Race Subgroups

The following was provided in a 10/18/07 S-006 submission in response to a request for this information. Note sample sizes were small in some subgroups such that results are difficult to interpret.

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Attachment Q.1.1:
Adjusted Mean Change from Baseline to Week 3 in Y-MRS Total Score (CN138135), by Race, LOCF Data Set, Efficacy Sample

	Adjusted Mean Changes from Baseline (SE) (Mean Actual Score for Baseline) (a)			Pairwise Comparisons (b) Difference in Adjusted Means (95% CI)			
Visit	Placebo	Lithium	Aripiprazole	Lithium - Placebo		Aripiprazole - Placebo	
WHITE							
	N= 117	N= 98	N= 95				
Baseline	29.35 (0.54)	29.43 (0.59)	28.83 (0.60)	0.08	(-1.50,1.66)	-0.52	(-2.11,1.07)
Week 3	-9.49 (0.92)	-11.70 (1.01)	-11.32 (1.02)	-2.21	(-4.90,0.48)	-1.82	(-4.54,0.89)
NON-WHITE							
	N= 46	N= 57	N= 59				
Baseline	28.11 (0.84)	28.96 (0.76)	27.98 (0.74)	0.86	(-1.38,3.09)	-0.13	(-2.34,2.09)
Week 3	-7.41 (1.38)	-12.31 (1.24)	-14.78 (1.22)	-4.90	(-8.58,-1.22)	-7.37	(-11.02,-3.73)

p-value for treatment by race interaction: 0.066 (c)

(a) Y-MRS Total Score is from 0 to 60.
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment, is used for baseline.
ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline at Week 3.
Means, differences in means, 95% CI for the differences are based on the ANOVA/ANCOVA model.
(c) ANCOVA model, controlling for baseline, treatment, race, and treatment by race interaction is used.

Results of other subgroup analyses are provided in Appendix 10.2 of this submission and failed to reveal any key clinical issues impacting on overall conclusions and recommendations in this review.

6.1.5 Clinical Microbiology

Not applicable to this sNDA.

6.1.6 Efficacy Conclusions

Studies were positive on the primary and key secondary variables, pending Biometric input. See the last section of this review for any key issues and recommendations.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The main focus of the review of safety results was on the following database:

- The safety results from the integrated PBO controlled, short-term Bipolar I-mania/mixed dataset (includes pivotal trials, integrated with data from similar trials).

This dataset is most relevant to this N19 submission since the sponsor proposes to reduce the starting dose (from 30 mg to 15 mg daily) of an already approved indication (Bipolar I-mania).

The review of N20 focuses more on safety findings of adjunctive treatment groups in Study C-134 since this parallel submission is for an adjunctive Bipolar I claim.

Additional secondary dataset results are summarized in this review and are outlined in the next subsection below.

Given the proposed claim (for a lower starting dose-level; 15 mg/day) for an already approved claim the primary focus of the safety review is of the following dataset:

- **Pooled 3-week Short-term Dataset** (Trials CN-135, -162, -007, -009, -074 and aborted trials -062 and -077):
- ITT safety sample size: 753 placebo and 917 Arip subjects
- This dataset includes:
  - Flexible dose trials (15-30 mg/day of Arip):
    - Pivotal Studies C-135 and C-162 of this sNDA: 15 mg starting daily-dose-level.
    - Studies C-135 and C-162 (previously reviewed and in labeling for the Bipolar-mania/mixed claim): 30 mg starting daily-dose-level.
    - Aborted Study -077: 30 mg starting dose level
- Fixed dose trials (placebo, 15 and 30 mg Arip groups)
  - Study C-007 (approximately 130 Ss/group in each group)
  - The aborted Study -062 (only 16-20 Ss/group)

Secondary safety datasets
Although section 4 of this review outlines each dataset the following provides more information relevant to dosing and more specific information on trials included in each dataset.

6-Week Adjunctive Unpooled Study C-134
Study C-134 is a pivotal trial for an adjunctive Bipolar-mania/mixed claim proposed in a parallel sNDA N20 which cross-references N19 for the safety results. Safety results of this study are found in Module 2.7.4 of N19.

Study C-134 was conducted on subjects, identified as "partial nonresponders" during a 2-week monotherapy phase of valproate or lithium treatment (130 placebo and 253 Arip subjects). These subjects were randomized (stratified by mood stabilizer) to 6 weeks of DB placebo or Arip (flexible 15-30 mg daily dose; starting dose was 15 mg).

Reviewer comment. *For the purposes of the review for N19, these results of Study C-134 are only briefly summarized in this review (refer to the review of N20 for a more focused review of safety and efficacy results from this study). Clinical parameter results are only provided in the review of N20, with some exceptions, as specified in applicable subsections below.*

Unpooled 12-Week Active-Controlled Bipolar Trial Dataset (New Trials -135 and -162 and Trial -008): Each study in this unpooled dataset had an active comparator phase (without a placebo group). The results for the active treatment groups were provided in Module 2.7.4 for each study separately (unpooled). The following outlines the design of each Study:

- Trials -135 and -162 had the following phases:
  - A 3-week PBO controlled DB phase that also had active comparator groups of either lithium (900-1500 mg/day of lithium) in Study -135 or haloperidol (5-15 mg/day) in Study -162. Data from the PBO and Arip groups of this phase was included in the previously described "Pooled Short-term Bipolar dataset" and also provided the efficacy results described in Section 6 of this review (to support the proposed claim).
  - A 9 week, non-PBO controlled, active comparator phase followed the 3-week PBO controlled phase. Subjects previously assigned to placebo were switched to Arip, while other subjects were continued on their assigned treatment (all subjects remained blinded to treatment). The subjects who had 12 continuous weeks of active treatment (subjects who were not previously assigned to placebo) were included in the unpooled 12 –week active-controlled safety dataset.
- Study -008 had a
  - 12-week active comparator phase (followed by a 14-week extension phase).
    - Haloperidol was the active comparator drug: a flexible dose of 10-15 mg/day.
    - Arip treatment: a flexible dose of 15 to 30 mg daily.

Review Comments. *The main focus of the review of this 12-week dataset was on the results from the new trials C-135 and C-162. Study -008 was among other older trials previously subject to review (as specified on page 57 of Module 2.7.4).*

Clinical parameter results of each of the 12-week dataset could not be found in Module 2.7.4. However, since results were not PBO controlled they are difficult to interpret. Therefore, this review only focused on deaths, SAEs and ADOs from this dataset.

All Arip-Treated Dataset: This dataset comes from completed and ongoing Phase II-IV trials and includes OL and PBO controlled trials. Although, a subset of these results were previously subject to review (as in a previous sNDA submission) the number of Ss is larger in the current submission (since some trials are ongoing) and included Ss exposed to longterm treatment (as in OL extension trials). Data from trials within a given diagnostic category is pooled (Bipolar, schizophrenia, Major depressive disorder, Dementia patient populations). Only results from Arip treated subjects are presented in Module 2.7.4.

Reviewer comments. *The sample sizes of the All-Arip dataset were larger than in this previously reviewed dataset (for the N18 submission). This dataset is more difficult to interpret such that the main focus of this dataset was on the incidence of SAEs and ADOs*

Additional Datasets in Module 2.7.4 that were not Subject To Review

Additional datasets included in Module 2.7.4 (and included in the table in Section 4.2 of this review) were not subject to review (unless otherwise specified in a safety section of this review, accordingly). *These additional datasets were not reviewed for one of the following reasons or combination of reasons:*

- *Previously subject to review (e.g. a maintenance Treatment Bipolar Study C-010, as specified on page 57 of Module 2.7.4).*
- (b) (4)
- (b) (4)

7.1.1 Deaths

The sponsor notes (among Ss receiving Arip), as specified in Section 2.1.2.5 of Module 2.7.4.:

- 7 deaths reported since the last Arip safety update report (dated October 2005)
- 9 deaths reported since the schizophrenia sNDA (submitted June 2005)
- 1 additional subject who died of overdose of heroin in the maintenance trial, CN-010 (subject CN138010-134-341).

Reviewer Comments on the reported deaths. *In summary reported deaths in Arip treated subjects occurred in patients with pre-existing conditions and/or other risk factors, concomitant medications or substance intoxication or were deaths that are expected of the patient population.*

The following subject in the adjunctive treatment, Bipolar Study C-134 is potentially notable given the nature of remarkable events preceding her death (respiratory distress, severe bradycardia, severe hypotension, severe pulmonary hypoventilation, and moderate syncope);

although she had pre-existing conditions (sleep apnea and obesity). A review of the narrative revealed that the patient was hospitalized on Days 322-3223 of Arip-lithium treatment due to lithium overdose (but the level was not markedly elevation; 1.05 nmol/l). She was not described as having any other events at that time, except for ongoing weight gain. Yet, within 5 hours of discharge she returned to the emergency room with the reported SAE of type II respiratory failure and developed other "life-threatening" cardiorespiratory events, as summarized below.

The following in-text summary was copied from page 206 of Module 2.7.4:

> CN138134-17-106 was a 49-year-old female with a history of Bipolar I Disorder, obesity and obstructive sleep apnea who died of pulmonary alveolar hypoventilation. On Day 365, while taking aripiprazole 30 mg and lithium 750 mg, the patient accidentally overdosed on lithium. Her lithium level was 1.05 mmol/L and she had a hospital course complicated by respiratory distress, severe bradycardia, severe hypotension, severe pulmonary hypoventilation, and moderate syncope. She was admitted to the intensive care unit and placed on a ventilator due to her symptoms. The investigator considered the respiratory failure, pulmonary hypoventilation, bradycardia, hypotension and syncope to have a possible relationship to the study medication. After her admission to the intensive care unit, she developed type II respiratory failure, cardiac arrhythmias and mild cardiac failure. Obstructive sleep apnea and pulmonary hypoventilation were noted to have contributed to her death. A total of 4 ECGs were performed throughout the study and no ECG abnormalities were noted prior to the SAE.

This S is described in more detail in the review of N20 since this study was receiving adjunctive treatment in the pivotal trial for N20.

The following table outlines deaths in each dataset.

Deaths			
Short-term Bipolar Trial Dataset			
Subject Number	**Baseline Information**	**Death**	**Time of Death Relative to Arip Treatment**
CN138074-18-252	Bipolar-mania diagnosis	Hydrocodone intoxication at autopsy	Found dead at his home, 5 days after his last dose
6-Week Adjunctive Bipolar Trial C-134 Dataset			
No deaths			
Unpooled 12-week Active Controlled Bipolar Trial Dataset			
CN138162-3-433	62-year old woman, coronary artery disease, diabetes and chronic gastritis	Respiratory arrest with pulmonary necrosis and lung abscess at autopsy	Day 83: stopped Arip (30 mg/day) due to mania on day 20 of Arip (previously on DB PBO)
Additional events: • Hospitalized for "gastric bleeding and poorly controlled diabetes" on Day 60. • Developed pneumonia, perforated duodenal ulcer • Underwent abdominal surgery on Day 62.			

On Days 62-83: developed "expansion of both lungs occurred, complicated with abscess formation and mortification" reported in her SAE update.			
CN138162-84-606	48-year-old female Bipolar disorder cocaine abuse, & other conditions	"Accidental death due to probable multiple drug effects" (cocaine, alcohol, diphenhydramine, and aripiprazole) noted in the coroner's report.	Found dead in his home by a third party, 21 days after his last known dose of Arip treatment

All Arip-Treated Dataset

Enumeration of Deaths as of 2/14/07 Provided by the Sponsor

Table 2.1.2.5A: Incidence of Deaths by Patient-Exposure Years: All Aripiprazole Treated Patients by Indication and Overall, Safety Sample

		Bipolar-Mania	Bipolar-Depression	MDD	Dementia	Schizophrenia	All Ari*
Bipolar Mania sNDA/Type II	Number of Patients	N=2626	N=593	N=1055	N=894	N=8215	N=13543
	Patient-Exposure Years	546.8	157.8	474.8	763.0	5648.0	7618.9
	N (%) of Deaths	5 (0.2)	1 (0.2)	0 (0.0)	161 (18.0)	45 (0.5)	212 (1.6)
	Per Patient-Exposure Year	0.009	0.006	0.000	0.211	0.008	0.028

*: bipolar mania, bipolar depression, MDD, dementia, schizophrenia, Psychosis associated with Parkinson's Disease, alcoholism

9 Deaths Since the June 2005 Schizophrenia sNDA (as specified on page 205 of Module 2.7.4)

Bipolar I-mania trials:

CN138134-17-106 (see text above), CN138162-3-433 (see above), CN138162-84-606 (see above)

(b) (4)

Subject Number	Baseline Information	Death	Time of Death Relative to Arip Treatment
CN138146-37-390	52-year-old male Hypertension, obese, asthma, gastro-esophageal reflux, +1 pitting edema	Died due to "cardiac disease"	Died approximately 45 days post-dose (discontinued due to leg tremors)

Reviewer Comment. *He had multiple risk factors and died over month post-dose.*
One potentially notable event was that was likely to be drug-related:

- *Ketones in his urine (on Day 139; 80 mg/dl)*
- *Not present at baseline*
- *Significantly decreased after treatment cessation on Day 155 (15 mg/dl).*

He also lost over 30 lbs of body weight (from 327 lbs on day 56 to 276 lbs on Day 155; dieting), which may have played a role.

Schizophrenia Trials

Reviewer Comment: *All 4 newly reported deaths were completed suicides. Note the following:*

- *2 Ss (*CN138100-262-952, CN138152-159-494*) died days to months after treatment cessation.*
- *2 Ss (*CN138166-36-1, CN138166-22-9*) died during treatment, but the latter S had significant psychosocial stressors (loss of child and family conflict).*

Dementia Trials

Subject Number	Baseline Information	Death	Time of Death Relative to

			Arip Treatment
CN138006-73-189	85 year old female, Alzheimer's disease, cardiac disease & other major medical conditions, multiple concomitant drugs	"cardiac arrest"	2 days following Arip treatment cessation (after reciving1856 days of treatment).

Deaths in Blinded Studies
No deaths were reported in blinded Phase II-IV studies.

7.1.2 Other Serious Adverse Events

The sponsor did not describe any individual subjects (in the in-text section on SAEs: Section 2.1.3 of Module 2.7.4). No new or clinically remarkable observations are noted by the sponsor.

The sponsor's tables on the incidence of SAEs follow reviewer comments below.

Reviewer Comments of Results on SAEs in each Safety Dataset
A review of the in-text tables in Module 2.7.4 (for datasets subject to review as previously discussed under Section 7 of this review) revealed the following observations among Bipolar I (b) (4) *study populations for each of the safety datasets reviewed (Tables 2.1.3.1-3, 2.1.3.5).*

The results on the incidence of SAEs failed to show any evidence for a new safety signal, as follows:

- *The Preferred Term AEs shown in the summary tables were generally SAEs that are expected of Arip treatment, the patient population (or of the general population), or were isolated events.*
- *Most preferred term (PT) SAEs were reported in <1% of Bipolar I Arip-treated subjects in each safety dataset*
- *None of the reported PT SAEs reached an incidence of 3% or more among the Arip-treated Bipolar I groups.*
- *Among the few PT SAEs reaching an incidence of at least 2% in the Bipolar I Arip-treated groups (in each safety dataset):*
  - *Mania most consistently reached ≥2% incidence level across several of the datasets (including the All-Arip dataset, which is not shown below)*
  - *Treatment groups showed a similar incidence of these PT SAEs or failed to show consistent group differences (based on numerical comparisons).*
  - *In the All-Arip dataset (results not shown below) the diagnostic groups also failed to show group differences or inconsistent groups differences on the incidence of these PT SAEs (based on numerical comparisons).*

The sponsor also does not make note of any individual subject(s) in Section 2.1.3 of Module 2.7.4.

Refer to the review of N20 for more detailed results from the 6-week Adjunctive trial dataset and any other adjunctive treatment results in Bipolar I-mania patients that are relevant to the proposed claim for N20.

Sponsor's Summary Tables

The following are the sponsor's in-text summary tables for the Pooled Short-term Bipolar I Trial Dataset, the One Adjunctive Bipolar I trial dataset and for the Unpooled 12-Week Active Controlled Bipolar Trials Dataset. The sponsor also shows results for SAEs with at least an incidence of 0.5% in any diagnostic group for the All-Arip Treated dataset in Table 2.1.3.5 of Module 2.7.4 which is not shown in this review.

Table 2.1.3.1: Incidence of Treatment-Emergent SAEs: 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	753	917
NUMBER OF MALE PATIENTS	349	433
NUMBER OF FEMALE PATIENTS	404	484
NUMBER OF PATIENTS WITH >=1 AES	33(4.4)	55(6.0)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	25(3.3)	41(4.5)
MANIA	12(1.6)	19(2.1)
SUICIDAL IDEATION	2(0.3)	5(0.5)
DEPRESSION	2(0.3)	4(0.4)
SUICIDE ATTEMPT	1(0.1)	4(0.4)
PSYCHOTIC DISORDER	1(0.1)	3(0.3)
ANXIETY	0	2(0.2)
BIPOLAR DISORDER	3(0.4)	2(0.2)
BIPOLAR I DISORDER	1(0.1)	2(0.2)
INSOMNIA	0	2(0.2)
BORDERLINE PERSONALITY DISORDER	0	1(0.1)
DEPRESSION SUICIDAL	1(0.1)	1(0.1)
DRUG DEPENDENCE	0	1(0.1)
MENTAL DISORDER	0	1(0.1)
PARANOIA	0	1(0.1)
THINKING ABNORMAL	0	1(0.1)
AFFECTIVE DISORDER	1(0.1)	0
AGITATION	2(0.3)	0
SUICIDAL BEHAVIOUR	1(0.1)	0
NERVOUS SYSTEM DISORDERS	3(0.4)	8(0.9)
CONVULSION	0	2(0.2)
CERVICAL CORD COMPRESSION	0	1(0.1)
DISTURBANCE IN ATTENTION	0	1(0.1)
EXTRAPYRAMIDAL DISORDER	0	1(0.1)
JUDGEMENT IMPAIRED	0	1(0.1)
NEUROLEPTIC MALIGNANT SYNDROME	0	1(0.1)
SYNCOPE	1(0.1)	1(0.1)
GRAND MAL CONVULSION	2(0.3)	0
LOSS OF CONSCIOUSNESS	1(0.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2(0.3)	3(0.3)
CHEST PAIN	1(0.1)	3(0.3)
CHEST DISCOMFORT	1(0.1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	3(0.3)
OVERDOSE	0	2(0.2)
DRUG TOXICITY	0	1(0.1)

GASTROINTESTINAL DISORDERS	1(0.1)	2(0.2)
ABDOMINAL PAIN	0	1(0.1)
PANCREATITIS	0	1(0.1)
INTESTINAL OBSTRUCTION	1(0.1)	0
INFECTIONS AND INFESTATIONS	0	1(0.1)
PNEUMONIA	0	1(0.1)
INVESTIGATIONS	0	1(0.1)
BLOOD PRESSURE INCREASED	0	1(0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1(0.1)
MUSCULOSKELETAL PAIN	0	1(0.1)
PAIN IN JAW	0	1(0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1(0.1)
BREAST CANCER	0	1(0.1)
SURGICAL AND MEDICAL PROCEDURES	0	1(0.1)
PSYCHOSOCIAL SUPPORT	0	1(0.1)
VASCULAR DISORDERS	0	1(0.1)
HYPOTENSION	0	1(0.1)
CARDIAC DISORDERS	2(0.3)	0
SUPRAVENTRICULAR TACHYCARDIA	1(0.1)	0
TACHYCARDIA	1(0.1)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1(0.1)	0
URTICARIA	1(0.1)	0

MedDRA Version: 9.1

Reviewer Comment on the 2 cases of overdose: *The undersigned reviewer found subjects 138162-31-97 and 138009-3-24 listed as an overdose in Appendix 2.1.3.1 of Module 2.7.4. The former subject was in one of the new pivotal trials (Study -162) and had increased psychosis leading to an adverse dropout (ADO) on Day 15 but had an overdose with quetiapine and clonazepam 11 days after Arip treatment cessation (according to the narrative found in the CSR).*

Table 2.1.3.2: Incidence of Treatment-Emergent SAEs: 6-Week Combination Therapy Study in Acute Bipolar Mania (CN138134), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	130	253
NUMBER OF MALE PATIENTS	55	122
NUMBER OF FEMALE PATIENTS	75	131
NUMBER OF PATIENTS WITH >=1 AES	3(2.3)	8(3.2)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	3(2.3)	6(2.4)
ANXIETY	0	1(0.4)
BIPOLAR I DISORDER	0	1(0.4)
CONFUSIONAL STATE	0	1(0.4)
MANIA	2(1.5)	1(0.4)
SUICIDAL IDEATION	0	1(0.4)
SUICIDE ATTEMPT	0	1(0.4)
DEPRESSION	1(0.8)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1(0.4)
OVERDOSE	0	1(0.4)
NERVOUS SYSTEM DISORDERS	0	1(0.4)
AKATHISIA	0	1(0.4)

MedDRA Version: 9.1

Incidence of SAEs in the 12-week Safety Dataset (Table 2.1.3.3 in Module 2.7.4)

	CN138-008		CN138-162		CN138-135	
	Haloperidol	Aripiprazole	Haloperidol	Aripiprazole	Lithium	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	169	175	165	166	159	154
NUMBER OF MALE PATIENTS	55	76	72	71	83	78
NUMBER OF FEMALE PATIENTS	114	99	93	95	76	76
NUMBER OF PATIENTS WITH >=1 AES	12(7.1)	4(2.3)	5(3.0)	19(11.4)	13(8.2)	19(12.3)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	4(2.4)	3(1.7)	1(0.6)	14(8.4)	10(6.3)	13(8.4)
DEPRESSION	1(0.6)	1(0.6)	0	2(1.2)	0	1(0.6)
HYPOMANIA	0	1(0.6)	0	0	0	0
MANIA	2(1.2)	1(0.6)	1(0.6)	4(2.4)	4(2.5)	4(2.6)
AGITATION	0	0	0	0	1(0.6)	0
ANXIETY	1(0.6)	0	0	0	1(0.6)	0
BIPOLAR DISORDER	0	0	0	3(1.8)	3(1.9)	1(0.6)
BIPOLAR I DISORDER	0	0	0	3(1.8)	0	1(0.6)
CONFUSIONAL STATE	0	0	0	0	1(0.6)	1(0.6)
DEPRESSION SUICIDAL	0	0	0	0	0	1(0.6)
DEPRESSIVE SYMPTOM	0	0	0	0	1(0.6)	1(0.6)
DISORIENTATION	0	0	0	0	1(0.6)	0
INSOMNIA	0	0	0	1(0.6)	0	0
PARANOIA	0	0	0	0	0	1(0.6)
PSYCHOTIC DISORDER	0	0	0	1(0.6)	0	0
SELF-INJURIOUS IDEATION	0	0	0	0	1(0.6)	0
SUICIDAL BEHAVIOUR	0	0	0	0	1(0.6)	0
SUICIDAL IDEATION	0	0	0	0	1(0.6)	3(1.9)
SUICIDE ATTEMPT	0	0	0	1(0.6)	1(0.6)	2(1.3)
SURGICAL AND MEDICAL PROCEDURES	3(1.8)	1(0.6)	1(0.6)	1(0.6)	0	0
HERNIA REPAIR	0	1(0.6)	0	0	0	0
PSYCHOSOCIAL SUPPORT	3(1.8)	0	1(0.6)	1(0.6)	0	0
GASTROINTESTINAL DISORDERS	0	0	0	1(0.6)	0	1(0.6)
INTESTINAL OBSTRUCTION	0	0	0	0	0	1(0.6)
PANCREATITIS	0	0	0	1(0.6)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	0	1(0.6)	0	0
CHEST PAIN	0	0	0	1(0.6)	0	0
INFECTIONS AND INFESTATIONS	0	0	0	1(0.6)	0	2(1.3)
CELLULITIS	0	0	0	0	0	1(0.6)
PNEUMONIA	0	0	0	1(0.6)	0	1(0.6)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1(0.6)	0	1(0.6)	1(0.6)	4(2.5)	0
ALCOHOL POISONING	0	0	0	0	1(0.6)	0
DRUG TOXICITY	0	0	0	0	1(0.6)	0
EXPOSURE TO TOXIC AGENT	1(0.6)	0	0	0	0	0
MEDICATION ERROR	0	0	0	0	1(0.6)	0

INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1(0.6)	0	1(0.6)	1(0.6)	4(2.5)	0
OVERDOSE	0	0	0	1(0.6)	1(0.6)	0
TREATMENT NONCOMPLIANCE	0	0	1(0.6)	0	0	0
INVESTIGATIONS	1(0.6)	0	0	0	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	1(0.6)	0	0	0	0	0
BLOOD LACTATE DEHYDROGENASE INCREASED	1(0.6)	0	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	0	0	1(0.6)
BREAST CANCER	0	0	0	0	0	1(0.6)
NERVOUS SYSTEM DISORDERS	3(1.8)	0	1(0.6)	0	1(0.6)	3(1.9)
CERVICAL CORD COMPRESSION	0	0	0	0	0	1(0.6)
CONVULSION	0	0	0	0	0	1(0.6)
DISTURBANCE IN ATTENTION	0	0	0	0	0	1(0.6)
DYSTONIA	1(0.6)	0	0	0	0	0
ENCEPHALOPATHY	0	0	0	0	1(0.6)	0
EXTRAPYRAMIDAL DISORDER	1(0.6)	0	1(0.6)	0	0	0
STUPOR	1(0.6)	0	0	0	0	0
RENAL AND URINARY DISORDERS	0	0	0	0	1(0.6)	0
RENAL FAILURE	0	0	0	0	1(0.6)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	1(0.6)	0	0	0
F OVARIAN CYST	0	0	1(1.1)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	1(0.6)	0	0
PNEUMOTHORAX	0	0	0	1(0.6)	0	0
SOCIAL CIRCUMSTANCES	0	0	0	0	0	2(1.3)
SEXUAL ASSAULT VICTIM	0	0	0	0	0	1(0.6)
SUBSTANCE ABUSE	0	0	0	0	0	1(0.6)

(M) Incidence of AE adjusted for males (F) Incidence of AE adjusted for females
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The following table (in the Appendix pdf file "sum-clin-safety-A.pdf file) shows a listing of SAEs in blinded Bipolar trials:

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Appendix 2.1.3.6:
Listing of SAEs in Patients Blinded to Treatment: Ongoing Phase II/III/IV Studies, by Indication

Indication=Bipolar-Mania

Patient Uniq_ID	Patient Uniq_ID2	Age	Gender	Race	Comb. trt.*	Prot. Of Report	AE Phase	Stdy# Day Of AE Start	Last# Day Of Cur. Trt.	Onset Dose (mg)	Severity	Adverse Event	New Event	New Ari	Related To Drug
138392-6-61		59	F	White	LAMO	138392	DB Mnt.	121	215		Mod	NEPHROLITHIASIS	Y		Unrel.
138392-34-168		43	M	White	LAMO	138392	DB Mnt.	123	167		Mod	INGUINAL HERNIA REPAIR	Y		Unrel.
138392-42-265		58	M	White	LAMO	138392	DB Mnt.	3	6		Sev	MENTAL STATUS CHANGES	Y		Unrel.
138392-54-56		44	F	White	LAMO	138392	DB Mnt.	11	55		Mod	VULVAL CANCER	Y		Unrel.
138392-67-356		60	M	White	LAMO	138392	DB Mnt.	35	76		Mod	CHEST PAIN	Y		Not l.
						138392	DB Mnt.	35	76		Mld	DIZZINESS	Y		Not l.
						138392	DB Mnt.	35	76		Mod	HYPERTENSION	Y		Not l.
						138392	DB Mnt.	36	76		Mod	VENTRICULAR FIBRILLATION	Y		Unrel.

*: CLOZ=CLOZAPINE, LAMO=LAMOTRIGINE, RISP=RISPERIDONE, SERT=SERTRALINE
#: Based on first day of dosing of specified treatment group.
New_Event = New event since the 120 Update -113 database cut-off.
New_Ari = Either "new event" reported on aripiprazole, or an event previously reported in the 120 Update -113 database as "blinded"
Severity abbreviations: Mld=Mild, Mod=Moderate, Sev=Severe, Vsv=Very Severe
Related to Drug abbreviations: Prob.=Probable, Poss.=Possible, Unrel.=Unrelated, Not l.=Not likely
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7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

See Appendix 10.1 for the disposition of subjects in the new pivotal placebo controlled Bipolar trials conducted to show efficacy for this NDA (when using a 15 mg, instead of a 30 mg starting dose level) and for a parallel NDA N20 (for an adjunctive Bipolar-mania, mixed claim).

7.1.3.2 Adverse events associated with dropouts

Reviewer Comments on the Integrated Monotherapy Bipolar trial Results
The safety profile of ADOs does not suggest a new and clinically remarkable safety signal with Arip monotherapy in Bipolar I-mania patients (as compared to results described in approved labeling). The review of N20 focuses on potential adjunctive subgroup differences on some AEs (primarily akathisia and tremor).

A review of the sponsor's summary tables (Tables 2.1.4.1-3 and 2.1.4.5 in Module 2.7.4) failed to reveal any new, clinically remarkable safety signals with Arip treatment, as follows:

- *PT AEs leading to ADOs among Arip Bipolar patients did not show evidence for a new and clinically remarkable safety signal (were generally expected with Arip or adjunctive trial treatment, expected of the patient population, and/or were isolated events)*
- *The following observations are noted regarding the incidence of PT AEs leading to ADOs:*
  - *Unexpected treatment group differences were not revealed on the incidence of ADOs among the PBO controlled safety datasets.*
  - *The incidence of most PT AEs were only approximately ≤1% (in Bipolar I, Arip treated Ss in each safety dataset)*
  - *Akathisia, mania, tremor and depression were generally most commonly reported among Arip treated subjects (generally in ≥2% of subjects).*

A review of individual cases as follows was unrevealing for a new and unexpected safety signal:

- *The sponsor also does not make note of any individual subject(s) in Section 2.1.4 of Module 2.7.4, except for the following (as found in the in-text summary)*
  - ADO of "hepatic failure" was reported in 1 Arip-valproate treated S (CN138134-135-575) with a history of hepatitis (but ALT 48 U/l and AST 20 U/l at baseline). He developed "hepatic failure" leading to an ADO on Day 19 (ALT=96 U/l, AST=48 U/l), requiring "no further treatment." The event "persisted at the time of the last follow-up."

  Comment: *Refer to Depakote™ labeling which specifies that patients with* (b) (4) *this drug. Also refer to the bolded warning in Depakote™ labeling describing cases of hepatic failure that led to death. Upon further inquiry about this S, the above elevations normalized and the subjects was reported to show no clinical signs of failure.*

- *A selected review of narratives (in subjects in the 2 new pivotal trials Study C-135 and C-162) failed to yield evidence for a new and unexpected safety signal (e.g. the given event was isolated, expected of the population, occurred in patients with pre-existing conditions and/or risk factors and/or the events were adequately described in approved labeling).*

<u>All-Arip treated Dataset:</u> subjects the following observations are noted (in addition to previously summarized observations, as noted by the sponsor):

- *Depression was:*
  - *Most common in the Bipolar-mania diagnostic group (2.7%) compared to*
  - *< 1% in the*
    - (b) (4)
    - *In other diagnostic groups.*
- *In light of the above observation note that:*
  - *Suicidality or Suicide <0.5% (were not included in the sponsor's summary Table 2.1.4.5 of ADOs with an incidence of ≥0.5%)*
- *Not unexpectedly, mania was reported in 2.2% in the Bipolar-mania group compared to ≤ 1% of subjects in other diagnostic groups.*

It is not clear to the undersigned reviewer why the incidence of depression was numerically greater in the Arip Ss of Bipolar-mania trials (b) (4) *Given the nature of this dataset these results are difficult to interpret.*

The following are copies of the sponsor's summary tables for selected safety datasets.

Table 2.1.4.1: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Medication: 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	753	917
NUMBER OF MALE PATIENTS	349	433
NUMBER OF FEMALE PATIENTS	404	484
NUMBER OF PATIENTS WITH >=1 AES	72(9.6)	101(11.0)
SYSTEM ORGAN CLASS / PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	52(6.9)	62(6.8)
MANIA	15(2.0)	22(2.4)
ANXIETY	5(0.7)	10(1.1)
AGITATION	9(1.2)	6(0.7)
RESTLESSNESS	1(0.1)	6(0.7)
INSOMNIA	5(0.7)	5(0.5)
DEPRESSION	4(0.5)	4(0.4)
PSYCHOTIC DISORDER	4(0.5)	4(0.4)
BIPOLAR I DISORDER	4(0.5)	3(0.3)
SUICIDE ATTEMPT	0	3(0.3)
BIPOLAR DISORDER	5(0.7)	2(0.2)
DEPRESSIVE SYMPTOM	2(0.3)	2(0.2)
PARANOIA	1(0.1)	2(0.2)
SUICIDAL IDEATION	0	2(0.2)
ABNORMAL DREAMS	0	1(0.1)
AGGRESSION	1(0.1)	1(0.1)
BRADYPHRENIA	0	1(0.1)
DELUSIONAL PERCEPTION	0	1(0.1)
HOSTILITY	0	1(0.1)
IMPULSIVE BEHAVIOUR	0	1(0.1)

MOOD ALTERED	0	1(0.1)
NERVOUSNESS	0	1(0.1)
THINKING ABNORMAL	0	1(0.1)
ANGER	1(0.1)	0
DELUSION	2(0.3)	0
FLIGHT OF IDEAS	1(0.1)	0
GRANDIOSITY	1(0.1)	0
LOGORRHOEA	2(0.3)	0
MENTAL DISORDER	1(0.1)	0
SUICIDAL BEHAVIOUR	1(0.1)	0
NERVOUS SYSTEM DISORDERS	9(1.2)	35(3.8)
AKATHISIA	2(0.3)	19(2.1)
EXTRAPYRAMIDAL DISORDER	0	5(0.5)
DISTURBANCE IN ATTENTION	0	2(0.2)
DIZZINESS	2(0.3)	2(0.2)
DYSTONIA	2(0.3)	2(0.2)
HEADACHE	1(0.1)	2(0.2)
TREMOR	0	2(0.2)
CONVULSION	0	1(0.1)
SEDATION	0	1(0.1)
SYNCOPE	0	1(0.1)
GRAND MAL CONVULSION	1(0.1)	0
HYPOAESTHESIA	1(0.1)	0
MYOCLONUS	1(0.1)	0
PARAESTHESIA	1(0.1)	0
TENSION HEADACHE	1(0.1)	0
GASTROINTESTINAL DISORDERS	5(0.7)	9(1.0)
NAUSEA	3(0.4)	7(0.8)
VOMITING	2(0.3)	3(0.3)
ABDOMINAL DISTENSION	0	1(0.1)
DIARRHOEA	2(0.3)	1(0.1)
ABDOMINAL PAIN	1(0.1)	0
INTESTINAL OBSTRUCTION	1(0.1)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4(0.5)	4(0.4)
MUSCULOSKELETAL STIFFNESS	2(0.3)	2(0.2)
BACK PAIN	0	1(0.1)
MUSCLE RIGIDITY	0	1(0.1)
JOINT STIFFNESS	1(0.1)	0
MUSCLE TIGHTNESS	2(0.3)	0
MUSCULAR WEAKNESS	1(0.1)	0
EYE DISORDERS	1(0.1)	3(0.3)
EYE PAIN	0	1(0.1)
VISION BLURRED	0	1(0.1)
VISUAL DISTURBANCE	0	1(0.1)
BLEPHAROSPASM	1(0.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6(0.8)	2(0.2)
ADVERSE EVENT	1(0.1)	1(0.1)
FATIGUE	0	1(0.1)
IRRITABILITY	3(0.4)	1(0.1)
CHEST DISCOMFORT	1(0.1)	0
CHEST PAIN	1(0.1)	0
FEELING HOT	1(0.1)	0

VASCULAR DISORDERS	0	2(0.2)
HYPOTENSION	0	1(0.1)
ORTHOSTATIC HYPOTENSION	0	1(0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1(0.1)
DRUG TOXICITY	0	1(0.1)
INVESTIGATIONS	4(0.5)	1(0.1)
HEART RATE INCREASED	0	1(0.1)
ALANINE AMINOTRANSFERASE INCREASED	1(0.1)	0
ASPARTATE AMINOTRANSFERASE INCREASED	1(0.1)	0
BLOOD CREATINE PHOSPHOKINASE INCREASED	2(0.3)	0
BLOOD CREATINE PHOSPHOKINASE MB INCREASED	1(0.1)	0
HEPATIC ENZYME INCREASED	2(0.3)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1(0.1)
BREAST CANCER	0	1(0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3(0.4)	1(0.1)
RASH GENERALISED	0	1(0.1)
PRURITUS	1(0.1)	0
RASH	1(0.1)	0
URTICARIA	1(0.1)	0
CARDIAC DISORDERS	1(0.1)	0
PALPITATIONS	1(0.1)	0
RENAL AND URINARY DISORDERS	2(0.3)	0
HAEMATURIA	1(0.1)	0
POLLAKIURIA	1(0.1)	0

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Table 2.1.4.2: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Medication: 6-Week Combination Therapy Study in Acute Bipolar Mania (CN138134), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	130	253
NUMBER OF MALE PATIENTS	55	122
NUMBER OF FEMALE PATIENTS	75	131
NUMBER OF PATIENTS WITH >=1 AES	8(6.2)	30(11.9)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	2(1.5)	18(7.1)
AKATHISIA	1(0.8)	13(5.1)
TREMOR	1(0.8)	5(2.0)
DISTURBANCE IN ATTENTION	0	2(0.8)
SEDATION	0	2(0.8)
DIZZINESS	0	1(0.4)
SOMNOLENCE	0	1(0.4)
PSYCHIATRIC DISORDERS	6(4.6)	11(4.3)
AGITATION	0	2(0.8)
DEPRESSION	4(3.1)	2(0.8)
ANXIETY	0	1(0.4)
DEPRESSIVE SYMPTOM	0	1(0.4)
MANIA	1(0.8)	1(0.4)
NERVOUSNESS	0	1(0.4)
RESTLESSNESS	0	1(0.4)
SUICIDAL IDEATION	0	1(0.4)
SUICIDE ATTEMPT	0	1(0.4)
BIPOLAR I DISORDER	1(0.8)	0

GASTROINTESTINAL DISORDERS	0	6(2.4)
DIARRHOEA	0	2(0.8)
DRY MOUTH	0	2(0.8)
NAUSEA	0	2(0.8)
ABDOMINAL DISCOMFORT	0	1(0.4)
CONSTIPATION	0	1(0.4)
IRRITABLE BOWEL SYNDROME	0	1(0.4)
LIP DRY	0	1(0.4)
RECTAL HAEMORRHAGE	0	1(0.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	2(0.8)
ARTHRALGIA	0	1(0.4)
MUSCLE FATIGUE	0	1(0.4)
MUSCULOSKELETAL STIFFNESS	0	1(0.4)
EYE DISORDERS	0	1(0.4)
PHOTOPHOBIA	0	1(0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1(0.8)	1(0.4)
FATIGUE	1(0.8)	1(0.4)
IRRITABILITY	1(0.8)	0
HEPATOBILIARY DISORDERS	0	1(0.4)
HEPATIC FAILURE	0	1(0.4)
INFECTIONS AND INFESTATIONS	0	1(0.4)
LOWER RESPIRATORY TRACT INFECTION	0	1(0.4)
INVESTIGATIONS	0	1(0.4)
BLOOD CREATINE PHOSPHOKINASE INCREASED	0	1(0.4)
METABOLISM AND NUTRITION DISORDERS	0	1(0.4)
INCREASED APPETITE	0	1(0.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1(0.4)
DRY SKIN	0	1(0.4)

Table 2.1.4.3: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Medication: 12-Week Active-Controlled Studies in Acute Bipolar Mania (CN138008, CN138162, CN138135), Safety Sample

	CN138-008		CN138-162		CN138-135	
	Haloperidol	Aripiprazole	Haloperidol	Aripiprazole	Lithium	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	169	175	165	166	159	154
NUMBER OF MALE PATIENTS	55	76	72	71	83	78
NUMBER OF FEMALE PATIENTS	114	99	93	95	76	76
NUMBER OF PATIENTS WITH >=1 AES	83(49.1)	33(18.9)	18(10.9)	24(14.5)	28(17.6)	31(20.1)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	59(34.9)	19(10.9)	10(6.1)	3(1.8)	8(5.0)	10(6.5)
AKATHISIA	24(14.2)	9(5.1)	2(1.2)	1(0.6)	2(1.3)	5(3.2)
DIZZINESS	0	3(1.7)	0	0	0	1(0.6)
EXTRAPYRAMIDAL DISORDER	19(11.2)	3(1.7)	4(2.4)	1(0.6)	0	1(0.6)
TREMOR	7(4.1)	3(1.7)	1(0.6)	0	3(1.9)	0
PARKINSONISM	11(6.5)	2(1.1)	1(0.6)	0	0	0
COORDINATION ABNORMAL	0	1(0.6)	0	0	0	0
DYSKINESIA	1(0.6)	1(0.6)	0	0	0	0
DYSTONIA	5(3.0)	1(0.6)	2(1.2)	0	0	2(1.3)
HYPERSOMNIA	0	1(0.6)	0	0	0	0
SEDATION	0	1(0.6)	0	1(0.6)	0	0
DISTURBANCE IN ATTENTION	0	0	0	0	0	1(0.6)
DYSARTHRIA	1(0.6)	0	0	0	1(0.6)	0
ENCEPHALOPATHY	0	0	0	0	1(0.6)	0
HEADACHE	1(0.6)	0	0	0	2(1.3)	2(1.3)
HYPERKINESIA	1(0.6)	0	0	0	0	0
MYOCLONUS	1(0.6)	0	0	0	0	0
NEUROLEPTIC MALIGNANT SYNDROME	1(0.6)	0	0	0	0	0
RESTLESS LEGS SYNDROME	1(0.6)	0	0	0	0	0
SOMNOLENCE	1(0.6)	0	0	0	0	0
STUPOR	1(0.6)	0	0	0	0	0

PSYCHIATRIC DISORDERS	16(9.5)	14(8.0)	7(4.2)	21(12.7)	14(8.8)	19(12.3)
DEPRESSION	6(3.6)	11(6.3)	1(0.6)	4(2.4)	2(1.3)	2(1.3)
ANXIETY	3(1.8)	2(1.1)	0	2(1.2)	1(0.6)	2(1.3)
AGITATION	0	1(0.6)	0	0	0	0
DYSPHORIA	0	1(0.6)	0	0	0	0
ILLUSION	0	1(0.6)	0	0	0	0
INSOMNIA	0	1(0.6)	1(0.6)	2(1.2)	0	2(1.3)
MANIA	2(1.2)	1(0.6)	1(0.6)	9(5.4)	4(2.5)	2(1.3)
AGGRESSION	0	0	0	0	1(0.6)	0
BIPOLAR DISORDER	0	0	0	1(0.6)	3(1.9)	1(0.6)
BIPOLAR I DISORDER	0	0	2(1.2)	4(2.4)	0	1(0.6)
CONFUSIONAL STATE	0	0	1(0.6)	0	0	1(0.6)
DEPRESSED MOOD	1(0.6)	0	0	0	0	0
DEPRESSIVE SYMPTOM	0	0	0	0	3(1.9)	4(2.6)
EARLY MORNING AWAKENING	1(0.6)	0	0	0	0	0
MOOD ALTERED	0	0	0	0	0	1(0.6)
NIGHTMARE	0	0	1(0.6)	0	0	0
PANIC ATTACK	2(1.2)	0	0	0	0	0
PARANOIA	0	0	0	0	0	1(0.6)
PSYCHOTIC DISORDER	0	0	0	2(1.2)	1(0.6)	0
RESTLESSNESS	2(1.2)	0	0	0	0	1(0.6)
SUICIDAL BEHAVIOUR	0	0	0	0	1(0.6)	0
SUICIDAL IDEATION	0	0	0	0	0	3(1.9)
SUICIDE ATTEMPT	0	0	0	1(0.6)	0	1(0.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	15(8.9)	5(2.9)	2(1.2)	1(0.6)	0	1(0.6)
MUSCULOSKELETAL STIFFNESS	6(3.6)	2(1.1)	0	0	0	1(0.6)
JAW DISORDER	0	1(0.6)	0	0	0	0
MUSCLE RIGIDITY	8(4.7)	1(0.6)	1(0.6)	1(0.6)	0	0
MUSCULAR WEAKNESS	0	1(0.6)	0	0	0	0
BACK PAIN	0	0	1(0.6)	0	0	0
JOINT STIFFNESS	1(0.6)	0	0	0	0	0
GASTROINTESTINAL DISORDERS	5(3.0)	4(2.3)	1(0.6)	1(0.6)	6(3.8)	2(1.3)
NAUSEA	1(0.6)	3(1.7)	0	1(0.6)	3(1.9)	1(0.6)
ABDOMINAL SYMPTOM	0	1(0.6)	0	0	0	0
SALIVARY HYPERSECRETION	4(2.4)	1(0.6)	0	0	0	0
ABDOMINAL DISTENSION	0	0	0	0	0	1(0.6)
DIARRHOEA	0	0	0	0	2(1.3)	0
DRY MOUTH	0	0	1(0.6)	0	0	0
VOMITING	1(0.6)	0	0	0	4(2.5)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2(1.2)	3(1.7)	0	0	1(0.6)	0
ASTHENIA	1(0.6)	1(0.6)	0	0	1(0.6)	0
FACE OEDEMA	0	1(0.6)	0	0	0	0
MALAISE	0	1(0.6)	0	0	0	0
CHEST DISCOMFORT	1(0.6)	0	0	0	0	0
EAR AND LABYRINTH DISORDERS	0	1(0.6)	0	0	0	0
EAR PAIN	0	1(0.6)	0	0	0	0
CARDIAC DISORDERS	1(0.6)	0	0	0	0	0
PALPITATIONS	1(0.6)	0	0	0	0	0
EYE DISORDERS	1(0.6)	0	1(0.6)	0	1(0.6)	2(1.3)
EYE PAIN	0	0	0	0	0	1(0.6)
OCULAR HYPERAEMIA	0	0	0	0	1(0.6)	0
OCULOGYRATION	1(0.6)	0	0	0	0	0
VISION BLURRED	0	0	0	0	0	1(0.6)
VISUAL DISTURBANCE	0	0	1(0.6)	0	0	0
HEPATOBILIARY DISORDERS	1(0.6)	0	0	0	0	0
HEPATITIS	1(0.6)	0	0	0	0	0

INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1(0.6)	0	2(1.3)	0
ALCOHOL POISONING	0	0	0	0	1(0.6)	0
DRUG TOXICITY	0	0	0	0	1(0.6)	0
TREATMENT NONCOMPLIANCE	0	0	1(0.6)	0	0	0
INVESTIGATIONS	2(1.2)	0	1(0.6)	0	1(0.6)	0
ASPARTATE AMINOTRANSFERASE INCREASED	1(0.6)	0	0	0	0	0
BLOOD CREATINE PHOSPHOKINASE INCREASED	1(0.6)	0	0	0	0	0
BLOOD LACTATE DEHYDROGENASE INCREASED	1(0.6)	0	0	0	0	0
WEIGHT INCREASED	0	0	0	0	1(0.6)	0
WHITE BLOOD CELL COUNT DECREASED	0	0	1(0.6)	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	0	0	1(0.6)
BREAST CANCER	0	0	0	0	0	1(0.6)
RENAL AND URINARY DISORDERS	0	0	1(0.6)	0	1(0.6)	0
POLLAKIURIA	0	0	1(0.6)	0	0	0
RENAL FAILURE	0	0	0	0	1(0.6)	0
URINARY INCONTINENCE	0	0	1(0.6)	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1(0.6)	0	0	0	0	0
GALACTORRHOEA	1(0.6)	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	1(0.6)	0	0
PNEUMOTHORAX	0	0	0	1(0.6)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2(1.2)	0	0	0	1(0.6)	1(0.6)
ACNE	0	0	0	0	1(0.6)	0
HYPERHIDROSIS	1(0.6)	0	0	0	0	0
PRURITUS GENERALISED	1(0.6)	0	0	0	0	0
RASH	1(0.6)	0	0	0	0	0
SKIN HYPERPIGMENTATION	0	0	0	0	0	1(0.6)
SOCIAL CIRCUMSTANCES	0	0	0	0	0	1(0.6)
SUBSTANCE ABUSE	0	0	0	0	0	1(0.6)
VASCULAR DISORDERS	1(0.6)	0	0	0	0	0
HYPERTENSION	1(0.6)	0	0	0	0	0

7.1.3.3 Other significant adverse events

Refer to Sections 7.1.4, 7.1.7.3.3, 7.1.8.3.3, and 7.1.9.3.3.

7.1.4 Other Search Strategies

The sponsor searched their AE database for the following AEs of "special interest" in the 3-week Placebo controlled Bipolar trial dataset and in the All-Arip treated dataset, unless otherwise specified (and searches were also generally conducted in other safety datasets described in Sections 4 and 7.1 of this review):

- Extrapyramidal Symptoms (EPS)
- Neuroleptic Malignant Syndrome (NMS)
- Seizures
- Orthostatic Hypotension
- Suicide
- Somnolence or sedation
- Metabolic and glucose measurement abnormalities: these results were of laboratory parameters and regarding individual subjects noted by the sponsor. The results on a special search for diabetes/hyperglycemia-related AEs are described in this section below. Other results based on laboratory or other clinical parameter measures are described in other sections of this review as follows. Routine laboratory parameter results are addressed in the laboratory section of this review (Section 7.1.7 for routine

laboratory parameters relevant to glucose and lipid profile parameters). Results of special laboratory parameters of glucose metabolism are summarized in Section 7.1.7.5. Results on body weight related measures are covered in Section 7.1.8 (vital sign measures).

Reviewer Comments.
Before summarizing the sponsor results please note the following for consideration.

The rationale for the sponsor's selection cannot be found by the undersigned reviewer for all AEs of "special interest." It is also not clear if the sponsor conducted searches for verbatim and/or preferred terms for a given category with some exceptions, such as suicide-related AEs in which search methods are described on page 294 of Module 2.7.4. Results on the incidence of some of the special interest AEs are provided by Preferred Terms.

The interpretation of the results can be limited by the search methods employed and a number of other factors that include several relevant to the given dataset being searched (and to the trial designs, among other factors). Therefore, the interpretation of the results is limited but serves as an attempt to capture clinically meaningful cases with an AE of "special interest."

Diabetes/hyperglycemia-related AEs
Based on a special search strategy described on page 319 of Module 2.7.4 the following outline provides the incidence of these AEs and of ADOs due these AEs (as found in the in-text Section 2.1.5.7 of Module 2.7.4) for selected datasets, as follows (selected for review for the purposes of this N19 submission).

- 3-week Short-term PBO controlled Bipolar trial dataset and 6-week A Trial Dataset (Study C-134):
  - The incidence of these AEs: 0 to <1% (in any given treatment group)
  - No ADOs were reported.
- All-Arip Safety dataset
  - AEs: 0.4% in Bipolar-mania trials compared to 1.1% (0.016 per patient exposure years) in schizophrenia trials.
  - No ADOs

The sponsor did not describe any individual cases.

Orthostasis.
Orthostatic Hypotension
Clinical Reviewer Comments. *A search of orthostatic hypotension related AEs revealed the following results:*

- *Pooled 3-week Placebo Controlled Bipolar Phase 3 trial dataset: no clinically remarkable and unexpected treatment group difference was found (generally <1% treatment group difference on the incidence of any given AE).*
- *6-week Adjunctive Bipolar Trial: see the below results (copied from Module 2.7.4):*

Table 2.1.5.4F: Incidence of Orthostatic-Related AEs: 6-Week Combination Therapy in Acute Bipolar Mania (CN138134), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	130	253
NUMBER OF MALE PATIENTS	55	122
NUMBER OF FEMALE PATIENTS	75	131
NUMBER OF PATIENTS WITH >=1 AES	2(1.5)	13(5.1)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	1(0.8)	12(4.7)
DIZZINESS	1(0.8)	11(4.3)
DIZZINESS POSTURAL	0	1(0.4)
CARDIAC DISORDERS	1(0.8)	1(0.4)
TACHYCARDIA	1(0.8)	1(0.4)

MedDRA Version: 9.1

In addition to the above, regarding the 6-week Adjunctive trial:

- *Only 1 subject in the Arip group met outlier criteria for orthostatic hypotension (out of 195 total Arip subjects).*
- *Treatment groups were not significantly different on mean change from baseline to treatment endpoint on orthostatic systolic BP (the difference between supine and standing BPs) and the group mean change was small (<1 bpm) in the Arip group.*

Results from the All-Arip treatment dataset could not be found.

Suicide.

Pooled 3-week Short-term Dataset Results:

The following table was provided by the sponsor.

Table 2.1.5.5A: Incidence of Treatment-Emergent Suicide-Related AEs: 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

	Placebo	Aripiprazole
#PATIENTS / #PATIENT-YEARS SCREENED FOR AES	753 / 31.2	917 / 41.0
MALE #PATIENTS / #PATIENT-YEARS	349 / 14.7	433 / 18.8
FEMALE #PATIENTS / #PATIENT-YEARS	404 / 16.6	484 / 22.2
NUMBER OF PATIENTS WITH >=1 AE	7(0.93) [0.224]	16(1.74) [0.390]
SUICIDALITY EVENT CATEGORIZATION PREFERRED TERM	INCIDENCE(%) [per PEY]	INCIDENCE(%) [per PEY]
SUICIDAL IDEATION	6(0.79) [0.192]	13(1.41) [0.317]
SUICIDAL IDEATION	5(0.66) [0.160]	12(1.30) [0.292]
DEPRESSION SUICIDAL	1(0.13) [0.032]	1(0.10) [0.024]
SUICIDE ATTEMPT	1(0.13) [0.032]	5(0.54) [0.122]
SUICIDE ATTEMPT	1(0.13) [0.032]	4(0.43) [0.097]
SUICIDAL BEHAVIOUR	1(0.13) [0.032]	1(0.10) [0.024]

PEY = Patient exposure years

Incidence of Suicidality Defined on the Basis of Scores on Item 10 of the MADRS

The sponsor also conducted an analyses of results on Item 10 of the MADRS (Item 10 is a rating of suicidal thoughts ranging from 0=enjoying life to 6=having active preparations for suicide).

The sponsor defined a treatment-emergent suicidal ideation in a given subject as a change from baseline score of 0-2 to an on-treatment score of 5-6. The incidence of suicidality based on this definition was as follows:

- 0.5% (4/804 subjects) and 0.2% (1/632 subjects) in the Arip and PBO groups (p=0.39).

Reviewer comment on selecting a 0-2 baseline score on Item 10: *Note that a score of 2= "…only fleeting suicidal thoughts."*

Reviewer Comments on Suicidality Results. *The incidence of suicidal related AEs was numerically greater in the Arip compared to PBO subjects as shown in the table above (statistical comparisons were not found). However, the incidence was small and the treatment group difference was <1% and generally 0 to <0.5% on most categories shown in the sponsor's table (above). Pivotal Bipolar monotherapy trials in this review and described in approved labeling (2 Bipolar trials) failed to show worsening on the MADRS scale (as shown in Table 3.2.1.3 H in the Summary of Clinical Efficacy module).*

Approved labeling includes a subsection (in Section 5 of labeling) on suicidality in Bipolar patients that adequately addresses suicidality risk in this patient population.

<u>6-week Adjunctive Trial Dataset:</u>
The incidence of suicide related AEs:

- 0.8% (2/253) and 0% in Arip and PBO treatment groups, respectively.
  - Among the 2 Arip subjects (subjects CN138134-115-477 and -104-244):
  - 1 had suicide ideation (-104-244)
    Reviewer Comment: *the S was reported as having improved and upon gaining insight on the adverse impact of his illness on his level of function, he developed suicidality*
  - The other a suicide attempt *(CN138134-115-477):*
    Reviewer Comment: *the S had a history of polysubstance abuse and appeared to exhibit poor impulse control ("suddenly felt severe depression" and consumed alcohol and buspirone, "wanting to die" on Day 6 of valproate-Arip DB treatment).*
  - The above events were reported as an ADO and SAE
  - Both Ss were receiving valproate adjunctive treatment

<u>An additional S with Suicidality in Study C-134</u>
Reviewer comment. *The undersigned reviewer found a third subject with suicidal thoughts (subject CN138134-40-212, upon review of the CSR) in Study -134. This S had developed a depressive episode following mania and had major psychosocial stressors (loss of work, marital conflict). This subject is listed in the line listings as having the AE of Bipolar disorder (in Table S.6.23 of SAEs), which is generally consistent with the narrative description for the narrative, but may explain why this S was missed from the sponsor's special search for suicidal-related AEs.*

Because the above (additional) S was not included in the sponsor's search the undersigned reviewer conducted a word search for "suic" in the narrative section of the pdf file of the CSR in the submission (the Adobe Acrobat "find" tool was used for the search). No additional subjects were found from this word search among the narratives provided in the CSR.

Maintenance Treatment Study CN138010

The incidence of these AEs in the maintenance trial:

- 2.4%, 1.3% in PBO and Arip groups, respectively).
- 0 Arip Ss met the definition for suicidality based on the MADRS-Item 10 score (as previously defined).

All-Arip Treated Dataset

Reviewer Comment. *Table 2.1.5.5I in Module 2.7.4 shows:*

- *A low incidence (per patient years of exposure) of each AE category or AE term*
- *The Bipolar-mania trials failed to show clinically remarkable differences in the incidence of these AEs compared to other diagnostic groups.*

The incidence of suicidal related AEs in the Bipolar-mania trials (number of subjects and incidence per patient years shown below):

- Completed suicide (1 subject or 0.002% incidence per patient years): the sponsor notes this S was incorrectly coded since the patient did not die.
- Suicidal ideation (40 Ss; 0.073%) compared to:
  - Schizophrenia trials (106 Ss; 0.019%)
- Suicide attempt (10 Ss; 0.018%) compared to:
  - Schizophrenia trials (59 Ss; 0.01%)

Somnolence/Sedation

Reviewer comments and conclusions. *A review of in-text information found in Section 2.1.5.6 of Module 2.7.4 did not reveal any clinically remarkable and unexpected finding related to somnolence or sedation.*

The overall incidence of these events reported as AEs or as ADOs was as follows for each dataset (found in Section 2.1.5.6):

- *3-week Short-term PBO controlled Bipolar trial dataset:*
  - *AEs: 12.8% and 6.0% in the Arip and PBO groups.*
  - *ADOs (due to somnolence or sedation as noted by the sponsor): 0.1% and 0%, in Arip and PBO groups, respectively.*
- *6-week Adjunctive Trial Dataset (Study C-134):*
  - *AEs: 6.3% and 3.8% in the Arip and PBO groups.*
  - *ADOs (due to somnolence or sedation as noted by the sponsor): 0.4% and 0%, in Arip and PBO groups, respectively.*

The sponsor did not describe any individual cases.

Seizures.

The following is the sponsor's summary of their search methods (on page 148 of Module 2.7.4):

> A comprehensive search of the AE database for all Phase 2/3/4 studies was conducted to identify patients with a seizure-related AE using the following terms: seizure, convulsion, grand mal, petit mal, epilepsy, fits, electroencephalogram, EEG, and lobe. Terms were then assessed to determine the appropriateness of the included entries.

The following summarizes the results for each dataset (incidence of Arip and PBO groups provided, as found in the in-text Section 2.1.5.3 of Module 2.7.4):

- 3-week Short-term PBO controlled Bipolar trial dataset:
  - Convulsion: 0.2 (2/917), 0 (0/753)
  - Grand mal convulsion: 0% and 0.3%
- 6-week Adjunctive Trial Dataset (Study C-134):
  - No subjects
- Active Controlled Trial (unpooled) dataset:
  - 1 subject (CN138135-44-137), also included in the All-Arip dataset below.
- Maintenance Trial (CN138010):
  - No subjects
- All-Arip Treated Dataset:
  - Bipolar-mania trials: 5/2626 (0.2%)
  - Dementia trials: 1.7%
  - Trials of other diagnostic groups ((b) (4) Major depressive disorder, and schizophrenia trials): 0-0.3%

Reviewer Comment. *The results do not suggest a new, clinically remarkable safety signal (refer to labeling for a section on seizures under Warnings/Precautions).*

Reviewer comment on the 5 Ss *with seizure-related AEs (convulsion or clonic convulsion was reported): CN138007-14-175, CN138007-34-61, CN138007-56-444, CN138134-96-296, and CN138135-44-137.*

The sponsor provided in-text summary descriptions of each of the above, 5 All-Arip treated Bipolar Ss. Note the following:

- *It is not clear in the summary descriptions how seizure or convulsion was diagnosed in each S (e.g. details on the clinical presentation are not included in the in-text descriptions).*
- *A history of seizures or risk factors is not described in each subject except for subject CN138007-34-61 (this S used amphetamines and was receiving olanzapine "within 14 days" of the event).*
- *S CN138007-14-175 continued treatment after resolution of her seizure (seizure was reported on Day 13 of Arip)*
- CN138007-56-444 and CN138135-44-137: *the event occurred on Days 3 and 50 in each respective subject and lead to an ADO on the day of the event.*

- CN138134-96-296: *This 25 year old patient had clinic convulsion reported as a non-serious AE on Day 183 of lithium-Arip (15mg/day) of treatment and also had loss of consciousness and headache (resolved on the same day).*

NMS: The sponsor summarizes results of a search of the All-Arip treated AE database for NMS (in Section 2.1.5.2 of Module 2.7.4). Only 3 out of 13543 (0.02%) subjects were found (as described on page 280 of Module 2.7.4). The sponsor notes that these 3 subjects were reported in previous submissions under the NDA (October 2001 and June 2005 submissions with no new cases since the 120-Day safety update Report dated October 2005, as described on page 280 of Module 2.7.4).

EPS
Section 2.1.5.1 of Module 2.7.4 provides the incidence of AEs (Preferred Term & Organ System) using a categorization system for grouping AEs into 5 categories: dystonic events, akathisia events, Parkinsonian event, Dyskinetic Events, Residual Events (pages 258-259 of the Module provides more details). Results from ratings scales were also provided.

Each subsection below summarizes some of the results found in Section 2.1.5.1 of Module 2.7.4 for each of the datasets selected for review (incidence of Arip and PBO groups provided for AE categories and results from rating scales).

<u>3-week Short-term PBO controlled Bipolar trial dataset:</u>

- EPS-related events (excludes akathisia-related events): 16% (148/917), 8% (63/753)
- Akathisia-related events: 13% and 4%
- Other common Preferred Term event categories (incidence of ≥5% in Arip Ss):
  - Tremor: 6% and 3%
  - Extrapyramidal disorder: 5%, 2%
- Tardive dyskinesia: 0%, 0.1% (1 subject)
- ADOs due to EPS-related AEs: 2.9%, 0.7% with akathisia as the most common AE leading to an ADO (2.1%, 0.3%)

Rating Scale results showed:

- Statistically significant worsening was observed on the SAS total score and the Barnes Akathisia Global Clinical Assessment scale (Arip; 0.50, PBO; -0.01 and Arip; 0.21, PBO; -0.05 on each scale, respectively).
- No statistical group difference was observed on the AIMS total score.

<u>6-week Adjunctive Trial Dataset (Study C-134) in Arip and PBO Ss, respectively:</u>

- EPS-related events (excludes akathisia-related events): 15% (39/253), 8% (11/130)
- Akathisia-related events: 19% and 5% (also a common event under other categories shown in Table 2.1.5.1E).
- Other common Preferred Term event categories (incidence of ≥5% in Arip Ss):
  - Tremor: 9% and 6%
  - Extrapyramidal disorder: 5%, 1%

- Tardive dyskinesia: not reported (not found in Table 2.1.5.1E)
- ADOs due to EPS-related AEs: 5.9%, 1.5%
    - All of these ADOs were due to:
        - Akathisia (Arip; 5.1%, PBO; 0.8%)
        - Tremor (Arip; 2.0%, PBO; 0.8%)

Adjunctive Subgroups of Study C-134:
Akathisia and tremor in each DB treatment group within each adjunctive treatment subgroup (Arip and PBO groups, respectively):

- Lithium:
    - Akathisia: 28%, 4%
    - Tremor: 13%, 8%
- Valproate
    - Akathisia: 12%, 6%
    - Tremor: 6%, 5%

Rating Scale results:

- Statistically significant worsening was observed on the SAS total score and the Barnes Akathisia Global Clinical Assessment scale (Arip; 0.73, PBO; 0.07 and Arip; 0.30, PBO; 0.11 on each scale, respectively).
- No statistical group difference was observed on the AIMS total score.

All-Arip Treated Dataset:

- Results were not found (this dataset included results from non-PBO controlled trials and ongoing OL trials).

Reviewer Comment. *The above results and as found in the in-text section 2.1.5.1 of Module 2.7.4 fail to reveal a clinically remarkable and new safety signal, except for a possible adjunctive treatment by DB treatment group interaction effect on events of akathisia and tremor.*

The results on these events in adjunctive treatment groups in Study C-134 suggest a greater effect of Arip compared to PBO treatment group in lithium Ss compared to that observed in valproate subjects as follows (the difference on the incidence of each of these events between the Arip and PBO DB treatment groups are shown for each adjunctive subgroup below):

- *Akathisia*
    - *DB Treatment group difference in lithium Ss: 24%*
    - *DB Treatment group difference in valproate Ss: 6%*
- *Tremor*
    - *DB Treatment group difference in lithium Ss: 5%*
    - *DB Treatment group difference in valproate Ss: 1%*

The above results are relevant to N20 are therefore addressed in the last Section of the review of N20. These results are not considered relevant to N19 since Study C-134 was of a focused patient population of "partial nonresponders" (based on their ratings during monotherapy with

a "mood stabilizer") and involved adjunctive treatment in order to seek approval for an adjunctive treatment claim.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Generally standard methods for monitoring and reporting for adverse events (AEs) were employed in the sponsor's trials. Any special rating scales that might be considered as elicited AEs are also described, elsewhere, in the appropriate subsection of this review.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The MedDRA classification system was used. The version used for each pivotal MDD trial was the version that was available at the time of the database lock.

Reviewer Comments. *Each AE categorization system has its inherent limitations. The MedDRA system is now considered the preferred categorization system by the Agency at this time, to the knowledge of the undersigned reviewer.*

7.1.5.3 Incidence of common adverse events

The following tables were provided by the sponsor.

Table 2.1A-1: Incidence of Treatment-Emergent AEs Reported in at Least 2 Percent of Patients in the Aripiprazole Group:3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	753	917
NUMBER OF MALE PATIENTS	349	433
NUMBER OF FEMALE PATIENTS	404	484
NUMBER OF PATIENTS WITH >=1 AES	540(71.7)	759(82.8)
SYSTEM ORGAN CLASS		
PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)

NERVOUS SYSTEM DISORDERS	288(38.2)	481(52.5)
HEADACHE	162(21.5)	213(23.2)
AKATHISIA	27(3.6)	119(13.0)
DIZZINESS	56(7.4)	73(8.0)
SEDATION	24(3.2)	71(7.7)
TREMOR	24(3.2)	57(6.2)
EXTRAPYRAMIDAL DISORDER	13(1.7)	49(5.3)
SOMNOLENCE	22(2.9)	48(5.2)
GASTROINTESTINAL DISORDERS	264(35.1)	418(45.6)
NAUSEA	87(11.6)	156(17.0)
CONSTIPATION	44(5.8)	99(10.8)
VOMITING	37(4.9)	77(8.4)
DYSPEPSIA	39(5.2)	73(8.0)
DIARRHOEA	61(8.1)	70(7.6)
DRY MOUTH	27(3.6)	45(4.9)
STOMACH DISCOMFORT	12(1.6)	27(2.9)
ABDOMINAL DISCOMFORT	12(1.6)	22(2.4)
GASTROINTESTINAL DISORDERS	264(35.1)	418(45.6)
TOOTHACHE	14(1.9)	20(2.2)
ABDOMINAL PAIN	22(2.9)	19(2.1)
SALIVARY HYPERSECRETION	3(0.4)	19(2.1)
PSYCHIATRIC DISORDERS	241(32.0)	325(35.4)
INSOMNIA	76(10.1)	105(11.5)
ANXIETY	58(7.7)	88(9.6)
AGITATION	57(7.6)	76(8.3)
RESTLESSNESS	17(2.3)	52(5.7)
MANIA	32(4.2)	36(3.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	130(17.3)	192(20.9)
MUSCULOSKELETAL STIFFNESS	21(2.8)	39(4.3)
PAIN IN EXTREMITY	17(2.3)	39(4.3)
BACK PAIN	31(4.1)	35(3.8)
ARTHRALGIA	18(2.4)	24(2.6)
MUSCLE SPASMS	9(1.2)	21(2.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	130(17.3)	192(20.9)
MYALGIA	9(1.2)	21(2.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	102(13.5)	135(14.7)
FATIGUE	27(3.6)	51(5.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	48(6.4)	98(10.7)
COUGH	14(1.9)	24(2.6)
PHARYNGOLARYNGEAL PAIN	15(2.0)	23(2.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	65(8.6)	63(6.9)
RASH	21(2.8)	29(3.2)
EYE DISORDERS	26(3.5)	52(5.7)
VISION BLURRED	9(1.2)	28(3.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	23(3.1)	24(2.6)
F DYSMENORRHOEA	12(3.0)	13(2.7)

(M) Incidence of AE adjusted for males (F) Incidence of AE adjusted for females
Schizophrenia studies include 31-93-202, 31-94-202, 31-97-201, 31-97-202, and CN138-001.
Bipolar mania studies include CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, and CN138162.
MedDRA Version: 9.1

The following table is provided in this review (as found in Module 2.7.4), since the sponsor's proposed labeling shows results of the Bipolar monotherapy trials pooled with results from the schizophrenia trials, consistent with pooling methods in the approved version of labeling (the below table corresponds to Table (b)(4) in proposed labeling, in Item 2 markup.pdf file).

1 page immediately following is withheld for b(4), draft labeling.

The following table provides results of the adjunctive trial C-134. Refer to the review of N20 for a discussion of these results.

Table 2.1B-1: Incidence of Treatment-Emergent AEs Reported in at Least 2 Percent of Patients in the Aripiprazole Group: 6-Week Combination Therapy Study in Acute Bipolar Mania (CN138134), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	130	253
NUMBER OF MALE PATIENTS	55	122
NUMBER OF FEMALE PATIENTS	75	131
NUMBER OF PATIENTS WITH >=1 AES	70(53.8)	157(62.1)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	27(20.8)	92(36.4)
AKATHISIA	7(5.4)	47(18.6)
TREMOR	8(6.2)	23(9.1)
HEADACHE	8(6.2)	14(5.5)
EXTRAPYRAMIDAL DISORDER	1(0.8)	12(4.7)
DIZZINESS	1(0.8)	11(4.3)
SEDATION	2(1.5)	11(4.3)
PSYCHIATRIC DISORDERS	18(13.8)	52(20.6)
INSOMNIA	5(3.8)	20(7.9)
ANXIETY	1(0.8)	9(3.6)
DEPRESSION	4(3.1)	7(2.8)
RESTLESSNESS	1(0.8)	6(2.4)
GASTROINTESTINAL DISORDERS	21(16.2)	49(19.4)
NAUSEA	6(4.6)	21(8.3)
DIARRHOEA	7(5.4)	11(4.3)
VOMITING	0	10(4.0)
SALIVARY HYPERSECRETION	2(1.5)	9(3.6)
DRY MOUTH	1(0.8)	6(2.4)
INFECTIONS AND INFESTATIONS	14(10.8)	26(10.3)
NASOPHARYNGITIS	3(2.3)	7(2.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	9(6.9)	22(8.7)
FATIGUE	5(3.8)	7(2.8)
INVESTIGATIONS	5(3.8)	14(5.5)
WEIGHT INCREASED	1(0.8)	6(2.4)

The incidence of AEs for a particular System Organ Class is the incidence of all AEs in that System Organ Class.
MedDRA Version: 9.1

7.1.5.4 Common adverse event tables

See the previous section.

7.1.5.5 Identifying common and drug-related adverse events

Only the results from the placebo controlled Bipolar trial datasets were reviewed for common AEs for reasons that follow. Placebo controlled trial results are most interpretable and applicable to this NDA (as previously discussed in Sections 7.1 and 4.3 of this review).

The sponsor lists common AEs (≥5% incidence in Arip patients that was at least twice that of placebo) for each dataset, as outlined below.

3 Week placebo controlled Bipolar Trial Dataset (see the previous summary table): akathisia, sedation, extrapyramidal disorder, and restlessness

Reviewer Comment. *The sponsor did not include tremor which was reported in 3.2% and 6.2% of Arip and PBO subjects respectively (it appears that the sponsor did not round off the numbers to the nearest whole integer before determining if the incidence met the criteria for identifying common and drug related AEs). This AE is noted since proposed labeling does include this AE (as either a common AE in Table* (b)(4) *of proposed labeling).*

See the last section of this review for further comments and recommendations relevant to proposed labeling (in which it is recommended that the results by indication be presented separately, rather than as pooled results and that tremor be included in labeling, as discussed in more detail in Section 9).

6-Week Adjunctive Treatment Bipolar Trial -134:
akathisia, insomnia, and extrapyramidal disorder.
Reviewer Comments. *The review of N20 provides additional comments regarding the 6-week adjunctive trial dataset.*

7.1.5.6 Additional analyses and explorations

The sponsor conducted subgroup analyses of common AEs for subgroups categorized by intrinsic factors (e.g. age, gender, and "race"). The following paragraphs outline key findings are noted by the undersigned review (as provided by the sponsor), regarding the integrated dataset of the 3-week, monotherapy, Bipolar trials.

Reviewer Comment of the Results of Subgroup Analyses on the Basis of Gender, Age or "Race"
Appendix 10.3 provides a summary of the sponsor's results. As discussed in Appendix 10.3, the undersigned reviewer concludes that the integrated 3-week monotherapy Bipolar trial dataset failed to show subgroup differences (for gender, age-group or "race" subgroups). However, some of the results are difficult to interpret due to insufficient samples sizes (e.g. few patients over 65 years old) or due to other confounding variables (e.g. a high incidence in placebo subjects in a given demographic subgroup).

The review of N20 focuses on safety results relevant to the proposed adjunctive treatment claim.

7.1.6 Less Common Adverse Events

See previous sections on AE results.

Reviewer Comments. *A review of less common AEs (defined as an AE with a <2% incidence in Arip subjects) was not conducted for reasons that follow. Only 2 new trials were integrated within the monotherapy dataset (involving trials that were submitted in previous NDAs) and the 2 new trials used a smaller starting dose-level that past trials. The review of N20 focuses on*

events in C-134, since this adjunctive Bipolar trial is relevant to N20. Other safety datasets have less relevant to the current sNDA or involved OL treatment (such that results were more difficult to interpret with respect to a Bipolar monotherapy indication for a 15 mg starting dose-level). Moreover, results from these additional trials or datasets were previous submitted under the NDA.

7.1.7 Overview of laboratory testing in the development program

Refer to the Schedule of Events table in Appendix 10.1 for study schedules employed in the pivotal Phase 3 trials (two 3-week Bipolar studies -135 and -162 and the adjunctive 6-week Bipolar trial -134). See tables providing outlier criteria in Appendix 10.3 of this review.

Reviewer Comments.

The sponsor generally showed results on "measures of central tendency" using a median change from the baseline value to endpoint or by using a % median change or median change in value.

Results of mean change, standard deviations and range of values were generally not found in the sponsor's summary tables and summary of results, unless otherwise specified in this review (as found in in-text sections of Module 2.7.4).

Statistical analyses of the results of outliers or on "measures of central tendency" could generally not be found in the in-text sections of Module 2.7.4 unless otherwise specified in this review. Therefore, comparisons of results across groups or over time-intervals are based on numerical comparisons, unless otherwise specified.

The incidence of outliers on a given parameter (as found in in-text summary tables of Module 2.7.4) generally was based on results of subjects having either normal baseline values or baseline values that did not meet outlier criteria. It is not clear how the sponsor selected one of these methods over the other method for presenting these results in the in-text table.

As previous discussed in this review, the primary focus of the review of safety results was on information found in in-text sections of Module 2.7.4, unless otherwise specified below.

7.1.7.1 Selection of studies and analyses for drug-control comparisons of laboratory values

Only the placebo controlled Bipolar trial integrated (pooled) safety datasets were reviewed for reasons previously discussed in Sections 4.3 and 7.1 of this review. Some additional results were reviewed as specified in corresponding sections below.

Results on the 12-week active comparator trials could not be found for laboratory parameters in Module 2.7.4.

The results of the 6-week, Adjunctive Bipolar I-mania/mixed Trial C-134 are not provided in the current review, unless there was a noteworthy observation relevant to this N19 submission. The review of N20 focuses on safety results of Study C-134 since these results are relevant to the proposed claim in N20 (for adjunctive treatment).

7.1.7.2 Standard analyses and explorations of laboratory data

7.1.7.2.1 Analyses focused on measures of central tendency

Pooled 3-week Short-term Dataset Results:

Chemistry Parameters

The sponsor notes the following observations on the median percent change on each chemistry parameter (electrolytes, LFTs, BUN, Cr, Prolactin, Ca, Uric acid):

- ALT, Uric acid and CPK and calcium showed increases and prolactin showed a decrease in Arip treated patients compared to placebo patient
- The greatest changes were observed with ALT, CPK and Prolactin
- However, these changes were "not clinically meaningful."

Results are shown below (copied from the submission):

Table 3.1.1.3: Median Percent Change from Baseline to Endpoint, Serum Chemistry and Electrolyte Measurements: 3 Week Placebo Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

	Placebo		Aripiprazole	
Laboratory Test	N	Median % Change	N	Median % Change

	Placebo		Aripiprazole	
Laboratory Test	N	Median % Change	N	Median % Change

Laboratory Test	N	Median % Change	N	Median % Change
AST (SGOT)	617	0.0	767	0.0
ALT (SGPT)	617	0.0	766	6.6
Alkaline Phosphatase	617	0.0	766	-1.0
LDH	612	-0.8	765	-2.0
Total Protein	617	0.0	767	0.0
Blood Urea Nitrogen	620	0.0	767	0.0
Creatinine	619	0.0	766	0.0
Uric Acid	615	0.0	765	2.8
Bilirubin (Total)	617	0.0	766	0.0
CPK	612	8.5	763	15.7
Prolactin	608	-14.3	763	-50.0
Sodium	620	0.0	765	0.0
Potassium	617	0.0	763	-2.3
Chloride	620	0.0	764	0.0
Calcium	619	0.0	766	1.0

Reviewer Comments. *Note that similar to results on outliers (shown later in subject 7.1.7.3.2 of this review) that the median increase in CPK is numerically greater in Arip compared to placebo subjects. In light of the results on CPK note that:*

- *The magnitude of group differences is difficult to interpret due to highly variable between subject and within subject variance on this parameter.*
- *It is not clear to the undersigned reviewer if elevations in ALT, uric acid and calcium observed in Arip subjects were associated with elevations in CPK (the sponsor does not provide any further comments on these elevations other than that previously noted in this review).*

Hematology Parameter Results

The sponsor notes the following hematology results (on median % change in each treatment group):

- "No clinically meaningful" differences were observed between the treatment groups.

Reviewer Comments. *An examination of Table 3.1.2.3 in Module 2.7.4 fails to show any evidence for a new and clinically remarkable safety signal.*

Lipid Profile and Glucose-related Parameters

Reviewer Comments. *Results (shown below) on the median percent change on fasting and non-fasting lipid profile parameters, fasting and non-fasting glucose parameters and on HGbA1C levels were not clinically remarkable and unexpected.*

The following is the sponsor's summary table with the results, but first note the following: *Note the footnote of this table specifying that only results of -135 and -162 were actually analyzed (rather than all the trials listed in the sponsor's title for this table).*

Table 2.1.5.7B-1: Median Percent Change from Baseline to Endpoint, Metabolic and Glucose Laboratory Measurements: 3-Week Placebo Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

	Placebo		Aripiprazole	
Laboratory Test	N	Median % Change	N	Median % Change
Cholesterol Total				
Fasting	343	-1.0	414	-2.4
Non-Fasting	130	-1.6	167	1.5
HDL Cholesterol(a)				
Fasting	223	-3.9	234	2.1
Non-Fasting	23	5.2	10	-4.4
LDL Cholesterol(a)				
Fasting	221	0.5	233	-3.0
Non-Fasting	23	3.9	10	3.7
Triglycerides(a)				
Fasting	221	-6.3	233	-8.7
Non-Fasting	23	-27.4	10	-28.6
Glucose				
Fasting	340	0.0	415	3.6
Non-Fasting	136	3.0	172	5.3
HBg A1C	308	0.0	419	0.0

(a) Analyzed for CN138135, CN138162 only.

Single 6-Week Adjunctive Treatment Trial dataset

These results are described in more detail in the review of N20. *However, in light of above observations on CPK (regarding other datasets) the following results on CPK are noted for the DB phase of the 6-week adjunctive Study C-134:*

- *A numerical trend for a % median increase in CPK was observed in the Arip group, while the PBO group showed a trend for a % median decrease in CPK as shown below (copied excerpts of the sponsor's table):*

Table 3.2.1.3: Median Percent Change from Baseline to Endpoint, Serum Chemistry and Electrolyte Measurements: 6 Week Combination Therapy in Acute Bipolar Mania (CN138134), Safety Sample

	Placebo		Aripiprazole	
Laboratory Test	N	Median % Change	N	Median % Change

CPK	127	-3.1	236	1.5
Uric Acid	126	0.0	236	2.0

The magnitude of the above trends is not clinically remarkable.

Maintenance Trial results on the median % change on CPK

Reviewer Comments. *Because of results on CPK described above the undersigned reviewer examined Table 3.3.1.2 for results on the median % change on CPK in the maintenance trial (and other chemistry parameters).*

The median % change in CPK in Arip and placebo groups was 9.6 and 1.0, respectively.

The magnitude of the above median % changes are not clinically remarkable.

All-Arip Treated Bipolar Patients

Descriptive statistical results could not be found for this dataset in Module 2.7.4.

Reviewer Comments on Lipid/Glucose-related Parameters: *Results on the median percent change over time-intervals for lipid and glucose related parameters were found in Table 2.1.5.7W. The results do not reveal a clinically remarkable unexpected safety signal, but are difficult to interpret given the nature of this dataset (e.g. involving multiple trials that used different study designs, among other limitations with this dataset)..*

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

Pooled 3-week Short-term Dataset Results:

Chemistry Parameters

The sponsor shows in-text tables summarizing the incidence of outliers on chemistry parameters among subjects with normal baseline values (electrolytes, LFTs, BUN, Cr, Prolactin, Ca, Uric acid) in Section 3.1.1.1 of Module 2.7.4 (Tables 3.1.1 A&B in Module 2.7.4).

The sponsor notes the following observations:

- No Arip subject had simultaneous elevations in liver enzymes and bilirubin
- Among subjects with normal baseline values, increased CPK outliers were reported in 3.2% of Arip subjects (20 subjects), compared to 1.6% placebo subjects (8 subjects). Among the 20 Arip treated CPK outliers 6 subjects had the following concurrent SAEs:
  - Exacerbation of mania in 4 subjects
  - Seizure in 1 subject
  - NMS in 1 subject which is not summarized (in the in-text Section 3.1.1)
- The "incidence of treatment emergent-potentially clinically relevant increase in CPK" was 3.5% and 2.0% in Arip and placebo subjects (as specified on pages 366-

367 of Module 2.7.4). ***Reviewer Comment.*** *This statement appears to be based on the incidence of all subjects who were found to meet outlier criteria during the DB phase, independent of their baseline values, although the sponsor does not specify this distinction of these results compared to results described in the previous paragraph of Section 3.1.1.1 of Module 2.7.4 (these results are described on pp 366-367 of Module 2.7.4).*

- No ADOs were reported in Arip subjects due to chemistry abnormalities.
- The sponsor does not describe any individual subject with potentially clinically remarkable values.
-

Table 3.1.1.1A: Incidence of Treatment-Emergent Serum Chemistry Measurements of Potential Clinical Relevance: 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

		Number of Patients with Potentially Clinically Relevant Abnormality(a)/Number Assessed (%)(b)	
#PTS IN SAFETY SAMPLE		Placebo 753	Aripiprazole 917
LAB MEASUREMENT	CRITERION	INCIDENCE(%)	INCIDENCE(%)
AST (SGOT)	>= 3xULN	1/ 572(0.2)	3/ 718(0.4)
ALT (SGPT)	>= 3xULN	1/ 537(0.2)	2/ 673(0.3)
Alkaline Phosphatase (ALP)	>= 3xULN	0/ 579(0.0)	0/ 713(0.0)
Lactate Dehydrogenase (LD)	>= 3xULN	0/ 552(0.0)	0/ 680(0.0)
Blood Urea Nitrogen	>= 30mg/dL	1/ 606(0.2)	3/ 740(0.4)
Creatinine	>= 2.0mg/dL	0/ 618(0.0)	2/ 758(0.3)
Uric Acid	Abnormal(c)	2/ 573(0.3)	2/ 700(0.3)
Bilirubin, Total	>= 2.0mg/dL	1/ 613(0.2)	1/ 764(0.1)
Creatine kinase (CK)	>= 3xULN	8/ 490(1.6)	20/ 618(3.2)
Prolactin	> ULN	48/ 464(10.3)	25/ 562(4.4)

(a) Criteria for identifying potentially clinically relevant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (see Appendix 1.1C).
(b) Includes only patients with a baseline value within normal limits.
(c) Uric acid: Abnormal: >= 10.5 mg/dL (men); >= 8.5 mg/dL (women).

Hematology Parameters

The sponsor notes the following hematology results:

- ≤1% incidence of outliers in any given treatment group on any given parameter (as shown in Table 3.1.2.1 in Module 2.7.4).
- No ADOs in Arip treated subjects were due to hematological abnormalities.
- The sponsor does not describe any individual subject with potentially clinically remarkable values.

Lipid Profile and Glucose Parameters

Results on the incidence of outliers on fasting and non-fasting lipid profile parameters, fasting and non-fasting glucose parameters and on HGbA1C levels were not clinically remarkable based on in-text results in Section 2.1.5.7 of Module 2.7.4.

The sponsor notes:

- That the incidence of hyperglycemia or diabetes related AEs (as defined in Section 2.5.7 of Module 2.7.4) was 0.43% and 0.53% in Arip and placebo groups in which each of these AEs were based on laboratory findings.
- That no ADOs due to hyperglycemia-related AEs occurred.

Reviewer Comment. *The following cholesterol results show a numerically greater incidence of outliers in Arip compared to placebo subjects (extracted from the sponsor's Table 2.1.5.7A in Module 2.7.4 which showed results among those subjects that did not meet abnormality criteria at baseline).*

Incidence of Treatment-Emergent Metabolic and Glucose Laboratory Measurements of Potential Clinical Relevance: 3-Week Placebo Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074,CN138077, CN138135, CN138162), Safety Sample

		Number of Patients with Potentially Clinically Relevant Abnormality(a)/Number Assessed (%)(b)	
#PTS IN SAFETY SAMPLE		Placebo 753	Aripiprazole 917
LAB MEASUREMENT	CRITERION	INCIDENCE(%)	INCIDENCE(%)
Cholesterol Total	>= 240 mg/dL		
Fasting		14/ 301(4.7)	21/ 364(5.8)
Non-Fasting		7/ 111(6.3)	12/ 143(8.4)

Single 6-Week Adjunctive Treatment Trial dataset and CPK Results

In light of previously discussed observations on CPK, the following observations on CPK in the adjunctive study C-134 are noted:

- *No Arip S met outlier criteria for elevated CPK,*
- *4.6% of PBO Ss were outliers on CPK*
- *The only ADO (CN138134-15-23) that was reported to be due to elevated CPK in this study was subject who was manic which could have been at least a contributing factor. However, the observed elevations in CPK improved upon discontinuation of treatment (but did not reach baseline values). Yet, the sponsor does not note whether or not the patient's mental status improved, as well (e.g. if standard pharmacotherapy was initiated and if the patient's mania was improving).*
- *An ADO due to "hepatic failure" in an Arip-Valproate treated S (CN138134-135-575) was also previously described in Section 7.1.3.2 of this review (on ADOs), that was not reported as an SAE and was not unexpected (due to the S's past history of hepatitis and hepatic failure cases and deaths described in approved labeling for valproate).*

Maintenance Trial CPK Results

The incidence of outliers on CPK in this study was:

- Arip: 4.6%
- PBO: 3.1%

No Arip S was an outlier on any other chemistry parameter, except for prolactin (3.3%).

All-Arip Treated Bipolar Patients

Chemistry Parameters

The sponsor notes the following observations in Bipolar-mania patients in Section 3.4.1.1 of Module 2.7.4:

- No Arip treated Bipolar-mania subject had simultaneous outlier values for elevated bilirubin and liver enzyme values (AST or ALT)

- CPK (incidence; 2.6%) and Prolactin (7.1%) were most frequently reported as showing outlier values (compared to schizophrenia trials showing an incidence of 6.5% and 4.7% of each parameter respectively).
- Among the 43 Arip treated Bipolar-mania patients with outlier CPK values 13 had concurrent SAEs as follows:
  - 1 "convulsion"
  - 1 NMS
  - 1 chest pain ("non-cardiac")
  - 1 hypomania
  - 1 loss of consciousness
  - 1 pancreatitis
  - 2 exacerbated Bipolar disorder
  - 7 mania/aggravated or exacerbated

Reviewer Comments. *Examination of results of Table 3.4.1.1 showed an incidence of ≤1% on each chemistry parameter (as specified, previously), except for CPK and Prolactin, as outlined above. Given the nature of this dataset, it is difficult to interpret the values across diagnostic groups and in the absence of placebo groups.*

Elevations in CPK are expected in the patient population (and in the 13 Ss with concurrent SAEs, given the nature of these SAEs. Elevations in prolactin are also expected of antipsychotic drugs and approved labeling for Abilify™ includes a section addressing this observation.

Hematology Parameters
Hematology results are described as showing similar values in the Bipolar-manic diagnostic group to values observed in other diagnostic groups (the sponsor shows the incidence of outliers for each diagnostic group among subjects with normal baseline values in the in-text summary Table 3.4.2.1 of Module 2.7.4).
Reviewer comments. *Examination of the results in Table 3.4.2.1 show values of ≤1%.*

Lipid Profile and Glucose-related Parameters
Reviewer Comments: *A review of Table 2.1.5.7U in Module 2.7.4 failed to reveal any clinically remarkable differences between the Bipolar mania diagnostic group from the* (b) (4) *Schizophrenia diagnostic groups. Although, these results are difficult to interpret given the nature of the dataset, as previously discussed.*

The sponsor does not describe any individual Ss included in this dataset (in Section 2.1.5.7 of Module 2.7.4).

7.1.7.2.3 Marked outliers and dropouts for laboratory abnormalities

See previous subsections.

7.1.7.3 Additional analyses and explorations

See the next section. Section 2.1.5.6 of Module 2.7.4 describes special AE search strategies for diabetes/hyperglycemic-related AEs. Refer to Section 7.1.4 of this review for these results.

7.1.7.4 Special assessments

Results on parameters using a model that is believed to assess pancreatic beta-cell function was provided (referred by the sponsor as HOMA2-%B or %B in this review) and insulin resistance (HOMA2-IR or IR in this review).

Reviewer Comment. *These results were difficult to interpret due to wide variance in the quartile median values or inconsistent values over time (some of these results were also previously subject to review). Moreover, the sponsor is proposing a lower starting dose level of 15 mg that was previously approved for Bipolar I monotherapy.*

7.1.8 Vital Signs and Weight

7.1.8.1 Overview of vital signs and weight testing in the development program

Refer to the Schedule of Events table in Appendix 10.1 for study schedules employed in the pivotal Phase 3 trials (two 3-week Bipolar studies -135 and -162 and the adjunctive Bipolar trial -134). See tables providing outlier criteria in Appendix 10.3 of this review.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Only the placebo controlled Bipolar trial integrated (pooled) safety datasets were reviewed for reasons previously discussed in Sections 4.3 and 7.1 of this review. Some additional results were reviewed as specified in corresponding sections below.

Results on the 12-week active comparator trials could not be found for vital sign parameters in Module 2.7.4 (only results of deaths, SAEs and AEs were found on Module 2.7.4 for this safety dataset).

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Pooled 3-week Short-term Dataset Results:

Vital Sign and Weight Parameter Results

The sponsor concludes that no "clinically meaningful treatment differences" were observed on median change from baseline to endpoint on vital sign parameters (the sponsor provides the in-text summary Table 4.1.1.3 with these results).

Adjusted mean change from baseline to treatment endpoint in body weight showed no statistically significant treatment group differences.

Reviewer Comments. *The results in Tables 4.1.1.3 and 2.1.5.7 C of Module 2.7.4 are consistent with the sponsor's conclusion that no clinically remarkable differences were observed.*

Orthostatic hypotension parameter results

Reviewer Comments. *Results of Table 2.1.5.4 B in Module 2.7.4 shows little to no treatment group difference (between Arip and placebo) on the model based mean change from baseline to endpoint on orthostatic blood pressure (from supine to standing measures).*

All-Arip Treated Bipolar Patients

Statistical descriptive statistical results on vital sign parameters could not be found in Section 4 of Module 2.7.4 on vital sign parameters.

Reviewer Comments. *Results on mean and median change in body weight, BMI and waist circumference over each time-interval (<3 weeks, 4-12 weeks, 13-25 weeks and ≥26 weeks) of the All-Arip treated Bipolar mania trials was found in Table 2.1.5.7AA (in-text table) in Module 2.7.4. Mean and median changes were generally small to absent for each time-interval except for the last 2 time intervals. The last 2 time intervals showed more consistent mean and median increases with the greatest increase occurring at the final time-interval of ≥26 weeks (mean change of 2.8 kg in body weight).*

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Pooled 3-week Short-term Dataset Results:

The sponsor notes the following observations on vital sign results in Section 4.1.1.1 of Module 2.7.4:

- Treatment groups were similar on the incidence of outliers except for increased standing heart rate : 3.5% (30/866) in Arip subjects and 1.3% (9/708) in placebo subjects
- ADOs due to each of the following AEs hypotension, orthostatic hypotension, syncope, and heart rate increased were reported in 1 Arip subject (for each AE).

The sponsor notes no statistically significant treatment group difference on the incidence of patients with weight gain.

The sponsor did not describe any individual subjects other than noting the above ADOs.

Reviewer Comments. *A review of Tables 4.1.1.1 and 2.1.5.7C (on the incidence of outliers) is consistent with the sponsor's overall conclusion for no statistically significant treatment group differences on the incidence of outliers of each parameter, summarized above. The incidence of*

outliers in the Arip group was generally small as follows. Except for increased standing heart rate the incidence of outliers was generally <1% for other parameters with a few parameters showing an incidence of <2% (in which treatment groups were similar on the incidence of each of these parameters). The incidence of weight gain was 2.7% and 2.2% in PBO and Arip subjects respectively.

Orthostatic hypotension parameter results

Reviewer Comments. *Results of Table 2.1.5.4 A in Module 2.7.4 shows little to no treatment group difference (between Arip and placebo) on the incidence of outliers on orthostatic vital sign parameters.*

The sponsor reports one ADO due to orthostatic hypotension among Arip subjects.

All-Arip Treated Bipolar Patients

The sponsor notes that increased standing heart rate showed the greatest incidence of outliers in Bipolar mania trials (as shown in Table 4.4.1.1 in Section 4.4.1.1 of Module 2.7.4). The sponsor does not note any clinically remarkable subjects, ADOs or SAEs in this section of the module.

The sponsor notes that the incidence of outliers on weight gain in Bipolar-mania trials was:

- Less than the incidence observed in Schizophrenia trials.
- Increased over time, regardless if Arip was given as a monotherapy or as adjunctive treatment (with "mood stabilizers").

The sponsor does not summarize or note any individual clinically remarkable subjects (including any ADOs, SAEs or AEs) on weight parameters.

Reviewer Comments. *The results of Table 4.4.1.1 generally show in incidence of <1% of outliers on vital sign parameters in the Bipolar-mania diagnostic group of this safety All-Arip treated safety dataset except for the following parameters in which the incidence did not exceed 2.9% (N= 2626 subjects in the safety dataset): decrease in systolic blood pressure at standing (2.2%), decrease in systolic blood pressure at sitting (2.6%), increase in diastolic blood pressure at sitting (2.0%) and standing increased hear rate (2.9%). These results are difficult to interpret (given the limitations with this safety dataset) but do not suggest a new and unexpected safety signal.*

Results on orthostatic hypotension measures could not be found.

Results on weight parameters in the All-Arip, Bipolar-mania-trial dataset failed to reveal any clinically remarkable, new findings.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Refer to the Schedule of Events table in Appendix 10.1 for study schedules employed in the pivotal Phase 3 trials (two 3-week Bipolar studies -135 and -162 and the adjunctive Bipolar trial -134). See tables providing outlier criteria in Appendix 10.3 of this review.

QTcE interval was calculated as follows: QT raw/$RR^{0.36}$ as a method that the sponsor states was recommended by the Agency's Neuropsychopharmacological Division (as stated in Section 4.1.2.4 on page 406 of Module 2.7.4). The exponential correction was derived from baseline ECG-QT interval data collected from all Phase 2-4 trials (except for dementia and pediatric trials and data was only used from trials that did not enroll patients from previous BMS or OPC sponsored trials). QTc F and QTcB were also calculated according to methods summarized on page 406 of Module 2.7.4.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Only the placebo controlled Bipolar trial integrated (pooled) safety datasets were reviewed for reasons previously discussed in Sections 4.3 and 7.1 of this review. Some additional results were reviewed as specified in corresponding sections below.

Results on the 12-week active comparator trials could not be found for ECG parameters in Module 2.7.4 (only results of deaths, SAEs and AEs were found on Module 2.7.4 for this safety dataset).

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Pooled 3-week Short-term Dataset Results:

Results on Heart Rate, PR, QRS and RR Parameters

The sponsor notes in Section 4.1.2.3 of Module 2.7.4 that no "clinically relevant" treatment group differences were observed on PR and QRS interval results as shown in Table 4.1.2.3 (on mean and median changes from baseline to endpoint) except for the following:

- PR interval decreased (on the mean and median change) while heart rate increased (mean and median change) in the Arip group while the placebo group showed the changes in the opposite direction for each of these parameters.

The following results are extracted from Table 4.1.2.3.

Mean and Median Change from Baseline for the Minimum, Maximum, and Endpoint On-Treatment ECG Value: 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162),Safety Sample

	Placebo				Aripiprazole			
ECG Parameter	N	Mean	(SE)	Median	N	Mean	(SE)	Median
RR (msec)								
Maximum	620	5.42	(6.02)	2.50	753	-21.46	(5.47)	-18.00
Minimum	620	3.12	(5.92)	0.50	753	-25.78	(5.51)	-24.00
Endpoint	612	5.27	(6.05)	2.00	746	-22.12	(5.51)	-19.50
Heart Rate (bpm)								
Maximum	620	-0.08	(0.55)	0.00	753	2.51	(0.52)	2.00
Minimum	620	-0.27	(0.55)	0.00	753	2.07	(0.51)	2.00
Endpoint	612	-0.27	(0.56)	0.00	746	2.11	(0.52)	2.00

Reviewer Comments. *Results of Table 4.1.2.3 are consistent with the sponsor's conclusions and results do not show a clinically remarkable and unexpected safety signal.*

Results on QTc Parameters

The table below was copied from Table 4.1.2.4.A of Module 2.7.4. Refer to footnote a of this table for the sponsor's method for calculating QTcE interval.

Analysis of QTc (Fractional Exponent Correction): 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

	Fractional Exponent Correction [a]				
	Placebo		Aripiprazole		p-value [e]
Sample Size [b]	612		745		
Mean Baseline QTcE (msec)	393.3		392.2		0.343
Mean Change at Endpoint (SE)	-0.28	(0.69)	-1.16	(0.63)	0.343
Mean Change at Max QTcE (SE)	0.03	(0.69)	-0.80	(0.62)	0.370

[a] QTcE=Fractional exponent correction (QT/RR**0.36).
[b] Includes all patients with both a baseline and an endpoint measurement.
[c] Includes all patients with an on-study measurement.
[d] Includes all patients with both a baseline and an on-study measurement.
[e] Comparisons of means were done by ANCOVA controlling for baseline QTc.
Comparisons of proportions were done by Fisher's exact test.

Reviewer Comments. *Results show no group differences. Tables 4.1.2.4 B-D of Module 2.7.4 shows results with subjects in each treatment group categorized into subgroups on the basis of gender, age and race. These results also fail to show clinically remarkable findings.*

All-Arip Treated Bipolar Patients

Results on Heart Rate, PR, QRS and RR Parameters

Only results on the incidence of outliers were found in Section 4 of Module 2.7.4 for this dataset and these results are summarized in the next subsection of this review.

Results on QTc Parameters

Only results on the incidence of outliers could be found in Module 2.7.4.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Pooled 3-week Short-term Dataset Results:

Incidence of ECG Abnormalities

The sponsor notes the following observation regarding results on the incidence of ECG abnormalities, as shown in Table 4.1.2.1 of Section 4.1.2.1 of Module 2.7.4 (abnormalities of rate, rhythm, conduction, infarction as specified and using outlier criteria as shown in Appendix 10.3 of this review):

- The incidence was low (<1%) for any parameter in each treatment group.

The sponsor does not note any clinically remarkable subject, ADO or SAE (in section 4.1.21 of Module 2.7.4).

Incidence of QTc Outliers

The following table summarizes results provided by the sponsor (copied from Table 4.1.2.4.A).

Analysis of QTc (Fractional Exponent Correction): 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

	Fractional Exponent Correction [a]		
	Placebo	Aripiprazole	p-value [e]
	Number of Patients/Number Assessed (%)		
>450 msec [c]	5/623 (0.8)	0/757 (0.0)	0.019
>500 msec [c]	0/623 (0.0)	0/757 (0.0)	1.000
>=30 msec increase [d]	35/620 (5.6)	50/752 (6.6)	0.500
>=60 msec increase [d]	2/620 (0.3)	3/752 (0.4)	1.000

[a] QTcE=Fractional exponent correction (QT/RR**0.36).
[b] Includes all patients with both a baseline and an endpoint measurement.
[c] Includes all patients with an on-study measurement.
[d] Includes all patients with both a baseline and an on-study measurement.
[e] Comparisons of means were done by ANCOVA controlling for baseline QTc.
Comparisons of proportions were done by Fisher's exact test.

Reviewer Comments. *A review of results in Table 4.1.2.1(as summarized above) and in Tables 4.1.2.4 A-D (results on QTcE that included results of gender, age and race subgroups) failed to reveal a clinically remarkable, unexpected new safety signal (results on QTcE outliers by race subgroups for the "other" category were the most difficult to interpret due to small sample sizes).*

The typical outlier parameter results for PR, RR, QT and QRS parameters could not be found in Module 2.7.4, but were incorporated with results on the incidence of ECG abnormalities (refer to Appendix 10.3 of this review for outlier criteria employed).

All-Arip Treated Bipolar Patients

Incidence of ECG Abnormalities

The sponsor notes that bradycardia, sinus bradycardia were most frequently reported in Bipolar-mania trials and in trials of other diagnostic subgroups. The sponsor does not describe any individual subjects with ECG abnormalities in Section 4.4.2.1 of Module 2.7.4.

Reviewer Comments. *A review of the Bipolar-mania diagnostic subgroup results found in Table 4.4.2.1A of Module 2.7.4 shows that the above 2 most frequently reported ADOs were only reported in 1.3% of subjects. Other PT ADO body system and AE categories showed an incidence of 0 in the majority of PT categories with only a few showing an incidence of <1%. In light of symmetrical T wave inversion observations in the adjunctive 6-week trial it is noted that this ECG abnormality was reported 13/2122 subjects (0.6%) of the Bipolar-mania diagnostic group in the All-Arip treated dataset compared to* (b) (4) *0/ 982 subjects (0.0%) in the MDD group, 32/ 848 subjects (3.8%) in the Dementia group and 69/4272 subjects (1.6) in the Schizophrenia group. These results are difficult to interpret but fail to reveal evidence for a T-wave inversion safety signal in the Bipolar-mania group (the greater incidence in Schizophrenia and dementia groups may be reflecting greater comorbidity for cardiac related conditions that are known to exist in these patient populations, although results are difficult to interpret).*

Incidence of QTc Outliers

The sponsor notes the following results on outliers on increased QTcE interval:

- None of the subjects in the Bipolar-mania trails had QTc > 500 msec
- The incidence of QTc>450msec in the Bipolar-mania diagnostic group was 0.6% (13 subjects) compared to 1.9% in all diagnostic groups, combined.
- The incidence of increased QTc of ≥ 30 msec was 7.9% in the bipolar mania trials compared to 14.8% in the schizophrenia trials and compared to an overall incidence of 12.3% (for all diagnostic groups combined).

Reviewer Comments. *The above results are difficult to interpret.*

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Refer to previous subsections.

7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

Abilify is not a therapeutic protein.

7.1.11 Human Carcinogenicity

Human carcinogenicity was not systematically evaluated in clinical trials included in this NDA submission and a section on this topic could not be found in Module 2.7.4. Appendix 2.1B-1A in Module 2.7.4 shows the incidence of Treatment Emergent AEs for the All Arip safety dataset for each patient diagnostic subgroup (MDD, Bipolar-mania, (b) (4) Dementia, and Schizophrenia) and for all subjects combined. The table shows the following results under the Neoplasms…and unspecified" category (copied from the sponsor's table).

Reviewer comments. *The results in the above table fail to differ remarkably from results previously provided in the review of N18 under this NDA (this previous clinical review was conducted by the undersigned reviewer).*

7.1.12 Special Safety Studies

None were found in Module 2.7.4 and CSRs provided were of pivotal efficacy trials.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Refer to approved labeling. The sponsor does not describe any new findings in Section 5.6-7 of Module 2.7.4.

7.1.14 Human Reproduction and Pregnancy Data

A search of the All-Arip treated Phase II-IV database of reported cases since Oct-2005 (since the last Safety Update Report submission) was conducted as described in Section 5.4 of Module 2.7.4. The search revealed:

- 26 cases with positive pregnancy results,
- 11 cases of pregnancy listed as a reason for discontinuing treatment (on the end-of-study form)
- 8 cases of "AE terms related to pregnancy."

The following 12 cases with confirmed pregnancies in Arip Ss in clinical trials had additional information. The cases were described as having one of the following outcomes: abortion was induced in most cases, in several cases the outcome is unknown, spontaneous abortion occurred in 2 cases and a normal healthy infant was delivered in 1 S.

Reviewer Comment. *The above results do not suggest a new, clinically remarkable safety signal that would warrant a change in approved labeling.*

7.1.15 Assessment of Effect on Growth

This N19 is for an adult indication. Refer to Section 8.4 of this review.

7.1.16 Overdose Experience

Reviewer Comment. *Section 5.5 of Module 2.7.4 briefly summarizes 14 cases involving Arip overdoses of greater than 60 mg. One S (C…134-17-106) was previously described in this review that involved a S also being treated with lithium ("accidental overdosed" on lithium) and developed SAEs and eventually died.*

Several other cases involved Ss on other concomitant medications or an overdose on multiple drugs. Irreversible sequelaea were not noted for any of the cases except for the above death. In several cases Ss returned to the study and/or did not require treatment.

The results as found in Section 5.5 of Module 2.7.4 fail to reveal any clinically remarkable new observations warranting a change in approved labeling under "Overdosage."

7.1.17 Postmarketing Experience

Refer to Section 2.6 of this review regarding the US marketing history of Arip relevant to this NDA.

Section 6 of Module 2.7.4 provides information on worldwide experience and on postmarketing safety surveillance. A summary of safety observations or potentially remarkable cases could not be found in this section of the submission. The sponsor lists past safety related topics of "Cumulative Review" in past Periodic Safety Update Reports (PSURs) previously submitted under the NDA (up to their specified cut-off date). The sponsor lists past Periodic Adverse Drug Reports (PSURs) submitted under the NDA, as well (as of the specified cut-off date). The sponsor provides a list of safety topics in past PSURs and updated in the CCSI (as specified in Table 6.2.1B in Module 2.7.4). A summary of findings cannot be found in Section 6 of Module 2.7.4. The sponsor indicates that since the first approval of Arip in July 17, 2002, the benefit to risk ratio of Arip "remains favorable" and that the accumulated postmarketing information "has been reflected in the Company Core Safety Information, the Summary of Product Characteristics and in the indicating US Prescribing Information." The sponsor states that their review of Arip AE data from spontaneous postmarketing reports and from clinical trials (as provided in their Periodic Adverse Drug Experience Reports) "indicated an overall benefit risk profile similar to and consistent with the previously established clinical trial experience as described in the exiting USPI for Abilify.®"

7.2 Adequacy of Patient Exposure and Safety Assessments

Exposure is adequate for the purposes of this review (refer to Sections 4, 7 and Appendix 10.1 for more information on exposure). Also see Section 7.2.1.3 below for additional information.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Refer to Sections 4, 7 and Appendix 10.1 for more information on exposure.

Also see Section 7.2.1.3 below for additional information.

7.2.1.1 Study type and design/patient enumeration

Refer to Sections 4 and 7 of this review.

7.2.1.2 Demographics

Refer to Sections 6 and Appendix 10.1 for information on demographics of the population and Section 4 and 7 regarding patient populations.

7.2.1.3 Extent of exposure (dose/duration)

Exposure to Study drug
The following outlines key observations on exposure during the 3-week, PBO controlled, DB Phase 2 of each pivotal trial (for Studies C-135 and C-162) as shown in Table 6.1 of each CSR:

- Arip exposure:
  - Approximately 40% of Subjects were receiving 1 tablet of Arip at week 3 in the OC dataset
  - The mean weekly, mean daily dose during week 1 treatment: 17.1 mg/day and 17.8 mg/day, in each study respectively.
  - The mean weekly, mean daily dose on subsequently weeks was approximately 23.2 for each subsequent week of Phase 2 and approximately 23 *on most subsequent weekly intervals during Phase 3 (through Day 91).*

The following tables are copied from each CSR.

Study C-135

Table S.4.6:
Number of Patients Receiving Study Medication at Week 3, by Dose Level, OC Data Set, Efficacy Sample

	Placebo N=90						Lithium N=93			Aripiprazole N=94		
Week	# of Caps.	N	(%)	# of Tablets	N	(%)	Dose (mg)	N	(%)	Dose (mg)	N	(%)
3	missing	1	(1.1)	missing	1	(1.1)	missing	0		missing	1	(1.1)
	< 3	4	(4.4)	< 1	4	(4.4)	< 900	4	(4.3)	< 15	9	(9.6)
	3	14	(15.6)	1	18	(20.0)	900	29	(31.2)	15	35	(37.2)
	4	38	(42.2)	2	67	(74.4)	1200	32	(34.4)	30	49	(52.1)
	5	32	(35.6)	> 2	0		1500	27	(29.0)	> 30	0	
	> 5	1	(1.1)				> 1500	1	(1.1)			

Note: The number of capsules or tablets and the dose level for a particular patient is the dose on the day prior to the Week 3 (OC) Y-MRS assessment.

Treatment groups according to the randomized treatment code.

Study C-162

Table S.4.6:
Number of Patients Receiving Study Medication at Week 3, by Dose Level, OC Data Set, Efficacy Sample

	Placebo N=117						Haloperidol N=129			Aripiprazole N=139		
Week	# of Caps.	N	(%)	# of Tablets	N	(%)	Dose (mg)	N	(%)	Dose (mg)	N	(%)
3	missing	0		missing	0		missing	0		missing	0	
	< 1	2	(1.7)	< 1	3	(2.6)	< 5	2	(1.6)	< 15	4	(2.9)
	1	46	(39.3)	1	44	(37.6)	5	62	(48.1)	15	59	(42.4)
	2	39	(33.3)	2	69	(59.0)	10	40	(31.0)	30	76	(54.7)
	3	30	(25.6)	> 2	1	(0.9)	15	25	(19.4)	> 30	0	
	> 3	0					> 15	0				

Note: The number of capsules or tablets and the dose level for a particular patient is the dose on the day prior to the Week 3 (OC) Y-MRS assessment.

Treatment groups according to the randomized treatment code.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Refer to Sections 4 and Sections 7.1.14-7.1.15.

7.2.2.1 Other studies

Refer to Sections 4 and 7.1.

7.2.2.2 Postmarketing experience

Refer to Sections 2.6 and 7.1.17 of this review.

7.2.2.3 Literature

Section 8.6 summarizes the results of the search. This section discusses the methods of the search. The Otsuka Pharmaceutical Company (OPC) and Bristol-Myers Squibb (BMS) conducted searches involving 11 databases (for online bibliographic references) and a medical scientific literature database in Japan. The BMS search (in which 11 databases were searched) is noted to have been a basic index searches (rather than a full text search) since the databases were not full text databases. These searches were conducted using the various search terms for the drug name, brand names, codes and Chem. Abs. Registry numbers. Additional searches were conducted on other databases and using other or additional search terms as described in the literature.pdf in Item 8 of the submission.

Curriculum vitae were included for individuals who conducted the searches and who reviewed the search results.

7.2.3 Adequacy of Special Animal and/or In Vitro Testing

Not applicable to this NDA since Abilify is already approved.

7.2.4 Adequacy of Routine Clinical Testing

See previous subsections of Section 7.1 of this review for comments relevant to potential limitations with clinical parameter results.

Pivotal trials and longterm OL adjunctive trials, relevant to this sNDA included routine clinical testing (that are typical for trials for this indication) and are adequate for the purposes of this review.

7.2.5 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The studies conducted are adequate for the purposes of this NDA.

7.2.6 Assessment of Quality and Completeness of Data

See Sections 4.3, 4.4 and 4.5 of this review. Overall the quality and completeness of the data were adequate, pending a final report from DSI.

7.2.7 Additional Submissions, Including Safety Update

A Safety update report was not submitted. The information provided in this review is sufficient for the purposes of this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

See previous sections of this review and the final section of this review for any major issues or potential issues.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Safety results from pivotal trials and trials relevant to this sNDA were pooled in a manner that is adequate for the purposes of this review. Refer to Sections 4 and 7.1 for additional comments and the last section of this review for any key issues that impact on recommendations.

7.4.1.2 Combining data

See the previous section.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Pivotal trials C-135 and C-162 were not designed to examine dose dependent effects. Other previous monotherapy trials (that were part of the integrated safety dataset for the 3-week Bipolar monotherapy trials) included 2 fixed dose, parallel group trials (all trials in this dataset were placebo controlled Phase III trials). These 2 studies were also follows:

- Fixed dose trials (placebo, 15 and 30 mg Arip groups)
  - Study C-007 (approximately 130 Ss/group in each group)
  - The aborted Study -062 (only 16-20 Ss/group)

According to results described in the Clinical Summary of Efficacy section of the sNDA, (b) (4) The CSR was not provided for this study. (b) (4) the

safety results of this study were integrated with results from the other monotherapy trials (also note that it is one of the earlier pivotal trials). Moreover, these safety results (and safety results of other past monotherapy trials, except for pivotal trials C-135 and C-162) were provided in past submissions under this NDA (as specified on page 57 in Module 2.7.4).

7.4.2.2 Explorations for time dependency for adverse findings

Refer to Section 7.1.5.6 for any additional explorative analyses.

7.4.2.3 Explorations for drug-demographic interactions

Refer to Section 7.1.5.6. Results discussed in Section 7.1.5.6 failed to reveal any remarkable or interpretable findings when stratifying subjects by age, gender or "race."

7.4.2.4 Explorations for drug-disease interactions

No studies were conducted to examine drug-disease interactions.

7.4.2.5 Explorations for drug-drug interactions

See section 5.1 of this review regarding PK results in past Phase I trials of concomitant valproate or lithium treatment (as found in approved labeling). Previous subsections of 7.1 describe safety results in adjunctive safety groups in Study C-134 (between placebo and Arip groups within each adjunctive subgroup). No other studies on drug-drug interactions were found in the submission. Refer to Section 9 of this review for any major issues, from a clinical perspective.

7.4.3 Causality Determination

It is difficult to determine causality of Arip treatment based on preliminary exploratory analyses of data for revealing potential predictors.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

See Section 6 and appendix 10.1of this review for the dosing regimen used for the pivotal Study C-134.
See Section 7.2.1 on adequacy of exposure and dose-levels employed and note reviewer comments in Section 7.2.1.3.

8.2 Drug-Drug Interactions

Drug-drug interactions were not examined (as stated in Section 5.2 of Module 2.7.5).
The review of N20 focuses on safety results from Study C-134 and examines potential subgroups differences between the adjunctive treatment subgroups (Arip and PBO treatment groups within each adjunctive lithium and valproate subgroup).

8.3 Special Populations

Refer to Sections 7.1.5.6 and 7.4.2.3. Results discussed in these previous sections failed to reveal any remarkable findings.

The sponsor did not conduct any trials that systematically evaluated special populations.

8.4 Pediatrics

The sponsor requests a waiver from conducting pediatric trials for this sNDA (this request was found in the cover letter of the N19 submission). The sponsor notes in their cover letter that they recently completed a pediatric Bipolar trial (31-03-240) and that they plan to submit the results of this study as a separate sNDA in order to fulfill a pediatric postmarketing commitment for S-002.

Reviewer Comment. *A deferral (rather than a waiver) is recommended contingent upon the review of their upcoming sNDA for a pediatric Bipolar I indication.*

8.5 Advisory Committee Meeting

A meeting is not planned for this sNDA.

8.6 Literature Review

OPC and BMS searched various databases of the medical and scientific literature using methods described in Section 7.2.2.3 of this review. A summary of the search results could not be found in the literature.pdf file of submission. However, it is noted that the search results were reviewed by (b) (6), MD, Robert Berman, MD and Vlad Coric, MD. These individuals also certified that efficacy and/or safety findings based on their literature review did not alter or adversely affect conclusions about efficacy and/or safety in the NDA submission (as specified in Item 8 literature.pdf file of the submission).

8.7 Postmarketing Risk Management Plan

No specific postmarketing risk management plan is needed for this NDA.

8.8 Other Relevant Materials

No other relevant materials are needed for the purposes of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy
The 2 pivotal (3-week) monotherapy Bipolar-I trials (Studies C-135 and C-162) are positive for efficacy, pending confirmation by the Biometrics Team. These studies adequately demonstrate efficacy when using a starting daily dose level of 15 mg (with the option of increasing the dose to 30 mg (b) (4) based on the following observations (as described in more detail in Section 6.1.4 and Appendices 10.1 and 10.2 of this review):

- The 3-week treatment phase revealed positive results on the primary and key secondary variables (YMRS and CGI-BP-S) for efficacy.
- Preliminary results over time revealed the following (based on analyses of the OC dataset over each time-point):
  - Study -135 showed significant treatment group differences (or at least numerical trends) as early as Day 4 of treatment
  - Study -162 showed minimal to small treatment group differences during early time time-points.
- Results on exposure described in Section 7.1.2.3 of this review showed that:
  - Approximately 40% of Subjects were receiving 1 tablet of Arip at week 3 in the OC dataset.

Consequently, from a clinical perspective, it is reasonable to recommend a 15 mg starting dose.

Safety
The safety results in this review support the adequate safety of a 15 mg starting dose.

9.2 Recommendation on Regulatory Action

An approvable action is recommended, from a clinical perspective.
The following are contingencies on the Agencies decision on approving this NDA:

- Confirmation of efficacy results by the Biometric Team
- Input from the Division of Scientific Investigations.
- Negotiation of labeling.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no recommendations for specific risk management activities.

9.3.2 Required Phase 4 Commitments

None are recommended.

9.3.3 Other Phase 4 Requests

None are recommended.

9.4 Labeling Review

Key labeling issues, from a clinical perspective were identified as outlined below. Upon request the sponsor provided a 9-6-07 side-by-side, annotated labeling, since annotated labeling was not found in the original submission ("annotated Abilify Current to PLR Comverson.qxp" 8/29/2007). Excerpts of proposed labeling are provided below. To the knowledge of the undersigned reviewer, the sponsor has not yet submitted labeling that is updated to reflect the most recently approved version of labeling (the version of the recently approved N18 application). To the knowledge of the undersigned reviewer this updated version is being requested by the project manager assigned to this NDA.

Note that some of the proposed text (shown below) is regarding an adjunctive claim that the sponsor is also seeking in a parallel application (N20) submitted under this NDA. These proposed changes are being addressed in the review of N20.

(b) (4)

3 Pages withheld. b(4) Draft Labeling

10 APPENDICES

10.1 Review of Individual Study Reports of Pivotal Trails (Corresponding to Sections 6 and7 of this Review).

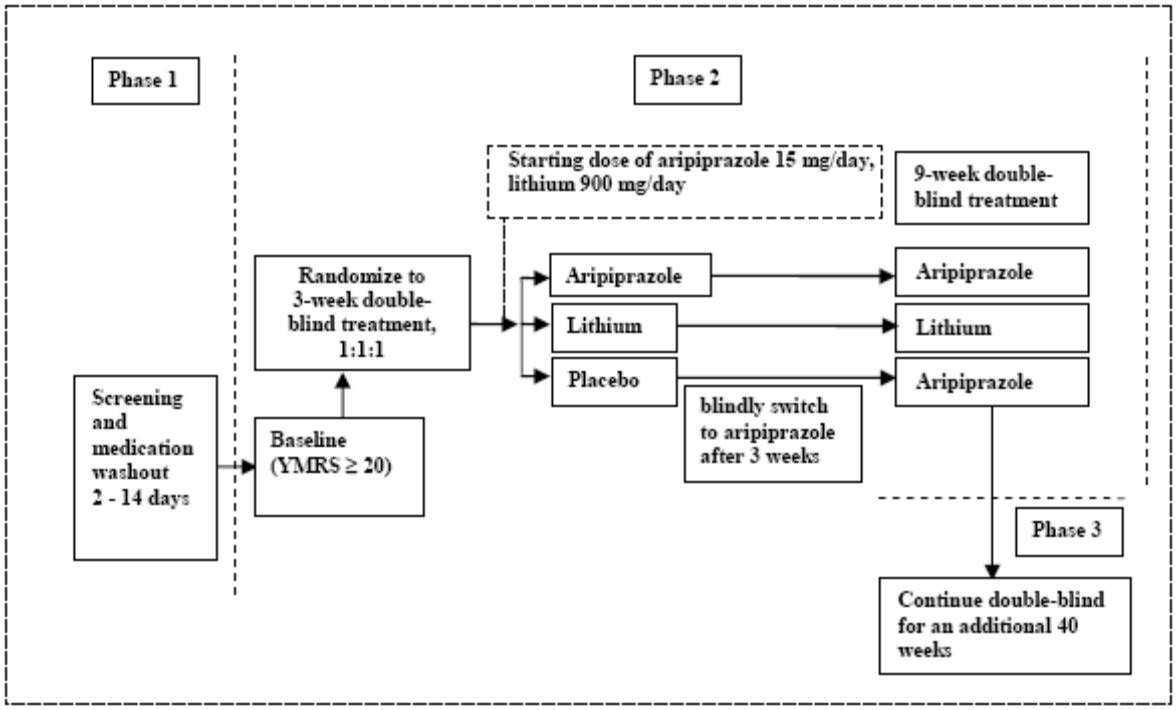
This appendix summarizes pivotal efficacy trials for N19 (Studies -135 and -162) and for N20 (-134) under this NDA since these trials were the new Bipolar trials that also provided new safety data, as well as providing key efficacy results. A separate review of N20 is being conducted in parallel with N19 that will contain more details. However, since safety results are provided for Study -134 (conducted for an adjunctive Bipolar claim for N20) the study design for this study is briefly summarized and the disposition of subjects is also provided for this study in this appendix.

Pivotal Studies -135 and -165

Refer to Section 6 of this review for a summary of the study design and efficacy results on primary and key secondary results. This appendix provides additional information on the study design or on other aspects of study results. Appendix 10.2 provides supplemental tables of efficacy results.

Study -135

Figure 3.1: Study Schema



Study -162

The study schema for Study C-162 is similar to the above schema, except Haloperidol treatment was used as an active comparator instead of lithium.

Study -135

The following tables show the study schedule for Phases 2 and 3 (as provided by the sponsor).

Table 3.5.1: Flow Chart/Time and Events Schedule

	Screening and Psychotropic Washout[a]		Double-Blind Treatment											
	2 to 14 days[a]		12 Weeks											
	Screening Day -2 to Day -14	Day 1 Baseline	Day 2	Day 4	Week 1[b]	Day 10	Week 2[b]	Week 3[b]	Week 4[b]	Week 5[b]	Week 6[b]	Week 8[b]	Week 10[b]	Week 12/ET[b]
PROCEDURE														
Informed Consent	X													
DSM-IV TR Dx Criteria (confirmed by the MINI)	X													
Entrance Criteria	X													
Medical and Psychiatric History	X													
Previous Medications	X													
Randomization and Study Drug Administration[c]		X[c]												
EFFICACY														
Y-MRS[d]	X[d]	X[d,e]	X	X	X	X	X	X	X	X	X	X	X	X
MADRS[d]	X[d]	X[d,e]	X	X	X	X	X	X	X	X	X	X	X	X
CGI-BP Severity		X[e]	X	X	X	X	X	X	X	X	X	X	X	X

Table 3.5.1: Flow Chart/Time and Events Schedule

	Screening and Psychotropic Washout[a]		Double-Blind Treatment											
	2 to 14 days[a]		12 Weeks											
	Screening Day -2 to Day -14	Day 1 Baseline	Day 2	Day 4	Week 1[b]	Day 10	Week 2[b]	Week 3[b]	Week 4[b]	Week 5[b]	Week 6[b]	Week 8[b]	Week 10[b]	Week 12/ET[b]
CGI-BP Change from Preceding Phase			X	X	X	X	X	X	X	X	X	X	X	X
PANSS		X[e]						X						X
OUTCOME														
LIFE-RIFT		X						X						X
IWQOL		X						X						X
Resource Utilization		X						X						X
SAFETY														
Physical Exam	X													X
Vital Signs[f]	X	X[e,g]			X		X	X[g]				X		X[g]
12-Lead ECG	X	X						X						X
Clinical Laboratory Tests (serum, hematology, urine, prolactin)[h]	X	X[e]						X				X		X

Table 3.5.1: Flow Chart/Time and Events Schedule

	Screening and Psychotropic Washout[a]		Double-Blind Treatment											
	2 to 14 days[a]		12 Weeks											
	Screening Day -2 to Day -14	Day 1 Baseline	Day 2	Day 4	Week 1[b]	Day 10	Week 2[b]	Week 3[b]	Week 4[b]	Week 5[b]	Week 6[b]	Week 8[b]	Week 10[b]	Week 12/ET[b]
Lithium Level[l]	X				X		X	X	X		X	X	X	X
HOMA-IR[j]		X						X						X
Pharmacogenomic Blood Sample[k]		X												
Pregnancy Test (WOCBP)[l]	X	X[l]						X				X		X
Drug Screen/Blood Alcohol Test[m]	X	----------	------	-------	---------	--------	---------	X	--------	---------	---------	---------	--------	X
SAS/AIMS		X[e]						X				X		X
Barnes Akathisia		X[e]			X		X	X			X	X		X
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X
OTHER														
Concomitant Therapy			X	X	X	X	X	X	X	X	X	X	X	X
Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X

Source: Appendix 1.1

[a] Minimum 2 day antipsychotic washout.

[b] Visits done at the end of each week (or at early termination). End of study assessments done prior to initiating new psychotropic medication.

[c] After all baseline assessments were completed and patient eligibility was confirmed, patients were randomized to double-blind treatment. The first dose of study medication was administered on Day 1 after the completion of baseline assessments.

[d] Y-MRS must have been ≥ 20 at screening and baseline, and less than a 25% decrease between these assessments. The MADRS must have been ≤ 17 at baseline with a ≤ 4 point increase between screening and baseline. No concomitant benzodiazepines were administered within 8 hours and no anticholinergics were administered within 12 hours of any efficacy and safety scale assessments.

[e] Baseline assessments were done prior to the first dose of study medication; the Y-MRS must have been the first efficacy evaluation performed at the baseline visit.

[f] Vital signs included supine and standing/sitting blood pressure and pulse. Blood pressure was taken before blood was drawn.

[g] Vital signs included weight at baseline, Week 3, and Week 12/Early Termination.

[h] Clinical laboratory tests were done fasting. Screening labs included valproic acid, carbamazepine, and oxcarbazepine to verify sub therapeutic levels of mood stabilizers.

[i] All patients had regular blood draws for lithium assays with periodic sham (false) levels reported for aripiprazole and placebo patients to maintain the blind. Blood was drawn 8 - 12 hours after the ingestion of study medication capsule(s).. Additional lithium levels were performed approximately 5 – 7 days after a dosage adjustment. In addition, unscheduled lithium levels were performed at any time at the discretion of the investigator. All lithium levels were done through the central laboratory.

[j] The homeostasis model assessment of insulin resistance (HOMA-IR) is a method for diagnosing and assessing insulin resistance and beta-cell function in order to evaluate potential coronary artery disease and/or carotid arteriosclerosis (fasting serum insulin [mU/mL] x fasting blood glucose [mmol/L]/22.5).

[k] A site specific amendment provided information on pharmacogenomic procedures. For sites participating, patients consented (via a separate pharmacogenomics consent form) to providing this blood sample.

[l] A serum or urine pregnancy test was performed within 72 hours of the first administration of study medication, and at the Week 3, Week 8, and Week 12/Early Termination visits. Baseline pregnancy test did not need to be performed if screening pregnancy test was within 72 hours of first dose of study medication.

[m] Drug screen for cocaine must have been negative prior to randomization.

The study schedule for Study -162 was provided in the CSR of the submission and did not show any remarkable deviation from the above study schedule that would impact on conclusions and recommendations in Section 9 of this review.

Treatment Schedule for Allowable Dose Adjustments in Phase 2

The following table outlines the flexible treatment schedule in Phase 2 (showing lithium treatment for Study C-135 and Haloperidol treatment for Study C-162, while both studies used the same treatment regimen for Arip). Dose adjustments were made as clinically indicated (lithium serum levels were assessed in the study by a specialized laboratory that was unblinded and independent from the central laboratory). The table specifies the allowable dosage adjustments (excerpts copied from Table 3.4.4. of each CSR):

Table 3.4.4: Dosing Regimens

	Dosing Regimen Aripiprazole / placebo			Dosing Regimen Lithium / placebo		
Study Day	Daily Dose	Dosing Frequency	Number of Tablets	Daily Dose	Dosing Frequency	Number of Capsules
Day 1 - Day 3	15 mg	QD	1	900 mg	TID	3
Day 4 - Day 6	15 - 30 mg	QD	1-2	900-1200 mg	TID	3-4
Day 7 - End study	15- 30 mg	QD	1-2	900, 1200 or 1500 mg	TID	3, 4 or 5

	Dosing Regimen Haloperidol / Placebo		
Study Day	Daily Dose	Dosing Frequency	Number of Capsules
Day 1 - Day 3	5 mg	QD	1
Day 4 - Day 6	5 - 10 mg	QD	1-2
Day 7 - End study	5, 10, or 15 mg	QD	1, 2 or 3

Prohibited Medications:

A number of psychotropic agents (antidepressants, antipsychotics, sleep aids, herbal supplements. 3A4 or 2D6 inducers, and mood stabilizers) were prohibited, as specified in the protocol. Limited use of other drugs (e.g. benzodiazepines, drugs for treating extrapyramidal side effects and others) was permitted, as specified in the protocol. See a subsection below on concomitant medication use during the 3-week DB phase 2 of each study.

Disposition through the 3-Week Placebo Controlled Phase 2
The following tables were extracted from the sponsor's tables on the disposition of subjects.

Study -162: Disposition of Subjects during the 3-week Placebo Controlled Phase 2

Number of Patients (%)

Patient Status	Placebo	Haloperidol	Aripiprazole	Total
ENROLLED	-	-	-	614
BASELINE FAILURES	-	-	-	129
RANDOMIZED	153	165	167	485
DISCONTINUED PRIOR TO END OF WEEK 3	44(28.8)	44(26.7)	41(24.6)	129(26.6)
LACK OF EFFICACY	14(9.2)	10(6.1)	9(5.4)	33(6.8)
ADVERSE EVENT	16(10.5)	8(4.8)	14(8.4)	38(7.8)
WITHDREW CONSENT	11(7.2)	19(11.5)	14(8.4)	44(9.1)
LOST TO FOLLOW-UP	2(1.3)	4(2.4)	2(1.2)	8(1.6)
POOR/NON-COMPLIANCE	0	1(0.6)	1(0.6)	2(0.4)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1(0.7)	2(1.2)	1(0.6)	4(0.8)
COMPLETED WEEK 3	109(71.2)	121(73.3)	126(75.4)	356(73.4)

Study -135: Disposition of Subjects during the 3-week Placebo Controlled Phase 2

Number of Patients (%)

Patient Status	Placebo	Lithium	Aripiprazole	Total
ENROLLED	-	-	-	715
BASELINE FAILURES	-	-	-	235
RANDOMIZED	165	160	155	480
DISCONTINUED PRIOR TO END OF WEEK 3	87(52.7)	82(51.3)	82(52.9)	251(52.3)
LACK OF EFFICACY	36(21.8)	26(16.3)	9(5.8)	71(14.8)
ADVERSE EVENT	13(7.9)	20(12.5)	23(14.8)	56(11.7)
WITHDREW CONSENT	25(15.2)	28(17.5)	32(20.6)	85(17.7)
LOST TO FOLLOW-UP	10(6.1)	5(3.1)	15(9.7)	30(6.3)
POOR/NON-COMPLIANCE	1(0.6)	2(1.3)	1(0.6)	4(0.8)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1(0.6)	1(0.6)	1(0.6)	3(0.6)
ADMINISTRATIVE REASON BY SPONSOR	1(0.6)	0	0	1(0.2)
OTHER	0	0	1(0.6)	1(0.2)
COMPLETED WEEK 3	78(47.3)	78(48.8)	73(47.1)	229(47.7)

Concomitant Medication Use

The following tables summarize concomitant medication use during Phase 2 of each study (copied from the CSRs).

Study C-135

Table 6.5A: Summary of Concomitant CNS Medications up to End of Week 3, Safety Sample

BODY SYSTEM CONCOMITANT MEDICATION	Number(%) of Patients Placebo N=164	 Lithium N=159	 Aripiprazole N=154
ANY CNS MEDICATIONS	152(92.7)	150(94.3)	149(96.8)
NERVOUS SYSTEM			
ANTICHOLINERGIC	10(6.1)	12(7.5)	30(19.5)
ANTIDEPRESSANT	0	1(0.6)	0
ANTIEPILEPTIC	2(1.2)	2(1.3)	2(1.3)
ANTIMIGRAINE PREP	1(0.6)	2(1.3)	3(1.9)
ANTIPSYCHOTIC	4(2.4)	3(1.9)	1(0.6)
ANXIOLYTIC	143(87.2)	141(88.7)	141(91.6)
DOPAMINERGIC	0	1(0.6)	0
HYPNOTIC & SEDATIVE	8(4.9)	5(3.1)	6(3.9)
OPIOID	2(1.2)	3(1.9)	5(3.2)
OTHER ANALGESIC & ANTIPYRETIC	112(68.3)	106(66.7)	101(65.6)

Table 6.5A: Summary of Concomitant CNS Medications up to End of Week 3, Safety Sample

BODY SYSTEM CONCOMITANT MEDICATION	Number(%) of Patients Placebo N=153	 Haloperidol N=165	 Aripiprazole N=166
ANY CNS MEDICATIONS	101(66.0)	127(77.0)	121(72.9)
NERVOUS SYSTEM			
ANALGESIC	0	1(0.6)	1(0.6)
ANTICHOLINERGIC	10(6.5)	73(44.2)	25(15.1)
ANTIEPILEPTIC	4(2.6)	1(0.6)	2(1.2)
ANTIMIGRAINE PREP	1(0.7)	0	0
ANTIPSYCHOTIC	5(3.3)	1(0.6)	2(1.2)
ANXIOLYTIC	90(58.8)	88(53.3)	108(65.1)
HYPNOTIC & SEDATIVE	5(3.3)	1(0.6)	8(4.8)
OPIOID	0	2(1.2)	2(1.2)
OTHER ANALGESIC & ANTIPYRETIC	42(27.5)	44(26.7)	44(26.5)
PSYCHOSTIMULANT	0	1(0.6)	0

Reviewer Comments on EPS medication use. *The CSRs also provide summary tables of EPS medication use during Phase 2 of each study (Tables 6.5.C in each CSR) and as expected EPS drug use was numerically greater in Arip groups compared to PBO groups.*

Exposure to Study drug

The following outlines key observations on exposure during the 3-week, PBO controlled, DB Phase 2 of each pivotal trial (for Studies C-135 and C-162) as shown in Table 6.1 of each CSR:

- Arip exposure:
  - The mean weekly, mean daily dose during week 1 treatment: 17.1 mg/day and 17.8 mg/day, in each study respectively.
  - The mean weekly, mean daily dose on subsequently weeks was approximately 23.2 for each subsequent week of Phase 2. ***Reviewer comment.*** *The mean weekly, mean daily dose-level on subsequent weeks (during Phase 3) was approximately 23 on most weekly intervals (through Day 91).*

- Haloperidol exposure (in Study C-162:
  - ***Reviewer comment.*** *Exposures started with a mean weekly, mean daily dose level of 5.8 mg in week 1 following by approximately7 to 9 mg daily dose-levels on subsequent weeks through Day 91.*
  -
- Lithium exposure (in Study C-135):
  - ***Reviewer comment.*** *Exposures started with a mean weekly, mean daily dose level of 930 mg in week 1 followed by approximately 1200 mg daily dose-levels on subsequent weeks through Day 91.*

The following tables are copied from each CSR.

Study C-135

Table S.4.6:
Number of Patients Receiving Study Medication at Week 3, by Dose Level, OC Data Set, Efficacy Sample

	Placebo N=90						Lithium N=93			Aripiprazole N=94		
Week	# of Caps.	N	(%)	# of Tablets	N	(%)	Dose (mg)	N	(%)	Dose (mg)	N	(%)
3	missing	1	(1.1)	missing	1	(1.1)	missing	0		missing	1	(1.1)
	< 3	4	(4.4)	< 1	4	(4.4)	< 900	4	(4.3)	< 15	9	(9.6)
	3	14	(15.6)	1	18	(20.0)	900	29	(31.2)	15	35	(37.2)
	4	38	(42.2)	2	67	(74.4)	1200	32	(34.4)	30	49	(52.1)
	5	32	(35.6)	> 2	0		1500	27	(29.0)	> 30	0	
	> 5	1	(1.1)				> 1500	1	(1.1)			

Note: The number of capsules or tablets and the dose level for a particular patient is the dose on the day prior to the Week 3 (OC) Y-MRS assessment.

Treatment groups according to the randomized treatment code.

Study C-162

Table S.4.6:
Number of Patients Receiving Study Medication at Week 3, by Dose Level, OC Data Set, Efficacy Sample

	Placebo N=117						Haloperidol N=129			Aripiprazole N=139		
Week	# of Caps.	N	(%)	# of Tablets	N	(%)	Dose (mg)	N	(%)	Dose (mg)	N	(%)
3	missing	0		missing	0		missing	0		missing	0	
	< 1	2	(1.7)	< 1	3	(2.6)	< 5	2	(1.6)	< 15	4	(2.9)
	1	46	(39.3)	1	44	(37.6)	5	62	(48.1)	15	59	(42.4)
	2	39	(33.3)	2	69	(59.0)	10	40	(31.0)	30	76	(54.7)
	3	30	(25.6)	> 2	1	(0.9)	15	25	(19.4)	> 30	0	
	> 3	0					> 15	0				

Note: The number of capsules or tablets and the dose level for a particular patient is the dose on the day prior to the Week 3 (OC) Y-MRS assessment.

Treatment groups according to the randomized treatment code.

Baseline Demographic and Psychiatric Features
The following outlines demographic features of randomized Ss in each pivotal trial:

- Mean age: approximately 40 years in each study.
- 52% or 44% were male, in Studies C-135 and -162, respectively
- 66% or 56% of Ss were "white," in Studies C-135 and -162, respectively
- Mean weight: 89.4 kg in Study C-135 and 78 kg in Study C-162
- Mean BMI was approximately 30 in each study and 63% or 43% of Ss were in the BMI category of > 27, in studies C-135 and -162, respectively.

Refer to Appendix 10.2 for efficacy rating values at baseline.

Reviewer Comment. *Demographic and psychiatric features were adequate for the purposes of this review. Treatment groups were generally, and adequately, similar for the purposes of this review.*

A review of Table 5.3.3 (in each CSR) which provides descriptive statistical results on baseline efficacy scores revealed the following observations:

- *Treatment groups were also generally similar on mean and median scores at baseline on the primary and key secondary variables.*
- *Values at baseline were generally consistent with the diagnostic and enrichment eligibility criteria employed in each study and with the indication of Bipolar-mania/mixed (for the proposed 15 mg starting dose level).*

Study -134 (Adjunctive Bipolar Trial)
This is a new trial conducted for N20 (submitted as a parallel supplemental NDA) but is included in safety results for N19. Therefore, the study design of this study is briefly summarized here. A more comprehensive description of this study and the study results is provided in the review of N20.

Study Design
Study C-134 was a multicenter (US and non-US), double-blind (DB), randomized, placebo (PBO) controlled study of Bipolar I patients (in the mixed or manic episode) who were identified as partial non-responders to valproate or lithium open-label (OL) monotherapy (during a 2-week monotherapy phase). Subjects underwent a 6-week DB add-on phase, following the 2-week lead-in phase. During the DB phase subjects were randomized to either:

- DB Arip (15-30 mg/day; N=384 randomized) or
- PBO treatment (N=131 randomized)

DB treatment was given as an adjunctive treatment to their ongoing OL valproate or lithium treatment, using a flexible dose, parallel group design (15 mg starting dose of Arip).

Ss could enter a 46-week OL phase of this study (received adjunctive treatment).

10.2 Appendix to the Integrated Review of Efficacy (Section 6)

Efficacy Results of Study -135 (Table 2D in Module 2.7.3)

	Placebo	Lithium	Aripiprazole
Primary Efficacy Measure			
Y-MRS Total Score	N = 163	N = 155	N = 154
Mean Baseline	28.90	29.22	28.53
Mean Change at Week 3 (LOCF)	-9.01	-12.03**	-12.64**
Key Secondary Efficacy Measure			
CGI-BP Severity of Illness (mania) Score	N = 162	N = 154	N = 153
Mean Baseline	4.60	4.54	4.55
Mean Change at Week 3 (LOCF)	-1.06	-1.34*	-1.48**
Other Secondary Efficacy Measure at Week 3			
Response Rate (LOCF)	N = 163	N = 155	N = 154
Number of Responders[a] at Week 3 (%)	56 (34.4)	71 (45.8)	72 (46.8)
Ratio of Response Rates vs Placebo	--	1.33*	1.31*
Secondary Efficacy Measures at Week 12			
Y-MRS Total Score	--	N = 155	N = 154
Mean Baseline	--	29.22	28.53
Mean Change at Week 12 (LOCF)	--	-12.71	-14.48
Treatment Difference[b] (95% CI)		-1.78 (-4.02, 0.47)	
CGI-BP Severity of Illness (mania) Score		N = 154	N = 153
Mean Baseline	--	4.54	4.55
Mean Change at Week 12 (LOCF)	--	-1.53	-1.70
Treatment Difference[b] (95% CI)		-0.18 (-0.47, 0.12)	
Response Rate (LOCF)		N = 155	N = 154
Number of Responders[a] at Week 12 (%)	--	76 (49.0)	87 (56.5)
Ratio of Response Rates vs lithium (95% CI)			1.13 (0.92, 1.39)

Source: CN138135 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

[a] A responder is a patient with at least a 50% decrease from baseline on the Y-MRS Total Score.

[b] Difference in adjusted treatment means: aripiprazole-lithium.

Efficacy Results of Study -162 (Table 2E in Module 2.7.3)

	Placebo	Haloperidol	Aripiprazole
Primary Efficacy Measure			
Y-MRS Total Score	N = 152	N = 161	N = 166
Mean Baseline	28.82	28.01	28.35
Mean Change at Week 3 (LOCF)	-9.70	-12.83**	-11.98*
Key Secondary Efficacy Measures			
CGI-BP Severity of Illness (mania) Score	N = 151	N = 161	N = 166
Mean Baseline	4.60	4.46	4.50
Mean Change at Week 3 (LOCF)	-1.17	-1.56**	-1.44*
Other Secondary Efficacy Measure at Week 3			
Response Rate (LOCF)	N = 152	N = 161	N = 166
Number of Responders[a] at Week 3 (%)	58 (38.2)	80 (49.7)	78 (47.0)
Ratio of Response Rates vs Placebo	--	1.26	1.19
Secondary Efficacy Measures at Week 12			
Y-MRS Total Score		N = 161	N = 166
Mean Baseline	--	28.01	28.35
Mean Change at Week 12 (LOCF)	--	-17.84	-17.16
Treatment Difference[b] (95% CI)		0.68 (-1.64, 3.00)	
CGI-BP Severity of Illness (mania) Score		N = 161	N = 166
Mean Baseline		4.46	4.50
Mean Change at Week 12 (LOCF)	--	-2.19	-2.11
Treatment Difference[b] (95% CI)		0.08 (-0.22, 0.37)	
Response Rate		N = 161	N = 166
Number of Responders[a] at Week 12 (%)	--	119 (73.9)	120 (72.3)
Ratio of Response Rates vs haloperidol (95%CI)			1.01 (0.89, 1.14)

Source: CN138135 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

[a] A responder is a patient with at least a 50% decrease from baseline on the Y-MRS Total Score.

[b] Difference in adjusted treatment means: aripiprazole-haloperidol.

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Table S.5.8:
Adjusted Mean Change from Baseline to Week 3 in Y-MRS Total Score,
by Psychotic Features at Baseline, LOCF Data Set, Efficacy Sample

	Adjusted Mean Changes from Baseline (SE) (Mean Actual Score for Baseline) (a)			Pairwise Comparisons (b) Difference in Adjusted Means (95% CI)			
Visit	Placebo	Lithium	Aripiprazole	Lithium - Placebo		Aripiprazole - Placebo	
Patients Without Psychotic Features at Baseline							
	N= 122	N= 117	N= 123				
Baseline	27.61 (0.45)	27.91 (0.46)	27.22 (0.44)	0.30	(-0.96,1.55)	-0.39	(-1.63,0.85)
Week 3	-9.52 (0.83)	-12.25 (0.85)	-12.03 (0.83)	-2.73	(-5.06,-0.40)	-2.50	(-4.80,-0.20)
Patients With Psychotic Features at Baseline							
	N= 41	N= 38	N= 31				
Baseline	33.15 (0.98)	33.42 (1.02)	33.61 (1.13)	0.27	(-2.53,3.08)	0.47	(-2.50,3.43)
Week 3	-7.12 (1.81)	-11.11 (1.88)	-14.78 (2.08)	-3.99	(-9.15,1.18)	-7.66	(-13.12,-2.20)

p-value for treatment by psychotic features at baseline interaction: 0.130 (c)

(a) Y-MRS Total Score is from 0 to 60.
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment, is used for baseline.
ANCOVA model, controlling for treatment and baseline value, is used
for mean change from baseline at Week 3.
Means, differences in means, 95% CI for the differences are based on the ANOVA/ANCOVA model.
(c) ANCOVA model, controlling for baseline, treatment, psychotic features at baseline, and
treatment by psychotic features at baseline interaction is used.

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Table S.5.9:
Adjusted Mean Change from Baseline to Week 3 in Y-MRS Total Score,
by Psychotic Features at Baseline, LOCF Data Set, Efficacy Sample

	Adjusted Mean Changes from Baseline (SE) (Mean Actual Score for Baseline) (a)			Pairwise Comparisons (b) Difference in Adjusted Means (95% CI)			
Visit	Placebo	Haloperidol	Aripiprazole	Haloperidol - Placebo		Aripiprazole - Placebo	
Patients Without Psychotic Features at Baseline							
	N= 135	N= 149	N= 149				
Baseline	27.65 (0.46)	26.99 (0.44)	27.40 (0.44)	-0.67	(-1.91,0.58)	-0.26	(-1.50,0.99)
Week 3	-9.95 (0.82)	-13.27 (0.78)	-12.03 (0.78)	-3.32	(-5.56,-1.08)	-2.09	(-4.32,0.15)
Patients With Psychotic Features at Baseline							
	N= 17	N= 12	N= 17				
Baseline	34.00 (1.48)	35.25 (1.77)	33.41 (1.48)	1.25	(-3.40,5.90)	-0.59	(-4.82,3.64)
Week 3	-6.87 (3.18)	-9.38 (3.81)	-13.57 (3.19)	-2.50	(-12.53,7.52)	-6.69	(-15.79,2.41)

p-value for treatment by psychotic features at baseline interaction: 0.296 (c)

(a) Y-MRS Total Score is from 0 to 60.
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment, is used for baseline.
ANCOVA model, controlling for treatment and baseline value, is used
for mean change from baseline at Week 3.
Means, differences in means, 95% CI for the differences are based on the ANOVA/ANCOVA model.
(c) ANCOVA model, controlling for baseline, treatment, psychotic features at baseline, and
treatment by psychotic features at baseline interaction is used.

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Table S.5.9:
Adjusted Mean Change from Baseline to Week 3 in Y-MRS Total Score,
by Type of Bipolar Episode, LOCF Data Set, Efficacy Sample

	Adjusted Mean Changes from Baseline (SE) (Mean Actual Score for Baseline) (a)			Pairwise Comparisons (b) Difference in Adjusted Means (95% CI)			
Visit	Placebo	Lithium	Aripiprazole	Lithium - Placebo		Aripiprazole - Placebo	
Manic							
	N= 103	N= 97	N= 88				
Baseline	29.28 (0.55)	29.11 (0.56)	28.43 (0.59)	-0.17	(-1.71,1.37)	-0.85	(-2.43,0.73)
Week 3	-8.22 (0.95)	-10.40 (0.97)	-11.94 (1.02)	-2.18	(-4.85,0.49)	-3.73	(-6.47,-0.98)
Mixed							
	N= 60	N= 58	N= 66				
Baseline	28.52 (0.81)	29.50 (0.82)	28.61 (0.77)	0.98	(-1.28,3.25)	0.09	(-2.11,2.28)
Week 3	-10.15 (1.28)	-14.47 (1.30)	-13.52 (1.22)	-4.32	(-7.93,-0.71)	-3.37	(-6.86,0.12)

p-value for treatment by type of bipolar episode interaction: 0.429 (c)

(a) Y-MRS Total Score is from 0 to 60.
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment, is used for baseline.
ANCOVA model, controlling for treatment and baseline value, is used
for mean change from baseline at Week 3.
Means, differences in means, 95% CI for the differences are based on the ANOVA/ANCOVA model.
(c) ANCOVA model, controlling for baseline, treatment, type of bipolar episode, and
treatment by type of bipolar episode interaction is used.

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Table S.5.10:
Adjusted Mean Change from Baseline to Week 3 in Y-MRS Total Score,
by Type of Bipolar Episode, LOCF Data Set, Efficacy Sample

	Adjusted Mean Changes from Baseline (SE) (Mean Actual Score for Baseline) (a)			Pairwise Comparisons (b) Difference in Adjusted Means (95% CI)			
Visit	Placebo	Haloperidol	Aripiprazole	Haloperidol - Placebo		Aripiprazole - Placebo	
Manic							
	N= 124	N= 133	N= 132				
Baseline	28.31 (0.53)	27.75 (0.51)	28.17 (0.51)	-0.55	(-2.00,0.89)	-0.13	(-1.58,1.31)
Week 3	-8.67 (0.90)	-12.77 (0.87)	-11.93 (0.87)	-4.10	(-6.57,-1.63)	-3.26	(-5.73,-0.78)
Mixed							
	N= 28	N= 28	N= 34				
Baseline	28.61 (1.01)	26.89 (1.01)	27.38 (0.92)	-1.71	(-4.55,1.12)	-1.22	(-3.93,1.48)
Week 3	-13.36 (1.80)	-14.30 (1.79)	-13.19 (1.62)	-0.94	(-6.00,4.12)	0.17	(-4.65,4.98)

p-value for treatment by type of bipolar episode interaction: 0.321 (c)

(a) Y-MRS Total Score is from 0 to 60.
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment, is used for baseline.
ANCOVA model, controlling for treatment and baseline value, is used
for mean change from baseline at Week 3.
Means, differences in means, 95% CI for the differences are based on the ANOVA/ANCOVA model.
(c) ANCOVA model, controlling for baseline, treatment, type of bipolar episode, and
treatment by type of bipolar episode interaction is used.

Table 3.3.1: **Y-MRS Total Score: Mean Change from Baseline to Week 3 by Population Subgroup: 3-Week Placebo - Controlled Comparisons (CN138007, CN138009, CN138074, CN138135, CN138162), LOCF Data, Efficacy Sample**

Subgroup Value	Placebo N	Placebo Mean (SE)	Aripiprazole N	Aripiprazole Mean (SE)	Treatment Comparison Aripiprazole - Placebo (a) Diff	(95% CI)	P-value	Treatment by Subgroup Interaction P-value (b)
Gender								
Male	333	-7.5 (0.6)	393	-10.7 (0.6)	-3.2	(-4.8, -1.6)	<.001	
Female	366	-8.1 (0.6)	442	-11.3 (0.5)	-3.1	(-4.6, -1.7)	<.001	0.980
Age								
<=50	573	-7.9 (0.4)	692	-11.1 (0.4)	-3.2	(-4.4, -2.0)	<.001	
>50	126	-7.5 (1.0)	143	-10.6 (1.0)	-3.0	(-5.9, -0.2)	0.038	0.923
Race								
Black	134	-6.9 (0.9)	156	-10.6 (0.8)	-3.7	(-6.0, -1.4)	0.002	
White	503	-7.7 (0.5)	596	-10.9 (0.4)	-3.2	(-4.5, -1.9)	<.001	
Other (c)	62	-10.0 (1.5)	83	-11.9 (1.4)	-1.9	(-5.9, 2.1)	0.344	0.828
Presence of Psychotic Symptoms								
Yes	143	-6.3 (1.1)	157	-11.5 (1.1)	-5.2	(-8.2, -2.2)	<.001	
No	555	-8.3 (0.4)	677	-11.0 (0.4)	-2.7	(-3.8, -1.6)	<.001	0.105
Type of Episode								
Mixed	232	-9.0 (0.7)	294	-11.3 (0.6)	-2.2	(-4.0, -0.5)	0.012	
Manic	467	-7.3 (0.5)	541	-11.0 (0.5)	-3.7	(-5.0, -2.3)	<.001	0.071

(a) ANCOVA model with treatment, and study as main effects, and baseline Y-MRS Total Score as covariate.
(b) ANCOVA model with treatment, study and subgroup as main effects, baseline Y-MRS Total Score as covariate, and treatment-by-subgroup as interaction effect.
(c) Includes Hispanic, Asian, and other race/ethnicity groups.
(d) Rapid Cyclers were to be excluded from CN138135 and CN138162.
PROGRAM SOURCE: /wwbdm/clin/proj/cn/138/bipolar_maint_cse/val/stats/eff_by_diff.sas RUN DATE: 02APR07 04:43

Preliminary Efficacy Results of Additional Subgroup Analyses on the Primary Efficacy Variable

Age-Subgroup Analyses of the Primary Efficacy Variable for Each Pivotal Trial

Results for each pivotal trial could not be found. However, results of all 3-week Bipolar Phase III trials, combined, were found in the sum-clin-efficacy.pdf file in the submission, as described in the next subsection, below.

Psychotic Feature Subgroups

Study C-162 only had 17 PBO and 17 Arip Ss who had psychotic features, while Study C-135 had approximately 40 Ss in each of these treatment groups. Despite the small sample sizes this subgroup at least showed trends for greater efficacy in the Arip group than the PBO group. The non-psychotic subgroup showed results consistent with a positive effect of Arip over PBO treatment.

Mixed and Manic Type Subgroups

The mixed type subgroup in Study C-162 was small (approximately 30 Ss/treatment group) and treatment group differences (between Arip and PBO groups) on the adjusted mean change from baseline on the YMRS score was only 0.17 in this subgroup. However, Study C-135 had at least 60 Ss in each treatment group (Arip and PBO) within the mixed type subgroup and this subgroup showed efficacy results similar to those of the manic type subgroup (treatment group difference on the adjusted mean change in the YMRS of -3.4 and -3.7, respectively, in favor of improvement in the Arip groups).

See a subsection below on subgroup analyses of an integrated efficacy dataset (found in the Summary of Clinical Efficacy section, Module 2.7.3) that shows a trend for a treatment group by subgroup (by type of Bipolar) interaction effect. However, each subgroup showed adequate evidence for efficacy when analyzed separately (as shown later below).

Preliminary Subgroup Analyses on Efficacy in the Integrated Monotherapy-Trial Dataset

The sponsor also provided results of subgroup analyses for the integrated short-term Phase III, PBO controlled trial dataset in the Summary of Clinical Efficacy module for most of the previously described subgroups (refer to Section 4 of this review describing this dataset for the safety datasets). It is important to note the following regarding these results (Table 3.3.1 in the Module 2.7.3):

- *No significant treatment group by subgroup interaction effects were reported for any of the subgroup analyses except for trends for a significant interaction effect for the following subgroup analysis (note that Table 3.3.1 does not include all subgroup analyses results for all previously discussed subgroups, such as subgroup analyses by country or region):*
  - *Type of episode (manic and mixed subgroups) showed small trends of influencing treatment group main effects, as follows (excerpt of the above table):*

Subgroup Value	Placebo N	Placebo Mean (SE)	Aripiprazole N	Aripiprazole Mean (SE)	Treatment Comparison Aripiprazole - Placebo (a) Diff	(95% CI)	P-value	Treatment by Subgroup Interaction P-value (b)
Gender								

Subgroup Value	Placebo N	Placebo Mean (SE)	Aripiprazole N	Aripiprazole Mean (SE)	Treatment Comparison Aripiprazole - Placebo (a) Diff	(95% CI)	P-value	Treatment by Subgroup Interaction P-value (b)
Type of Episode								
Mixed	232	-9.0 (0.7)	294	-11.3 (0.6)	-2.2	(-4.0, -0.5)	0.012	
Manic	467	-7.3 (0.5)	541	-11.0 (0.5)	-3.7	(-5.0, -2.3)	<.001	0.071

(a) ANCOVA model with treatment, and study as main effects, and baseline Y-MRS Total Score as covariate.
(b) ANCOVA model with treatment, study and subgroup as main effects, baseline Y-MRS Total Score as covariate, and treatment-by-subgroup as interaction effect.

- *Note results of age subgroups, that may be reflecting a smaller sample size and greater variability in the older group (refer to confidence intervals for this subgroup), as copied below:*

Subgroup Value	Placebo N	Placebo Mean (SE)	Aripiprazole N	Aripiprazole Mean (SE)	Treatment Comparison Aripiprazole - Placebo (a) Diff	(95% CI)	P-value	Treatment by Subgroup Interaction P-value (b)
Age								
<=50	573	-7.9 (0.4)	692	-11.1 (0.4)	-3.2	(-4.4, -2.0)	<.001	
>50	126	-7.5 (1.0)	143	-10.6 (1.0)	-3.0	(-5.9, -0.2)	0.038	0.923

- *It is notable that both psychotic and nonpsychotic subgroups showed treatment group differences reaching a p<0.001*

Subgroup Value	Placebo N	Placebo Mean (SE)	Aripiprazole N	Aripiprazole Mean (SE)	Treatment Comparison Aripiprazole - Placebo (a) Diff	(95% CI)	P-value	Treatment by Subgroup Interaction P-value (b)
Presence of Psychotic Symptoms								
Yes	143	-6.3 (1.1)	157	-11.5 (1.1)	-5.2	(-8.2, -2.2)	<.001	
No	555	-8.3 (0.4)	677	-11.0 (0.4)	-2.7	(-3.8, -1.6)	<.001	0.105

- *Note that these results may be diluted by 1 out of the 5 trials included in this safety dataset that did not show significant overall treatment group differences on the primary efficacy variable (in the primary analysis).*

Preliminary Efficacy Results on Ratings of Manic Symptoms compared to Results on (b) (4) Psychotic Symptoms

Reviewer Comments. *Note that the following based on a review of efficacy results in Table 7.1 of each CSR (with correcting for multiple comparisons):*

- *Efficacy variables rating manic symptoms were generally positive for efficacy (as previously shown) and secondary efficacy ratings of mania generally showed results similar to those of the primary and key secondary variables.*
- *A measures of psychotic symptoms (PANSS PSS) also reached a level of significance (p<0.01) in favor of Arip over PBO treatment. PANSS total score and other subscales on the PANNS generally showed at least trends for improvement in the Arip compared to PBO groups.*
- (b) (4)

(b) (4)

(b) (4)

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	1166	1843
NUMBER OF MALE PATIENTS	658	1132
NUMBER OF FEMALE PATIENTS	508	711
NUMBER OF PATIENTS WITH >=1 AES	902(77.4)	1603(87.0)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	492(42.2)	886(48.1)
AGITATION	199(17.1)	350(19.0)
INSOMNIA	153(13.1)	326(17.7)
ANXIETY	157(13.5)	320(17.4)
RESTLESSNESS	33(2.8)	89(4.8)
PSYCHOTIC DISORDER	37(3.2)	62(3.4)
MANIA	34(2.9)	37(2.0)

In light of the above observations on psychotic efficacy ratings note that 23% of Ss in Study C-135 and 10% of subjects in Study C-162 had psychotic features at baseline. Yet as previously noted efficacy was demonstrated in favor of Arip over PBO among Ss without psychotic features (and a treatment group by psychotic feature interaction effect was not revealed).

10.3 Appendix to the Integrated Review of Safety (Section 7)

Adjunctive Bipolar Study -134

Schedule of Assessments for Study C-134

	PHASE 1					PHASE 2		PHASE 3							
	Screening and Psychotropic Washout[a]					Li/valproate Monotherapy[b] and Baseline		Double-Blind Treatment							
	3 days to 4 weeks					2 Weeks		6 Weeks							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[c]	Week 1 (+/-2 days)	Week 2 (+/-2 days)	Day 4 (+1 day)	Week 1[d] (+/-2 days)	Week 2[d] (+/-2 days)	Week 3[d] (+/-2 days)	Week 4[d] (+/-2 days)	Week 5[d] (+/-2 days)	Week 6 /ET[d] (+/-2 days)	Protocol Section
PROCEDURE															
Informed Consent	X														6.1/10.2
Demographic Data	X														5
Entrance Criteria	X				X[e]		X[e]								5
Medical History	X														5/7
Psychiatric History	X														5
Previous Medications	X														5
DSM-IV-TR/MINI[f]	X														3.1
EFFICACY[g]															
Y-MRS					X[h]		X[i]	X	X	X	X	X	X	X	7.3.5.1
MADRS							X	X	X	X	X	X	X	X	7.3.5.2
CGI-BP							X	X[j]	X	X	X	X	X	X	7.3.5.3
PANSS							X		X		X			X	7.3.5.4
SAFETY															
Physical Exam	X[k]													X	7.3.2.4
Vital Signs[l]	X					X	X[m]	X	X	X	X[m]	X	X	X[m]	7.3.2.5
12 Lead ECG	X						X[n]							X	7.3.2.6
Clinical Laboratory Tests (chemistry, hematology, urine)[o,p]	X						X[n]				X			X	7.3.4
-Prolactin level							X[n]				X			X	7.3.4
Lithium/Valproate levels	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	3.1.2/ 6.2.3
Pregnancy Test (WOCBP)[s]	X	X					X	X			X			X	5/7.3.4
Drug Screen/Blood Alcohol Test[t]	X						X----	---------	---------	---------	X	---------	---------	X	5/7.3.4
SAS/AIMS/Barnes Akathisia							X		X	X	X	X	X	X	7.3.2
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9

OUTCOMES RESEARCH															
SF-36 Health Survey[u]							X							X	7.3.9.1
LIFE-RIFT Tool[v]							X							X	7.3.9.2
OTHER															
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.4
Study Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.2
Drug Accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3/8.4
Baseline Visit Form							X								7.2.2
End of Study Form														X[w]	3.1.4

[a] The purpose of Phase 1 is to start patient on mood stabilizer or to confirm therapeutic level of mood stabilizer, and to washout concomitant medications. The total number of visits in Phase I will vary based on a patient's incoming therapeutic regimen (i.e., the need for varying washouts), including therapeutic serum levels of the mood stabilizer. Mood stabilizer serum levels should be assessed approximately 12 hours after the last dose on the 5-7th day of initiation or dose modification. This phase can be extended for up to two weeks with permission of the BMS Medical Monitor

[b] The purpose of Phase 2 is to confirm partial nonresponsiveness to mood stabilizers (therapeutic level must be maintained throughout 2 weeks). The main requirement for entry into this phase is a Y-MRS Total Score of ≥ 16

[c] This visit, prior to Phase 2, must be completed for all subjects who have achieved stable therapeutic levels and washout criteria

[d] Visits to be done at the end of each week (or at early termination)

[e] Assess Y-MRS and serum therapeutic levels as per Inclusion Criteria 7, 8 and 9

[f] Bipolar I Disorder, with or without psychotic features, defined by the DSM-IV-TR, and confirmed by the M.I.N.I.

[g] Please refer to Table 6.4.1 for required washout periods for benzodiazepines, anticholinergics, and propanolol by study phase

[h] Y-MRS must be ≥ 16 for patients to be eligible to enter Phase 2. Y-MRS should be conducted at the visit that the investigator expects the patient to have a therapeutic lithium or valproate level. If the central laboratory does not confirm a therapeutic level (causing Phase 1 to be extended) the Y-MRS does not need to be repeated prior to entering Phase 2.

[i] Baseline Y-MRS must be ≥ 16 and ≤ 25% decrease in case of decrease of Y-MRS from Phase 1. Note that Y-MRS total score can remain the same or increase (no limits to the increase) between the Phase 1 and Phase 2 assessments

[j] CGI-BP Change from Preceding Phase will be done starting at Day 4 (to refer to preceding phase of the baseline/end of Phase 2), while CGI-BP Severity of Illness will be done at all timepoints from Baseline (end of Phase 2) forward

[k] Height is to be measured at the screening visit

[l] Vital signs to include supine and standing/sitting blood pressure and pulse. Blood pressure should be taken before blood is drawn.

[m] To include weight at Baseline, Week 3, and Week 6/Early Termination

[n] Procedures to be completed at the end of Week 2 in Phase 2

[o] Clinical laboratory tests should be done fasting (10 hours minimum)

[p] Prothrombin time and partial thromboplastin time to be performed at screening for patients receiving valproate. TSH (with reflexive T4) to be performed at screening for all patients.

[q] Serum levels of lithium/valproate will be assessed 5-7 days (approximately 12 hours after last dose) after initializing dose or making a dose modification, and at approximately weekly intervals thereafter to confirm therapeutic serum levels. Unscheduled lithium or valproate levels may be performed at any time, based on the investigator's judgment

[r] Serum levels of lithium/valproate will be taken weekly to confirm patients are at therapeutic levels

[s] A serum or urine pregnancy test should be performed within 72 hours of the first administration of study medication, and at the Screening, Visit 2 of Phase 1, Baseline, Day 4, Week 3, and Week 6/Early Termination visits

[t] Drug screen for cocaine must be negative prior to randomization. Drug screen and/or blood alcohol level testing may be repeated at any time during the study at the discretion of the investigator. BMS should be contacted to discuss positive drug screen and/or blood alcohol level at the screening visit.

[u] 36-Item Short Form Health Survey

[v] Longitudinal Interval Follow-up Evaluation- Rating Impaired Functioning Tool

[w] The End of Study Form/Extension Baseline form should be completed when the patient completes the study, or upon early termination

Appendix 1.1C: Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry[a]	
AST (SGOT)	≥ 3 x upper limit of normal (ULN)
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
LDH	≥ 3 x ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
CPK	≥ 3 x ULN
Prolactin	> ULN
Hematology[a]	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from Baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from Baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2800/ mm^3 or ≥ 16,000/ mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Platelet count	≤ 75,000/ mm^3 or ≥ 700,000/ mm^3
Urinalysis[a]	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units

Appendix 1.1D: Criteria for Identifying Abnormal Vital Signs of Potential Clinical Relevance

Vital Sign	Criterion Value	Change from Baseline
Heart rate[a]	120 bpm	≥ 15 bpm increase
	50 bpm	≥ 15 bpm decrease
Systolic blood pressure[a]	180 mmHg	≥ 20 mmHg increase
	90 mmHg	≥ 20 mmHg decrease
Diastolic blood pressure[a]	105 mmHg	≥ 15 mmHg increase
	50 mmHg	≥ 15 mmHg decrease
Orthostatic Hypotension[b]	≥ 20 mmHg decrease in systolic blood pressure and a 25 bpm increase in heart rate from supine to standing	

[a] As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

[b] Blood pressure measurements were obtained after a patient had been supine for 5 minutes. A repeat measurement was then taken after the patient had been standing for 2 minutes.

Appendix 1.1E: Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	≥ 2 per 10 seconds	any increase
Ventricular premature beat	≥ 1 per 10 seconds	any increase
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 0.20 second	increase of ≥ 0.05 second
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 0.12 second	increase of ≥ 0.02 second
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post study entry
ST/T Morphological		
Myocardial ischemia	all	not present → present
Symmetrical T-wave inversions	all	not present → present
Increase in QT_C	$QT_C > 450$	

[a] Criteria developed for a previous BMS filing based upon discussions with the FDA Division of Neuropharmacological Drug Products.

[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c] No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d] No current diagnosis of left bundle branch block or right bundle branch block.

Results of the Incidence of Common AEs for Demographic Subgroups (corresponds to Sections 7.1.5.6, 7.4.2.3, and Section 8.3

The sponsor conducted subgroup analyses of common AEs for subgroups categorized by intrinsic factors (e.g. age, gender, and "race"). The following paragraphs outline key findings are noted by the undersigned review (as provided by the sponsor), regarding the integrated dataset of the 3-week, monotherapy, Bipolar trials.

Reviewer Comment of the Results of Subgroup Analyses on the Basis of Gender, Age or "Race"

As discussed below (refer to reviewer comments that follow the sponsor's results in the following paragraphs), the undersigned reviewer concludes that the integrated 3-week monotherapy Bipolar trial dataset failed to show subgroup differences (for gender, age-group or "race" subgroups). However, some of the results are difficult to interpret due to insufficient samples sizes (e.g. few patients over 65 years old) or due to other confounding variables (e.g. a high incidence in placebo subjects in a given demographic subgroup).

Potential Age-group Differences on the Incidence of Common AEs

The sponsor states that the overall incidence of common AEs was similar across the three following age-groups for each treatment group (Arip or PBO): 18-50 year old, 51-64 year old, ≥65 year old. However, the sponsor notes that the sample size for patients in the ≥ 65 year old subgroup is small (1.7% of all Ss in the 3-week placebo-controlled comparisons). However, statistical testing (Breslow Day-Test) revealed significant differences between the 18 - 50 year old and ≥ 50 year old subgroups for events of somnolence, diarrhea, and fatigue as follows:

- Somnolence showed: A greater treatment group difference (between Arip and PBO Ss) in the older age-group than in the younger age-group (in which the incidence was greater in Arip versus PBO Ss).
- Diarrhea and fatigue each showed:
  - A higher incidence in Arip compared to PBO treatment groups within the younger age-group
  - A lower incidence in Arip compared to PBO treatment groups within the older age-group.

The following shows the above results (copied excerpts of Table 2.1.1.1A in the appendix to Module 2.7.4).

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Appendix 2.1.1.1A:
Breslow-Day Test of Significance for Incidence of Treatment-Emergent AEs, by Age (at Least 5 Percent of Patients in the Pooled Aripiprazole Group): 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania
(CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

	18-50 Years		>=51 Years				
	Placebo	Aripiprazole	Placebo	Aripiprazole			
NUMBER OF PATIENTS SCREENED FOR AES	618	759	135	158			
NUMBER OF MALE PATIENTS	290	364	59	69			
NUMBER OF FEMALE PATIENTS	328	395	76	89			
NUMBER OF PATIENTS WITH >=1 AES	444(71.8)	628(82.7)	96(71.1)	131(82.9)			
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	_bdchi	DF	PVAL

SOMNOLENCE	21 (3.4)	37 (4.9)	1 (0.7)	11 (7.0)	3.95	1	0.047
DIARRHOEA	42 (6.8)	62 (8.2)	19 (14.1)	8 (5.1)	7.84	1	0.005
FATIGUE	22 (3.6)	50 (6.6)	5 (3.7)	1 (0.6)	6.70	1	0.010

Reviewer Comment. *These results are based on multiple group comparisons (including comparisons on additional AEs not shown) and are difficult to interpret. These results are considered as preliminary and do not provide sufficient reason to recommend any changes in approved labeling.*

Potential Gender Subgroup Differences on the Incidence of Common AEs

The sponsor notes that the overall incidence of common AEs was similar across female and male subgroups (Arip or PBO).

Upon statistical analyses of results (Breslow-Day test) the sponsor notes significant differences between gender subgroups on the common AEs of akathisia as follows:

- Akathisia showed a greater treatment group difference (between Arip and PBO groups, with a greater incidence in the Arip group) among men than women. The sponsor attributes this observation to a higher incidence of akathisia in the PBO group among women.

The following is an excerpt from the sponsor's Table 2.1.1.1 B (in the appendix of Module 2.7.4.

Appendix 2.1.1.1B:
Breslow-Day Test of Significance for Incidence of Treatment-Emergent AEs, by Gender (at Least 5 Percent of Patients in the Pooled Aripiprazole Group): 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138062, CN138074, CN138077, CN138135, CN138162), Safety Sample

	Men		Women				
	Placebo	Aripiprazole	Placebo	Aripiprazole			
NUMBER OF PATIENTS SCREENED FOR AES	349	433	404	484			
NUMBER OF MALE PATIENTS	349	433	0	0			
NUMBER OF FEMALE PATIENTS	0	0	404	484			
NUMBER OF PATIENTS WITH >=1 AES	239 (68.5)	361 (83.4)	301 (74.5)	398 (82.2)			
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	_bdchi	DF	PVAL
AKATHISIA	6 (1.7)	53 (12.2)	21 (5.2)	66 (13.6)	4.21	1	0.040

Reviewer Comment. *These results are difficult to interpret, as the sponsor suggested (and since p values were not corrected for multiple comparisons).*

No Significant "Race" Subgroup Differences on the Incidence of Common AEs

Reviewer comments. *The Asian and Other subgroups had insufficient sample sizes to allow for adequate interpretation of the results. The larger "Black" and "White" subgroups failed to show differences on common AEs (based on results shown in Section 2.1.1 of Module 2.7.4)*

10.4 Line-by-Line Labeling Review

A line-by-line review was not conducted. See Section 9.4 on key labeling issues.

REFERENCES

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/s/

Karen Brugge
2/25/2008 08:08:33 PM
MEDICAL OFFICER

Gwen Zornberg
3/5/2008 08:49:22 PM
MEDICAL OFFICER
Dr. Brugge recommends an approvable action contingent upon final agreement on labeling and the final biometrics consultation.
I concur with the approvable recommendation given agreement with the sponsors on labeling for the lower
15 mg starting dose..

ADDENDUM CLINICAL REVIEW

Application Type	NDA
Submission Number	21436
Submission Code	SE1 N019
Letter Date	7/11/07
Stamp Date	7/11/07
PDUFA Goal Date	5/11/08
Reviewer Due Date	3/11/08
Reviewer Name	Karen Brugge, MD
Review Completion Date	2/28/08
Established Name	Aripiprazole
Trade Name	Abilify®
Therapeutic Class	atypical antipsychotic
Applicant	Otsuka Pharmaceutical Developmental & Commercialization, Inc
Priority Designation	S
Formulation	2, 5, 10, 15, 20, 30 mg oral tablet
Dosing Regimen	(b) (4) 15 mg/day starting dose
Indication	Lower starting dose of 15 mg/day
Intended Population	Bipolar I Disorder

This addendum is being submitted due to an inadvertent error (regarding referencing the correct paragraphs for Section 14.2 for corresponding recommendations). These recommendations appear as a subsection entitled "Section 14.2…(under Clinical Studies)" of the original review of this NDA21436 N20. The following reflects the corrected version of the subsection on "Section 14.2…Studies)" under Section 9.4 of the clinical review of this submission (regarding the incidence of adverse dropouts).

(b) (4)

<u>The above changes regarding monotherapy trials are acceptable to the undersigned reviewer except for the following recommended changes for Section 14.2:</u>

1 (b) (4)

(b) (4)

The efficacy of ABILIFY in the treatment of acute manic episodes was established in four 3-week, placebo-controlled studies in hospitalized patients who met the DSMIV 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.

3. It is recommended that the third paragraph of Section 14.2 also be revised as follows:
   - (b) (4)

   Recommended Text: Therefore it is recommended that the first paragraph of Section 14.2 be replaced by the following text (while noting that shorter sentences are used for enhancing clarity and flow):

   (b) (4)

Biometric confirmation of efficacy results is pending at the time of this writing.

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/s/

Karen Brugge
2/28/2008 04:41:45 PM
MEDICAL OFFICER

Gwen Zornberg
3/4/2008 08:59:19 AM
MEDICAL OFFICER
I concur with Dr. Brugge's recommendations to remove the
(b) (4)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21436
Submission Code	SE1 N020
Letter Date	7/11/07
Stamp Date	7/11/07
PDUFA Goal Date	5/11/08
Reviewer Due Date	3/11/08
Reviewer Name	Karen Brugge, MD
Review Completion Date	2/25/08
Established Name	Aripiprazole
Trade Name	Abilify®
Therapeutic Class	atypical antipsychotic
Applicant	Otsuka Pharmaceutical Developmental & Commercialization, Inc
Priority Designation	S
Formulation	2, 5, 10, 15, 20, 30 mg oral tablet
Dosing Regimen	(b) (4) 15 mg/day starting dose
Indication	Adjunctive treatment (lithium or valproate)
Intended Population	Bipolar I Disorder

Table of Contents

EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that this NDA be approved, from a clinical perspective. Final decision for final approval will be contingent on:

- Finalized Input from other Disciplines assigned to the sNDA (Biometric Team and the Division of Scientific Investigations)
- Negotiation of Labeling.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no recommendations for specific risk management activities.

1.2.2 Required Phase 4 Commitments

Results from Study C-134 (shown in Sections 7 and summarized in Section 9.1 of this review) suggest a potential interaction effect of Arip and lithium on the incidence of primarily akathisia. Akathisia is poorly understood. Lithium has a narrow therapeutic index and is associated with severe and life-threatening events that include CNS effects. Restlessness and giddiness may be confused with akathisia and is an event that is generally a sign of lithium toxicity, although some patients may experience this event at lower plasma levels than others. Therefore, it is worthwhile to consider an examination of akathisia against other more serious adverse events, particularly in patients receiving adjunctive treatment with lithium (e.g. consider a search for adverse events characteristic of lithium toxicity and akathisia). Also consider interaction effects with antidepressants on akathisia, as well (refer to the review of N18).

It is recommended that OSE be consulted for considering approaches to address this potential safety signal.

It is also recommended that the Division consider requiring that the sponsor be involved with searching their database as well. Consider the following. Initially the sponsor could be required to propose an approach (methods) for examining their existing databases to address this potential signal and that OSE be consulted on their proposal.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor proposes a new claim that Aripiprazole (Arip) is effective as an adjunctive therapy (with lithium or valproate) for the acute treatment of manic or mixed episodes of Bipolar I disorder (with or without psychotic features).

A monotherapy claim for the indication of Bipolar I disorder (mixed/manic) is already approved for this drug. Therefore the sponsor only conducted one pivotal trial, Study CN138134 (C-134) to support the proposed adjunctive claim.

1.3.2 Efficacy

Study Design
Study C-134 was a multicenter (US and non-US), double-blind (DB), randomized, placebo (PBO) controlled study of Bipolar I patients (in the mixed or manic episode) who were identified as "partial non-responders" (which was operationally defined) to valproate or lithium open-label (OL) monotherapy (during a 2-week monotherapy phase). Subjects underwent a 6-week DB add-on phase, following the 2-week lead-in phase. During the DB phase subjects were randomized to either:

- DB Arip (15-30 mg/day; N=384 randomized) or
- PBO treatment (N=131 randomized)

The above DB treatment was added onto the subject's ongoing OL adjunctive treatment of valproate or lithium. A flexible dose, parallel group design was employed for this DB phase using a starting dose of 15 mg of Arip that could be increased to 30 mg as early as Day 7 of treatment (at the investigator's clinical discretion). Plasma levels of valproate and lithium were followed during OL monotherapy and DB adjunctive treatment to assure adequate stability of level within therapeutic range.

Results on the Primary and Key Secondary Efficacy Variables
The study showed superiority of the Arip group over the PBO group on the primary and key secondary variables as follows:

- Primary efficacy variable: significantly greater improvement on the mean change from baseline to treatment endpoint on the Young Mania Rating Scale total score ($p<0.01$)

- Key secondary variable: significantly greater improvement than the placebo group on the Clinical Global Impression-Bipolar Severity of Illness ($p<0.025$)

Section 6 of this Review provides more details on this study and the study results relevant to efficacy.

1.3.3 Safety

The focus of the safety review was on results from the pivotal adjunctive Study C-134. The overall safety profile of serious adverse events (SAEs) and adverse dropouts (ADOs) in Study C-134 did not reveal a new clinically remarkable safety signal. The highest incidence of akathisia (reported as an AE leading to an ADO or reported as an AE) was observed in the lithium-Arip subgroup of Study C-134, when numerically compared to the incidence observed in the PBO-lithium subgroup and each valproate subgroup (PBO and Arip valproate-subgroups). Results on additional AEs also suggested adjunctive subgroup differences but the treatment group differences (between Arip and PBO) appeared to be less robust. These results are only considered preliminary since Study C-134 was not designed for interpreting results that are based on comparisons between multiple adjunctive subgroups on multiple outcome measures (the interpretation of the results is limited by the small sample sizes, the multiple treatment group comparisons that were based on numerical comparisons, by the non-randomized, non-stratified assignment of subjects to valproate or lithium, among other factors to consider). Moreover, the AEs that were suggestive of showing subgroup differences are AEs that are known to occur with either study drug alone (with Arip or the adjunctive drug). These results are summarized in Section 7.1 of this review.

Longterm OL adjunctive safety data from the ongoing 46 week OL phase of Study C-134 and of the OL stabilization phase of the ongoing Study C-189 were also provided as unpooled results (upon request in a 1/8/08 submission). The results failed to reveal a clinically remarkable new safety signal.

Module 2.7.4 in the N19 submission is cross-referenced in the current N20 submission for safety results from additional datasets (of clinical trials). These additional datasets were not the primary focus of the review for the N20 application, since they involved different patient populations or different treatment regimens (among other limitations). These results are described in more detail in the review of N19. A clinically remarkable new safety signal was not revealed.

Section 7 of this review provides details on safety results from primary and secondary datasources.

Finally there is extensive experience with Arip treatment in Bipolar I and other patient populations that include patients receiving concomitant lithium and valproate.

1.3.4 Dosing Regimen and Administration

Refer to Section 1.3.2 for the dosing regimen in Study C-134. The starting dose of 15 mg is lower than the 30 mg dose that is recommended for acute monotherapy of Bipolar I disorder.

The flexible daily-dose range of 15 mg to 30 mg in Study C-134 is consistent with the dose range used in the pivotal monotherapy of Bipolar I (mania/mixed) trials that supported the approval of Arip monotherapy for this indication.

1.3.5 Drug-Drug Interactions

This submission did not include new Phase I trial results on drug-drug interaction effects. Drug-drug interaction studies (using lithium or valproate) were previously conducted and subject to review (with the results described in approved labeling).

Study C-134 was not designed to make direct comparisons between the adjunctive subgroups or to monotherapy.

1.3.6 Special Populations

Studies on special populations were not conducted, since they were not required for the purpose of this program.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor is seeking approval of Abilify as an adjunctive treatment with lithium or valproate in adult patients with Bipolar I-acute mania or mixed, with or without psychotic features. The sponsor conducted a pivotal Phase III trial, Study CN138134 (C-134). This 6-week study is part of a postmarketing commitment for S-002 and S-005 (these supplemental NDAs were for acute and maintenance monotherapy treatment claims for this indication). The sponsor claims that this study:

- Shows efficacy and safety for their proposed indication
- Fulfills their Phase IV commitment for S-002 (b) (4) in providing short-term data on adjunctive treatment with "mood stabilizers."

The sponsor cross-references N19 for safety information, as specified in Sections 2.5, 4 and Section 7 of this review.

Abilify (aripiprazole) is an atypical neuroleptic that is approved for Schizophrenia and other psychiatric indications as described in approved labeling. It is among a drug class of atypical neuroleptics approved for schizophrenia (and in some cases for other psychiatric indications).

2.2 Currently Available Treatment for Indications

Several atypical neuroleptic agents are approved for acute monotherapy treatment of Bipolar I (mania/mixed). Zyprexa® (oral olanzapine formulation), Seroquel,® and Risperdal® are approved as an adjunctive treatment (with lithium or valproate) for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

Abilify® has been on the market for a number of years. This drug was first approved in the US on November 15, 2002 for schizophrenia and September 29, 2004 for Bipolar I, mixed or manic. See sections in this review discussing the postmarketing experience with the drug.

The sponsor notes (on page 465 of Module 2.7.4 of N19) that Aripiprazole (Arip) has not be withdrawn from the market (from any country).

2.4 Important Issues with Pharmacologically Related Products

Refer to labeling of approved drugs in this drug class that describe important issues relevant to safety.

2.5 Presubmission Regulatory Activity

The sponsor refers to the following presubmission activities:

- The sponsor conducted Study C-134 to fulfill their Phase IV commitment for S-002 and S-005 in providing short-term data on adjunctive treatment with "mood stabilizers."
- The protocol of Study C-134 was previously subject to review under IND42776.
- The sponsor refers to a February 26, 2007 pre-sNDA meeting. Based on discussions during this meeting, the sponsor is submitting N19 and N20, as parallel NDA submissions. The sponsor seeks approval for a 15 mg monotherapy starting dose in the N19 submission which also provides integrated safety and efficacy data and other safety data from Bipolar trials. The sponsor cross-references N19.
- IND 42776 is referenced (the IND in which the protocol for Study C-134 was submitted).
- As previously discussed in Section 2.1, Study C-134 is also part of a Phase IV commitment to provide data on short-term adjunctive treatment with "mood stabilizers") for S-002 and S-005 (for the acute and maintenance monotherapy claims for Bipolar disorders, as previously specified).
- IND73863 is referenced regarding monotherapy Bipolar trials that were conducted in support of S-002 and S-005 (for acute and monotherapy claims).

2.6 Other Relevant Background Information

The sponsor provided postmarketing and foreign marketing information in the parallel NDA 21436 N19 submission (cross-referenced for N20).

The following is copied from the N19 review:

> Abilify® is approved for the indications of schizophrenia and/or bipolar mania in approximately 40 countries (the sponsor lists the countries in Table 6.1.A in Section 6 of Module 2.7.4). Arip was first approved for schizophrenia in Mexico on July 17, 2002 and later in the USA on November 15, 2002.
>
> The sponsor notes (on page 465 of Module 2.7.4) that Arip has not been withdrawn for the market (in any country).
>
> The sponsor also lists a number of marketing applications that are under review in other countries (as of 12/31/06).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

This is a supplemental NDA for an adjunctive treatment claim (with valproate and lithium) for an already approved indication of Bipolar I mixed/mania (approved for monotherapy treatment). The only new information in this NDA is efficacy trial data and safety results.

3.1 Animal Pharmacology/Toxicology

No new preclinical data is provided (as specified in the guide.pdf file). Therefore this sNDA is not assigned to a preclinical reviewer.

3.2 Biometrics

The undersigned reviewer is not aware of any major issues from the Biometrics Team at the time of this writing (a final review is pending at this time). Dr. Phillip Dinh is the assigned Biometric reviewer.

3.3 Division of Scientific Investigations

Division of Scientific Investigations (DSI) reviewer Dr. Dianne Tesch is assigned to this NDA and DSI inspections are underway at the time of this writing.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The following table lists the datasources that were reviewed, as described in more detail in subsections that follow.

TABLE 4.3.1: ITEMS THE REVIEWED

Submission Date	Items Reviewed in N20 and the Cross-referenced N19 Submission
7/11/07	Clinical Study Report (selected sections): Study C…134 (Studies C-135 and C…162 were reviewed in N19 for N19) Module 2.7.4 in N19: in-text and selected appendices/attachments and selected narratives (narratives were provided in Appendix 2.2B) Proposed Labeling (side-by-side version) Financial Disclosure Certification Literature Search Item 8 (litserach.pdf) Selected Case Report Forms
1/18/08	Responses to inquiries (refer to 12/6/07 questions e-mail (Telecon) document under the NDA. In-text responses and selected Attachments were reviewed.

4.2 Tables of Clinical Studies

The following table shows the single efficacy trial.

Efficacy Studies*	
Phase 3 Study C-134	Multicenter (US and non-US), DB, randomized, PBO controlled study of Bipolar I patients (in the mixed or manic episode) who were identified as partial non-responders to valproate or lithium monotherapy (during a 2-week monotherapy treatment). Subjects underwent a 6-week DB phase of adjunctive Arip (15-30 mg/day) or PBO treatment using a flexible dose, parallel group design). The study has an ongoing 46-week OL adjunctive phase for safety data.
Total randomized:**	Placebo: 131 subjects Arip: 253 subjects
Total completers:**	Placebo: 111 subjects Arip: 199 subjects
Total of ITT Efficacy Subjects:**	Placebo: 130 subjects Arip: 247 subjects

*Arip=aripiprazole OL=open-label DB=double-blind SB=single blind PBO=placebo
** Based on results on disposition in Table 5.1A in the Clinical Study Report (CSR).

Safety Studies*	
Phase 3 Study C-134	See the above. The DB phase provide PBO controlled safety results that were summarized in Module 2.7.4 of N19 (cross-referenced in the current N20 submission) and results were also found in the CSR provided for this phase.
Total completers:**	Placebo: 111 subjects Arip: 199 subjects
Total of ITT Safety Subjects:***	Placebo: 130 subjects Arip: 253 subjects
Additional Adjunctive (lithium or valproate) Safety databases	The sponsor cross-references N19. Also described in the review of N19.
Unpooled Longterm Adjunctive Treatment Bipolar Databases available from ongoing Trials (results provided upon request in a 1/18/08 submission)	Study C-134: The ongoing OL 46-week extension phase of the above pivotal Study C…134 of Bipolar I patients (15-30 mg flexible dose of Arip and lithium or valproate). Study C-189: 13-24 week stabilization phase of OL adjunctive of the an ongoing adjunctive maintenance trial, Study C…189 of Bipolar I patients (15-30 mg flexible dose of Arip and lithium or valproate).
Exposure:	These trials are ongoing. A total of 74 subjects and 146 subjects exposed to ≥360 days and ≥270 days of treatment, respectively (only 38 subjects in Study C-189 were exposed to 90-179 days of treatment) as found in the 1/18/08 submission. Refer to Section 7.2.1.3 for details.

* Arip=aripiprazole OL=open-label DB=double-blind SB=single blind PBO=placebo
** Based on results on disposition in Table 5.1A in the CSR.

The sponsor cross-references N19 for safety results in Module 2.7.4 that include results from Study C-134. These safety datasets are shown in a table in the review of N19 and safety results are described in the review of N19.

Each trial used lithium or valproate treatment and a 15-30 mg flexible daily dose of adjunctive Arip treatment. These trials are ongoing. A total of 74 subjects and 146 subjects exposed to ≥360 days and ≥270 days of treatment, respectively, in Bipolar mania trial which included the 2 above adjunctive longer-term trials Table 1.2.5.1A of Module 2.7.4.
Refer to Section 7.2.1.3 on exposure to study drug in these trials.

4.3 Review Strategy

Efficacy results of Study C-134 were reviewed (along with additional relevant information as described in Section 6 of this review) in order to determine if the study adequately demonstrated efficacy for the proposed claim.

The primary focus of the safety review was on results from the pivotal adjunctive Study C-134.

Longterm OL adjunctive safety results (unpooled results) were provided upon request (in a 1/18/08 submission). Refer to Section 4.2 regarding this dataset (included in the table in Section 4.2 of this review). The interpretation of OL datasets are limited by the nature of the OL study design and the studies are also ongoing. The 1/18/08 provided information on exposure for this dataset, as well, and longterm exposure was limited. Therefore, the primary focus of the review of this dataset was on deaths, serious adverse events (SAEs) and adverse dropouts (ADOs).

The N19 submission is cross-referenced in the current N20 submission for safety results from additional (secondary) datasets (of clinical trials) that were not the primary focus of this review, since they involved different patient populations or different treatment regimens (among other limitations with interpreting these results).

4.4 Data Quality and Integrity

DSI has not conveyed any key concerns to the undersigned reviewer at the time of this writing.

All pivotal trials include protocols describing methods for quality assurance (in Section 4.2 of the Clinical Study Report). Appendix 10.1 of this review summarizes protocol deviations in each study. Section 6 notes that the per protocol population analyses on the primary efficacy variable revealed positive efficacy results.

The following was copied from the review of N19 since it includes information relevant to the current submission.

Comparisons between arbitrarily selected Case Report Forms (CRFs) with corresponding narratives revealed adequate accuracy (no inconsistencies were found, as described in detail below).

Methods of the CRF and Narrative Audit
CRF to Narrative comparisons for each arbitrarily selected subject of each pivotal trial revealed no inconsistencies as follows (SAE terms were compared for each subject but other items were also arbitrarily selected for a given subject, as specified below):

- *Subject CN138135-28-388: Comparisons were made on: SAE terms, the timing of the SAE relative to onset of DB treatment and additional descriptive information regarding the SAE (a quote was provided from the SAE form in the CRF). The information matched.*
- *Subject CN138162-16-38: Comparisons were made on: SAE terms, the timing of the SAE relative to onset of DB treatment and additional descriptive information regarding the SAE (comments in a supplemental report). The information matched.*
- *Subject CN138134-49-25: Compared the age, gender, SAE terms and timing relative to DB treatment and AE terms (ongoing at the time and comments quoted from the SAE from). The information matched.*

Inconsistencies or Problems Found Upon Review of the NDA (cross-reference N19 and N20)
Subsections of this review note some inconsistencies (or apparent inconsistencies) that were found upon review of sections of the submission and are described in the sections of this review to which they apply. The nature of these problems found by the undersigned reviewer, did not alter overall conclusions and therefore did not have a significant impact on the quality of the information reviewed. Moreover, the sponsor's 1/18/98 response submission provided information that also did not lead to altering overall conclusions of the information that was originally provided (e.g. regarding cases of hepatic impairment, identifying SAEs and ADOs during OL adjunctive phases of ongoing trials).

The following copied text (see below) is regarding one inconsistency that is perhaps most notable to the undersigned reviewer. Yet this discrepancy did not alter conclusions and recommendations in Section 9 for reasons that follow. This was the only subject (S) with seizure (a tonic clonic episode) found in the adjunctive trials and the sponsor captured this S in their special search for seizures (as described in Section 7.1.4 of this review). It appears that the episode occurred after the S was hospitalized for a reported SAE of worsening Bipolar disorder. There was also evidence for noncompliance based on her lithium levels which is consistent with a worsening of mania. The S also had a history of hypothyroidism and thyroid hormone replacement therapy (which is a risk for seizure). Consequently, the exclusion of the tonic clonic event in the narrative does not alter overall conclusions and recommendations regarding the regulatory action and for labeling in this review. Text below is of copied excerpts from Section 7.1.4 of this review in a section that discusses the sponsor's special search of their AE database for events of seizure:

Seizures

The only lithium-Arip treated subject reported by the sponsor to have an AE of seizure was the following subject:

- CN138134-96-296, a 25-year-old woman, was started on aripiprazole 15 mg/day co-administered with lithium. On Day 183, during the extension phase of the study and while she was still on treatment, she experienced a non-serious AE of clonic convulsion. The event was reported as moderate in severity and possibly related to study treatment. The patient also experienced loss of consciousness for one minute and headache. All events resolved on the day of onset.

The above subject was found by the sponsor by conducting a search of the AE database for all Phase 2/3/4 studies using the following search terms: seizure, convulsion, grand mal, petit mal, epilepsy, fits, EEG, electroencephalogram, and lobe.

Reviewer Comments. *Limitations and potential limitations with the sponsor's search methods are discussed in the Section 7.1.4 of the review of N19. It is not clear if the sponsor searched verbatim terms, as well as preferred terms. The search did not include syncope (as above).*

It should be noted that a description of the above tonic clonic episode and loss of consciousness was not found in the patient's narrative summary in Appendix 2.2B in the Appendix pdf of Module 2.7.4 of N19.

The narrative has this patient listed as SAE of worsening Bipolar disorder (manic episode) leading to hospitalization on Day 183 (worsening of Bipolar disorder was reported on Day 178). It is not clear why the narrative does not include this information. The narrative indicates that "no other events were ongoing at the time of this event." The following is a copy of the narrative found in the Appendix 2.2B:

Patient CN138134-96-296: Hospitalized due to SAE of worsening of bipolar disorder to manic episode

Patient CN138134-96-296, a 25-year-old female with Bipolar I Disorder and relevant medical history of neuralgic headache, hypothyroidism, and tobacco use, was assigned to lithium at screening. At the end of the monotherapy phase, the patient was randomized to receive aripiprazole 15 mg on Day 1 of the double-blind phase. The patient completed treatment with aripiprazole 15 mg in the double-blind phase on Day 43, and continued in the open-label extension phase.

Per supplemental report, on Day 178 (Day 135 of extension phase), at an aripiprazole dose of 15 mg and a lithium dose of 1500 mg (the most recent lithium level 0.79 mmol/l on Day 141), the patient experienced worsening of bipolar disorder to manic episode. Per SAE report, "the investigator reported that the patient experienced the acute manic episode secondary to noncompliance with her dosing of lithium and possibly aripiprazole." The patient was hospitalized on Day 183 (Day 140 of extension phase), at an aripiprazole dose of 15 mg and 1500-mg lithium for mania. On the following day, her serum lithium level was 0.24 mmol/l (baseline value: 0.79 mmol/l). Treatment was implemented during her hospitalization; however, the details were not reported. The investigator considered the manic episode moderate in intensity with a possible relationship to study medication.

No other events were ongoing at the time of this event. Concomitant medication taken within 14 days prior to the manic episode was levothyroxine.

There were no potentially clinically relevant laboratory, vital sign, or ECG abnormalities reported during the study.

It is important to note that a 3rd case of suicidality was found by the undersigned reviewer (based on the term being found in a narrative summary) but was not found in the sponsor's special search of cases of suicidality or in summary tables, as described in this review.

The above discrepancies were found for single cases for a given type of event (in one case, a single subject with suicidality, in the other case a single subject with seizure that did not appear to be captured in all relevant sections of Module 2.7.4) that do not impact on the interpretation of the sponsor's results on overall incidence of events or on reviewer conclusions in Section 9 of this review.

4.5 Compliance with Good Clinical Practices

DSI has not conveyed any key concerns to the undersigned reviewer at the time of this writing.

The knowledge of the undersigned reviewer, Study C…134 was conducted in accordance to the Declaration of Helsinki and Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines (this aspect of the study is discussed on page 81 of the CSR).

4.6 Financial Disclosures

The below excerpt from the submission summarizes financial disclosure information.
Reviewer Comment. *The sponsor included adequate financial information for the purposes of this review. Only 1 investigator had disclosable*

information.

(b) (4) Financial Disclosure Letters (b) (4) and Forms ((b) (4)) were mailed with prepaid return mailers to the following:

CN138-134: 112 investigators and 336 subinvestigators

As of June 4, 2007, BMS has received a total of 112 statements of the 112 investigators, and 1 individual had disclosable information reported. In addition, BMS received a total of 336 statements of the 336 subinvestigators.

5 CLINICAL PHARMACOLOGY

Since the submission does not include new OCPB related data this sNDA was not assigned to an OCPB reviewer.

5.1 Pharmacokinetics

Current approved labeling has sections on Arip-drug interaction effects on PK during concomitant valproate or lithium treatment which is also relevant to the current N20 submission.

Labeling specifies that no dose adjustments are needed for either of these two concomitant drugs. Although, the following PK changes are described in approved labeling (using 30 mg/day of Arip treatment):

- A 25% decrease in Cmax and AUC of Arip with valproate (500-1500 mg/day) adjunctive treatment at steady state
- A less than 20% increase in Cmax and AUC (of Arip or the dehydro-Arip) was observed with 21 days of lithium (1200-1800 mg/day).

Additional results using lower dose-levels of lithium (900 mg/day) or valproate (1000 mg/day) are described as well (in approved labeling) given with 30 mg of Arip (daily) are unremarkable.

The sponsor notes no new data (as specified in the guide.pdf file of the N20 submission or in the guide.pdf file of submission N19). Module 2.7.4 of N19 has a Section 5.3 on "Drug Interactions." The sponsor notes that there are the following drug interaction studies involving either lithium or valproate coadministration:

- Studies CN138021 and CN138023 (patient with schizophrenia or schizoaffective disorder using lithium and valproate in each study, respectively)

The sponsor notes that results from these trials were previously reported (in a "Schizophrenia Integrated Summary of Safety/Marketing Authorization Application dated October 2001/November 2001"). The sponsor concludes that these studies showed no "clinically relevant" effects on the PK of Arip.

Reviewer Comment. *Refer to Sections 7.1, 7.1.4.1, 7.1.4.2, 7.1.5.6 discussing potential Arip-lithium interaction effects on the incidence of akathisia (includes ADOs and AEs), possibly tremor (reported as AEs) and on additional less common AEs. In light of these observations,*

note the above increases with Cmax during lithium (in contrast to valproate). However, Study C-134 was not designed for interpreting results from each adjunctive subgroup (e.g. due to small sample sizes, multiple treatment group comparisons and the likelihood for selection bias, given the methods employed for assigning subjects to a given "mood stabilizer" as described in Section 6 of this review).

The sponsor also notes 2 healthy volunteer Phase I trials involving either lithium or valproate coadministration with results that were previously reported (in the "schizophrenia sNDA/Type II Variation [June 2005]"). The sponsor concludes that these studies showed no "meaningful effects" of Arip on PK of each of these concomitant drugs.

The sponsor also describes studies involving coadministration with lamotrigine (an ongoing study) or carbamazepine (submitted in the schizophrenia 2001 marketing application, specified above).

Approved labeling does not include any PK results from trials involving carbamazepine or lamotrigine. However, N20 is regarding adjunctive treatment with only lithium or valproate (as the sponsor specifies in proposed labeling, and as shown in Section 9.4 of this review).

5.2 Pharmacodynamics

The submission does not include new information on the pharmacodynamic properties of Arip.

5.3 Exposure-Response Relationships

The placebo controlled pivotal trial employed a flexible dose design, as described in Section 6 of this review. Consequently, the study was not designed to examine the relationship of dose and efficacy.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

A monotherapy claim for the indication of Bipolar I-mixed/manic is already approved for this drug. The sponsor conducted Study C-134 to support the proposed adjunctive (lithium or valproate) treatment claim for this indication.

6.1.1 Methods

Study C…-134 was the pivotal efficacy trial intended to support the proposed claim. The study was a multicenter (US and non-US), DB, randomized, PBO controlled study of Bipolar I patients (in the mixed or manic episode) who were identified as partial non-responders to valproate or lithium monotherapy (during a 2-week monotherapy treatment). Subjects (Ss) underwent a 6-week DB add-on phase in which DB Arip (15-30 mg/day; N=384 randomized) or PBO treatment

(N=131 randomized) was given as an adjunctive treatment to their ongoing valproate or lithium treatment. DB treatment was given using a flexible dose, parallel group design (15 mg starting dose of Arip). See section 6.1.3 below for more details on the study design.

6.1.2 General Discussion of Endpoints

Young-Mania Rating Scale (YMRS) total score was the primary efficacy variable
The Clinical Global Impression-Bipolar Version-Severity Illness Score (CGI-PB-S) for mania is specified in the CSR as the key secondary variable.

Reviewer Comment. *The above variables are acceptable primary and key secondary, respectively endpoints for a pivotal Phase III efficacy trial for a Bipolar I-mania/mixed claim and are appropriate for Study C-134 as the pivotal trial for this NDA.*

6.1.3 Study Design

Reviewer comment. *The study is adequately designed for the purposes of this review.*

The study is a multi-center (16 countries including the US), randomized, double-blind (DB), placebo-controlled, flexible dose study that used a parallel group design.

Study Phases and Overall Treatment Methods
Generally healthy adult (≥18 years old) patients with Bipolar I (mixed or manic episode) underwent the following study phases:

- Phase 1: 3-day to 4 week phase for:
  - Screening
  - Psychotropic washout.
    - Achieving therapeutic levels (as defined later) of lithium or valproate OL monotherapy.

  Subjects may have already been receiving either lithium or valproate treatment (also referred to as "mood stabilizers") prior to study entry.
- 2-week observational Phase 2 during OL monotherapy (lithium or valproate):
  - Subjects who entered this phase had to meet the following criteria:
    - Confirmed therapeutic levels of lithium (i.e., 0.6 to 1.0 mmol/L) or valproate (i.e., 50 to 125 µg/mL)
    - YMRS≥16
  - Subjects continued OL monotherapy during Phase 2.
  - "Partial nonresponders" (PNRs) were identified during this phase and were defined as subjects meeting both of the following criteria:
    - YMRS≥16 at the end of Phase 2 (as well as at baseline)
    - ≤25% improvement (decrease), no change, or worsening (increase) on the YMRS total score (between Phase 1 and the end of Phase 2)

- 6-week DB Phase 3: PNRs entered this phase and were randomized (2:1, stratified by "mood stabilizer" treatment) to either of the following DB adjunctive treatments (as OL lithium or valproate treatment was continued):
  - Arip (15 mg starting dose with the option to increase the dose to 30 mg daily on Day 7 or thereafter, as clinically indicated)
  - Placebo (PBO)

Treatment was given without regard to meals.

46-week OL Adjunctive Phase 4

Subjects had the option to enter in a 46-week OL Phase 4 (OL Arip with lithium or Arip adjunctive treatment). This phase was conducted in order to obtain longterm safety data and is not described further in this section of the review (refer to Section 7 of this review for safety results during longterm OL adjunctive treatment).

Eligibility Criteria:

The following outlines key criteria:

- Subjects had to meet DSM-IV-TR criteria for Bipolar I-mixed or manic episode, with or without psychotic features (the Mini International Neuropsychiatric Interview was employed).
- Patients may be receiving ongoing lithium or valproate prior to study entry (but this was not a requirement to be eligible). Patients who were not already receiving one of these 2 drugs was assigned to one of them by the investigator.
- Subjects could not be:
  - In their first manic or mixed episode.
  - Could not be rapid cyclers (as defined by having ≥4 manic or depressive episodes/year)
  - Hospitalized for over 3 weeks with their current episode.
  - Refractory to treatment for manic symptoms (failed ≥2 treatments such as with a mood stabilizer or an antipsychotic drug, excluding treatment of the current episode, unless permission was granted by BMS medical monitor to include the patient).
  - Nonresponsive to Arip treatment, if given in the past.
  - Could not meet other specified Axis I disorders (using DS-IV-TR criteria)
  - Could not exceed prespecified cut-off values on clinical parameters (QTc, LFTs, Cr, neutrophil count, platelets and others).
  - Could not have history of thyroid pathology (with some exceptions as permitted by the sponsor)
- Additional criteria were included.

Treatment Methods

The following outlines lithium or valproate treatment during Phase 2:

- Lithium (Camcolit®):
  - US sites: 500-1500 mg daily

        - Starting dose was 900 mg for subjects not previously receiving this treatment,
        - 300 mg increments were allowed, as needed, in order to maintain therapeutic levels
    - Non-US sites: 600-1500 mg
        - Starting dose was 1000 mg for patients not previously receiving this drug
        - Used 250 mg increments, as needed to maintain therapeutic levels
- Valproate (Depakote®):
    - 500-2500 mg daily
        - Starting dose of 750 mg in divided doses, twice daily (if not previously receiving this drug)
        - Used 250 mg increments, as needed to maintain therapeutic levels.
- Dose increases only allowed for achieving or maintaining therapeutic levels and dose decreases allowed for achieving tolerability (as long as therapeutic levels were maintained).
- Serum levels were obtained approximately every 5 to 7 days after starting treatment or after adjusting the dose and approximately weekly thereafter (to verify that therapeutic levels were being maintained at 0.6 to 1.0 mmol/l lithium or 50 to 125 µg/ml valproate).

Phase 3 Treatment was as follows:

- OL lithium or valproate monotherapy was continued at the dose in which therapeutic serum levels were maintained during Phase 2 (dose adjustments were permitted in order to maintain therapeutic levels)
- DB Arip group received a 15 mg starting dose with the option to increase the dose to 30 mg daily on Day 7 or thereafter, as clinically indicated (15 or 30 mg daily, flexible dose)
- Serum valproate or lithium levels were obtained weekly.

Reviewer Comment: (b) (4)

See the last section of this review for further comment and recommendations regarding proposed labeling.

Concomitant Medications.
Restrictions and prohibition of concomitant medications were specified. Refer to Appendix 10.1 for details on common concomitant medications used during the DB phase of the study.

The study flow chart is provided in Section 10.1 of this review and includes efficacy assessments at multiple time-points, as specified.

Statistical Analyses
The following outlines key aspects of the methods (using the LOCF dataset):

- Primary efficacy variable: The mean change from baseline to treatment endpoint of the DB phase on the total YMRS score.
- Key Secondary variable (specified in the CSR): The mean change from baseline to treatment endpoint of the DB phase on the CGI-BP-S mania score.
- Statistical Test: The sponsor employed an ANCOVA model with DB treatment as the main effect and the baseline score as a covariate and "mood stabilizer" adjunctive subgroups as a factor in the model.
- Method of Correcting for Multiple Comparisons (on primary and key secondary variables): a hierarchical testing procedure was employed, such that key secondary analysis was not conducted unless the primary efficacy analysis was positive ($p<0.05$).
- Methods of Conducting Subgroup Analyses: Subgroup analyses was conducted to determine the potential influence of a given subgroup on the mean change from baseline to treatment endpoint (Week 6, LOCF) on each efficacy variable (on the primary and on the key secondary efficacy variables) for each of the following subgroups:
  - "Mood stabilizer"
  - Gender
  - Study sites categorized by regions (US, non-US)
  - Study sites categorized by country
  - Each study center
  - Psychotic features (present versus absent)
  - Type of current episode of Bipolar disorder (manic versus mixed)

  The statistical test used for each subgroup analyses was an ANCOVA model with baseline as a covariate and with the given subgroup category and treatment group as the factors in the model.

Reviewer comments. *The undersigned reviewer discussed with the Biometric review the possibility of conducting an additional analyses given the narrow score range on the key secondary variable (CGI-BP-S). Biometrics plans on conducting an additional sensitivity analyses since results on this key secondary variable only show small, although significant treatment group differences. These results are pending at the time of this writing.*

Refer to the last section of this review for additional comments and recommendations (Section 9).

6.1.4 Efficacy Findings

Disposition, Exposure, Concomitant Medication Use, Protocol Deviations, Baseline Demographic and Psychiatric Features

Results on disposition, concomitant medications, baseline demographic and psychiatric features are summarized in Appendix 10.1 of this review. Results on Exposure are provided in Section 7.2 of this review.

Reviewer Comments. *These results (described in Appendix 10.1) fail to show findings that are considered substantial enough to render the study inadequate as a pivotal efficacy trial for the purposes of this review.*

Efficacy Results

The following outlines efficacy results on the primary and key secondary variables, respectively, as found in Section 7.1 of the CSR (refer to Appendix 10.2 for summary tables showing more details, as provided by the sponsor):

- The Arip group showed a significantly greater improvement than the placebo group on the YMRS total score ($p<0.01$)
- The Arip group showed a significantly greater improvement than the placebo group on the CGI-BP-S mania score ($p<0.025$)
- Statistically significant treatment group by subgroup interaction effects were not revealed by the sponsor on the primary or key secondary variables (for each subgroup analyses, as previously listed and including gender, "mood stabilizer" and study center, among others).

Primary, Key Secondary and Other Secondary Efficacy Results of Study -134 (copied from Table 2H in Module 2.7.3)

	Placebo	Aripiprazole
Primary Efficacy Measure		
Y-MRS Total Score	N = 130	N = 247
Mean Baseline	22.72	23.12
Mean Change at Week 6 (LOCF)	-10.70	-13.31**
Key Secondary Efficacy Measure		
CGI-BP Severity of Illness (mania) Score	N = 130	N = 346
Mean Baseline	4.12	4.21
Mean Change at Week 6 (LOCF)	-1.56	-1.89*
Other Secondary Efficacy Measures		
Response Rate (LOCF)	N = 130	N = 247
Number of Responders[a] at Week 6 (%)	63 (48.5)	155 (62.8)
Ratio of Response Rates vs Placebo (95% CI)	--	1.29 (1.06, 1.58)**
Remission Rate (LOCF)	N =130	N =247
Number in Remission[b] at Week 6 (%)	66 (50.8)	163 (66.0)
Ratio of Remission Rates vs Placebo (95% CI)	--	1.30 (1.07, 1.57)**

Source: CN138134 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

a Response on the Y-MRS scale is defined as ≥ 50% improvement from baseline in Y-MRS Total Score.

b Remission on the Y-MRS scale is defined as a Y-MRS Total score ≤ 12.

Reviewer comments on Primary, Key Secondary and Secondary Analyses. *Refer to Appendix 10.2 showing additional efficacy results, while key reviewer comments are provided below.*

Refer to previous reviewer comments regarding the statistical test methods employed for the key secondary variable. For reasons previously discussed (regarding the potential issue of parametric versus non-parametric tests and the small range of scores on this measure), the undersigned reviewer consulted with the Biometric Team on considering an additional analysis on the CGI-BP-S. Also note that the mean treatment group difference on this variable is only 0.23. The Biometric Team plans to conduct a sensitivity analysis (results remain pending at the time of this writing).

The results of additional (non-key) secondary analyses generally show at least trends for greater improvement in the Arip compared to PBO groups that were consistent with the results on the primary and key secondary analyses.

Refer to appendix 10.1 regarding protocol deviations and analysis of primary efficacy data from the per-protocol population. The CSR describes the methods for defining the per protocol population and for the analyses conducted. The sponsor's per protocol population results showed a significantly greater improvement on the YMRS in Arip compared to PBO subjects ($p<0.001$).

Subgroup Analyses on the Primary Efficacy Variable
Subgroup analyses by gender, US versus non-US sites, by "mood stabilizer" did not show significant treatment group interaction effects on the primary efficacy variable. The following subsections discuss results of various subgroup analyses (tables are copied from the submission).

A key caveat regarding most of the results below is that Study C-134 was not designed for examining these subgroups on efficacy and in most cases samples sizes are small. Therefore the results are considered as preliminary.

<u>*Subgroup Analyses on the Basis of Age*</u>
The following results were provided in a (b) (4) *submission in response to a request for this information. Sample sizes (in the upper age-group) were insufficient for results to be considered interpretable.*

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Attachment Q.4.2:
Adjusted Mean Change from Baseline to Week 6 in Y-MRS Total Score,
by Age, LOCF Data Set, Efficacy Sample

Subgroup	Visit	Placebo N	Placebo Mean (a) (SE)	Aripiprazole N	Aripiprazole Mean (a) (SE)	Treatment Comparison (b) Aripiprazole - Placebo Difference	(95% CI)
<= 50							
Mean Baseline		97	22.86 (0.52)	184	23.12 (0.37)	0.26	(-0.99,1.50)
Mean Change from Baseline to Week 6		97	-10.78 (0.81)	184	-13.04 (0.58)	-2.26	(-4.20,-0.31)
> 50							
Mean Baseline		33	22.38 (1.09)	63	22.93 (0.85)	0.55	(-2.16,3.27)
Mean Change from Baseline to Week 6		33	-10.57 (1.38)	63	-14.05 (1.07)	-3.48	(-6.91,-0.06)

p-value for treatment by age interaction: 0.484 (c)

(a) Y-MRS Total Score is from 0 to 60.
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment and mood stabilizer, is used for baseline.
ANCOVA model, controlling for treatment, mood stabilizer and baseline value, is used for mean change from baseline
Means, differences in means, 95% CI for the differences are based on the ANOVA/ANCOVA model.
(c) ANCOVA model, controlling for baseline, treatment, mood stabilizer, age, and
treatment by age interaction is used.

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Attachment Q.4.5:
Adjusted Mean Change from Baseline to Week 6 in CGI-BP Severity of Illness (Mania) Score,
by Age, LOCF Data Set, Efficacy Sample

Subgroup	Visit	Placebo N	Placebo Mean (a) (SE)	Aripiprazole N	Aripiprazole Mean (a) (SE)	Treatment Comparison (b) Aripiprazole - Placebo Difference	(95% CI)
<= 50							
Mean Baseline		97	4.09 (0.07)	183	4.19 (0.05)	0.11	(-0.07,0.28)
Mean Change from Baseline to Week 6		97	-1.52 (0.13)	183	-1.85 (0.09)	-0.33	(-0.63,-0.03)
> 50							
Mean Baseline		33	4.23 (0.14)	63	4.26 (0.11)	0.03	(-0.33,0.38)
Mean Change from Baseline to Week 6		33	-1.69 (0.23)	63	-2.00 (0.18)	-0.31	(-0.89,0.27)

p-value for treatment by age interaction: 0.971 (c)

(a) CGI-BP Severity of Illness (Mania) is from 1 (Normal) to 7 (very severely ill).
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment and mood stabilizer, is used for baseline.
ANCOVA model, controlling for treatment, mood stabilizer and baseline value, is used for mean change from baseline
Means, differences in means, 95% CI for the differences are based on the ANOVA/ANCOVA model.
(c) ANCOVA model, controlling for baseline, treatment, mood stabilizer, age, and
treatment by age interaction is used.

<u>Gender Subgroups</u>
The following table is copied from the submission.

Table S.5.14:
Adjusted Mean Change from Baseline to Week 6 in Y-MRS Total Score,
by Gender, LOCF Data Set, Efficacy Sample

Subgroup	Visit	Placebo N	Placebo Mean (a) (SE)	Aripiprazole N	Aripiprazole Mean (a) (SE)	Treatment Comparison (b) Aripiprazole - Placebo Difference	(95% CI)
MALE							
Mean Baseline		55	22.46 (0.65)	118	23.53 (0.44)	1.07	(-0.47,2.61)
Mean Change from Baseline to Week 6		55	-10.55 (1.08)	118	-13.40 (0.74)	-2.85	(-5.42,-0.29)
FEMALE							
Mean Baseline		75	22.89 (0.68)	129	22.73 (0.52)	-0.16	(-1.82,1.50)
Mean Change from Baseline to Week 6		75	-10.63 (0.89)	129	-13.26 (0.68)	-2.63	(-4.82,-0.45)

p-value for treatment by gender interaction: 0.911 (c)

Y-MRS Total Score is from 0 to 60.
A negative change from baseline signifies improvement.
ANOVA model, controlling for treatment and mood stabilizer, is used for baseline.
ANCOVA model, controlling for treatment, mood stabilizer and baseline value, is used for mean change from baseline
Means, differences in means, 95% CI for the differences are based on the ANOVA/ANCOVA model.
ANCOVA model, controlling for baseline, treatment, mood stabilizer, gender, and
treatment by gender interaction is used.

Mood Stabilizer Subgroups

As previously noted the sponsor reports no treatment group by "mood stabilizer" interaction effects on the primary efficacy variable. However, the following results are noted since they suggest a greater treatment group effect in the valproate subgroup on the primary, key secondary and PANSS efficacy variables than the lithium subgroup, while the latter subgroup showed greater trends for a treatment group effect on measures used to assess depressive symptoms. Observations noted and outline below are based on a review of Table 7.1.A (in the CSR) that shows efficacy results (on each efficacy rating measure) of each DB treatment group and of each "mood stabilizer" subgroup within each DB treatment group (refer to Appendix 10.2 of this review for a copy of Table 7.1A, shown as a series of tables):

- *The lithium subgroup did not reach statistical significance for a DB treatment group effect on most variables including*
  - *The primary and key secondary variables: p value > 0.25).*
  - *And other secondary efficacy variables tended to approach a p value of >0.05, except for the following variables that approached this level of significance:*
  - *CGI-BP S for depression (p=0.066)*
  - *MADRS total score (p=0.073)*
- *The valproate subgroup reached a p<0.05 for a DB treatment group effect on the following efficacy variables and also appeared to show a numerically greater magnitude for greater treatment group effects than observed in the lithium subgroup on a number of these variables):*
  - *Primary and key secondary efficacy variables (p<0.01 for each variable)*
  - *CGI-BP change for mania (subjects are rated on the degree of change from the preceding phase; on the degree of improvement or worsening, or showing no change); p<0.05*
  - *PANSS PSS (p<0.01)*
  - *PANSS Total score (p<0.025)*

- *PANSS hostility and cognitive subscale scores, each ($p<0.01$)*

- *Overall DB treatment group effects (with "mood stabilizer" subgroups, combined) reached $p<0.05$ on the primary and key secondary variables, as previously noted, in addition to the following efficacy variables:*
  - *CGI-BP-S overall ($p<0.05$)*
  - *CGI-BP (mania or overall, each) change from preceding phase ($p<0.05$)*
  - *PANSS total score ($p<0.025$)*
  - *PANSS PSS score ($p<0.01$)*
  - *PANSS hostility and cognitive subscale scores, each ($p<0.01$)*

The above results suggest a greater treatment group effect in the valproate subgroup on the primary, key secondary and PANSS efficacy variables than the lithium subgroup, (b) (4)

Upon examination of efficacy results by week of DB treatment (for LOCF and OC datasets, Tables S.5.6 and S.5.7, respectively as found in the CSR), the lithium group at least showed trends for greater improvement in the Arip compared to PBO Ss.

Potential subgroup differences on AEs of depression are described in Section 7 of this review (refer to Section 7.1 for a synopsis) that appear to be consistent with treatment subgroup differences observed on ratings of depression (above).

As a final but critical comment, the above subgroup comparisons can only be considered as preliminary due to the multiple comparisons that were made, together with small sample sizes and the non-randomized, non-stratified methods for assigning Ss to a given "mood stabilizer."

Psychotic Subgroups

The PANSS PSS was highly significant for a treatment group effect that could be a factor in influencing primary efficacy results. Moreover, this level of significance ($p<0.01$) was comparable to the level of significance reached for the primary efficacy variable (YMRS). The sponsor reports no treatment group by psychotic subgroup (presence versus absence) interaction effects on the primary and key secondary variables. Upon review of S.5.17 in the CSR it is noted that only 5 PBO Ss and 15 Arip Ss with psychotic features were included in this efficacy analysis. Therefore, it is difficult to interpret the results of this subgroup analysis. Yet, it is notable that the analyses of the primary efficacy variable for only those Ss without psychotic features were consistent with the results of the primary efficacy analyses as shown below (excerpt copied from Table S.5.17 of the CSR).

Table S.5.17:
Adjusted Mean Change from Baseline to Week 6 in Y-MRS Total Score,
by Psychotic Features at Baseline, LOCF Data Set, Efficacy Sample

Subgroup	Visit	Placebo N	Placebo Mean (a) (SE)	Aripiprazole N	Aripiprazole Mean (a) (SE)	Treatment Comparison (b) Aripiprazole - Placebo Difference	(95% CI)
PATIENTS WHITHOUT PSYCHOTIC FEATURES AT BASELINE							
Mean Baseline		125	22.46 (0.43)	230	22.58 (0.32)	0.12	(-0.92,1.16)
Mean Change from Baseline to Week 6		125	-10.30 (0.71)	230	-12.77 (0.52)	-2.47	(-4.18,-0.76)

Consequently, given the small sample size of psychotic subjects in the trial, along with results showing efficacy in the larger subgroup of non-psychotic subjects (based on the diagnosis during screening in the study), the presence of psychotic features does not suggest a significant influence on the primary efficacy results.

The following shows results from an integrated efficacy dataset (also provided in the review of N19 and copied from Module 2.7.3) that suggest efficacy may occur with the psychotic subgroup as well in monotherapy trials, although no interaction effects were revealed:

Subgroup Value	Placebo N	Placebo Mean (SE)	Aripiprazole N	Aripiprazole Mean (SE)	Treatment Comparison Aripiprazole - Placebo (a) Diff	(95% CI)	P-value	Treatment by Subgroup Interaction P-value (b)
Presence of Psychotic Symptoms								
Yes	143	-6.3 (1.1)	157	-11.5 (1.1)	-5.2	(-8.2, -2.2)	<.001	
No	555	-8.3 (0.4)	677	-11.0 (0.4)	-2.7	(-3.8, -1.6)	<.001	0.105

<u>*Mixed and Manic Subgroups and Failure to Show Efficacy in the Mixed Subgroup*</u>
Subgroup analyses of mixed and manic subgroups showed no interaction effects. However, the sample size of the PBO mixed group was only 33 Ss (N=61 in the Arip mixed group).

Upon review of Table S5.18 in the CSR for the adjunctive Study C-134, the treatment group difference (between Arip and PBO groups) in each subgroup was as follows (on the adjusted mean change of the YMRS):

- *Mixed subgroup: only -0.41*
- *Manic subgroup: -3.18.*

The observation of no to little treatment group difference in the mixed group may be spurious due to the small sample size.

Refer to the review of N19 showing efficacy on the YMRS in both mixed and manic subgroups in one of the 2 pivotal monotherapy trials that was reviewed. One of these 2 studies, Trail C-135, had larger sample sizes in the mixed subgroup (at least 60 Ss/treatment group). The treatment group difference in this monotherapy study (on the adjusted mean change on the YMRS) was:

- *Mixed subgroup: -3.4*
- *Manic subgroup: -3.7*

The other monotherapy trial, Study C-162 revealed:

- *No significant treatment effect in the mixed group.*
- *Yet the sample size of mixed Bipolar Ss was small: only approximately 30 Ss in each treatment group.*

Perhaps failure to show efficacy in the mixed group in the monotherapy study C-162 and in Study C-134 may be due to insufficient sample sizes.

A, subgroup analyses of an integrated monotherapy dataset showed small trends for a treatment group by subgroup interaction effect, but each subgroup showed adequate evidence for efficacy as follows (copied from the review of N19):

Subgroup Value	Placebo N	Placebo Mean (SE)	Aripiprazole N	Aripiprazole Mean (SE)	Treatment Comparison Aripiprazole - Placebo (a) Diff	(95% CI)	P-value	Treatment by Subgroup Interaction P-value (b)
Type of Episode								
Mixed	232	-9.0 (0.7)	294	-11.3 (0.6)	-2.2	(-4.0, -0.5)	0.012	
Manic	467	-7.3 (0.5)	541	-11.0 (0.5)	-3.7	(-5.0, -2.3)	<.001	0.071

(a) ANCOVA model with treatment, and study as main effects, and baseline Y-MRS Total Score as covariate.
(b) ANCOVA model with treatment, study and subgroup as main effects, baseline Y-MRS Total Score as covariate, and treatment-by-subgroup as interaction effect.

Note that the above results may be diluted by 1 out of the 5 trials included in this safety dataset that did not show significant overall treatment group differences on the primary efficacy variable (in the primary analysis).

The above observations are only considered as preliminary given a number of key limitations with interpreting the results in this manner. The results do not provide sufficient evidence to alter conclusions and recommendations in Section 9 of this review.

6.1.5 Clinical Microbiology

The undersigned reviewer is not aware of any special safety studies that were conducted for this sNDA.

6.1.6 Efficacy Conclusions

Study C…134 is positive for efficacy. See previous review comments. See Section 9 of this review for additional reviewer comments and for reviewer recommendations.

7 INTEGRATED REVIEW OF SAFETY

7.1 Synopsis, Methods and Review Strategy

Synopsis

The focus of this safety review is on results from the pivotal adjunctive Study C-134. The overall safety profile of serious adverse events (SAEs) and adverse dropouts (ADOs) in Study C-134 did not reveal a clinically remarkable and new safety signal. However, results on akathisia show the highest incidence of this event in the lithium-Arip subgroup of Study C-134, when numerically compared to the PBO-lithium Ss and the valproate subgroup, as shown later.

The N19 submission is cross-referenced in the current N20 submission (which provides Module 2.7.4). Safety observations from additional datasets summarized in the review of N19 (and that are not included in the current review) failed to reveal a clinically remarkable new safety signal.

The following is a synopsis of the safety results relevant to N20.

The Incidence of SAEs and ADOs

The incidence of SAEs and ADOs summarized in Section 7.1.2 of this review fail to reveal a clinically remarkable new safety signal.

Isolated SAEs and ADOs

Isolated SAEs and ADOs were noted by the undersigned reviewer in this review (the sponsor also noted a few of these Ss, as described in this review).

1 Death in Study C-134.

The most remarkable was a death during the OL extension phase of Study C-134. S C…134-14-106 is described in detail in Section 7.1.1 of this review. The following outlines some key information relevant to the clinical events that occurred in this S:

- *She was an obese 49 year old female who was receiving OL Arip and lithium (she had an otherwise unremarkable medical history and was receiving no concomitant medications).*
- *She was initially hospitalized for one night for an accidental overdose of lithium (level of 1.05 nmol/l) and was discharged on the following day.*
- *She developed drowsiness, slurred speech and dyspnea within 5 hours after discharge and was returned to the hospital by ambulance*
- *En route to the hospital (while in the ambulance) she developed severe bradycardia and hypotension and required resuscitation.*
- *She was admitted with type II respiratory failure, obstructive sleep apnea, and pulmonary hypoventilation.*

A more detailed description of this subject is provided in Section 7.1.1 of this review (including information provided in a 1/18/08 submission in response to inquiries about this S and other

inquiries). Based on the information provided by the sponsor the undersigned reviewer concludes the following. The events in this S are complicated and it is difficult to ascertain the potential role of Arip with these events.

1 S with loss of consciousness (ADO), *described in Section 7.1.2 of this review (C...134-15-32) had hypomania (SAE) and loss of consciousness (SAE leading to an ADO). This S "fell asleep" after receiving 10 mg of diazepam, orally. She could not be awakened, with a clinically remarkable Glasgow score of 3. The patient woke up "in less than an hour." QTcF was increased to 464 msec on the same day of this event that resolved at post-treatment. No other ECG or vital sign abnormalities were described. Moreover, this some question on whether or not she was compliant given her low lithium levels upon hospitalization. The S also had an upper-respiratory infection.*

Other cases of LOC (characterized by some as profound sedation) have been reported with an IM olanzapine formulation (under review in an NDA at the time of this writing) and isolated cases have been reported with other antipsychotic agents (that include oral formulations). However, it is not clear if these olanzapine cases are related to events of LOC or sedation observed in Arip Ss described in this review.

Additional individual Ss deaths, SAEs or ADOs are described in Sections 7.1.1-3 and in Appendix 10.3 of this review. Observations from these individual Ss do not justify reason for altering overall conclusions and recommendations relevant to this sNDA as provided in Section 9 of this review (for reasons discussed in this review).

<u>Observations in Adjunctive Subgroups of Study C-134</u>
The following sections in this review discuss potential interaction effects with primarily lithium and Arip adjunctive treatment:

- *Section 7.1.3.2 (on ADOs),*
- *Section 7.1.4.1 (refer to a subsection on "Adjunctive Subgroup Differences on EPS-related AEs),*
- *Section 7.1.4.2 (the sponsor's 1/18/08 response to questions regarding potential drug-drug interaction effects on safety) and*
- *Section 7.1.5.6 of observations by the undersigned reviewer that led to this inquiry.*

A number of limitations exist with the interpretation of these results such that results are considered preliminary (observations are based on multiple numerical comparisons on multiple dependent variables, together with small samples sizes and also given the non-randomized, non-stratified study design for assigning Ss to a "mood stabilizer," among other factors to consider).

Refer to the last section of this review for recommendations.

<u>Suicidality in Valproate-Arip Subjects and the Incidence of AEs of Depression in Adjunctive Subgroups</u>
Refer to Section 7.1.2 describing SAEs of suicidality and potentially related observations (regarding psychiatric AEs) among the adjunctive subgroups. These results are considered

speculative due to a number of limitations with making subgroup comparisons as previously noted.

Clinical Parameter Results
Results on clinical parameters failed to reveal a clinically remarkable new safety signal (that is not already described in approved labeling of the study drugs involved).

Methods and Review Strategy
Refer to Section 4 describing the trials, databases and review strategy.

7.1.1 Deaths

Deaths in Adjunctive Trials

Only one death was reported that occurred during adjunctive treatment (based on the line listing in Appendix 2.1.2.5 of the All-arip treated dataset in the appendix to Module 2.7.4 of N19). This subject had SAEs starting on Day 322 of the extension phase of Study C-134 and died on Day 416). The S is described in the review of N19. However, since this S is relevant to the current N20 submission a description of the S is also provided below (using text that is generally similar to text provided in the review of N19).

Subject C…134-17-106 was in the adjunctive treatment, Bipolar Study C-134. She experienced clinically remarkable events preceding her death (respiratory distress, severe bradycardia, severe hypotension, severe pulmonary hypoventilation, and moderate syncope); although she may have had pre-existing conditions contributing to these events (possibly sleep apnea and obesity). A review of the narrative revealed that the patient was hospitalized on Days 322-3223 of Arip-lithium treatment due to lithium overdose (but the level was not markedly elevation; 1.05 nmol/l). She was not described as having any other events at that time, except for ongoing weight gain. Yet, within 5 hours of discharge she returned to the emergency room with the reported SAE of type II respiratory failure and developed other "life-threatening" cardiorespiratory events, as summarized below.

The following description copy of the narrative on this subject was not provided in the review of N19, since this death occurred in the pivotal trial C-134 that is

more relevant to the current N20 sNDA:

Patient CN138134-17-106: Death due to SAE of pulmonary alveolar hypoventilation, discontinued due to SAEs of cardiac arrythmias, mild cardiac failure, obstructive sleep apnea, severe bradycardia, severe hypotension, syncope, and type II respiratory failure

Patient CN138134-17-106, a 49-year-old female with Bipolar I Disorder and relevant medical history of obesity (per supplemental report), was assigned to lithium at screening. At the end of the monotherapy phase, the patient was randomized to receive placebo on Day 1 of the double-blind phase. The patient was administered placebo and completed the double-blind phase on Day 43, and continued in the open-label extension phase.

On Day 365 (Day 322 of the extension phase), while at a dose of 30 mg aripiprazole and 750 mg lithium (the most recent lithium level was 0.42 mmol/L on Day 240), the patient accidentally overdosed on lithium and was taken to the hospital. The overdose was not a suicide attempt. Per SAE report, the patient's lithium level was 1.05 mmol/L. The investigator considered the overdose mild in intensity with a certain relationship to study medication. She was discharged on Day 366 (Day 323 of extension phase) and the event resolved without sequela. One other event ongoing at the onset of overdose was weight gain, which the investigator considered moderate in intensity with a possible relationship to the study medication. There were no concomitant medications taken within 14 days prior to the overdose.

Five hours after hospital discharge on Day 366 (Day 323 of extension phase), per SAE report, the patient was in type II respiratory failure and developed life-threatening severe bradycardia, severe hypotension, severe pulmonary hypoventilation, moderate syncope and cardiac arrythmias resulting in admission to the

Continued on the next page

ICU, ventilation, and discontinuation of study medication that same day. Lithium level at that time was 0.7 mmol/l. She was treated with atropine, flumazenil and cefotaxime. The bradycardia, hypotension, and syncope resolved in less than 24 hours, and the investigator considered them to have a possible relationship to the study medication. Cardiac arrythmias were assessed as moderate and possibly related to the study medication. The respiratory failure and pulmonary hypoventilation were both severe in intensity and had a possible relationship to the study medication.

On Day 366, the patient also experienced an SAE of obstructive sleep apnea, prolonging hospitalization and possibly contributing to continuing respiratory status problems, which the investigator considered mild and not related to study medication.

On Day 369, per SAE report, the patient went on a ventilator due to continued severe type II respiratory failure. Continuing episodic arrythmic events resulting in bradycardia and associated hypotension and syncope were reported per supplemental report. The patient was extubated on Day 371 and reintubated on Day 373. She was treated with acetaminophen, furosemide, ipratropium, and macrogol oral compound powder, and continued on atropine and flumenazil.

On Day 373 the patient experienced an SAE of mild cardiac failure, which the investigator considered mild and not related to study drug. She was treated with dobutamine, enoxaparin, hetastarch, insulin, iron, midazolam, morphine, remifentanil, magnesium sulfate, and sodium acid phosphate, cefotaxime, dexmedetomidine and flumazenil and continued on furosemide. The mild cardiac failure resolved on Day 376. On Day 378, the cardiac arrythmias were downgraded from moderate to mild in intensity. She received triamcinolone and remifentanil. The type II respiratory failure, improved in intensity from severe to moderate. On Day 380, the arrythmias resolved.

On Day 400, the respiratory failure became severe in intensity. On Day 404, the patient suffered from pulmonary alveolar hypoventilation considered severe in intensity and not related to study medication. On Day 416, the patient died. At the time of death, the patient's ongoing events of respiratory failure, cardiac arrythmias, and obstructive sleep apnea had not resolved.

Per SAE report, the cause of death was pulmonary alveolar hypoventilation secondary to nonserious morbid obesity. In the opinion of the investigator, the patient's confounding comorbidities were contributing factors to the fatal outcome. These included a morbid obesity, as well as suspicion of a possible Pickwick syndrome, and a suspicion of sick sinus syndrome. Further work-up was not provided. Patient's weight gain during the study was associated with lithium therapy and considered a nonserious adverse event.

There were no potentially clinically relevant ECG abnormalities reported during the study. Potentially clinically relevant (*) laboratory and vital sign abnormalities that occurred during the study are shown in the following table.

Test	Reference Range/ Units	Pre-randomization	Day 1	Day 22	Day 43	Day 72	Day 128	Day 240	Day 369
Uric acid	2.4 - 6.5 mg/dL	9.1*	7.7	9.6*	9.6*	11.6*	8.2	8.9*	NA
White blood cell count	4 - 10.3 x 10^3 c/uL	19.2*	18.3*	16.6*	22.5*	19.9*	16.3*	15.4	NA
Neutrophils	2.0 - 7.5 x10^9/L	NA	NA	NA	NA	NA	NA	NA	9.08*
Monocytes	0.2 - 1.0 x10^9/L	NA	NA	NA	NA	NA	NA	NA	1.42*
Hemoglobin	11.5 - 16.5 g/dL	NA	NA	NA	NA	NA	NA	NA	8.4*
Hematocrit	0.36 - 0.47 L/L	NA	NA	NA	NA	NA	NA	NA	.26*

Red Blood Cells	3.8 - 5.8 /pl	NA	NA	NA	NA	NA	NA	NA	2.80*
Potassium	3.5 - 5.1 mmol/L	NA	NA	NA	NA	NA	NA	NA	3.3*
Bicarbonate	21 - 29 mmol/L	NA	NA	NA	NA	NA	NA	NA	31*
Calcium	2.15 mmol/L	NA	NA	NA	NA	NA	NA	NA	2.02*
C-reactive Protein	0 - 1 ng/L	NA	NA	NA	NA	NA	NA	NA	161.5*
Blood pressure	180-150/90-50 mmHg	NA	NA	NA	NA	NA	NA	NA	70/20*
Heart Rate	≥120 - ≤50 bpm	NA	NA	NA	NA	NA	NA	NA	20*

The following additional information was provided in a 1/18/08 submission (upon inquiry about this S).

On Day 365 the S had admitted to taking more lithium "than she should have, to try to sleep, but denied overdose." She was found to be drowsy, with slight bilateral tremor, ataxia and dyspnea on examination. Vital signs and Glasgow Coma Scale rating were normal during her initial hospitalization on Day 365-366 and she was released at 1700 hours on day 366.

Continued on the next page

The following additional information is copied from the 1/18/08 submission:

At 2300hrs on Day 366, the patient's family contacted the principal investigator to report that the patient was drowsy, slurring her speech, and having difficulty breathing. The family confirmed that no further medications had been taken, as the patient was on constant watch since hospital discharge. The patient was transported to the hospital by ambulance. In the ambulance, the patient had severe bradycardia and hypotension, and required resuscitation. The patient was admitted to the hospital with type II respiratory failure, obstructive sleep apnea and pulmonary hypoventilation. The differential diagnosis was lithium toxicity causing the delayed severe bradycardia and hypotension, Pickwickian Syndrome, and acute respiratory infection. Clinically the patient presented with obesity, short neck, high pCO2 levels, flushed face, peripheral edema, and apnotic episodes resulting in severe bradycardia and hypotension. The family confirmed signs of sleep apnea. The hospital clinicians considered that the patient was unable to sustain adequate air entry and that the severe bradycardia and hypotension were related to apnotic events.

The investigator also notes in his response that the increased WBC count pre-randomization and at various times during the trial mainly consisted of neutrophilia, were attributed to resolving viral infection, and were not considered to be of clinical significance.

Based on the information provided by the sponsor, this S had a complicated clinical presentation and it is difficult to ascertain the potential role of Arip with these events.

7.1.2 Other Serious Adverse Events

Note the following: This subsection and subsections that follow that describe SAEs and ADOs are organized as follows:

1) Results on the Incidence of the Events
   a) First, the sponsor's summary tables on the incidence of the events are provided
   b) Reviewer comments (if needed) on the results of these tables, follow the tables.
2) Descriptions of Individual Ss
   a) A description of any individual S noted by the sponsor
   b) A description of any additional individual Ss noted by the undersigned reviewer (selected narratives were reviewed and noted).

Short Term DB Phase of Study C-134

The Sponsor's Summary Tables on the Incidence of SAEs (for each adjunctive subgroup)

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Table S.6.21:
Incidence of Treatment-Emergent Serious Adverse Events, Lithium Patients, Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	50	106
NUMBER OF MALE PATIENTS	22	52
NUMBER OF FEMALE PATIENTS	28	54
NUMBER OF PATIENTS WITH >=1 SAE	1(2.0)	1(0.9)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	0(0.0)	1(0.9)
AKATHISIA	0	1(0.9)
PSYCHIATRIC DISORDERS	1(2.0)	0(0.0)
DEPRESSION	1(2.0)	0

(M)/(F) Incidence of AEs adjusted for Males/Females.
Patients may have more than one SAE, but were counted in the overall total only once.
Each patient was also counted at most once for a particular SAE, even if the SAE occurred more than once for the same patient.
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Table S.6.22:
Incidence of Treatment-Emergent Serious Adverse Events, Valproate Patients, Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	80	147
NUMBER OF MALE PATIENTS	33	70
NUMBER OF FEMALE PATIENTS	47	77
NUMBER OF PATIENTS WITH >=1 SAE	2(2.5)	7(4.8)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	2(2.5)	6(4.1)
ANXIETY	0	1(0.7)
BIPOLAR I DISORDER	0	1(0.7)
CONFUSIONAL STATE	0	1(0.7)
MANIA	2(2.5)	1(0.7)
SUICIDAL IDEATION	0	1(0.7)
SUICIDE ATTEMPT	0	1(0.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0(0.0)	1(0.7)
OVERDOSE	0	1(0.7)

(M)/(F) Incidence of AEs adjusted for Males/Females.
Patients may have more than one SAE, but were counted in the overall total only once.
Each patient was also counted at most once for a particular SAE, even if the SAE occurred more than once for the same patient.
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The review of N19 (cross-referenced in N20) provides the incidence of the subgroups combined.

Reviewer Comments on the Incidence of SAEs

Suicidality in Valproate and Lithium Subgroups and the Incidence of Psychiatric Disorder AEs

Reviewer Comment. *The undersigned reviewer found a third S with suicidality (as discussed later regarding individual Ss with SAEs). Given this additional S the incidence of suicidality is as follows:*

- *3 valproate-Arip Ss (2%; 3/147) had suicidality compared to*
- *No Valproate PBO Ss (N=80) and*
- *No lithium-Arip or lithium PBO Ss (out of 106 and 50 Ss, respectively).*

The observation of all 3 cases occurring in the valproate-Arip subgroup may be serendipitous and suicidality is an expected event in this patient population.
A review of the narratives of these Ss revealed that:

- *At least 2 Ss had risk factors (S C…-115-477 and C…-40-212) and*
- *The third S had improvement of mania and developed insight on their debilitated state.*

These Ss are discussed in more detail in Appendix 10.3 of this review. In the opinion of the undersigned reviewer, it is unlikely that the suicidality in these Ss was due to valproate-Arip treatment (except for the S showing efficacy and who developed insight on his debilitated state).

In light of the 3 valproate-Arip Ss with suicidality (an event not reported in valproate-PBO Ss or lithium Ss), it is important to note the following subgroup differences on the incidence of psychiatric AEs.

- *The valproate-Arip subgroup had at least twice the incidence of psychiatric disorder AEs compared to valproate-PBO group while.*
- *Note that the majority of psychiatric disorder AEs in valproate-Arip was insomnia.*
- *Depression AEs occurred in 3.4% (5 Ss total) compared to 0 Ss in the Valproate-Arip and valproate-PBO subgroups, respectively.*

Appendix 2.1B-3:
Incidence of Treatment-Emergent AEs That Occurred in at Least 2 Percent of Patients in the Aripiprazole Group by Mood Stabilizer: 6-Week Combination Therapy Study in Acute Bipolar Mania (CN138134), Safety Sample

	Lithium		Valproate	
	Placebo	Aripiprazole	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	50	106	80	147
NUMBER OF MALE PATIENTS	22	52	33	70
NUMBER OF FEMALE PATIENTS	28	54	47	77
NUMBER OF PATIENTS WITH >=1 AES	30(60.0)	74(69.8)	40(50.0)	83(56.5)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	11(22.0)	23(21.7)	7(8.8)	29(19.7)
INSOMNIA	4(8.0)	8(7.5)	1(1.3)	12(8.2)
ANXIETY	0	6(5.7)	1(1.3)	3(2.0)
RESTLESSNESS	1(2.0)	3(2.8)	0	3(2.0)
DEPRESSION	4(8.0)	2(1.9)	0	5(3.4)

It is difficult to draw any final conclusions on the basis these results, given the multiple comparisons, potential floor effects on at lease some AEs, and sample size considerations, among other limitations with these data (and given the study design, as previously noted).

Another problem with interpreting the above results are differences in reporting rates in the PBO adjunctive subgroups (as shown above).

Section 6.1.4 of this review shows results of adjunctive subgroups on ratings of depression, mania or psychosis that may be consistent with some of the observations in comparing the 2 subgroups. However, adjunctive subgroups did not show a worsening of depressive symptoms (based on group mean change from baseline to treatment endpoint on efficacy ratings). These observations are only considered speculative given the limitations with interpreting these results.

Individual SAEs in the DB Phase of Study C-134

The sponsor does not note any individual S with an SAE in Section 2.1.3.2 in Module 2.7.4 (regarding SAEs in the DB phase of Study C-134).

Reviewer Comment on Individual SAEs. *The following are SAEs noted by the undersigned reviewer.*

A Possible Discrepancy between the Narrative, A Line Listing, and the above Table Regarding S C...134-42-108 with ***SAE of Akathisia***

Appendix 10.3 includes a discussion on apparent inconsistencies found in the sponsor summary table (shown in this review) compared to a line listing of SAEs and the narrative of S C…134-42-108 regarding the ***SAE term of somnolence.*** *However, these apparent inconsistencies do not alter overall conclusions regarding the safety profile, conclusions or recommendations in this review.*

An SAE of Overdose

The narrative of the S with an SAE term of overdose was reviewed since overdose could represent suicidality (S CN138134-22-13). The SAE was reported as accidental (took 45 mg of Arip instead of 15 mg on Day 2) and no other AEs or clinically remarkable events are described.

S with an SAE of Confusion

Confusion was found regarding the S below and the narrative of this S was reviewed (since it's vague yet suggests a clinically remarkable and potentially unexpected event). The following is a copy of the narrative of the subject with confusion to "space" and time in a 55 year old obese female on Day 40 of Arip-valproate treatment. This S had loss of appetite and depression as ongoing events but was not receiving any concomitant medications:

Patient CN138134-93-213: Hospitalized due to SAE of confusion

Patient CN138134-93-213, a 55-year-old female with Bipolar I Disorder and relevant medical history of obesity, was assigned to valproate at screening. At the end of the monotherapy phase, the patient was randomized to receive aripiprazole 15 mg on Day 1 of the double-blind phase.

On Day 40, at an aripiprazole dose of 15 mg and a valproate dose of 500 mg (the most recent valproate level 62.3 ug/mL on Day 36), the patient was hospitalized for confusion. Per SAE report, she was "moderately space- and time-disoriented." The investigator considered the event moderate in intensity with a possible relationship to study medication. This event was ongoing at the time of last follow-up.

Other events ongoing at the time of the confusion were appetite loss and depression. The investigator considered the appetite loss moderate in intensity, the depression mild in intensity, and the relationship to study medication possible for both events. No concomitant medications were taken within 14 days prior to the onset of the SAE of confusion.

There were no potentially clinically relevant laboratory, vital sign, or ECG abnormalities reported during the study.

This event is not unexpected for valproate and current approved labeling for Arip has a section 5.8 on potential cognitive and motor impairment. Moreover, cognitive impairment has been observed in patients with depressive symptoms.

OL Extension Phase of the Adjunctive Treatment Study C-134

The Incidence of SAEs

Upon request the sponsor provided the following results on SAEs (tables below were copied form their 1/18/08 response submission).

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Attachment Q.1C.1.1:
Incidence of Treatment-Emergent SAEs by Acute Phase Treatment and Overall:
Open Label Extension Phase in Study CN138134, Safety Sample

	Prior Treatment Placebo	Prior Treatment Aripiprazole	Overall
NUMBER OF PATIENTS SCREENED FOR AES	103	178	281
NUMBER OF MALE PATIENTS	43	89	132
NUMBER OF FEMALE PATIENTS	60	89	149
NUMBER OF PATIENTS WITH >=1 AES	11(10.7)	13(7.3)	24(8.5)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	10(9.7)	10(5.6)	20(7.1)
DEPRESSION	4(3.9)	3(1.7)	7(2.5)
MANIA	3(2.9)	2(1.1)	5(1.8)
BIPOLAR I DISORDER	0	3(1.7)	3(1.1)
MAJOR DEPRESSION	2(1.9)	0	2(0.7)
BIPOLAR DISORDER	0	1(0.6)	1(0.4)
DEPRESSIVE SYMPTOM	0	1(0.6)	1(0.4)
HYPOMANIA	1(1.0)	0	1(0.4)
SUICIDAL IDEATION	0	1(0.6)	1(0.4)
NERVOUS SYSTEM DISORDERS	3(2.9)	1(0.6)	4(1.4)
AKATHISIA	1(1.0)	0	1(0.4)
LOSS OF CONSCIOUSNESS	1(1.0)	0	1(0.4)
SOMNOLENCE	0	1(0.6)	1(0.4)
SYNCOPE	1(1.0)	0	1(0.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1(1.0)	2(1.1)	3(1.1)
OVERDOSE	1(1.0)	1(0.6)	2(0.7)
THERAPEUTIC AGENT TOXICITY	0	1(0.6)	1(0.4)
VASCULAR DISORDERS	1(1.0)	1(0.6)	2(0.7)
HYPERTENSION	0	1(0.6)	1(0.4)
HYPOTENSION	1(1.0)	0	1(0.4)
CARDIAC DISORDERS	1(1.0)	0	1(0.4)
ARRHYTHMIA	1(1.0)	0	1(0.4)
BRADYCARDIA	1(1.0)	0	1(0.4)
CARDIAC FAILURE	1(1.0)	0	1(0.4)
METABOLISM AND NUTRITION DISORDERS	0	1(0.6)	1(0.4)
DEHYDRATION	0	1(0.6)	1(0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1(1.0)	0	1(0.4)
HYPOVENTILATION	1(1.0)	0	1(0.4)
RESPIRATORY FAILURE	1(1.0)	0	1(0.4)
SLEEP APNOEA SYNDROME	1(1.0)	0	1(0.4)

The incidence of AEs for a particular System Organ Class is the incidence of all AEs in that System Organ Class.
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The following tables show the incidence of SAEs by adjunctive subgroups.

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Attachment Q.1C.1.2:
Incidence of Treatment-Emergent SAEs by Acute Phase Treatment and Overall:
Open Label Extension Phase in Study CN138134 (Lithium Patients Only), Safety Sample

	Prior Treatment Placebo	Prior Treatment Aripiprazole	Overall
NUMBER OF PATIENTS SCREENED FOR AES	36	70	106
NUMBER OF MALE PATIENTS	18	37	55
NUMBER OF FEMALE PATIENTS	18	33	51
NUMBER OF PATIENTS WITH >=1 AES	6(16.7)	7(10.0)	13(12.3)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	5(13.9)	5(7.1)	10(9.4)
DEPRESSION	2(5.6)	2(2.9)	4(3.8)
MANIA	1(2.8)	1(1.4)	2(1.9)
BIPOLAR I DISORDER	0	1(1.4)	1(0.9)
HYPOMANIA	1(2.8)	0	1(0.9)
MAJOR DEPRESSION	1(2.8)	0	1(0.9)
SUICIDAL IDEATION	0	1(1.4)	1(0.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1(2.8)	2(2.9)	3(2.8)
OVERDOSE	1(2.8)	1(1.4)	2(1.9)
THERAPEUTIC AGENT TOXICITY	0	1(1.4)	1(0.9)
NERVOUS SYSTEM DISORDERS	2(5.6)	1(1.4)	3(2.8)
LOSS OF CONSCIOUSNESS	1(2.8)	0	1(0.9)
SOMNOLENCE	0	1(1.4)	1(0.9)
SYNCOPE	1(2.8)	0	1(0.9)
CARDIAC DISORDERS	1(2.8)	0	1(0.9)
ARRHYTHMIA	1(2.8)	0	1(0.9)
BRADYCARDIA	1(2.8)	0	1(0.9)
CARDIAC DISORDERS	1(2.8)	0	1(0.9)
CARDIAC FAILURE	1(2.8)	0	1(0.9)
METABOLISM AND NUTRITION DISORDERS	0	1(1.4)	1(0.9)
DEHYDRATION	0	1(1.4)	1(0.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1(2.8)	0	1(0.9)
HYPOVENTILATION	1(2.8)	0	1(0.9)
RESPIRATORY FAILURE	1(2.8)	0	1(0.9)
SLEEP APNOEA SYNDROME	1(2.8)	0	1(0.9)
VASCULAR DISORDERS	1(2.8)	0	1(0.9)
HYPOTENSION	1(2.8)	0	1(0.9)

Reviewer Comment on Isolated SAEs of Respiratory, Vascular, Cardiac and Syncope in the Above Table. *Based on a review of the bolded PT SAE terms that were found in the narrative section in Appendix 2.2B of Module 2.7.4 of N19 (starting on page 5518 of the appendix) the above isolated cardiac, respiratory, and vascular disorder events and the SAE of syncope were all found as bolded SAE terms in the narrative of one S. This S was previously described in this review (Section 7.1.1), as a lithium-Arip treated S who died after initially presenting with "lithium overdose" reported as an SAE(S C...134-17-106).*

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Attachment Q.1C.1.3:
Incidence of Treatment-Emergent SAEs by Acute Phase Treatment and Overall:
Open Label Extension Phase in Study CN138134 (Valproate Patients Only), Safety Sample

	Prior Treatment Placebo	Prior Treatment Aripiprazole	Overall
NUMBER OF PATIENTS SCREENED FOR AES	67	108	175
NUMBER OF MALE PATIENTS	25	52	77
NUMBER OF FEMALE PATIENTS	42	56	98
NUMBER OF PATIENTS WITH >=1 AES	5(7.5)	6(5.6)	11(6.3)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	5(7.5)	5(4.6)	10(5.7)
DEPRESSION	2(3.0)	1(0.9)	3(1.7)
MANIA	2(3.0)	1(0.9)	3(1.7)
BIPOLAR I DISORDER	0	2(1.9)	2(1.1)
BIPOLAR DISORDER	0	1(0.9)	1(0.6)
DEPRESSIVE SYMPTOM	0	1(0.9)	1(0.6)
MAJOR DEPRESSION	1(1.5)	0	1(0.6)
NERVOUS SYSTEM DISORDERS	1(1.5)	0	1(0.6)
AKATHISIA	1(1.5)	0	1(0.6)
VASCULAR DISORDERS	0	1(0.9)	1(0.6)
HYPERTENSION	0	1(0.9)	1(0.6)

Reviewer Comments on the Incidence of SAEs. *It is difficult to interpret OL results (no PBO group). The overall incidence of events fails to reveal evidence for a clinically remarkable new safety signal.*

It is noted that most events are expected of the patient population, the study trial conditions, the study drugs, were complicated by other factors and/or were isolated events (refer to selected cases below).

Individual Ss with SAEs in the OL Phase of Study C-134

The sponsor does not note any individual S with an SAE during the OL Phase of Study C-134 (in Section 2.1.3.5 on SAEs in the All-Arip dataset that included Ss in the OL phase of Study C-134).

Selected narratives were reviewed and the Ss are summarized.

Patient CN138134-17-106 who died: *The S with vascular, respiratory, and cardiac disorder SAEs who also had the SAE of syncope was previous described Section 7.1.1 of this review.*

A S with loss of conscious (138134-15-32): *the narrative was reviewed since this term is clinically remarkable event and reported as an isolated SAE is unexpected. The narrative (copied from the submission) is shown below since it describes both loss of consciousness and QTcB prolongation and a non-Arip etiology was not reported.*

Patient CN138134-15-32: Hospitalized due to SAE of hypomania, discontinued due to SAE of loss of consciousness

Patient CN138134-15-32, a 52-year-old female with Bipolar I Disorder and relevant medical history of rheumatoid arthritis and allergies, was assigned to lithium at screening. At the end of the monotherapy phase, the patient was randomized to receive placebo on Day 1 of the double-blind phase. The patient completed treatment with placebo in the double-blind phase on Day 42, and continued in the open-label extension phase.

On Day 99 (Day 57 of extension phase), at an aripiprazole dose of 15 mg and a lithium dose of 0 mg (patient's last dose of lithium 500 mg was Day 95; lithium level was 0.5 mEq/L on Day 99), the patient experienced SAEs of hypomania and loss of consciousness and was hospitalized. Per SAE report, the patient had a hypomanic episode at home, and was sedated with diazepam in order to transport her to the hospital. At the hospital, she fell asleep and the staff was unable to wake her up. At the time of hospitalization, the patient had a QTcB interval of 499 msec. Study medication was discontinued due to loss of consciousness, and the patient received remedial therapy with clotiapine. The patient revived in less than an hour, and the hypomania resolved on Day 100 (Day 58 of extension phase). The investigator considered both of these events severe in intensity, the hypomania to have a possible relationship to study medication, and the loss of consciousness not likely related to study medication.

At the time of these events, the patient was also experiencing ongoing headaches and flu, both of which the investigator considered to be moderate in intensity and not likely related to study medication. No concomitant medication was taken within 14 days prior to the event.

There were no potentially clinically relevant vital sign or laboratory abnormalities reported during the study. Potentially clinically relevant (*) ECG abnormalities that occurred during the study are shown in the following table.

Test	Reference Range/Units	Pre-randomization	Day 43	Day 99	Day 105
QTc (Bazett)	> 450 msec	449	433	499*	422

Additional information on S C…134-15-32 Obtained Upon Inquiry

The sponsor was inquired about the above S and in a 1/18/07 response submission the sponsor noted that Arip and lithium were discontinued on Day 99 (according to the investigator SAE reporting). The CRF data specifies Day 94 for the last dose of lithium. The sponsor speculates that missed doses of lithium on Days 95-98 were due to patient noncompliance. On Day 99 the patient was given 10 mg diazepam orally for violent and aggressive behaviors (reported to have hypomania) at 1400 hours and the patient was hospitalized. One hour after receiving diazepam the S "fell asleep" and "could not be awakened." The Glasglow Coma scale score was 3. The S "regained consciousness" and was admitted for observation at 1830 hours. The sponsor provided additional laboratory and ECG results (QTraw and QTc values and heart rate) showing elevated CPK, AST (elevated to 53 u/l on Day 99, only), negative alcohol and drug screen, unremarkable ECG findings except for possibly the following: QTcF of 464 msec on Day 99 (compared to 433 at baseline on Day 43 and 389 on Day 105). The following is additional information copied from the response submission:

> The differential diagnosis at the time of hospitalization included CVA, brain hemmorhage, cardiovascular cause, or severe reaction to diazepam. A CT scan was performed and showed no abnormalities. Physical examination showed no changes from baseline. Serum toxicology screen and urinalysis were normal. An upper respiratory tract infection was diagnosed and treated. No other symptoms associated with the loss of consciousness occurred. The sedation with diazepam, possibly complicated by the URI, is felt by the investigator to be the cause of the loss of consciousness.

The sponsor was asked to provide copies of admission and discharge summaries but none could be found in the response submission (for any of the Ss in which this information was requested).

See previous reviewer comments in which this case does not alter conclusions and recommendations in Section 9 of this review.

Note that the previously described S (C...17-106) who died was also receiving Arip and lithium (and had elevated levels associated with an accidental overdose). This S was also reported to be initially drowsy (among other events) and developed syncope and more life-threatening SAEs of cardiac arrhythmias, respiratory failure among other SAEs. However, the clinical presentation of this S was complicated, as previously described.

Reviewer Comment of an Additional S with an SAE of Somnolence: *In light of the above S one other S had a potentially related* ***SAE of somnolence****, but the narrative of this S did not describe any episodes of loss of consciousness with this S (Patient CN138134-42-108). This S had* ***akathisia as an SAE that led to discontinuation*** *of the study drug (the narrative does not describe any somnolence or any unexpected and clinically remarkable events in this S).*

Reviewer Comment of S 138134-11-120 **(SAEs of therapeutic agent toxicity and dehydration).** *This was narrative reviewed since it involved lithium toxicity. However, the narrative failed to provide any clear role of Arip treatment in the events of this S that are known to occur with lithium treatment and in light of other factors that were likely contributory (e.g. was also receiving hydrochlorothiazide, had poor fluid and food intake for 5 days prior to the SAEs, her most recent lithium level was in the toxic range of 2.4 mEq/l several days before).*

S 138134-14-3 (SAEs of mania, suicidal ideation and overdose) *is noted due to suicidal ideation. The narrative describes the S as having "relationship problems," "panic-like attack," and depressive symptoms.*

Patient CN138134-22-13 (SAE of overdose). *The overdose was described as accidental (45 mg of Arip daily for 3 days).*

Longterm Ongoing Maintenance to Relapse Study C-189
The following table was copied from the sponsor's 1/18/08 response submission.

Attachment Q.1C.1.7:
Incidence of Treatment-Emergent SAEs by Combination Treatment and Overall:
Open Label Stabilization Phase in Study CN138189, Safety Sample

	Mood Stabilizer Lithium	Mood Stabilizer Valproate	Overall
NUMBER OF PATIENTS SCREENED FOR AES	45	87	132
NUMBER OF MALE PATIENTS	22	40	62
NUMBER OF FEMALE PATIENTS	23	47	70
NUMBER OF PATIENTS WITH >=1 AES	0	3(3.4)	3(2.3)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1(1.1)	1(0.8)
ACCIDENTIAL OVERDOSE	0	1(1.1)	1(0.8)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1(1.1)	1(0.8)
F UTERINE LEIOMYOMA	0	1(2.1)	1(1.4)
PSYCHIATRIC DISORDERS	0	1(1.1)	1(0.8)
BIPOLAR I DISORDER	0	1(1.1)	1(0.8)

(M) Incidence of AE adjusted for males (F) Incidence of AE adjusted for females
The incidence of AEs for a particular System Organ Class is the incidence of all AEs in that System Organ Class.
MedDRA Version: 9.1

Reviewer Comments on the Above Results. *The above results fail to reveal evidence for a clinically remarkable, new safety signal for Arip or adjunctive treatment.*

Individual Ss
The sponsor does not note any individual Ss in Section 2.1.3.5 of Module 2.7.4.

Reviewer Comments on Individual Ss. *The AE terms listed above were not unexpected for the population or for the study drugs and/or were isolated events. Therefore the narratives of the above events were not reviewed, except to verify that the "accidental overdose" (reported in S C…189-23-110) was not associated with suicidality or did not lead to any clinically remarkable events or sequelea associated with Arip overdose, as follows. Based on the narrative summary, "the patient misunderstood instructions to titrate" Arip and took 60 mg of Arip on days 17-26 without developing AEs (except for "bloating" on Day 22) or clinical abnormalities.*

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

See Section 4 of this review for a table enumerating ITT Safety subjects in each safety dataset.

The following provides more details on the disposition of subjects (overall dropout profile) for the pivotal efficacy trial which is the source of placebo controlled trial safety results used to support the proposed adjunctive treatment claim.

The following are excerpts from Table 5.1.B in the CSR of Study C-134 (the below excerpts were selected in order to show the disposition of randomized subjects in DB and disposition of subjects during the OL extension phases).

Number of Patients (%)

Patient Status	Placebo	Aripiprazole	Total
RANDOMIZED @	131	253	384
DISCONTINUED DURING DOUBLE-BLIND PHASE (d)	20 (15.3)	54 (21.3)	74 (19.3)
LACK OF EFFICACY	6 (4.6)	12 (4.7)	18 (4.7)
ADVERSE EVENT	7 (5.3)	23 (9.1)	30 (7.8)
SUBJECT WITHDREW CONSENT	5 (3.8)	9 (3.6)	14 (3.6)
LOST TO FOLLOW-UP	1 (0.8)	4 (1.6)	5 (1.3)
POOR/NON-COMPLIANCE	0	3 (1.2)	3 (0.8)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.8)	1 (0.4)	2 (0.5)
OTHER	0	1 (0.4)	1 (0.3)
MISSING @	0	1 (0.4)	1 (0.3)
COMPLETED 6-WEEK DOUBLE-BLIND PHASE (d)	111 (84.7)	199 (78.7)	310 (80.7)
DID NOT ENTER THE EXTENSION PHASE (d)	7 (5.3)	20 (7.9)	27 (7.0)
LACK OF EFFICACY	2 (1.5)	4 (1.6)	6 (1.6)
ADVERSE EVENT	1 (0.8)	6 (2.4)	7 (1.8)
SUBJECT WITHDREW CONSENT	0	6 (2.4)	6 (1.6)
POOR/NON-COMPLIANCE	1 (0.8)	0	1 (0.3)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.4)	1 (0.3)
ADMINISTRATIVE REASON BY SPONSOR	0	1 (0.4)	1 (0.3)
OTHER	3 (2.3)	2 (0.8)	5 (1.3)
ENTERED THE OPEN-LABEL EXTENSION PHASE (d)	104 (79.4)	179 (70.8)	283 (73.7)

(a) Percentages are based on the number of patients enrolled
(b) Percentages are based on the number of patients who completed Phase 1 (Screening and Psychotropic Washout)
(c) Percentages are based on the number of patients who entered Phase 2 (Mood Stabilizer Monotherapy and Baseline)
@ Patient CN138134-67-43 received double-blind study medication during Phase 2 in error

(d) Percentages are based on the number of patients randomized using the randomized treatment
@ Patient CN138134-67-43 received double-blind study medication during Phase 2 in error

Refer to Section 7.2.1.3 of this review for results on exposure for the DB phase and the ongoing OL extension phase of Study C-134 and for the OL stabilization (pre-DB) phase of the ongoing maintenance trial C-189.

7.1.3.2 Adverse events associated with dropouts

Short Term Adjunctive DB Phase of Study C-134

The Sponsor's Summary Tables of ADOs for Each Adjunctive Subgroup
The review of N19 provides the sponsor's table on the incidence of ADOs for the adjunctive subgroups combined, while tables below are of results in each subgroup (copied form the CSR).

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Table S.6.25:
Incidence of Treatment-Emergent Adverse Events That Led to Discontinuation,
Lithium Patients, Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	50	106
NUMBER OF MALE PATIENTS	22	52
NUMBER OF FEMALE PATIENTS	28	54
NUMBER OF PATIENTS WITH >=1 AE LEADING TO DISCONTINUATION	5(10.0)	16(15.1)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	1(2.0)	12(11.3)
AKATHISIA	0	9(8.5)
TREMOR	1(2.0)	3(2.8)
DISTURBANCE IN ATTENTION	0	1(0.9)
SEDATION	0	1(0.9)
SOMNOLENCE	0	1(0.9)
PSYCHIATRIC DISORDERS	4(8.0)	6(5.7)
AGITATION	0	1(0.9)
ANXIETY	0	1(0.9)
DEPRESSIVE SYMPTOM	0	1(0.9)
MANIA	0	1(0.9)
NERVOUSNESS	0	1(0.9)
RESTLESSNESS	0	1(0.9)
DEPRESSION	4(8.0)	0
GASTROINTESTINAL DISORDERS	0(0.0)	5(4.7)
DRY MOUTH	0	2(1.9)
NAUSEA	0	2(1.9)
GASTROINTESTINAL DISORDERS	0(0.0)	5(4.7)
ABDOMINAL DISCOMFORT	0	1(0.9)
CONSTIPATION	0	1(0.9)
DIARRHOEA	0	1(0.9)
LIP DRY	0	1(0.9)
RECTAL HAEMORRHAGE	0	1(0.9)
EYE DISORDERS	0(0.0)	1(0.9)
PHOTOPHOBIA	0	1(0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1(2.0)	1(0.9)
FATIGUE	1(2.0)	1(0.9)
IRRITABILITY	1(2.0)	0
INFECTIONS AND INFESTATIONS	0(0.0)	1(0.9)
LOWER RESPIRATORY TRACT INFECTION	0	1(0.9)
INVESTIGATIONS	0(0.0)	1(0.9)
BLOOD CREATINE PHOSPHOKINASE INCREASED	0	1(0.9)
METABOLISM AND NUTRITION DISORDERS	0(0.0)	1(0.9)
INCREASED APPETITE	0	1(0.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0(0.0)	1(0.9)
DRY SKIN	0	1(0.9)

(M)/(F) Incidence of AEs adjusted for Males/Females.
Patients may have more than one AE, but were counted in the overall total only once.
Each patient was also counted at most once for a particular AE, even if the AE occurred more than once for the same patient.
MedDRA Version: 9.1

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Table S.6.26:
Incidence of Treatment-Emergent Adverse Events That Led to Discontinuation,
Valproate Patients, Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	80	147
NUMBER OF MALE PATIENTS	33	70
NUMBER OF FEMALE PATIENTS	47	77
NUMBER OF PATIENTS WITH >=1 AE LEADING TO DISCONTINUATION	3(3.8)	14(9.5)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	1(1.3)	6(4.1)
AKATHISIA	1(1.3)	4(2.7)
TREMOR	0	2(1.4)
DISTURBANCE IN ATTENTION	0	1(0.7)
DIZZINESS	0	1(0.7)
SEDATION	0	1(0.7)
PSYCHIATRIC DISORDERS	2(2.5)	5(3.4)
DEPRESSION	0	2(1.4)
AGITATION	0	1(0.7)
SUICIDAL IDEATION	0	1(0.7)
SUICIDE ATTEMPT	0	1(0.7)
BIPOLAR I DISORDER	1(1.3)	0
MANIA	1(1.3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0(0.0)	2(1.4)
ARTHRALGIA	0	1(0.7)
MUSCLE FATIGUE	0	1(0.7)
MUSCULOSKELETAL STIFFNESS	0	1(0.7)
GASTROINTESTINAL DISORDERS	0(0.0)	1(0.7)
DIARRHOEA	0	1(0.7)
IRRITABLE BOWEL SYNDROME	0	1(0.7)
HEPATOBILIARY DISORDERS	0(0.0)	1(0.7)
HEPATIC FAILURE	0	1(0.7)

(M)/(F) Incidence of AEs adjusted for Males/Females.
Patients may have more than one AE, but were counted in the overall total only once.
Each patient was also counted at most once for a particular AE, even if the AE occurred more than once for the same patient.
MedDRA Version: 9.1

The sponsor notes in Module 2.7.4 (Section 2.1.4.2.6) that:

- Tremor and akathisia were most prominent in lithium-Arip treated subjects compared to the incidence of each of these types of ADOs in the valp-Arip group.

Reviewer Comments. *The Lithium-Arip and Lithium-PBO subgroups had a similar incidence of ADOs due to tremor (2.8%, 2.0%).*

Reviewer Comments on the Incidence of ADOs

Overall ADOs were reported in 12% and 6% of Arip and PBO groups, as specified in Section 6 of proposed labeling (refer to lines 1077-1079 of Item 2 markup.pdf of proposed labeling).

Akathisia was the most common AE leading to an ADO in Arip Ss (3%, 1% in the Arip and PBO groups).

A Potential Lithium-Arip Treatment Interaction Effect Based on the Incidence of ADOs and AEs

When examining the incidence of ADOs by PT AE categories, a lithium-Arip interaction effect on common ADOs (incidence of ≥5% in the Arip adjunctive group) is suggested by results shown below. Only common AEs (organ system and preferred term AEs) leading to an ADO are shown in the table (AEs with an incidence of ≥5% among any given Arip adjunctive subgroup). Results from an integrated bipolar monotherapy trial dataset are also shown for numerical comparison.

The Incidence of Common AEs Leading to ADOs Among any Given Arip-adjunctive Subgroup in the DB Phase of Study C-134 and as Compared to the Incidence in 3-week Monotherapy Bipolar-I trials (integrated dataset)

Adjunctive Subgroup	*Lithium*			*Valproate*			*Monotherapy***		
Treatment Group	*Arip N=106*	*PBO N=50*	*Delta**	*Arip N=147*	*PBO N=80*	*Delta**	*Arip N=917*	*PBO N=753*	*Delta**
System Organ Class Preferred Term									
Nervous System disorder	*11*	*2*	***9***	*4*	*1*	***3***	*4*	*1*	***3***
Akathisia	*9*	*0*	***9***	*3*	*1*	***2***	*2*	*0.3*	***2***
Gastrointestinal disorder	*5*	*0*	***5***	*1*	*0*	***1***	*1*	*1*	***0***

**Delta is the difference in the incidence between Arip and PBO groups within the adjunctive subgroup.*

*** These results are from the integrated Bipolar I (mania/mixed) monotherapy trial dataset (Trials C..007, -009, -062, -074, -077, -135 and -162) and were provided in summary tables in the parallel N19 submission. These results are also shown in Table 2.1.4.1 in Section 7.1.3.2 in the review of N19.*

One caveat regarding comparisons between Study C-134 and the monotherapy trial results is that treatment in the monotherapy trials was only 3-weeks long compared to 6-weeks of adjunctive treatment in Study C-134. However, the starting dose of Arip in Study C-134 was lower (only 15 mg) than that of most of the monotherapy trials (30 mg). Moreover, the treatment group difference (delta) in the valproate subgroup on the incidence of each of the above ADO categories was similar to that observed in the monotherapy trials (despite the longer duration of the DB phase in the adjunctive trial).

Additional observations based on a special search for extrapyramidal system-related AEs also provided results suggestive of an Arip-lithium interaction effect on akathisia and other events, as discussed in Sections 7.1.4.1 and 7.1.5.6 of this review.

Individual ADOs in the DB Phase of Study C-134

"Hepatic Failure" reported in a Valproate S

The sponsor noted (in Section 2.1.4.2 of Module 2.7.4) an ADO of "hepatic failure" in an Arip-valproate treated S (CN138134-135-575) with a history of hepatitis (but ALT 48 U/l and AST 20 U/l at baseline). The ADO occurred on Day 19 (ALT=96 U/l, AST=48 U/l) and "no further treatment" was required. The event "persisted at the time of the last follow-up."

Comment on the above event: *Refer to Depakote™ labeling which specifies that patients with* (b) (4) *this drug. Also refer to*

the bolded warning in Depakote™ labeling describing cases of hepatic failure that led to death. The narrative summary of the above S did not describe increase bilirubin or jaundice (but AE if "itchiness" was first reported on Day 3 of treatment). The S had a history of hepatitis.

It is not clear why hepatic failure was reported in the above ADO. Upon request the sponsor provided more information on this S (in 1/18/08 submission). The S did not show clinical evidence of failure based on the information provided (elevations normalized and no clinical signs suggestive of failure were described).

The sponsor does not note any ADOs in lithium treated Ss.

Individual ADOs noted by the Undersigned Reviewer

Photophobia

One ADO of photophobia is noted here in this review for the following reasons. This event is an atypical event (e.g. rarely reported in Arip Ss) and given observed results on AEs of photophobia as summarized later. This S was reported in the narrative to have "light sensitivity" (S C…-15-79), as well as akathisia, tremor and nausea leading to the ADO. The S was receiving lithium with Arip on Day 9 and a lithium level of only 0.6 mEq/l on Day 8. Most, if not all of these events are likely to be related to one or the other study drug. No other events or clinical abnormalities were described in the narrative of this S.

Photophobia is listed as a rare event under "Other Adverse Events Observed…" section of labeling. However this AE was not a rare event in Study C-134 as follows. Photophobia and visual disturbance were each reported as AEs in 3% of lithium-Arip Ss. Photophobia was not reported in any lithium-PBO treated S or in any S in the valproate subgroup (receiving PBO or Arip). Refer to Section 7.1.4.2 on a potential interaction effect of Arip-lithium treatment for at least the more common AEs (it is difficult to interpret results based on multiple subgroup comparisons, particularly regarding less common events).

Additional ADOs in Appendix 10.3 of this review

Refer to Appendix 10.3 for additional ADOs (noted by the undersigned reviewer) that are not considered as events that warrant a change in recommendations in conclusions and recommendations in Sections 1 and 9 of this review.

Appendix 10.3 also describes a review of bolded terms in the narrative section of ADOs (due to find any additional clinically remarkable and expected AE terms leading to an ADO). One potentially notable S was found and described in Appendix 10.3.

Appendix 10.3 also describes additional Ss with sedation or somnolence based on a special search conducted on the narratives (as described in Appendix 10.3).

Extension Phase of the Adjunctive Treatment Study C-134

Since the incidence of ADOs in the OL extension phase could not be found in N19 or N20 submission the sponsor was asked to provide this information (these ADOs were integrated with the All-Arip dataset that included multiple trials of different duration and study design).

The following table was copied from the sponsor's 1/18/08 response submission for ADOs in of Ss who received OL treatment during the 46-week OL adjunctive phase of Study C-134.

Attachment Q.1C.1.4:
Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Therapy by Acute Phase Treatment and Overall:
Open Label Extension Phase in Study CN138134, Safety Sample

	Prior Treatment Placebo	Prior Treatment Aripiprazole	Overall
NUMBER OF PATIENTS SCREENED FOR AES	103	178	281
NUMBER OF MALE PATIENTS	43	89	132
NUMBER OF FEMALE PATIENTS	60	89	149
NUMBER OF PATIENTS WITH >=1 AES	18(17.5)	12(6.7)	30(10.7)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
PSYCHIATRIC DISORDERS	11(10.7)	8(4.5)	19(6.8)
DEPRESSION	4(3.9)	2(1.1)	6(2.1)
MANIA	2(1.9)	1(0.6)	3(1.1)
M PREMATURE EJACULATION	0	1(1.1)	1(0.8)
MAJOR DEPRESSION	2(1.9)	0	2(0.7)
ALCOHOLISM	0	1(0.6)	1(0.4)
BIPOLAR DISORDER	0	1(0.6)	1(0.4)
BIPOLAR I DISORDER	0	1(0.6)	1(0.4)
DEPRESSIVE SYMPTOM	1(1.0)	0	1(0.4)
INSOMNIA	1(1.0)	0	1(0.4)
PSYCHOTIC DISORDER	0	1(0.6)	1(0.4)
RESTLESSNESS	1(1.0)	0	1(0.4)
NERVOUS SYSTEM DISORDERS	9(8.7)	4(2.2)	13(4.6)
AKATHISIA	2(1.9)	0	2(0.7)
EXTRAPYRAMIDAL DISORDER	1(1.0)	1(0.6)	2(0.7)
SEDATION	1(1.0)	1(0.6)	2(0.7)
DYSTONIA	1(1.0)	0	1(0.4)
HYPERKINESIA	1(1.0)	0	1(0.4)
NERVOUS SYSTEM DISORDERS	9(8.7)	4(2.2)	13(4.6)
HYPERSOMNIA	0	1(0.6)	1(0.4)
LOSS OF CONSCIOUSNESS	1(1.0)	0	1(0.4)
MEMORY IMPAIRMENT	1(1.0)	0	1(0.4)
PSYCHOMOTOR SKILLS IMPAIRED	0	1(0.6)	1(0.4)
SYNCOPE	1(1.0)	0	1(0.4)
TREMOR	1(1.0)	0	1(0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2(1.9)	0	2(0.7)
FATIGUE	2(1.9)	0	2(0.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1(1.0)	1(0.6)	2(0.7)
OVERDOSE	1(1.0)	1(0.6)	2(0.7)
CARDIAC DISORDERS	1(1.0)	0	1(0.4)
ARRHYTHMIA	1(1.0)	0	1(0.4)
BRADYCARDIA	1(1.0)	0	1(0.4)
CARDIAC FAILURE	1(1.0)	0	1(0.4)
HEPATOBILIARY DISORDERS	0	1(0.6)	1(0.4)
HEPATIC FUNCTION ABNORMAL	0	1(0.6)	1(0.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1(1.0)	0	1(0.4)
MUSCLE SPASMS	1(1.0)	0	1(0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1(1.0)	0	1(0.4)
HYPOVENTILATION	1(1.0)	0	1(0.4)
RESPIRATORY FAILURE	1(1.0)	0	1(0.4)
SLEEP APNOEA SYNDROME	1(1.0)	0	1(0.4)
VASCULAR DISORDERS	1(1.0)	0	1(0.4)
HYPOTENSION	1(1.0)	0	1(0.4)

Individual ADOs

The sponsor does not note any individual ADOs in Section 2.1.4.5 of Module 2.7.4 (All-Arip dataset ADOs that includes Arip Ss in the extension phase of C-134).

The undersigned reviewer notes the following individual ADOs
Refer to the previous section on SAEs that included Ss with events leading to ADOs (subjects 138134-17-106 and 138134-15-32 were previously summarized.

ADOs due to Liver Impairment
An ADO due to "liver failure" (elevated enzymes but no evidence of failure) in a previously summarized Valproate-Arip S that occurred on Day 19 during the DB phase (C…134-135-575).

"Hepatic function abnormal" was reported in S # C…134-95-257 on Day 43 of Arip-valproate treatment (on Day 1 of the extension phase). This S was listed in the ADO line listing found in Appendix 2.1.4.5 B of Module 2.7.4. See the narrative below (ADO of liver impairment) since this event could be drug related.

Patient CN138134-95-257: Discontinuation due to an AE of liver impairment

Patient CN138134-95-257, a 50-year-old male with Bipolar I Disorder and a relevant medical history of hypertension, was assigned to valproate at screening. At the end of the monotherapy phase, the patient was randomized to receive aripiprazole 15 mg on Day 1 of the double-blind phase. The patient completed the double-blind phase at aripiprazole 30 mg on Day 42, and continued in the open-label extension phase.

On Day 43 (Day 1of the extension phase), while at a dose of 30 mg aripiprazole and 1000 mg valproate (the most recent valproate level was 69.8 µg/mL on Day 43), the patient experienced liver impairment. The investigator considered the event moderate in intensity and certainly related to study medication. No remedial treatment was required. Study medication was discontinued on Day 52 (valproate) and Day 56 (aripiprazole) due to the event, whose outcome date is unknown.

No other events were ongoing at the time of this event. Concomitant medication taken within 14 days prior to the onset of the event was lercandipine.

No potentially clinically relevant vital sign abnormalities were reported during the study. Potentially clinically relevant (*) ECG and laboratory abnormalities that occurred during the study is shown in the following table.

Test	Reference Range/Units	Day -23	Day 1	Day 43
QTc (Bazett)	> 450 msec	450*	422	428
Alanine aminotransferase	8 - 45 U/L	15	17	164*
Aspartate aminotransferase	11 - 39 U/L	21	21	101

The sponsor was asked if any other Ss had liver related events and the sponsor responded (in their 1/18/08 submission) noting no additional ADOs (or SAEs) in Studies C-134 or C-189 in patients receiving valproate and Arip.

Only 3 additional Ss were noted to have increased hepatic enzymes but were not reported as AEs exceeding outlier criteria and did not require treatment or discontinuation of treatment (Ss C...134-25-147, C..134-96-114 and C...134-146-466). These Ss had transient elevations of approximately 3 times the upper limit of normal or less with no reported elevations in bilirubin.

Depakote labeling includes a black box warning on hepatoxicity.

Sedation or Loss of Consciousness
See Section 7.1.1 and 7.1.2 for cases of loss of consciousness and/or sedation, as well as Appendix 10.3 for additional cases (ADOs).

A word search for "seda" (searches words starting with these letters) was conducted (using the adobe acrobat search tool) to find any Ss in the narrative section of Ss in Study C-134 (starts on page 5518) in Appendix 2.2B of the Appendix pdf file of Module 2.7.4. None of the Ss found had syncopal episodes reported in the narratives (except for the 1 previously summarized S with an SAE of loss of consciousness after 10 mg diazepam and Arip treatment, S C…134-15-32). A search for "loss of" and for "synco" failed to reveal any additional Ss listed under Study C…134 in the narratives (in Appendix 2.2B).

Clarification on Problems Encountered by the Undersigned Reviewer on Line listings
Some subjects (in the sponsors line listing) may have had their events during the DB phase rather than the extension phase since study day numbers found on line listings provided in Attachments Q.5.11 and Q.5.11 did not appear to show a consistent numbering system (this line listing was provided in response to a request for line listings that included had verbatim). This inconsistency was found based on a comparison between the narrative and line listing regarding the study numbers specified of selected subjects. The sponsor was asked about these line listing and in response the sponsor explained that the line listings are correct (as specified in their 1/18/08 submission).

Longterm Ongoing Maintenance to Relapse Study C-189

The following table was copied from the sponsor's response submission dated 1/18/08.

Attachment Q.1C.1.8:
Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Therapy by Combination Treatment and Overall:
Open Label Stabilization Phase in Study CN138189, Safety Sample

	Mood Stabilizer Lithium	Mood Stabilizer Valproate	Overall
NUMBER OF PATIENTS SCREENED FOR AES	45	87	132
NUMBER OF MALE PATIENTS	22	40	62
NUMBER OF FEMALE PATIENTS	23	47	70
NUMBER OF PATIENTS WITH >=1 AES	6(13.3)	12(13.8)	18(13.6)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	2(4.4)	7(8.0)	9(6.8)
AKATHISIA	2(4.4)	2(2.3)	4(3.0)
SEDATION	0	4(4.6)	4(3.0)
DYSARTHRIA	0	2(2.3)	2(1.5)
COGNITIVE DISORDER	0	1(1.1)	1(0.8)
TREMOR	1(2.2)	0	1(0.8)
PSYCHIATRIC DISORDERS	4(8.9)	4(4.6)	8(6.1)
RESTLESSNESS	1(2.2)	1(1.1)	2(1.5)
ANXIETY	1(2.2)	0	1(0.8)
BIPOLAR I DISORDER	0	1(1.1)	1(0.8)
DEPRESSION	0	1(1.1)	1(0.8)
INSOMNIA	1(2.2)	0	1(0.8)
ORGASM ABNORMAL	0	1(1.1)	1(0.8)
PANIC REACTION	1(2.2)	0	1(0.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1(2.2)	2(2.3)	3(2.3)
FATIGUE	0	2(2.3)	2(1.5)
IRRITABILITY	1(2.2)	0	1(0.8)
GASTROINTESTINAL DISORDERS	1(2.2)	1(1.1)	2(1.5)
SALIVARY HYPERSECRETION	1(2.2)	0	1(0.8)
VOMITING	0	1(1.1)	1(0.8)
INFECTIONS AND INFESTATIONS	0	1(1.1)	1(0.8)
NASOPHARYNGITIS	0	1(1.1)	1(0.8)

The incidence of AEs for a particular System Organ Class is the incidence of all AEs in that System Organ Class.
MedDRA Version: 9.1

Reviewer Comments. *The above results do not show evidence for a new and clinically remarkable safety signal (some events are expected of the study drugs or the patient population or were isolated events).*

Individual ADOs

The sponsor does not note any individual ADOs in Section 2.1.4.5 of Module 2.7.4 (the section on ADOs of All-Arip treated Ss).

Individual ADOs noted by the Undersigned Reviewer

Individual ADOs are provided in Appendix 10.3. Although these cases are noted they do not provide sufficient reason for altering conclusions and recommendations in Sections 1 and 9 of this review.

7.1.3.3 Other significant adverse events

See previous sections and subsections that follow involving special searches and subsections on outliers and "marked outliers" under each clinical parameter section of this review (under 7.1.4, 7.1.5, and so on), as well as other safety related sections.

7.1.4 Other Search Strategies

Selected reviewer searches were conducted in narrative sections of the submission (of SAEs or ADOs) and are described in previous sections in which they apply.

Searches conducted by the sponsor either in the original submission or upon request are described in this section of the review.

7.1.4.1 Sponsor Search Strategies

Reviewer Comments. *Results of sponsor search strategies for AEs of "special interest" are summarized in the review of N19. The only notable individual Arip S (in Study C…134) that was described in this section of AEs of "special interest" in the N19 review or that is not described elsewhere in this review is the following S.*

Seizures

The only lithium-Arip treated subject reported by the sponsor to have an AE of seizure was the following subject during the OL phase of Study C-134:

- CN138134-96-296, a 25-year-old woman, was started on aripiprazole 15 mg/day co-administered with lithium. On Day 183, during the extension phase of the study and while she was still on treatment, she experienced a non-serious AE of clonic convulsion. The event was reported as moderate in severity and possibly related to study treatment. The patient also experienced loss of consciousness for one minute and headache. All events resolved on the day of onset.

The above subject was found by the sponsor by conducting a search of the AE database for all Phase 2/3/4 studies using the following search terms: seizure, convulsion, grand mal, petit mal, epilepsy, fits, EEG, electroencephalogram, and lobe.

Reviewer Comments.

A review of the narrative of the above S failed to reveal any new and clinically remarkable safety signal (not already addressed in labeling). The S had a history of hypothyroidism, was receiving thyroid replacement therapy (a risk factor for seizure) and there was suggestion of noncompliance (based on lithium levels). As discussed later and in Section 4.4 of this review the narrative of this S did not described the above event (that apparently occurred while she was hospitalized).

It is not clear if the sponsor searched verbatim terms, as well as preferred terms and other limitations require consideration when interpreting the results of their search for seizures (as described in Module 2.7.4 of N19).

Events of Loss of Consciousness and Tonic Clonic Episode in the Narrative of S C…-96-296
It should be noted that a description of the above events of tonic clonic episode and loss of consciousness were not found in the patient's narrative summary in Appendix 2.2B in the Appendix pdf of Module 2.7.4 of N19.

The narrative specifies the SAE of worsening Bipolar disorder (manic episode) leading to hospitalization on Day 183 (worsening of Bipolar disorder was reported on Day 178). It is not clear why the narrative does not include this information. The narrative indicates that treatment was implemented during her hospitalization, however details were not reported." It is also stated that "no other events were ongoing at the time of this event." Refer to Section 4.4 of this review which includes a copy of the narrative on this S (as found in the Appendix 2.2B).

EPS-related AEs
The following observations and reviewer comments that follow are copied from the review of N19.

> Section 2.1.5.1 of Module 2.7.4 provides the incidence of AEs (Preferred Term & Organ System) using a categorization system for grouping AEs into 5 categories: dystonic events, akathisia events, Parkinsonian event, Dyskinetic Events, Residual Events (pages 258-259 of the Module provides more details). Results from ratings scales were also provided.

EPS-related AEs in Study C-134 (copied from the review of N19):

- EPS-related events (excludes akathisia-related events): 15% (39/253), 8% (11/130)
- Akathisia-related events: 19% and 5% (also a common event under other categories shown in Table 2.1.5.1E).
- Other common Preferred Term event categories (incidence of ≥5% in Arip Ss):
  - Tremor: 9% and 6%
  - Extrapyramidal disorder: 5%, 1%
- Tardive dyskinesia: not reported (not found in Table 2.1.5.1E)
- ADOs due to EPS-related AEs: 5.9%, 1.5% in which all of these ADOs were due to akathisia or tremor (Arip; 5.1%, PBO; 0.8% and Arip; 2.0%, PBO; 0.8% for each type of ADO, respectively)

Rating Scale results coped from the review of N19:

- Statistically significant worsening was observed on the SAS total score and the Barnes Akathisia Global Clinical Assessment scale (Arip; 0.73, PBO; 0.07 and Arip; 0.30, PBO; 0.11 on each scale, respectively).
- No statistical group difference was observed on the AIMS total score.

Adjunctive Subgroup Differences on EPS-related AEs

The following table shows EPS-related AEs by adjunctive subgroups for common AEs (≥5% incidence) in any given Arip group (excerpts of Appendix 2.1.5.1E in Module 2.7.4).

Appendix 2.1.5.1E:
Incidence of Treatment-Emergent EPS-Related AEs by Mood Stabilizer:
6-Week Combination Therapy Study in Acute Bipolar Mania (CN138134), Safety Sample

	Lithium		Valproate	
	Placebo	Aripiprazole	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	50	106	80	147
NUMBER OF MALE PATIENTS	22	52	33	70
NUMBER OF FEMALE PATIENTS	28	54	47	77
NUMBER OF PATIENTS WITH >=1 AES	6(12.0)	40(37.7)	12(15.0)	31(21.1)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
EPS-RELATED AE	6(12.0)	40(37.7)	12(15.0)	31(21.1)
AKATHISIA EVENTS	2(4.0)	30(28.3)	5(6.3)	17(11.6)
NON-AKATHISIA EVENTS	4(8.0)	18(17.0)	7(8.8)	21(14.3)
AKATHISIA EVENTS	2(4.0)	30(28.3)	5(6.3)	17(11.6)
AKATHISIA	2(4.0)	30(28.3)	5(6.3)	17(11.6)
PARKINSONISM EVENTS	4(8.0)	17(16.0)	5(6.3)	17(11.6)
TREMOR	4(8.0)	14(13.2)	4(5.0)	9(6.1)
EXTRAPYRAMIDAL DISORDER	0	2(1.9)	1(1.3)	10(6.8)

Reviewer Comment. *In light of the previous adjunctive group differences on the incidence of ADOs of akathisia (also observed with the incidence of ADOs due to nervous system and gastrointestinal disorder AEs), note the following treatment group differences (between Arip and PBO groups) on the incidence of EPS-related AEs within each adjunctive subgroup (based on the above results):*

- *Akathisia*
  - *DB Treatment group difference in lithium Ss: 24%*
  - *DB Treatment group difference in valproate Ss: 6%*
- *Tremor*
  - *DB Treatment group difference in lithium Ss: 5%*
  - *DB Treatment group difference in valproate Ss: 1%*

See the last section of this review for additional comments and recommendations.

7.1.4.2 Additional Search Strategies or Data Analyses Relevant to a Potential Adjunctive Treatment Interaction Effect

The sponsor was asked to explore their data for a potential interaction effect of Arip and lithium treatment, given the narrow therapeutic index with lithium and in light of adjunctive treatment group differences on ADOs and AEs. Appendix 10.3 summarizes selected results from the sponsors 1/18/08 submission, while subsections below describe potentially positive findings (but

these are only considered as preliminary due to limitations with making these subgroup comparisons for reasons previously described).

The Incidence of AEs in each Adjunctive Subgroup
Given the higher incidence of akathisia and tremor in lithium-Arip subjects compared to other subgroups (as previously described in this review), the sponsor acknowledges that "lithium may be exaggerating the effects of antipsychotics." The sponsor attributes akathisia to an effect of adjunctive treatment as an EPS AE.

In response to the question of potential Valproate-Arip interaction effects, the sponsor concludes that the valproate subgroup did not show evidence for a potential interaction effect of Arip and valproate treatment (based on the incidence of AEs specified in their response).

Refer to Sections 7.1, and 7.1.5 of this review regarding observations on these AES.

Reviewer Comment. *A potential masking effect on at least some of the more common AEs does not appear to exist based on the incidence of AEs (as noted by the sponsor). However, a potential masking effect on other less common AEs that are known to be associated with lithium toxicity may exist, but such a potential masking effect may be difficult to detect due in Study C-134 (e.g. due to a potential floor effect). Also consider the potential for confusing an AE as being due to one drug versus the other (e.g. sedative effects, restlessness) in which the events may be attributed to Arip when they may actually be early signs of lithium toxicity. Akathisia is one possible example in the potential for confusing this event as being due to Arip rather than the event being considered restlessness observed with lithium. However, patients with lithium toxicity often present with multiple AEs that can generally be detected by the clinician and often also by the patient who has experience with lithium treatment. A discussion of akathisia follows.*

Additional Analyses of AEs of Akathisia and Tremor
The sponsor was asked to conduct several analyses regarding akathisia and tremor, in order to better characterize these events as representing lithium versus Arip induced effects (e.g. since restlessness and giddiness associated with lithium may be confused as akathisia associated with Arip). However, the sponsor identified several limitations with how these AEs were recorded (e.g. investigators were not instructed to differentiate fine from coarse tremor when reporting tremor). Therefore the results of their analyses are not summarized in this review.

AEs Leading to Dose Reduction
The question regarding AEs associated with dose reduction was addressed by the sponsor, but the sponsor notes a number of limitations with the analyses of their data that they conducted. The key problem with their analyses is that the reason for a dose reduction of a "mood stabilizer" was not recorded (the CRFs do not specify the reason for dose reductions). Consequently, the sponsor conducted an analyses of AEs that coincide with a dose reduction that was maintained over a period of at least 3 consecutive days.

D*espite the key limitations with interpreting the results provided upon requested (and as noted by the sponsor), the largest treatment group difference (between Arip and PBO Ss) on AEs temporally associated with dose reductions (of at least 3 days in duration) was observed with akathisia in the lithium subgroup, as follows:*

- *Treatment group differences (between Arip and PBO) on the incidence of overall AEs:*
  - *12% in the lithium group versus 3% in the valproate group.*
- *Treatment group differences on akathisia:*
  - *7% in the lithium subgroup versus 1% in the valproate subgroup.*

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Generally standard methods for monitoring and reporting for adverse events (AEs) were employed in the sponsor's trials. Any special rating scales that might be considered as elicited AEs are also described, elsewhere, in the appropriate subsection of this review.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The MedDRA classification system was used. The version used for each pivotal MDD trial was the version that was available at the time of the database lock.

Reviewer Comments. *Each AE categorization system has its inherent limitations. The MedDRA system is now considered the preferred categorization system by the Agency at this time, to the knowledge of the undersigned reviewer.*

7.1.5.3 Incidence of common adverse events

The incidence of AEs (independent of the type of AE) during the 6-week DB adjunctive phase of Study -134 was less than the incidence of AEs in the 3-week monotherapy trial dataset as follows:

- Study -134: 62% and 54% in Arip and PBO Ss,
- 3-week monotherapy Bipolar trial dataset: 83% and 72%, respectively (refer to the review of N19 for details).

7.1.5.4 Common adverse event tables

The following table of AE results is shown, as shown in the review of the N19 parallel submission to this N20 submission (as provided by the sponsor).

Table 2.1B-1: Incidence of Treatment-Emergent AEs Reported in at Least 2 Percent of Patients in the Aripiprazole Group: 6-Week Combination Therapy Study in Acute Bipolar Mania (CN138134), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	130	253
NUMBER OF MALE PATIENTS	55	122
NUMBER OF FEMALE PATIENTS	75	131
NUMBER OF PATIENTS WITH >=1 AES	70(53.8)	157(62.1)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	27(20.8)	92(36.4)
AKATHISIA	7(5.4)	47(18.6)
TREMOR	8(6.2)	23(9.1)
HEADACHE	8(6.2)	14(5.5)
EXTRAPYRAMIDAL DISORDER	1(0.8)	12(4.7)
DIZZINESS	1(0.8)	11(4.3)
SEDATION	2(1.5)	11(4.3)
PSYCHIATRIC DISORDERS	18(13.8)	52(20.6)
INSOMNIA	5(3.8)	20(7.9)
ANXIETY	1(0.8)	9(3.6)
DEPRESSION	4(3.1)	7(2.8)
RESTLESSNESS	1(0.8)	6(2.4)
GASTROINTESTINAL DISORDERS	21(16.2)	49(19.4)
NAUSEA	6(4.6)	21(8.3)
DIARRHOEA	7(5.4)	11(4.3)
VOMITING	0	10(4.0)
SALIVARY HYPERSECRETION	2(1.5)	9(3.6)
DRY MOUTH	1(0.8)	6(2.4)
INFECTIONS AND INFESTATIONS	14(10.8)	26(10.3)
NASOPHARYNGITIS	3(2.3)	7(2.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	9(6.9)	22(8.7)
FATIGUE	5(3.8)	7(2.8)
INVESTIGATIONS	5(3.8)	14(5.5)
WEIGHT INCREASED	1(0.8)	6(2.4)

The incidence of AEs for a particular System Organ Class is the incidence of all AEs in that System Organ Class.
MedDRA Version: 9.1

Refer to the review of N19 for results of the 3-week monotherapy trials.

7.1.5.5 Identifying common and drug-related adverse events

The following results were also provided in the review of N19. However, reviewer comments that follow are specific to N20 (and were not included in the review of N19).

Common AEs (≥5% incidence in Arip patients that was at least twice that of placebo) in the DB phase of Study C-134:

akathisia, insomnia, and extrapyramidal disorder.

The above results are compared to the following common AEs (meeting the above criteria) in the 3-week placebo controlled Bipolar Trial Dataset (see table below):

akathisia, sedation, extrapyramidal disorder, and restlessness

Reviewer Comments. *Note that insomnia was among the common AEs (meeting the above specified criteria) in the 6-week adjunctive phase Study -134 while sedation (instead of insomnia) was among the common AEs in the 3-week monotherapy trials. See the next section for results of each adjunctive treatment group in Study -134.*

7.1.5.6 Additional analyses and explorations

The Incidence of AEs by Adjunctive Treatment Subgroups in Study C-134

Results Noted by the Sponsor

A summary of results of AEs by adjunctive treatment subgroups cannot be found in Module 2.7.4 of N19 (section 2.1B). However, in the CSR for Study -134 (in Section 8.5.1) the sponsor describes several aspects of their results that includes the following observation regarding the incidence of AEs for each adjunctive treatment subgroup:

> Akathisia and tremor showed a higher incidence in the Lithium-Arip subgroup (28% and 13%, respectively) than in the Valp-Arip subgroup (12% and 6%, respectively).

Reviewer Comments. *See Appendix 10.3 for results of the incidence of AEs of PBO and Arip groups within each adjunctive treatment subgroup, as found in the submission (for AEs with an incidence of ≥2% in Arip groups).*

While the following results can only be considered as preliminary (as previously discussed) some of these results show robust findings on akathisia. The greatest treatment group difference (between Arip and PBO groups) was observed on the incidence of AEs of akathisia or tremor in the lithium adjunctive subgroup as numerically compared to the treatment group difference on incidence in the valproate adjunctive subgroup as shown in the following table (and as provided in more detail later)

	Study C-134 Adjunctive Bipolar I mania/mixed		***Monotherapy Bipolar Trials mania/mixed****	***Adjunctive MDD Trials***	***All-Arip Dataset*** These results only show the incidence in Arip treated subjects (not delta)***		
	Lithium	***Valproate***					
	*Delta**	*Delta**	*Delta**	*Delta**	*Bipolar I (mania), or Bipolar I (depressed) or MDD trials*	*Schizophrenia trials*	*"Dementia" Trials*
AEs							
Akathisia	***24%***	*6%*	*9%*	***21%***	***16-25%***	*7%*	*0.4%*
Tremor	***5%***	*1%*	*3%*				
ADOs							
Akathisia	***9%***	*2%*	*2%*		***3-5%***	*0.2%*	*0.9%*

**Delta is the difference between Arip and PBO groups (for Study C-134 this difference is provided for each of the adjunctive subgroups, as specified, and for the adjunctive MDD trials this difference is provided for all adjunctive Ss, since most of these Ss were receiving SSRIs). The MDD trial dataset is of 2 adjunctive MDD short-term Phase III trials in which most of the Ss received SSRIs (with a small number receiving venlafaxine instead) with Arip or PBO. These trials and the results were included in the review of N18 for a MDD adjunctive claim*

***These results are from the integrated Bipolar I (mania/mixed) monotherapy trial dataset (Trials C..007, -009, -062, -074, -077, -135 and -162) and were provided in summary tables in the parallel N19 submission. These results are also shown in Table 2.1.4.1 in Section 7.1.3.2 in the review of N19.*

****These results are from All-Arip treatment dataset as found in Module 2.7.4 of N19. The incidence for the Arip-treated Ss within a give patient population is shown (of integrated trial datasets of trials examining a given patient population).*

The following table is copied from Section 7.1.3.2 to allow for comparisons with results of the above table (for the convenience of the reader):

The Incidence of Common AEs Leading to ADOs Among any Given Arip-adjunctive Subgroup in the DB Phase of Study C-134 and as Compared to the Incidence in 3-week Monotherapy Bipolar-I trials (integrated dataset)

Adjunctive Subgroup	*Lithium*			*Valproate*			*Monotherapy***		
Treatment Group	*Arip N=106*	*PBO N=50*	*Delta**	*Arip N=147*	*PBO N=80*	*Delta**	*Arip N=917*	*PBO N=753*	*Delta**
System Organ Class Preferred Term									
Nervous System disorder	*11*	*2*	***9***	*4*	*1*	***3***	*4*	*1*	***3***
Akathisia	*9*	*0*	***9***	*3*	*1*	***2***	*2*	*0.3*	***2***
Gastrointestinal disorder	*5*	*0*	***5***	*1*	*0*	***1***	*1*	*1*	***0***

**Delta is the difference in the incidence between Arip and PBO groups within the adjunctive subgroup.*

*** These results are from the integrated Bipolar I (mania/mixed) monotherapy trial dataset (Trials C...007, -009, -062, -074, -077, -135 and -162) and were provided in summary tables in the parallel N19 submission. These results are also shown in Table 2.1.4.1 in Section 7.1.3.2 in the review of N19.*

Adjunctive MDD Trials

The table above also provides results from the MDD All-Arip dataset (in the above table). To the knowledge of the undersigned reviewer, this dataset mostly represents Ss receiving adjunctive treatment (primarily SSRIs with only a small proportion of Ss receiving venlafaxine or a related drug).

As discussed in the review of N18 for an adjunctive MDD claim (in which the adjunctive MDD trial results were reviewed), a potential exaggerated effect of adjunctive antidepressant-Arip treatment was observed on the incidence of at least the following events in the 2 pivotal adjunctive MDD trials (the incidence in the adjunctive Arip and adjunctive PBO groups are shown):

- *Overall ADOs: 6% and 2%*
- *AEs of akathisia: 25% and 4%*

The large majority of these Ss were receiving SSRIs.

The Sponsor's Explanation for the Above Results and Reviewer Comments

Given the above results on ADOs and AEs due to akathisia the sponsor was asked to explain these results. The sponsor's 1/18/08 provides a number of plausible explanations such as the following:

- *Previous antipsychotic exposure may influence risk of akathisia (less risk with past exposure). Previous exposure (as defined by the sponsor) appeared to be much less in*

the Bipolar and MDD patients (17% and <1%, respectively) than in the Schizophrenia patients (79%), as estimated by the sponsor and based on a number of assumptions regarding these estimates (as discussed on pages 59-60 of the 1/18/08 response submission).

- *Other differences or potential differences in the patient populations were noted (age, inpatient versus outpatient, more acutely psychotic versus less psychotic) that could lead to differences in the reporting rates of akathisia. These explanations are plausible explanations.*
- *The sponsor also notes possible differences to the sensitivity of MDD and Bipolar patients to EPS and cites some past studies showing the incidence of EPS in these populations.*

Although the sponsor's explanations are plausible, the sponsor fails to address the potential role of adjunctive treatment. Moreover, the sponsor does not explain treatment group differences among the subgroups of Study C-134. Finally the sponsor does not address the potential role of adjunctive treatment when making preliminary comparisons of these results to those of the monotherapy trials and the adjunctive MDD trials. Yet these comparisons can only be considered as preliminary given the nature of these datasets and limitations with multiple comparisons.

The study design of Study C-134 with respect to treatment with lithium and valproate also presents difficulties with interpreting the results of adjunctive subgroups.

Refer to Section 9 of this review for further comment.

Results of Additional Common AEs among Adjunctive Treatment Subgroups

Lithium Adjunctive Subgroups

The Incidence of Common AEs in Lithium-Arip subjects (AEs with an incidence of 5% that was at least twice that of placebo & Additional AEs)			
Organ System *Adverse Event*	***Arip***	***PBO***	***Treatment Group Difference***
Nervous System	*45%*	*22%*	***23%***
Akathisia	*28%*	*4%*	***24%***
Tremor	*13%*	*8%*	***5%***
Anxiety	*6%*	*0%*	***6%***
Nausea	*8%*	*2%*	***6%***
Eye disorders	*7%*	*0%*	***7%***
Photophobia	*3%*	*0%*	***3%***
Visual Disturbance	*3%*	*0%*	***3%***

Respiratory system, Thoracic, Mediastinal System	*5%*	*0%*	***5%***
Nasal Congestion	*2%*	*0%*	***2%***

Valproate Adjunctive Subgroups:

The Incidence of common AEs in Valproate-Arip subjects (AEs with an incidence of 5% that was at least twice that of placebo)			
Organ System *Adverse Event*	***Arip***	***PBO***	***Treatment Group Difference***
Extrapyramidal System	*7%*	*1%*	***6%***
Dizziness	*5%*	*0%*	***5%***
Sedation	*5%*	*1%*	***4%***
Vomiting	*5%*	*1%*	***4%***
Psychiatric System	*20%*	*9%*	***11%***
Insomnia	*8%*	*1%*	***7%***

Given the above incidence of Psychiatric System AEs (20%, 9%, respectively) the following less common AEs (at least 2% and twice that of PBO

- *Depression*
- *Agitation*
- *Anxiety*
- *Restlessness*

- *Suicidal (1 Arip subject, no PBO Ss)*
- *Suicidal Attempt (1 Arip subject, no PBO Ss)*

The following less common AEs are noted since they are investigational AEs and given Valp reported events of thrombocytopenia and hepatoxicity (reported in 1 Arip subject and no placebo subjects, each):

- *Urinary RBC,*
- *Increased hepatic enzymes (refer to sections 7.1.3.2 and 7.1.7 of this review).*

EPS, Insomnia and Sedation

Extrapyramidal AEs and insomnia were common in adjunctive subgroups combined (with a incidence of at least twice that of placebo) as follows:

- *EPS AEs: 4.7% and 0.8%, in Arip and PBO treatment groups, respectively and*
- *Insomnia: 7.8% and 3.8%, respectively*

Most of these AEs were reported among valproate-Arip Ss (as shown later). These AEs were not common in the Arip-lithium subgroup (incidence of ≤2%).

Insomnia
Since insomnia was a common AE (with an incidence of ≥5% and at least twice that of PBO) in the adjunctive trial C-134 but not in the 3-week monotherapy trial dataset the following treatment group differences (between Arip and PBO groups) on the incidence of this AE are noted for each of these datasets (as provided in more detail later):

- *Adjunctive Lithium Treatment group difference (Arip versus PBO): 0%*
- *Adjunctive Valp Treatment group difference (Arip versus PBO): 7%*
- *3-week Monotherapy Bipolar trials showed the following treatment group differences, between Arip and PBO groups (results on AEs are shown in more detail in the review of N19): 2%*

Sedation
Since sedation was a common AE (with an incidence of ≥5% and at least twice that of PBO) in the 3-week monotherapy trial dataset but not in the adjunctive trial the following treatment group differences (between Arip and PBO groups) on the incidence of this AE are noted for each of these datasets (as shown in more detail later):

- *Adjunctive Lithium Treatment group difference (Arip versus PBO): 2%*
- *Adjunctive Valp Treatment group difference (Arip versus PBO): 4%*
- *3-week Monotherapy Bipolar trials showed the following treatment group differences, between Arip and PBO groups (results on AEs are shown in more detail in the review of N19): 5%*

The following subsections describe AE results of each adjunctive subgroup in more detail.

7.1.6 Less Common Adverse Events

See the previous section which includes less common AEs also see a summary table of less common AEs (incidence of ≥2% among Arip Ss) by treatment subgroups in Appendix 10.3 of this review.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Refer to the Schedule of Events table in Appendix 10.1 for the study schedule.

This review focuses on results of Study C-134 found in Module 2.7.4 and in the CSR.

The sponsor generally showed results on "measures of central tendency" using a median change from the baseline value or by using a % median change or median change in value for study -

134 and for other safety datasets (in the review of N19). The change from baseline to the highest value (and in some cases also to the lowest value) was provided in the CSR, while results on mean changes from baseline to endpoint (LOCF dataset) or to each time-point (OC dataset) could not be found.

Statistical analyses of comparing groups or time-points on the results of outliers or on "measures of central tendency" could generally not be found in the in-text sections of Module 2.7.4 unless otherwise specified in this review. Therefore, comparisons of results across groups or over time-intervals are based on numerical comparisons, unless otherwise specified.

The incidence of outliers on a given parameter (as found in in-text summary tables of Module 2.7.4) generally was based on results of subjects having either normal baseline values or baseline values that did not meet outlier criteria. It is not clear how the sponsor selected one of these methods over the other method for presenting these results in the in-text table.

As previous discussed in this review, the primary focus of the review of safety results was on information found in in-text sections of Module 2.7.4 and the CSR, unless otherwise specified below.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Reviewer Comments. *This review focuses on results of the pivotal and only adjunctive Bipolar trial conducted (Study C-134). The review of N19 provides results on this trial and additional Bipolar trials. Overall conclusions of results of Study -134 are discussed in this review and of any observations in numerical differences between Valp and Lithium adjunctive subgroups.*

An examination of potential interaction effects of lithium or valproate adjunctive treatment on the incidence of outliers was not conducted or reviewed by the undersigned reviewer since the number of outliers was small such that results are difficult to interpret (moreover in some subgroups the samples sizes were also small). Moreover, given the study design of Study C-134 it is difficult to interpret results based on treatment subgroup comparisons on multiple dependent variables.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Reviewer Comments. *No clinically remarkable new findings were revealed in Study C-134. Results on the mean or median change from baseline to endpoint of each DB treatment group within each adjunctive treatment group could not be found in Module 2.7.4 of N19 or in the CSR of Study C-134. The CSR only provided results on median change from baseline to the highest value.*

The following is the sponsor's tables in Module 2.7.4.

Median Percent Change from Baseline to Endpoint in Each Clinical Parameter in the 6-week Adjunctive Phase of Study C-134

	Placebo		Aripiprazole	
Laboratory Test	N	Median % Change	N	Median % Change
AST (SGOT)	127	10.0	235	0.0
ALT (SGPT)	127	13.3	235	9.1
Alkaline Phosphatase	127	-2.2	236	-2.5
LDH	126	1.3	233	-5.9
Total Protein	126	0.0	236	0.0
Blood Urea Nitrogen	126	1.0	235	0.4
Creatinine	126	0.0	236	0.9
Uric Acid	126	0.0	236	2.0
Bilirubin (Total)	126	0.0	235	0.0
CPK	127	-3.1	236	1.5
Prolactin	116	0.0	226	-16.7
Sodium	126	0.0	235	0.0
Potassium	126	-2.2	234	0.0
Chloride	126	0.0	235	0.0
Calcium	126	0.0	236	0.0

Hematocrit	124	0.0	230	0.0
Hemoglobin	124	-0.3	231	0.0
WBC	124	-3.6	231	0.1
Eosinophils (relative)	122	2.5	231	0.0
Neutrophils (absolute)	122	-9.0	231	0.0
Platelet Count	124	-2.3	228	0.2
Cholesterol Total				
Fasting	115	0.9	204	0.5
Non-Fasting	13	-4.4	22	3.5
HDL Cholesterol				
Fasting	115	1.8	204	2.3
Non-Fasting	13	-1.8	21	3.6
LDL Cholesterol				
Fasting	115	0.0	204	-1.3
Non-Fasting	13	-13.5	21	-0.7
Triglycerides				
Fasting	114	-3.6	204	1.8
Non-Fasting	13	5.5	21	22.0
Glucose				
Fasting	115	0.0	201	1.2
Non-Fasting	13	-5.4	22	2.4

(a) This study did not measure HBg A1C.

The following results were found in the sponsor's 1/18/08 submission (in response to questions). The results are excerpts from the sponsor's table and were perhaps the most notable, since the lithium subgroup showed a mean increase of fasting glucose of up to 9.1 on any given time-point in the Arip group, as compared to 0 to -3.4 mean change observed in the PBO group and as compared to valproate Ss.

Attachment Q.6.8:
Descriptive Statistics for Change from Baseline in Laboratory Measurements,
Lithium Patients, Safety Sample

	Change from Baseline (Actual Value for Baseline)											
	Placebo						Aripiprazole					
Visit	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Fasting Glucose (mg/dL)												
Baseline	47	96.6	14.6	74.0	95.0	162.0	82	91.4	15.5	52.0	92.0	164.0
Week 3	37	-3.4	19.3	-97.0	-2.0	24.0	69	9.1	34.7	-34.0	5.0	254.0
Week 6	36	-0.7	14.4	-57.0	0.0	20.0	69	3.2	13.5	-32.0	2.0	46.0
Week 6 (LOCF)	47	0.1	13.8	-57.0	0.0	31.0	82	5.6	30.9	-32.0	2.0	254.0

Attachment Q.6.9:
Descriptive Statistics for Change from Baseline in Laboratory Measurements,
Valproate Patients, Safety Sample

	Change from Baseline (Actual Value for Baseline)											
	Placebo						Aripiprazole					
Visit	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Fasting Glucose (mg/dL)												
Baseline	68	89.1	15.4	61.0	86.0	162.0	119	91.9	18.0	67.0	90.0	191.0
Week 3	55	1.0	12.6	-42.0	2.0	26.0	94	1.8	15.2	-83.0	2.5	33.0
Week 6	59	-2.2	14.2	-52.0	-2.0	31.0	96	0.5	11.7	-44.0	1.0	29.0
Week 6 (LOCF)	68	-2.1	14.3	-52.0	-1.0	31.0	119	-0.3	14.6	-83.0	0.0	29.0

It is important to note that the incidence of outliers in the lithium subgroup was similar in Arip and PBO groups (13% in each group as shown in Table S.7.2 of the CSR).

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Chemistry Parameters

The sponsor shows summary tables on the incidence of outliers on chemistry parameters among subjects with normal baseline values in Section 3.2.1 of Module 2.7.4 (Tables 3.2.1.1.A&B in Module 2.7.4). The sponsor notes the following chemistry parameter observations:

- The incidences of outliers (with normal baseline values) among Arip or placebo treated subjects receiving valproate or lithium were "generally low."
- The sponsor does not describe any clinically remarkable or potentially clinically remarkable subjects in this in-text section of Module 2.7.4 except for 1 ADO as summarized below.
- 1 Arip treated ADO occurred due to elevated CPK who was summarized as follows (in the in-text summary):

> One patient in the aripiprazole group (CN138134-15-23) discontinued because of increased CPK (Appendix 2.1.4.2) and worsening of mania on Day 21 of double-blind treatment. This patient received aripiprazole with lithium and had a CPK measurement of 255 U/L at baseline and 912 U/L at discontinuation. A follow-up value obtained 5 days after discontinuing aripiprazole treatment was 421 U/L.

Reviewer Comment. *An examination of Tables 3.2.1.1A-B (on the incidence of outliers with normal baseline values in each treatment group) fails to reveal any evidence for a new, clinically remarkable safety signal with Arip treatment.*

Hematology Parameters

The sponsor provides a summary table (Table 3.2.2.1 in Module 2.7.4) of the incidence on outliers on hematology parameters (in subjects with normal baseline values) in Section 3.2.2.1 of Module 2.7.4. The sponsor notes the following observations:

- The incidence values in the table are low.
- No Arip subject was an ADO due to abnormal hematology values.
- The sponsor does not describe any individual subject with potentially clinically remarkable values.

Reviewer Comments. *Examination of numerical values on the incidence of outliers of Table 3.2.2.1 fail to show any evidence for a clinically remarkable and new safety signal with Arip treatment.*

Lipid Profile and Glucose Parameters

The sponsor's in-text summary table (Table 2.1.5.7F) shows results among those subject that did not meet abnormality criteria at baseline. The sponsor notes:

- That few subjects met outlier criteria
- No hyperglycemia or diabetes-related AEs were reported in this trial

- No ADOs due to hyperglycemia or diabetes-related AEs were reported in this trial.

Reviewer Comments: *No unexpected remarkable finding was revealed upon review of Table 2.1.5.7F in Module 2.7.4. LDL cholesterol results showed the following numerically greater incidence of outliers in Arip compared to placebo patients (extracted from the aforementioned table).*

Number of Patients with Potentially Clinically Relevant Abnormality(a)/Number Assessed (%)(b)

#PTS IN SAFETY SAMPLE LAB MEASUREMENT	CRITERION	Placebo 130 INCIDENCE(%)	Aripiprazole 253 INCIDENCE(%)
LDL Cholesterol	>= 160 mg/dL		
Fasting		1/ 110(0.9)	4/ 192(2.1)
Non-Fasting		0/ 13(0.0)	1/ 21(4.8)

(a) Criteria for identifying potentially clinically relevant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (see Appendix 1.1C).
(b) Includes only patients not meeting criteria at baseline.

In light of a few subjects with elevated liver enzymes or related ADOs (in Valp-Arip subjects), previously noted in this review, the following LFT outliers are noted among the Adjunctive-Arip group (Valp and lithium subjects, combined:

- 1/242 (0.4%) of Adjunctive-Arip subjects had any elevation in liver enzymes
- 2/242 (0.8%) had elevated bilirubin (compared to 1/127;0.8% of PBO-Valp subjects).

The number of above outliers for a given LFT parameter that were Valp-Arip subjects is as follows (as found in supplemental CSR table S.7.3):

- *1/147 outliers on liver enzyme parameters (the 1 subject was an outlier on ALT)*
- *0 outliers were found on elevated total bilirubin*

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

See previous subsections on SAEs and ADOs and the special search Section 7.1.4.2.

The sponsor did not note or describe any individual subjects in Section 8.6 of the CSR. However, in Section 8.4 of the CSR (on ADOs) the sponsor notes the following 2 ADOs in Arip treated subjects:

- CN138134-15-23 (lithium treated): an ADO due to increased CPK and worsening of mania on Day 21 of double-blind treatment (CPK levels: 255 U/L at baseline and 912 U/L on day 23, at discontinuation).

Reviewer Comments. *The above patient was also manic which can be associated with CPK elevations.*

- CN138134-135-575 (valproate treated): ADO on Day 21 due to "liver failure" reported on Day 19 in a patient with a history of hepatitis C. On Day 21 ALT was 96 U/L and AST was 48 U/L.

Reviewer Comments. *See previous reviewer comments on this patient in Section 7.1.3.2 in which there was no evidence of "liver failure" in this S (based on additional information*

provided by the sponsor in their 1/18/08 submission in which elevations of ALAT and AST normalized and there was no description of other events that would suggest liver failure).

C…134-95-257: a previously described S with "liver impairment" leading to an ADO on Day 1 of the extension phase of Study C-134 while receiving valproate and Arip during the previous DB phase through Day 1 of the extension phase (when elevated AST and ALT of approximately 3 times the ULN, were found). This subject was previously described in Section 7.1.3.2 on ADOs.

7.1.7.4 Additional analyses and explorations

Refer to the special search Section 7.1.4.2.

7.1.7.5 Special assessments

Reviewer Comments. *Prolactin levels were monitored and results failed to show a remarkable and new safety signal.*

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Refer to the Schedule of Events table in Appendix 10.1 for the study schedule.
See previous reviewer comments in 7.1.7.1 regarding the nature of the results that were found.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.7.2 for the selection of studies/analyses.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Single 6-Week Adjunctive Treatment Trial dataset

The sponsor concludes in Section 4.2.1.3 of Module 2.7.4 that no "clinically relevant" differences were observed between the treatment groups on mean and median change from baseline to endpoint on vital sign parameters (as shown in Table 4.2.1.3 in the Module 2.7.4).

Adjusted mean change from baseline to treatment endpoint in body weight showed no statistically significant treatment group differences.

Reviewer Comments. *The results in Tables 4.2.1.3 and 2.1.5.7 H of Module 2.7.4 are consistent with the sponsor's conclusion that no clinically remarkable differences were observed. Mean and median changes on vital sign parameters were small to absent in the Arip group (mean changes ranged from -1.60 to 0.01 and median change was 0).*

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Single 6-Week Adjunctive Treatment Trial dataset

The sponsor notes the following observations in Section 4.2.1.1 of Module 2.7.4:

- Treatment groups were similar on the incidence of outliers
- No ADOs due to vital sign outliers were reported among Arip subjects.

No statistically significant treatment group differences on the incidence of weight gain or loss was observed.

The sponsor does not summarize or note any individual clinically remarkable subjects (including any ADOs, SAEs or AEs) on weight parameters.

Reviewer Comments. *A review of Tables 4.2.1.1 and 2.1.5.7I (on the incidence of outliers) is consistent with the sponsor's overall conclusion (see the above first bulleted item). The incidence of outliers in the Arip group was <1% for each vital sign parameter.*

The incidence of outliers on weight gain was 3.9% and 3.0% in PBO and Arip groups, respectively.

Orthostatic hypotension parameter results

Reviewer Comments. *Results of Table 2.1.5.4 D in Module 2.7.4 shows little to no treatment group difference (between Arip and placebo) on the incidence of outliers on orthostatic vital sign parameters (only 1 subject met outlier criteria who was in the Arip group; 1/195 total subjects compared to 0/98 placebo subjects).*

The sponsor reports one ADO due to dizziness among Arip subjects. A search in the narratives for a subject with dizziness in the CSR for Study -134 revealed a Patient CN138134-133-569 who had dizziness and inability to focus and concentrate on Day 1 of adjunctive Arip treatment (added to ongoing valproate) who did not have any other AEs or clinically remarkable observations noted in the narrative.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Reviewer Comments. *See the previous subsections and subsections on ADOs and SAEs.*

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Refer to the Schedule of Events table in Appendix 10.1 for the study schedule.
See previous reviewer comments in 7.1.7.1 regarding the nature of the results that were found.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.7.2 for the selection of studies/analyses.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Reviewer Comments. *No new and clinically remarkable results were revealed in each DB treatment group (Arip and PBO) in Study C-134, as follows.*

Single 6-Week Adjunctive Treatment Trial dataset
Results on Heart Rate, PR, QRS and RR Parameters
The sponsor notes (in Section 4.2.2.3 of Module) similar observations on mean and median changes on ECG parameters that they noted for the short-term 3-week dataset (as summarized above in this review).

Reviewer Comments. *Results of Table 4.2.2.3 are consistent with the sponsor's conclusions and results do not show a clinically remarkable and unexpected safety signal. As observed in the 3-week trials (as described in the review of N19), small changes in RR (mean and median decreases) and heart rate (mean and median increases) were observed in the Arip group and were also observed in the placebo group, but occurred in the opposite direction in the placebo group. These small changes generally were numerically smaller in magnitude in this 6-week study compared to changes observed in the 3-week trial dataset.*

Results on QTc Parameters
The following results were copied from Table 2.2.4.2A

Analysis of QTc (Fractional Exponent Correction): 6 Week Combination Therapy in Acute Bipolar Mania (CN138134), Safety Sample

	Fractional Exponent Correction [a]				
	Placebo		Aripiprazole		p-value [e]
Sample Size [b]	117		215		
Mean Baseline QTcE (msec)	400.4		400.1		0.912
Mean Change at Endpoint (SE)	-0.64	(1.65)	-0.58	(1.22)	0.978
Mean Change at Max QTcE (SE)	0.33	(1.65)	0.77	(1.20)	0.828

Reviewer Comments. *The results are unremarkable. The results of each treatment group by gender, race or age-groups (as shown in Tables 2.2.4.2 B-D in Module 2.7.4) were generally unremarkable or sample sizes were insufficient to interpret the results (for some subgroups).*

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Incidence of ECG Abnormalities

No Arip treated subject met outlier criteria for any given ECG abnormality except for:

- 3 Arip subjects (1.3%) with symmetrical T-wave inversion compared to no placebo subjects (according to Tables S.7.12 and S.7.13 in the 1/18/08 response submission 2 of these 3 Ss were in the valproate Arip group and 1 S was in the lithium-Arip group.
- The sponsor reports no ADOs due to ECG abnormalities.

Incidence of QTc Outliers

The following table was copied from Table 4.2.2.4A in Module 2.7.4.

Analysis of QTc (Fractional Exponent Correction): 6 Week Combination Therapy in Acute Bipolar Mania (CN138134), Safety Sample

	Fractional Exponent Correction [a]		
	Placebo	Aripiprazole	p-value [e]
	Number of Patients/Number Assessed (%)		
>450 msec [c]	0/119 (0.0)	4/226 (1.8)	0.303
>500 msec [c]	0/119 (0.0)	0/226 (0.0)	1.000
>=30 msec increase [d]	9/119 (7.6)	19/226 (8.4)	0.839
>=60 msec increase [d]	0/119 (0.0)	1/226 (0.4)	1.000

[a] QTcE=Fractional exponent correction (QT/RR**0.36).
[b] Includes all patients with both a baseline and an endpoint measurement.
[c] Includes all patients with an on-study measurement.
[d] Includes all patients with both a baseline and an on-study measurement.
[e] Comparisons of means were done by ANCOVA controlling for baseline QTc.
Comparisons of proportions were done by Fisher's exact test.

The sponsor notes the following observation among adjunctive treatment subgroups:

- 4 (1.8%) Arip subjects (3 in the lithium subgroup, 1 in the valproate subgroup) had QTcE intervals > 450 msec versus 0 patients on placebo.

- The incidence of outliers on QTcE > 450 msec was:
  - 3.1% in the Arip-lithium group (3 subjects)
  - 0.0% in lithium-placebo group
  - 0.8% in the Arip-valproate group (1 subject)
  - 0.0% the valproate-placebo group.

Reviewer Comment. *Note that only 4 total subjects met this outlier criterion and no subject met the outlier criterion of > 500 msec. Also note that the maximum QTcE outlier value among all Arip subjects was 461 msec (as shown below). Only a 0.8% incidence of outliers was reported for a ≥60 msec QTcE increase in the Arip-valproate group (which would correspond to only 1 subject meeting this criterion) and in no subjects in other subgroups. Since only a few subjects met these outlier criteria the results are difficult to interpret with respect to a potential adjunctive treatment effect (e.g. possible floor effects versus the cases only being sporadic events associated with non-drug-related factors). The number of subjects with a ≥30 msec QTcE increase was larger (see above table for the number of subjects). Yet, the incidence of outliers on this parameter was generally similar among adjunctive treatment subgroups (as shown below). Consequently, the sponsor's results on adjunctive treatment subgroups do not provide evidence for a safety signal on QT interval associated with adjunctive treatment.*

- The incidence of outliers on a ≥ 60 msec increase was:
  - 0.8% in the Arip-valproate group
  - No outliers occurred in the other subgroups;
- The incidence of outliers on ≥ 30 msec increase was:
  - 8.2% in the Arip-lithium group,
  - 8.5% in the Arip-valproate group,
  - 6.7% in the lithium-placebo group
  - 8.1% in the valproate-placebo group.
- The maximum QTcE value reported in the following adjunctive groups were:
  - 453 msec in the Arip-lithium group
  - 461 msec in the Arip-valporate group

Results on QTcB were also found but are not described since it is difficult to interpret these results, since the Bazett's method is based on the assumption that heart rate was decreased or abnormally low (and values are likely to be misleading higher among Arip treated subjects since results on heart rate suggest no change to a numerically small trend for an increase in heart rate).

Reviewer Comments on Outliers on Increased QTcE interval with Treatment Groups Subdivided into Subgroups on the Basis of Gender, Age or Race

The sponsor shows the incidence of outliers on increased QTcE interval with treatment groups subdivided into gender, age or race subgroups in Tables 4.2.2.4B-D in Module 2.7.4. A, potential gender by treatment interaction effect was not suggested by results in Table 4.2.2.4 B. However, the sample size of most subgroups was insufficient for results to be considered adequately interpretable.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

A description of individual subjects could not be found in the CSR (in Sections 8.7, 8.3 or 8.4) except enumeration of outliers (or the incidence of outliers), except that the sponsor notes that the one patient with a QTcB change of >60 msec had this increased value over 30 days after their last dose.

Section 4.2.2 of Module 2.7.4 does not describe any individual subjects (aside from enumerating the subjects with a given abnormality). The sponsor notes that no ADOs occurred due to an ECG abnormality.

Refer to previous sections of this review for outliers and ADOs due to ECG abnormalities.

7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

Abilify is not a therapeutic protein.

7.1.11 Human Carcinogenicity

The following is copied from the review of N19.
Human carcinogenicity was not systematically evaluated in clinical trials included in this NDA submission and a section on this topic could not be found in Module 2.7.4. Appendix 2.1B-1A in Module 2.7.4 shows the incidence of Treatment Emergent AEs for the All Arip safety dataset for each patient diagnostic subgroup (MDD, Bipolar-mania, Bipolar-depression, Dementia, and Schizophrenia) and for all subjects combined. The table shows the following results under the "Neoplasms…and unspecified" category (copied from the sponsor's table).

Reviewer comments. *The results in the above table fail to differ remarkably from results previously provided in the review of N18 under this NDA (this previous clinical review was conducted by the undersigned reviewer).*

7.1.12 Special Safety Studies

The undersigned could not find any special safety studies in the submission.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The undersigned reviewer is not aware of any special studies or data analyses on this topic for this sNDA (refer to approved labeling for this information).

7.1.14 Human Reproduction and Pregnancy Data

Reviewer Comment. *As described in the review of N19 no new and clinically remarkable findings were found in Module 2.7.4 of N19.*

7.1.15 Assessment of Effect on Growth

This sNDA is on the adult population and information on effects on growth was not found.

7.1.16 Overdose Experience

The following was copied from the review of N19.
Reviewer Comment. *Section 5.5 of Module 2.7.4 briefly summarizes 14 cases involving Arip overdoses of greater than 60 mg.*

One S (C…134-17-106) was previously described in this review that involved a S also being treated with lithium ("accidental overdosed" on lithium) and developed SAEs and eventually died.

Several other cases described in Section 5.5 of Module 2.7.4 involved Ss on other concomitant medications or an overdose on multiple drugs. Irreversible sequelaea were not noted for any of the cases except for the above death. In several cases Ss returned to the study and/or did not require treatment.

The results as found in Section 5.5 of Module 2.7.4 fail to reveal any clinically remarkable new observations warranting a change in approved labeling under "Overdosage."

7.1.17 Postmarketing Experience

Refer to Section 2.6 of this review regarding the US marketing history of Arip relevant to this NDA.

The following was copied from the review of N19:

> Section 6 of Module 2.7.4 provides information on worldwide experience and on postmarketing safety surveillance. A summary of safety observations or potentially remarkable cases could not be found in this section of the submission. The sponsor lists past safety related topics of "Cumulative Review" in past Periodic Safety Update Reports (PSURs) previously submitted under the NDA (up to their specified cut-off date). The sponsor lists past Periodic Adverse Drug Reports (PSURs) submitted under the NDA, as well (as of the specified cut-off date). The sponsor provides a list of safety topics in past PSURs and updated in the CCSI (as specified in Table 6.2.1B in Module 2.7.4). A summary of findings cannot

be found in Section 6 of Module 2.7.4. The sponsor indicates that since the first approval of Arip in July 17, 2002, the benefit to risk ratio of Arip "remains favorable" and that the accumulated postmarketing information "has been reflected in the Company Core Safety Information, the Summary of Product Characteristics and in the indicating US Prescribing Information." The sponsor states that their review of Arip AE data from spontaneous postmarketing reports and from clinical trials (as provided in their Periodic Adverse Drug Experience Reports) "indicated an overall benefit risk profile similar to and consistent with the previously established clinical trial experience as described in the exiting USPI for Abilify.®"

7.2 Adequacy of Patient Exposure and Safety Assessments

See subsections below and Section 9 of this review for any key issues relevant to the overall recommendations for this NDA.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See subsections below.

7.2.1.1 Study type and design/patient enumeration

See Sections 4, 6 and 7 of this review.

7.2.1.2 Demographics

Refer to Appendix 10.1 and the review of N19 for demographic information on study populations in Bipolar trials that provided safety results. Demographic features of patients in the pivotal trial Study C…134 are discussed in Appendix 10.1 and were generally consistent with those of the general population of patients with Bipolar I disorder.

7.2.1.3 Extent of exposure (dose/duration)

DB Phase of Study C-134
Exposure in the pivotal efficacy Study C…134 is discussed in detail on Appendix 10.1 of this review. For the convenience of the reader the following outlines some key observations on exposure (the items below are excerpts copied from Appendix 10.1):

- 111 PBO and 199 Arip subjects completed the DB phase (as listed in Table 5.1.A of the CSR).
- A total of 130 PBO and 247 Arip subjects were in the ITT efficacy population (randomized subjects who had at least one dose of study drug and at least one efficacy assessment after starting the study drug).

- Mean weekly doses of Arip during the DB phase were as follows:
  - 15.5 mg/day in the first week
  - 17.3-19.0 mg/day in subsequent weeks

The following table enumerates Ss by mean daily dose categories (as provided by the sponsor).

Table 6.1: Number of Patients Receiving Double-Blind Study Medication and Mean and Range of Weekly Mean Daily Dose, Safety Sample

	Placebo		Aripiprazole			
Days	N	(%)	N	(%)	Mean (mg/day)	Min - Max (mg/day)
1 - 7	130	(100)	253	(100)	15.5	10.7 - 45.0
8 - 14	129	(99.2)	242	(95.7)	17.3	6.0 - 30.0
15 - 21	124	(95.4)	233	(92.1)	18.4	7.5 - 30.0
22 - 28	123	(94.6)	217	(85.8)	18.8	2.1 - 30.0
29 - 35	119	(91.5)	208	(82.2)	18.7	6.4 - 30.0
36 - 42	115	(88.5)	197	(77.9)	19.0	8.6 - 40.7
43 - 49	46	(35.4)	81	(32.0)	18.5	12.0 - 45.0
> 49	6	(4.6)	14	(5.5)	18.6	15.0 - 45.0

The following table was copied from the submission in which the sponsor notes that the majority of patients received the 15 mg daily dose-level of Arip during the DB phase.

Table 1.2.2.1B: Number and Percentage of Patients Who Received Aripiprazole by Overall Mean Dose Category and Duration of Therapy: 6-Week Combination Therapy in Acute Bipolar Mania (CN138134), Safety Sample

Total Dur. of Trt (days)	Unavailable(a) N (%)	<=17.5 N (%)	>17.5-<=25 N (%)	>25 N (%)	Total N (%)
1-7	0	10 (4.0)	0	1 (0.4)	11 (4.3)
8-14	0	8 (3.2)	1 (0.4)	0	9 (3.6)
15-21	0	14 (5.5)	2 (0.8)	0	16 (6.3)
22-28	0	8 (3.2)	1 (0.4)	0	9 (3.6)
29-35	0	6 (2.4)	4 (1.6)	1 (0.4)	11 (4.3)
36-42	0	78 (30.8)	18 (7.1)	20 (7.9)	116 (45.8)
>42	0	58 (22.9)	13 (5.1)	10 (4.0)	81 (32.0)
Total	0	182 (71.9)	39 (15.4)	32 (12.6)	253 (100.0)

(a) Dosage data not available as of data cut-off date.

Reviewer comment on valproate and lithium subgroups. *As discussed in more detail on appendix 10.1 of this review, these subgroups were adequately similar on Arip exposure and number of days of DB treatment (of Arip or PBO).*

The majority of subjects received the 15 mg rather than the 30 mg dose level as reflected in the following observation (taken from tables similar to that of the above table but presenting results for each adjunctive subgroup; these tables are shown in Appendix 10.1 of this review):

- *A total of 12 Lithium Ss were in the >25 mg dose-category (generally after 29-35 weeks of treatment)*
- *A total of 19 Valproate Ss were in the >25 mg dose-category (after either 36-42 or 42 weeks)*

See additional comments in the last section of this review.
Exposure to lithium or valproate treatment was adequate for the purposes of this review.

Exposure in the Ongoing OL Phase of Study C-134 and the OL Stabilization Phase of the Ongoing Study C-189

The sponsor provided upon request, exposure to longterm OL adjunctive treatment during the OL extension phase of Study C-134 (ongoing) and during the OL stabilization (pre-DB) phase of the ongoing maintenance trial, Study C-189.

Reviewer Comment. *Based on results below, the majority of Ss in the OL phase of each study received a mean daily dose of over 12.5 mg to 17.5 mg during at least one time interval. Longterm exposure does not meet ICH guidelines. However, the exposure on the basis of dose and duration is adequate for the purposes of this review given extensive experience with Arip involving patient populations commonly receiving concomitant medications (and include lithium and valproate). Moreover, drug-drug interaction Phase I studies were previously conducted and subject to review (as described in approved labeling).*

OL Phase of Study C-134

Attachment Q.1B.2:
Cumulative Number of Patients Who Received Aripiprazole by Duration of Exposure: Open Label Extension Phase in Study CN138134 by Combination Treatment and Overall, Safety Sample

Patient Exposure Years	Lithium 41.2		Valproate 62.5		Total 103.7	
Duration of Treatment	N	(%)	N	(%)	N	(%)
>= 1 day	106	(100.0)	175	(100.0)	281	(100.0)
>= 21 days	101	(95.3)	148	(84.6)	249	(88.6)
>= 42 days	77	(72.6)	114	(65.1)	191	(68.0)
>= 90 days	54	(50.9)	75	(42.9)	129	(45.9)
>=180 days	36	(34.0)	58	(33.1)	94	(33.5)
>=270 days	19	(17.9)	35	(20.0)	54	(19.2)
>=360 days	0	(0.0)	0	(0.0)	0	(0.0)
>=540 days	0	(0.0)	0	(0.0)	0	(0.0)
>=720 days	0	(0.0)	0	(0.0)	0	(0.0)

Attachment Q.1B.3:
Number and Percentage of Patients Who Received Aripiprazole by Overall Mean Dose Category and Duration of Therapy: Combined Double-blind Acute Phase and Open Label Phase in Study CN138134, Open Label Extension Phase Safety Sample

Total Dur. of Trt (days)	Unavailable(a) N	(%)	<=12.5 N	(%)	>12.5 - <=17.5 N	(%)	>17.5 - <=25 N	(%)	>25 - <=32.5 N	(%)	> 32.5 N	(%)	Total N	(%)
1-20	0		1	(0.4)	10	(3.6)	1	(0.4)	3	(1.1)	0		15	(5.3)
21-41	0		2	(0.7)	17	(6.0)	1	(0.4)	8	(2.8)	0		28	(10.0)
42-89	0		11	(3.9)	38	(13.5)	9	(3.2)	15	(5.3)	0		73	(26.0)
90-119	0		0		14	(5.0)	1	(0.4)	1	(0.4)	0		16	(5.7)
120-149	0		0		19	(6.8)	3	(1.1)	7	(2.5)	0		29	(10.3)
150-179	0		0		8	(2.8)	0		2	(0.7)	0		10	(3.6)
180-269	0		2	(0.7)	22	(7.8)	7	(2.5)	5	(1.8)	0		36	(12.8)
270-359	0		1	(0.4)	33	(11.7)	2	(0.7)	4	(1.4)	1	(0.4)	41	(14.6)
360-719	0		0		26	(9.3)	4	(1.4)	3	(1.1)	0		33	(11.7)
Total	0		17	(6.0)	187	(66.5)	28	(10.0)	48	(17.1)	1	(0.4)	281	(100.0)

OL Stabilization Phase of Study C-189

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Attachment Q.1B.9:
Cumulative Number of Patients Who Received Aripiprazole by Duration of Exposure: Open Label Stabilization Phase in Study CN138189 by Combination Treatment and Overall, Safety Sample

Patient Exposure Years	Lithium 7.8		Valproate 15.7		Total 23.5	
Duration of Treatment	N	(%)	N	(%)	N	(%)
>= 1 day	45	(100.0)	87	(100.0)	132	(100.0)
>= 21 days	36	(80.0)	62	(71.3)	98	(74.2)
>= 42 days	27	(60.0)	54	(62.1)	81	(61.4)
>= 90 days	12	(26.7)	26	(29.9)	38	(28.8)
>=180 days	1	(2.2)	1	(1.1)	2	(1.5)
>=270 days	0	(0.0)	0	(0.0)	0	(0.0)
>=360 days	0	(0.0)	0	(0.0)	0	(0.0)
>=540 days	0	(0.0)	0	(0.0)	0	(0.0)
>=720 days	0	(0.0)	0	(0.0)	0	(0.0)

Attachment Q.1B.10:
Number and Percentage of Patients Who Received Aripiprazole by Overall Mean Dose Category and Duration of Therapy: Open Label Stabilization Phase in Study CN138189, Safety Sample

Total Dur. of Trt (days)	Unavailable(a) N	(%)	<=12.5 N	(%)	>12.5 - <=17.5 N	(%)	>17.5 - <=25 N	(%)	>25 - <=32.5 N	(%)	> 32.5 N	(%)	Total N	(%)
1-20	1	(0.8)	2	(1.5)	27	(20.5)	2	(1.5)	2	(1.5)	0		34	(25.8)
21-41	0		4	(3.0)	9	(6.8)	4	(3.0)	0		0		17	(12.9)
42-89	0		8	(6.1)	15	(11.4)	6	(4.5)	14	(10.6)	0		43	(32.6)
90-119	0		5	(3.8)	4	(3.0)	2	(1.5)	7	(5.3)	0		18	(13.6)
120-149	0		2	(1.5)	6	(4.5)	0		5	(3.8)	0		13	(9.8)
150-179	0		1	(0.8)	1	(0.8)	1	(0.8)	2	(1.5)	0		5	(3.8)
180-269	0		0		1	(0.8)	1	(0.8)	0		0		2	(1.5)
Total	1	(0.8)	22	(16.7)	63	(47.7)	16	(12.1)	30	(22.7)	0		132	(100.0)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

See subsections below. Section 9 outlines any key issues.

7.2.2.1 Other studies

The undersigned review is not aware of any other secondary safety datasources from clinical studies. Refer to Section 4 of this review for various safety datasources and review strategies.

7.2.2.2 Postmarketing experience

See sections 2.6 and 7.1.17 of this review.

7.2.2.3 Literature

Section 8.6 summarizes the results of the search. This section discusses the methods of the search. The Otsuka Pharmaceutical Company (OPC) and Bristol-Myers Squibb (BMS) conducted searches involving 11 databases (for online bibliographic references) and a medical scientific literature database in Japan. The BMS search (in which 11 databases were searched) is noted to have been a basic index searches (rather than a full text search) since the databases were not full text databases. These searches were conducted using the various search terms for the drug name, brand names, codes and Chem. Abs. Registry numbers. Additional searches were conducted on other databases and using other or additional search terms as described in the literature.pdf in Item 8 of the submission.

Curriculum vitae were included for individuals who conducted the searches and who reviewed the search results.

The overall clinical experience is adequate and as described in related sections of this review (e.g. refer to Section 7.2.1 of this review), from a clinical perspective and for the purposes of this NDA.

7.2.3 Adequacy of Special Animal and/or In Vitro Testing

Not applicable to this NDA since Abilify is already approved.

7.2.4 Adequacy of Routine Clinical Testing

See previous subsections of Section 7.1 of this review for comments relevant to potential limitations with clinical parameter results.

Pivotal trials and longterm OL adjunctive trials, relevant to this sNDA included routine clinical testing (that are typical for trials for this indication) and are adequate for the purposes of this review.

7.2.5 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The studies conducted are adequate for the purposes of this NDA.

7.2.6 Assessment of Quality and Completeness of Data

See Sections 4.3, 4.4 and 4.5 of this review. Overall the quality and completeness of the data was adequate, pending a final report from DSI. Previous subsections generally note minor problems, inconsistencies or other relevant aspects of results, upon review. Some of these problems were also adequately addressed in response to inquiries to the sponsor. No major issues were identified relevant to the quality and completeness of the data.

7.2.7 Additional Submissions, Including Safety Update

A Safety update report was not submitted. The sponsor responded to inquires (see section 4.1 of this review for submission dates). Key information found in their 1/18/08 response submission was incorporated in sections of this review, where applicable. This additional information, together with information provided in the original submission (cross-referencing N19), are sufficient for the purposes of this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

See previous sections of this review and the final section of this review for any major issues or potential issues.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Only 1 pivotal trial was submitted for efficacy results and the sponsor cross-referenced N19 for safety information. The review of N19 discusses pooling of the safety results from other trials which was adequate for the purposes of the review of N19 and N20.

7.4.1.2 Combining data

See the previous section.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Study C-134 used a flexible dose design such that dose dependency on findings was not explored.

7.4.2.2 Explorations for time dependency for adverse findings

Refer to Section 7.1.5.6.

7.4.2.3 Explorations for drug-demographic interactions

It is difficult to interpret results on drug-demographic interactions given study design of Study C-134 (and other limitations with interpreting results on the basis of multiple comparisons, multiple dependent variables among other key limitations).

7.4.2.4 Explorations for drug-disease interactions

No studies were conducted to examine drug-disease interactions.

7.4.2.5 Explorations for drug-drug interactions

See section 5.1 of this review regarding PK results in past Phase I trials of concomitant valproate or lithium treatment (as found in approved labeling). Previous subsections of 7.1 describe safety results in adjunctive safety groups in Study C-134 (between placebo and Arip groups within each adjunctive subgroup). No other studies on drug-drug interactions were found in the submission. Refer to Section 9 of this review for any major issues, from a clinical perspective.

7.4.3 Causality Determination

It is difficult to determine causality of Arip treatment based on preliminary exploratory analyses of data for revealing potential predictors.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

See Section 6 and appendix 10.1of this review for the dosing regimen used for the pivotal Study C-134.
See Section 7.2.1 on adequacy of exposure and dose-levels employed and note reviewer comments in Section 7.2.1.3.

See the last section of this review for any key issues, additional comments and recommendations relevant to proposed labeling.

8.2 Drug-Drug Interactions

Safety results on AEs and possibly some ADOs (as discussed in Section 7 of this review) may suggest an exaggerated (more robust) adverse effect with Lithium-Arip combination treatment on nervous system AEs, mostly due to akathisia. A possible exaggerated effect was observed with other AEs (that are AEs that are reported or expected of one or the other drug, when given alone). Valproate-Arip combination may also have an exaggerated effect on insomnia. However, the overall safety profile (the nature of the AEs) was generally expected for Arip or the concomitant "mood stabilizer."

Section 9 of this review provides an outline of the key safety findings with adjunctive treatment and provides recommendations.

Approved labeling currently provides Phase I results on potential PK interactions between Arip and lithium or valproate. Dose adjustments are not recommended in approved labeling.

See the last section of this review for additional comments and recommendations, relevant to the maximum recommended dose during adjunctive treatment.

8.3 Special Populations

No new information was found on special population trials.

8.4 Pediatrics

The following was copied from the review of N19.

The sponsor requests a waiver from conducting pediatric trials for this sNDA (this request was found in the cover letter of the N19 submission). The sponsor notes in their cover letter that they recently completed a pediatric Bipolar trial (31-03-240) and that they plan to submit the results of this study as a separate sNDA in order to fulfill a pediatric postmarketing commitment for S-002.

Reviewer Comment. *A deferral (rather than a waiver) is recommended contingent upon the review of their upcoming sNDA for a pediatric Bipolar I indication.*

8.5 Advisory Committee Meeting

A meeting will not be held on this sNDA.

8.6 Literature Review

OPC and BMS searched various databases of the medical and scientific literature using methods described in Section 7.2.2.3 of this review. A summary of the search results could not be found in the literature.pdf file of submission. However, it is noted that the search results were reviewed by (b) (6), MD, Robert Berman, MD and Vlad Coric, MD. These individuals also certified that efficacy and/or safety findings based on their literature review did not alter or adversely affect conclusions about efficacy and/or safety in the NDA submission (as specified in Item 8 literature.pdf file of the submission). Dr. Berman also notes the following (copied from the submission):

> In addition, this is to certify that we have thoroughly searched the published literature for reports of studies evaluating the efficacy of adjunctive aripiprazole for the treatment of Bipolar Mania through Dec 1, 2006. In our opinion, there were no publications reporting on data that provided sufficient basis for the approval of adjunctive ABILIFY (aripiprazole) for the treatment of Bipolar Mania without reference to the clinical investigations contained in the application.

8.7 Postmarketing Risk Management Plan

A postmarketing risk management plan could not be found in the submission.

8.8 Other Relevant Materials

No other information could found.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy
From a clinical perspective, the pivotal trial (Study C-134) was positive for efficacy of adjunctive therapy (lithium and valproate) for acute treatment of Bipolar I, mixed or mania, from a clinical perspective, pending confirmation by Biometrics.

Pending confirmation from Biometrics, Study C-134 showed efficacy on the primary and key secondary variables (mean change from baseline to endpoint on the YMRS and on the CGI-BP-S score, respectively). The Biometric reviewer was consulted by the undersigned reviewer on conducting an additional analyses of this parameter (refer to section 6.1.3 of this review). The Biometric reviewer plans on conducting an additional sensitivity analyses on this key secondary variable.

Section 6 of this review provides more details on efficacy and safety, respectively.

Safety

The focus of the safety review was on results from the pivotal adjunctive Study C-134. The overall safety profile of serious adverse events (SAEs) and adverse dropouts (ADOs) in Study C-134 did not reveal a clinically remarkable and new safety signal. However, results on the incidence of AEs suggest interaction effects with akathisia and other AEs.

Possible Lithium-Arip Interaction Effect on Akathisia and Possibly Other AEs

The highest incidence of akathisia (reported as an AE leading to an ADO or reported as an AE) was observed in the lithium-Arip subgroup of Study C-134, when numerically compared to incidence observed in each valproate subgroup (PBO and Arip valproate-subgroups). Results on additional AEs also suggest adjunctive subgroup differences on the incidence of these events. The treatment group differences (between Arip and PBO) on these additional AEs appeared to be less robust and are more difficult to interpret.

Tables below are copied from subsections of Section 7 of this review.

The following table is copied from Section 7.1.3.2 to allow for comparisons with results of the above table (for the convenience of the reader):

The Incidence of Common AEs Leading to ADOs Among any Given Arip-adjunctive Subgroup in the DB Phase of Study C-134 and as Compared to the Incidence in 3-week Monotherapy Bipolar-I trials (integrated dataset)

Adjunctive Subgroup	*Lithium*			*Valproate*			*Monotherapy***		
Treatment Group	*Arip N=106*	*PBO N=50*	*Delta**	*Arip N=147*	*PBO N=80*	*Delta**	*Arip N=917*	*PBO N=753*	*Delta**
System Organ Class Preferred Term									
Nervous System disorder	*11*	*2*	***9***	*4*	*1*	***3***	*4*	*1*	***3***
Akathisia	*9*	*0*	***9***	*3*	*1*	***2***	*2*	*0.3*	***2***
Gastrointestinal disorder	*5*	*0*	***5***	*1*	*0*	***1***	*1*	*1*	***0***

**Delta is the difference in the incidence between Arip and PBO groups within the adjunctive subgroup.*

*** These results are from the integrated Bipolar I (mania/mixed) monotherapy trial dataset (Trials C...007, -009, -062, -074, -077, -135 and -162) and were provided in summary tables in the parallel N19 submission. These results are also shown in Table 2.1.4.1 in Section 7.1.3.2 in the review of N19.*

The following table is copied from Section 7.1.5.6 of this review.

Treatment Group Differences (Between Arip and PBO group; Delta) on the Incidence of ADOs and AEs of Akathisia and of AEs of Tremor in Various Clinical Trial Database

	Study C-134 Adjunctive Bipolar I mania/mixed		*Monotherapy Bipolar Trials mania/mixed***	*Adjunctive MDD Trials*	*All-Arip Dataset*** These results only show the incidence in Arip treated subjects (not delta)*		
	Lithium	*Valproate*					
	*Delta**	*Delta**	*Delta**	*Delta**	*Bipolar I (mania), or*	*Schizophrenia trials*	*"Dementia" Trials*

					Bipolar I (depressed) or MDD trials		
AEs							
Akathisia	***24%***	*6%*	*9%*	***21%***	***16-25%***	*7%*	*0.4%*
Tremor	***5%***	*1%*	*3%*				
ADOs							
Akathisia	***9%***	*2%*	*2%*		***3-5%***	*0.2%*	*0.9%*

**Delta is the difference between Arip and PBO groups (for Study C-134 this difference is provided for each of the adjunctive subgroups, as specified, and for the adjunctive MDD trials this difference is provided for all adjunctive Ss, since most of these Ss were receiving SSRIs). The MDD trial dataset is of 2 adjunctive MDD short-term Phase III trials in which most of the Ss received SSRIs (with a small number receiving venlafaxine instead) with Arip or PBO. These trials and the results were included in the review of N18 for a MDD adjunctive claim*

***These results are from the integrated Bipolar I (mania/mixed) monotherapy trial dataset (Trials C..007, -009, -062, -074, -077, -135 and -162) and were provided in summary tables in the parallel N19 submission. These results are also shown in Table 2.1.4.1 in Section 7.1.3.2 in the review of N19.*

****These results are from All-Arip treatment dataset as found in Module 2.7.4 of N19. The incidence for the Arip-treated Ss within a give patient population is shown (of integrated trial datasets of trials examining a given patient population).*

The following tables provide results of common AEs for each subgroup (copied from Section 7.1.5.6 of this review).

Lithium Adjunctive Subgroups

The Incidence of Common AEs in Lithium-Arip subjects (AEs with an incidence of 5% that was at least twice that of placebo & Additional AEs)			
Organ System *Adverse Event*	***Arip***	***PBO***	***Treatment Group Difference***
Nervous System	*45%*	*22%*	***23%***
Akathisia	*28%*	*4%*	***24%***
Tremor	*13%*	*8%*	***5%***
Anxiety	*6%*	*0%*	***6%***
Nausea	*8%*	*2%*	***6%***
Eye disorders	*7%*	*0%*	***7%***
Photophobia	*3%*	*0%*	***3%***
Visual Disturbance	*3%*	*0%*	***3%***
Respiratory system, Thoracic, Mediastinal System	*5%*	*0%*	***5%***
Nasal Congestion	*2%*	*0%*	***2%***

Valproate Adjunctive Subgroups:

The Incidence of common AEs in Valproate-Arip subjects (AEs with an incidence of 5% that was at least twice that of placebo)			
Organ System *Adverse Event*	***Arip***	***PBO***	***Treatment Group Difference***
Extrapyramidal System	*7%*	*1%*	***6%***
Dizziness	*5%*	*0%*	***5%***
Sedation	*5%*	*1%*	***4%***
Vomiting	*5%*	*1%*	***4%***
Psychiatric System	*20%*	*9%*	***11%***
Insomnia	*8%*	*1%*	***7%***

These results are only considered preliminary since Study C-134 was not designed for interpreting results that are based on comparisons between multiple adjunctive subgroups on multiple outcome measures (the interpretation of the results is limited by the small sample sizes, by the multiple comparisons which were non-statistical comparisons, n among other factors to consider). Moreover, the AEs that were suggestive of showing subgroup differences are AEs that are known to occur with either study drug alone (with Arip or the adjunctive drug).

Refer to the following sections in this review for more detailed discussions on potential interaction effects with primarily lithium and Arip adjunctive treatment:

- Section 7.1.3.2 (on ADOs),
- Section 7.1.4.1 (refer to a subsection on "Adjunctive Subgroup Differences on EPS-related AEs),
- Section 7.1.4.2: This section discusses the sponsor's 1/18/08 response to questions regarding potential drug-drug interaction effects on safety. One potentially notable finding in the sponsor's response is the following (copied from Section 7.1.4.2):
  Despite the key limitations with interpreting the results provided upon requested (and as noted by the sponsor), the largest treatment group difference (between Arip and PBO Ss) on AEs temporally associated with dose reductions (of at least 3 days in duration) was observed with akathisia in the lithium subgroup, as follows:
  - *Treatment group differences (between Arip and PBO) on the incidence of overall AEs:*
    - *12% in the lithium group versus 3% in the valproate group.*
  - *Treatment group differences on akathisia:*
    - *7% in the lithium subgroup versus 1% in the valproate subgroup.*

These results are considered, preliminary.

Refer to Sections 9.3.2 for recommendations on Phase 4 activities and in Section 9.4 regarding recommending a minimum interval of 7 days when increasing the daily dose level from the initial 15 mg starting dose level to the 30 mg dose level.

Additional Comments on Safety
Longterm OL adjunctive safety data from the ongoing 46 week OL phase of Study C-134 and of the OL stabilization phase of the ongoing Study C-189 were also provided as unpooled results (upon request in a 1/18/08 submission). These results failed to reveal a clinically remarkable new safety signal.

Module 2.7.4 in the N19 submission is cross-referenced in the current N20 submission for safety results from additional datasets (of clinical trials). These additional datasets were not the primary focus of the review for the N20 application, since they involved different patient populations or different treatment regimens (among other limitations). These results are described in more detail in the review of N19 and they failed to reveal a clinically remarkable new safety signal.

Section 7 of this review provides details on safety results from primary and secondary datasources.

Finally there is extensive experience with Arip treatment in Bipolar I and other patient populations that include patients receiving concomitant lithium and valproate.

9.2 Recommendation on Regulatory Action

It is recommended that this NDA be approved, from a clinical perspective. Final decision for final approval will be contingent on:

- Finalized Input from other Disciplines assigned to the sNDA (Biometric Team and the Division of Scientific Investigations)
- Negotiation of Labeling.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no recommendations for specific risk management activities.

9.3.2 Required Phase 4 Commitments

Results from Study C-134 (shown in Sections 7 and summarized in Section 9.1 of this review) suggest a potential interaction effect of Arip and lithium on the incidence of primarily akathisia. Akathisia is poorly understood. Lithium has a narrow therapeutic index and is associated with

severe and life-threatening events that include CNS effects. Restlessness and giddiness may be confused with akathisia and is an event that is generally a sign of lithium toxicity, although some patients may experience this event at lower plasma levels than others. Therefore, it is worthwhile to consider an examination of akathisia against other more serious adverse events, particularly in patients receiving adjunctive treatment with lithium (e.g. consider a search for adverse events characteristic of lithium toxicity and akathisia). Also consider interaction effects with antidepressants on akathisia, as well (refer to the review of N18).

It is recommended that OSE be consulted for considering approaches to address this potential safety signal.

It is also recommended that the Division consider requiring that the sponsor be involved with searching their database as well. Consider the following. Initially the sponsor could be required to propose an approach (methods) for examining their existing databases to address this potential signal and that OSE be consulted on their proposal.

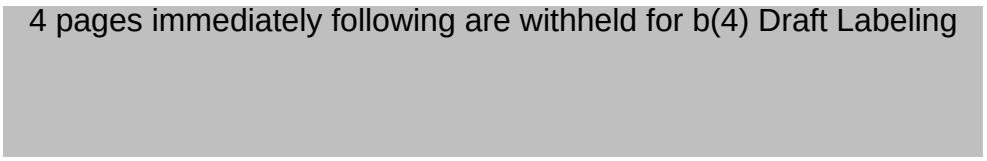
9.3.3 Other Phase 4 Requests

None are recommended.

9.4 Labeling Review

Key labeling issues, from a clinical perspective were identified as outlined below. Upon request the sponsor provided a 9-6-07 side-by-side, annotated labeling, since annotated labeling was not found in the original submission ("annotated Abilify Current to PLR Comverson.qxp" 8/29/2007). Excerpts of proposed labeling are provided below. To the knowledge of the undersigned reviewer, the sponsor has not yet submitted labeling that is updated to reflect the most recently approved version of labeling (the version of the recently approved N18 application). To the knowledge of the undersigned reviewer this updated version is being requested by the project manager assigned to this NDA.

Any proposed text (copied below) relevant to a 15 mg starting dose for monotherapy of Bipolar I is addressed in a separate review of a parallel N19 application under NDA21436 (in which the sponsor seeks this additional claim). Reviewer comments and recommendations below only pertain to proposed changes on adjunctive treatment of Bipolar I, relevant to the N20 submission.



(b) (4)

9.5 Comments to Applicant

None are recommended, from a clinical perspective.

APPENDICES

10.1 Review of Individual Study Reports

The only pivotal trial for this NDA is Study C-134 which is summarized in Section 6 of this review. This appendix provides additional information regarding this study.

Schedule of Assessments for Study C-134

	PHASE 1					PHASE 2		PHASE 3							
	Screening and Psychotropic Washout[a]					Li/valproate Monotherapy and Baseline[b]		Double-Blind Treatment							
	3 days to 4 weeks					2 Weeks		6 Weeks							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[c]	Week 1 (+/-2 days)	Week 2 (+/-2 days)	Day 4 (+1 day)	Week 1[d] (+/-2 days)	Week 2[d] (+/-2 days)	Week 3[d] (+/-2 days)	Week 4[d] (+/-2 days)	Week 5[d] (+/-2 days)	Week 6 /ET[d] (+/-2 days)	Protocol Section
PROCEDURE															
Informed Consent	X														6.1/10.2
Demographic Data	X														5
Entrance Criteria	X				X[e]		X[e]								5
Medical History	X														5/7
Psychiatric History	X														5
Previous Medications	X														5
DSM-IV-TR/MINI[f]	X														3.1
EFFICACY[g]															
Y-MRS					X[h]		X[i]	X	X	X	X	X	X	X	7.3.5.1
MADRS							X	X	X	X	X	X	X	X	7.3.5.2
CGI-BP							X	X[j]	X	X	X	X	X	X	7.3.5.3
PANSS							X		X		X			X	7.3.5.4
SAFETY															
Physical Exam	X[k]													X	7.3.2.4
Vital Signs[l]	X					X	X[m]	X	X	X	X[m]	X	X	X[m]	7.3.2.5
12 Lead ECG	X						X[n]							X	7.3.2.6

Clinical Laboratory Tests (chemistry, hematology, urine)[o,p]	X						X[n]				X			X	7.3.4
-Prolactin level							X[n]				X			X	7.3.4
Lithium/Valproate levels	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	3.1.2/ 6.2.3
Pregnancy Test (WOCBP)[s]	X	X					X	X			X			X	5/7.3.4
Drug Screen/Blood Alcohol Test[t]	X						X----	---------	----------	----------	X	----------	----------	X	5/7.3.4
SAS/AIMS/Barnes Akathisia							X		X	X	X	X	X	X	7.3.2
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9
OUTCOMES RESEARCH															
SF-36 Health Survey[u]							X							X	7.3.9.1
LIFE-RIFT Tool[v]							X							X	7.3.9.2
OTHER															
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.4
Study Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.2
Drug Accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3/8.4
Baseline Visit Form							X								7.2.2
End of Study Form														X[w]	3.1.4

[a] The purpose of Phase 1 is to start patient on mood stabilizer or to confirm therapeutic level of mood stabilizer, and to washout concomitant medications. The total number of visits in Phase I will vary based on a patient's incoming therapeutic regimen (i.e., the need for varying washouts), including therapeutic serum levels of the mood stabilizer. Mood stabilizer serum levels should be assessed approximately 12 hours after the last dose on the 5-7th day of initiation or dose modification. This phase can be extended for up to two weeks with permission of the BMS Medical Monitor

[b] The purpose of Phase 2 is to confirm partial nonresponsiveness to mood stabilizers (therapeutic level must be maintained throughout 2 weeks). The main requirement for entry into this phase is a Y-MRS Total Score of ≥ 16

[c] This visit, prior to Phase 2, must be completed for all subjects who have achieved stable therapeutic levels and washout criteria

[d] Visits to be done at the end of each week (or at early termination)

[e] Assess Y-MRS and serum therapeutic levels as per Inclusion Criteria 7, 8 and 9

[f] Bipolar I Disorder, with or without psychotic features, defined by the DSM-IV-TR, and confirmed by the M.I.N.I.

[g] Please refer to Table 6.4.1 for required washout periods for benzodiazepines, anticholinergics, and propanolol by study phase

[h] Y-MRS must be ≥ 16 for patients to be eligible to enter Phase 2. Y-MRS should be conducted at the visit that the investigator expects the patient to have a therapeutic lithium or valproate level. If the central laboratory does not confirm a therapeutic level (causing Phase 1 to be extended) the Y-MRS does not need to be repeated prior to entering Phase 2.

[i] Baseline Y-MRS must be ≥ 16 and ≤ 25% decrease in case of decrease of Y-MRS from Phase 1. Note that Y-MRS total score can remain the same or increase (no limits to the increase) between the Phase 1 and Phase 2 assessments

[j] CGI-BP Change from Preceding Phase will be done starting at Day 4 (to refer to preceding phase of the baseline/end of Phase 2), while CGI-BP Severity of Illness will be done at all timepoints from Baseline (end of Phase 2) forward

[k] Height is to be measured at the screening visit

[l] Vital signs to include supine and standing/sitting blood pressure and pulse. Blood pressure should be taken before blood is drawn.

[m] To include weight at Baseline, Week 3, and Week 6/Early Termination

[n] Procedures to be completed at the end of Week 2 in Phase 2

[o] Clinical laboratory tests should be done fasting (10 hours minimum)

[p] Prothrombin time and partial thromboplastin time to be performed at screening for patients receiving valproate. TSH (with reflexive T4) to be performed at screening for all patients.

[q] Serum levels of lithium/valproate will be assessed 5-7 days (approximately 12 hours after last dose) after initializing dose or making a dose modification, and at approximately weekly intervals thereafter to confirm therapeutic serum levels. Unscheduled lithium or valproate levels may be performed at any time, based on the investigator's judgment

[r] Serum levels of lithium/valproate will be taken weekly to confirm patients are at therapeutic levels

[s] A serum or urine pregnancy test should be performed within 72 hours of the first administration of study medication, and at the Screening, Visit 2 of Phase 1, Baseline, Day 4, Week 3, and Week 6/Early Termination visits

[t] Drug screen for cocaine must be negative prior to randomization. Drug screen and/or blood alcohol level testing may be repeated at any time during the study at the discretion of the investigator. BMS should be contacted to discuss positive drug screen and/or blood alcohol level at the screening visit.

[u] 36-Item Short Form Health Survey

[v] Longitudinal Interval Follow-up Evaluation- Rating Impaired Functioning Tool

[w] The End of Study Form/Extension Baseline form should be completed when the patient completes the study, or upon early termination

Protocol Amendments. The CSR of the study includes a section summarizing protocol amendments and provides a summary table outline the changes relative to sample sizes of Ss (enrolled and randomized) and dates of the protocol changes (Section 4.5 of the CSR).

Reviewer Comment. *A review of the in-text information of Section 4.5 failed to reveal a sufficient reason to render the pivotal study inadequate for the purposes of the review.*

Protocol Deviations and Per Protocol Population Analyses on the Primary Efficacy Variable.

Reviewer comments. *Table 4.3 in the CSR shows protocol deviations "considered to be potentially clinically relevant that were captured in the database and those that were considered to be clinical study management issues (not found in the database)."*

Based on a review of Table 4.3 the treatment groups were generally balanced on protocol deviations (PDs) and the number of subjects within a given category of PDs was generally small within each treatment group (0 to approximately 10 subjects in a given treatment group) with some exceptions. The following table (excerpts of Table 4.3 in the CSR) shows the most common types of PDs. While Arip subjects tended to receive more of some of the prohibited (e.g. anticholinergics, benzodiazepines) treatment group differences were not substantial enough to consider the study as inadequate for showing efficacy (while Arip and PBO treatment was DB). Moreover the per protocol population analyses of efficacy results showed significantly greater improvement on the YRMS in the Arip (N=201 per protocol Arip subjects) compared to the PBO groups (N=110 per protocol PBO subjects; p<0.001).

Table 4.3: Protocol Deviations of Clinical Relevance

	Number of Patients		
	Placebo	Aripiprazole	Total
Poor study drug compliance			
Treated patients with study medication not administrated per protocol	10	14	24
Mood stabilizer medication not administrated per protocol	12	22	40
Use of prohibited concomitant medications			
benzopdiazepines during Phase 3 [c]	24	37	61
Treated patients who used anticholinergics within 12 hours of efficacy or safety rating scales at any assessment during Phase 3	1	12	13
Treated patients who used more than 2 mg/day benztropine or biperiden during Phase 3	0	8	8

Disposition. Refer to Section 7.1.3.1 of this review.

Demographic Features and Baseline Psychiatric Status.

Reviewer Comments. *Treatment groups were generally similar on demographic features (as outlined in Table 5.3.1 of the CSR). The majority of subjects were at US sites (28% of subjects), female (54%), and "white" (91%) and the mean age of subjects was 42 years (range of 18-68 years). Treatment groups were also generally similar on key psychiatric features at baseline and as outlined below.*

The following outlines some key psychiatric features of the randomized subjects at baseline (as found in sections 5.3.2-3 of the CSR or in Tables 5.3.2 or 5.3.3. in this section of the CSR):

- 75% were manic and 25% were in the mixed episode
- 5% had psychotic features
- Baseline Mean Y-MRS total score was 23.1±5.4 units (median score of 22.0)
- Baseline mean CGI-BP overall was 4.1±0.9 (median score of 4.0, range of 1-7)
- Baseline mean PANSS positive subscale score was 13.7±5.3 units (median of 13, range of 7-37 units)
- Baseline mean MADRS total score of 10.1±7.1 unites (median of 8.0, range of 0-37).
- Mean or median age of onset of depressive or manic/mixed episodes was generally at approximate 24 to 27 years of age.
- Mean and median total number of manic episodes in a given patient's lifetime was 9.9±11.8 (range of 1-80) and 5.0, respectively.

Exposure during the DB Phase.
111 PBO and 199 Arip subjects completed the DB phase (as listed in Table 6.1. of the CSR). A total of 130 PBO and 247 Arip subjects were in the ITT efficacy population (randomized subjects who had at least one dose of study drug and at least one efficacy assessment after starting the study drug).
Mean weekly doses of Arip during the DB phase were as follows:

- 15.5 mg/day in the first week
- 17.3-19.0 mg/day in subsequent weeks

Reviewer Comments on Exposure in "mood stabilizer" subgroups.
A review of Tables S.4.2-3 in the appendix of the CSR revealed that valproate and lithium subgroups were generally similar on exposure of DB treatment (on the mean weekly dose-level of Arip treatment), as shown below.

Table S.4.2:
Number of Patients Receiving Double-Blind Study Medication and Mean and Range of Weekly Mean Daily Dose, Lithium Patients, Safety Sample

	Placebo		Aripiprazole			
Days	N	(%)	N	(%)	Mean (mg/day)	Min - Max (mg/day)
1 - 7	50	(100)	106	(100)	15.6	10.7 - 45.0
8 - 14	49	(98.0)	101	(95.3)	17.4	6.4 - 30.0
15 - 21	47	(94.0)	98	(92.5)	18.4	7.5 - 30.0
22 - 28	47	(94.0)	89	(84.0)	19.3	10.7 - 30.0
29 - 35	45	(90.0)	85	(80.2)	18.9	12.9 - 30.0
36 - 42	41	(82.0)	78	(73.6)	19.2	15.0 - 30.0
43 - 49	20	(40.0)	31	(29.2)	18.4	15.0 - 30.0
> 49	3	(6.0)	8	(7.5)	17.5	15.0 - 30.0

Table S.4.3:
Number of Patients Receiving Double-Blind Study Medication and Mean and Range of Weekly Mean Daily Dose, Valproate Patients, Safety Sample

	Placebo		Aripiprazole			
Days	N	(%)	N	(%)	Mean (mg/day)	Min - Max (mg/day)
1 - 7	80	(100)	147	(100)	15.5	10.7 - 30.0
8 - 14	80	(100)	141	(95.9)	17.3	6.0 - 30.0
15 - 21	77	(96.3)	135	(91.8)	18.3	10.7 - 30.0
22 - 28	76	(95.0)	128	(87.1)	18.3	2.1 - 30.0
29 - 35	74	(92.5)	123	(83.7)	18.6	6.4 - 30.0
36 - 42	74	(92.5)	119	(81.0)	18.9	8.6 - 40.7
43 - 49	26	(32.5)	50	(34.0)	18.5	12.0 - 45.0
> 49	3	(3.8)	6	(4.1)	20.0	15.0 - 45.0

Weekly exposure of lithium or valproate treatment as shown below was adequate.

The following tables were copied from the sponsor's supplemental tables (attached to the CSR).

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Table S.4.4:
Number of Patients Receiving Lithium and Mean and Range of Weekly Mean Daily Lithium Dose during 6-Week Double-Blind Treatment Phase, Safety Sample

		Placebo				Aripiprazole			
	Days	N	(%)	Mean	Min - Max	N	(%)	Mean	Min - Max
Lithium Dosing	1 - 7	50	(100)	991.2	500.0 - 1500.0	105	(100)	1135.8	500.0 - 1800.0
	8 - 14	49	(98.0)	1005.2	500.0 - 1500.0	101	(96.2)	1146.5	500.0 - 1800.0
	15 - 21	47	(94.0)	1009.2	464.3 - 1500.0	96	(91.4)	1148.7	500.0 - 1800.0
	22 - 28	47	(94.0)	1008.3	625.0 - 1500.0	89	(84.8)	1138.3	464.3 - 1800.0
	29 - 35	45	(90.0)	994.8	625.0 - 1500.0	85	(81.0)	1158.2	500.0 - 1800.0
	36 - 42	40	(80.0)	985.3	520.0 - 1500.0	78	(74.3)	1160.3	500.0 - 1750.0
	43 - 49	19	(38.0)	977.6	500.0 - 1500.0	31	(29.5)	1129.0	750.0 - 1500.0
	> 49	3	(6.0)	972.4	900.0 - 1017.2	8	(7.6)	1031.3	900.0 - 1250.0

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Table S.4.5:
Number of Patients Receiving Valproate and Mean and Range of Weekly Mean Daily Valproate Dose during 6-Week Double-Blind Treatment Phase, Safety Sample

		Placebo				Aripiprazole			
	Days	N	(%)	Mean	Min - Max	N	(%)	Mean	Min - Max
Valproate Dosing	1 - 7	80	(100)	1207.6	571.4 - 2250.0	146	(100)	1203.9	500.0 - 3000.0
	8 - 14	79	(98.8)	1182.2	714.3 - 2250.0	139	(95.2)	1205.4	464.3 - 3000.0
	15 - 21	76	(95.0)	1168.1	428.6 - 2250.0	134	(91.8)	1195.6	464.3 - 3000.0
	22 - 28	75	(93.8)	1171.0	500.0 - 2250.0	127	(87.0)	1203.2	166.7 - 3000.0
	29 - 35	74	(92.5)	1178.2	500.0 - 2250.0	121	(82.9)	1219.3	250.0 - 3000.0
	36 - 42	74	(92.5)	1178.9	500.0 - 2250.0	118	(80.8)	1225.3	250.0 - 3000.0
	43 - 49	25	(31.3)	1165.0	500.0 - 2250.0	49	(33.6)	1258.7	500.0 - 3000.0
	> 49	3	(3.8)	1166.7	750.0 - 1500.0	6	(4.1)	1705.6	1250.0 - 2500.0

The following table (copied from the CSR) shows the incidence of Ss in each adjunctive subgroup with serum levels of the concomitant "mood stabilizer" within therapeutic range (as specified below):

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Table S.4.8:
Number and Percentage of Patients with Mood Stabilizer Plasma Levels within Therapeutic Range, Safety Sample

	Lithium		Valproate	
	Placebo	Aripiprazole	Placebo	Aripiprazole
Visit (c)	Number (a)/Number Assessed(%)	Number (a)/Number Assessed(%)	Number (a)/Number Assessed(%)	Number (a)/Number Assessed(%)
Day 4	30/ 35 (85.7)	55/ 70 (78.6)	46/ 53 (86.8)	83/ 95 (87.4)
Week 1	38/ 46 (82.6)	69/ 86 (80.2)	69/ 73 (94.5)	112/129 (86.8)
Week 2	30/ 43 (69.8)	76/ 92 (82.6)	68/ 74 (91.9)	111/129 (86.0)
Week 3	33/ 45 (73.3)	66/ 87 (75.9)	65/ 73 (89.0)	103/126 (81.7)
Week 4	31/ 42 (73.8)	67/ 86 (77.9)	62/ 68 (91.2)	98/121 (81.0)
Week 5	29/ 36 (80.6)	63/ 74 (85.1)	60/ 71 (84.5)	97/115 (84.3)
Week 6	27/ 39 (69.2)	60/ 76 (78.9)	58/ 70 (82.9)	93/114 (81.6)

(a) Therapeutic range for Lithium: 0.6 - 1.0 mmol/L.
(b) Therapeutic range for Valproate: 50 - 125 ug/mL.
(c) For each timepoint, the last observation within the study day interval is used.

Exposure During the OL Extension Phase (as discussed in Section 7.2.1.3 of this review)
The following are tables on exposure copied from the 1/18/08 response submission.

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Attachment Q.1B.7:
Number and Percentage of Patients Who Received Aripiprazole by Overall Mean Dose Category and Duration of Therapy:
Open Label Extension Phase in Study CN138134 (Lithium Patients Only), Safety Sample

Total Dur. of Trt (days)	N	Unavailable(a) (%)	<=12.5 N	(%)	>12.5 - <=17.5 N	(%)	>17.5 - <=25 N	(%)	>25 - <=32.5 N	(%)	> 32.5 N	(%)	Total N	(%)
1-20	0		0		5	(4.7)	0		0		0		5	(4.7)
21-41	0		2	(1.9)	12	(11.3)	4	(3.8)	6	(5.7)	0		24	(22.6)
42-89	0		1	(0.9)	15	(14.2)	1	(0.9)	6	(5.7)	0		23	(21.7)
90-119	0		0		3	(2.8)	0		0		0		3	(2.8)
120-149	0		0		5	(4.7)	2	(1.9)	1	(0.9)	0		8	(7.5)
150-179	0		0		5	(4.7)	1	(0.9)	1	(0.9)	0		7	(6.6)
180-269	0		1	(0.9)	14	(13.2)	1	(0.9)	0		1	(0.9)	17	(16.0)
270-359	0		0		12	(11.3)	3	(2.8)	4	(3.8)	0		19	(17.9)
Total	0		4	(3.8)	71	(67.0)	12	(11.3)	18	(17.0)	1	(0.9)	106	(100.0)

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Attachment Q.1B.8:
Number and Percentage of Patients Who Received Aripiprazole by Overall Mean Dose Category and Duration of Therapy:
Open Label Extension Phase in Study CN138134 (Valproate Patients Only), Safety Sample

Total Dur. of Trt (days)	N	Unavailable(a) (%)	<=12.5 N	(%)	>12.5 - <=17.5 N	(%)	>17.5 - <=25 N	(%)	>25 - <=32.5 N	(%)	> 32.5 N	(%)	Total N	(%)
1-20	0		7	(4.0)	14	(8.0)	1	(0.6)	5	(2.9)	0		27	(15.4)
21-41	0		5	(2.9)	20	(11.4)	0		9	(5.1)	0		34	(19.4)
42-89	0		1	(0.6)	28	(16.0)	3	(1.7)	7	(4.0)	0		39	(22.3)
90-119	0		0		5	(2.9)	0		2	(1.1)	0		7	(4.0)
120-149	0		0		2	(1.1)	0		2	(1.1)	1	(0.6)	5	(2.9)
150-179	0		0		4	(2.3)	0		1	(0.6)	0		5	(2.9)
180-269	0		1	(0.6)	16	(9.1)	4	(2.3)	2	(1.1)	0		23	(13.1)
270-359	0		1	(0.6)	29	(16.6)	2	(1.1)	3	(1.7)	0		35	(20.0)
Total	0		15	(8.6)	118	(67.4)	10	(5.7)	31	(17.7)	1	(0.6)	175	(100.0)

Concomitant medications used during the DB Phase.
The following outlines the most frequently used medications, as summarized by the sponsor:

- Anxiolytics (20.9% Arip Ss, 24.6% PBO Ss)
- Other analgesics and antipyretics (21.3% Arip Ss, 23.1% PBO Ss).

Reviewer comment. *Treatment groups were balanced on the above commonly used concomitant medications.*

The sponsor notes that concomitant medication for the potential treatment of EPS occurred in 18.6% of Arip Ss and 6.9% PBO Ss.

In light of the above exposures on concomitant use of anxiolytic agents the following table is of excerpts copied from the sponsor's summary table outlining methods on allowed and prohibited use of concomitant medications.

Table 3.4.7: Restricted Concomitant Medication

	Phase 1 (Screening & Psychotropic Washout)	Phase 2 (Lithium/Valproate Monotherapy and Baseline)	Phase 3 (Double-Blind Treatment)
Benzodiazepines[b] (for escalating manic symptoms or insomnia)	Taper off	≤ 4mg/day lorazepam or equivalents during Week 1 and 3 mg/day lorazepam or equivalents during Week 2	≤ 2mg/day lorazepam or equivalents for a maximum of 10 days (cumulative) Permitted only through Week 4

[b] Patients were permitted adjunctive use of benzodiazepines. Alprazolam, estazolam, and triazolam were not allowed. No benzodiazepines were allowed within 8 hours of efficacy or safety rating scale assessments during all phases of the study.

Reviewer comments. *Refer to the previous subsection on PDs involving patients using benzodiazepine related agents. As previously noted the per protocol population analysis on the primary efficacy variable was positive for efficacy. The exposure on concomitant medications is not considered substantial enough to render the study inadequate as a pivotal efficacy trial for the purposes of this review.*

10.2 Appendix to the Integrated Review of Efficacy (Tables were provided by the sponsor and refer to Section 6 for details)

Table 7.1A: Summary of Efficacy Results for Changes from Baseline and Changes from Preceding Phase at Week 6, LOCF Data Set, Efficacy Sample

Measurement / Mood Stabilizer	Placebo N	Placebo Baseline: Mean (SE)	Placebo Change: Mean (SE)	Aripiprazole N	Aripiprazole Baseline: Mean (SE)	Aripiprazole Change: Mean (SE)	Treatment Comparison Aripiprazole–Placebo Difference (95% CI)	p-value
Primary Efficacy Endpoint: Y-MRS Total Score								
Overall	130	22.72 (0.47)	-10.70 (0.69)	247	23.12 (0.34)	-13.31 (0.50)	-2.62 (-4.29 , -0.95)	0.002
Lithium	50	22.28 (0.63)	-10.75 (1.11)	102	22.31 (0.44)	-12.35 (0.77)	-1.60 (-4.27 , 1.07)	0.238
Valproate	80	23.25 (0.66)	-10.72 (0.88)	145	23.88 (0.49)	-14.00 (0.65)	-3.29 (-5.44 , -1.14)	0.003
Key Secondary Efficacy Endpoint: CGI-BP Severity of Illness (Mania)								
Overall	130	4.12 (0.06)	-1.56 (0.11)	246	4.21 (0.05)	-1.89 (0.08)	-0.33 (-0.60 , -0.07)	0.014
Lithium	50	4.04 (0.09)	-1.51 (0.18)	102	4.06 (0.06)	-1.63 (0.12)	-0.12 (-0.54 , 0.31)	0.584
Valproate	80	4.23 (0.09)	-1.61 (0.14)	144	4.35 (0.06)	-2.09 (0.10)	-0.48 (-0.82 , -0.13)	0.007
Other Efficacy Endpoints:								
CGI-BP Severity of Illness (Depression)								
Overall	130	1.74 (0.10)	0.03 (0.08)	246	1.79 (0.07)	-0.09 (0.06)	-0.12 (-0.32 , 0.09)	0.262
Lithium	50	1.84 (0.17)	0.28 (0.14)	102	1.77 (0.12)	-0.04 (0.10)	-0.32 (-0.66 , 0.02)	0.066
Valproate	80	1.66 (0.13)	-0.18 (0.10)	144	1.78 (0.10)	-0.16 (0.08)	0.02 (-0.23 , 0.28)	0.871

Table 7.1A: Summary of Efficacy Results for Changes from Baseline and Changes from Preceding Phase at Week 6, LOCF Data Set, Efficacy Sample

Measurement / Mood Stabilizer	Placebo N	Placebo Baseline: Mean (SE)	Placebo Change: Mean (SE)	Aripiprazole N	Aripiprazole Baseline: Mean (SE)	Aripiprazole Change: Mean (SE)	Treatment Comparison Aripiprazole–Placebo Difference (95% CI)	p-value
CGI-BP Severity of Illness (Overall)								
Overall	130	4.05 (0.08)	-1.29 (0.11)	246	4.12 (0.06)	-1.55 (0.08)	-0.27 (-0.53 , 0.00)	0.048
Lithium	50	4.10 (0.11)	-1.19 (0.17)	102	4.05 (0.08)	-1.43 (0.12)	-0.23 (-0.65 , 0.19)	0.274
Valproate	80	4.04 (0.11)	-1.37 (0.14)	144	4.19 (0.08)	-1.67 (0.10)	-0.30 (-0.64 , 0.04)	0.083
CGI-BP Change from Preceding Phase (Mania)								
Overall	130	-	2.64 (0.12)	246	-	2.33 (0.09)	-0.31 (-0.60 , -0.02)	0.037
Lithium	50	-	2.56 (0.19)	102	-	2.42 (0.14)	-0.13 (-0.60 , 0.33)	0.572
Valproate	80	-	2.69 (0.15)	144	-	2.26 (0.11)	-0.42 (-0.79 , -0.05)	0.025
CGI-BP Change from Preceding Phase (Depression)								
Overall	130	-	3.77 (0.10)	246	-	3.64 (0.07)	-0.14 (-0.38 , 0.10)	0.254
Lithium	50	-	3.93 (0.17)	102	-	3.64 (0.12)	-0.29 (-0.69 , 0.11)	0.149
Valproate	80	-	3.65 (0.12)	144	-	3.61 (0.09)	-0.03 (-0.33 , 0.26)	0.818
CGI BP Change from Preceding Phase (Overall)								
Overall	130	-	2.90 (0.12)	246	-	2.57 (0.09)	-0.33 (-0.62 , -0.03)	0.029
Lithium	50	-	2.88 (0.20)	102	-	2.61 (0.14)	-0.28 (-0.76 , 0.21)	0.263
Valproate	80	-	2.89 (0.15)	144	-	2.54 (0.11)	-0.35 (-0.73 , 0.02)	0.063

Table 7.1A: Summary of Efficacy Results for Changes from Baseline and Changes from Preceding Phase at Week 6, LOCF Data Set, Efficacy Sample

Measurement / Mood Stabilizer	Placebo N	Placebo Baseline: Mean (SE)	Placebo Change: Mean (SE)	Aripiprazole N	Aripiprazole Baseline: Mean (SE)	Aripiprazole Change: Mean (SE)	Treatment Comparison Aripiprazole–Placebo Difference (95% CI)	p-value
MADRS Total Score								
Overall	130	10.12 (0.64)	-1.12 (0.63)	246	10.07 (0.46)	-2.33 (0.46)	-1.21 (-2.72 , 0.30)	0.117
Lithium	50	10.80 (1.07)	0.53 (1.05)	102	10.01 (0.75)	-1.78 (0.73)	-2.31 (-4.83 , 0.22)	0.073
Valproate	80	9.63 (0.77)	-2.58 (0.76)	144	10.06 (0.58)	-2.98 (0.57)	-0.40 (-2.28 , 1.48)	0.674
PANSS Total Score								
Overall	129	50.78 (1.56)	-6.43 (1.00)	243	52.68 (1.14)	-9.55 (0.73)	-3.12 (-5.52 , -0.71)	0.011
Lithium	49	48.94 (2.16)	-5.33 (1.64)	102	50.32 (1.50)	-7.20 (1.14)	-1.88 (-5.83 , 2.07)	0.349
Valproate	80	52.76 (2.13)	-7.41 (1.23)	141	55.00 (1.60)	-11.34 (0.93)	-3.93 (-6.97 , -0.88)	0.012
PANSS Positive Subscale Score								
Overall	129	13.01 (0.47)	-2.91 (0.34)	243	13.92 (0.34)	-4.12 (0.24)	-1.21 (-2.02 , -0.40)	0.004
Lithium	49	12.49 (0.68)	-2.76 (0.54)	102	13.34 (0.47)	-3.54 (0.37)	-0.78 (-2.08 , 0.52)	0.238
Valproate	80	13.55 (0.62)	-3.03 (0.42)	141	14.49 (0.47)	-4.52 (0.32)	-1.48 (-2.53 , -0.44)	0.005
PANSS Negative Subscale Score								
Overall	129	9.67 (0.41)	-0.41 (0.25)	243	9.81 (0.30)	-0.70 (0.18)	-0.29 (-0.88 , 0.30)	0.336
Lithium	49	9.45 (0.58)	-0.18 (0.40)	102	9.20 (0.40)	-0.29 (0.28)	-0.10 (-1.06 , 0.85)	0.832
Valproate	80	10.00 (0.55)	-0.63 (0.31)	141	10.39 (0.42)	-1.02 (0.23)	-0.39 (-1.15 , 0.37)	0.316

Table 7.1A: Summary of Efficacy Results for Changes from Baseline and Changes from Preceding Phase at Week 6, LOCF Data Set, Efficacy Sample

Measurement / Mood Stabilizer	Placebo N	Placebo Baseline: Mean (SE)	Placebo Change: Mean (SE)	Aripiprazole N	Aripiprazole Baseline: Mean (SE)	Aripiprazole Change: Mean (SE)	Treatment Comparison Aripiprazole–Placebo Difference (95% CI)	p-value
PANSS Cognitive Subscale Score								
Overall	129	13.43 (0.52)	-2.00 (0.30)	243	14.00 (0.38)	-3.05 (0.22)	-1.05 (-1.78 , -0.31)	0.005
Lithium	49	12.35 (0.63)	-1.44 (0.47)	102	12.94 (0.44)	-2.08 (0.32)	-0.64 (-1.77 , 0.48)	0.260
Valproate	80	14.51 (0.75)	-2.46 (0.39)	141	15.06 (0.56)	-3.76 (0.29)	-1.30 (-2.27 , -0.34)	0.008
PANSS Hostility Subscale Score								
Overall	129	8.46 (0.30)	-2.09 (0.23)	243	8.82 (0.22)	-3.01 (0.17)	-0.91 (-1.46 , -0.36)	0.001
Lithium	49	7.96 (0.42)	-1.84 (0.35)	102	8.25 (0.29)	-2.42 (0.24)	-0.58 (-1.43 , 0.26)	0.175
Valproate	80	8.98 (0.42)	-2.29 (0.29)	141	9.38 (0.32)	-3.42 (0.22)	-1.12 (-1.85 , -0.40)	0.002

Results for the Overall Efficacy are obtained from:
ANOVA model, controlling for treatment and mood stabilizer for baseline.
ANCOVA model, controlling for treatment, mood stabilizer and baseline value for mean change from baseline.
ANCOVA model, controlling for treatment, mood stabilizer and baseline CGI-BP Severity for mean change from preceding phase.
Means, differences in means, 95% CI for the differences, and p-values are based on the ANOVA/ANCOVA model.

Results for the Lithium and Valproate Subgroup are obtained from:
ANOVA model, controlling for treatment for baseline.
ANCOVA model, controlling for treatment and baseline value for mean change from baseline.
ANCOVA model, controlling for treatment and baseline CGI-BP Severity for mean change from preceding phase.
Means, differences in means, 95% CI for the differences, and p-values are based on the ANOVA/ANCOVA model.
SE = standard error

Table 7.2A: Adjusted Mean Change from Baseline in Y-MRS Total Score, LOCF Data Set, Efficacy Sample

	Visit	Placebo N	Placebo Mean (a) (SE)	Aripiprazole N	Aripiprazole Mean (a) (SE)	Treatment Comparisons (b) Aripiprazole – Placebo Difference (95% CI)	p-value
Mean Baseline		130	22.72 (0.47)	247	23.12 (0.34)	0.40 (-0.74,1.54)	0.494
Mean Change from Baseline to	Day 4	97	-2.94 (0.45)	191	-3.59 (0.32)	-0.65 (-1.73,0.44)	0.243
	Week 1	130	-4.31 (0.49)	247	-5.68 (0.36)	-1.37 (-2.56,-0.18)	0.024
	Week 2	130	-6.61 (0.56)	247	-8.16 (0.41)	-1.55 (-2.91,-0.19)	0.026
	Week 3	130	-8.12 (0.60)	247	-10.33 (0.44)	-2.21 (-3.66,-0.77)	0.003
	Week 4	130	-9.48 (0.63)	247	-11.16 (0.45)	-1.68 (-3.19,-0.17)	0.029
	Week 5	130	-10.15 (0.67)	247	-12.41 (0.48)	-2.25 (-3.86,-0.65)	0.006
	Week 6	130	-10.70 (0.69)	247	-13.31 (0.50)	-2.62 (-4.29,-0.95)	0.002

(a) Y-MRS Total Score is from 0 to 60.
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment and mood stabilizer, is used for baseline.
ANCOVA model, controlling for treatment, mood stabilizer and baseline value, is used for mean change from baseline.
Means, differences in means, 95% CI for the differences, and p-values are based on the ANOVA/ANCOVA model.

Table 7.3A: Adjusted Mean Change from Baseline in CGI-BP Severity of Illness (Mania) Score, LOCF Data Set, Efficacy Sample

		Placebo			Aripiprazole			Treatment Comparisons (b) Aripiprazole - Placebo		
	Visit	N	Mean (a)	(SE)	N	Mean (a)	(SE)	Difference	(95% CI)	p-value
Mean Baseline		130	4.12	(0.06)	246	4.21	(0.05)	0.08	(-0.07,0.24)	0.302
Mean Change from Baseline to	Day 4	97	-0.38	(0.07)	191	-0.36	(0.05)	0.01	(-0.15,0.17)	0.892
	Week 1	130	-0.56	(0.08)	246	-0.63	(0.06)	-0.07	(-0.26,0.11)	0.421
	Week 2	130	-0.92	(0.09)	246	-1.03	(0.06)	-0.11	(-0.33,0.10)	0.303
	Week 3	130	-1.16	(0.10)	246	-1.42	(0.07)	-0.26	(-0.50,-0.02)	0.031
	Week 4	130	-1.30	(0.10)	246	-1.55	(0.07)	-0.25	(-0.49,-0.01)	0.042
	Week 5	130	-1.48	(0.10)	246	-1.75	(0.08)	-0.27	(-0.52,-0.02)	0.036
	Week 6	130	-1.56	(0.11)	246	-1.89	(0.08)	-0.33	(-0.60,-0.07)	0.014

(a) CGI-BP Severity (Mania) Score is from 1 (normal) to 7 (very severely ill).
A negative change from baseline signifies improvement.
(b) ANOVA model, controlling for treatment and mood stabilizer, is used for baseline.
ANCOVA model, controlling for treatment, mood stabilizer and baseline value, is used for mean change from baseline.
Means, differences in means, 95% CI for the differences, and p-values are based on the ANOVA/ANCOVA model.

PROGRAM SOURCE: /wwbdm/clin/proj/cn/138/134/val/stats/eff_ancova_tables.sas RUN DATE: 08MAR07 08:02

10.3 Appendix to the Integrated Review of Safety (Section 7)

A Possible Discrepancy between the Narrative, A Line Listing of Ss, and the above Table Regarding S C...134-42-108) as Discussed in Section 7.1.2 of this Review

Upon review of bolded SAE terms found in the narrative section of the Appendix to Module 2.7.4 (Supplemental Table S.6.23A of the CSR) the undersigned review found that the Arip subject with the SAE of akathisia also had the SAE of somnolence reported on Day 12 (CN138134-42-108). This subject was also an ADO. The narrative specifies the following:

"Patient CN138134-42-108: Discontinued due to SAEs of akathisia and somnolence"

Yet the narrative description that follows the above heading for this patient does not mention somnolence and instead indicates that akathisia occurred and progressed to an SAE that resulted in hospitalization of the patient and resulted in early dropout (an ADO). This subject is also listed in the line listing as having an SAE of akathisia (Table S.6.23). The possible presence of somnolence in this subject does not alter overall conclusions that no new and clinically remarkable findings were revealed (both events are known to occur with Arip treatment).

Suicidality in 3 Arip-valproate Subjects (1 SAE of Bipolar disorder and 2 SAEs and ADOs of suicidal related events, as discussed in Section 7.1.2 of this review

Refer to the previous discussion on suicidality and psychiatric related AEs. Given these observations and the high risk for mortality associated with suicidality, the narratives of the 3 Ss with suicidality were reviewed. Based on observations described below these events do not provide adequate evidence for a new and unexpected safety signal (events were not unexpected for the patient population and/or the course of their Bipolar I disorder, and/or involved additional factors or risk factor). However, the potential role of the study drugs cannot be ruled out.

Subject CN138134-40-212: *The Arip subject with the SAE of Bipolar I Disorder (as found in the line listing in Table S.6.23 in the CSR) had the SAE of Bipolar disorder-depression. The S was found by the undersigned reviewer to also have suicidal thoughts (this observation was found as a result of reviewing the narrative summary on this S). The S had suicidal thoughts after having lost work and experiencing marital difficulties. The depressive episode occurred 29 days after resolution of a manic episode. Prior to this SAE the S was having a manic episode that was reported as an SAE of "exacerbation of Bipolar disorder" that began on Day -8 during valproate monotherapy (per narrative of subject CN138134-40-212 in Table S.6.23A of the CSR). The subsequent depressive episode continued for the remainder of the DB phase. The S also had akathisia and agitation among other ongoing AEs at the time of the SAE of "Bipolar disorder-depression."*

Patient CN138134-104-244*: Based on a reviewer of this S's narrative the S appeared to have developed suicidality associated with improvement of his Bipolar disorder and while gaining insight on the adverse effect of his illness on his level of function. This clinical presentation has been reported in a number of psychiatric patients.*

Patient CN138134-115-477 *had a history of polysubstance abuse and appeared to exhibit poor impulse control ("suddenly felt severe depression" and consumed alcohol and buspirone, "wanting to die" on Day 6 of valproate-Arip DB treatment). This behavior appears consistent with his past history and underlying psychiatric conditions. The potential role of the study drugs cannot be ruled out but appear to be unlikely.*

Individual ADOs in the DB Phase of Study C-134 as Noted by the Sponsor or by the Undersigned review (corresponds to Section 7.1.3.2 of this review)

Additional Individual Ss noted by the Undersigned Reviewer

Elevated CPK
Section 7.1.3.3 of this review regarding S CN…134-135-575 who an ADO due to elevated CPK while receiving Arip and lithium treatment. This S was also manic (which can lead to elevated CPK).

ADO of Rectal Hemorrhage
Rectal hemorrhage is unexpected; therefore the narrative of S CN138134-124-225 who developed this AE was reviewed. This Arip-lithium treated S also had diarrhea associated with rectal hemorrhage and was likely a key factor in the development of rectal hemorrhage. She had a number of other AEs at that time that included nausea, vomiting, decreased concentration, and restlessness among others. These additional AEs, as well as the diarrhea are not unexpected events for Arip and/or lithium. The S had bradycardia at baseline and on subsequent study days (HR was as low as 42 bpm). She was a 26 year old with history of tobacco use, infrequent alcohol and cannabis use. Marijuana and/or nicotine can affect vital signs.

ADO of Elevated Lithium noted in a 1/18/08 Response Submission that cannot be Found in the Sponsor's Table S.6.25 in the CSR (and as shown in Section 7.1.3.2 of this review)
Only 1 ADO was reported due to this event (as noted in the 1/18/08 response submission). Prior to this submission the undersigned reviewer found this S (C…134-111-341) among the narratives in the CSR of Study C...134 (in the original N20 submission).

Note that despite the above ADO of "elevated lithium," the term "elevated lithium" or a related term cannot be found in the sponsor's table S.6.25 on ADOs (in the CSR that is shown in Section 7.1.3.2. of this review). Section 7.1.4.2 of this submission discusses cases of elevated lithium or lithium toxicity provided upon request in a 1/18/08 submission.

An SAE of lithium toxicity occurred in another S C...134-11-120 is summarized in Section 7.1.2 of this review.

An additional S is described (S C…-17-106) in Section 7.1.2 of this review who first had an SAE of "lithium overdose" and had AEs that were consistent with lithium toxicity. Within hours after this initial SAE her condition progressed to life-threatening SAEs that culminated in her death. The clinical presentation of this S was complicated.

A review of Bolded Text in the Narrative Section of ADOs in the DB Phase of Study C-134 (Table S.6.27A of the CSR)
A possible discrepancy between the sponsor's table and the narrative of an ADO due to elevated lithium was found (in which this term or a related term cannot be found in the above summary table). Therefore, the undersigned reviewer conducted a review of the bolded terms (ADO) that

appear in as headings for each narrative in the CSR (Table S.6.27A). This review was conducted to find any bolded terms that are unexpected for the population or the study drugs involved. None were revealed other than those described in this review.

A S with Multiple AEs leading to an ADO (agitation/restlessness in limbs/dry mouth/dry skin around lips, gastrointestinal burning, tremor in hands, increased appetite, and others)
S CN138134-119-276 was found upon review of the bolded terms in the narrative table (see the previous paragraph) and is described due to the large number of AE terms reported as AEs leading to the ADO. These events are expected of either lithium and/or Arip.

The following provides more details on this S. The ADO occurred on Day 8 of the DB phase, although some of the events started on Day 1 of treatment (arip and lithium) and additional AEs were reported during treatment (e.g. nausea, sleepiness). The lithium level was 0.8 mEq/l on Day 1 and 0.6 mEq/l on Day 6 (after a dose increase from 600 mg to 1200 mg daily). No potentially clinically relevant abnormalities on clinical parameters were described.

ADOs due to Sedation, Somnolence or Loss of Consciousness in the DB Phase of Study C…134, as Discussed in Section 7.1.3.2 of this review.

Sedation or Loss of Consciousness
Because of an atypical case of an SAE of loss of consciousness associated with sedation (SC...134-17-106 described in Section 7.1 who eventually died and an ADO and SAE in S C…134-15-32 described in Section 7.1.2 a review of bolded AE terms (that appear in the narrative section in Table S.6.27A in the CSR) was conducted to look for these events or potentially related events (e.g. syncope, somnolence). 3 additional Ss were found from this search but these Ss were not described as having syncopal episodes or profound sedation. These Ss are summarized below.

C...-148-590: Somnolence was reported on Day 31. Additional AEs were reported that are AEs expected with lithium or Arip treatment (e.g. hand tremors, dry mouth, dry skin, nervousness). The narrative does not describe any syncopal events in this S. The ADO occurred on Day 38. One observation described in the narrative was a HR of 50 bpm on Day 22 (compared to 78 or 104 at baseline or other assessments during treatment). It is not clear why bradycardia occurred but this event occurred before the somnolence was reported. Her medical history includes occasional cannabis abuse and tobacco abuse which can affect vital signs. One consideration is the potential role of these 2 substances regarding the appearance of bradycardia and other AEs (consider the role of intoxication or withdrawal). The narrative does not note the use of these substances at the time of these events (and drug testing is not described).

Patient CN138134-151-475: this S had agitation and sedation reported but not other AEs or clinical abnormalities noted in the narrative.

Patient CN138134-79-60: *this S had agitation and sedation reported but not other AEs or clinical abnormalities noted in the narrative.*

Patient CN138134-133-569: this S did not have sedation or loss of consciousness reported as AEs leading to an ADO but is noted since he had potentially related AE terms that were bolded terms in the narrative (as AEs leading to the ADO). Dizziness and inability to concentrate/focus were listed and were reported on Day 1 of Arip and valproate treatment. No other events or clinical abnormalities are described in the narrative.

Selected ADOs in Study C-189 (OL Stabilization Phase)

ADOs of "Slurred Speech" or Dysarthria

A review of the narrative for S C...189-19-58 (slurred speech leading to an ADO) and S CN138189-18-264 (slurred speech, sedation, and akathisia reported as AEs leading to an ADO) did not reveal anything new or clinically remarkable that is not already adequately addressed in approved labeling of the study drugs (valproate and Arip). The latter S also had other events that were ongoing at that time (vomiting and elevated blood pressure). It is not clear why the patient's blood pressure was elevated (BP was 170/112 supine on Day 1 of 15 mg Arip and 750 mg valproate that normalized at the next assessment performed on Day 7 after discontinuing treatment on Day 6). This S had risk factors for atherosclerotic disease (46 year old male, history of tobacco use) and had a history of headaches. The other events were continuing when the S withdrew from the study. No other clinical abnormalities were noted. Acetaminophen was the only concomitant medication. Another consideration that may explain the vomiting, sedation, and dysarthria is the possibility of a hyperammonia that is reported with valproate treatment. Depakote labeling describes this condition (characterized by several of the events reported in this S), and emphasizes the importance of increased risk for developing this condition in patients with urea cycle disorders (e.g. with inborn errors of metabolism or decreased hepatic mitochondrial activity). The narrative of this patient does not describe any testing of ammonia levels. The events (slurred speech, sedation and akathisia) "were continuing when the patient discontinued the trial due to these adverse events." However, the time of the S's last dose relative to when he was last assessed is not clear to the undersigned reviewer.

"Slurred speech" was reported in S C…189-19-5) and is an AE reported in patients receiving valproate. This S did not have vomiting, mental status-related or somnolence-related AEs reported as ongoing events during the time of the "slurred speech."

ADOs of Sedation in the OL Phase of Study C-189

An S with the SAE of loss of consciousness was previously summarized in which this event appeared to be due to profound sedation following 10 mg diazepam and Arip. 3 Ss with related AEs that led to ADOs occurred in the OL stabilization phase of Study -189. None these additional Ss were described as experiencing an episode of loss of consciousness (or profound sedation). These S were also not reported to have also received diazepam or related drug as follows:

- ***Patient CN138189-23-60:*** *had* ***"daytime sedation"*** *reported leading to an ADO. This S also had sweating, tremulousness, increased insomnia, increased appetite and nausea reported. The S had a history of marijuana use. No other clinical abnormalities were noted in the narrative during treatment.*
- ***Patient CN138189-19-152*** *had* ***sedation*** *leading to an ADO. This event was described as "mild" to "moderate" and no clinically remarkable abnormalities were reported (loss of consciousness was also not noted).*
- ***Patient CN138189-23-193*** *was an ADO due to* ***sedation*** *that was "moderate." No other abnormalities were noted.*

Fatigue and Cognitive Impairment in a S in Study C-189

Patient CN138189-5-34: the narrative of this S was reviewed because "cognitive impairment" is vague (and potentially serious) and the S also had fatigue (both reported on Day 1). The narrative did not describe any other abnormalities (except for increased thirst listed as an ongoing event at the time). This S was receiving valproate and Arip and study drug was stopped on Day 6.

Additional Search Strategies for a Potential Arip-Lithium Interaction Effect on Adverse Events (Provided Upon Request in a 1/18/08 Submission)
Corresponds to Section 7.1.4.2 of this Review

The sponsor was asked to explore their data for a potential interaction effect of Arip and lithium treatment, given the narrow therapeutic index with lithium and in light of adjunctive treatment group differences on ADOs and AEs. Section 7.1.4.2 and the below summarize selected results from the sponsors 1/18/08 submission (results described in Section 7.1.4.2 are potentially positive findings, given the caveat that these results are only considered as preliminary due to limitations with making these subgroup comparisons).

An Analyses of AEs Against Lithium Levels

The sponsor was asked to consider an analysis of AEs against lithium levels and to analyze AE data. However, the sample size of subjects in Study C-134 with elevated levels was insufficient to yield interpretable results (e.g. only 16 subjects with levels of ≥1.2 mEq/l). Therefore the sponsor did not analyze AEs against lithium levels.

Few subjects were reported to have lithium toxicity (e.g. reported as an SAE or AE leading to an ADO). These subjects are already described in previous sections in this review including one S who died (S C…17-106) initially presented with "lithium overdose" involving a lithium level of 1.05 mEq/l. This level is not remarkably high, given the life-threatening events (including arrhythmias) that followed, culminating in her death. However, this S was morbidly obese and was observed to have episodes of apnea, among other SAEs such that her clinical presentation was complicated.

Potential Lithium-Arip Interactions Effects on the Cardiovascular System

The sponsor was asked to provide results from any adjunctive studies with cardiovascular parameters (ECG, vital signs) near Tmax. The sponsor only described one small Phase I trial, while another Phase I trial described did not have assessments near Tmax. Both studies (Studies CN138021 and CN138127) failed to reveal a clinically remarkable signal.

Refer to Sections 7.1.8 and 7.1.9 for vital sign and ECG (and QT interval) results that did not reveal a new and clinically remarkable safety signal in Study C-134.

Table of the Incidence of AEs in Adjunctive Subgroups
Corresponds to Section 7.1.5.6 of this Review

Incidence of Treatment-Emergent AEs That Occurred in at Least 2 Percent of Patients in the Aripiprazole Group by Mood Stabilizer: 6-Week Combination Therapy Study in Acute Bipolar Mania (CN138134), Safety Sample

	Lithium		Valproate	
	Placebo	Aripiprazole	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	50	106	80	147
NUMBER OF MALE PATIENTS	22	52	33	70
NUMBER OF FEMALE PATIENTS	28	54	47	77
NUMBER OF PATIENTS WITH >=1 AES	30(60.0)	74(69.8)	40(50.0)	83(56.5)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	11(22.0)	48(45.3)	16(20.0)	44(29.9)
AKATHISIA	2(4.0)	30(28.3)	5(6.3)	17(11.6)
TREMOR	4(8.0)	14(13.2)	4(5.0)	9(6.1)
HEADACHE	3(6.0)	5(4.7)	5(6.3)	9(6.1)
DIZZINESS	1(2.0)	4(3.8)	0	7(4.8)
SEDATION	1(2.0)	4(3.8)	1(1.3)	7(4.8)
EXTRAPYRAMIDAL DISORDER	0	2(1.9)	1(1.3)	10(6.8)
PSYCHIATRIC DISORDERS	11(22.0)	23(21.7)	7(8.8)	29(19.7)
INSOMNIA	4(8.0)	8(7.5)	1(1.3)	12(8.2)
ANXIETY	0	6(5.7)	1(1.3)	3(2.0)
RESTLESSNESS	1(2.0)	3(2.8)	0	3(2.0)
DEPRESSION	4(8.0)	2(1.9)	0	5(3.4)
GASTROINTESTINAL DISORDERS	5(10.0)	20(18.9)	16(20.0)	29(19.7)
NAUSEA	1(2.0)	8(7.5)	5(6.3)	13(8.8)
DIARRHOEA	2(4.0)	4(3.8)	5(6.3)	7(4.8)
SALIVARY HYPERSECRETION	1(2.0)	4(3.8)	1(1.3)	5(3.4)
DRY MOUTH	1(2.0)	3(2.8)	0	3(2.0)
VOMITING	0	3(2.8)	0	7(4.8)
INFECTIONS AND INFESTATIONS	4(8.0)	13(12.3)	10(12.5)	13(8.8)
NASOPHARYNGITIS	2(4.0)	3(2.8)	1(1.3)	4(2.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4(8.0)	9(8.5)	5(6.3)	13(8.8)
FATIGUE	2(4.0)	2(1.9)	3(3.8)	5(3.4)
INVESTIGATIONS	1(2.0)	7(6.6)	4(5.0)	7(4.8)
WEIGHT INCREASED	0	3(2.8)	1(1.3)	3(2.0)

The incidence of AEs for a particular System Organ Class is the incidence of all AEs in that System Organ Class.
MedDRA Version: 9.1

10.4 Line-by-Line Labeling Review

A line-by-line review was not conducted. See Section 9.4 on key labeling issues.

REFERENCES

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/s/

Karen Brugge
2/25/2008 08:12:50 PM
MEDICAL OFFICER

Gwen Zornberg
3/5/2008 09:01:55 PM
MEDICAL OFFICER
Dr. Brugge recommends that this supplemental NDA be approved for aripiprazole in the adjunctive treatment of bipolar disorder (manic or mixed), given final agreement on labeling and no evidence to preclude approval from DSI.

ADDENDUM CLINICAL REVIEW

Application Type	NDA
Submission Number	21436
Submission Code	SE1 N020
Letter Date	7/11/07
Stamp Date	7/11/07
PDUFA Goal Date	5/11/08
Due Date	3/11/08
Reviewer Name	Karen Brugge, MD
Review Completion Date	2/28/08
Established Name	Aripiprazole
Trade Name	Abilify®
Therapeutic Class	atypical antipsychotic
Applicant	Otsuka Pharmaceutical Developmental & Commercialization, Inc
Priority Designation	S
Formulation	2, 5, 10, 15, 20, 30 mg oral tablet
Dosing Regimen	(b) (4) 15 mg/day starting dose
Indication	Adjunctive treatment (lithium or valproate)
Intended Population	Bipolar I Disorder

This addendum is being submitted due to an inadvertent error (regarding the incidence of adverse dropouts due to akathisia and tremor) regarding recommendations labeling for Section 6 of proposed labeling. These recommendations appear as a subsection "Key Safety Sections" under Section 9.4 of the original review of this NDA21436 N20. The following reflects the corrected version of this subsection ("Key Safety Sections" under Section 9.4) of the clinical review of this submission (regarding the incidence of adverse dropouts).

Key Safety Sections

(b) (4)

ADOs and Common AEs in Bipolar Monotherapy Trials under Section 6.2

The following recommendations are provided for revised sections of ADOs and common AEs in the monotherapy dataset.

ADOs and Common AEs

(b) (4)

(b) (4)

he below table is an excerpt of the Table 8.4 in the CSR.

Table 8.4: Incidence of Treatment-Emergent Adverse Events That Led to Discontinuation, Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	130	255
NUMBER OF MALE PATIENTS	55	122
NUMBER OF FEMALE PATIENTS	75	121
NUMBER OF PATIENTS WITH >=1 AE LEADING TO DISCONTINUATION	8(6.2)	30(11.9)
SYSTEM ORGAN CLASS / PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	2(1.5)	18(7.1)
AKATHISIA	1(0.8)	13(5.1)
TREMOR	1(0.8)	5(2.0)
DISTURBANCE IN ATTENTION	0	2(0.8)
SEDATION	0	2(0.8)
DIZZINESS	0	1(0.4)
SOMNOLENCE	0	1(0.4)
PSYCHIATRIC DISORDERS	6(4.6)	11(4.3)
AGITATION	0	2(0.8)
DEPRESSION	4(3.1)	2(0.8)
ANXIETY	0	1(0.4)
DEPRESSIVE SYMPTOM	0	1(0.4)
MANIA	1(0.8)	1(0.4)
NERVOUSNESS	0	1(0.4)
RESTLESSNESS	0	1(0.4)
SUICIDAL IDEATION	0	1(0.4)
SUICIDE ATTEMPT	0	1(0.4)

(b) (4)

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/s/

Karen Brugge
2/28/2008 04:46:29 PM
MEDICAL OFFICER

Gwen Zornberg
3/4/2008 09:17:31 AM
MEDICAL OFFICER
I concur with Dr. Brugge's recommendation to include in labeling the elevated risk observed of akathisia and tremor associated with discontinuation in the adjunctive aripiprazole group compared to adjunctive placebo.

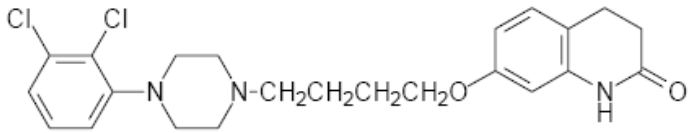
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S-019, S-020, S-022
21-713/S-014, S-015, S-017
21-729/S-006, S-007, S-009
21-866/S-006, S-007, S-009

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1

	1. ORGANIZATION ONDQA/DPE/Branch VII	2. NDA NUMBER 21-436
3. NAME AND ADDRESS OF APPLICANT (*City and State*) Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Blvd. Rockville, MD 20850		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)
6. NAME OF DRUG Abilify®	7. NONPROPRIETARY NAME Aripiprazole	SE2-019 / 07-11-2007
8. SUPPLEMENT PROVIDES FOR: Treatment of Bipolar I Disorder, Manic or Mixed, 15 mg starting dose.		9. AMENDMENTS DATES
10. PHARMACOLOGICAL CATEGORY Schizophrenia	11. HOW DISPENSED RX ✓ OTC	12. RELATED IND/sNDA/DMF
13. DOSAGE FORM(S) Tablets (21-436) Oral Solution (21-713) Orally Disintegrating Tablet (21-729) Injection (21-866)	14. POTENCY 2 mg, 5 mg, 10 mg, 15 mg, 20 mg & 30 mg 1 mg/mL (b) (4) 150 mL (b) (4) bottles) 10 mg, 15 mg (b) (4) 9.75 mg/1.3 mL	21-713/S-014 (08-28-2007) 21-729/S-006 (08-28-2007) 21-866/S-006 (08-28-2007)
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT: 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril $C_{23}H_{27}Cl_2N_3O_2$ 448.39 		16. RECORDS AND REPORTS CURRENT YES__ NO REVIEWED YES__ NO

17. COMMENTS

This bundled efficacy supplement provides for the use of Abilify in the treatment of bipolar I disorder, manic or mixed and a new 15 mg starting dose. The applicant has not provided any new CMC information other than some minor formatting changes to table numbers in How Supplied section of the labeling. The applicant has submitted a claim for categorical exclusion from filing an environmental assessment document under 21 CFR 25.31 (b); the expected introduction concentration (EIC) of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The applicant's claim is found to be acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Provided information is found to be adequate. This supplement and others in this bundle are recommended for approval from the standpoint of chemistry, manufacturing and controls.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Nallaperumal Chidambaram, Ph.D.		02-29-2007

DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: D. Bates HFD-130	Branch Chief: James Vidra Ph.D.

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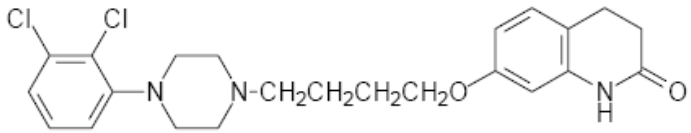
/s/

Nallaperumal Chidambaram
2/29/2008 11:00:44 AM
CHEMIST

Jim Vidra
2/29/2008 12:54:57 PM
CHEMIST

CHEMIST'S REVIEW #1

1. ORGANIZATION ONDQA/DPE/Branch VII		2. NDA NUMBER 21-436	
3. NAME AND ADDRESS OF APPLICANT (*City and State*) Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Blvd. Rockville, MD 20850		4. AF NUMBER	
		5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG Abilify®	7. NONPROPRIETARY NAME Aripiprazole	SE1-020	07-11-2007
8. SUPPLEMENT PROVIDES FOR: Adjunctive treatment of bipolar disorder, manic or mixed.		9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Schizophrenia	11. HOW DISPENSED RX ✓ OTC	12. RELATED IND/sNDA/DMF	
13. DOSAGE FORM(S) Tablets (21-436) Oral Solution (21-713) Orally Disintegrating Tablet (21-729) Injection (21-866)	14. POTENCY 2 mg, 5 mg, 10 mg, 15 mg, 20 mg & 30 mg 1 mg/mL (b) (4) 150 mL (b) (4) bottles) 10 mg, 15 mg, (b) (4) 9.75 mg/1.3 mL	21-713/S-015 (08-28-2007) 21-729/S-007 (08-28-2007) 21-866/S-007 (08-28-2007)	
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT: 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril $C_{23}H_{27}Cl_2N_3O_2$ 448.39 		16. RECORDS AND REPORTS CURRENT YES__ NO REVIEWED YES__ NO	

17. COMMENTS

This bundled efficacy supplement provides for the use of Abilify in the adjunctive treatment of bipolar disorder, manic or mixed. The applicant has not provided any new CMC information other than some minor formatting changes to table numbers in How Supplied section of the labeling. The applicant has submitted a claim for categorical exclusion from filing an environmental assessment document under 21 CFR 25.31 (b); the expected introduction concentration (EIC) of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The applicant's claim is found to be acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Provided information is found to be adequate. This supplement and others in this bundle are recommended for approval from the standpoint of chemistry, manufacturing and controls.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Nallaperumal Chidambaram, Ph.D.		02-29-2007

DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: D. Bates HFD-130	Branch Chief: James Vidra Ph.D.

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/s/

Nallaperumal Chidambaram
2/29/2008 11:03:25 AM
CHEMIST

Jim Vidra
2/29/2008 12:55:47 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S-019, S-020, S-022
21-713/S-014, S-015, S-017
21-729/S-006, S-007, S-009
21-866/S-006, S-007, S-009

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/Serial Number:	21-436 / S019
Drug Name:	Abilify (Aripiprazole)
Indication(s):	Treatment of Bipolar I Disorder, manic or mixed
Applicant:	Otsuka Pharmaceutical and Bristol-Meyers Squibb
Date(s):	Received: July 11, 2007;
	PDUFA Due Date: May 11, 2008
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewers:	Phillip Dinh, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.
	H.M. James Hung, Ph.D.
Medical Division:	Division of Psychiatric Products, HFD-130
Clinical Team:	Karen Brugge M.D., Medical Reviewer, HFD-130
	Gwen Zornberg M.D., Sc.D., Medical Team Leader, HFD-130
Project Manager:	Doris Bates Ph.D., HFD-130

Keywords: Analysis of covariance, Clinical studies, Endpoint analysis/LOCF, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Aripiprazole, at a starting dose of 15 mg/day and an option to titrate up to 30 mg/day, was efficacious in the acute treatment of bipolar I disorder as demonstrated by lowering the change from baseline in the Young Mania Rating Scale (YMRS) total score. The efficacy was supported by the results on the key secondary endpoint, Clinical Global Impression-Bipolar Version (CGI-BP) Severity of Illness Score (mania).

1.2 Brief Overview of Clinical Studies

This submission contains two studies that are similar in design. They were multi-center, randomized, double-blind, placebo-controlled studies that consisted of three phases. Phase 1 was a screening and washout period that lasted from 2 to 14 days. Phase 2 was a double-blind treatment phase that lasted for 12 weeks. Efficacy assessments were evaluated at week 3 to demonstrate the acute effect of aripiprazole against placebo. After week 3, patients who were randomized to placebo were switched to aripiprazole. Efficacy was evaluated again at week 12 to demonstrate that the effect observed at week 3 was maintained to week 12. The starting dose for aripiprazole was 15 mg/day with an option to increase to 30 mg/day. The primary efficacy outcome was the change from baseline in the Young Mania Rating Scale (YMRS) total score. The key secondary efficacy outcome was the change from baseline in the Clinical Global Impression-Bipolar Version (CGI-BP) Severity of Illness Score (mania).

Study CN138135 enrolled 715 patients from the United States who were diagnosed with bipolar I disorder. A total of 480 patients between the ages of 18 and 69 were randomized. Besides placebo and aripiprazole, the study also included lithium for assay sensitivity purpose.

Study CN138162 enrolled 614 patients from Bulgaria, Croatia, Mexico, Peru, Russia, South Africa, and the United States. A total of 485 subjects between the ages of 18 and 76 were randomized. Haloperidol was included in the study for assay sensitivity purpose.

Since only the acute 3-week period is required for the United States registration, this review will evaluate only the data on this 3-week period.

1.3 Statistical Issues and Findings

For both studies, this reviewer confirmed the sponsor's findings based on the primary and key secondary analyses. Aripiprazole was superior to placebo in lowering the YMRS total score and CGI-BP (mania) score at week 3.

Study CN138162 was an international study and the subgroup results for the U.S. sample did not suggest a separation between treatment and placebo. However, study CN138135 was a U.S. study and was positive.

The following table summarizes the treatment differences and p-values of the comparisons between aripiprazole and placebo for the primary endpoint and key secondary endpoint. The results on the CGI-BP (mania) score appeared weaker and less robust under supportive analyses as compared to the results on the primary endpoint. Study CN138135 had about 50% dropout rate prior to the end of Week 3. This high dropout rate appeared to impact the efficacy negatively. The treatment differences diminished for both the YMRS total score and the CGI-BP (mania) score.

Table 1. Summary of treatment effects

	Study CN138135				Study CN138162			
	YMRS		**CGI-BP (mania)**		**YMRS**		**CGI-BP (mania)**	
	Treatment difference	P-value	Treatment difference	P-value	Treatment difference	P-value	Treatment difference	P-value
ANCOVA (LOCF)	-3.63	<0.001	-0.43	0.002	-2.28	0.039	-0.27	0.044
ANCOVA (OC)	-1.92	0.107	-0.25	0.134	-1.87	0.068	-0.28	0.051
MMRM (OC)	-2.62	0.024	-0.29*	0.067*	-2.38	0.030	-0.29*	0.058*
Wilcoxon rank-sum test (LOCF)	- - -	0.001	- - -	0.003	- - -	0.045	- - -	0.069

(Source: Clinical Study Reports:
Study cn138135 [Table 7.1, page 119; Table 7.1.2B, page 128; Table 7.1.3B, page 132; Table S.5.120, page 593; Table S.5.10, page 461; Table S.5.18, page 472]
Study cn138162 [Table 7.1, page 119; Table 7.1.2B, page 127; Table 7.1.3B, page 131; Table S.5.122, page 571; Table S.5.11, page 430; Table S.5.19, page 443])
(*) reviewer's results

2. INTRODUCTION

2.1 Overview

This document contains a statistical evaluation of aripiprazole as an acute treatment for patients with bipolar I disorder with a starting dose of 15 mg/day.

According to the sponsor, bipolar I disorder is a lifelong episodic illness characterized by manic or depressive episodes followed by symptom-free periods. The estimated prevalence of bipolar disorder is 0.4% to 1.6%. The age of onset for a first manic episode is usually in the early 20's. Current Expert Consensus Guidelines recommend lithium or valproate as a first-line treatment for manic symptoms associated with bipolar I disorder. However, lithium has a slow onset of action and narrow therapeutic window that are undesirable. Liver toxicity is a rare but recognized side effect of valproate. Both lithium and valproate require dose adjustments that may complicate the treatment strategy.

Aripiprazole is currently indicated in the United States for the treatment in adults with acute schizophrenia, maintaining stability in schizophrenia, treatment of acute manic and mixed episodes associated with bipolar disorder, and for maintaining efficacy in adult patients with bipolar I disorder. The effective starting dose in acute treatment of bipolar I disorder was 30 mg/day. In this application, the sponsor submitted two multicenter, randomized, double-blind, placebo-controlled, parallel-group studies (CN138135 and CN 138162). The purpose of these studies is to demonstrate the efficacy and safety of aripiprazole as an acute treatment of bipolar I disorder at a starting dose of 15 mg/day.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room:
\\Cdsesub1\n21436\S_019\2007-07-11\crt\datasets

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study CN138135

3.1.1.1 Objectives

Primary: The primary objective was to evaluate the efficacy of aripiprazole monotherapy as acute and maintenance therapy for the treatment of acutely manic patients with bipolar I disorder, manic or mixed.

Secondary: The secondary objective was to evaluate the safety and tolerability of aripiprazole in this same patient population.

3.1.1.2 Study Design

This was a United States multi-center, randomized, double-blind, placebo-controlled study with three treatment groups. Patients with bipolar I disorder were randomized to receive aripiprazole, placebo, or lithium in a 1:1:1 ratio for three weeks, and either aripiprazole or lithium for an additional 9 weeks. Patients who were randomized to placebo were blindly switched to receive aripiprazole treatment at the end of Week 3. Since only the acute 3-week period is required for the United States registration, this review will focus on this 3-week period.

The study consisted of three phases. Phase 1 was a screening and washout period. Mood stabilizers were tapered off. Prohibited medications were discontinued. Phase 2 was a double-blind treatment phase. The purpose of this phase was to demonstrate the efficacy of aripiprazole relative to placebo at Week 3 and to demonstrate that this effect was maintained to Week 12. Phase 3 was a double-blind extension phase (40 weeks). The result of this extension phase was not part of this submission. Figure 1 captures the three phases of the study.

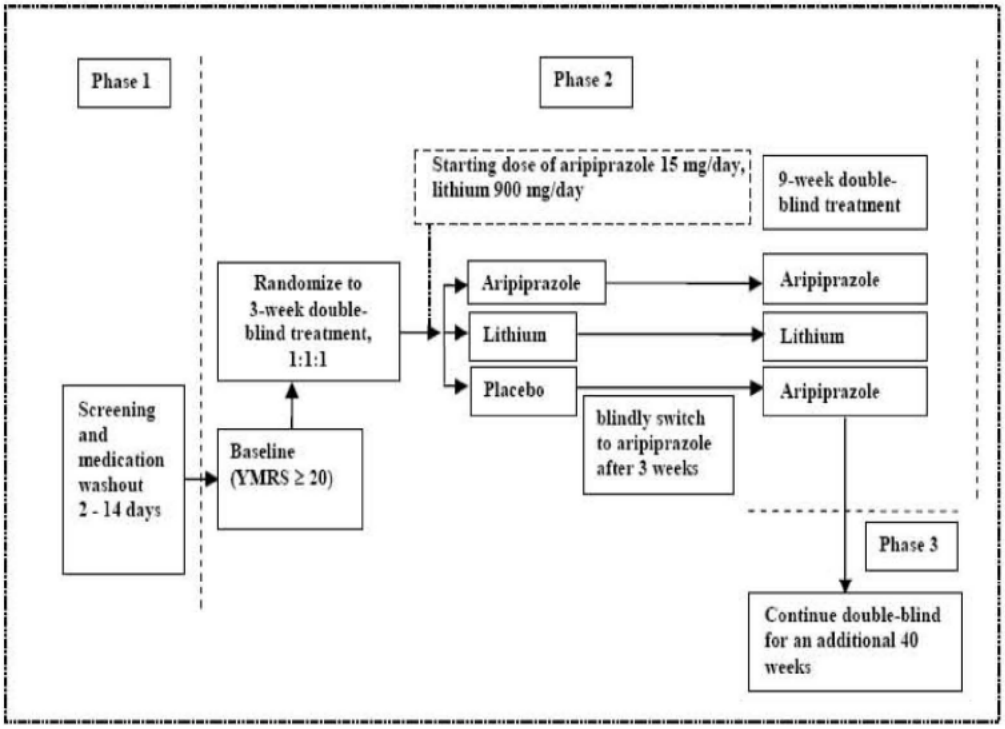

Figure 1. Study CN138135 Schema

(Source: Clinical Study Report: Study cn138135; Figure 3.1, page 49)

The starting dose for aripiprazole was 15 mg/day with an option to increase to 30 mg/day. Lithium was initiated at 900 mg/day in divided doses with an option to increase to 1200 mg/day at Day 4, and 1500 mg/day at Day 7. At any time, the dose could be decreased for tolerability. Lithium dosing may decrease or increase to maintain the lithium blood level.

3.1.1.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary efficacy endpoint was the mean change from baseline to Week 3 (LOCF) in the Young Mania Rating Scale (YMRS) total score. The primary endpoint was evaluated by an ANCOVA model with baseline YMRS score as a covariate and treatment and study center as main effects. Efficacy was assessed on Baseline, Days 2, 4, 7, and 10, Weeks 2, 3, 4, 5, 6, 8, and 10.

Key secondary endpoint and analysis: The key secondary efficacy endpoint was the mean change from baseline to Week 3 (LOCF) in the Clinical Global Impression-Bipolar Version (CGI-BP) Severity of Illness Score (mania). The key secondary endpoint was analyzed by an ANCOVA model with baseline CGI-BP Severity of Illness (mania) as a covariate and treatment and study center as main effects.

3.1.1.4 Efficacy Results

3.1.1.4.1 Study Population

The study included male and female hospitalized patients who had bipolar I disorder and displayed an acute manic or mixed episode, with or without psychotic features. Subjects must have an YMRS total score of at least 20 at screening and at the end of phase 1 (baseline) with less than a 25% decrease between these two visits. In addition, the MADRS total score must be ≤ 17 at the end of phase 1 (baseline), with no more than 4 points increase between screening and baseline, with measurements at least 2 days apart.

Between April 2004 and July 2006, 715 subjects in the United States enrolled in the study and 480 were randomized to receive aripiprazole, lithium, or placebo in a 1:1:1 ratio. Table 2 summarizes the disposition of the study. About 52% of the subjects discontinued prior to the end of week 3. The main reasons for the discontinuation were lack of efficacy, consent withdrawals, and adverse events. More patients dropped out in the aripiprazole group due to consent withdrawal and adverse events than in the placebo group. On the other hand, more patients dropped out in the placebo arm due to lack of efficacy than in the aripiprazole arm.

Table 2. Study 135: Disposition of patients in the acute phase

	Aripiprazole	Lithium	Placebo	Total
Enrolled				715
Randomized	155	160	165	480
Discontinued prior to end of week 3: N (%)	82 (52.9)	82 (51.3)	87 (52.7)	251 (52.3)
Lack of efficacy	9 (5.8)	26 (16.3)	36 (21.8)	71 (14.8)
Adverse event	23 (14.8)	20 (12.5)	13 (7.9)	56 (11.7)
Withdrew consent	32 (20.6)	28 (17.5)	25 (15.2)	85 (17.7)
Lost to follow-up	15 (9.7)	5 (3.1)	10 (6.1)	30 (6.3)
Poor/non-compliance	1 (0.6)	2 (1.3)	1 (0.6)	4 (0.8)
Subject no longer met Study criteria	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
Administrative reason by sponsor	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Other	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Completed week 3	73 (47.1)	78 (48.8)	78 (47.3)	229 (47.7)

(Source: Clinical Study Report: Study cn138135; Tables 5.1A, page 91)

Table 3 summarizes the demographic and baseline disease characteristics in the randomized sample. The male to female ratio was roughly 1 to 1. The average age of patients in the sample was about 40 years old. The majority of subjects were white and African Americans. On average, at baseline, the YMRS total score was 28.9 and the CGI-BP (mania) score was 4.6. Overall, the distribution of these demographic variables and baseline disease characteristics appeared balanced across the treatment arms.

Table 3. Study 135: Demographic and baseline disease characteristics (randomized sample)

	Aripiprazole (N = 155)	Lithium (N = 160)	Placebo (N = 165)	Total (N = 480)
Female	76 (49.0%)	76 (47.5%)	79 (47.9%)	231 (48.1%)
Age (*)				
Mean (SD)	39.6 (10.6)	39.6 (10.5)	39.8 (11.3)	39.7 (10.8)
Range	18 – 69	18 – 65	18 – 65	18 – 69
Race (% of patients)				
White	96 (61.9%)	103 (64.4%)	118 (71.5%)	317 (66.0%)
African American	55 (35.5%)	54 (33.8%)	44 (26.7%)	153 (31.9%)
Others	4 (2.6%)	3 (1.8%)	3 (1.8%)	10 (2.1%)
BMI (*)				
Sample size	153	159	163	475
Mean (SD)	30.4 (7.8)	29.9 (7.5)	31.8 (7.6)	30.7 (7.6)
Range	10.4 – 64.0	17.1 – 67.2	18.0 – 55.0	10.4 – 67.2
YMRS (*)				
Mean (SD)	28.5 (5.6)	29.4 (5.9)	28.9 (5.9)	28.9 (5.8)
Range	20 – 45	20 – 51	20 – 49	20 – 51
CGI-BP Severity (mania) (*)				
Sample size	154	160	163	477
Mean (SD)	4.5 (0.7)	4.5 (0.7)	4.6 (0.7)	4.6 (0.7)
Range	3 – 6	2 – 6	3 – 6	2 – 6

(*) Characteristics at baseline
(Source: Clinical Study Report: Study cn138135; Tables 5.3.1 & 5.3.3, pages 98-99 & 106)

3.1.1.4.2 Sponsor's Efficacy Results for Primary and Key Secondary Endpoints
The primary efficacy measure was the average change from baseline to Week 3 (LOCF) in the YMRS total score. A hierarchical testing procedure was employed to control the family-wise type I error rate. Aripiprazole was compared to placebo at a 0.05 level of significance. If the difference between aripiprazole and placebo was statistically significant, lithium was compared to placebo. If this comparison was also statistically significant, then aripiprazole was compared to placebo on the key secondary endpoint (CGI-BP (mania) score).

Table 4 summarizes the results of the primary and key secondary analyses. Aripiprazole was statistically significantly different from placebo on the primary endpoint as well as on the key secondary endpoint. Lithium was also statistically significantly different from placebo.

Table 4. Study 135: Primary and key secondary efficacy analyses: YMRS total score and CGI-BP (mania) score, change from baseline to Week 3 (LOCF); Sponsor's Results

	Placebo	Aripiprazole	Lithium
YMRS Total Score			
Sample size	163	154	155
LS Means	-9.01	-12.64	-12.03
Difference from placebo		-3.63	-3.03
(95 % confidence intervals)		(-5.75, -1.51)	(-5.13, -0.92)
Unadjusted p-values		<0.001	0.005
CGI-BP (mania) Score			
Sample size	162	153	154
LS Means	-1.06	-1.48	-1.34
Difference from placebo		-0.43	-0.28
(95 % confidence intervals)		(-0.70, -0.15)	(-0.56, -0.01)
Unadjusted p-values		0.002	0.041

(Source: Clinical Study Report: Study cn138135; Table 7.1, page 119)

3.1.1.4.3 Sponsor's Other Efficacy Results

Change from baseline up to Week 3: The changes from baseline in the YMRS total score and the CGI-BP (mania) score over time are presented in Table 5. The treatment difference was in favor of aripiprazole in Weeks 1, 2 and 3.

Table 5. Study 135: Adjusted mean change from baseline up to end of week 3 in YMRS Total Score and CGI-BP (mania) Score (LOCF); Sponsor's Results

	Placebo	Lithium	Aripiprazole	Lithium – Placebo		Aripiprazole – Placebo	
				Diff. in Adj. Means	p-value*	Diff. in Adj. Means	p-value*
YMRS							
Week 1	-6.52	-8.25	-10.06	-1.73 (-3.38, -0.08)	0.04	-3.54 (-5.19, -1.88)	<0.001
Week 2	-8.71	-12.09	-13.00	-3.38 (-5.37, -1.39)	<0.001	-4.29 (-6.29, -2.28)	<0.001
Week 3	-9.01	-12.03	-12.64	-3.03 (-5.13, -0.92)	0.005	-3.63 (-5.75, -1.51)	<0.001
CGI-BP (mania)							
Week 1	-0.60	-0.76	-1.02	-0.17 (-0.37, 0.04)	0.111	-0.42 (-0.63, -0.21)	<0.001
Week 2	-0.94	-1.24	-1.43	-0.30 (-0.55, -0.04)	0.021	-0.49 (-0.74, -0.23)	<0.001
Week 3	-1.06	-1.34	-1.48	-0.28 (-0.56, -0.01)	0.041	-0.43 (-0.70, -0.15)	0.002

(Source: Clinical Study Report: Study cn138135; Tables 7.1.2A & 7.1.3A, pages 127 & 131)
*Reviewer's note: p-values are not adjusted for multiple comparisons

Analyses on the primary endpoint and key secondary endpoint based on observed cases (OC):

Analyses on the primary and key secondary endpoints based on observed cases did not corroborate with the LOCF analyses. These models did not include centers as a factor in the model according to the protocol. Both aripiprazole and lithium groups showed improvements over placebo. However, the numerical differences diminished as compared to the LOCF analyses.

Table 6. Study 135: YMRS total score and CGI-BP (mania) score, change from baseline to Week 3 (OC); Sponsor's Results

	Placebo	Aripiprazole	Lithium
YMRS Total Score			
Sample size	90	94	93
LS Means	-12.81	-14.73	-15.79
Difference from placebo		-1.92	-2.98
(95 % confidence intervals)		(-4.26, 0.42)	(-5.33, -0.63)
Unadjusted p-values		0.107	0.013
CGI-BP (mania) Score			
Sample size	90	93	91
LS Means	-1.52	-1.77	-1.81
Difference from placebo		-0.25	-0.29
(95 % confidence intervals)		(-0.57, 0.08)	(-0.62, 0.04)
Unadjusted p-values		0.134	0.081

(Source: Clinical Study Report: Study cn138135; Tables 7.1.2B & 7.1.3B, pages 128 & 132)

Analysis on the primary endpoint based on a mixed model for repeated measures (MMRM):

The sponsor conducted a mixed model for repeated measures to assess the sensitivity of the primary results. The model included the baseline YMRS total score as a covariate, terms for treatment, pooled center, time, baseline by time, and treatment by time interaction. The model specified an unstructured covariance matrix. The results of the longitudinal analysis on the mean changes from baseline up to week 3 in YMRS total score agreed with the results of the primary efficacy analysis.

Table 7. Study 135: YMRS total score, change from baseline to Week 3 (OC); Sponsor's Results based on MMRM

	Placebo	Aripiprazole	Lithium
YMRS Total Score			
LS Means	-11.84	-14.47	-14.52
Difference from placebo		-2.62	-2.67
(95 % confidence intervals)		(-4.89, -0.35)	(-4.93, -0.41)
Unadjusted p-values		0.024	0.021

(Source: Clinical Study Report: Study cn138135; Table S.5.120, page 593)

3.1.1.4.5 Statistical Reviewer's Results and Comments

This reviewer confirmed the findings on the primary and key secondary endpoints as presented in Table 4.

As an exploratory analysis for the primary endpoint, a treatment-by-center interaction was added to the primary analysis model. The interaction term was not significant at the 0.05 level (p-value = 0.084). The results of this analysis did not appear to impact the conclusion on the primary endpoint.

The longitudinal analysis of the key secondary endpoint (CGI-BP (mania)) based on an MMRM model is presented in Table 8. The model included the CGI-BP (mania) score as a covariate, pooled centers, visits, and treatments as fixed factors, treatment-by-visits and baseline-by-visits interactions. The within subject covariance matrix was unstructured. The method of estimation was restricted maximum likelihood. The degrees of freedom were approximated by the Kenward-Roger's method. The results did not suggest a separation between aripiprazole and placebo in the CGI-BP (mania) score at week 3.

Table 8. Study 135: CGI-BP (mania) score, change from baseline to Week 3 (OC); Reviewer's Results based on MMRM

	Placebo	Aripiprazole	Lithium
CGI-BP (mania) score			
LS Means	-1.43	-1.72	-1.62
Difference from placebo		-0.29	-0.19
(95 % confidence intervals)		(-0.60, 0.02)	(-0.50, 0.12)
Unadjusted p-values		0.067	0.221

(Source: reviewer's results)

The CGI-BP (mania) score was an ordered categorical variable with seven levels (a score of 1 represents normal and a score of 7 represent very severely ill). The key secondary analysis, the ANCOVA model, and the MMRM model above were more suited for continuous outcomes. As a sensitivity exploratory analysis, this reviewer also confirmed the sponsor's findings on a Wilcoxon (van Elteren) analysis using a modified ridit score. The results were consistent in supporting the key secondary analysis ($p = 0.003$) based on the ANOVA (row mean scores differ) statistic (CN138135 Study Report: Table S.5.18, page 472).

Out of the 480 randomized patients, 251 (52.3%) discontinued from the study prior to the end of week 3. These dropouts appeared to affect the efficacy results on the CGI-BP (mania) score. The OC analyses did not corroborate with the LOCF analyses. The MMRM analysis on CGI-BP (mania) score did not suggest a separation between aripiprazole and placebo. For the YMRS total score, the treatment difference diminished as compared to the primary analysis.

3.1.1 Study CN138162

3.1.1.1 Objectives

Primary: The primary objective was to evaluate the efficacy of aripiprazole monotherapy as acute and maintenance therapy for the treatment of acutely manic patients with bipolar I disorder, manic or mixed.

Secondary: The secondary objective was to evaluate the safety and tolerability of aripiprazole in this same patient population.

3.1.1.2 Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study with three treatment groups. Patients with bipolar I disorder were randomized to receive aripiprazole, placebo, or haloperidol in a 1:1:1 ratio for three weeks, and either aripiprazole or haloperidol for an additional 9 weeks.

The study consisted of two phases. Phase 1 was a screening and washout period. Mood stabilizers were tapered off over a reasonable period of time. Prohibited medications were discontinued. Phase 2 was a double-blind treatment phase. The purpose of this phase was to evaluate the efficacy of aripiprazole in improving manic symptomatology relative to placebo at Week 3 and to demonstrate that this effect was maintained to Week 12. Because the results up to Week 12 are not required for the United States registration, this review will focus on the Week 3 evaluation. Figure 2 captures the design of the study.

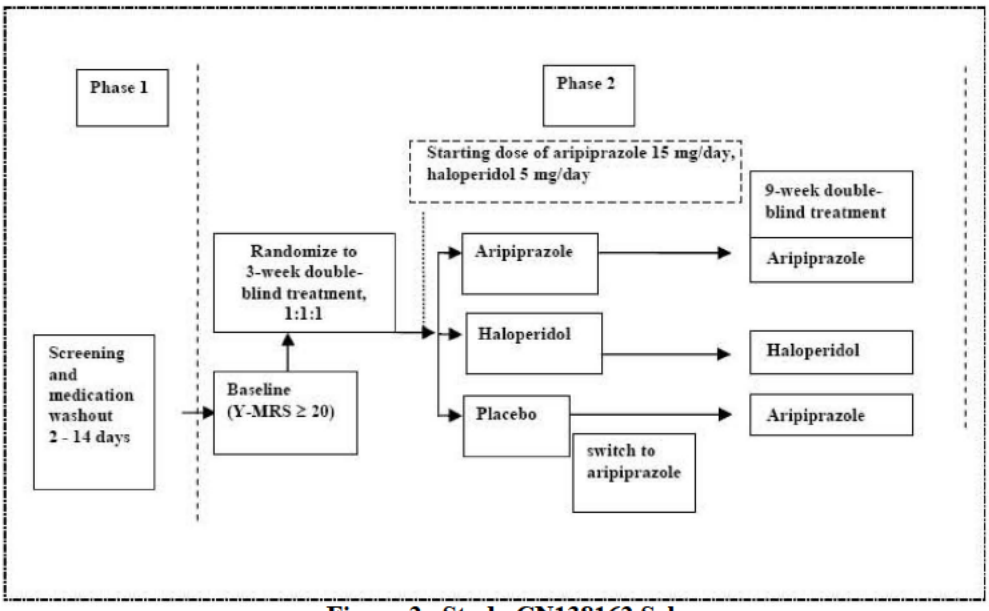

Figure 2. Study CN138162 Schema

(Source: Clinical Study Report: Study cn138162; Figure 3.1, page 49)

The starting dose for aripiprazole was 15 mg/day with an option to increase to 30 mg/day. Haloperidol was initiated at 5 mg/day with an option to increase to 10 mg/day at Day 4, and 15 mg/day at Day 7 or beyond. At any time, the dose could be decreased for tolerability.

3.1.1.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary efficacy endpoint was the mean change from baseline to Week 3 (LOCF) in the Young Mania Rating Scale (YMRS) total score. The primary endpoint was evaluated by an ANCOVA model with the baseline YMRS score as a covariate, treatment and study center as main effects. Efficacy was assessed on Baseline, Days 2, 4, 7, and 10, Weeks 2, 3, 4, 5, 6, 8, and 10.

Key secondary endpoint and analysis: The key secondary efficacy endpoint was the mean change from baseline to Week 3 (LOCF) in the Clinical Global Impression-Bipolar Version (CGI-BP) Severity of Illness Score (mania). The key secondary endpoint was analyzed by an ANCOVA model with the baseline CGI-BP Severity of Illness (mania) as a covariate, treatment and study center as main effects.

3.1.1.4 Efficacy Results

3.1.1.4.1 Study Population

The study included male and female hospitalized patients, at least 18 years of age, who had bipolar I disorder and displayed acute manic or mixed episode, with or without psychotic features. Subjects must have an YMRS total score of at least 20 at screening and at the end of phase 1 (baseline) with less than a 25% decrease between the two visits. In addition, the MADRS total score must be ≤ 17 at the end of phase 1 (baseline), with no more than a 4-point increase between screening and baseline, with measurements at least 2 days apart.

Between December 2004 and January 2007, 614 patients from Bulgaria, Croatia, Mexico, Peru, Russia, South Africa, and the United States enrolled in the study. Four hundreds and eighty-five (485) subjects were randomized to receive aripiprazole, haloperidol, or placebo in a 1:1:1 ratio. Table 9 summarizes the disposition of the study. About 27% of the subjects discontinued the study prior to the end of week 3. The main reasons for the discontinuation were lack of efficacy, adverse events, and consent withdrawals. There were more subjects discontinuing due to lack of efficacy in the placebo arm than in aripiprazole arm or haloperidol arm.

Table 9. Study 162: Disposition of patients in the acute phase

	Aripiprazole	Haloperidol	Placebo	Total
Enrolled				614
Randomized	167	165	153	485
Discontinued prior to end of week 3: N (%)	41 (24.6)	44 (26.7)	44 (28.8)	129 (26.6)
Lack of efficacy	9 (5.4)	10 (6.1)	14 (9.2)	33 (6.8)
Adverse event	14 (8.4)	8 (4.8)	16 (10.5)	38 (7.8)
Withdrew consent	14 (8.4)	19 (11.5)	11 (7.2)	44 (9.1)
Lost to follow-up	2 (1.2)	4 (2.4)	2 (1.3)	8 (1.6)
Poor/non-compliance	1 (0.6)	1 (0.6)	0 (0.0)	2 (0.4)
Subject no longer met study criteria	1 (0.6)	2 (1.2)	1 (0.7)	4 (0.8)
Completed week 3	126 (75.4)	121 (73.3)	109 (71.2)	356 (73.4)

(Source: Clinical Study Report: Study cn138162; Tables 5.1A, page 92)

Table 10 captures the demographic and baseline disease characteristics in the randomized sample. There were slightly more females than males. The average age was 41 years old and ranged from 18 to 76 years. Similar to Study cn138135,

the majority of subjects were white and black/African American. The average YMRS total score at baseline was 28 and CGI-BP (mania) was 4.5.

Table 10. Study 162: Demographic and baseline disease characteristics (randomized sample)

	Aripiprazole (N = 167)	Haloperidol (N = 165)	Placebo (N = 153)	Total (N = 485)
Female	95 (56.7%)	93 (56.4%)	82 (53.6%)	270 (55.7%)
Age (*)				
Mean (SD)	40.5 (11.8)	41.6 (12.0)	40.2 (12.0)	40.8 (11.9)
Range	18 – 68	18 – 76	18 – 70	18 – 76
Race (% of patients)				
White	131 (78.4%)	127 (77.0%)	122 (79.7%)	380 (78.4%)
Black	26 (15.6%)	26 (15.8%)	25 (16.3%)	77 (15.9%)
Others	10 (6.0%)	12 (7.2%)	6 (4.0%)	28 (5.8%)
BMI (*)				
Sample size	166	164	153	483
Mean (SD)	27.5 (6.2)	27.3 (5.4)	27.6 (7.2)	27.5 (6.3)
Range	16.9 – 54	18.3 – 48.1	15.9 – 59.5	15.9 – 59.5
YMRS (*)				
Mean (SD)	28.0 (5.8)	27.6 (5.6)	28.3 (5.8)	28.0 (5.7)
Range	14 – 50	10 – 42	19 – 45	10 – 50
CGI-BP Severity (mania) (*)				
Sample size	167	165	152	484
Mean (SD)	4.4 (0.7)	4.4 (0.7)	4.5 (0.8)	4.5 (0.7)
Range	3 – 6	2 – 6	3 – 7	2 – 7

(*) Characteristics at baseline
(Source: Clinical Study Report: Study cn138162; Tables 5.3.1 & 5.3.3, pages 98-99 & 106)

3.1.1.4.2 Sponsor's Efficacy Results for Primary and Key Secondary Endpoints

The primary efficacy measure was the change from baseline to Week 3 (LOCF) in the YMRS total score. A hierarchical testing procedure was employed to control the family-wise type I error rate. Aripiprazole was compared to placebo at a 0.05 level of significance. If the difference between aripiprazole and placebo was statistically significant, haloperidol was compared to placebo. If this comparison was also statistically significant, then aripiprazole was compared to placebo on the key secondary endpoint (CGI-BP (mania)).

Table 11 summarizes the results of the primary and key secondary analyses. Aripiprazole was statistically significantly different from placebo on the primary

endpoint as well as on the key secondary endpoint. Haloperidol was also statistically significantly different from placebo.

Table 11. Study 162: Primary and key secondary efficacy analyses: YMRS total score and CGI-BP (mania) score, change from baseline to Week 3 (LOCF); Sponsor's Results

	Placebo	Aripiprazole	Haloperidol
YMRS total score			
Sample size	152	166	161
LS Means	-9.70	-11.98	-12.83
Difference from placebo		-2.28	-3.13
(95 % confidence intervals)		(-4.44, -0.11)	(-5.31, -0.94)
Unadjusted p-values		0.039	0.005
CGI-BP (mania) score			
Sample size	151	166	161
LS Means	-1.17	-1.44	-1.56
Difference from placebo		-0.27	-0.39
(95 % confidence intervals)		(-0.54, -0.01)	(-0.66, -0.13)
Unadjusted p-values		0.044	0.004

(Source: Clinical Study Report: Study cn138162; Table 7.1, page 119)

3.1.1.4.3 Sponsor's Other Efficacy Results

Change from baseline up to Week 3: The changes from baseline in the YMRS total score and the CGI-BP (mania) score over time are presented in Table 12. The treatment difference was in favor of aripiprazole in Weeks 2 and 3.

Table 12. Study 162: Adjusted mean change from baseline up to end of week 3 in YMRS total score and CGI-BP (mania) score (LOCF); Sponsor's Results

	Placebo	Haloperidol	Aripiprazole	Haloperidol - Placebo		Aripiprazole - Placebo	
				Diff. in Adj. Means	p-value*	Diff. in Adj. Means	p-value*
YMRS							
Week 1	-5.94	-7.56	-6.91	-1.61 (-3.00, -0.23)	0.022	-0.97 (-2.34, 0.40)	0.165
Week 2	-8.81	-11.51	-10.71	-2.69 (-4.60, -0.79)	0.006	-1.90 (-3.78, -0.01)	0.049
Week 3	-9.97	-12.83	-11.98	-3.13 (-5.31, -0.94)	0.005	-2.28 (-4.44, -0.11)	0.039
CGI-BP (mania)							
Week 1	-0.48	-0.67	-0.62	-0.19 (-0.35, -0.03)	0.021	-0.15 (-0.30, 0.01)	0.074
Week 2	-0.95	-1.32	-1.23	-0.38 (-0.61, -0.14)	0.002	-0.28 (-0.51, -0.05)	0.018
Week 3	-1.17	-1.56	-1.44	-0.39 (-0.66, -0.13)	0.004	-0.27 (-0.54, -0.01)	0.044

(Source: Clinical Study Report: Study cn138162; Tables 7.1.2A & 7.1.3A, pages 126 & 130)
*Reviewer's note: p-values are not adjusted for multiple comparisons

Analyses on the primary endpoint and key secondary endpoint based on observed cases (OC):

The results on observed cases analyses did not corroborate with the LOCF analyses on the primary and key secondary endpoints. The numerical differences were in favor of aripiprazole for both the YMRS total score and the CGI-BP (mania) score.

For the YMRS total score, the treatment differences diminished as compared to the LOCF analysis.

Table 13. Study 162: YMRS total score and CGI-BP (mania) score, change from baseline to Week 3 (OC); Sponsor's Results

	Placebo	Aripiprazole	Haloperidol
YMRS total score			
Sample size	117	139	129
LS Means	-12.44	-14.30	-14.34
Difference from placebo		-1.87	-1.91
(95 % confidence intervals)		(-3.87, 0.14)	(-3.95, 0.13)
Unadjusted p-values		0.068	0.067
CGI-BP (mania) score			
Sample size	116	139	129
LS Means	-1.40	-1.68	-1.74
Difference from placebo		-0.28	-0.34
(95 % confidence intervals)		(-0.55, 0.00)	(-0.62, -0.05)
Unadjusted p-values		0.051	0.020

(Source: Clinical Study Report: Study cn138162; Tables 7.1.2B & 7.1.3B, pages 127 & 131)

Analysis on the primary endpoint based on a mixed model for repeated measures (MMRM):
The results of the longitudinal analysis on the mean changes from baseline up to week 3 in YMRS total score agreed with the results of the primary efficacy analysis.

Table 14. Study 162: YMRS total score, change from baseline to Week 3 (OC); Sponsor's Results based on MMRM

	Placebo	Aripiprazole	Haloperidol
YMRS total score			
LS Means	-10.88	-13.26	-14.23
Difference from placebo		-2.38	-3.36
(95 % confidence intervals)		(-4.53, -0.23)	(-5.53, -1.18)
Unadjusted p-values		0.030	0.003

(Source: Clinical Study Report: Study cn138162; Table S.5.122, page 571)

3.1.1.4.5 Statistical Reviewer's Results and Comments
This reviewer confirmed the findings on the primary and key secondary endpoints as presented in Table 11.

As an exploratory analysis for the primary endpoint, a treatment-by-center interaction was added to the primary analysis model. The treatment-by-center interaction p-value was 0.001 suggesting a treatment-by-center interaction effect. However, the results did not seem to alter the primary analysis results.

Because patients from this study were from multiple countries, an exploratory analysis with model terms for baseline YMRS total score, treatment, country, treatment-by-country interaction was performed. The p-value for the treatment-by-country interaction was 0.070.

This reviewer performed an MMRM analysis on the change from baseline in the CGI-BP (mania) score. The results are summarized in Table 14. The model included the baseline CGI-BP (mania) as a covariate, pooled study center, treatment, and visits as fixed factors, baseline-by-visit and treatment-by-visit interactions. The covariance matrix was unstructured. The method of estimation was restricted maximum likelihood (ReML). The degrees of freedom were estimated by the Satterthwaite's method. The results did not seem to corroborate with the key secondary analysis based on an ANCOVA model with missing values imputed by the LOCF method.

Table 15. Study 162: CGI-BP (mania) score, change from baseline to Week 3 (OC); Reviewer's Results based on MMRM

	Placebo	Aripiprazole	Haloperidol
CGI-BP (mania) score			
LS Means	-1.29	-1.58	-1.70
Difference from placebo		-0.29	-0.42
(95 % confidence intervals)		(-0.59, 0.01)	(-0.72, -0.11)
Unadjusted p-values		0.058	0.007

(Source: Reviewer's results)

CGI-BP (mania) score was an ordered categorical variable with seven levels (a score of 1 represents normal and a score of 7 represent very severely ill). The key secondary analysis, ANCOVA model, and the MMRM model above were more suited for a continuous outcome. As a sensitivity exploratory analysis, this reviewer also confirmed the sponsor's findings on a Wilcoxon (van Elteren) analysis using a modified ridit score. The results did not seem to suggest a separation between aripiprazole and placebo ($p = 0.069$) based on the ANOVA (row mean scores differ) statistic (CN138162 Study Report: Table S.5.19, page 443).

While the results on the YMRS total score appeared more robust under various analyses, the results on the CGI-BP (mania) score appeared weaker and less robust.

3.2 Evaluation of Safety

Please refer to the clinical review for safety evaluation and report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study 138135

4.1.1.1 Gender

The primary and secondary analyses stratified by gender are presented in Table 16. These models did not include centers as a factor according to the Statistical Analysis Plan. For both male and female, aripiprazole resulted in a numerical improvement over the placebo group at Week 3. However, aripiprazole female patients appeared to have a smaller numerical improvement than aripiprazole male patients.

Table 16. Study 135: Efficacy analyses by gender: YMRS and CGI-BP (mania) total scores, change from baseline to Week 3 (LOCF); Sponsor's Results

	Placebo	Aripiprazole	Lithium
YMRS total score			
Male			
Sample size	84	78	82
LS Means	-8.11	-12.90	-10.48
Difference from placebo		-4.78	-2.37
(95 % confidence intervals)		(-7.90, -1.67)	(5.45, 0.71)
Female			
Sample size	79	76	73
LS Means	-9.69	-12.36	-13.63
Difference from placebo		-2.67	-3.94
(95% confidence intervals)		(-5.70, 0.35)	(-7.00, -0.89)
CGI-BP (mania) score			
Male			
Sample size	84	77	81
LS Means	-0.93	-1.44	-1.18
Difference from placebo		-0.51	-0.25
(95% confidence intervals)		(-0.90, -0.12)	(-0.64, 0.13)
Female			
Sample size	78	76	73
LS Means	-1.19	-1.52	-1.47
Difference from placebo		-0.34	-0.28
(95% confidence intervals)		(-0.76, 0.09)	(-0.71, 0.15)

(Source: cn138135 Study Report: Tables S.5.7 and S.5.15, pages 458 and 469)

4.1.1.2 Race

Since the majority of subjects were white (65.7%) and African American (32.2%), race was dichotomized to either white or African Americans/others. The analyses stratified by race are presented below. These models did not include centers as a

factor according to the Statistical Analysis Plan. A bigger numerical treatment difference was seen among the African American/others patients than among the white patients.

Table 17. Study 135: Efficacy analyses by race: YMRS and CGI-BP (mania) total scores, change from baseline to Week 3 (LOCF)

	Placebo	Aripiprazole	Lithium
YMRS total score			
White			
Sample size	117	95	98
LS Means	-9.49	-11.32	-11.70
Difference from placebo		-1.82	-2.21
(95 % confidence intervals)		(-4.54, 0.89)	(-4.90, 0.48)
African Americans/Others			
Sample size	46	59	57
LS Means	-7.41	-14.78	-12.31
Difference from placebo		-7.37	-4.90
(95% confidence intervals)		(-11.02, -3.73)	(-8.58, -1.22)
CGI-BP (mania) score			
White			
Sample size	116	95	98
LS Means	-1.19	-1.34	-1.38
Difference from placebo		-0.15	-0.19
(95 % confidence intervals)		(-0.52, 0.22)	(-0.56, 0.17)
African Americans/Others			
Sample size	46	58	56
LS Means	-0.72	-1.69	-1.21
Difference from placebo		-0.97	-0.49
(95% confidence intervals)		(-1.41, -0.52)	(-0.94, -0.05)

(Source: Sponsor's communication on October 18, 2007 in response to the filing letter; Attachment Q.1.1 and reviewer's results)

4.1.1.3 Age

Since the majority of subjects in this study were between the age of 18 and 65, the analysis stratified by age is omitted.

4.1.2 Study 138162

4.1.2.1 Gender

The primary and key secondary analyses stratified by gender are presented in Table 18. These models did not include centers as a factor according to the Statistical Analysis Plan. Both females and males showed a numerical improvement over placebo.

Table 18. Study 162: Efficacy analyses by gender: YMRS and CGI-BP (mania) total scores, change from baseline to Week 3 (LOCF); Sponsor's Results

	Placebo	Aripiprazole	Haloperidol
YMRS total score			
Male			
Sample size	71	71	68
LS Means	-8.79	-11.76	-11.22
Difference from placebo		-2.97	-2.42
(95 % confidence intervals)		(-6.23, 0.29)	(-5.72, 0.87)
Female			
Sample size	81	95	93
LS Means	-10.19	-12.47	-14.41
Difference from placebo		-2.29	-4.22
(95% confidence intervals)		(-5.29, 0.71)	(-7.25, -1.20)
CGI-BP (mania) score			
Male			
Sample size	70	71	68
LS Means	-0.97	-1.34	-1.25
Difference from placebo		-0.37	-0.28
(95 % confidence intervals)		(-0.78, 0.04)	(-0.69, 0.14)
Female			
Sample size	81	95	93
LS Means	-1.18	-1.47	-1.76
Difference from placebo		-0.29	-0.58
(95% confidence intervals)		(-0.68, 0.10)	(-0.98, -0.19)

(Source: cn138162 Study Report: Tables S.5.8 and S.5.16, pages 427 & 440)

4.1.2.2 Race

Subjects from this study were white (78.3%), black/African American (15.9%), other races (5.8%). The primary analysis stratified by race is presented below. The models did not include centers as a factor according to the Statistical Analysis Plan. For this study, white patients appeared to have a greater improvement as compared to black/other patients.

Table 19. Study 162: Efficacy analyses by race: YMRS and CGI-BP (mania) total scores, change from baseline to Week 3 (LOCF); Reviewer's Results

	Placebo	Aripiprazole	Lithium
YMRS total score			
White			
Sample size	121	130	124
LS Means	-8.81	-11.74	-12.67
Difference from placebo		-2.92	-3.86
(95 % confidence intervals)		(-5.43, -0.42)	(-6.40, -1.32)
Black/Others			
Sample size	31	36	37
LS Means	-12.46	-13.79	-14.19
Difference from placebo		-1.33	-1.73
(95% confidence intervals)		(-6.10, 3.44)	(-6.47, 3.01)
CGI-BP (mania) score			
White			
Sample size	121	130	124
LS Means	-1.09	-1.43	-1.60
Difference from placebo		-0.34	-0.51
(95 % confidence intervals)		(-0.67, -0.01)	(-0.84, -0.18)
Black/Others			
Sample size	30	36	37
LS Means	-1.06	-1.36	-1.35
Difference from placebo		-0.30	-0.29
(95% confidence intervals)		(-0.87, 0.27)	(-0.86, 0.27)

(Source: Reviewer's results)

4.1.2.3 Age

Since only 2.1% of subjects were over 65 years old, this reviewer omitted the analysis stratified by age.

4.2 Other Subgroups

4.2.1 Study 138162

4.2.1.1 Geographical Region

The primary analysis stratified by geographical region (U.S. versus non-U.S.) is presented below. The models included treatment as a factor and baseline score as a covariate. Among the U.S. patients, the treatment effects were numerically better for placebo group than for aripiprazole and haloperidol groups. For the YMRS total score, this could be explained by a large placebo effect that was seen for U.S. patients. Among the non-U.S. patients, both aripiprazole and haloperidol arms showed numerical improvements over the placebo arm.

Table 20. Study 162: Efficacy analysis by region: YMRS and CGI-BP (mania) total scores, change from baseline to Week 3 (LOCF)

	Placebo	Aripiprazole	Haloperidol
YMRS total score			
U.S.			
Sample size	46	47	46
LS Means	-12.49	-12.39	-11.98
Difference from placebo		0.10	0.50
(95 % confidence intervals)		(-3.94, 4.13)	(-3.55, 4.55)
Non-U.S.			
Sample size	106	119	115
LS Means	-8.34	-12.09	-13.40
Difference from placebo		-3.75	-5.07
(95% confidence intervals)		(-6.39, -1.11)	(-7.74, -2.40)
CGI-BP (mania) score			
U.S.			
Sample size	46	47	46
LS Means	-1.10	-1.09	-1.00
Difference from placebo		0.01	0.10
(95 % confidence intervals)		(-0.42, 0.44)	(-0.33, 0.53)
Non-U.S.			
Sample size	105	119	145
LS Means	-1.08	-1.55	-1.76
Difference from placebo		-0.47	-0.68
(95% confidence intervals)		(-0.83, -0.12)	(-1.04, -0.32)

(Source: Sponsor's communication on October 18, 2007 in response to the filing letter; Attachment Q.1.3 and Reviewer's results)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For both studies, this reviewer confirmed the sponsor's findings based on the primary and key secondary analyses. Aripiprazole was superior to placebo in lowering the YMRS total score and CGI-BP (mania) score at week 3.

Study CN138162 was an international study and the subgroup results for the U.S. sample did not suggest a separation between treatment and placebo. However, study CN138135 was a U.S. study and was positive.

The following table summarizes the treatment differences and p-values of the comparisons between aripiprazole and placebo for the primary endpoint and key secondary endpoint. The results on the CGI-BP (mania) score appeared weaker and less robust under supportive analyses as compared to the results on the primary endpoint. Study CN138135 had about 50% dropout rate prior to the end of Week 3. This high dropout rate appeared to impact the efficacy negatively. The treatment differences diminished for both the YMRS total score and the CGI-BP (mania) score.

Table 21. Summary of treatment effects

	Study CN138135				Study CN138162			
	YMRS		**CGI-BP (mania)**		**YMRS**		**CGI-BP (mania)**	
	Treatment difference	P-value	Treatment difference	P-value	Treatment difference	P-value	Treatment difference	P-value
ANCOVA (LOCF)	-3.63	<0.001	-0.43	0.002	-2.28	0.039	-0.27	0.044
ANCOVA (OC)	-1.92	0.107	-0.25	0.134	-1.87	0.068	-0.28	0.051
MMRM (OC)	-2.62	0.024	-0.29*	0.067*	-2.38	0.030	-0.29*	0.058*
Wilcoxon rank-sum test (LOCF)	- - -	0.001	- - -	0.003	- - -	0.045	- - -	0.069

(Source: Clinical Study Reports:
Study cn138135 [Table 7.1, page 119; Table 7.1.2B, page 128; Table 7.1.3B, page 132; Table S.5.120, page 593; Table S.5.10, page 461; Table S.5.18, page 472]
Study cn138162 [Table 7.1, page 119; Table 7.1.2B, page 127; Table 7.1.3B, page 131; Table S.5.122, page 571; Table S.5.11, page 430; Table S.5.19, page 443])
(*) reviewer's results

5.2 Conclusions and Recommendations

Aripiprazole, at a starting dose of 15 mg/day and an option to titrate up to 30 mg/day, was efficacious in the acute treatment of bipolar I disorder as demonstrated by lowering the change from baseline in the Young Mania Rating Scale (YMRS) total score. The efficacy was supported by the results on the key secondary endpoint, Clinical Global Impression-Bipolar Version (CGI-BP) Severity of Illness Score (mania).

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Phillip Dinh
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James Hung
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-436 / S020
Drug Name:	Abilify (Aripiprazole)
Indication(s):	Adjunctive Treatment of Bipolar I Disorder, manic or mixed
Applicant:	Bristol-Meyers Squibb Company
Date(s):	Received: July 11, 2007;
	PDUFA Due Date: May 11, 2008
Review Priority:	Standard
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Statistical Reviewers:	Phillip Dinh, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.
	H.M. James Hung, Ph.D.
Medical Division:	Division of Psychiatric Products, HFD-130
Clinical Team:	Karen Brugge M.D., Medical Reviewer, HFD-130
	Gwen Zornberg M.D., Sc.D., Medical Team Leader, HFD-130
Project Manager:	Doris Bates Ph.D., HFD-130

Keywords: Clinical studies, NDA review, One study application

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results of study CN138134 demonstrated that aripiprazole, in combination with lithium or valproate, was efficacious in the acute treatment of patients with bipolar I disorder who were partially nonresponsive to lithium or valproate monotherapy. The starting dose of aripiprazole was 15 mg/day with an option to titrate to 30 mg/day.

1.2 Brief Overview of Clinical Studies

Study CN138134 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study. Patients who were partially nonresponsive to lithium or valproate were randomized to receive, in combination with lithium or valproate, either aripiprazole or placebo in a 2:1 ratio. The starting dose was 15 mg/day with an option to titrate to 30 mg/day. The randomized sample included 384 subjects between the age of 18 and 68 who were diagnosed with bipolar I disorder. The primary endpoint was the change from baseline to Week 6 in the Young Mania Rating Scale (YMRS) total score. The key secondary endpoint was the change from baseline to Week 6 in the Clinical Global Impression-Bipolar mania (CGI-BP (mania)) score.

1.3 Statistical Issues and Findings

This reviewer confirmed the sponsor's findings that aripiprazole (flexibly dosed), in combination to lithium or valproate, were superior to lithium or valproate monotherapy in the acute treatment of bipolar I disorder in patients who were partially nonresponsive to lithium or valproate monotherapy. The efficacy was demonstrated on the primary endpoint (change from baseline to Week 6 in the YMRS total score) and the key secondary endpoint (change from baseline to Week 6 in the CGI-BP (mania) score).

2. INTRODUCTION

2.1 Overview

This document contains a statistical evaluation of aripiprazole as an adjunctive treatment for patients with bipolar I disorder who are partially nonresponsive to lithium or valproate monotherapy.

According to the sponsor, bipolar I disorder is a lifelong episodic illness characterized by manic or depressive episodes followed by symptom-free periods. The estimated prevalence of bipolar disorder is 0.4% to 1.6%. The age of onset for a first manic episode is usually in the early 20's. Current Expert Consensus Guidelines recommend lithium or valproate as a first-line treatment for manic symptoms associated with bipolar I disorder. However, up to 40% of patients respond poorly to monotherapy. When monotherapy fails, the guidelines recommend combination therapies.

Aripiprazole is currently indicated in the United States for the treatment in adults with acute schizophrenia, maintenance of stability in schizophrenia, treatment of acute manic and mixed episodes associated with bipolar disorder, and for maintaining efficacy in adult patients with bipolar I disorder. In this application, the sponsor submitted one multi-center, randomized, double-blind, placebo-controlled, parallel group study (Study CN138134). The purpose of the study was to demonstrate the efficacy and safety of aripiprazole, in combination with valproate or lithium, in the acute treatment of bipolar I disorder, manic and mixed episodes. The target patients were those with bipolar I disorder who were partially nonresponsive to lithium or valproate monotherapy.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room:
\\Cdsesub1\n21436\S_020\2007-07-11\crt\datasets\

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Objectives

Primary: The primary objective was to compare the efficacy of aripiprazole in combination with lithium or valproate to lithium or valproate monotherapy in the treatment of patients with Bipolar I Disorder, manic or mixed episode, with or without psychotic features, partially nonresponsive to lithium or valproate monotherapy.

Secondary: The secondary objective was to evaluate the safety and tolerability of aripiprazole in combination with lithium or valproate in this same population.

3.1.2 Study Design

Study CN138134 was a multi-center, randomized, double-blind, placebo-controlled, parallel group study. Patients who were partially nonresponsive to lithium or valproate monotherapy were randomly assigned to receive either aripiprazole or placebo in a 2:1 ratio, in combination with lithium or valproate, for 6 weeks. The starting dose for aripiprazole was 15 mg/day and could be increased to 30 mg/day after Week 1.

The study consisted of four phases. Phase 1 was a 3-day to 4-week screening and psychotropic washout phase. Phase 2 was a 2-week period used to confirm that patients were partially nonresponsive to mood stabilizers. In phase 3, patients who met criteria were randomized to a 6-week, double-blind phase. Patients were randomized in a 2:1 ratio stratified by mood stabilizer and study center. Phase 4 was a 46-week open label extension phase. Phase 4 was ongoing and was not part of this application. Figure 1 captures the study schema. In this figure as well as in all subsequent figures and tables, 'Aripiprazole' refers to the group of patients who received aripiprazole in combination with lithium or valproate and 'Placebo' refers to the group of patients who received placebo in combination with lithium or valproate.

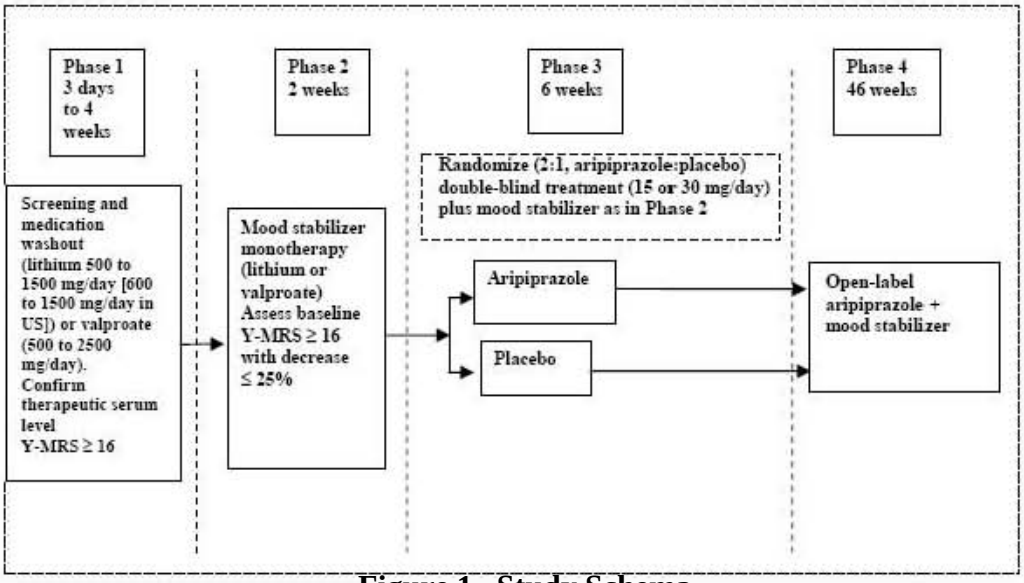

Figure 1. Study Schema

(Source: CN138134 Study Report: Figure 3.1, page 42)

3.1.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary efficacy endpoint was the mean change from baseline to endpoint (Week 6 LOCF) in the YMRS total score. The primary efficacy analysis model was an ANCOVA model with baseline score as a covariate, type of mood stabilizer (lithium or valproate) and treatment as main effects.

Key Secondary endpoint and analysis: The key secondary efficacy endpoint was the mean change from baseline to endpoint (Week 6 LOCF) in the CGI-BP Severity of Illness score (mania). The key secondary endpoint was analyzed by an ANCOVA model with baseline CGI-BP Severity of Illness (mania) as a covariate, treatment and type of mood stabilizer as main effects. A sequential testing approach was pre-specified. The key secondary endpoint was tested only if aripiprazole was statistically significantly different from placebo on the primary endpoint.

The primary and key secondary efficacy endpoints for phase 3 were assessed on Day 4, Weeks 1, 2, 3, 4, 5, and 6 or last visit before discontinuation.

3.1.4 Efficacy Results

3.1.4.1 Study Population

Patients came from Australia, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, Italy, Netherlands, Poland, Portugal, Russia, South Africa, Spain, United Kingdom, and USA. Between October 2004 and November 2006, six hundreds and twenty three (623) subjects were screened and 384 were randomized in a 2:1 ratio to receive either aripiprazole or placebo. About 81% of subjects completed the study. The last patient visit in phase 3 was in January 2007. The main reasons for patients to discontinue were adverse events and lack of efficacy. There were slightly more subjects dropping out in the aripiprazole group than in the placebo group overall. There were also slightly more subjects dropping out due to adverse events in the aripiprazole group than in the placebo group. Table 1 captures the disposition of patients in the study.

Table 1. Disposition of patients (number of patients (%))

	Aripiprazole	Placebo	Total
Enrolled			623
Randomized	253	131	384
Discontinued during double-blind phase	54 (21.3)	20 (15.3)	74 (19.3)
Adverse event	23 (9.1)	7 (5.3)	30 (7.8)
Lack of efficacy	12 (4.7)	6 (4.6)	18 (4.7)
Lost to follow-up	4 (1.6)	1 (0.8)	5 (1.3)
Poor/Non-compliance	3 (1.2)	0 (0.0)	3 (0.8)
Subject no longer met study criteria	1 (0.4)	1 (0.8)	2 (0.5)
Subject withdrew consent	9 (3.6)	5 (3.8)	14 (3.6)
Other	1 (0.4)	0 (0.0)	1 (0.3)
Missing	1 (0.4)	0 (0.0)	1 (0.3)
Completed double-blind phase	199 (78.7)	111 (84.7)	310 (80.7)

(Source: CN138134 Study Report: Table 5.1A, pages 90-91)

Patients diagnosed with bipolar I disorder, experienced a manic or mixed episode, were partially nonresponsive to lithium or valproate therapy were recruited to participate in the study. Partial nonresponsive was defined as follows:

- Patients having YMRS total score $\geq$ 16 during the phase 1, and 2 weeks after achieving a therapeutic level of lithium or valproate
- If the YMRS total score decreased between phase 1 and the end of phase 2, the score could only decrease by $\leq$ 25%

Roughly 50% of subjects in the efficacy sample were female. The average age was 42 years and ranged from 18 to 68 years. Most subjects were white. The baseline body mass index (BMI), YMRS total score, and CGI-BP Severity of Illness (mania) score were relatively similar for aripiprazole group and placebo group. There were more patients receiving valproate than lithium. Table 2 summarizes demographic and baseline disease characteristics in the efficacy sample.

Table 2. Demographic and baseline characteristics (randomized sample)

	Aripiprazole (N = 253)	Placebo (N = 131)	Total (N = 384)
Female	131 (51.8%)	76 (58.0%)	207 (53.9%)
Age (*)			
Mean (SD)	42.2 (11.6)	41.7 (12.1)	42.0 (11.8)
Range	18 – 68	18 – 66	18 – 68
Race (% of patients)			
White	232 (91.7%)	118 (90.1%)	350 (91.2%)
Other	21 (8.3%)	13 (9.9%)	34 (8.9%)
BMI (*)			
Mean (SD)	28.4 (6.0)	27.2 (5.8)	28.0 (6.0)
Range	17.0 – 55.0	17 – 47.6	17.0 – 55.0
Mood stabilizer			
Lithium	106 (41.9%)	51 (38.9%)	157 (40.9%)
Valproate	147 (58.1%)	80 (61.1%)	227 (59.1%)
YMRS (*)			
Mean (SD)	23.2 (5.7)	23.0 (4.9)	23.1 (5.4)
Range	1 – 47	14 – 38	1 – 47
CGI-BP Severity (mania) (*)			
Mean (SD)	4.2 (0.8)	4.2 (0.7)	4.2 (0.7)
Range	2 – 7	2 – 6	2 – 7

(*) Characteristics at baseline
(Source: CN138134 Study Report: Tables 5.3.1 & 5.3.3, pages 95-97, 104)

3.1.4.2 Sponsor's Efficacy Results for Primary and Key Secondary Endpoints

The primary efficacy endpoint was the mean change from baseline to Week 6. Missing values were imputed by the last-observation-carried-forward (LOCF) method. The primary analysis model was an ANCOVA with baseline YMRS total score as a covariate, mood stabilizer (lithium or valproate) and treatment as factors.

The key secondary endpoint was the change from baseline to endpoint in the CGI-BP Severity of Illness (mania) score. The key secondary endpoint was analyzed by an ANCOVA model with baseline CGI-BP Severity of Illness (mania) score as a covariate, treatment and mood stabilizer as factors.

Table 3 presents the primary and key secondary analyses results. Aripiprazole added to lithium or valproate showed statistically

significantly greater improvement than placebo added to lithium or valproate in lowering the YMRS total score and CGI-BP (mania) score from baseline to Week 6.

Table 3. Primary and key secondary efficacy analyses: YMRS and CGI-BP (mania) total scores, change from baseline at Week 6 (LOCF)

	Aripiprazole	Placebo
YMRS total score		
Sample size (N)	247	130
LS Means (SE)	-13.31 (0.50)	-10.70 (0.69)
Difference from placebo (95% CI)	-2.62 (-4.29, -0.95)	
P-value	0.002	
CGI-BP (mania) score		
Sample size (N)	246	130
LS Means (SE)	-1.89 (0.08)	-1.56 (0.11)
Difference from placebo (95% CI)	-0.33 (-0.60, -0.07)	
P-value	0.014	

(Source: CN138134 Study Report: Table 7.1A, page 113)

3.1.4.3 Sponsor's Other Efficacy Results

Mixed-model for repeated measures (MMRM) on the primary endpoint:
The sponsor's analysis of the primary endpoint based on an MMRM model is presented in Table 4. The model included treatment, time, and mood stabilizers as factors, treatment-by-time, baseline-by-time interactions, and baseline score as a covariate. The within subject covariance matrix was unstructured. The results are consistent with the primary analysis.

Table 4. Primary endpoint analysis: YMRS total score, change from baseline at Week 6 (MMRM)

	Aripiprazole	Placebo
Sample size (N)	194	113
LS Means (SE)	-14.58 (0.49)	-11.20 (0.66)
Difference from placebo (95% CI)	-3.38 (-4.99, -1.78)	
P-value	< 0.001	

(Source: CN138134 Study Report: Table 7.2C, page 123)

Primary and key secondary endpoints analyses based on an ANCOVA model on observed cases (OC):
Table 5 presents ANCOVA analyses of the primary endpoint and key secondary endpoint based on observed cases. The ANCOVA models included baseline total score as a covariate, treatment and mood stabilizers as factors. The results are consistent with the primary and key secondary analyses.

Table 5. Primary and key secondary endpoint analyses: YMRS total score, change from baseline at Week 6 (OC)

	Aripiprazole	Placebo
YMRS total score		
Sample size (N)	194	113
LS Means (SE)	-15.08 (0.49)	-11.11 (0.65)
Difference from placebo (95% CI)	-3.97 (-5.55, -2.39)	
P-value	<0.001	
CGI-BP (mania) score		
Sample size (N)	193	113
LS Means (SE)	-2.16 (0.08)	-1.60 (0.11)
Difference from placebo (95% CI)	-0.56 (-0.82, -0.29)	
P-value	< 0.001	

(Source: CN138134 Study Report: Tables 7.2B & 7.3B, pages 122 & 127)

Primary and key secondary endpoints analyses over time:
The sponsor's analyses of YMRS total score and CGI-BP (mania) score over time are summarized in Table 6. Aripiprazole was numerically superior to placebo from week 1 to week 6 for YMRS total score and from week 3 to week 6 for CGI-BP (mania) score.

Table 6. Adjusted Mean Change from Baseline Over Time in YMRS and CGI-BP (mania) Total Scores (LOCF)

Week	Aripiprazole N	Aripiprazole LS Mean	Placebo N	Placebo LS Mean	Difference (P-value*) Aripiprazole vs. placebo
YMRS total score					
Day 4	191	- 3.59	97	- 2.94	-0.65 (0.243)
Week 1	247	- 5.68	130	- 4.31	-1.37 (0.024)
Week 2	247	- 8.16	130	- 6.61	-1.55 (0.026)
Week 3	247	-10.33	130	- 8.12	-2.21 (0.003)
Week 4	247	-11.16	130	- 9.48	-1.68 (0.029)
Week 5	247	-12.41	130	-10.15	-2.25 (0.006)
Week 6	247	-13.31	130	-10.70	-2.62 (0.002)
CGI-BP (mania) score					
Day 4	191	-0.36	97	-0.38	0.01 (0.892)
Week 1	246	-0.63	130	-0.56	-0.07 (0.421)
Week 2	246	-1.03	130	-0.92	-0.11 (0.303)
Week 3	246	-1.42	130	-1.16	-0.26 (0.031)
Week 4	246	-1.55	130	-1.30	-0.25 (0.042)
Week 5	246	-1.75	130	-1.48	-0.27 (0.036)
Week 6	246	-1.89	130	-1.56	-0.33 (0.014)

(Source: CN138134 Study Report: Tables 7.2A & 7.3A, pages 120 & 126)
*Reviewer's note: P-values are not adjusted for multiplicity

3.1.4.5 Statistical Reviewer's Results and Comments

This reviewer confirmed the findings for primary and key secondary endpoints as presented in Table 3.

As an exploratory analysis for the primary endpoint, treatment-by-region (U.S. versus non-U.S.) and (U.S. versus Eastern Europe versus Western Europe/Australia/South Africa) interactions were added to the primary analysis model. The treatment-by-region interactions p-values were 0.839 and 0.106, respectively, suggesting there were no treatment-by-region interactions. The results from these analyses did not seem to alter the primary conclusion.

This reviewer also performed analyses based on the mixed effect models for repeated measures (MMRM) for the key secondary endpoint. The model included the change from baseline to each post baseline visit in CGI-BP (mania) score as a dependent variable; baseline CGI-BP (mania) score as a covariate; mood stabilizers, treatment group, and visit week as fixed effect factors; and a treatment-by-visit fixed effect interaction. The within subject covariance matrix was unstructured. The method of estimation was restricted maximum likelihood (ReML). The denominator degrees of freedom were approximated using the Satterthwaite approach. The results are presented in Table 7 and are supportive of the key secondary analysis.

Table 7. MMRM analysis on the CGI-BP (mania) score

	Aripiprazole	Placebo
Sample size (N)	193	113
LS Means	-2.11	-1.61
Difference from placebo (95% CI)	-0.50 (-0.79, -0.21)	
P-value	<0.001	

(Source: Reviewer's results)

CGI-BP (mania) score was an ordered categorical variable with seven levels (a score of 1 represents normal and a score of 7 represent very severely ill). The key secondary analysis was an ANCOVA model that was more suited for a continuous outcome. As a sensitivity exploratory analysis, this reviewer also confirmed the sponsor's analysis using the Wilcoxon rank-sum test stratified by mood stabilizers. The results were consistent in supporting the key secondary analysis ($p = 0.013$, Study Report: Table S.5.31, page 409).

Because aripiprazole was used as an adjunctive therapy to lithium or valproate and lithium and valproate were flexibly-dosed, it is of interest to see if the effect of aripiprazole was confounded by the dosing of lithium and valproate. Reproduced in Table 8 are the weekly average daily dose of lithium and valproate in the two treatment arms. For both lithium and

valproate groups, aripiprazole patients received a higher dose of lithium or valproate, on average, than placebo patients. However, upon discussing with the medical division, the difference was deemed clinically insignificant to impact the efficacy results.

Table 8. Number of patients receiving lithium or valproate and the weekly average dose (safety sample)

		Placebo			Aripiprazole		
	Days	N	Mean	Min-Max	N	Mean	Min-Max
Lithium dosing	1-7	50	991.2	500.0-1500.0	105	1135.8	500.0-1800.0
	8-14	49	1005.2	500.0-1500.0	101	1146.5	500.0-1800.0
	15-21	47	1009.2	464.3-1500.0	96	1148.7	500.0-1800.0
	22-28	47	1008.3	625.0-1500.0	89	1138.3	464.3-1800.0
	29-35	45	994.8	625.0-1500.0	85	1158.2	500.0-1800.0
	36-42	40	985.3	520.0-1500.0	78	1160.3	500.0-1750.0
	43-49	19	977.6	500.0-1500.0	31	1129.0	750.0-1500.0
	> 49	3	972.4	900.0-1017.2	8	1031.3	900.0-1250.0
Valproate dosing	1-7	80	1207.6	571.4-2250.0	146	1203.9	500.0-3000.0
	8-14	79	1182.2	714.3-2250.0	139	1205.4	464.3-3000.0
	15-21	76	1168.1	428.6-2250.0	134	1195.6	464.3-3000.0
	22-28	75	1171.0	500.0-2250.0	127	1203.2	166.7-3000.0
	29-35	74	1178.2	500.0-2250.0	121	1219.3	250.0-3000.0
	36-42	74	1178.9	500.0-2250.0	118	1225.3	250.0-3000.0
	43-49	25	1165.0	500.0-2250.0	49	1258.7	500.0-3000.0
	> 49	3	1166.7	750.0-1500.0	6	1705.6	1250.0-2500.0

(Source: CN138134 Study Report: Tables S.4.4 & S.4.5, pages 355 & 356)

3.2 Evaluation of Safety

Please refer to the clinical review for safety evaluation and report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Gender

The primary and key secondary efficacy analyses stratified by gender are presented below. The magnitudes of difference between aripiprazole and placebo appeared similar for male and female subjects.

Table 9. Primary and key secondary efficacy analyses by gender: YMRS and CGI-BP (mania) total scores, change from baseline at Week 6 (LOCF)

	Aripiprazole	Placebo
YMRS total score		
Female		
Sample size (N)	129	75
LS Means (SE)	-13.3 (0.68)	-10.6 (0.89)
Difference from placebo (95% CI)	-2.63 (-4.82, -0.45)	
Male		
Sample size (N)	118	55
LS Means (SE)	-13.4 (0.74)	-10.6 (1.08)
Difference from placebo (95% CI)	-2.85 (-5.42, -0.29)	
CGI-BP (mania) score		
Female		
Sample size (N)	128	75
LS Means (SE)	-1.8 (0.11)	-1.5 (0.15)
Difference from placebo (95% CI)	-0.32 (-0.69, 0.04)	
Male		
Sample size (N)	118	55
LS Means (SE)	-1.9 (0.11)	-1.6 (0.17)
Difference from placebo (95% CI)	-0.33 (-0.73, 0.06)	

(Source: CN138134 Study Report: Tables S.5.14 & S.5.26, pages 390 & 403)

4.1.2 Race

Because more than 90% of subjects are white, this reviewer omitted the analysis stratified by race.

4.1.3 Age

Because 98% of subjects in this study were between the age of 18 and 65, this reviewer omitted the analysis stratified by age.

4.2 Other Subgroups

4.2.1 U.S. versus non-U.S.

Presented below are analyses stratified by geographical regions (U.S. versus non-U.S.). Numerical evidence suggested a similar treatment effects for U.S. and non-U.S. patients. For the key secondary endpoint, the treatment effects appeared slightly lower for U.S. patients than non-U.S. patients.

Table 10. Primary and key secondary efficacy analyses (U.S. versus non-U.S.): YMRS and CGI-BP (mania) total scores, change from baseline at Week 6 (LOCF)

	Aripiprazole	Placebo
YMRS total score		
U.S.		
Sample size (N)	67	34
LS Means (SE)	-11.6 (0.95)	-9.2 (1.32)
Difference from placebo (95% CI)	-2.39 (-5.61, 0.83)	
Non-U.S.		
Sample size (N)	180	96
LS Means (SE)	-14.1 (0.60)	-11.4 (0.82)
Difference from placebo (95% CI)	-2.71 (-4.67, -0.75)	
CGI-BP (mania) score		
U.S.		
Sample size (N)	66	34
LS Means (SE)	-1.5 (0.16)	-1.3 (0.22)
Difference from placebo (95% CI)	-0.23 (-0.77, 0.30)	
Non-U.S.		
Sample size (N)	180	96
LS Means (SE)	-2.1 (0.09)	-1.7 (0.13)
Difference from placebo (95% CI)	-0.38 (-0.68, -0.07)	

(Source: CN138134 Study Report: Tables S.5.15 & S.5.27, pages 391 & 404)

4.2.2 Regions

Table 11 presents analyses stratified by geographical regions (U.S., Eastern Europe, Western Europe including South Africa and Australia). Eastern Europe included Bulgaria, Czech Republic, Estonia, Hungary, Poland, and Russia. Western Europe included France, Germany, Italy, Netherlands, Portugal, Spain, and United Kingdom. For the primary endpoint, numerical evidence suggested the results were consistent for the U.S. and Eastern European populations and the effect among the Western Europeans was smaller than the effects seen in the U.S. and Eastern European populations. For the key secondary endpoint, the effects appeared larger among the Eastern Europeans than among the U.S. and Western Europeans.

Table 11. Primary and key secondary efficacy analyses by region: YMRS and CGI-BP (mania) total scores, change from baseline at Week 6 (LOCF)

	Aripiprazole	Placebo
YMRS total score		
U.S.		
Sample size (N)	67	34
LS Means (SE)	-11.6 (0.95)	-9.2 (1.32)
Difference from placebo (95% CI)	-2.39 (-5.61, 0.83)	
Eastern Europe		
Sample size (N)	89	45
LS Means (SE)	-14.9 (0.79)	-10.1 (1.12)
Difference from placebo (95% CI)	-4.74 (-7.39, -2.09)	
Western Europe & Australia & South Africa		
Sample size (N)	91	51
LS Means (SE)	-13.2 (0.88)	-12.6 (1.16)
Difference from placebo (95% CI)	-0.59 (-3.41, 2.22)	
CGI-BP (mania) score		
U.S.		
Sample size (N)	66	34
LS Means (SE)	-1.5 (0.16)	-1.3 (0.22)
Difference from placebo (95% CI)	-0.23 (-0.77, 0.30)	
Eastern Europe		
Sample size (N)	89	45
LS Means (SE)	-2.2 (0.13)	-1.6 (0.18)
Difference from placebo (95% CI)	-0.64 (-1.08, -0.21)	
Western Europe & Australia & South Africa		
Sample size (N)	91	51
LS Means (SE)	-1.9 (0.13)	-1.8 (0.18)
Difference from placebo (95% CI)	-0.11 (-0.54, 0.32)	

(Source: Reviewer's results)

4.2.3 *Mood stabilizers*

Table 12 summarizes analyses stratified by mood stabilizers (lithium versus valproate). It appears that those who took valproate had larger mean changes from baseline than those who took lithium on both primary and key secondary endpoints.

Table 12. Primary and key secondary efficacy analysis by mood stabilizers: YMRS and CGI-BP (mania) total scores, change from baseline at Week 6 (LOCF)

	Aripiprazole	Placebo
YMRS total score		
Lithium		
Sample size (N)	102	50
LS Means (SE)	-12.3 (0.77)	-10.7 (1.11)
Difference from placebo (95% CI)	-1.60 (-4.27, 1.07)	
Valproate		
Sample size (N)	145	80
LS Means (SE)	-14.0 (0.65)	-10.7 (0.88)
Difference from placebo (95% CI)	-3.29 (-5.44, -1.14)	
CGI-BP (mania) score		
Lithium		
Sample size (N)	102	50
LS Means (SE)	-1.6 (0.12)	-1.5 (0.18)
Difference from placebo (95% CI)	-0.12 (-0.54, 0.31)	
Valproate		
Sample size (N)	144	80
LS Means (SE)	-2.1 (0.10)	-1.6 (0.14)
Difference from placebo (95% CI)	-0.48 (-0.82, -0.13)	

(Source: CN138134 Study Report: Tables S.5.6, S.5.8, S.5.22, & S.5.24, pages 382, 384, 399, & 401. Results are based on an ANCOVA model with treatment as a factor and baseline score as a covariate)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This reviewer confirmed the sponsor's findings that aripiprazole (flexibly dosed), in combination to lithium or valproate, were superior to lithium or valproate monotherapy in the acute treatment of bipolar I disorder in patients who were partially nonresponsive to lithium or valproate monotherapy. The efficacy was demonstrated on the primary endpoint (change from baseline to Week 6 in the YMRS total score) and the key secondary endpoint (change from baseline to Week 6 in the CGI-BP (mania) score).

5.2 Conclusions and Recommendations

The results of study CN138134 demonstrated that aripiprazole, in combination with lithium or valproate, was efficacious in the acute treatment of patients with bipolar I disorder who were partially nonresponsive to lithium or valproate monotherapy. The starting dose of aripiprazole was 15 mg/day with an option to titrate to 30 mg/day.

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Phillip Dinh
3/3/2008 01:03:47 PM
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Peiling Yang
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BIOMETRICS

James Hung
3/3/2008 01:14:29 PM
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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

ADDENDUM STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-436 / S020
Drug Name:	Abilify (Aripiprazole)
Indication(s):	Adjunctive Treatment of Bipolar I Disorder, manic or mixed
Applicant:	Bristol-Meyers Squibb Company
Date(s):	Received: July 11, 2007; PDUFA Due Date: May 11, 2008
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewers:	Phillip Dinh, Ph.D.
Concurring Reviewers:	Yeh-Fong Chen, Ph.D. H.M. James Hung, Ph.D.
Medical Division:	Division of Psychiatric Products, HFD-130
Clinical Team:	Karen Brugge M.D., Medical Reviewer, HFD-130 Gwen Zornberg M.D., Sc.D., Medical Team Leader, HFD-130
Project Manager:	Doris Bates Ph.D., HFD-130

Keywords: Clinical studies, NDA review, One study application

This addendum is submitted following the inspection results for site # 122. The Division of Scientific Investigations recommended that data from this site may be unreliable to support the efficacy results. At the time of this development, the statistical review has been signed off (on March 3, 2008). This addendum reflects additional analyses of the primary and key secondary efficacy variables. These additional analyses suggest that the efficacy conclusions remain unchanged.

Table 1 summarizes the primary and key secondary efficacy results as reported in the original statistical review (Table 3, page 10).

Table 1. Primary and key secondary efficacy analyses: YMRS and CGI-BP (mania) total scores, change from baseline at Week 6 (LOCF)

	Aripiprazole	Placebo
YMRS total score		
Sample size (N)	247	130
LS Means (SE)	-13.31 (0.50)	-10.70 (0.69)
Difference from placebo (95% CI)	-2.62 (-4.29, -0.95)	
P-value	0.002	
CGI-BP (mania) score		
Sample size (N)	246	130
LS Means (SE)	-1.89 (0.08)	-1.56 (0.11)
Difference from placebo (95% CI)	-0.33 (-0.60, -0.07)	
P-value	0.014	

(Source: CN138134 Study Report: Table 7.1A, page 113)

Site 122 contributed 13 randomized subjects to study CN138134. Table 2 summarizes the results excluding data from site # 122. It seems that the efficacy conclusions remain unchanged.

Table 2. Primary and key secondary efficacy analyses: YMRS and CGI-BP (mania) total scores, change from baseline at Week 6 (LOCF)
(Excluding site # 122)

	Aripiprazole	Placebo
YMRS total score		
Sample size (N)	238	126
LS Means	-13.27	-10.69
Difference from placebo (95% CI)	-2.58 (-4.27, -0.89)	
P-value	0.003	
CGI-BP (mania) score		
Sample size (N)	237	126
LS Means	-1.87	-1.55
Difference from placebo (95% CI)	-0.32 (-0.59, -0.05)	
P-value	0.020	

(Source: Reviewer's results)

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/s/

Phillip Dinh
4/11/2008 02:49:11 PM
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Yeh-Fong Chen
4/11/2008 02:51:49 PM
BIOMETRICS
I am acting for Dr. Peiling Yang.

James Hung
4/16/2008 08:26:18 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S-019, S-020, S-022
21-713/S-014, S-015, S-017
21-729/S-006, S-007, S-009
21-866/S-006, S-007, S-009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA (Serial Number):	**21436 SN(b) (4)**
Sponsor :	**Bristol-Meyers Squibb**
Drug:	**Aripiprazole**
Formulation:	**Tablets**
Proposed Indication:	**Bipolar Disorder**
Material Submitted:	**Drug/Drug Interaction Study**
Correspondence Date:	**December 27, 2007**
Reviewer:	Andre Jackson

STUDY CN138402-EFFECTS OF ARIPIPRAZOLE ON THE STEADY-STATE PHARMACOKINETICS OF LAMOTRIGINE IN SUBJECTS WITH BIPOLAR I DISORDER

Primary Objective

The primary objective of this study was to determine the effect of aripiprazole (10 to 30 mg/day) on the steady-state PK of lamotrigine in subjects with Bipolar I Disorder.

Study Design

This was an open-label, non-randomized, controlled study in subjects with Bipolar I Disorder, who had been clinically stable on a stable regimen of at least 100 mg lamotrigine and other allowed medications for at least 4 weeks prior to screening. Subjects unable to tolerate 10 mg aripiprazole were discontinued from the study. Subjects unable to tolerate 20 or 30 mg aripiprazole returned to their previously maximum tolerated dose provided this dose was at least 10 mg.

Selection of Doses

A dose range of 10 to 30 mg of aripiprazole and ≥ 100 mg lamotrigine was selected for this study (similar to doses in the CN138392 study). Lamotrigine is commonly titrated up in dose over a number of weeks due to acute tolerability issues. Therefore, subjects with Bipolar I Disorder already on a stable dose of lamotrigine for at least 4 weeks were enrolled in this study. In order for any metabolic enzyme or transporter induction or inhibition due to aripiprazole dosing to become apparent, subjects were on a dose of at least 10 mg aripiprazole for a minimum of 2 weeks. To maximize the possibility of observing a pharmacokinetic interaction between aripiprazole and lamotrigine, aripiprazole was titrated up to the maximum tolerated dose of 10, 20 or 30 mg daily.

DEMOGRAPHICS

Table 8.3.1:
Summary of Demographic Characteristics

	Total N=18
Age (yrs)	
N	18
Mean	39
Standard Deviation	9
Median	40
Min-Max	27-55
Q1-Q3	31-43
Age Category n(%)	
< 65 years	18(100)
>= 65 years	0
Not Reported	0
Gender n(%)	
Male	12(67)
Female	6(33)
Not Reported	0
Race n(%)	
WHITE	11(61)
BLACK/AFRICAN AMERICAN	7(39)
ASIAN	0
OTHER	0
Not Reported	0
Ethnicity n(%)	
Not Hispanic/Latino	16(89)
Hispanic/Latino	2(11)
Not Reported	0

Pharmacokinetics: Blood Collection

Study Day	Time (Relative To Dosing) Hour	Blood Sample for Lamotrigine	Blood Sample for Aripiprazole and Dehydro-Aripiprazole
-1	0 (pre-dose)	x	
-1	0.5	x	
-1	1	x	
-1	2	x	
-1	3	x	
-1	4	x	
-1	5	x	
-1	6	x	
-1	8	x	
-1	10	x	
-1	12	x	
-1	16	x	
-1	20	x	
1	0 (pre-dose)	x	
14	0 (pre-dose)	x	x
14	0.5	x	
14	1	x	
14	2	x	
14	3	x	
14	4	x	
14	5	x	
14	6	x	
14	8	x	
14	10	x	
14	12	x	
14	16	x	
14	20	x	
15	0 (pre-dose)	x	x

ANALYTICAL

ASSAY VALIDATION

Analytical

STUDY PERIOD: Study Initiation Date: (b) (4)
Study Completion Date: (b) (4)

Assay Dates Aripiprazole (b) (4) and (b) (4)
Total Storage: (b) (4)

Assay Dates Lamotrigine (b) (4) and (b) (4)
Total Storage: (b) (4)

Parameter	Lamotrigine	Aripiprazole

RESULTS

Figure 1. Dose-Normalized Plasma Concentration vs. Time Profile for Lamotrigine Administered Alone and with Aripiprazole

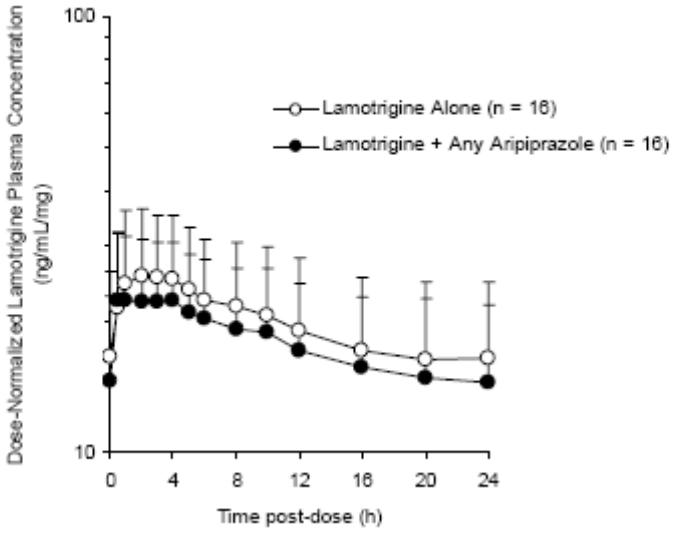

Table 1. Summary of Results of the Statistical Analyses of Lamotrigine Pharmacokinetic Parameters Untransformed Scale N=16.

Pharmacokinetic Parameter	Geometric Mean	Geometric Mean	Point Estimate and 90% Confidence Interval
	Treatment A	Treatment B	
Dose-normalized C_{max} ((ng/mL)/mg)	26	23	0.898 (0.829, 0.972)
Dose-normalized AUC(TAU) ((ng•h/mL)/mg)	434	394	0.909 (0.849, 0.973)
Treatments:			
A=Lamotrigine 100-400mg QD,			
B= Lamotrigine 100-400mg + Any Aripiprazole			

Pharmacokinetics of Aripiprazole

Table 2. Summary Statistics for Aripiprazole Cmin

Pharmacokinetic Parameter	Treatment B (N=16)	
	Day 14 - 0hr	Day 14 - 24hr
Cmin (ng/mL)		
Geom. Mean		
CV (%)	261.06 (35.77)	251.92 (40.94)
Treatment B= Lamotrigine 100-400mg + Any Aripiprazole		

DISCUSSION

Aripiprazole dosed to steady-state did not alter the steady-state pharmacokinetics of lamotrigine. Lamotrigine is predominantly metabolized by

glucuronic acid conjugation, and aripiprazole does not undergo direct glucuronidation. Aripiprazole is primarily metabolized by the cytochrome P450 enzymes, CYP2D6 and CYP3A4. Lamotrigine does not inhibit the metabolism of drugs eliminated primarily by CYP2D6 or CYP3A4. Aripiprazole has not been shown to cause clinically important pharmacokinetic interactions with drugs metabolized through glucuronidation (lorazepam and valproic acid). Based on their respective routes of metabolism and lack of major inhibitory or inductive effects on relevant drug metabolizing enzyme systems, the potential for a drug-drug interaction between aripiprazole and lamotrigine was anticipated to be low.

COMMENT

The study conducted by the firm clearly shows that there is no drug-drug interaction of Aripiprazole on Lamotrigine.

LABELLING:

Lamotrigine

Coadministration of 10 mg/day to 30 mg/day oral doses of aripiprazole for 14 days to patients with Bipolar I Disorder had no effect on the steady-state pharmacokinetics of 100 mg/day to 400 mg/day lamotrigine, a UDP-glucuronosyltransferase 1A4 substrate. No dosage adjustment of lamotrigine is required when aripiprazole is added to lamotrigine.

COMMENT:

The sponsor's proposed labeling is acceptable to OCP.

SIGNATURES

Andre Jackson_____

RD/FT Initialed by Raman Baweja, Ph.D.
Team Leader_____

Cc-NDA 21436, HFD-860(Jackson, Baweja,Mehta), Central Documents Room(Biopharm-CDR)
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/s/

Andre Jackson
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BIOPHARMACEUTICS

Raman Baweja
4/14/2008 03:52:36 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S-019, S-020, S-022
21-713/S-014, S-015, S-017
21-729/S-006, S-007, S-009
21-866/S-006, S-007, S-009

OTHER REVIEW(S)

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: April 7, 2008

TO: Doris Bates, Ph.D., Regulatory Project Manager
Karen Brugge, Medical Officer

FROM: Dianne Tesch, Consumer Safety Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Joseph P. Salewski
Acting Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA or IND: 21-436/SE#019/020

APPLICANT: Otsuka Pharmaceutical Company, Ltd.

DRUG: Abilify (aripiprazole)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: 1. 21-436 S-019, Study 162: (b) (4) 15 mg starting dose in the treatment of Bipolar Disorder

2. 21-436 S-020, Study 134: Adjunctive therapy in the treatment of Bipolar I Disorder with lithium or valproate

CONSULTATION REQUEST DATE: September 6, 2007

DIVISION ACTION GOAL DATE: February 11, 2008

PDUFA DATE: May 11, 2008

I. BACKGROUND:

Bipolar I Disorder is a lifelong episodic illness characterized by manic or depressive episodes followed by symptom-free periods. Psychotic symptoms (delusions, hallucinations, thought disorders) often accompany the manic phase of bipolar disorder. The lifetime prevalence of bipolar disorder is estimated to be 0.4% to 1.6%. The mean age at onset for a first manic episode is the early 20's.

Aripiprazole is a novel dopamine-serotonin stabilizer approved in the U.S. and other countries in tablet form for the management of schizophrenia, and for the acute treatment of mania in patients with bipolar disorder; it is also approved in the U.S. and other countries for maintenance treatment of bipolar disorder. Aripiprazole has also been shown superior to placebo in treating acute bipolar mania in hospitalized patients with Bipolar I Disorder.

(b) (4)

Study 162

The primary objective of Study 162 was to evaluate the efficacy of aripiprazole monotherapy as acute and maintenance therapy for the treatment of acutely manic patients with Bipolar I Disorder, Manic or Mixed. The secondary objective was to evaluate the safety and tolerability of the drug in this population.

The primary efficacy measure was the mean change from baseline to Week 3 in Young-Mania Rating Scale (Y-MRS) Total Score.

The key secondary efficacy measure was the mean change in baseline in the CGI-BP Severity of Illness Score (mania).

Study 134

The primary objective of Study 134 was to compare the efficacy of aripiprazole with placebo in combination with lithium or valproate to lithium or valproate monotherapy, as measured by the Y-MRS, in the treatment of Bipolar I patients with a manic or mixed episode, with or without psychotic features, partially nonresponsive to lithium or valproate monotherapy.

The primary efficacy measure was the mean change from baseline to endpoint in Y-MRS Total Score.

The key secondary efficacy measure was the mean change in baseline in the CGI-BP Severity of Illness Score (mania).

Both investigators were chosen for inspection because they were high enrollers.

Protocol #B: Protocol CN138162: A Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Aripiprazole Monotherapy in the Treatment of Acutely Manic Patients with Bipolar I Disorder

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State or Country	Indication: Protocol #: and # of Subjects:	Insp. Date	Final Classification
Richard Weisler, M.D., Raleigh, NC	Protocol A: CN138134	11/6/07-11/16/07	OAI (probable - pending OC review)
Adam Lowy, M.D., Washington, D.C.	Protocol B: CN138162	11/26/07-11/30/07	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-R = Response Requested = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

Protocol #A: Protocol CN138134: Efficacy of Aripiprazole in Combination With Valproate or Lithium in the Treatment of Mania in Patients with Bipolar I Disorder Partially Nonresponsive to Valproate or Lithium Monotherapy

Richard Weisler, M.D., 700 Spring Forest Rd., Suite 125, Raleigh, NC 27609

a. Nineteen subjects were screened, and thirteen were randomized. All of the records were reviewed for this inspection. There were no limitations to the inspection.

b. The inspection revealed significant discrepancies in drug accountability. Specifically, Subjects 336, 350, 358, 448, and 454 received blinded medication not assigned to them by the Interactive Voice Response System (IVRS). Subject 554 was randomized, with double blind bottles assigned one week prior to completion of the baseline phase, and open label medication was assigned at the week 3 and week 5 visits of the double-blind phase. Furthermore, one subject was randomized who had a Young Mania Rating Scale (YMRS) of 9 at the end of screening. The protocol required a score of $\geq$ 16.

c. Given the drug accountability issues the data from Subjects 336, 350, 358, 448, and 454 is considered unreliable and should not be used in support of the application.

Adam F. Lowy, M.D., 4228 Wisconsin Ave., Washington, D.C. 20016

a. Twenty-five subjects were screened between March 23, 2005 and September 14, 2006. Ten subjects completed the study. Eleven records were reviewed in depth for the data audit.

b. There were no regulatory violations at this site.

c. The data are considered acceptable in support of the application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

There were no data integrity issues found at Dr. Lowy's site. There were serious drug accountability issues at Dr. Weisler's site. Five subjects as noted above received medication not assigned to them by the IVRS, and a sixth subject received open label medication during the double blind phase of the study. Data from Subjects 336, 350, 358, 448, 454 and 554 are considered unreliable and should not be included in the efficacy analysis.

{See appended electronic signature page}

Dianne D. Tesch, Consumer Safety Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Joseph P. Salewski
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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

/s/

Dianne Tesch
4/8/2008 11:04:38 AM
CSO

Joseph Salewski
4/8/2008 01:24:13 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S-019, S-020, S-022
21-713/S-014, S-015, S-017
21-729/S-006, S-007, S-009
21-866/S-006, S-007, S-009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

Doctype	Number	Supp. Type	Supp. No.	Proprietary Name Generic Name	Dosage Form & Strengths
NDA #	21436	SE2	019	Abilify (aripiprazole)	Tablets 2, 5, 10, 15, 20, 30 mg
NDA #	21713	SE2	014	Abilify (aripiprazole)	Oral Solution 1 mg / mL
NDA #	21729	SE2	006	Abilify (aripiprazole)	DISCMELT Orally Disintegrating Tablet 10, 15 mg
NDA #	21866	SE2	006	Abilify (aripiprazole)	Injection for Intramuscular Use 9.75 mg / 1.3 mL

Applicant: Otsuka Pharmaceutical Co., Ltd
Agent for Applicant (if applicable): Otsuka Pharmaceutical Development & Commercialization, Ind.
Collaborative Business Partner for Applicant and Agent: Bristol-Myers Squibb Company

Approval Date, If Known PDUFA Goal Date is May 11, 2008 for S-019, June 29, 2008 for all others listed.

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 ☐

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8
505(b)(1) SE2 for change in dosing regimen.

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?

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?

Yes.

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).

NDA 21436 Abilify (aripiprazole) Tablets

#			2, 5, 10, 15, 20, 30 mg
NDA	21713	Abilify (aripiprazole)	Oral Solution
#			1 mg / mL
NDA	21729	Abilify (aripiprazole)	DISCMELT Orally Disintegrating Tablet
#			10, 15 mg
NDA	21866	Abilify (aripiprazole)	Injection for Intramuscular Use
#			9.75 mg / 1.3 mL

2. Combination product. ***Not Applicable***

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).

NDA#

NDA#

NDA#

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 ☐

A clinical investigation was required to establish the lower initial starting dosage.

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:

Investigation 1: Study CN 138135
Investigation 2: Study CN138162

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"):

Investigation 1: Study CN 138135
Investigation 2: Study CN138162

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 Study CN138135 :

IND # 42776	YES ☑	NO ☐
		Explain:

Investigation #2 Study CN138162 ! !
IND # 42776 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?

NOT APPLICABLE

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:

==========

Exclusivity Summary
NDA 21-436 / SE2-019, NDA 21-713 / SE2-014, NDA 21-729 / SE2-006, NDA 21-866 / SE2-006

Name of person completing form: Doris J. Bates, Ph.D.
Title: Regulatory Health Project Manager
Date: April 13, 2008

Name of Office/Division Director signing form: Thomas P. Laughren, M.D.
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Doris Bates
5/5/2008 04:06:43 PM

Thomas Laughren
5/6/2008 08:40:51 AM

EXCLUSIVITY SUMMARY

Doctype	Number	Supp. Type	Supp. No.	Proprietary Name Generic Name	Dosage Form & Strengths
NDA #	21436	SE1	020	Abilify (aripiprazole)	Tablets 2, 5, 10, 15, 20, 30 mg
NDA #	21713	SE1	015	Abilify (aripiprazole)	Oral Solution 1 mg / mL
NDA #	21729	SE1	007	Abilify (aripiprazole)	DISCMELT Orally Disintegrating Tablet 10, 15 mg
NDA #	21866	SE1	007	Abilify (aripiprazole)	Injection for Intramuscular Use 9.75 mg / 1.3 mL

Applicant: Otsuka Pharmaceutical Co., Ltd
Agent for Applicant (if applicable): Otsuka Pharmaceutical Development & Commercialization, Inc.
Collaborative Business Partner for Applicant and Agent: Bristol-Myers Squibb Company

Approval Date, If Known PDUFA Goal Date is May 11, 2008 for S-020, June 29, 2008 for all others listed.

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 ☐

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8
505(b)(1) SE1 for new indication.

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?

THREE

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?

Yes.

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).

NDA #	21436	Abilify (aripiprazole)	Tablets 2, 5, 10, 15, 20, 30 mg
NDA #	21713	Abilify (aripiprazole)	Oral Solution 1 mg / mL
NDA #	21729	Abilify (aripiprazole)	DISCMELT Orally Disintegrating Tablet 10, 15 mg
NDA #	21866	Abilify (aripiprazole)	Injection for Intramuscular Use 9.75 mg / 1.3 mL

2. Combination product. ***Not Applicable.***

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).

NDA#

NDA#

NDA#

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:

Only one Investigation was required for this supplement: Study CN138134.

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 ☐
Investigation #3	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 ☐
Investigation #3	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"):

Investigation 1: Study CN138134.

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 Study CN138134 : **note*: for this indication only one study was required.***

IND #42776 YES ☑ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #3 !
!
IND # 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?

NOT APPLICABLE

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: Doris J. Bates, Ph.D.

Exclusivity Summary
NDA 21-436 / SE1-020, NDA 21-713 / SE1-015, NDA 21-729 / SE1-007, NDA 21-866 / SE1-007

Title: Regulatory Health Project Manager
Date: April 13, 2008

Name of Office/Division Director signing form: Thomas P. Laughren, M.D.
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Doris Bates
5/5/2008 04:09:39 PM

Thomas Laughren
5/6/2008 08:41:27 AM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#, Supplement Number, Trade and Generic Names and Dosage Forms:

NDA 21-436	SE2-019	Abilify (aripiprazole) Tablets 2, 5, 10, 15, 20, 30 mg
NDA 21-713	SE2-014	Abilify (aripiprazole) Oral Solution 1 mg / mL
NDA 21-729	SE2-006	Abilify (aripiprazole) DISCMELT Orally Disintegrating Tablets 10, 15 mg
NDA 21-866	SE2-006	Abilify (aripiprazole) Intramuscular Injection 9.75 mg / 1.3 mL

Division Name: Div. of Psychiatry Products, HFD-130

Stamp Date: 11-JUL-2007 PDUFA Goal Date: 11-MAY-2008

Applicant/Sponsor: Otsuka Pharmaceutical Development and Commercialization, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):

ORAL FORMULATIONS	-Acute and maintenance treatment of schizophrenia [adults] -Acute treatment of schizophrenia [adolescents aged 13 to 17 years] -Treatment of acute manic or mixed episodes associated with bipolar disorder [adults, pediatric patients aged 10 to 17] -Maintenance treatment of manic or mixed episodes associated with bipolar disorder [adults] -Adjunctive therapy with antidepressants in treatment of major depressive disorder [adult]
INJECTABLE FORMULATION	-Agitation associated with schizophrenia [adult] -Agitation associated with bipolar disorder [adult]

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue

No ***XX*** Please proceed to Question 2.

If Yes, NDA/BLA#: Supplement #: PMC #:

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s); ☐ indication(s); ☐ dosage form; **XX** dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):**ONE**
(Attach a completed Pediatric Page for each indication in current application.)

Indication:

NDA 21-436 SE2-019 **NDA 21-713 SE2-014** **NDA 21-729 SE2-006** **NDA 21-866 SE2-006**	**Monotherapy in the treatment of bipolar disorder, manic or mixed [approved indication] with a new lower starting dose of 15 mg [already approved dosage strength; new dosing regimen].**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

XX No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

XX Yes: (Complete Section A.)

☐ No: Please check all that apply:

- ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- ☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)
- ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
- ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

XX Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): (b) (4) [redacted]

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

XX Justification attached. *Justification: the approved pediatric starting dose is 2 mg,* (b) (4) [redacted] *Requiring studies in pediatric patients with a starting dose of 15 mg is not feasible for any pediatric age group, using any formulation of the drug..*

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed):

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may <u>only</u> cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E

and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason:

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#, Supplement Number, Trade and Generic Names and Dosage Forms:

NDA 21-436	SE1-020	Abilify (aripiprazole) Tablets 2, 5, 10, 15, 20, 30 mg
NDA 21-713	SE1-015	Abilify (aripiprazole) Oral Solution 1 mg / mL
NDA 21-729	SE1-007	Abilify (aripiprazole) DISCMELT Orally Disintegrating Tablets 10, 15 mg
NDA 21-866	SE1-007	Abilify (aripiprazole) Intramuscular Injection 9.75 mg / 1.3 mL

Division Name: Div. of Psychiatry Products, HFD-130
Stamp Date: 11-JUL-2007 PDUFA Goal Date: 11-MAY-2008
Applicant/Sponsor: Otsuka Pharmaceutical Development and Commercialization, Inc.
Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):

ORAL FORMULATIONS	-Acute and maintenance treatment of schizophrenia [adults] -Acute treatment of schizophrenia [adolescents aged 13 to 17 years] -Treatment of acute manic or mixed episodes associated with bipolar disorder [adults, pediatric patients aged 10 to 17] -Maintenance treatment of manic or mixed episodes associated with bipolar disorder [adults] -Adjunctive therapy with antidepressants in treatment of major depressive disorder [adult]
INJECTABLE FORMULATION	-Agitation associated with schizophrenia [adult] -Agitation associated with bipolar disorder [adult]

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue

No ***XX*** Please proceed to Question 2.

If Yes, NDA/BLA#: Supplement #: PMC #:

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s); **XX** indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Pediatric use for each pediatric subpopulation must be addressed for <u>each indication</u> covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):**ONE**
(Attach a completed Pediatric Page for <u>each</u> indication in current application.)

Indication:

NDA 21-436 SE1-020 **NDA 21-713 SE1-015** **NDA 21-729 SE1-007** **NDA 21-866 SE1-007**	**Adjunctive treatment with lithium or valproate for acute treatment of bipolar disorder, manic or mixed, using the same 15 mg starting dose provided for under SE2-019.**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

XX No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

XX No: Please check all that apply:

XX Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

XX Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
XX	Neonate	0 yrs	1 yr	X	☐	☐	☐
XX	Other	1 yr	9 yr	X	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? X No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? X No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

XX Disease/condition does not exist in children [cannot be reliably diagnosed in these age groups]

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed):

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric

subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason:

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
XX	Other	10 yr	17 yr	XX	XX
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? XX No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? XX No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

MINUTES: FILING MEETING

NDA 21-436 / SE2-019 and SE1-020
NDA 21-713 / SE2-014 and SE1-015
NDA 21-729 / SE2-006 and SE1-007
NDA 21-866 / SE2-006 and SE1-007

Abilify (aripiprazole) Tablets, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg; Oral Solution, 1 mg/mL; DISCMELT Orally Disintegrating Tablets, 10 mg & 15 mg; Injection for Intramuscular Use, 9.75 mg/1.3 mL

SE2-019 etc.: acute bipolar, 15 mg starting dose
SE1-020 etc: acute bipolar: adj tx. w. Li or valproate and with 15 mg starting dose

Applicant: Otsuka Pharmaceutical Co., Ltd
Agent for Applicant (if applicable): Otsuka Pharmaceutical Development & Commercialization, Ind.
Collaborative Business Partner for Applicant and Agent: Bristol-Myers Squibb Company

Date/Time/Place: Thursday, September 6, 2007: 2:00 - 3:00 P.M.; WO 22 Rm 4270
Participants: see below.

Reviewer Roster:

Discipline	**Team Leader /Reviewer**
Division Director:	Laughren
Clinical Team Leader II	Khin
Regulatory Project Management:	Bates
Clinical [Deputy Director and Clinical Reviewer]	Mathis/Brugge
Clinical Safety:	---
Controlled Substances:	---
DDRE:	---
Statistical:	Yang/Dinh
Nonclinical Pharmacology:	---
Statistical Nonclin Pharmacology:	---
Clinical Pharmacology:	---
Chemistry [PAL]:	Chidambaram
Environmental Assessment (if needed):	---
Microbiology, sterility:	---
Microbiology, clinical (for antimicrobial products only):	---
DSI:	Tesch
DDMAC:	---

Other Consults:
505(b)(2)? No

NDA 21-436 S-019 and S-020 were submitted and received on July 11, 2007 and therefore have May 11, 2008 Goal Dates. The remaining six applications were submitted August 28, 2007 and received August 29, 2007, and therefore have June 29, 2008 goal dates. Because these are duplicates by cross reference and require no additional review, the May 11, 2008 Goal Date is targeted for all eight supplements.

LETTER DATE: July 11, 2007 for 019, 020	STAMP DATE: July 11, 2007 for 019, 020
FILING DATE:	September 9, 2007 for 019, 020
74-DAY LETTER ISSUE DATE:	September 23, 2007 for both [9/21 in actuality]
DATE OF MIDCYCLE MEETING:	~Dec. 11, 2007
DSI CI SUMMARY NEEDED BY	February 11, 2008
DATE OF MONTH 8 MEETING	~March 11, 2008

PDUFA GOALDATE: MAY 11, 2008

ACTION LETTER SIGNATORY AUTHORITY: ***Division Director*** or Office Director

NDA 21-436 / SE2-019 and SE1-020
NDA 21-713 / SE2-014 and SE1-015
NDA 21-729 / SE2-006 and SE1-007
NDA 21-866 / SE2-006 and SE1-007

DATE REVIEWS ARE DUE:

To Team Leaders:	Feb. 25, 2008
To Clinical Team Leader:	March 11, 2008
To Division Director:	April 18, 2008

Background: SE2-019: adds a provision for use of a 15 mg/day starting dose or aripiprazole in the monotherapy treatment of bipolar disorder, manic or mixed. SE1-020: provides for the use of aripiprazole as adjunctive therapy with lithium or valproate mood stabilizers in the treatment of bipolar disorder, manic or mixed, using a 15 mg/day starting dose.

SE1-020 is submitted in fulfillment of a post marketing commitment, related to SE1-002 and SE1-005 for NDA 21-436, to perform short term studies on the use of Abilify as adjunctive treatment of bipolar disorder (acute, manic or mixed) in combination with lithium or valproate. The PMC language, with status summary, is captured in the Additional Comments at the end of these minutes:

The additional SE1 and SE2 submissions are cross referenced efficacy supplements necessitated by the use of a single package insert for all four dosage forms of the drug. User Fees will be waived for these six submissions, since no additional clinical data will be reviewed for them.

Meeting Details:

Per reviewers, are all parts in English or English translation? ***YES*** X NO

CLINICAL ***FILE*** X REFUSE TO FILE

- Clinical site inspection needed? ***YES*** X NO
- Domestic or foreign? ***Domestic*** X Foreign
- Advisory Committee Meeting needed? YES, date if known _____ ***NO*** X
- Is application affected by AIP ***N/A*** X YES NO
- Has Division made a recommendation regarding exception to the AIP to permit review based on medical necessity or public health significance? ***N/A*** X YES NO

Summarize Clinical Issues. ***See 74-day letter.***

- Clinical Questions for 74-Day Letter? N/A ***YES*** NO

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE

STATISTICS N/A FILE X REFUSE TO FILE

- Questions for 74-Day Letter? ***YES***

CLINICAL PHARMACOLOGY ***N/A*** X FILE REFUSE TO FILE

- Biopharm. inspection needed? YES NO
- Domestic or foreign? Domestic | | Foreign | |

NONCLINICAL PHARMACOLOGY ***N/A*** X FILE REFUSE TO FILE

- GLP inspection needed? YES NO
- Carc Studies? YES NO
- Date of CAC

NDA 21-436 / SE2-019 and SE1-020
NDA 21-713 / SE2-014 and SE1-015
NDA 21-729 / SE2-006 and SE1-007
NDA 21-866 / SE2-006 and SE1-007

CHEMISTRY	N/A	***FILE***	X	REFUSE TO FILE	
• Establishment(s) ready for inspection?		***N/A***		YES	NO
• Microbiology consult needed? YES		***N/A***			NO X
• Other expert consult needed?				***NO***	***X***
• Methods validation needed?				***NO***	
• Questions for 74-Day Letter?				***NO***	***X***

ELECTRONIC SUBMISSION:
No comments.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

The application is unsuitable for filing. See attached summary of deficiencies.

X The application, on its face, appears to be sufficiently well-organized and indexed to permit filing. This decision does not guarantee that no deficiencies will be identified during review. It also does not guarantee a first cycle approval action.

No filing issues identified.

X Filing review issues to be communicated by Day 74

ACTION ITEMS / COMMENTS:

Pediatric Waiver granted.

74-day letter to be sent.

Status of responses to existing Phase 4 Commitments for bipolar submissions will be assessed separately and addressed in separate correspondence.

Doris J. Bates, Ph.D.
Regulatory Project Manager, HFD-130

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/s/

Doris Bates
5/5/2008 04:26:17 PM

Bates, Doris J

From: Bates, Doris J
Sent: Monday, April 21, 2008 4:09 PM
To: 'Susan.Behling@bms.com'; 'Mallikaarjun, Kusuma'
Cc: Bates, Doris J
Subject: NDA 21-436 S-019, S-020, and others: Responses to Questions 17APR08

Importance: High

Hello Susan, hello Kusuma

Here are responses to the questions remaining from our email exchange on April 17 - if further clarification is needed please feel free to check back with me.

First - we have included S-022 [and its counterparts for the other NDAs] in this labeling, as we intend to include it in the final action.

Second - with regard to the acute/maintenance question re schizophrenia: since I'm not the PM for this indication, I have checked with Dr. Laughren, and the reasoning behind our revision is as follows.

Clinically, patients with schizophrenia - and most other psychiatric disorders - need treatment beyond the acute episode; this will be true regardless of whether or not a maintenance study has been done at the time of initial approval of a drug.

The exception is bipolar disorder. In bipolar, it is not uncommon to manage the acute episode with one drug, sometimes as adjunctive therapy and sometimes as monotherapy. Once the patient is stabilized, the practitioner may choose to continue the initial regimen, or change it to remove or replace one or more of the drugs that were given to treat the acute episode.

We therefore are continuing to make a distinction between acute and maintenance treatment in the case of bipolar disorder. We will also continue to describe both acute and maintenance clinical trials for all other psychiatric disorders for which they are conducted and approval is granted, but we will not make a distinction between acute and maintenance treatment, as separate indications per se, except in the case of bipolar disorder.

Hopefully this explanation will help; if you have questions about any of this, please let me know; Dr. Laughren is willing to explain further if this will help.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
4/21/2008 04:18:12 PM
CSO

This message explains the distinction between bipolar disorder and other psychiatric disorders, in terms of labeling for acute and maintenance indications.

Bates, Doris J

From: Bates, Doris J
Sent: Thursday, December 06, 2007 2:10 PM
To: 'Susan.Behling@bms.com'
Cc: 'Mallikaarjun, Kusuma'; Bates, Doris J
Subject: RE: NDA 21-436 S-019 and S-020: Statistical and Clinical Requests
Importance: High

Good afternoon Dr. Mallikaarjun and Ms. Behling --

Our review team has discussed your November 29, 2007 requests for extended time to submit the clinical responses to our questions from November 16, 2007.

These responses were initially requested by January 7, 2008.

We are seeking to comply with Good Review Management Practices in our evaluation of this submission. Therefore, we are now asking for the requested data any time on or before January 18, 2008. Beyond that point, we may have difficulty completing review of all materials within the first review cycle.

Please note that review of all materials within the first cycle does not necessarily guarantee an approval action in one cycle. If further questions arise upon our review of your response, for example, we will be hard pressed to turn around a further cycle of query, response, and review within the first cycle time frame. The sooner we receive your reply, however, the sooner we can review it, and communicate any further questions that might arise.

Please feel free to follow up with us if you have any questions.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

From: Susan.Behling@bms.com [mailto:Susan.Behling@bms.com]
Sent: Thursday, December 06, 2007 11:23 AM
To: Bates, Doris J; Brugge, Karen; Dinh, Phillip
Cc: Mallikaarjun, Kusuma
Subject: Re: NDA 21-436 S-019 and S-020: Statistical and Clinical Requests
Importance: High

Dear Drs. Bates, Brugge and Dinh: I just received a 'bounce back' notice for an e-mail that I sent you that included the protocol for the CN138189 study in response to the request below (1.c iv).. It seems that the

size of the file is too large for the server to receive. We'll explore other options for getting it to you expeditiously. However, since it is an IND study, the protocol is available to you in IND 73863 (current version of the protocol submitted September 13, 2007, Serial # 014).)

We propose to use the last observation prior to the first aripiprazole treatment as the baseline for the requested safety assessments in the study. Please let us know if you prefer an alternative.

I recently sent a request to extend our submission date for these clinical responses to early February but I have not received confirmation that this is acceptable. We would greatly appreciate your response to this proposal.

Best regards,

Sue

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/s/

Doris Bates
12/6/2007 02:45:12 PM
CSO
See email for date and time of transmittal to applicant.

Bates, Doris J

From: Bates, Doris J
Sent: Friday, November 16, 2007 6:40 PM
To: 'Mallikaarjun, Kusuma'; 'Susan.Behling@bms.com'
Cc: Brugge, Karen; Dinh, Phillip; Bates, Doris J
Subject: NDA 21-436 S-019 and S-020: Statistical and Clinical Requests
Importance: High

Dear Dr. Mallikaarjun and Ms. Behling:

Please refer to the above referenced supplemental NDAs. This email forwards questions from our statistical and clinical reviewers. Note that our clinical reviewer has requested the clinical information be provided no later than January 7, 2008; we would appreciate receiving the statistical information as soon as possible.

I have included both the clinical and statistical reviewers as CC recipients to this message. Please 'reply to all' if responding via email to facilitate their receipt of the information.

As always, we appreciate an e-copy of information whenever possible, and a single amendment to the official file to add the replies to the formal record should be made subsequently.

Statistical Questions: Relate to S-019.

1. Please identify the variables and the datasets used to generate Tables 6.1, (page 110 of 9701) and 5.1A (page 91 of 9701) for study CN138135 report. Please also include the SAS codes to generate these tables.

2. Please identify the variables and the datasets used to generate Tables 6.1, (page 110 of 9298) and 5.1A (page 92 of 9298) for study CN138162 report. Please also include the SAS codes to generate these tables.

Clinical Questions: SNDA reference is included for each question.

We request the following safety-related information regarding NDA 21-436 N20, Abilify in the Adjunctive Treatment of bipolar disorder, manic or mixed states (which cross-references N19 for safety information and is also the submission for a new Abilify starting dose of 15 mg). If any information below is provided in either of these submissions please clarify the exact location where the information can be found. Please send to us your response as soon as possible, but no later than 1/7/2008 (if you cannot make this deadline please notify us by 26 November 2007).

1) We cannot find longterm safety data in your submission on adjunctive treatment in N19 (for N20) with lithium or valproate other than integrated safety information on deaths, serious adverse events (SAEs) and adverse dropouts (ADOs) in the All-aripiprazole treated dataset. It is our understanding that the only longterm adjunctive trials in your bipolar disorder program (in patients using lithium or valproate) are ongoing trials involving OL treatment (results from a 46-week extension phase of Study CN138134 and from the OL phases of an ongoing maintenance trial Study CN138189). Please verify this and provide the following information for the OL phase of each longterm trial using adjunctive lithium or valproate:
   a. Provide a copy of the protocol (we can only find the protocol for Study C-134).
   b. Provide information on exposure for each study (using tables as found in Module 2.7.4)
   c. Provide information on safety (for adjunctive OL phases of the trials) as follows (and also provide the same information for each adjunctive treatment subgroup; lithium and valproate subgroups:
      i. Incidence of SAEs and ADOs
      ii. Incidence of AEs during the adjunctive OL phase and over time (e.g. by each visit) during the OL phase. Please distinguish fine tremor versus coarse tremors, if the information exists (and AEs of tremor that coincided with extrapyramidal events). If this information does not exist explain why.
      iii. Incidence of AEs leading to dose reductions of valproate or lithium (if the reported AE was elevated or toxic levels rather than a symptom or sign, then provide a summary of the subject regarding why drug levels were drawn and any AEs or clinical abnormalities coinciding with or leading to having levels drawn on that subject). Please distinguish fine tremor versus coarse tremors, if the information exists (and AEs of tremor that coincided with extrapyramidal events). If

this information does not exist explain why.

iv. The mean±SD, median and range at baseline (pre-dose) and mean±SD, median and range in the change from baseline to treatment endpoint (LOCF dataset using the last on-treatment value) and the change from baseline to each time-point (OC dataset) of each clinical parameter. Please send us a protocol for Study C-189 so that we may clarify which baseline value(s) to use (in the case the study has multiple OL phases).

v. The incidence of outliers on each clinical parameter.

d. It is our understanding that you have provided narratives on patients who experience SAEs or AE discontinuations for these ongoing trials in Module 2.7.4 (in the appendix section) and in line listings (as well as those provided with verbatim terms upon our request). If not, then please provide the narratives.

e. Please provide verbatim/preferred term line listings for ADOs and SAEs reported during the OL extension phase of Study -134 and for the OL adjunctive phase of Study -189 (line listings provided already under the NDA do not clearly separate and delineate events that occurred during the OL phase versus the DB phase. We found some inconsistencies between the study day numbers in the line listings compared to the narratives, further adding to the difficulty in finding these subjects). Please specify the study day (during the OL phase) when the ADO or SAE was reported and specify if the given ADO was an SAE. For the line listing of SAEs (specify if the SAE was also an ADO). Please include other information that is generally included in your line listings (e.g. age, gender, adjunctive treatment, dose of aripiprazole).

2) We cannot find any discussion in N19 or N20 that focuses on potential interaction effects of Arip with concomitant valproate or lithium on safety. Please provide a summary of any key, clinically remarkable findings relevant to this topic. We are also interested in any results relevant to potential effects of aripiprazole on lithium toxicity given the narrow therapeutic index for this drug. For example, is there evidence for a masking effect on detecting early stages of lithium toxicity during aripiprazole treatment (e.g. diarrhea, nausea, vomiting may be masked by potential aripiprazole effects on this organ system, or fine tremor is masked by extrapyramidal symptoms)? Is there evidence suggestive of an effect in which aripiprazole exaggerates lithium toxicity? There may be a possible interaction between aripiprazole and lithium or valproate related to cardiac conduction effects, CNS effects and possibly other effects such as tremor. It is hypothetically possible that potential interaction effects, if they are identified, could be dependent on lithium levels. For example, it is possible that masking effects could occur at serum lithium levels between 1.2 mEq/l and 1.5 mEq/l, while an exaggerated effect may occur at the higher end of the toxic range such as at serum levels >1.5 mEq). Perhaps the AE profile (the type of AEs), the severity of AEs, or the incidence of AEs relevant to the adverse effects of lithium may be altered by adjunctive aripiprazole at each given lithium level (e.g. low versus moderate versus high levels). Consequently, an examination of AEs against lithium levels in Arip subjects and compared to placebo subjects of Study C-134 may be revealing (and/or examination of the data is some other manner). Please distinguish fine tremor versus coarse tremors, if the information exists (and AEs of tremor that coincided with extrapyramidal events). If this information does not exist explain why. Consider approaches to analyzing your safety data to explore a possible masking or exaggerated effect that will be most interpretable. Please provide your data-based justification for your conclusions on potential interaction effects with concomitant Abilify. Also examine potential arip-lithium interaction effects on the cardiovascular system near Tmax (e.g. consider using Phase I data that includes data collected near Tmax).

Additionally, please provide information on the incidence of AEs leading to dose reductions of valproate or lithium in the DB and OL adjunctive extension phase of Study C-134 (consider a comparison to the incidence of dose reductions due to elevated levels revealed on scheduled blood draws or categorizing subjects by serum levels or some other manner of examining the results for a potential masking effect or exaggerated effect at a given serum level).

3) Please provide more information on the following subjects and we request that the information be provided from a clinical perspective (we request that a medical doctor with appropriate training and clinical experience review the information and write up the response that you provide us):

a. 138134-15-32: please explain why lithium was discontinued on Day 95. Please provide information on the differential diagnosis and diagnostic work-up (with the results) regarding the loss of consciousness and describe this episode, from a clinical perspective (please include the timing of assessment results relative to the timing of this episode and relative to baseline pre-treatment values). Please include QT raw values and QTc values if heart rate was altered or abnormal (using the appropriate correction method). Please include any information relevant to potential risk factors, concomitant drugs and clinical information relevant to potential etiologies or contributing factors. Include copies of the hospital admission and discharge summaries.

b. 138134-17-106: please explain why there was an “overdose” of lithium (e.g. please describe actual doses of drug received and lithium levels and information relevant to how the overdose occurred). Please describe her clinical presentation on day 365 through the time she arrived to the hospital on Day 366 (e.g. include information relevant to showing signs and symptoms of lithium toxicity, any drugs received over this time-period and any other relevant clinical information on her clinical status, the differential diagnosis of events leading to her re-admission to the hospital, the differential diagnosis and work-up with clinical results over this time-period). Please include any information relevant to potential risk factors, concomitant drugs and clinical information relevant to potential etiologies or contributing factors. Also,

include copies of the hospital admission and discharge summaries. Include her lithium levels, relative to actual treatment received during the trial, through Day 366.

Also explain why she had a high WBC at pre-randomization and multiple time-points during the study (please explain this from a clinical perspective that reflects a differential diagnosis that includes risk factors and concomitant drugs, on the diagnostic work-up and the results regarding the etiology or contributing factors)?

c. 138134-111-341: It is not clear from the narrative summary, why this subject's lithium levels increased at a lithium dose level of 600 mg daily (after Aripiprazole was added to lithium treatment) compared to a lithium level obtained while receiving 1200 mg daily (during monotherapy) and why lithium levels returned to baseline after stopping aripiprazole (but no mention of changing the dose). Please provide a clarification (using clinically relevant observations to support your explanation). Were any lithium levels drawn due to signs or symptoms of lithium toxicity? Please explain the reason for each level drawn and for any dose adjustments. Please summarize this subject from a clinical perspective regarding signs of symptoms of lithium toxicity relative to treatment and relative to lithium levels as well that may suggest a potential interaction effect of adding Arip treatment to lithium treatment (also refer to Item 2 above regarding potential safety issues to consider).

d. 138134-135-575 (an ADO): why was this subject reported as "hepatic failure." We cannot find any description in the narrative of this subject regarding clinically relevant evidence of hepatic failure. It's not clear:

i. Why this event was reported on Day 19 (the narrative does not describe any events on that particular day that triggered the reporting of "hepatic failure," while LFT levels were obtained 3 days later (that revealed elevated enzymes).

ii. The narrative indicates that the event (not clear which event) persisted at follow-up. It is not clear what exactly persisted (elevated LFTs, AEs or other events) and for how long after the last dose of aripiprazole and valproate.

Please provide clarification on the above and a narrative summary of this subject with clinically relevant information to rule in or rule out drug-related liver effects (e.g. valproate versus aripiprazole versus the combination of treatment), the differential diagnosis, work-up and results of the work-up and clinical conclusions (with results to support the conclusions).

4) We found the above valproate subject and subject 138134 -95-257 (ADO) with liver related events. Were there any other valproate subjects with liver related events in any of the Bipolar trials using valproate adjunctive treatment? Please summarize these additional subjects (or provide the exact location of the narrative summary in the N19 submission).

5) Akathisia was most commonly reported as an AE leading to early dropout (ADO) and was most commonly reported as an AE in the Bipolar-mania, Bipolar-depression and MDD groups compared to other diagnostic groups in the All-aripiprazole (Arip)-treated dataset (in Table 2.1.4.5 of Module 2.7.4 in N19). This is outlined in the following:

a. Incidence of ADOs due to akathisia in Bipolar mania, Bipolar-depressed, and MDD groups ranged from 3-5% in any given group compared to 0.2 and 0.9% in the dementia and schizophrenia groups.

b. Incidence of AEs of akathisia Bipolar mania, Bipolar-depressed, and MDD groups ranged from 16-25% in any given group compared to 0.4 and 7.3% in the dementia and schizophrenia groups. Please provide an explanation for these results (and provide results to support your rationale and conclusions).

How do you account for the above diagnostic group differences (please provide results to support your conclusions)?

6) It appears that Module 2.7.4 of N19 provides median change from baseline to endpoint on clinical parameters for each safety dataset, including results from Study C-134. The CSR for Study C-134 appears to show median change in values from baseline to the highest value (or lowest value) of each clinical parameter. Please clarify what baseline value was used. Please provide the mean (±SD), median change, and range of values from baseline to each time-point (OC dataset) and to endpoint (LOCF dataset, using the last on-treatment value in the DB phase) for each clinical parameter in Study C-134. Please provide this information for each DB treatment group (placebo and aripiprazole groups) and for each DB treatment group within each adjunctive treatment subgroup (valproate and lithium subgroups).

Please feel free to contact me if you have any questions regarding this message.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

White Oak Federal Research Center

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/s/

Doris Bates
11/16/2007 07:04:33 PM
CSO
Sent on 16NOV07 at time indicated in email printout.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

SUPPLEMENTAL NDA FILED:
FILING REVIEW ISSUES IDENTIFIED
(CLINICAL / STATISTICS)

NDA 21-436/S-019
NDA 21-713/S-014
NDA 21-729/S-006
NDA 21-866/S-006
NDA 21-436/S-020
NDA 21-713/S-015
NDA 21-729/S-007
NDA 21-866/S-007

Otsuka Pharmaceutical Development and Commercialization Inc.
Attn: Kusuma Mallikaarjun, Ph.D.
Senior Director, Regulatory Affairs
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Mallikaarjun:

Please refer to your supplemental new drug applications (sNDAs) for NDA 21-436, referenced above, which were submitted and received on July 11, 2007 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ABILIFY (aripiprazole) Tablets. Please also refer to letters of cross reference submitted on August 28, 2007 and received August 29, 2007 for NDAs 21-713, 21-729, and 21-866.

Supplemental applications 21-436/S- 019, NDA 21-713/S-014, NDA 21-729/S-006, and NDA 21-866/S-006 provide for the use of a starting dose of 15 mg/day of aripiprazole as monotherapy in the acute treatment of Bipolar I Disorder.

Supplemental applications NDA 21-436/S-020, NDA 21-713/S-015,NDA 21-729/S-007, and NDA 21-866/S-007 provide for the use of aripiprazole as adjunctive treatment to the mood stabilizers lithium or valproate, including the starting dose of 15 mg/day aripiprazole.

We have completed our filing review for these supplemental applications and have determined that your applications are sufficiently complete to permit a substantive review. As you were informed via secure e-mail, the applications have been filed on September 4, 2007 under section 505(b) of the Act and in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following review issues:

Clinical

Please refer to our secure electronic mail message dated August 22, 2007, in which we made the following requests:

1. S-019: Please refer to page 365, Module 2.7.4, regarding narratives. Are all aripiprazole-treated subjects, in all bipolar trials, included in the narratives in Appendix 2.2B and in the line listings in Appendix 2.2A? [i.e., are all subjects listed in both Appendices]? Does this also include placebo patients, or are they only included in the CSRs? We need, if possible, one document including narratives for all subjects, or minimally for all aripiprazole treated subjects. S-020: Please provide similar information for this supplement as well, since we are having the same difficulty locating narratives here as for S-019.

2. S-019: In Module 2.7.4, some hyperlinks are not working. See p. 205, hyperlink to Appendix 2.1.2.5. When this link is clicked, we get an error message indicating that the linked file does not exist. Please contact the EDR, and submit a replacement Module 2.7.4. with working hyperlinks. S-020: Please check this module also for S-020, as similar problems seem to exist.

3. S-019 and S-020: In your submitted labeling, we note inconsistencies between the side-by-side labeling presentations [with annotation] and the clean copy. Please submit one set of side-by-side annotated labeling which includes all of the changes proposed in both supplements, clearly indicating all additions and deletions with reference to the currently approved labeling. Please clearly reference the basis for each proposed change and indicate the exact location in the submissions where the supporting data may be found. You may submit identical labeling to S-019 and to S-020. We understand that not all hyperlinks may work within each supplement since links to information included only in S-020 won't be accessible within S-019, and vice versa. Please also submit a clean and marked up WORD file including all proposed changes within a single document.

4. S-020: We were unable to locate subgroup analyses of efficacy results for Study 134. Please provide these results [by gender, by age, and by race or ethnicity], or indicate where we can find them in the submission.

5. S020: With regard to line listings for deaths, serious adverse events [SAEs], and adverse dropouts [ADOs], we cannot tell which SAEs resulted in ADOs. Please provide this information in line listing format. Also, we are not able to tell whether the AE terms in the current line listings are preferred or verbatim terms. Please explain, clearly differentiate verbatim and preferred terms, and provide verbatim terms where omitted. Finally, it appears that the line listings for all-aripiprazole-treated subjects include subjects also listed in other line listings [e.g., subjects listed in Appendix 2.1.3.1 are a subset of the subjects listed in Appendix 2.1.3.5]. Please indicate whether our understanding is correct.

You have contacted us on August 22, 23, and 30, 2007, and on September 4 and 6, 2007, regarding responses to the above questions. They are included in this letter verbatim, as originally transmitted to you, for ease of reference.

Statistics

1. Please provide subgroup primary efficacy analyses by gender, race, and geographical regions (U.S. vs. non-US) for studies CN138135 and CN138162.

2. If available, please share with us the SAS programs to generate all tables and figures in the study reports.

Please respond to the above requests for additional information as soon as possible. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Please also note that our filing review is only a preliminary evaluation of the application, and is not indicative of all deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have any questions, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, by phone at (301) 796-2260 or via secure electronic mail at doris.bates@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren

9/17/2007 05:08:00 PM

DSI CONSULT: Request for Clinical Inspections

Date: September 6, 2007

To: Joseph Salewski, Acting Branch Chief, GCP2, HFD-47

CC: Leslie Ball, M.D., Acting Director, DSI, HFD-45
Thomas Laughren, M.D., Director, HFD-130

From: Doris J. Bates, Ph.D., Regulatory Project Manager, HFD-130
(Please see electronic signature page)

Subject: **Request for Clinical Inspections**
NDA 21-436 SE2-019
NDA 21-436 SE1-020
Otsuka Pharmaceutical Company, Ltd.
ABILIFY (aripiprazole) Tablets

Protocol/Site Identification:

As recently discussed with DSI representatives, the following protocols/sites essential for approval of the subject NDAs have been identified for inspection. These sites are listed in order of priority.

Indication	NDA and Site #	Site (Name and Address)	Number of Subjects
Addition of 15 mg starting dose in the Treatment of Bipolar I Disorder	NDA 21-436 S-019 Study 162 Site 29	Adam Lowy, MD (PI) Comprehensive NeuroScience, Inc. Psychiatric Institute of Washington 4428 Wisconsin Ave, NW Washington, DC 20016	22
Adjunctive Therapy in the Treatment of Bipolar I Disorder with lithium or valproate	NDA 21-426 S-020 Study 134 Site 122	Richard Weisler, MD, PA (PI) 700 Spring Forest Road Suite 125 Raleigh, NC 27609	19

Domestic Inspections:

We have requested inspections because (please check all that apply):

X Enrollment of large numbers of study subjects
High treatment responders (specify:)
Significant primary efficacy results pertinent to decision-making
There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
Other: SPECIFY

International Inspections: *None Requested*

We have requested inspections because (please check all that apply):

There are insufficient domestic data
Only foreign data are submitted to support an application
Domestic and foreign data show conflicting results pertinent to decision-making
There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by **February 11, 2008** (inspection summary goal date). We intend to issue an action letter on this application by (action goal date) **May 11, 2008**. We are willing to accept a draft of the Inspection Summary Results, in either hard copy or e-mail format, for the February 2008 request date.

Should you require any additional information, please contact Doris J. Bates, Ph.D. at 301-796-1040 or via e-mail at doris.bates@fda.hhs.gov.

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/s/

Doris Bates
9/14/2007 01:05:55 PM

Mitchell Mathis
9/14/2007 01:12:49 PM
For Dr. Laughren

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, August 22, 2007 2:16 PM
To: 'Mallikaarjun, Kusuma'; 'Susan.Behling@bms.com'
Cc: Bates, Doris J
Subject: URGENT: NDA 21-436 S-019 and S-020: Abilify, 15 mg starting dose and adjunctive treatment of bipolar with [lithium or valproate]
Importance: High

Dear Dr. Mallikaarjun and Ms. Behling:

We are conducting our filing review of the above referenced supplemental New Drug Applications and have the following urgent questions. Please respond by reply email on or before the close of business on September 4, 2007; we will also need a formal amendment to the supplements, but this may be submitted later.

1. **S-019:** Please refer to page 365, Module 2.7.4, regarding narratives. Are all aripiprazole-treated subjects, in all bipolar trials, included in the narratives in Appendix 2.2B and in the line listings in Appendix 2.2A? [i.e., are all subjects listed in both Appendices]? Does this also include placebo patients, or are they only included in the CSRs? We need, if possible, one document including narratives for all subjects, or minimally for all aripiprazole treated subjects. **S-020:** Please provide similar information for this supplement as well, since we are having the same difficulty locating narratives here as for S-019.

2. **S-019:** In Module 2.7.4, some hyperlinks are not working. See p. 205, hyperlink to Appendix 2.1.2.5. When this link is clicked, we get an error message indicating that the linked file does not exist. Please contact the EDR, and submit a replacement Module 2.7.4. with working hyperlinks. **S-020:** Please check this module also for S-020, as similar problems seem to exist.

3. **S-019 and S-020:** In your submitted labeling, we note inconsistencies between the side-by-side labeling presentations [with annotation] and the clean copy. Please submit one set of side-by-side annotated labeling which includes all of the changes proposed in both supplements, clearly indicating all additions and deletions with reference to the currently approved labeling. Please clearly reference the basis for each proposed change and indicate the exact location in the submissions where the supporting data may be found. You may submit identical labeling to S-019 and to S-020. We understand that not all hyperlinks may work within each supplement since links to information included only in S-020 won't be accessible within S-019, and vice versa. Please also submit a clean and marked up WORD file including all proposed changes within a single document.

4. **S-020:** We were unable to locate subgroup analyses of efficacy results for Study 134. Please provide these results [by gender, by age, and by race or ethnicity], or indicate where we can find them in the submission.

5. **S020:** With regard to line listings for deaths, serious adverse events [SAEs], and adverse dropouts [ADOs], we cannot tell which SAEs resulted in ADOs. Please provide this information in line listing format. Also, we are not able to tell whether the AE terms in the current line listings are preferred or verbatim terms. Please explain, clearly differentiate verbatim and preferred terms, and provide verbatim terms where omitted. Finally, it appears that the line listings for all-aripiprazole-treated subjects include subjects also listed in other

line listings [e.g., subjects listed in Appendix 2.1.3.1 are a subset of the subjects listed in Appendix 2.1.3.5]. Please indicate whether our understanding is correct.

If you have any questions about the above comments, please feel free to contact us by reply e-mail. Again, as we state above, a response by email to our questions will suffice for our immediate needs, but the supplements should be amended as soon as possible.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
8/22/2007 02:21:24 PM
CSO

Bates, Doris J

From: Bates, Doris J
Sent: Friday, July 20, 2007 12:28 PM
To: 'Mallikaarjun, Kusuma'; 'Susan.Behling@bms.com'
Cc: Bates, Doris J
Subject: Acknowledgement of Receipt of NDA 21-436 S-019 and S-020

Importance: High

Dear Dr. Mallikaarjun and Ms. Behling :

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Abilify (aripiprazole) Tablets
NDA Number: 21-436
Supplement number: S-019 and S-020
Review Priority Classification: Standard (S)
Date of supplement: July 11, 2007 [both submissions]
Date of receipt: July 11, 2007 [both submissions]

The supplemental applications propose the following changes:

S-019: Abilify at a starting dose of 15 mg/day (with allowed increases to 30 mg/day) in the treatment of patients with bipolar disorder, manic or mixed.

S-020: Abilify as adjunctive therapy to lithium or valproate, in the acute treatment of patients with bipolar disorder, manic or mixed.

Unless we notify you within 60 days of the receipt date that S-019 and/or S-020 is/are not sufficiently complete to permit a substantive review, they will be filed on September 9, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 11, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

We acknowledge receipt of your request for a waiver of pediatric studies for these two new applications, and we note your plans to submit pediatric studies for the acute bipolar mania monotherapy indication in August of 2007. Once this pediatric application is submitted and reviewed, we will notify you whether you have fulfilled the pediatric study requirement for this indication. In the meantime, we are waiving the requirement for additional pediatric studies in this indication, i.e., to support the 15 mg starting dose and to support the use of aripiprazole as adjunctive therapy with lithium or valproate in pediatric patients.

Please 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:

Thomas P. Laughren, M.D.
Director
Division of Psychiatry Products, HFD-130
Center for Drug Evaluation and Research
Food and Drug Administration
via Central Document Room
5901-B Ammendale Road

Beltsville, MD 20705-1266

If you have any questions, please contact me by phone at (301) 796-2260, fax at (301) 796-9838, or secure electronic mail at doris.bates@fda.hhs.gov .

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
7/20/2007 12:33:12 PM
CSO
Sent to applicant on Friday, July 20, 2007 at 12:28 PM.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-860 / Dr. Baweja			FROM: HFD-130 / Dr. Bates	
DATE July 16, 2007	IND NO. 42,776	NDA NO. 21436, SE2-019 21436, SE1-020	TYPE OF DOCUMENT Efficacy supplement new dosage Efficacy supplement new indication	DATE OF DOCUMENT 11JUL07 11JUL07
NAME OF DRUG Abilify (aripiprazole)	PRIORITY CONSIDERATION 019: S- due 11MAY08 020: S- due 11MAY08		CLASSIFICATION OF DRUG: S019: Bipolar disorder S020: Bipolar disorder	COMPLETION DATE: filing mtg 06SEP07 filing letter 23SEP07 PDUFA 11MAY08

NAME OF FIRM: Bristol-Myers Squibb / Otsuka America

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
New efficacy supplements – see filing meeting notice. EDR links: S-019: \\CDSESUB1\N21436\S_019\2007-07-11
S-020: \\CDSESUB1\N21436\S_020\2007-07-11

S-019 provides for starting dose of 15 mg; OCP review likely to be minimal to none, efficacy study performed and PLR format conversion has been addressed under SE1-018.

S-020 provides for maintenance tx as adjunctive med w. Lithium or valproate. Note the proposed labeling; OCP please advise if any revisions needed in text re concomitant use, etc.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Please see electronic signature on next page	☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
7/19/2007 04:16:27 PM
labeling review only requested for both S019 and S020.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-710 (Dr. Yang, Dr. Dinh)			FROM: HFD-130 (Dr. Bates)	
DATE July 16, 2007	IND NO. 42,776	NDA NO. 21436, SE2-019 21436, SE1-020	TYPE OF DOCUMENT Efficacy supplement new dosage Efficacy supplement new indication	DATE OF DOCUMENT 11JUL07 11JUL07
NAME OF DRUG ABILIFY (aripiprazole)	PRIORITY CONSIDERATION 019: S- due 11MAY08 020: S- due 11MAY08		CLASSIFICATION OF DRUG S019: Bipolar disorder S020: Bipolar disorder	COMPLETION DATE: filing mtg 06SEP07 filing letter 23SEP07 PDUFA 11MAY08

NAME OF FIRM: Bristol-Myers Squibb / Otsuka America

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☒ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☒ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
New efficacy supplements – see filing meeting notice. EDR links: S-019: \\CDSESUB1\N21436\S_019\2007-07-11
S-020: \\CDSESUB1\N21436\S_020\2007-07-11

I was not able to locate datasets in the EDR submission; please let me know if they should be requested.

SIGNATURE OF REQUESTER see electronic signature	METHOD OF DELIVERY (Check one) ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
7/19/2007 03:37:27 PM
If one common review is written for both supplements, please link review to both SE2 019 and SE1 020 under NDA 21436.

NDA REGULATORY FILING CHECKLIST

NDA #	21436	Efficacy Supplement Type	SE-	SE2	Supplement #	019
NDA #	21436	Efficacy Supplement Type	SE-	SE1	Supplement #	020
NDA #	21713	Efficacy Supplement Type	SE-	SE2	Supplement #	014
NDA #	21713	Efficacy Supplement Type	SE-	SE1	Supplement #	015
NDA #	21729	Efficacy Supplement Type	SE-	SE2	Supplement #	006
NDA #	21729	Efficacy Supplement Type	SE-	SE1	Supplement #	007
NDA #	21866	Efficacy Supplement Type	SE-	SE2	Supplement #	006
NDA #	21866	Efficacy Supplement Type	SE-	SE1	Supplement #	007

Proprietary Name, Established Name: Abilify (aripiprazole)
Dosage Form: Tablets / Oral Solution / Orally Disintegrating Tablet / Injection for Intramuscular Use
Strengths: 2, 5, 10, 15, 20, 30 mg/ 1 mg per mL/ 10, 15 mg / 9.75 mg/1.3 mL
Indication(s) requested:
SE2-019, 014, 006, 006: adds a provision for use of a 15 mg/day starting dose or aripiprazole in the monotherapy treatment of bipolar disorder, manic or mixed.
SE1-020, 015, 007, 007: provides for the use of aripiprazole as adjunctive therapy with lithium or valproate mood stabilizers in the treatment of bipolar disorder, manic or mixed, using a 15 mg/day starting dose.

Applicant: Otsuka Pharmaceutical Co., Ltd
Agent for Applicant (if applicable): Otsuka Pharmaceutical Development & Commercialization, Ind.
Collaborative Business Partner for Applicant and Agent: Bristol-Myers Squibb Company

NDA 21-436 S-019 and S-020 were submitted and received on July 11, 2007 and therefore have May 11, 2008 Goal Dates. The remaining six applications were submitted August 28, 2007 and received August 29, 2007, and therefore have June 29, 2008 goal dates. Because these are duplicates by cross reference and require no additional review, the May 11, 2008 Goal Date is targeted for all eight supplements.

Date of Application: 11JUL07 Date of Receipt: 11JUL07 Clock started: 11JUL07
Filing Meeting: 06SEP07 Filing Date: 09SEP07 Day 74: 23SEP07
User Fee Goal Date: 11MAY08
List referenced IND numbers:

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND Nos. 42,776; (b) (4) 71,501; 73,863; (b) (4)
NDA Nos. 21-713, 21-729; DMF Nos. (b) (4)

The following information applies to both sNDAs for 21-436 and by cross-reference to the others.

Type of Original NDA:	**(b)(1)**	**X**	(b)(2)	☐
AND (if applicable)				
Type of Supplement:	**(b)(1)**	**X**	(b)(2)	☐

Review Classification: **S**	**X**	P	☐
Resubmission after withdrawal?	☐	Resubmission after RTF?	☐
Chemical Classification: (1,2,3 etc.)		Other (orphan, OTC, etc.)	

Form 3397 (User Fee Cover Sheet) submitted: **YES** **X** NO ☐
User Fee Status: **Paid** **X** for **S-019 and S-020** Exempt (orphan, government) ☐ Waived (e.g., small business, public health) **X waived for all other submissions**
Is the application affected by the Application YES ☐ **NO** **X**

Version: 6/14/2006
This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the View' tab; drag the cursor down to 'Toolbars'; click on Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

NDA 21-436 / SE2-019 and SE1-020
NDA 21-713 / SE2-014 and SE1-015
NDA 21-729 / SE2-006 and SE1-007
NDA 21-866 / SE2-006 and SE1-007

Integrity Policy (AIP)?
If yes, explain:

If yes, has OC/DMPQ been notified of the submission?			***not applicable***	
Does each submission contain an accurate comprehensive index?	YES	**X**	NO	☐
Was form 356h included with an authorized signature for each submission?	YES	**X**	NO	☐
Is each submission complete as required under 21 CFR 314.50?	YES	**X**	NO	☐

Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐ NO x
2. This application is an eNDA or combined paper + eNDA YES x NO ☐
This application is: All electronic X Combined paper + eNDA ☐
This application is in: NDA format ☐ CTD format ☐ Combined NDA / CTD formats X
Does the eNDA follow the guidance? YES X NO ☐
(http://www.fda.gov/cder/guidance/2353fnl.pdf)

If combined paper + eNDA, which parts of the application were submitted in electronic format?
not applicable.

Additional comments:

3. This application is an eCTD NDA. YES ☐ NO X
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.
Additional comments:

Patent information submitted on form FDA 3542a? YES **X** NO ☐

Exclusivity requested? ***Yes for the SE1 apps. No for the SE2 apps.*** **YES** X NO X
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

5-year or 3-year exclusivity ***on the active moiety*** in any approved (b)(1) or (b)(2) application?	YES	**X to 11-15-07**	NO	☐
Does another drug have orphan drug exclusivity for the same indication?	YES	☐	**NO**	**X**
If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?			***not applicable***	

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
If yes, explain:

Correctly worded Debarment Certification included with authorized signature? **YES** **X** NO ☐

Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES **X** NO ☐ :
Waiver is requested in cover letter and is granted. Previously required pediatric studies in bipolar disorder are pending submission separately at time of filing for these supplements.

If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)?
YES **X** NO ☐

NDA 21-436 / SE2-019 and SE1-020
NDA 21-713 / SE2-014 and SE1-015
NDA 21-729 / SE2-006 and SE1-007
NDA 21-866 / SE2-006 and SE1-007

Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO **X**

If yes, contact PMHS
Financial Disclosure forms included with authorized signature? YES **X** NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

Field Copy Certification (that it is a true copy of the CMC technical section) ***not applicable***

PDUFA Goal dates correct in tracking system? YES **X** NO ☐

Drug name and applicant name correct in COMIS? YES **X** NO ☐ If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

End-of-Phase 2 Meeting(s)? Date(s) ***not applicable***

Pre-NDA Meeting(s)? Date(s) **February 26, 2007 - telecon. Minutes issued March 1, 2007.** NO ☐

Any SPA agreements? Date(s) ***not applicable, no SPAs*** NO ☐
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

Was electronic Content of Labeling submitted in SPL format? YES **X** NO ☐
If no, request in 74-day letter.

Was the PI submitted in PLR format? YES **X** NO ☐
Note: This is not the first PLR format submission of labeling for Abilify. SE1-017 and SE1-018 also include PLR formatted labeling.

All labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO **X**
If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO **X**
If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A no MedGuide or PPI **X** YES ☐ NO ☐

Risk Management Plan consulted to OSE/IO? N/A **X** YES ☐ NO ☐

If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA **X** YES ☐ NO ☐

Clinical
If a controlled substance, has a consult been sent to the Controlled Substance Staff? ***not applicable***
YES ☐ NO ☐

Chemistry
Did applicant request categorical exclusion for environmental assessment? YES **X** NO ☐
Establishment Evaluation Request (EER) submitted to DMPQ? **N/A** YES ☐ NO **X**
If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

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/s/

Doris Bates
5/5/2008 04:29:03 PM
CSO