# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***
**NDA 21-436/S-002**

***Trade Name:*** Abilify (NDA 21436/S-002)

***Generic Name:*** Aripiprazole

***Sponsor:*** Otsuka

***Approval Date:*** 09/29/2004

***Indications:*** ABILIFY is indicated for the treatment of schizophrenia.

ABILIFY is indicated for the treatment of acute manic and mixed episodes associated with Bipolar Disorder.

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***APPLICATION NUMBER:***

# NDA 21-436/S-002

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-436/S-002

# APPROVAL LETTER

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436 / S-002

Otsuka Maryland Research Institute
Attn: Dr. Kusuma Mallikaarjun
Director, Regulatory Affairs
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Mallikaarjun:

Please refer to your supplemental new drug application dated June 23, 2003, received June 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify® (aripiprazole) Tablets.

We also acknowledge receipt of your submissions dated May 26, 2004, July 19, 2004, and July 28, 2004. Your submission of July 28, 2004, as cross-referenced to the May 26 and July 19, 2004 submissions, constituted a Complete Response to our April 23, 2004 action letter.

This supplemental new drug application provides for the use of Abilify® Tablets in the treatment of acute manic or mixed episodes associated with Bipolar Disorder. We have completed our review of this supplemental application as amended. It is approved effective on the date of this letter for use as recommended in the enclosed agreed-upon labeling text.

**Pediatric Research Equity Act (PREA) Requirements: Phase 4 Commitment: Partial Waiver, Partial Deferral**

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 are waiving this requirement for children below the age of 10 years. We are deferring submission of your pediatric studies for ages 10 to 17 years (children and adolescents) under PREA until September 30, 2008.

The deferred pediatric studies required under Section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing commitments shall be reported annually according to 21 CFR 314.81. The associated commitments are listed below.

1. *Deferred pediatric studies under PREA.*
   You are required to assess the safety and effectiveness of Abilify as a treatment for bipolar disorder in pediatric patients ages 10 to 17 (children and adolescents).

   Final Report Submission: September 30, 2008

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment, whether submitted to the IND or the NDA, must be clearly designated "**Required Pediatric Study Commitments**".

**Pediatric Exclusivity**
Please note that Proposed Pediatric Study Requests and Pediatric Written Requests, which apply to pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act, are distinct from, and may need to be developed ***in addition to,*** pediatric studies under PREA as described above. Satisfaction of the requirements in Section 2 of PREA alone may not qualify you for pediatric exclusivity.

**Additional Phase 4 Commitments (Clinical)**
We remind you of your additional postmarketing commitments, agreed upon in two teleconferences on September 28, 2004 and your secure email of the same date. The commitments are summarized below.

2. *Clinical Efficacy and Safety: Adult clinical study to address efficacy and safety of aripiprazole as add-on therapy in bipolar disorder.*
   You have agreed to submit the results of a clinical study in adults, examining the acute efficacy and safety of aripiprazole as add-on therapy in bipolar patients currently taking mood stabilizers (e.g., lithium, valproate).

   *Final Report Submission:* September 30, 2007

3. *Clinical Efficacy and Safety: Adult clinical study to address longer-term efficacy and safety of aripiprazole as add-on therapy in bipolar disorder.*
   You have agreed to submit the results of a clinical study in adults examining the longer-term efficacy and safety of aripiprazole as add-on therapy in bipolar patients currently taking mood stabilizers (e.g., lithium, valproate).

   *Final Report Submission:* September 30, 2009

4. *Pharmacology / Toxicology: Juvenile animal toxicity study/ies to support pediatric studies of aripiprazole in bipolar disorder.*
   You have agreed to conduct and submit a juvenile animal study or studies to support pediatric studies of aripiprazole in bipolar disorder.

   *Final Report(s) Submission:* June 30, 2006.

Submit clinical protocols to your IND for this product. Submit nonclinical protocols and all final study reports to this NDA, including any final reports intended to support clinical efficacy claims or changes in labeling. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you

should include a status summary for each commitment in your annual report to this NDA. The status summary should include:

- expected summary completion dates,
- expected final report submission dates,
- any changes in plans since the last annual report,
- and, for clinical studies, the number of patients entered into each study.

All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

**Labeling**

The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplemental NDA 21-436 / S-002**." Approval of this submission by FDA is not required before the labeling is used.

**Introductory Promotional Materials**

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product in this indication. 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(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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 this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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 301-594-2850.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: agreed-upon labeling

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

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/s/

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Russell Katz
9/29/04 07:17:27 AM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-436/S-002

# APPROVABLE LETTER

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436 / S-002

Otsuka Maryland Research Institute
Attn: Dr. Kusuma Mallikaarjun
Director, Regulatory Affairs
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Mallikaarjun:

Please refer to your supplemental new drug application (sNDA), referenced above, dated June 23, 2003, received June 25, 2003, submitted on under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ABILIFY (aripiprazole) Tablets.

We also acknowledge receipt of your submissions dated September 12, 2003; October 23, 2003; November 26, 2003; December 16, 2003; and January 30, 2004.

This supplemental application provides for the use of aripiprazole in the treatment of acute manic episodes (two three week studies) in patients with Bipolar I Disorder.

We have completed our review of this application as amended, and it is approvable. Before this application may be approved, however, you must address the following comments and/or deficiencies:

**Clinical /Statistical**

1. As you are aware, 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 reference the deferral granted on May 9, 2003 for the pediatric study requirement for this application. Please see the pharmacology/toxicology comment below with respect to preclinical studies which will be required to support pediatric studies of this drug.
2. What effect does the presence or absence of psychotic symptoms have on the efficacy outcome of studies 009 and 074? We were not able to find an analysis that examined this interaction in the study reports.
3. We note that you have included, according to the intent-to-treat principle, patients with various protocol violations in your analyses. We are particularly interested in the effects on your primary analysis of including patients who did not have baseline valproate or lithium levels, patients with benzodiazepine use within 1 day of a rating having been done, patients with positive drug screens at anytime during the study, and patients who began the study within 30 days of taking fluoxetine or within 14 days of other antidepressants.

4. We were unable to find any record in the original protocol, subsequent amendment, or administrative letter to the Division designating key secondary efficacy variables for study 009 prior to breaking the data blind. Does this record exist?
5. You have pooled the controlled trials of schizophrenia and bipolar mania into one adverse event table in your initial version of draft labeling. (b) (4)
6. (b) (4)

**Pharmacology / Toxicology**

(b) (4), you were informed that juvenile animal studies would be needed to support pediatric studies of aripiprazole (b) (4) These studies will also be needed to support pediatric studies of aripiprazole in bipolar disorder.

Studies should be performed in rodent and nonrodent species and initiated as soon as possible. The studies should utilize animals of an age range and stage(s) of development that are comparable to the intended human population and the animals should be exposed to the drug for a period appropriate for the intended length of treatment in the proposed pediatric population.

In addition to the usual toxicological parameters and with a focus on the toxicities observed in adult animals, these studies should evaluate the effects of aripiprazole on growth, reproductive development, and neurological and neurobehavioral development. Reproductive effects need to be evaluated following cessation of treatment; there should be a washout period of appropriate duration (depending on the half-life of aripiprazole) between cessation of treatment and evaluation. In assessing neurobehavioral development, the effects of aripiprazole should be evaluated during treatment and after an appropriate washout period following the cessation of treatment (to evaluate potential long-term effects). To avoid the confounding effect of repeated neurobehavioral testing, separate groups of animals must be used at the two assessment times. However, to avoid unnecessary use of animals, the same group of animals may be used to evaluate neurobehavioral effects during treatment and the effects on reproductive parameters. The neurobehavioral tests should assess sensory function, motor function, and learning and memory. The neuropathological evaluation should include examination of all major brain

regions and cellular elements, with particular attention to alterations indicative of developmental insult.

We will be requesting these studies along with the pediatric study as a Phase 4 Commitment; please indicate a time frame within which you would expect to submit final reports for these studies.

**Chemistry, Manufacturing, and Controls**
We note your request for categorical exclusion from the environmental assessment requirements, as per 21 CFR 25.15 (d) and 21 CFR 25.31(a). We have reviewed this request, and it has been found acceptable. A categorical exclusion will be approved at the time of approval of the supplemental NDA.

**Labeling**
In addition to addressing the deficiencies listed above, you must submit draft labeling revised as presented in the attached draft labeling. We have included bracketed comments in the text to explain our changes.

We realize that you may have questions about our draft changes and points that you may wish to clarify and we are willing to meet with you via teleconference if you wish.

In addition to the changes we have indicated in the attached labeling, all other previous revisions to labeling, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that clearly shows all changes. If additional information relating to the safety or effectiveness of this drug becomes available, further revision of the labeling may be required.

**Safety Update**
When you respond to the above deficiencies please include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original sNDA submission.
   - Present tabulations of the new safety data combined with the original sNDA data.
   - Include tables that compare frequencies of adverse events in the original sNDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original sNDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of currently approved foreign labeling not previously submitted.

**Promotional Materials (Draft Format)**
In addition, please submit three copies of the introductory promotional materials that you propose to use for this product in this indication. 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:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed for the proposed new indication before approval of this supplemental application.

If you have any questions, please call Doris J. Bates, Regulatory Project Manager, at (301) 594-2850.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

35 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/

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Russell Katz

4/23/04 12:50:07 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-436/S-002

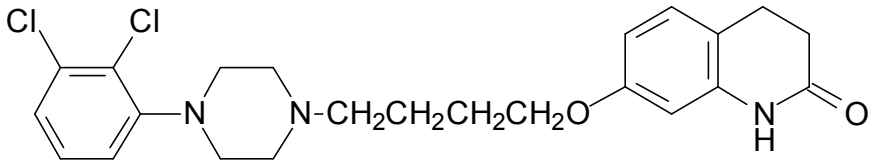
# LABELING

# ABILIFY® (aripiprazole) Tablets

**Rx only**

## DESCRIPTION

ABILIFY™ (aripiprazole) is a psychotropic drug that is available as tablets for oral administration. 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 5-mg, 10-mg, 15-mg, 20-mg, and 30-mg strengths. Inactive ingredients include lactose monohydrate, cornstarch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

## CLINICAL PHARMACOLOGY

### 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, 0.8, 1.7, 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, 15, 39, 57, 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.

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia and 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.

## 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.

### Absorption

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 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.

### Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent $D_2$-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, like quinidine in EMs, results in a 112% increase in aripiprazole plasma exposure, and dosing adjustment is needed (see **PRECAUTIONS: Drug-Drug Interactions**). 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.

## Special 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: Dosage in Special Populations**). The pharmacokinetics of aripiprazole in special populations are described below.

### 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.

### 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.

### Elderly

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 **PRECAUTIONS: Geriatric Use**).

### 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.

### 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.

### 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.

## Drug-Drug Interactions

### 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.

### 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- 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* (see **PRECAUTIONS: Drug-Drug Interactions**).

*Aripiprazole had no clinically important interactions with the following drugs:*

*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 (500-1500 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.

*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 (1200-1800 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.

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

*Warfarin:* Aripiprazole 10 mg per day for 14 days had no effect on the pharmacokinetics of R- 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 per 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.

## Clinical Studies

### Schizophrenia

The efficacy of ABILIFY in the treatment of schizophrenia was evaluated in four short-term (4- and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Three of the four 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 three 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 or 30 mg/day) and haloperidol (10 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 or 30 mg/day) and risperidone (6 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, 15, 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 fourth study, a 4-week trial (n=103) comparing ABILIFY in a range of 5 to 30 mg/day or haloperidol 5 to 20 mg/day to placebo, haloperidol was superior to placebo, in the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis, and in a responder analysis based on the CGI-severity score, the primary outcomes for that trial. ABILIFY was only significantly different compared to placebo in a responder analysis based on the CGI-severity score.

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

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 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 experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo.

### Bipolar Mania

The efficacy of ABILIFY in the treatment of acute manic episodes was established in two 3-week placebo-controlled trials in hospitalized patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes (in one trial, 21% of placebo and 42%

of ABILIFY-treated patients had data beyond two weeks). These trials included patients with or without psychotic features and 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 two positive 3-week placebo-controlled trials (n=268; n=248) which evaluated ABILIFY 15 or 30 mg/day, once daily (with a starting dose of 30 mg/day), ABILIFY was superior to placebo in the reduction of Y-MRS total score and CGI-BP Severity of Illness score (mania).

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.

# INDICATIONS AND USAGE

## Schizophrenia

ABILIFY is indicated for the treatment of schizophrenia. The efficacy of ABILIFY in the treatment of schizophrenia was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

The efficacy of ABILIFY in maintaining stability in patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those other medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks was demonstrated in a placebo-controlled trial (see **CLINICAL PHARMACOLOGY: Clinical Studies**). The physician who elects to use ABILIFY for

extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

## Bipolar Mania

ABILIFY is indicated for the treatment of acute manic and mixed episodes associated with Bipolar Disorder.

The efficacy of ABILIFY was established in two placebo-controlled trials (3-week) of inpatients with DSM-IV criteria for Bipolar I Disorder who were experiencing an acute manic or mixed episode with or without psychotic features (see **CLINICAL PHARMACOLOGY**). However, the effectiveness of ABILIFY for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been established in controlled clinical trials. Therefore, physicians who elect to use ABILIFY for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

# CONTRAINDICATIONS

ABILIFY is contraindicated in patients with a known hypersensitivity to the product.

# WARNINGS

## Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole treatment in the premarketing 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, etc) 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.

## 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.

## 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. 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.

# PRECAUTIONS

## General

### Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its $\alpha_1$-adrenergic receptor antagonism. The incidence of orthostatic hypotension associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%) and syncope (placebo 1%, aripiprazole 0.6%). The incidence of orthostatic hypotension associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on ABILIFY included: orthostatic hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%, aripiprazole 0.5%), and syncope (placebo 0.9%, aripiprazole 0.5%).

The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo (in schizophrenia: 14% among aripiprazole-treated patients and 12% among placebo-treated patients and in bipolar mania: 3% among aripiprazole-treated patients and 2% among placebo-treated patients).

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).

## Seizure

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients with schizophrenia in short-term, placebo-controlled trials. In short-term, placebo-controlled clinical trials of patients with bipolar mania, 0.3% (2/597) of aripiprazole-treated patients and 0.2% (1/436) placebo-treated patients experienced seizures. 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.

## Potential for Cognitive and Motor Impairment

In short-term, placebo-controlled trials of schizophrenia, somnolence was reported in 11% of patients on ABILIFY compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% (1/926) of patients with schizophrenia on ABILIFY in short-term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar mania, somnolence was reported in 14% of patients on ABILIFY compared to 7% of patients on placebo, but did not lead to discontinuation of any patients with bipolar mania. Despite the relatively modest increased incidence of somnolence compared to placebo, ABILIFY, like other antipsychotics, 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 therapy with ABILIFY does not affect them adversely.

## 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.

## Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. 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 **PRECAUTIONS:** *Use in Patients with Concomitant Illness*).

## Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. 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.

## Use in Patients with Concomitant Illness

*Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease:* In a flexible dose (2 to 15 mg/day), 10-week, placebo-controlled study of aripiprazole in elderly patients (mean age: 81.5 years; range: 56 to 95 years) with psychosis associated with Alzheimer's dementia, 4 of 105 patients (3.8%) who received ABILIFY died compared to no deaths among 102 patients who received placebo during or within 30 days after termination of the double-blind portion of the study. Three of the patients (age 92, 91, and 87 years) died following the discontinuation of ABILIFY in the double-blind phase of the study (causes of death were pneumonia, heart failure, and shock). The fourth patient (age 78 years) died following hip surgery while in the double-blind portion of the study. The treatment-emergent adverse events that were reported at an incidence of ≥5% and having a greater incidence than placebo in this study were accidental injury, somnolence, and bronchitis. Eight percent of the ABILIFY-treated patients reported somnolence compared to one percent of placebo patients. In a small pilot, open-label, ascending-dose, cohort study (n=30) in elderly patients with dementia, ABILIFY was associated in a dose-related fashion with somnolence.

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.

Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses (see **CLINICAL PHARMACOLOGY: Special Populations:** *Renal Impairment* and *Hepatic Impairment*) is limited.

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.

## Information for Patients

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

### 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.

### Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY.

### Nursing

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

### 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.

### Alcohol

Patients should be advised to avoid alcohol while taking ABILIFY.

### Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

## Drug-Drug Interactions

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally acting drugs and alcohol. Due to its $\alpha_1$-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

### 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:* 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 concomitant administration of ketoconazole with aripiprazole occurs, 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; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

*Quinidine:* 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 concomitant administration of quinidine with aripiprazole occurs. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When

the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

*Carbamazepine:* Coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) 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, aripiprazole dose should then be reduced.

No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**).

### 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- 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* (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**).

*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.

## 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, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m$^2$,

respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/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 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m$^2$). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m$^2$); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m$^2$).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- 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 shown to be due to a mechanism not considered relevant to humans.

### Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/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 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg.

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

## 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, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m$^2$ basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. 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 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 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 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and 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.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on $mg/m^2$) of aripiprazole during the period of organogenesis. 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 and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 30 and 100 mg/kg) and minor skeletal variations (100 mg/kg).

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, 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.

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.

## Labor and Delivery

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

## 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.

## Pediatric Use

Safety and effectiveness in pediatric and adolescent patients have not been established.

## Geriatric Use

Of the 7951 patients treated with aripiprazole in premarketing clinical trials, 991 (12%) were ≥65 years old and 789 (10%) were ≥75 years old. The majority (88%) of the 991 patients were diagnosed with dementia of the Alzheimer's type.

Placebo-controlled studies of aripiprazole in schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects (≥65 years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients.

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 **PRECAUTIONS:** *Use in Patients with Concomitant Illness*). 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.

## ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 7951 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5235 patient-years of exposure. A total of 2280 aripiprazole-treated patients were treated for at least 180 days and 1558 aripiprazole-treated patients had at least 1 year of exposure.

The conditions and duration of treatment with aripiprazole 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, modified COSTART dictionary terminology has been used initially 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 events 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; i.e., all reported events are included.

The prescriber should be aware that 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 prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

## Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of 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 aripiprazole was administered in doses ranging from 2 to 30 mg/day.

### Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

## Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

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

### Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, in patients with bipolar mania, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (11%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

## Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

Commonly observed adverse events 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 1. There were no adverse events in the short term trials of schizophrenia that met these criteria.

**Table 1: Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials in Patients with Bipolar Mania**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| | **Aripiprazole** | **Placebo** |
| **Adverse Event** | **(n=597)** | **(n=436)** |
| Accidental Injury | 6 | 3 |
| Constipation | 13 | 6 |
| Akathisia | 15 | 4 |

## Adverse Events Occurring at an Incidence of 2% or More Among Aripiprazole-Treated Patients and Greater than Placebo in Short-Term, Placebo-Controlled Trials

Table 2 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those events 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 2: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials**

| | Percentage of Patients Reporting Event[a] | |
|---|---|---|
| **Body System**<br>**Adverse Event** | **Aripiprazole**<br>**(n=1523)** | **Placebo**<br>**(n= 849)** |
| **Body as a Whole** | | |
| Headache | 31 | 26 |
| Asthenia | 8 | 7 |
| Accidental Injury | 5 | 4 |
| Peripheral Edema | 2 | 1 |
| **Cardiovascular System** | | |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Nausea | 16 | 12 |
| Dyspepsia | 15 | 13 |
| Vomiting | 11 | 6 |
| Constipation | 11 | 7 |
| **Musculoskeletal System** | | |
| Myalgia | 4 | 3 |
| **Nervous System** | | |
| Agitation | 25 | 24 |
| Anxiety | 20 | 17 |
| Insomnia | 20 | 15 |
| Somnolence | 12 | 8 |
| Akathisia | 12 | 5 |
| Lightheadedness | 11 | 8 |
| Extrapyramidal Syndrome | 6 | 4 |
| Tremor | 4 | 3 |
| Increased Salivation | 3 | 1 |
| **Respiratory System** | | |
| Pharyngitis | 4 | 3 |
| Rhinitis | 4 | 3 |
| Coughing | 3 | 2 |
| **Special Senses** | | |
| Blurred Vision | 3 | 1 |

[a] Events reported by at least 2% of patients treated with aripiprazole, except the following events, which had an incidence equal to or less than placebo: abdominal pain, back pain, dental pain, diarrhea, dry mouth, anorexia, psychosis, hypertonia, upper respiratory tract infection, rash, vaginitis[f], dysmenorrhea[f].

[f] Percentage based on gender total.

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

## Dose-Related Adverse Events

### Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in patients with schizophrenia comparing various fixed doses (2, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

### Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 17% vs. 12% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). In the 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 bipolar mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia, 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.

## Laboratory Test Abnormalities

A between group comparison for 3- to 6-week placebo-controlled trials 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 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, and total cholesterol measurements.

## Weight Gain

In 4- to 6-week trials in 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 3-week trials in mania the mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. -0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (3%) compared to placebo (2%).

Table 3 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:

**Table 3: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample**

| | BMI <23 | | BMI 23-27 | | BMI >27 | |
|---|---|---|---|---|---|---|
| | Placebo | Aripiprazole | Placebo | Aripiprazole | Placebo | Aripiprazole |
| 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 4 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 4: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample**

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

### ECG Changes

Between group comparisons for pooled, placebo-controlled trials in patients with schizophrenia, revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters; in fact, within the dose range of 10 to 30 mg/day, aripiprazole tended to slightly shorten the QTc interval. Aripiprazole was associated with a median increase in heart rate of 4 beats per minute compared to a 1 beat per minute increase among placebo patients.

## Additional Findings Observed in Clinical Trials

### Adverse Events in a Long-Term, Double-Blind, Placebo-Controlled Trial

The adverse events reported in a 26-week, double-blind trial comparing ABILIFY and placebo were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9% (13/153) for ABILIFY vs. 1% (2/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days), and were of limited duration (9/13 ≤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 for ABILIFY was 4% (34/859).

## Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 7951 patients. All reported events are included except those already listed in Table 1, or other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are 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); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

*Body as a Whole: Frequent* - flu syndrome, fever, chest pain, rigidity (including neck and extremity), neck pain, pelvic pain; *Infrequent* - face edema, suicide attempt, malaise, migraine, chills, photosensitivity, tightness (including abdomen, back, extremity, head, jaw, neck, and tongue), jaw pain, bloating, enlarged abdomen, chest tightness, throat pain; *Rare* - moniliasis, head heaviness, throat tightness, Mendelson's syndrome, heat stroke.

*Cardiovascular System: Frequent* - tachycardia (including ventricular and supraventricular), hypotension, bradycardia; *Infrequent* - palpitation, hemorrhage, heart failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris, pallor, cardiopulmonary arrest, phlebitis; *Rare* - bundle branch block, atrial flutter, vasovagal reaction, cardiomegaly, thrombophlebitis, cardiopulmonary failure.

*Digestive System: Frequent* - nausea and vomiting; *Infrequent* - increased appetite, dysphagia, gastroenteritis, flatulence, tooth caries, gastritis, gingivitis, gastrointestinal hemorrhage, hemorrhoids, gastroesophageal reflux, periodontal abscess, fecal incontinence, rectal hemorrhage, stomatitis, colitis, tongue edema, cholecystitis, mouth ulcer, oral moniliasis, eructation, fecal impaction, cholelithiasis; *Rare* - esophagitis, hematemesis, intestinal obstruction, gum hemorrhage, hepatitis, peptic ulcer, glossitis, melena, duodenal ulcer, cheilitis, hepatomegaly, pancreatitis.

*Endocrine System: Infrequent* - hypothyroidism; *Rare* - goiter, hyperthyroidism.

*Hemic/Lymphatic System: Frequent* - ecchymosis, anemia; *Infrequent* - hypochromic anemia, leukocytosis, leukopenia (including neutropenia), lymphadenopathy, eosinophilia, macrocytic anemia; *Rare* - thrombocythemia, thrombocytopenia, petechiae.

*Metabolic and Nutritional Disorders: Frequent* - weight loss, creatine phosphokinase increased, dehydration; *Infrequent* - edema, hyperglycemia, hypercholesteremia, hypokalemia, diabetes mellitus, hypoglycemia, hyperlipemia, SGPT increased, thirst, BUN increased, hyponatremia, SGOT increased, creatinine increased, cyanosis, alkaline phosphatase increased, bilirubinemia, iron deficiency anemia, hyperkalemia, hyperuricemia, obesity; *Rare* - lactic dehydrogenase increased, hypernatremia, gout, hypoglycemic reaction.

*Musculoskeletal System: Frequent* - muscle cramp; *Infrequent* - arthralgia, myasthenia, arthrosis, bone pain, arthritis, muscle weakness, spasm, bursitis, myopathy; *Rare* - rheumatoid arthritis, rhabdomyolysis, tendonitis, tenosynovitis.

*Nervous System: Frequent* - depression, nervousness, schizophrenic reaction, hallucination, hostility, confusion, paranoid reaction, suicidal thought, abnormal gait, manic reaction, delusions, abnormal dream; *Infrequent* - emotional lability, twitch, cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence, extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, panic attack, decreased libido, hypersomnia, dyskinesia, manic depressive reaction, ataxia, visual hallucination, cerebrovascular accident, hypokinesia, depersonalization, impaired memory, delirium, dysarthria, tardive dyskinesia, amnesia, hyperactivity, increased libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia, increased reflexes, akinesia, decreased consciousness, hyperesthesia, slowed thinking;

*Rare* - blunted affect, euphoria, incoordination, oculogyric crisis, obsessive thought, hypotonia, buccoglossal syndrome, decreased reflexes, derealization, intracranial hemorrhage.

*Respiratory System: Frequent* - sinusitis, dyspnea, pneumonia, asthma; *Infrequent* - epistaxis, hiccup, laryngitis, aspiration pneumonia; *Rare* - pulmonary edema, increased sputum, pulmonary embolism, hypoxia, respiratory failure, apnea, dry nasal passages, hemoptysis.

*Skin and Appendages: Frequent* - skin ulcer, sweating, dry skin; *Infrequent* - pruritus, vesiculobullous rash, acne, eczema, skin discoloration, alopecia, seborrhea, psoriasis; *Rare* - maculopapular rash, exfoliative dermatitis, urticaria.

*Special Senses: Frequent* - conjunctivitis; *Infrequent* - ear pain, dry eye, eye pain, tinnitus, cataract, otitis media, altered taste, blepharitis, eye hemorrhage, deafness; *Rare* - diplopia, frequent blinking, ptosis, otitis externa, amblyopia, photophobia.

*Urogenital System: Frequent* - urinary incontinence; *Infrequent* - urinary frequency, leukorrhea, urinary retention, cystitis, hematuria, dysuria, amenorrhea, vaginal hemorrhage, abnormal ejaculation, kidney failure, vaginal moniliasis, urinary urgency, gynecomastia, kidney calculus, albuminuria, breast pain, urinary burning; *Rare* - nocturia, polyuria, menorrhagia, anorgasmy, glycosuria, cervicitis, uterus hemorrhage, female lactation, urolithiasis, priapism.

## Other Events Observed During the Postmarketing Evaluation of Aripiprazole

Voluntary reports of adverse events in patients taking aripiprazole that have been received since market introduction and not listed above that may have no causal relationship with the drug include rare occurrences of allergic reaction (eg, anaphylactic reaction, angioedema, laryngospasm, pruritis, or urticaria).

# DRUG ABUSE AND DEPENDENCE

## Controlled Substance

ABILIFY (aripiprazole) is not a controlled substance.

## 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).

# OVERDOSAGE

## Human Experience

In premarketing clinical studies, involving more than 5500 patients, accidental or intentional acute overdosage of aripiprazole was identified in seven patients. In the two patients taking the largest identified amount, 180 mg, the only symptoms reported were somnolence and vomiting in one of the two patients. In the patients who were evaluated in hospital settings, including the two patients taking 180 mg, there were no observations indicating an adverse change in vital signs, laboratory assessments, or ECG. An uneventful, accidental overdose (15 mg) occurred in a non-patient, an 18-month-old child, with concomitant ingestion of ATIVAN® (2 mg).

## 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 QTc 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.

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ATIVAN® is a registered trademark of Wyeth Laboratories, a Wyeth-Ayerst Company.

*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.

# DOSAGE AND ADMINISTRATION

## Schizophrenia

### Usual Dose

The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, however, doses higher than 10 or 15 mg/day, the lowest doses in these trials, were not more effective than 10 or 15 mg/day. Dosage increases should not be made before 2 weeks, the time needed to achieve steady state.

### Dosage in Special Populations

Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status (see **CLINICAL PHARMACOLOGY: Special Populations**).

*Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP3A4 inhibitors:* When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

*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, aripiprazole dose should then be increased.

*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 (to 20 or 30 mg). Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 to 15 mg.

### Maintenance Therapy

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, demonstrated a benefit of such maintenance treatment (see **CLINICAL PHARMACOLOGY: Clinical Studies**). 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.

## Bipolar Mania

### Usual Dose

In clinical trials, the starting dose was 30 mg given once a day. A dose of 30 mg/day was found to be effective. Approximately 15% of patients had their dose decreased to 15 mg based on assessment of tolerability. The safety of doses above 30 mg/day has not been evaluated in clinical trials.

### Dosage in Special Populations

See *Dosage in Special Populations* under **DOSAGE AND ADMINISTRATION: Schizophrenia**.

### Maintenance Treatment

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with aripiprazole. 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 (i.e., beyond 3 weeks).

## ANIMAL TOXICOLOGY

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

## HOW SUPPLIED

ABILIFY™ (aripiprazole) Tablets are available in the following strengths and packages.

The 5-mg ABILIFY tablets are blue, modified rectangular tablets, debossed on one side with “A-007” and “5”.

Bottles of 30 NDC 59148-007-13

Blister of 100 NDC 59148-007-35

The 10-mg ABILIFY tablets are pink, modified rectangular tablets, debossed on one side with “A-008” and “10”.

Bottles of 30 NDC 59148-008-13

Blister of 100 NDC 59148-008-35

The 15-mg ABILIFY tablets are yellow, round tablets, debossed on one side with “A-009” and “15”.

Bottles of 30 NDC 59148-009-13

Blister of 100 NDC 59148-009-35

The 20-mg ABILIFY tablets are white, round tablets, debossed on one side with “A-010” and “20”.

Bottles of 30 NDC 59148-010-13

Blister of 100 NDC 59148-010-35

The 30-mg ABILIFY tablets are pink, round tablets, debossed on one side with “A-011” and “30”.

Bottles of 30 NDC 59148-011-13

Blister of 100 NDC 59148-011-35

## Storage

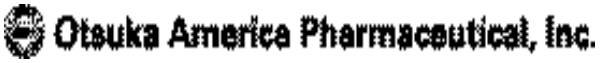
Store at 25º C (77º F); excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature].

Marketed by Otsuka America Pharmaceutical, Inc, Rockville, MD 20850 USA and Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Manufactured and Distributed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

U.S. Patent Nos. 4,734,416 and 5,006,528

**APPROVED AGREED-UPON LABELING**


Revised _____

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-436/S-002

# MEDICAL 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**

**DATE:** September 29, 2004

**FROM:** Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

**SUBJECT:** Recommendation for Approval Action for NDA 21-436 Supplement 002: Aripiprazole for the Acute Treatment of Bipolar Mania

**TO:** File, NDA 21-436
[Note: This memo should be filed with the July28, 2004 original submission of this NDA.]

**1.0 Background**
On 06-23-03, the sponsor submitted supplemental NDA 21-436 S002 to support the claim of efficacy for aripiprazole (Abilify) in the treatment of acute bipolar mania. The Division received a complete response to its April 23, 2004 Approvable Action letter on July 28, 2004. Teresa Podruchny, MD performed the primary review of this response as well as initial review of this supplement.

I agree with Dr. Podruchny that the sponsor has adequately addressed the items the Approvable Action letter of April 23, 2004 and the Division's attached draft labeling is acceptable to the sponsor. Dr. Podruchny and I have a few differences in recommendations for labeling and some other items and a discussion of these differences may be found in the clinical review section below.

**2.0 Chemistry**
Aripiprazole is an approved product and there were no chemistry issues in this review.

**3.0 Pharmacology/ Toxicology**
Aripiprazole is a marketed product and there are no pharmacology toxicology issues that bar the approval of this supplement. The April 23, 2004 Division action letter requested the firm to commit to performing juvenile animal studies that would be part of the pediatric development program for Abilify. (b) (4)

**4.0 Biopharmaceutics**
There were no human biopharmaceutical requirements included in the Division's April 23, 2004 action letter.

**5.0 Clinical**
The sponsor adequately addressed the clinical questions that remained from the initial review of this supplement.

- The sponsor has adequately presented data regarding the relationship between the presence or absence of psychotic symptoms and efficacy in studies 009 and 074. Patients generally showed improvement without respect to the presence or absence of psychotic symptoms.
- I believe that the sponsor has adequately addressed the effects of the protocol violations on the primary analysis (e.g. missing baseline valproate or lithium levels, benzodiazepine use within one day of a rating scale, positive drug screens at anytime during the study, and initiation of the study within 30 days of taking fluoxetine and within 14 days of other antidepressants). A re-analysis of the data both with and without these patients did not affect the overall positive outcome of the pivotal studies.
- (b) (4)
  A crucial part of designating a key secondary efficacy variable is receiving concurrence on the choice of the key secondary variable from the Division. This was not done for either study CN138009 or CN138074. Though an administrative letter exists that states the sponsor's plans for study CN138074, the Division was not made aware of this letter until the after the analysis was performed and had no part in agreeing with the decision. We likewise would have needed to approve of the use of the results of CN138009 before the analysis of study CN138074 was performed. That said, and even though these procedures were not followed, I recognize that adequate scientific study and analysis was made of the secondary variables (b) (4)

  (b) (4)

  (b) (4)

  I therefore believe that a CGI measure may be allowed in labeling, but encourage the sponsor to follow the Division's procedure for their key secondary analysis plans in the future.

- (b) (4)
  The sponsor noted that the adverse event profiles were generally similar (b) (4). The sponsor also included a table of common and drug-related adverse events for bipolar mania patients. I confirmed that the adverse event profiles were generally the same in bipolar and schizophrenia studies with the notable exception of akathisia and EPS syndrome that are both listed in the common-and-drug-related-adverse-event table. Therefore, I believe that the pooled common adverse event table is reasonable to retain in the service of simplifying labeling.

- [redacted] (b) (4) The sponsor did not exactly comply with this requirement, but I believe that they responded acceptably. The sponsor lumped the above terms excepting akathisia which was compared separately. I believe that this is appropriate given that many clinicians easily distinguish akathisia (15%-aripiperzole vs. 4% placebo) from the grouped involuntary movement terms associated with symptoms of EPS (17% aripiprazole vs. 12% placebo).
- The safety update did not identify unexpected or unlabeled adverse events that are not already under closer safety review. These unexpected and unlabeled events that are currently under review are the potential relationship of aripiprazole to pancreatitis and stroke in the demented elderly.
- Dr Podruchny suggests that the sponsor follow up on the priapism case reports. Priapism listed as a rare event in labeling. Reporting of priapism, especially for serious cases, will continue and I am not sure that we need the company to change its reporting practices or further follow-up previous reports unless they re-challenge patients with aripiprazole.
- Dr Podruchny notes that in the 3-week placebo-controlled trials, there was one suicide attempt in the aripiprazole group and none in the placebo group. Suicide related adverse events are commonly seen in the bipolar mixed and manic population. One case of a suicide attempt in the drug group versus none in the placebo group of this controlled trial population of this disorder is unfortunately expected. It is even more expected when the studies enroll more patients in the treatment groups as opposed to the placebo group. I therefore feel that further work-up of this case in this setting is not necessary.
- Dr Podruchny notes some exceptions in the list of Other Events Adverse Events. I believe that he other adverse events that are listed in the Other Adverse Events During Pre-marketing section of the draft proposed labeling seem reasonable at this time. This is always something that may be revisited over time.

**6.0 Non-US labeling**

In her review Dr Podruchny states,

> Currently, aripiprazole is approved in eleven countries: Mexico (2002), U.S. (2002), Puerto Rico (2002), Brazil (2003), Australia (2003), Peru (2003), Korea (2003), Ecuador (2004), Venezuela (2004), Columbia (2004), and Singapore (2004). Marketing applications are pending in another 11 countries and the EU.
>
> It is noted that the Australian label includes a section under Interactions for Antihypertensive Agents with the statement, "Due to its $a_1$ – adrenergic receptor antagonist activity, ABILIFY ™ has the potential to enhance the effect of certain antihypertensive agents." Additionally, this label includes under the Use in Pregnancy section descriptions of possible teratogenic effects in rats and rabbits and gives a rough estimate of the doses compared to human exposure.

[redacted] (b) (4) The potential for teratogenicity appears to be adequately addressed in current US labeling.

**7.0 Recommendations and Conclusions**

I believe that the sponsor has adequately addressed the concerns that were listed in the Division's Approvable Action letter of April 23, 2004. I therefore recommend that the Division take an approval action on supplement 002 Attached to this package is draft labeling.

Supplement 005, the use of aripiprazole monotherapy for the maintenance treatment of mania is currently under review. In addition to maintenance monotherapy data, I recommend that the sponsor agree to a phase 4 commitment to perform both acute and maintenance studies of the efficacy of treating patients with aripiprazole with an adjunctive mood stabilizer.

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/s/
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Paul Andreason
9/29/04 10:21:47 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
sNDA #21436-002

Sponsor: Otsuka/BMS
Drug: Aripiprazole (Abilify)
Indication: Acute Mania
Material Submitted: Response to 4-23-04 Approvable Letter
Correspondence Date(s): 05-26-04, 7-19-04, 7-28-04

I. Background

On 06-23-03, the sponsor submitted this supplemental NDA for the approval of aripiprazole (Abilify) in the treatment of acute mania in patients with Bipolar I Disorder.

An approvable letter was issued on 4-23-04 for supplement 002 indicating that before the application could be approved, the sponsor must address several areas of concern/deficiency:

1. preclinical studies that will be used to support pediatric studies of this drug, specifically for use in bipolar patients as a phase 4 commitment
2. the effect of the presence or absence of psychotic symptoms on primary efficacy in studies 009 and 074
3. the effects of certain protocol violations on the primary analysis
4. whether key secondary variables were defined in advance of breaking the blind in study 009
5. the table of adverse events which pooled schizophrenic and bipolar patients
6. the rate of EPS-related symptoms for drug treated and placebo treated patients
7. Revised draft labeling
8. Safety update

This submission contains their response. The initial response was sent on May 26, 2004, further information and analyses regarding question 3 were sent July 19, 2004 and the amended appendices to the CSR for studies 009 and 074 were sent July 28, 2004.

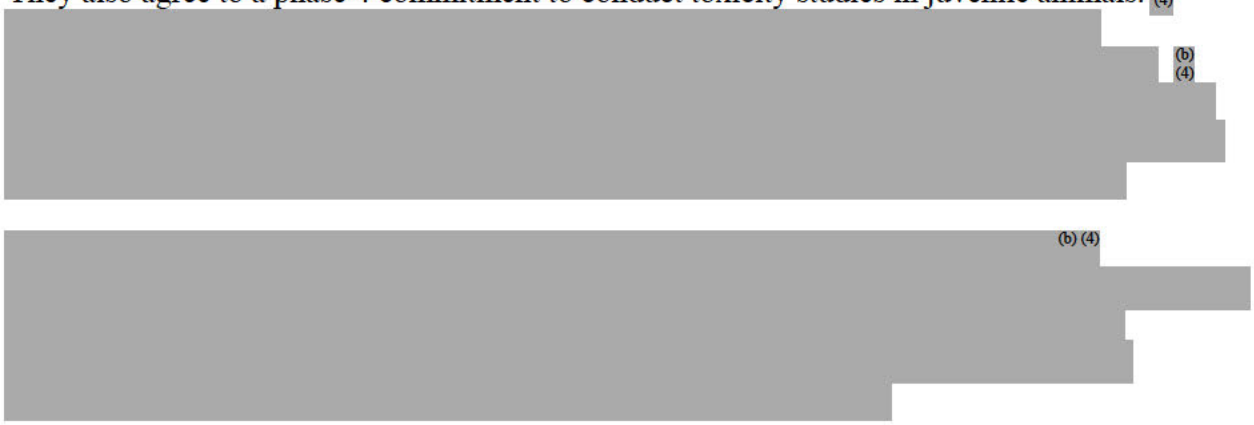
II. Clinical Data

**Question 1:** *As you are aware, all applicants 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 reference the deferral granted on May 9, 2003 for the pediatric study requirement for this application. Please see the pharmacology/toxicology comment below with respect to preclinical studies which will be required to support the pediatric studies of this drug.*

The sponsor has agreed to a phase 4 commitment to conduct a trial that will provide safety and efficacy data in pediatric patients with bipolar mania using aripiprazole. They propose to use the

same short-term study that will be conducted to meet the requirements of the written request for pediatric exclusivity and note this as been discussed between OPC and FDA. The study is anticipated to start in January/February 2005 and generate a clinical study report for submission in January/February 2008, if recruitment moves as anticipated.

They also agree to a phase 4 commitment to conduct toxicity studies in juvenile animals. (b) (4)




**Question 2:** *What effect does the presence or absence of psychotic symptoms have on the efficacy outcome of studies 009 and 074? We were unable to find an analysis that examined this interaction in the study reports.*

The sponsor notes that the criteria used were the same as those used in the aripiprazole schizophrenia trials. Patients were considered to have psychotic symptoms if at baseline, they had a PANSS total of $\geq 60$ and a score of $\geq 4$ (moderate) on 2 or more of these items: delusions, hallucinatory behavior, conceptual disorganization, or suspiciousness.

The sponsor provided a table of the results, Table 1, which is duplicated below.

**Table 1: Mean Change from Baseline in Y-MRS Total Score by the Presence of Psychotic Symptoms, LOCF Data Set, Efficacy Sample**

| | Y-MRS Total Score[a] | | | | |
|---|---|---|---|---|---|
| | Placebo | | Aripiprazole | | Aripiprazole vs Placebo |
| | N | Mean[b] | N | Mean[b] | P-value |
| **Protocol CN138009** | | | | | |
| **Subjects with Psychotic Symptoms[c]** | | | | | |
| Baseline Score | 37 | 34.74 | 26 | 33.97 | 0.568 |
| Change from Baseline to Week 3 | 37 | 0.88 | 26 | -8.63 | 0.014 |
| **Subjects without Psychotic Symptoms[c]** | | | | | |
| Baseline Score | 85 | 27.71 | 97 | 27.25 | 0.460 |
| Change from Baseline to Week 3 | 85 | -3.67 | 97 | -7.07 | 0.050 |
| **Protocol CN138074** | | | | | |
| **Subjects with Psychotic Symptoms[c]** | | | | | |
| Baseline Score | 17 | 34.83 | 18 | 33.59 | 0.564 |
| Change from Baseline to Week 3 | 17 | -9.39 | 18 | -13.72 | 0.431 |
| **Subjects without Psychotic Symptoms[c]** | | | | | |
| Baseline Score | 115 | 27.88 | 118 | 27.94 | 0.914 |
| Change from Baseline to Week 3 | 115 | -7.27 | 118 | -12.62 | < 0.001 |

Protocol CN138009 & CN138074

[a] Y-MRS Total Score is from 0 to 60. A negative change score signifies improvement.

[b] LS-Means from ANCOVA model, controlling for treatment, study center, and baseline value.

[c] Baseline psychotic symptoms were defined as PANSS Total Score ≥ 60 and a score ≥ 4 (moderate) on two or more of the following PANSS items: delusions, hallucinatory behavior, conceptual disorganization, or suspiciousness.

Conclusion: The number of patients in study 138074 who have psychotic symptoms is small and may account for the lack of significant difference seen between the aripiprazole and placebo patients. However, in each study, the subjects without psychotics symptoms experienced greater mean changes in YMRS scores when taking aripiprazole than when taking placebo ($p=0.05$ in CN138009 and $p<0.001$ in CN 138074). These data seem adequate to address the question and support that the efficacy results seen in the acute mania trials were not due exclusively to aripiprazole's action as an antipsychotic.

**Question 3:** *We note that you have included, according to the intent-to-treat principle, patients with various protocol violations in your analyses. We are particularly interested in the effects on your primary analysis of including patients who did not have baseline valproate or lithium levels, patients with benzodiazepine use within 1 day of a rating having been done, patients with positive drug screens at anytime during the study, and patients who began the study within 30 days of flouxetine or within 14 days of other antidepressants.*

Upon initial review, I was concerned that there appeared to be a fair number of protocol violations and that some patients DSI had noted as missing labs (lithium/valproate), were not listed in the appendix listings of these data. For example, neither Appendix 7.3A or 7.3B captured patients 009-23-29, 009-23-49, 009-23-56 (listed in Dr. Khin's review). As site inspections are limited to a discrete number of sites, whether such events could have been more widespread and yet not captured by the sponsor was a concern discussed internally during the original review cycle.

Early in my comparative audit of the appendices, I could not locate three patients from study 09 who had missing lithium or valproate levels (3-02, 43-104, 43-127) in the RA. We addressed this with the sponsor as we were concerned there may be discrepancies in the data.

The sponsor then performed a comparison of the two sets of appendices and concluded that in the majority of cases (July 19, 2004 submission), the differences between the RA and the CSR appendices resulted from differing criteria used in the identification of patients for inclusion. One difference was in the criteria delineated in the approvable letter versus those specified in the protocols. (Table 2.2, as provided by the sponsor, compares the two sets of criteria, and is reproduced in the appendix of this document). The second difference was that the RA included only those patients who were actually in the primary efficacy analysis set while the appendices in the CSRs included all randomized patients.

The company noted that another review of the database was conducted in order to ensure the accuracy of the RA. This review identified a number of patients who were either included or excluded in error from the RA sent on May 28, 2004. However, as many of these patients met at least one of the criteria specified in the approvable letter request, in the final outcome, they note there were only eight discrepancies between the CSR appendices and the RA due to an erroneous exclusion from the Response Appendix (1 in 009 and 7 in 074).

As discussed above, the sponsor performed a second sensitivity analysis and notes that for both analyses, the primary efficacy measure yielded statistically significant results in favor of aripiprazole even with or without exclusion of the protocol violators as specified in the AE letter. The table displaying the analysis, as presented in the July 19, 2004 submission, is reproduced below. (For reference, the efficacy data from the original submission CSRs are duplicated in the appendix of this document).

**Table 6: Mean Change from Baseline in Y-MRS Total Score, LOCF Dataset, Excludes Patients per FDA Request**

| | Y-MRS Total Score[a] | | | | |
|---|---|---|---|---|---|
| | Placebo | | Aripiprazole | | Aripiprazole vs Placebo |
| | N | Mean[b] | N | Mean[b] | P-value |
| **CN138009** | | | | | |
| Baseline Score | 32 | 29.85 | 40 | 28.62 | 0.321 |
| Change from Baseline to Week 3 | 32 | -5.61 | 40 | -13.05 | 0.017[c] |
| **CN138074** | | | | | |
| Baseline Score | 53 | 27.61 | 62 | 29.08 | 0.108 |
| Change from Baseline to Week 3 | 53 | -11.86 | 62 | -16.79 | 0.012[c] |

[a] Y-MRS Total Score is from 0 to 60. A negative change score signifies improvement.

[b] LS-Means from ANCOVA model, controlling for treatment, study center, and baseline value. There were 24 study centers used in the analysis sample for each of CN138009 and CN138074.

[c] The Analysis Plan specified study center as a covariate in the model. In the Analysis sample with patients excluded per FDA request it is questionable whether it is appropriate to include study center in the model with the smaller sample size and large number of centers (24 in the Analysis sample of each study). The above analysis includes study center in the model ( per Analysis Plan); if study center is excluded from the model, p= 0.011 for CN138009 and p= 0.005 for CN138074.

Note: Sample includes all patients in the primary analysis of Y-MRS who did not have any of the following exclusion reasons per our interpretation of the FDA request: missing valproate or lithium levels at randomization, positive drug screens after randomization, benzodiazepine use within 1 day of endpoint Y-MRS, fluoxetine use within 30 days of randomization or other antidepressants within 14 days of randomization.

Comments: Of the six patients that DSI reported as missing either lithium or valproate levels pre-randomization, the original CSR 009 appendix listing captured three. The amended appendix to the CSR (submitted July 28, 2004) contains all of these patients. However, one patient that Dr. Khin listed in study 074 (03-35), is still not listed in the new appendix for CSR 074.

I compared some of the original appendices from the CSRs to the amended CSR appendices (submitted July 28, 2004). Specifically, I looked at Appendix 7.3, "Psychotropic drugs at or before randomization". I chose this protocol violation listing because the explanation noted more than just a name clarification. The new listings in studies 009 and 074 display quite a few more patients because the sponsor's original program specifications had not searched for certain drugs such as zolpidem, zalepon, mirtazapine, nefazodone, antidepressants other than flouxetine within 7 days of randomization, and anticholinergic use. It appears there were errors in the original appendices. However, I believe the analyses performed on the RA and as part of answering Question 3 have incorporated these.

The sponsor is correct that our criteria were not always identical to the protocol specified criteria. Also, the explanations they offer regarding the differences between the patients listed in the RA and those in the original CSR appendices generally sound reasonable. What we still do not necessarily know is whether protocol violations were captured by the sponsor or incorporated subsequent to DSI inspection.

Conclusion: This is a complex issue. It is true that some of our criteria were different than the original criteria. The numbers of protocol violations of various types in the trials still seem fairly large to me and are somewhat bothersome, although some types of violations are less likely to

impact efficacy. They have dropped large numbers of patients and the studies remain significant. Additionally, the preliminary in-house analyses performed regarding protocol violators during the original review cycle, although perhaps not perfect in patient selection, did not cause the studies to lose significance. Given these factors and the randomization process, I think the trials, on balance, do meet the stated primary efficacy objectives.

Additionally, although the completion rates in these three week studies may reflect the difficulty in treating this patient population, the robustness of the drug, or some combination thereof, I think the completion rates should be described in the label. Study 009 had a forced discontinuation at week 2 based on CGI-BP criteria. In this study, 21% of the placebo group and 42% of the aripiprazole group completed 3 weeks of treatment. In study 074, in which there was no forced discontinuation, the completion rates are about equal between groups (52% placebo, 55%aripiprazole).

**Question 4:** *We were unable to find any record in the original protocol, subsequent amendment, or administrative letter to the Division designating key secondary efficacy variables for study 009 prior to breaking the data blind. Does this record exist?*

The sponsor confirmed that hierarchical testing was not pre-specified in protocol 009 and therefore, there is no record. They note, however, that hierarchical testing was prospectively planned for study 074 and that if the same methodology from study 074 was used on the results of 009, that the same secondary endpoints would remain statistically significant. (b) (4)

Comments: Study 009 was initiated March 22, 2000, completed July 06, 2001 and the report was generated April 23, 2003. Database lock for 009 occurred on July 31, 2001.

In September, 2001, (b) (4)

(b) (4)

**Question 5:** *You have pooled the controlled trials of schizophrenia and bipolar mania into one adverse event table in your initial version of draft labeling.* (b) (4)

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Please see the label section of this review.

**B. Foreign Regulatory Update**

Currently, aripiprazole is approved in eleven countries: Mexico (2002), U.S. (2002), Puerto Rico (2002), Brazil (2003), Australia (2003), Peru (2003), Korea (2003), Ecuador (2004), Venezuela (2004), Columbia (2004), and Singapore (2004). Marketing applications are pending in another 11 countries and the EU.

It is noted that the Australian label includes, under the Use in Pregnancy section, descriptions of possible teratogenic effects in rats and rabbits and gives a rough estimate of the doses compared to human exposure.

**C. Safety Update:**

Oral tablet: The updated safety database for all Phase 2/3 clinical studies using the oral tablet is comprised of 7951 aripiprazole-treated patients representing 5234.7 patient-exposure years. This is an increase of 464 patients since the 120 day update and 1397 patients since the original

ISS/ISE. As of January 16th, 2004, about 9,326 patients had received aripiprazole in Otsuka and BMS sponsored Phase 1-3 trials. (An updated exposure table displaying exposure per indication in the clinical trials is duplicated from the submission in the appendix of this document).

- 2280 patients for 180 days or more
- 1558 patients for at least 360 days
- 864 patients for at least 720 days
- (b) (4)
- schizophrenia patients in open-label studies 138060, 138087, and 138100, and 138114
- Alzheimer's psychosis study 138005-130 patients and 138004-360 patients
- Patients in studies of the IM formulation (schizophrenia, schizophreniform, schizoaffective, bipolar I, dementia)
- Patients in studies using the ODT (schizophrenia)
- (b) (4)

Line listings of the clinical trial deaths and serious adverse events in the phase 2/3 studies were reviewed. IM formulation and ODT data were not reviewed. Additional review of the safety data in the maintenance study will be performed as part of the review of that supplement (s005).

- A total of 199 deaths occurred in 7951 patients treated with aripiprazole
- 58 deaths occurred since the original material for this supplement was submitted
- 25 deaths are either newly reported (11) or newly unblinded (14) since the 120 day update
- the sponsor notes that 5 deaths, which were included in the total in the 120 day update and in the Maintenance ISS, were later found to have occurred > 30 days after the last dose of study medication and have been moved out of the count. The deaths are still listed in a subsection of the appendix listing all deaths.

**Oral Tablet Clinical Trial Data:**

**Death:** One death is reported in the maintenance study that was not covered in my original review (138010-47-85). This death was from pulmonary embolism and is noted to have occurred > 60 days after the last dose of study medication in the extension phase of study 010.

Twenty-five newly reported or previously blinded deaths in the aripiprazole group are included in this update. Twenty-four of the 25 deaths were in the Alzheimer's trials and one was in a schizophrenia trial.

Within the Alzheimer's patients, the average age was 82.3 years old with a range of 77-97 years old. The adverse events listed are not unexpected types of events seen in an elderly population with dementia. Whether these events are occurring at higher rates than the background cannot be determined from this line listing. The sponsor noted that when incidence of death was calculated by patient-year exposure by indication for the oral tablet, bipolar mania has an incidence of 0.010, schizophrenia, 0.009, and dementia 0.214.

One death by suicide occurred on day 147 in a patient with schizophrenia who experienced a psychotic decompensation on day 127 of an extension phase study resulting in an increase in his study drug dose. The investigator noted this patient had not attempted suicide in 10 years and felt the suicide was caused by psychosis and the decompensation probably related to study drug. It is difficult to assess causality in this case.

Comment: On January 30, 2003, the DNDP requested that the sponsor perform an analysis of cerebrovascular-related adverse events in elderly patients with dementia in the studies of aripiprazole. The sponsor notes that one additional study is available since that request.

**Non-Fatal Serious Adverse Events:** 22.1% of patients experienced at least 1 serious adverse event (SAE). This is similar to the acute ISS/ISE and the 120-day update (21.9%) and the maintenance ISS (22.0%). A total of 196 newly reported or previously blinded and now identified as having occurred while receiving aripiprazole treatment SAEs since the 120-day update are included in this submission. From the line listing, I identified eleven of these as bipolar patients*. (The maintenance bipolar study CN138010 is currently under review). There were 96 SAEs in the dementia population and 97 SAEs in the schizophrenia population.

Line listings of the SAEs were reviewed. With regard to the Alzheimer's and schizophrenia patients who experienced SAEs, there do not appear to be any types of SAEs that are rare and unexpected for the population.

- Within the bipolar population, most of the events were psychiatric in nature. One patient each experienced pruritis or paralysis (secondary to an MVA). One patient with a history of chronic recurrent pancreatitis experienced pancreatitis. One patient, with no previous cardiac history, experienced ventricular bigeminy after about 62 total days of dosing which was felt to be possibly related to treatment by the investigator. (b) (4) [redacted]
- Suicide attempt cumulative: In the bipolar population, there are three suicide attempts. One occurred in study CN138007 (day 2 of aripiprazole treatment), one in study 138010 during open label aripiprazole, and one in a placebo patient in CN138010 during the maintenance phase.

**SUMMARY:** Acute Bipolar Population: There are no obvious new safety concerns such as to preclude approval for the acute indication. The maintenance supplement (s005) is under review.

*An email of September 24th from the sponsor noted there were 12 total bipolar mania: 1 new and 11 previously unblinded.

**PSUR: POST MARKETING**

The company estimates that (b) (4) patients have been exposed to aripiprazole worldwide with (b) (4) patients exposed from (b) (4). These estimates are based on the total number of milligrams sold divided by (b) (4)

There are 516 Adverse drug reports (ADR) meeting the inclusion criteria defined in the E2C guideline that were received and/or validated by BMS for the six month period from July 17, 2003-January 16, 2004 from 17 countries included in this PSUR. Of these, 214 were classified as serious (184 spontaneous reports, 45 from clinical trials, and 2 from the literature) and 285 non-serious. Seventeen of the 516 reports were of death. Of these fatal outcome reports, 14 were spontaneous and 3 were from clinical trials. Twelve were initial reports and five were follow-up. Seventeen reports described overdose, one described pregnancy exposure, one of potential drug abuse, and four of suspected drug interactions.

Line listings for the spontaneous reports were reviewed for deaths and non-fatal, serious adverse events. Dr. Andreason assisted in selection of cases from the line listings of which the available reports were read. Additionally, either narratives or ADRs were read for all cases in which suicide was a cause of death and a report was contained in the submission.

(Synopses of some of the narratives read are in the appendix of this document.)

**Death:**

In general, the cases reviewed are confounded, lack details, lack specific causes of death, and are not easily interpreted.

**Serious Adverse Events:**

It appears there may be a possible signal with pancreatitis in the post marketing cases. Cumulatively, there are two cases of pancreatitis that involve teenagers with autism who developed cholecystitis and pancreatitis while on aripiprazole. Neither case is clean and I am uncertain whether autistic patients have a higher risk. However, pancreatitis is not a common event in non-autistic teenagers. (A case was seen in the clinical study 010. This occurred in a patient with a history of chronic pancreatitis.) Recently, the company was asked to further research the incidence of pancreatitis subsequent to a review of the FDA ADRs and the literature.

Torsades appeared on this list as an event, but with review of the narrative, I do not think this is likely attributable to aripiprazole. (See synopses in the appendix for further information)

There were four cases of priapism in this reporting period. One case is not confounded. One required surgery but is confounded by concomitant risperidone. Priapism is listed in the aripiprazole label as occurring rarely in the pre-marketing section. This appears to be based on one case in the schizophrenia population. I recommend we request the company seek more

information on the two cases that were lacking in detail,However I think this can be done after this action is taken.

**D. Label**

Label issues raised by the sponsor in this update:

1. The sponsor reports that based on a cumulative review of post-marketing ADRs in the PSUR submitted this time, it was recommended that "rare" allergic reaction (including anaphylactic reaction, angioedema, pruritis or uritcaria) be in the USPI in the post marketing section.

Comments: The sponsor notes that 24 reports of either anaphylactic reaction (4), hypersensitivity (7), Hypersensitivity and Swelling Face (1), Hypersensitivity and Face Oedema (1), Hypersensitivity and Urticaria (1), Asthma (2), Tongue Oedema (3) and Urticaria (5) were retrieved in a cumulative review of the BMS AE database for all medically confirmed spontaneous and literature cases and all serious, drug-related clinical trial cases of anaphylaxis/hypersensitivity received between July 17, 2002 and January 16, 2004 in which aripiprazole was suspect or interacting. Of these cumulative reports, 23 were spontaneous and one was from a clinical trial.

2. Overdose information will be updated and submitted as a labeling supplement as a CBE.
3. Based on new/additional clinical trial data, the sponsor is considering a CBE regarding the new data from the dementia trials and cerebrovascular-related adverse events as an update to the PRECAUTIONS section.
4. (b) (4)
5. (b) (4)
6. We suggested adding laryngospasm (b) (4) .

**RECOMMENDATIONS to proposed labeling submitted 5-26-04:**

The following items correspond to the bracketed comments in the side-by-side.pdf..

(b) (4)

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**Table 2.2: Criteria Used in CSR Deviation Appendices versus Response Appendix**

| | Response Appendix | CSR Protocol Deviation Appendices[a] |
|---|---|---|
| **Patient Population:** | All patients in the primary efficacy analysis | All patients in the randomized sample |
| **FDA-Requested Exclusions** | | |
| No Baseline Valproate or Lithium Level | No valproic acid level and/or lithium level on or before the randomization date | No valproic acid level and/or lithium level on or before the randomization date |
| Benzodiazepine Use Within 1 Day of a Rating Having Been Done | Any benzodiazepine use within 1 day of endpoint Y-MRS assessment | Excessive lorazepam use defined as the following:<br>> 6 mg on days 1-4<br>> 4 mg on days 5-7<br>> 2 mg on days 8-10<br>any dose after day 10 up to last day of study medication dosing<br>Other benzodiazepine use at any time between first and last day of study medication dosing |
| Patients With Positive Drug Screen at Any Time During the Study | Positive drug screen after randomization date | Positive drug screen before or after randomization date |
| Patients Who Began the Study Within 30 Days of Taking Fluoxetine or Within 14 Days of Other Antidepressants | Fluoxetine within 30 days prior to randomization date<br>Other antidepressants within 14 days prior to randomization date | Fluoxetine within 4 weeks prior to randomization date<br>Other antidepressants[b] within 1 day (CN138009) or 2 days (CN138074) prior to randomization date |

[a] Bolded text indicates differences between FDA-requested exclusions and the protocol deviations for the 2 studies captured in the CSR Deviation Appendices.

[b] Other antidepressants were captured in the category of psychotropic drugs.

**EFFICACY RESULTS:**

The summary of key efficacy results at endpoint is shown in the following table. The aripiprazole treatment group showed statistically greater improvement than placebo for the Y-MRS at Week 3. The aripiprazole group was also statistically superior to placebo on the secondary endpoints of CGI-BP Severity of Illness (mania) score, rate of discontinuation due to lack of efficacy, and response rate.

**Summary of Key Efficacy Results at Endpoint, LOCF Data Set, Efficacy Sample**

| | Treatment Group | |
|---|---|---|
| | **Placebo** | **Aripiprazole** |
| **PRIMARY EFFICACY ENDPOINT** | | |
| Y-MRS[a] | N = 122 | N = 123 |
| Mean Baseline | 29.68 | 28.16 |
| (95% CI) | (28.66, 30.69) | (27.13, 29.20) |
| Change at Week 3 | -3.35 | -8.15** |
| (95% CI) | (-5.75, -0.94) | (-10.60, -5.73) |

**Table 10: Summary of Efficacy Results at Endpoint, Efficacy Sample, LOCF Data Set**

| | Treatment Group | |
|---|---|---|
| **Variable** | **Placebo** | **Aripiprazole** |
| **PRIMARY EFFICACY ENDPOINT** | | |
| Y-MRS Total Score | N = 132 | N = 136 |
| Mean Baseline | 28.45 | 28.80 |
| (95% CI) | (27.47, 29.42) | (27.85, 29.76) |
| Mean Change at Week 3 | -7.19 | -12.52** |
| (95% CI) | (-9.30, -5.08) | (-14.59, -10.45) |
| **KEY SECONDARY ENDPOINTS** | | |
| Response Rate at Week 3[a] | N = 132 | N = 136 |
| N (%) | 42 (32%) | 72 (53%)** |
| (S.E.%) | (4.1%) | (4.3%) |

**Table 3: Number of Protocol Deviators, By Study, Deviation Type, and Treatment Group**

| | CN138009 | | CN138074 | |
|---|---|---|---|---|
| | **Placebo** | **Aripiprazole** | **Placebo** | **Aripiprazole** |
| No baseline valproate or lithium level | 8 | 7 | 7 | 5 |
| Benzodiazepine use within 1 day of endpoint Y-MRS | 58 | 43 | 48 | 40 |
| Positive drug screen after randomization | 1 | 3 | 6 | 5 |
| Fluoxetine within 30 days or antidepressant within 14 days of randomization | 45 | 48 | 40 | 27 |
| Any of the above deviations | 84 | 81 | 79 | 67 |

| | Bipolar Mania N = 1170 | | Dementia N = 788 | | Schizophrenia N = 5529 | | All Aripiprazole N = 7487 | |
|---|---|---|---|---|---|---|---|---|
| **Patient exposure years** | **153.5** | | **640.2** | | **3937.6** | | **4731.2** | |
| **Duration of Exposure** | **N** | **(%)** | **N** | **(%)** | **N** | **(%)** | **N** | **(%)** |
| ≥ 1 day | 1170 | (100.0) | 788 | (100.0) | 5529 | (100.0) | 7487 | (100.0) |
| ≥ 21 days | 703 | (60.1) | 734 | (93.1) | 4492 | (81.2) | 5929 | (79.2) |
| ≥ 42 days | 485 | (41.5) | 668 | (84.8) | 3673 | (66.4) | 4826 | (64.5) |
| ≥ 90 days | 189 | (16.2) | 570 | (72.3) | 2278 | (41.2) | 3037 | (40.6) |
| ≥ 180 days | 32 | (2.7) | 449 | (57.0) | 1586 | (28.7) | 2067 | (27.6) |
| ≥ 270 days | 5 | (0.4) | 366 | (46.4) | 1343 | (24.3) | 1714 | (22.9) |
| ≥ 360 days | 2 | (0.2) | 255 | (32.4) | 1168 | (21.1) | 1425 | (19.0) |
| ≥ 540 days | 2 | (0.2) | 158 | (20.1) | 867 | (15.7) | 1027 | (13.7) |
| ≥ 720 days | 0 | (0.0) | 91 | (11.5) | 724 | (13.1) | 815 | (10.9) |

**PSUR:**
**Deaths:**

**MFR#** 12369310 This was a 61 y.o. female bipolar patient with no history of cardiac problems, a history of bipolar disorder, who was taking multiple medications including nefazodone, sertraline, clonazepam, and conjugated estrogens. It is reported "her heartbeat slowed then stopped" and she died at home. While taking aripiprazole she experienced diarrhea and some type of unspecified gastrointestinal disorder and was hospitalized. Her death occurred at least 10 days after discharge from this hospitalization. The cause of death is unclear to me.

**MFR#** 12376281: In the narrative of this completed suicide, it indicates that this schizoaffective patient was suspected to have not been taking medications for the three weeks prior to the event. These patients are at higher risk of suicide and, if medications were stopped, this would be a reasonable explanation for the suicide.

**MFR**# 12412078: In the narrative of this completed suicide, it is noted the patient had a history of major depression with schizophrenic tendencies.

**MFR**# 12432993: This patient was found dead. The patient had multiple psychiatric and other medical historical diagnoses including major depression with psychosis, although no history of suicide attempt, was on several medications, including zolpidem, olanzapine, escitalopram, and aripiprazole, and may have been abusing diazepam. There is no known cause of death.

**MFR#** 12181277: This case was included in the last review. Follow-up in this PSUR notes there was no autopsy.

**MFR**# 12433512: This patient had a history of bipolar II depression, psychotic disorder, suicidal ideation and was experiencing suicidal ideation. She was on antipsychotics, antidepressants, and hydrocodone. The patient was noted to be confused a few days before her death. The exact cause of death is not known. This narrative cannot be meaningful interpreted.

**Serious Adverse Events:**

**Torsades:**
**MFR**# 12423612: This is a 59 year old female with Marfan syndrome, aortic valve replacement, diabetes, hypertension, stroke and depression who experienced a convulsion, QT prolongation, torsades and an embolic stroke 17 days after starting aripiprazole 30 mg daily for delusions. She was on several concomitant medications including risperidone and warfarin (INR 1.5) and was treated with dilantin for the seizure. The first EKG monitoring describes QT prolongation, with torsades occurring the next morning. She was electrically cardioverted. QT prolongation apparently continued intermittently for some time period after aripiprazole was discontinued, although it is unclear how long after discontinuation this was. As presented in the narrative, there appear to be other possible explanations for torsades.

**Reported "Serotonin Syndrome" (SS)**

**MFR**# 12330429: This is a case of a 16 year old male (96 kg) who reportedly experienced rhabdomyolysis, serotonin syndrome, hyponatremia, acute renal failure while taking aripiprazole 15 mg daily for bipolar disorder. He was also taking venlafaxine, risperidone, and zonisamide. On admission to the hospital with pain, spasm, sweats, and diarrhea, his CK was found to be 4008 and his sodium 127. The narrative indicates that his CPK decreased while aripiprazole treatment was interrupted for two days, however it looks like the risperidone was discontinued also. When aripiprazole was re-started and after one dose, his CPK increased (5439) All medications were discontinued. He was discharged with a CPK of 2019. The rhabdomyolysis was felt to be due to either increased activity, crushing injury, or serotonin syndrome. From the narrative, it is unclear to me that this was serotonin syndrome, however, some role of aripiprazole cannot be excluded in the CPK increases.

**MFR**# 12368635: This is a case of suspected serotonin syndrome in a patient taking ariprazole for the treatment of "schizoaffective disorder bipolar type". He was concomitantly on paroxetine, valproate, and haloperidol. It appears symptoms started about six days after beginning aripiprazole. He experienced two seizures and both aripiprazole and paroxetine were discontinued. He had no history of previous seizures. This patient was on an SSRI making aripiprazole less likely to be the primary suspect drug.

**Hepatobiliary:**

Pancreatitis: **MFR#** 12416244: This is a 17 year old with autism and "idiopathic hypersomnolence" who developed cholecystitis and pancreatitis after four months of aripiprazole 15 mg daily treatment. He was treated with a cholecsytectomy. Concomitant medication was venlafaxine.

Pancreatitis: **MFR#** 12291886 (from the last review cycle PSUR): This is an 18 year old with Asperger's on aripiprazole 15 mg daily who developed pancreatitis and gallstones four weeks after initiation of treatment. Citalopram was noted as a concomitant medication. This patient was scheduled for a cholecystectomy.

**MFR**#12396917: This is a 19 year old with a history of alcoholism and drug abuse who was hospitalized for schizophrenia. He began risperidone initially, this was discontinued, and he was started on aripiprazole. He developed nausea and vomiting and the hematocrit and LFTs are reported as elevated but exact values were not reported. Aripiprazole was discontinued 30 days after initiation and his labs reportedly improved. However, on quetiapine, his LFTs and cholesterol increased. An ultrasound showed a fatty liver.

**MFR** #12311239: (This is follow-up). This is a 34 year old who the sponsor notes developed drug-induced hepatitis while taking po aripiprazole 15 mg daily. This patient was taking other medications and reportedly had taken a month's worth of multivitamins a week before in a suicide attempt. Reportedly, two months before aripiprazole treatment, her AST and ALT were normal, returned to normal after medication discontinuation, and aripiprazole addition and discontinuation of olanzapine were the only recent changes to her medications. This case is confounded but aripiprazole may have played a contributory role.

**Priapism:** There were four cases of priapism in this reporting period (MFR#s: 12404083, 12472981, 12476230, and 12334074). The patient in MFR#12404083 required surgical intervention but was also taking risperidone. MFR#12476230 was on no concomitant medications and reportedly experienced priapism ½ hour after taking aripiprazole and with almost every time he took the medication. The other two reports (one in a 7 year old) contain too little information to be interpreted meaningfully.

**Rhabdomyolysis:**
**MFR**# 12362554: This is a 37 year old patient with schizoaffective disorder with a history of psychosis, depression, suicidal ideation, and past suicide attempt 20 years ago who was diagnosed with rhabdomyolysis, increased blood glucose, and increase ALT and AST after taking aripiprazole for about 3 weeks (dose not reported). This patient was taking concomitant escitalopram and rofecoxib. Reportedly, he began to complain, almost immediately after starting aripiprazole, of severe back pain and muscle spasms in both lower extremities. Admission labs indicate a CPK of 1111 U/L (38-174). He was treated with bicarbonate and three days after admission, was discharged. The psychiatrist reported his symptoms "dramatically" improved after discontinuation of aripiprazole. Although confounded, a contributory role of aripiprazole cannot be ruled out.

**Overdose:**
**MFR**# 12287546: 21 year old female who overdosed on aripiprazole and possibly on venlafaxine and escitalopram as well in a suicide attempt. This follow-up notes that she had a serum aripiprazole level of 222ng/mL and 195ng/mL 2 days post attempt but does not note whether the other drugs were detected or checked. She experienced a number of serious medical problems as a result of the overdose. This overdose information does not provide characterization of the profile of aripiprazole in overdose given the confounders.

**MFR**# 12461349: This overdose was a suicide attempt in a 56 year old female with a history of suicide attempt and depression who took an estimate of 420 mg of aripiprazole, 300 mg tramadol and 10.5 gram of gabapentin. She experienced seizures and hypotension (SBP=95mmHg). This is a confounded case of overdose.

**Withdrawal: MFR**# 12379814: This is a reported case of withdrawal in a child with too little information to be useful. The symptoms are listed as drooling and catatonia.

**Table 6.1.8: Y-MRS Total Score: Mean Change from Baseline to Week 3 by Population Subsets; 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, CN138074), LOCF Data Set, Efficacy Sample**

| Subgroup | Value | N | Placebo | N | Aripiprazole | Aripiprazole vs. Placebo P-value |
|---|---|---|---|---|---|---|
| **Gender** | Men | 178 | -6.9 | 244 | -9.6 | 0.019 |
| | Women | 206 | -6.9 | 271 | -10.5 | < 0.001 |
| **Age Group** | ≤ 50 | 313 | -7.1 | 424 | -10.3 | < 0.001 |
| | > 50 | 71 | -5.9 | 91 | -9.1 | 0.092 |
| **Race** | White | 279 | -6.7 | 386 | -10.3 | < 0.001 |
| | Black | 66 | -5.5 | 75 | -7.8 | 0.244 |
| | Other[a] | 39 | -8.8 | 54 | -11.0 | 0.407 |
| **Type of Episode** | Manic | 240 | -6.5 | 321 | -10.4 | < 0.001 |
| | Mixed | 144 | -7.4 | 194 | -9.7 | 0.044 |
| **Rapid Cycling** | No | 305 | -7.3 | 415 | -9.9 | 0.002 |
| | Yes | 79 | -5.5 | 100 | -10.6 | 0.001 |

In the **2 studies CN138009 and CN138074** pooled data LOCF, efficacy sample: The mean change from baseline in the patients with psychotic features at baseline was -4.97 in the placebo group and -12.25 in the aripiprazole group (p=.007). The mean change from baseline in the patients without psychotic symptoms was -5.90 in the placebo group and -10.50 in the aripiprazole group (p<0.001).

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/s/
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Teresa Podruchny
9/29/04 07:58:24 AM
MEDICAL OFFICER

Paul Andreason
9/29/04 09:47:35 AM
MEDICAL OFFICER
I recommend that supplement 002 be approved. Please see my memo to the file.

**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:** April 15, 2004

**FROM:** Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

**SUBJECT:** Aripiprazole in the Acute Treatment of Manic and Mixed Episodes in Patients with Bipolar Disorder Type I

**TO:** File, NDA 21-436 Supplements SE1-002 (b) (4)
[Note: This memo should be filed with the June 23, 2003 original submission of this NDA.]

## 1.0 BACKGROUND

Aripiprazole is a partial agonist at D2 and 5-HT1A receptors and an antagonist at 5HT2 receptors. This class of compounds previously referred to as "atypical antipsychotics" is now referred to as "dopamine system stabilizers," based on the hope that they will permit sufficient nigrostriatal DA activity to prevent EPS while at the same time reducing excessive DA activity in the mesolimbic pathways.

Abilify was approved for the treatment of (b) (4) schizophrenia on 11-15-02. Additionally, the Division approved supplemental NDA 21436-SE6-001 that focused on aripiprazole's use in the longer-term treatment of schizophrenia on August 28, 2003. Supplement 006 included the Division's required WARNING section language on the risk of diabetes mellitus and hyperglycemia. Supplement 006 was approved on April 8, 2004. Division approved labeling from supplement 006 is the basis document from which draft labeling for supplements 002 (b) (4).

Supplements SE1-002 (b) (4) constitute the sponsor's NDA supplement supporting the use of aripiprazole in the acute treatment of bipolar mania. (b) (4) Supplement 002 includes three 3-week placebo controlled trials of aripiprazole (CN138007, CN138009 and CN138074).

(b) (4)

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee

(PDAC).

Dr. Robert Temple of ODE-1 was briefed on these two supplements on March 29, 2003. Our preliminary conclusions presented in that briefing have not changed since that date.

## 2.0 CHEMISTRY

As aripiprazole tablets are already approved, there were no CMC issues requiring review for this NDA.

## 3.0 PHARMACOLOGY

As aripiprazole tablets are already approved, there were no pharm/tox labeling issues requiring review prior to an action for these NDA supplements.

## 4.0 BIOPHARMACEUTICS

As aripiprazole tablets are already approved, there were no biopharmaceutics issues requiring review for this NDA.

## 5.0 CLINICAL DATA

### 5.1 Efficacy Data

#### 5.1.1 Overview of Supplement 002

Supplement 002 consists of three completed 3-week placebo controlled trials of aripiprazole (CN138007, CN138009 and CN138074) (b) (4) . CN138007 was a 3-week, placebo controlled, multiple fixed dose study of aripiprazole that failed to show superiority over placebo in the acute treatment of mania. (b) (4)

Studies 009 and 074 were both pivotal 3-week, placebo controlled flexible dose studies that, on face, supported the efficacy of aripiprazole in the acute treatment of bipolar mania. Teresa Podruchny, MD was the primary clinical reviewer and Yeh-Fong Chen, PhD was the primary statistical reviewer. Both agreed with some reservation that the studies supported the efficacy of aripiprazole in the acute treatment of bipolar mania; however, Dr Podruchny felt that study 009 could only support a 2-week as opposed to the 3-week claim that the sponsor sought.

##### 5.1.1.1 Overview of Study CN138009

CN 138009 was, as the title implies, was " A Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Flexible Doses of Aripiprazole in the Treatment of Hospitalized Patients with Acute Mania" 40 Investigators from 38 U.S. centers randomized 262 patients: 132 to placebo and 130 to aripiprazole. At the end of week 2, there was a forced discontinuation of patients who failed to respond as defined by a CGI-BP change from preceding phase (mania) of 4-7. Patients who failed to respond were dropped from blinded treatment and offered open-label aripiprazole for week 3. The primary efficacy variable was the mean change from baseline to week 3 on YMRS using a LOCF analysis of the ITT dataset. This was evaluated using ANCOVA with an adjustment for baseline score and a control for study center.

**Recommendations and Conclusions on Study 009**

The sponsor concludes that there is a significant benefit of aripiprazole over placebo treatment by the primary efficacy analysis (p=0.002). This statement is true and I agree that the study supports the claim with the following caveats:

- According to Ni Khin, MD of DSI, data from Drs. Coskinas and DeSilva were classified as VAI-RR with deficiencies such as the failure to obtain serum lithium or divalproex levels on six subjects and the failure to report headache or diarrhea in four subjects. Dr. Rubenfaer's site was classified as VAI with deficiencies including failure of the site to obtain lithium levels on two patients and randomizing patients with positive drug screens without obtaining approval from the sponsor. Dr. Khin recommended that the Review Division consider exclusion and reanalysis of data from the subjects who did not meet all eligibility criteria and discussed with me her concern regarding the possibility of more widespread protocol violations. She recommended a re-examination of the data for protocol violations at sites other than those inspected. Otherwise, her review concludes that data from the centers inspected appear acceptable for use in support of this NDA. Some of the protocol violations were likely to have affected individual patient clinical response. I concur with Dr. Podruchny and Dr. Khin of DSI that the sponsor should re-analyze this study excluding these patients to examine the effect of these patients on the study outcome. I concur with Dr Podruchny that this re-analysis focus on excluding protocol violations in patients who did not have baseline labs to check therapeutic levels, patients with benzodiazepine use within 4 hours of rating scales or patients with excessive benzodiazepine use within 1 day of scales, perhaps patients with anticholinergic drugs within 4 hours of scales, patients with positive drug tests at randomization or during the study, and patients who started the study within 30-days of taking fluoxetine or within 14 days of taking other anti-depressants.

- Dr Podruchny notes there is no evaluation of the contribution of the presence or absence psychotic symptoms to the outcome of the study. This kind of analysis is essential in the evaluation of this drug class for the treatment of bipolar mania.

- Dr Podruchny argues that study 009 be described as a two week study as opposed to a three week study. She bases this recommendation on the forced discontinuation based on clinical improvement and the discrepant outcome of the LOCF and OC data. Placebo patients in the OC analysis were actually better than their aripiprazole treated OC counterparts at the three week point. Since the forced discontinuation could potentially bias the study by carrying forward poor scores of placebo treated patients that were potentially improving, we looked at week-2 LOCF data and found that aripiprazole showed significant improvement over placebo prior to the forced discontinuation. How we end up describing study 009 in labeling is somewhat moot if study 074 is positive. Since study 074 lacks the forced discontinuation, it is a bona fide 3-week study, and the duration of the proposed claim would be considered 3-weeks based on study 074. If the results of the above suggested exploratory analyses on protocol violations and contribution of psychotic symptoms do not significantly detract from the results of study 009, then I think that we can describe it as a three week study since it would remain positive at the protocol stated primary analysis endpoint.

- [redacted] (b) (4)

[redacted]

### 5.1.1.2 Overview of Study CN130974

CN 138074 was as the title implies, "A Multicenter, Randomized, Double-Blind Study of Aripiprazole Versus Placebo in the Treatment of Acutely Manic Patients with Bipolar Disorder." 29 U.S. Investigators at 29 sites; randomized 272 patients to either placebo (n=135) or aripiprazole (n=137). There was no forced discontinuation at week 2 as in study 009.

**Conclusions and Recommendations on Study 074**

- The primary efficacy analysis plan was the same as that in study CN138009, which was the LOCF analysis of the mean change in YMRS total score from baseline to end of week 3. Aripiprazole was significantly more effective than placebo on the analysis of the primary efficacy variable ($p<0.001$).

- The sponsor specified four key secondary variables; response rate, mean change from baseline in the CGI-BP Severity of Illness Score (mania), mean change from baseline in the PANSS Hostility Scale, and mean change from preceding phase score (mania). A hierarchical testing procedure was used for the analysis of key secondary variables and followed in sequence, as listed above, after the primary efficacy measure analysis was found statistically significant at $p \leq 0.05$. Analysis was to stop with the first comparison that failed to reach statistical significance. The analysis of these variables demonstrated a statistically significant difference in favor of aripiprazole on all key secondary variables; [redacted]

- Study 074 shares two similar potential problems with study 009 that need to be explored prior to potential approval of this claim: there is no evaluation of the contribution of the presence or absence psychotic symptoms to the outcome of the study, and there are several potentially significant protocol violations that should be differentially dropped in an exploratory analysis of their affect on final YMRS mean group values.

[redacted]

[redacted]

(b) (4)

(b) (4)

## 5.2 Safety Data

Teresa Podruchny, MD was the primary safety reviewer for supplements 002 (b) (4) Generally speaking, the safety profile of aripiprazole in patients with bipolar mania was qualitatively similar to that of patients with schizophrenia. There appear to be some differences in the reporting rates of some of the adverse events. The sponsor pools the controlled trials of schizophrenia and bipolar mania into one adverse event table in their draft labeling. (b) (4)

(b) (4)

(b) (4)

**Seizure**- The incidence of seizure in the bipolar mania studies was [redacted] vs. placebo [redacted] Both of these rates are higher than the reported seizure incidence in the schizophrenia studies [0.1% (1/926)]. Though the seizure rates are [redacted] higher in the aripiprazole treated bipolar manic patients over the schizophrenic patients, this still only represents one more patient in the aripiprazole treated bipolar manic population over the placebo or aripiprazole treated schizophrenic population. In other words, I find it hard to be convinced that this represents a true signal for increased seizure risk with aripiprazole treatment in the bipolar manic population.

**Orthostasis**-The incidence of orthostatic hypotension associated events from short-term, placebo-controlled trials in bipolar mania [redacted] on ABILIFY included: orthostatic hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%, aripiprazole 0.5%), and syncope (placebo [redacted], aripiprazole [redacted]). The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo (14% among aripiprazole-treated patients and 12% among placebo-treated patients, and in bipolar mania: 3% among aripiprazole-treated patients and 2% among placebo treated patients.)

**6.0 World Literature**
A world literature search was performed by the sponsor and reviewed by Dr. Podruchny. Dr Podruchny also performed a MEDLINE search for aripiprazole treatment associated safety data. Both the sponsor and Dr. Podruchny report found nothing that would adversely affect conclusions about the safety of aripiprazole.

**7.0 Foreign Regulatory Action**
To my knowledge, aripiprazole is not approved for the treatment of bipolar mania anywhere at this time.

**8.0 Psychopharmacological Drugs Advisory Committee (PDAC) Meeting**
As noted above we did not take this supplement to PDAC.

**9.0 DSI Inspections**
As noted above DSI inspections were performed as part of the review of this submission. According to Ni Khin, MD of DSI, data from Drs. Coskinas and DeSilva were classified as VAI-RR with deficiencies such as the failure to obtain serum lithium or divalproex levels on six subjects and the failure to report headache or diarrhea in four subjects. Dr. Rubenfaer's site was classified as VAI with deficiencies including failure of the site to obtain lithium levels on two patients and randomizing patients with positive drug screens without obtaining approval from the sponsor. Dr. Khin recommended that the Review Division consider exclusion and reanalysis of data from the subjects who did not meet all eligibility criteria and discussed with me her concern regarding the possibility of more widespread protocol violations. She recommended a re-examination of the data for protocol violations at sites other than those inspected. Otherwise, her review concludes that data from the centers inspected appear acceptable for use in support of this NDA. Some of the protocol violations were likely to have affected individual patient clinical response.

I concur with Dr. Khin of DSI that the sponsor should re-analyze both study 009 and study 074 excluding these patients to examine their effects on the study outcome.

## 10.0 Labeling and Approvable Action Letter for Supplement 002 (b) (4)

### 10.1 Labeling for Approvable action Letter

Draft labeling for approvable claims along with imbedded recommendations to the sponsor for draft labeling modifications are attached to these action letters.

### 10.2 Foreign Labeling

To my knowledge, aripiprazole is not approved for the treatment of bipolar mania anywhere at this time.

## 11.0 Conclusions and Recommendations

### Supplement 002

I believe that the sponsor has performed studies that may ultimately support the approval of a claim that aripiprazole is effective in the treatment of acute manic and mixed episodes in Bipolar Disorder. I therefore recommend that the Division issue an Approvable Action Letter for Supplement 002.

In order to reach final approval the sponsor needs to adequately respond to the Review Team's following questions and make appropriate changes in draft labeling.

- What does the presence or absence of psychotic symptoms have on the efficacy outcome of studies 009 and 074? We were not able to find an analysis that examined this interaction in the study reports.
- What is the effect on the outcomes of studies 009 and 074 of deleting patients with potentially clinically significant protocol violations from the analysis of the primary efficacy variable?
- We were unable to find any record in the original protocol, subsequent amendment, or administrative letter to the Division designating key secondary efficacy variables for study 009 prior to breaking the data blind. Does this record exist?
- The sponsor pools the controlled trials of schizophrenia and bipolar mania into one adverse event table in their draft labeling. (b) (4)
- (b) (4)


(b) (4)


(b) (4)

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/s/

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Paul Andreason
4/15/04 10:56:26 PM
MEDICAL OFFICER

# NDA 21436S002/ (b) (4)

# Sponsor: Otsuka-Bristol-Meyers Squibb

# Date Submitted: June 23, 2003

# User Fee Date: April 23, 2004

# Date Review Completed: April 14, 2004

# Reviewer: Teresa A. Podruchny, M.D.

# ***Table of Contents***

# Clinical Review for NDA 21-436

## *Executive Summary*

## I. Recommendations

### A. Recommendation on Approvability

I recommend that the Division consider an approvable action on supplemental NDA 21436/S002. This recommendation is contingent upon data re-analyses of both pivotal trials yielding significant results as outlined in the body of this review. With this said, it is my opinion that the data of study CN138009 provide support for two weeks of efficacy in acutely manic patients and that the data of study CN138074 provide support for both two and three weeks.

(b) (4)

### B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The sponsor has been issued a Pediatric Written Request and is in the process of implementing these studies.

## II. Summary of Clinical Findings

### A. Brief Overview of Clinical Program

The safety and efficacy of aripiprazole in the treatment of manic patients have been investigated in 8 completed phase 3 clinical trials: five 3-week placebo-controlled studies (CN138007, CN138009, CN138074, (b) (4) and (b) (4); one 26-week haloperidol controlled study, CN138008; one long term maintenance open-label study, CN 138037, and one long term maintenance placebo-substitution study, CN 138010.

The overall development program for aripiprazole includes studies in schizophrenic patients and Alzheimer' Disease.

### B. Efficacy

**S002:** Contingent upon statistically significant results after the requested re-analyses, the primary efficacy data from trial CN138009 and CN138074 meet the pre-agreed criteria for

efficacy and the results indicate that aripiprazole offers some utility over placebo in the treatment of acutely manic or mixed Bipolar I patients.

The low retention seen in CN138009, a three week trial, is somewhat bothersome and patients are not "well" upon study termination. However, those in the study and taking aripiprazole are doing better than the placebo patients and the difference likely is clinically meaningful. These results may reflect the difficulty in treating this population the robustness of the drug or some combination thereof. For these reasons, I believe the data can be viewed as supportive of some utility in the acute treatment of bipolar patients, again pending the results of reanalysis. (b) (4)

In study CN138074, the retention rates are about equal (by LOCF) between groups and just over 50%. Again, this may reflect the difficulty in treating these patients or it may reflect the actual robustness of the drug or some combination thereof. However, this study demonstrated efficacy at both weeks 2 and 3 by LOCF and OC analysis on the primary endpoint. Additionally, the four key secondary efficacy measures were all statistically significant in favor of aripiprazole.

Study CN138007, the only fixed dose study the sponsor completed is negative. The mean changes at week three are higher in all groups than those seen in CN138009 and CN138074.

(b) (4)

### C. Safety

There were two deaths in the acute bipolar mania trials. One of these patients had not taken study medication. One patient died 5 days after his last dose of medication from an overdose of hydrocodone on day 8. This death is not likely directly attributable to aripiprazole although it is possible continuing akathisia, which possibly was drug related versus part of his illness, could have contributed to this event.

The incidences of treatment emergent serious adverse events in the four pooled studies were similar for placebo and aripiprazole patients at 5.6% to 5.8%. Reaction manic occurred in slightly more aripiprazole patients (2.6% versus 2.2%) than the placebo patients. One "risk of suicide attempt" and two overdoses (anti insomnia medication, hydrocodone) occurred in the aripiprazole patient group. None occurred in the placebo group.

In the four pooled studies, the percentages of patients discontinuing secondary to a treatment emergent adverse event were 10.9% of the aripiprazole patients and 9.5% of the placebo patients.

Two of these events occurred at ≥ 2% in the aripiprazole group; reaction manic (2.5% versus 0.7%) and akathisia (2.3% versus 0.5 %).

In the four pooled placebo controlled trials, common and drug related adverse events as defined as occurring in at least 5% of the aripiprazole treated patients and at least 2x the incidence of the placebo group, were akathisia (15% versus 3.4%), accidental injury (5.8% versus 2.7%), and extrapyramidal syndrome(5.1% versus 2.2 %). Constipation, somnolence, and vomiting occurred at almost this level. Hyper-tension occurred in 3.0% of the aripiprazole patients versus 1.2% of the placebo patients.

More aripiprazole treated patients than placebo treated patients experienced a PCS increase in creatine phosphokinase with the median percent change higher in the placebo group by > 2 fold (15.7% versus 6.1%). Two aripiprazole treated patient discontinued a study secondary to either hypotension or orthostatic hypotension. No aripiprazole treated patient in this study pool experienced a QTcE >450msec. No patients in the acute trials discontinued secondary to EKG abnormalities.

Post marketing data suggest that anaphylaxis, laryngospasm, and torticollis have been reasonably associated with the use of aripiprazole and may be drug related. Future reporting of events such as DVT/PE and pancreatitis should be followed closely by the sponsor. A case of hyperammonemia and severe encephalopathy is inconclusive and cannot reasonably be directly attributed to drug.

### D. Dosing

Contingent upon the primary efficacy measures remaining positive for trials CN138009 and CN138074 after re-analyses, dosing recommendations are a starting dose of 15mg daily, titrated up to 30 mg per clinical response and tolerability.

### E. Special Populations

Neither supplement included studies of aripiprazole in special populations.

# *Clinical Review*

## I. Introduction and Background

### A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Aripiprazole, Abilify™, is an atypical antipsychotic approved in the U.S. for use in the treatment of the signs and symptoms of schizophrenia. It is a partial $D_2$ agonist; acting as an agonist in an animal model of dopaminergic hypoactivity and an antagonist in animal models of dopaminergic hyperactivity. Aripiprazole also is a 5-$HT_{1A}$ partial agonist and a 5-$HT_{1A/1c}$ antagonist.

### B. State of Armamentarium for Indication(s)

Drugs approved for use in the treatment of acute mania are lithium (mood stabilizer), valproate (anticonvulsant), and more recently, the atypical antipsychotics, olanzapine, quetiapine, and risperidone. (b) (4)

### C. Important Milestones in Product Development

The sponsor notes that aripiprazole has not been withdrawn from the market in any country. As of June 2, 2003, aripiprazole has been approved for marketing in the following countries:

- Mexico (Abiligize™, July 17, 2002 for schizophrenia and schizoaffective disorder)
- Brazil (April 11, 2003)
- USA (Abilify™, November 15, 2002, August 28, 2003, schizophrenia)
- Puerto Rico (November 25, 2002)
- Australia (May 21, 2003)
- Peru (May 20, 2003)

Marketing applications are under review:

- EU (submitted December, 2001)
- Switzerland (submitted March, 2002)
- Turkey (submitted January 07, 2003)
- Japan (submitted March 26, 2003)
- Malaysia (submitted May 3, 2002)

**History:** In September of 1999, Bristol-Myers Squibb (BMS) and Otsuka entered a co-development agreement with respect to the development of aripiprazole . This resulted in a development program to allow for additional indications beyond schizophrenia. In February of 2000, the sponsor (BMS and Otsuka) and the Division met to discuss the planned development for indications other than schizophrenia which included a program for acute mania and a relapse prevention study in bipolar disorder.

However, the original NDA submission of September 24, 2001 contained only the schizophrenia indications as one key bipolar study, CN138007, did not show efficacy on the primary efficacy variable.

A pre-NDA meeting was held between the Division and BMS on May 9, 2003 to discuss both efficacy and safety database issues relative to the mania submission(s). Meeting minutes reflect that at the time of this meeting, studies CN138007, CN138008, CN138009, and CN138074 were complete, study (b) (4), (b) (4)

The Division noted that, on-face, the program appeared sufficient to support short-term efficacy but that ultimately this was a review issue. (b) (4)

(b) (4)

On June 23, 2003, the sponsor submitted supplements 002 (b) (4), the subjects of this review.

(I refer the reader to the original NDA review by Drs. G. Dubitsky and R.Harris for a more detailed history of the development program acknowledge using this review as a source of information. The foreign marketing information above essentially was duplicated from the sponsor's submission.)

### D. Other Relevant Information

None to discuss.

### E. Important Issues with Pharmacologically Related Agents

Aripiprazole is a member of a class of drugs referred to as atypical antipsychotics. In general, these drugs are associated with fewer extrapyramidal side effects and are thought by some to possibly present a decreased risk of neuroleptic malignant syndrome when compared to older "typical" antipsychotics. Recently, language has been added to this class of drugs to describe the potential for hyperglycemia and diabetes mellitus. Additionally, clozapine carries a box warning for agranulocytosis.

## II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

**A. Statistical Review and Evaluation:** Yeh-Fong Chen, Ph.D. was the primary statistical reviewer for both supplements 002 (b) (4). Her review of supplement 002, the placebo-controlled trials in support of the acute mania indication, is complete. She concluded that

CN138007 is a failed study and that CN138009 has significant results on the primary endpoint by LOCF analysis. However, she notes that the interpretation of these significant findings should be considered due to the OC analysis which numerically favored placebo and which resulted from a large number and unbalanced dropouts at the end of visits. (b) (4)

Her review indicates that study CN138074 clearly demonstrated efficacy for the treatment of acute manic or mixed episodes in patients with a diagnosis of Bipolar I Disorder. Four secondary measures (response rate, CGI Severity Score (mania), PANSS Hostility sub-scale and CGI-BP Change from Preceding phase (mania) were amended as key secondary measures via a protocol administrative letter (Letter 1). Significant results were shown for all four key secondary endpoints.

(b) (4)

**B. DSI Clinical Site Inspections:** The Division of Scientific Investigations (DSI) conducted three domestic inspections: Dr. A. Cutler (PI site 009, CN138009 and site 018, CN138074), Drs. E. Coskinas and H. DeSilva (PIs site 023,CN138009 and site 028, CN138074), and Dr. L. Rubenfaer (PI site 003, CN138074). The formal results of these inspections were reported by Ni Khin, M.D., DSI Medical Officer, in the Clinical Inspection Summary dated March 24th, 2004 and are summarized below.

Dr. Cutler's data was deemed overall to appear acceptable and was classified as VAI (minor deviations from regulations, data acceptable). Data from Drs. Coskinas and DeSilva were classified as VAI-RR with deficiencies such as the failure to obtain serum lithium or divalproex levels on six subjects and the failure to report headache or diarrhea in four subjects. Dr. Rubenfaer's site was classified as VAI with deficiencies including failure of the site to obtain lithium levels on two patients and randomizing patients with positive drug screens without obtaining approval from the sponsor.

Dr. Khin recommended that the Review Division consider exclusion and reanalysis of data from the subjects who did not meet all eligibility criteria and discussed with me her concern regarding the possibility of more widespread protocol violations. She recommended a re-examination of the data for protocol violations at sites other than those inspected. Otherwise, her review concludes that data from the centers inspected appear acceptable for use in support of this NDA.

**C. Chemistry Review and Evaluation:** Sherita McLamore was the primary reviewing chemist for supplements 002 (b) (4). The drug product was found adequate in all categories reviewed and she recommended this supplement be approved.

**D. Biopharmaceutics Review and Evaluation:** The sponsor notes that no clinical pharmacology studies were conducted specifically to support the indication of acute bipolar mania. Dr. Kofi Kumi notes there are no proposed changes in the clinical pharmacology and bio-pharmaceutic sections of the approved label.

**E. Pharmacology-Toxicology Review and Evaluation:** (b) (4) Email from Dr. Lois Freed, a pharmacology-toxicology Team Leader in this Division, indicates that there are no pharmacological-toxicological issues that would impact actions taken by the Division.

## III. Human Pharmacokinetics and Pharmacodynamics

### A. Pharmacokinetics

There was no new pharmacokinetic information presented for review in this sNDA. However, there were three drug-drug interaction studies in the original NDA which have pertinence to the treatment of Bipolar I Disorder.

As per the review of the original NDA, drug interaction studies of aripiprazole with lithium, divalproex, and carbamazepine were conducted as part of the profile of aripiprazole in support of the original NDA application. These studies were conducted in patients with schizophrenia or schizoaffective disorder. Neither co-administration of lithium (1200-1800 mg/day) nor valproate (350-1500mg/day) had clinically significant effects on the pharmacokinetic profile of aripiprazole. Co-administration of carbamazepine 200mg twice a day in patients with schizophrenia or schizoaffective disorder increased the clearance of aripiprazole.

### B. Pharmacodynamics

There is no new pharmacodynamic information presented for review in this sNDA.

## IV. Description of Clinical Data and Sources

### A. Overall Data

The development program for mania consisted of 8 phase 3 clinical studies: Five 3-week placebo-controlled studies (CN138007, CN138009, CN138074, (b) (4) one 26-week active controlled study, CN138008; one long term maintenance open-label study, CN 138037, and one long term maintenance placebo-substitution study, CN 138010.

Efficacy results for trials CN 138007, CN 138009, CN 138074 (b) (4) are presented for supplements 002 (b) (4). Safety results from these studies and from (b) (4), CN138037, and CN 138010 are presented. The ISS and Update provide safety data for all aripiprazole treated patients in clinical trials, pooled data from studies CN138007, CN138009, (b) (4), and CN138074, and data from study CN138008. The focus of the safety review performed for this submission was the data from the bipolar mania trials and tabular line listings of deaths and serious, non-fatal adverse events as presented from the PSUR.

**B. Tables Listing the Clinical Trials**

| Trial | Design | Description | Number Patients | Efficacy Results |
|---|---|---|---|---|
| **138007** | Fixed dose<br>R, DB, PC | Hospitalized, Bipolar I, manic or mixed, YRMS ≥ 20, DB up to 3 weeks[a]<br><br>3 weeks with forced dc at 2 weeks based on CGI criteria | Enrolled=534<br>Randomized=401<br>131=15mg ari<br>136=30mg ari<br>134=placebo | No difference between groups on primary eff<br>Completed: 40% placebo, 43% ari 15mg, 40% ari 30mg |
| **138008 Non-IND** | Non-fixed, haloperidol versus ari<br>R, DB,<br>No placebo | Hospitalized or outpatient, Bipolar I manic or mixed, rapid cycling excluded, YRMS ≥ 20<br><br>3 phases: weeks 1-3 weeks 4-12 phase, extension weeks 13-26<br>forced dc at week 3 based on CGI criteria | Enrolled=372<br>Randomized=347<br>H: n=172<br>ari: n=175 | Primary 12 weeks: on-face, Ari won<br>Seconday: 3 weeks: no stat difference<br>Completed 1st 3 weeks: 55.2% H; 76.6% ari<br>12 weeks: 29.1% H, 50.9% ari |
| **138009** | Non-fixed dose<br>R, DB, PC | Hospitalized, Bipolar I manic or mixed, YMRS≥ 20, DB up to 3 weeks[a]<br><br>Forced dc week 2 per CGI | Enrolled=358<br>Randomized=262<br>130 =Ari 15 or 30mg<br>132 =Placebo | Prim:on face, ari wins<br>Completed 3 weeks<br>DB: Ari=42%, Placebo=21% |
| **138037** | Flexible dose, open label, long-term, | Bipolar I manic/ mixed who switched to open label in an acute study 138007,138009, (b) (4)<br><br>Stabilization =6-18 weeks<br>maintenance phases= 26 weeks<br>extension =50 weeks | Entered stabilization: 25<br>Dc'd stab:15<br>Completed stab:10<br>Entered Maint:8<br>Completed Maint:3<br>Entered Ext:2<br>Completed Ext:1 | Open label study |
| (b) (4) | | | | |
| **138074** | Non-fixed dose<br>R, DB, PC | Hospitalized, Bipolar I, manic or mixed, YMRS ≥ 20, up to 3 weeks of DB<br><br>No forced dc at week 2 | Enrolled=353<br>Randomized=272<br>137 = ari<br>135 = placebo | p≤ 0.01 on primary efficacy, on face ari wins<br>Completed db: 52% placebo, 55% ari |

| | | | | |
|---|---|---|---|---|
| **138010** | Non-fixed dose, R, DB, PC | In/or outpatients open label stabilization=6-18 weeks, if eligible-randomized to Maintenance=26 weeks Extension=74 weeks | Enrolled open label=633 Entered open label=567 Randomized: 83= placebo, 78= ari | P<0.02 on primary efficacy , on face ari wins 1° endpoint: time randomized to relapse in maint |
| [redacted] (b) (4) | | | | |

R=Randomized; DB=Double blind, PC= placebo-controlled, dc=discontinuation, YMRS-Young Mania Rating Scale, CGI=Clinical Global Impression Scale, Ari=aripiprazole, H=Haloperidol,

### C. Postmarketing Experience

The first 6-month periodic update safety report (PSUR) for aripiprazole was in March 13, 2003 and covered clinical and spontaneous reporting from July 17, 2002 to January 16, 2003. The 120-day safety update submission contained a 2nd PSUR which covered the period of January 17th, 2003 through July 16, 2003.

### D. Literature Review

The sponsor notes that a literature search was conducted for published articles from July 3, 2002, through March 13, 2003, pertaining to the safety of aripiprazole. Ms. Yuri Takagaki and Ms. Chuang conducted searches of 14 online databases, none full text, which resulted in 82 articles. MEDLINE and BIOSIS were among the databases searched. Drs. Margaretta Nyilas and Joy Parris signed certified statements that these articles had been reviewed in detail for safety data relevant to aripiprazole and that there were no findings that would adversely affect conclusions about the safety of aripiprazole with regard to this supplement.

I conducted a limited pub-med literature search using the term aripiprazole and the terms liver or hepatic or ammonia or ammonemia or encephalopathy. No articles were found that reported serious adverse events related to these terms.

## V. Clinical Review Methods

### A. How the Review was Conducted

Study reports for studies CN138007, CN138008 (12 week), CN138009, [redacted] (b) (4), CN138074, [redacted] (b) (4), as found in the June 23, 2003 submission, and the final study report for [redacted] (b) (4) submitted October 13, 2003 in the 120 day update were utilized in the preparation of this document.

The ISS-ISE, the 120-day update submitted for supplements 002 (b) (4) and some of the composite efficacy data from the placebo-controlled trials, as found in the ISS for supplement 005 dated January 01, 2004, were used in this review. CRT(.xpt) and CRF datasets, proposed labeling, various files found within the CLINSTAT-OTHER file, the OTHER file and the SUMMARY file from the June 23, 2003 submission, were reviewed. Narratives and additional information regarding patient disposition in the form of line listings sent by the sponsor were referred to and reviewed as needed.

Dr. Greg Dubitsky, a senior reviewer in this Division, reviewed and wrote sections of this review: the Special Issues, Orthostatic Changes section, the majority of the QT section, and the safety information for the blinded study. Additionally, he performed quality control audits.

### B. Overview of Materials Consulted in Review

Supplement 002 (b) (4) were electronic submissions. Meeting minutes of the May 2003, pre-NDA meeting as filed under IND 42,776 and the review of the original NDA submission were consulted to review regulatory history. Informal and formal consultation with the statistics reviewer, Dr. Chen, was utilized as was informal consultation with Dr. G. Dubitsky, a senior medical officer in this Division and one of the authors of the review of the original NDA.

### C. Overview of Methods Used to Evaluate Data Quality and Integrity

The sponsor notes that BMS conducted on-site monitoring by the clinical staff and that data from 16 investigational sites were audited for the "purpose of determining the validity of the study processes and methodologies employed to generate and document study data." This included verification of case report form data against supporting documentation for selected subjects.

DSI/OHRP inspections were conducted and the report results are summarized in section II B. of this document.

Greg Dubitsky, M.D., performed quality control checks of the safety data in the form of audits of random patients in trials CN138007, CN138009, CN138074 and CN138008, to compare adverse events and serious non-fatal adverse events as per the CRF data to the narrative to the data found in the line listings of JMP files. The data were acceptable. A list of the audited patients may be found in Appendix B of this document.

The COSTART Dictionary terms for Trials CN138007, CN138008, CN138009, CN13074, (b) (4) were reviewed for coding of Investigator terms to Primary terms using the JMP files issqadr2.xpt and issqadr3.xpt. Overall, it appears no major adverse events would be missed in this coding system. The results may be found in Appendix B of this review.

SAS transport files were submitted to the Division of Biometrics and were analyzed with respect to the efficacy variables.

### D.Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor noted trials CN138007, CN138008, CN138009, CN138074, and CN138010 were conducted in compliance with Good Clinical Practices (GCP) and in accordance with 21CFR part 50, IRB/IEC regulations of 21 CFR 56 and principles of the Declaration of Helsinki.

Signed certifications were submitted that noted that the use of persons listed as debarred by the FDA (as of April 9, 2003) did not occur in connection with the supplemental NDAs.

### E.Evaluation of Financial Disclosure

The sponsor requested statements of financial interests and arrangements from 419 investigators and 2790 sub-investigators involved with studies CN138-007, 008, 009, 1010, 037, (b) (4), 074, and (b) (4) 416/419 investigators responded by May 12, 2003. It is reported that no investigator had disclosable information. 2741/2790 of the sub-investigators submitted statements by the time this submission was written. It is reported that 6 had disclosable information with two of these either on multiple protocols or functioning at multiple sites within the same protocol. As the investigators were blinded, it is not likely that these significantly impacted the efficacy results.

## VI. Integrated Review of Efficacy

### A. Brief Statement of Conclusions

(b) (4)

**S002:** Contingent upon statistically significant results after the requested re-analyses, the primary efficacy data from trial CN138009 and CN138074 meet the pre-agreed criteria for efficacy and the results indicate that aripiprazole offers some utility over placebo in the treatment of acutely manic or mixed Bipolar I patients.

The low retention seen in CN138009, a three week trial, is somewhat bothersome and patients are not "well" upon study termination. However, those in the study and taking aripiprazole are doing better than the placebo patients and the difference likely is clinically meaningful. These results may reflect the difficulty in treating this population the robustness of the drug or some combination thereof. For these reasons, I believe the data can be viewed as supportive of some utility in the acute treatment of bipolar patients, again pending the results of reanalysis. (b) (4)

In study CN138074, the retention rates are about equal (by LOCF) between groups and just over 50%. Again, this may reflect the difficulty in treating these patients or it may reflect the actual robustness of the drug or some combination thereof. However, this study demonstrated efficacy

at both weeks 2 and 3 by LOCF and OC analysis on the primary endpoint. Additionally, the four key secondary efficacy measures were all statistically significant in favor of aripiprazole.

Study CN138007, the only fixed dose study the sponsor completed is negative. The mean changes at week three are higher in all groups than those seen in CN138009 and CN138074.

### B. General Approach to Review of the Efficacy of the Drug

(b) (4)

The submission for sNDA 21436 (b) (4) contained seven study reports. The study report for the longer term trial CN138010 was not reviewed. The focus of this review was on studies CN138009 and CN138074 as the two proposed positive studies and CN138007, which is negative. (b) (4) These study reports were reviewed briefly and are discussed in Appendix XIA of this document.

### C. Detailed Review of Trials by Indication

(b) (4)

(b) (4)

(b) (4)



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(b) (4)

## SUPPLEMENT 002: TRIALS CN1138007, CN138009, and CN138074

Three placebo-controlled trials were submitted; Trials CN138007, CN138009, and CN138074. Of these, CN138009 and CN138074 were non-fixed dose trials and CN138007 was a fixed dose study. Two other trials were started but not completed by the sponsor. (b) (4)

(b) (4)

**CN 138007** "A Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Two Fixed Doses of Aripiprazole in the Treatment of Hospitalized Patients with Acute Mania"

This study was conducted at 51 sites in the U.S., three in Mexico, and two in Argentina using 60 investigators. (The investigators are listed in a table in the appendix of this document.)

**Subjects:** 534 hospitalized Bipolar I patients with an acute manic or mixed episode and a baseline YMRS ≥ 20 were enrolled patients; 401 patients were randomized with 134 to placebo, 131 to 15-mg aripiprazole and 136 to 30 mg aripiprazole.

Exclusion criteria included:

- an Axis I diagnosis of a cognitive disorder or schizophrenia, or schizoaffective disorder
- not having had a previous manic episode or current episode of mania > 4 weeks
- lack of response to clozapine
- significant psychoactive or substance use disorder
- potentially therapeutic serum levels of lithium or divalproex sodium
- suicide risk
- seizure history
- the use, as protocol-specified, of other psychotropic medications.

**Baseline demographic** tables: Sponsor's tables, Table 8.3 and 8.4A:

**Table 8.3: Demographic Characteristics, Randomized Sample**

| Variable | | Placebo N = 134 | Aripiprazole 15 mg N = 131 | Aripiprazole 30 mg N = 136 | Total N = 401 |
|---|---|---|---|---|---|
| Age | Mean | 40.6 | 39.3 | 41.4 | 40.5 |
| (years) | Median | 40.5 | 39.0 | 42.0 | 40.0 |
| | Min - Max | 18.0 - 71.0 | 18.0 - 68.0 | 19.0 - 74.0 | 18.0 - 74.0 |
| | S. E. | 1.0 | 1.0 | 1.0 | 0.6 |
| Gender | Male | 65 (49) | 65 (50) | 62 (46) | 192 (48) |
| N (%) | Female | 69 (51) | 66 (50) | 74 (54) | 209 (52) |
| Race | White | 96 (72) | 99 (76) | 98 (72) | 293 (73) |
| N (%) | Black | 19 (14) | 19 (15) | 19 (14) | 57 (14) |
| | Asian/Pacific Islander | 0 | 1 (1) | 3 (2) | 4 (1) |
| | Hispanic/Latino | 17 (13) | 12 (9) | 16 (12) | 45 (11) |
| | Other | 2 (1) | 0 | 0 | 2 (< 1) |
| Weight (kg) | Mean | 84.8 | 88.8 | 84.8 | 86.1 |
| | Median | 80.6 | 85.1 | 81.3 | 81.9 |
| | Min-Max | 47.7 - 168.8 | 49.5 - 165.6 | 50.4 - 156.6 | 47.7 - 168.8 |
| | S.E. | 1.9 | 1.9 | 1.7 | 1.1 |
| | Missing | 5 | 4 | 2 | 11 |

Protocol CN138-007

**Table 8.4A: Psychiatric History of Bipolar Disorder, Randomized Sample**

| Variable | | Placebo N = 134 | Aripiprazole 15 mg N = 131 | Aripiprazole 30 mg N = 136 | Total N = 401 |
|---|---|---|---|---|---|
| Rapid Cycling | No | 104 (78) | 106 (81) | 109 (81) | 319 (80) |
| N (%) | Yes | 30 (22) | 25 (19) | 26 (19) | 81 (20) |
| | Missing | 0 | 0 | 1 | 1 |
| Type of Current Episode | Manic | 84 (63) | 77 (59) | 81 (60) | 242 (61) |
| N (%) | Mixed | 50 (37) | 54 (41) | 54 (40) | 158 (40) |
| | Missing | 0 | 0 | 1 | 1 |

Protocol CN138-007
Source: Appendix 8.4.2

**Design:**
Screening: 1-7 days and up to 14 with permission from BMS
Randomization:

- Eligible patients were randomized into a 3 week treatment phase of either a daily dose of 15 mg aripiprazole, 30 mg aripiprazole, or placebo.
- At the end of week 2, patients meeting CGI-BP severity scale (mania) ≤ 4 and CGI-BP Preceding phase (mania) ≤ 2 could be discharged and continue as outpatients.

- Patients not meeting these criteria remained hospitalized.
- Also at the end of week 2, there was a forced discontinuation of patients not improving as defined by CGI-BP change from preceding phase (mania) ≥ 4.

**Study conduct:**

- **Concomitant medications:** Patients were not allowed to use flouxetine within 4 weeks of randomization. Carbamazepine, valproic acid in any form, lithium in any form, neuroleptics, or other investigational drugs could not be used between baseline and the end of the study other than for tapering during the screening period.
- **Concomitant** benzodiazepine (lorazepam) use was allowed through day 10: up to 6mg/day on days 1-4, up to 4 mg/day on days 5-7, and up to 2mg/day on days 8-10. Lorazepam use was not allowed after day 10 and was not allowed within 4 hours of rating scales. EPS symptoms could not be treated in the screening period preceding randomization but could be treated as necessary with benztropine in the double-blind phase. No dose of an anticholinergic was to be given within 12 hours of rating scales. Generally, beta blockers and antihistamines were not allowed unless medically inappropriate to exclude.
- **Changes to the conduct of the trial:** There were six amendments and one administrative letter for this trial. The administrative letter addressed changes in the timing of an ECG and specified or clarified lab tests. Amendment 1 allowed for an optional collection of blood for pharmacogenomic banking at one site. Other amendments addressed changes such as in the allowable doses of lorazepam, adding IV midazolam for centers in Brazil, changing or clarifying safety data collection, and updating the CIB.

**Disposition:**

Of the 401 patients randomized, 216 (54%) completed 3 weeks of treatment and 185 (46%) discontinued early. The rates of completion were roughly the same for all three groups and are displayed in the sponsor-provided table below.

Aripiprazole
BMS-337039/OPC-14597

CN138-007
Clinical Study Report

**Table 8.1A: Disposition of Patients**

| Patient Status | Number (%) of Patients: Placebo | Aripiprazole 15 mg | Aripiprazole 30 mg | Total |
|---|---|---|---|---|
| **Enrolled Sample** | n/a | n/a | n/a | 534 |
| Baseline failures | n/a | n/a | n/a | 133 |
| **Randomized** | 134 | 131 | 136 | 401 |
| **Discontinued from Double-Blind Treatment** | 80(60) | 75(57) | 82(60) | 237(59) |
| Due to lack of response entered open-label aripiprazole[a] | 27(20) | 14(11) | 26(19) | 67(17) |
| Adverse Event | 9(7) | 20(15) | 9(7) | 38(9) |
| Lack of efficacy | 10(7) | 9(7) | 12(9) | 31(8) |
| Patient withdrew consent | 22(16) | 28(21) | 29(21) | 79(20) |
| Patient unreliability | 1(1) | 0 | 1(1) | 2(< 1) |
| Lost to follow-up | 3(2) | 3(2) | 4(3) | 10(2) |
| Other known cause[b] | 8(6) | 1(1) | 1(1) | 10(2) |
| **Completed Double-Blind Treatment** | 54(40) | 56(43) | 54(40) | 164(41) |

Protocol CN138-007

Source: Appendix 8.1.1[c]

[a] Patients not responding at Week 2, as indicated by CGI-BP Change from Preceding Phase (mania) score of four to seven, were placed on open-label aripiprazole.

[b] Other reasons for discontinuation may have included: pregnancy, other known cause (other), study terminated by sponsor, protocol violation, patient met withdrawal criteria, patient did not satisfy one or more screening criteria, or general inability to continue.

[c] Includes patients in double-blind and open-label treatment phases.

- **Use of concomitant medications** in the double-blind period safety sample: 91.73% of the placebo patients, 88.55% of the aripiprazole 15mg patients and 90.37 % of the aripiprazole 30mg patients used concomitant CNS drugs. The two most frequently administered CNS medication groups were anxiolytic medications and analgesic/antipyretic medications. Anxiolytic medication use was high in all groups (82% placebo; 79 % aripiprazole 15 mg; 86% aripiprazole 30mg). More aripiprazole-treated patients (18% for aripiprazole 15 and 30 mg) received an anticholinergic agent than placebo-treated patients (11%).
- **Protocol violations:** The sponsor submitted lists of protocol violations under multiple headings. These included missing or late informed consent documentation, randomization of patients with current manic episodes > 29 days, positive cocaine (9 aripiprazole, 3 placebo) or drug screens (multiple), missing lithium or valproic acid levels (about 17 aripiprazole and 10 placebo), lithium or valproic acid at or near randomization, other psychotropics at randomization, missing or positive pregnancy tests, missing or abnormal laboratory values or EKG measurements at screening, and prohibited or excessive medication use.

**Primary Efficacy:** The primary efficacy variable for the study was the mean change from baseline to week 3 on the YMRS as per ANCOVA.

The primary efficacy data is displayed as per the sponsor provided table, Table 10.



**Table 10: Summary of Efficacy Results at Endpoint, LOCF Data Set, Efficacy Sample**

| Variable | Treatment Group: Placebo | Aripiprazole 15 mg | Aripiprazole 30 mg |
|---|---|---|---|
| **PRIMARY EFFICACY ENDPOINT** | | | |
| Y-MRS | N = 130 | N = 127 | N = 129 |
| Mean Baseline | 28.27 | 27.94 | 27.83 |
| (95% CI) | (27.34, 29.20) | (26.99, 28.88) | 26.89, 28.77) |
| Change at Week 3 | -10.12 | -10.01 | -10.80 |
| (95% CI) | (-12.01, -8.24) | (-11.92, -8.09) | (-12.71, -8.90) |

There was no difference at any timepoint between aripiprazole at either dose and placebo by either LOCF or OC analysis. This data is contained in the sponsor's tables 10.1A and 10.1.B and is duplicated in Appendix B of this document.

**Conclusion:** Mean changes from baseline on YMRS scores were similar in all groups. There were no statistically significant differences on CGI-BP severity of illness (mania) or rate of discontinuation due to lack of efficacy or entry into the open-label phase between aripiprazole at either dose and placebo. This study does not demonstrate the efficacy of either dose of aripiprazole over placebo.

**CN 138009:** " A Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Flexible Doses of Aripiprazole in the Treatment of Hospitalized Patients with Acute Mania"

Sites: 40 Investigators from 38 U.S. centers (Investigators are listed in a table in the appendix.)

**Subjects:** The study population was intended to be similar to study CN138007.

- 18 years old and older with Bipolar I Disorder, acute manic or mixed episode requiring hospitalization, and YMRS ≥ 20.
- Exclusion criteria included: patients experiencing their first manic episode, patients with the current manic episode longer than 4 weeks, patients likely to need prohibited concomitant medications during the trial, patients with serum concentrations of lithium or divalproex > 0.6mmol/L or 50mcg/mL respectively, and patients with positive drug screen for cocaine. Patients with a + drug screen were to be discussed with BMS prior to randomization.
- At randomization, patients were not to have had the following: any recent treatment with a long acting antipsychotic with the last dose less than one full cycle plus 1 week, psychotropics within 1 day of randomization, fluoxetine treatment within the past 4 weeks, or ECT within the past 2 months unless cleared with BMS.
- Between the baseline visit and the end-of-study visit, patients could not use neuroleptics, fluoxetine, carbamazepine, lithium formulations, or valproic acid formulations.

- Concomitant lorazepam use was allowed in similar fashion as that of CN138007. No lorazepam use was allowed after day 10 and none was to be used within 4 hours before a scale. Otherwise, up to 6 mg/day on days 1-4, up to 4 mg/day on days 5-7, and up to 2 mg/day on days 8-10 were allowed. Anticholinergics were allowed in the double-blind period for the treatment of EPS (anti-cholinergic not to exceed 6mg/day of benztropine mesylate and none within 12 hours prior to efficacy or safety rating scales).
- Amendment #2 on March 28, 2000 increased the allowed doses of concomitant lorazepam from 2mg to 6mg on days 1 through 4, and from 1 mg to 4mg/day on days 5 through 7 and up and from none to 2 mg/day on days 8 through 10 and deleted the requirement that lorazepam not be administered within 4 hours of ratings and anti-cholinergic within 12 hours for the screening visit

**Design:** Similar to CN138007 except this is a flexible dose study.

- Screen 1-7 days. Amendment #3, July 20, 2000, extended the screening period up to 14 days, with BMS permission.
- Randomized to aripiprazole 30 mg daily (could decrease to 15mg if 30mg dose was not tolerated) or placebo.
- Hospitalized for a minimum of two weeks during the treatment phase. Amendment #3 (July 20, 2000) allowed patients whose symptoms of mania were much improved to be discharged from the hospital at the end of week 2. CGI-BP criteria were used: CGI-BP Severity (mania) $\leq 3$ AND CGI-BP Change from Preceding Phase (mania) score of $\leq 2$. Otherwise, if not meeting these criteria, the patient remained in the hospital.
- End of week 2: forced discontinuation: CGI-BP change from preceding phase (mania) of 4-7 were dropped from blinded treatment and offered open-label aripiprazole for week 3.
- Amendment #4, December 7, 2000: included allowance for patients to receive open-label aripiprazole at the end of week 2 if CGI-BP change from preceding phase scores $\geq 4$.
- Patients discontinued prior to week 2 due to lack of response or adverse events received one additional week of hospitalization for stabilization but did not go into other long term studies.

**Demographics:** 358 patients were enrolled with 262 randomized; 132 to placebo and 130 to aripiprazole. Patients were roughly similar with respect to the presence or absence of rapid cycling, the type of current episode, and age, gender, race, and body weight. Sponsor-provided tables of this data are below. It appears that baseline summary information regarding the presence or absence of psychotic symptoms and the length of time in the current manic episode was not provided.

**Table 8.3: Demographic Characteristics, Randomized Sample**

| Variable | | Placebo N = 132 | Aripiprazole N = 130 | Total N = 262 |
|---|---|---|---|---|
| Age | Mean | 40.5 | 40.5 | 40.5 |
| (years) | Median | 41.0 | 40.0 | 40.5 |
| | Range | 18.0 - 70.0 | 18.0 - 74.0 | 18.0 - 74.0 |
| | S. E. | 1.0 | 1.1 | 0.8 |
| Gender | Male | 55 (42) | 59 (45) | 114 (44) |
| N (%) | Female | 77 (58) | 71 (55) | 148 (56) |
| Race | White | 103 (78) | 95 (73) | 198 (76) |
| N (%) | Black | 20 (15) | 16 (12) | 36 (14) |
| | Asian/Pacific Islander | 1 (1) | 6 (5) | 7 (3) |
| | Hispanic/Latino | 5 (4) | 11 (8) | 16 (6) |
| | American/Alaskan Native | 1 (1) | 0 | 1 (0) |
| | Other | 2 (2) | 2 (2) | 4 (2) |
| Weight (kg) | Mean | 86.3 | 85.2 | 85.8 |
| | Median | 81.5 | 83.7 | 82.8 |
| | Min-Max | 46.8 - 184.5 | 47.7 - 147.1 | 46.8 - 184.5 |
| | S.E. | 2.1 | 1.8 | 1.4 |
| | Missing | 4 | 5 | 9 |

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**Table 8.4A: Psychiatric History of Bipolar Disorder, Randomized Sample**

| Variable | | Placebo N (%) N = 132 | Aripiprazole N (%) N = 130 | Total N (%) N = 262 |
|---|---|---|---|---|
| Rapid Cycling | No | 99 (75) | 102 (78) | 201 (77) |
| N (%) | Yes | 33 (25) | 28 (22) | 61 (23) |
| Current Episode | Manic | 83 (63) | 93 (72) | 176 (67) |
| N (%) | Mixed | 49 (37) | 37 (28) | 86 (33) |

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Source: Appendix 8.4.2

**End of Baseline Rating Scales:** Mean YRMS scores were similar across groups with the placebo mean at 29.1 (median 27.0) and the aripiprazole mean at 27.8 (median 26.0). The sponsor provided summary of this data may be found in Appendix B of this document.

**STUDY CONDUCT:**

- **Changes to the protocol:** There were 4 protocol amendments and one administrative letters. The first amendment, November 29, 1999, allowed for future pharmacogenomic analyses from randomized patients. The relevant parts of Amendments 2, 3, and 4 were discussed earlier. Amendment 4 also allowed day passes for days 10-21 with drug and alcohol screens upon return and eliminated the performance of a blood alcohol level at screening.
- **Unblinding:** The sponsor notes "No treatment codes were broken in this study."

**EFFICACY MEASURES:**

The primary efficacy variable was the mean change from baseline to week 3 on YMRS using the LOCF dataset. This was evaluated using ANCOVA with an adjustment for baseline score and a control for study center. Subgroup analyses were performed by gender using ANCOVA. Dropout cohort analysis plotting the change in YMRS score by treatment group was performed by grouping patients who had their last primary efficacy measure in the same week interval.

Key secondary measures were not defined in the protocol and were not determined at the pre-NDA meeting with the sponsor. Secondary efficacy analyses included the mean change from baseline to week 3 in the CGI-BP Severity of Illness (mania) score and the rate of discontinuation due to lack of efficacy or entry into the open-label aripiprazole phase at week 2 with a CGI-BP Change from Preceding Phase (mania) score of 4 to 7 by treatment group.

**CONCOMITANT THERAPY:**

The most frequently administered concomitant CNS drugs during double-blind therapy were anxiolytics (109/116 or 85.83% placebo and 108/117 or 85.04% aripiprazole and analgesic/antipyretics (81/116 or 63.78% placebo versus 85/117 or 66.93% aripiprazole). Sedative hypnotic use occurred in 10/116 (7.87% ) of the placebo patients and 12/117 (9.45%) of the aripiprazole patients. Anticholinergic use occurred in 6/116 (4.72%) of the placebo patients and 28/117 (22.05%) of the aripiprazole patients. Benztropine was the most commonly used anticholinergic.

**DOSING:** The mean week three aripiprazole dose was 27.38 mg.

**COMPLIANCE:** A summary of treatment compliance was not included with the study report.

**RESULTS:**

**Disposition:** 358 patients were enrolled with 262 randomized to double-blind treatment (132 placebo and 130 aripiprazole). 31% of the total patient population completed 3 weeks of double-blind treatment (21% placebo and 42% aripiprazole). Thirty-seven placebo patients and 17 aripiprazole patients entered open-label treatment due to lack of response as defined by the CGI-BP Change from Preceding Phase (mania). These numbers do not represent the numbers who were discontinued secondary to not meeting the criteria as entry into open-label was optional.

The sponsor's table of this information follows.

**Table 8.1A: Disposition of Patients**

| Patient Status | Number of Patients (%) | | |
|---|---|---|---|
| | Placebo | Aripiprazole | Total |
| **Enrolled** | n/a | n/a | 358 |
| Baseline failures | n/a | n/a | 96 |
| **Randomized** | 132 | 130 | 262 |
| **Discontinued from Double-Blind Treatment** | 104 (79) | 76 (58) | 180 (69) |
| Entered open-label treatment phase due to lack of response[a] | 37 (28) | 17 (13) | 54 (21) |
| Adverse event | 13 (10) | 14 (11) | 27 (10) |
| Lack of Efficacy | 16 (12) | 13 (10) | 29 (11) |
| Patient withdrew consent | 30 (23) | 28 (22) | 58 (22) |
| Patient unreliability | 0 | 3 (2) | 3 (1) |
| Lost to follow-up | 2 (2) | 1 (1) | 3 (1) |
| Pregnancy | 0 | 0 | 0 |
| Death | 0 | 0 | 0 |
| Other known cause[b] | 6 (5) | 0 | 6 (2) |
| **Completed Double-Blind Treatment** | 28 (21) | 54 (42) | 82 (31) |

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Source: Appendix 8.1.1[c]

[a] Patients not responding at Week 2, as indicated by CGI-BP Change from Preceding Phase (mania) score of 4 to 7, were offered open-label aripiprazole treatment.

[b] Other reasons for discontinuation may have included: pregnancy, other known cause (other), study terminated by sponsor, protocol violation, patient met withdrawal criteria, patient did not satisfy one or more screening criteria, or general inability to continue.

[c] Includes patients in double-blind and open-label treatment phases.

**Efficacy as per the sponsor:**

- **LOCF:** This was used for analysis of the primary efficacy measure. A statistically significant difference between placebo and aripiprazole groups on mean change from baseline to week 3 was seen. The difference at week two also is statistically significant favoring aripiprazole. The change in the YMRS for the treatment group is from about a 28 at baseline → about a 20 at the end of week 3 with 42% of the patients completing 3 weeks of aripiprazole treatment. The change in the YMRS for the placebo group is from about a 29 baseline → about a 26.3 at week 3 using LOCF data with 21% completing the double-blind period.

- LOCF data as per sponsor provided table follows.

**Table 10: Summary of Efficacy Results at Endpoint, LOCF Data Set, Efficacy Sample**

| Variable | Treatment Group: Placebo | Treatment Group: Aripiprazole |
|---|---|---|
| **PRIMARY EFFICACY ENDPOINT** | | |
| Y-MRS[a] | N = 122 | N = 123 |
| Mean Baseline | 29.68 | 28.16 |
| (95% CI) | (28.66, 30.69) | (27.13, 29.20) |
| Change at Week 3 | -3.35 | -8.15** |
| (95% CI) | (-5.75, -0.94) | (-10.60, -5.73) |
| **SECONDARY ENDPOINTS** | | |
| CGI -BP Severity of Illness (mania) | N = 122 | N = 124 |
| Mean Baseline | 4.74 | 4.56 |
| (95% CI) | (4.60, 4.88) | (4.42, 4.71) |
| Change at Week 3 | -0.39 | -1.00** |
| (95% CI) | (-0.68, -0.10) | (-1.30, -0.71) |
| Rate of discontinuation due to lack of efficacy or entry into open-label aripiprazole phase at Week 2 with a CGI-BP Change from Preceding Phase (mania) Score of 4 to 7. | 50/123 (41%) | 28/124 (23%)** |
| SE(%) | (4.4%) | (3.8%) |
| **OTHER EFFICACY ENDPOINTS** | | |
| CGI -BP Severity of Illness (depression) | N = 122 | N = 124 |
| Mean Baseline | 2.35 | 2.11 |
| (95% CI) | (2.13, 2.57) | (1.89, 2.34) |
| Change at Week 3 | 0.07 | -0.24* |
| (95% CI) | (-0.14, 0.28) | (-0.46, -0.02) |
| CGI -BP Severity of Illness (overall) | N = 122 | N = 124 |
| Mean Baseline | 4.78 | 4.55 |
| (95% CI) | (4.65, 4.91) | (4.42, 4.69) |
| Mean Change at Week 3 | -0.39 | -1.01** |
| (95% CI) | (-0.67, -0.12) | (-1.28, -0.74) |

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**Table 10.1A: Mean Change from Baseline in Y-MRS, LOCF Data Set, Efficacy Sample**

| | LOCF Data Set | | |
|---|---|---|---|
| | Mean Change from Baseline in Y-MRS[a] | | Pairwise Comparisons P-values[b] |
| Phase/ Variable | Placebo N = 122[c] | Aripiprazole N = 123[c] | Aripiprazole versus Placebo |
| Mean Baseline | 29.68 | 28.16 | .019 |
| **Double-Blind Treatment Phase** | | | |
| Day 4 | -2.80 | -5.66 | 0.004 |
| Week 1 | -3.56 | -7.44 | 0.002 |
| Day 10 | -3.71 | -8.24 | 0.001 |
| Week 2 | -3.13 | -8.32 | < 0.001 |
| Week 3 | -3.35 | -8.15 | 0.002 |
| Week 3: 95% confidence interval for treatment differences (Aripiprazole - Placebo) | -4.80 (-7.80, -1.80) | | |

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Source: Appendices 10.1.1A, 10.1.1B

[a] Y-MRS Total Score is from 0 to 60. A negative change score signifies improvement.

[b] ANCOVA, controlling for treatment, center, and baseline value. LS Means P-values for comparisons.

[c] At Day 4, N = 118 for Placebo, N = 118 for Aripiprazole; At Week 1, N = 121 for Placebo.

- **OC**: There are 72 placebo patients in the group at week 2 and 83 aripiprazole patients. The OC data are significantly in favor of aripiprazole at week 2 only (p=.001) with the mean changes of -5.74 for the placebo group and -11.54 for the aripiprazole group. At week 3, the OC data favor the placebo group numerically, although not statistically (p = 0.700) with a mean change of -16.17 in the placebo group (n = 29) and -15.43 in the aripiprazole group (n = 56). The placebo group of completers go from a mean baseline YMRS of 29 → 23 at week 2 → <13 at week 3. The aripiprazole group goes from a baseline YMRS of 28 →16.5 at week 2 → 12.5 at week 3.

- The sponsor provided table displaying the OC data is below.

**Table 10.1B: Mean Change from Baseline in Y-MRS, OC Data Set, Efficacy Sample**

| | OC Data Set | | | | |
|---|---|---|---|---|---|
| | Mean Change from Baseline in Y-MRS[a] | | | | Pairwise Comparisons P-values[b] |
| | Placebo | | Aripiprazole | | Aripiprazole vs Placebo |
| | N | Mean | N | Mean | |
| Mean Baseline | 122 | 29.11 | 123 | 27.93 | 0.129 |
| **Double-Blind Treatment Phase** | | | | | |
| Day 4 | 118 | -2.89 | 118 | -5.64 | 0.006 |
| Week 1 | 95 | -5.15 | 107 | -8.27 | 0.025 |
| Day 10 | 82 | -6.88 | 91 | -10.60 | 0.024 |
| Week 2 | 72 | -5.74 | 83 | -11.54 | 0.001 |
| Week 3 | 29 | -16.17 | 56 | -15.43 | 0.700 |
| Week 3: 95% confidence interval for treatment differences (Aripiprazole - Placebo) | | | | | 0.74 (-3.07, 4.56) |

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Source: Appendix 10.1.1A
[a] Y-MRS Total Score is from 0 to 60. A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment and baseline value. LS Means P-values for comparisons.

**Time to discontinuation:** The sponsor presented the time to discontinuation based on the number of days of dosing in the double-blind treatment period. Patients who entered open-label treatment were dropped from the double-blind treatment group. The sponsor notes that there is a statistical difference between the groups. There is fairly large attrition.

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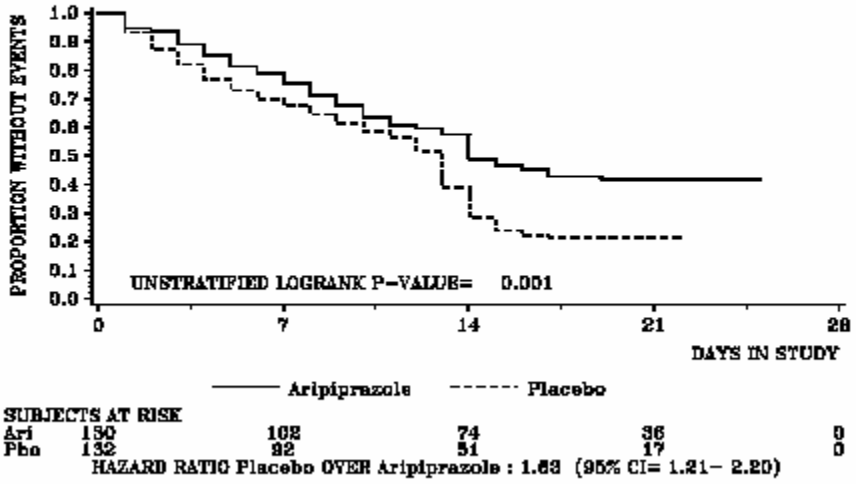
**Figure 8.1 Time to Discontinuation Due to All Reasons or Entry in Open-Label, Randomized Sample**




(Ari = aripiprazole, Pbo = Placebo)
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**Clinical Response:** Tables S.10.3.11A and B may be found in Appendix B of this document. These tables display the percentage of patients who lack a clinical response, which was defined as the failure to achieve a decrease of ≥ 5% from baseline on the YMRS. From these tables it appeared that more aripiprazole patients met this lack of clinical response criteria, which was statistically significant by the LOCF analysis.

Dr. Chen performed a re-analysis and it appears the sponsor reversed the numbers such that the placebo group data is reported for the aripiprazole patients. Histograms plotted by Dr. Chen to display the distribution of the people in each treatment group by percentage change in YMRS for weeks 2 and 3 using both LOCF and OC data. These histograms are included in Appendix B of this document.

**RESULTS ON DEPRESSION SCALES:**

The data from these scales are not part of the primary efficacy endpoint. However, I looked at these data as bipolar disorder has several states. Overall, the results on these scales do not indicate that aripiprazole precipitated depression.

- **MADRS:** Mean change from baseline MADRS total scores at week 3 for both LOCF and OC data were not statistically significant. LOCF data were: Placebo (n=79), mean baseline 14.26, week 3 -1.20; aripiprazole (n=99), mean baseline 13.80, week 3 -1.30; p values at baseline and week 3 respectively, 0.696 and 0.934. OC data favored placebo numerically with a mean change of -5.56 versus -3.99 in the aripiprazole group. This difference was not statistically significant.

- **CGI-BP Severity of Illness (Depression)LOCF:** Mean change from baseline in the CGI-BP Severity of Illness (Depression) LOCF data showed statistically greater improvement for the aripiprazole group at weeks 1, 2, and 3, although not at day 10.

| | Placebo | Aripiprazole | p value |
|---|---|---|---|
| # of patients | 122 | 124 | |
| Baseline | 2.35 | 2.11 | 0.09 |
| Week 1 | -0.01 | -0.25 | 0.20 |
| Day 10 | -0.02 | -0.20 | 0.151 |
| Week 2 | 0.04 | -0.30 | 0.014 |
| Week 3 | 0.07 | -0.40 | 0.026 |

**DISCUSSION/CONCERNS REGARDING EFFICACY RESULTS:**

1. **Protocol violations:**

- Protocol violations, the sponsor: The sponsor did not exclude any patients secondary to protocol violations and noted that protocol deviations of potential clinical relevance (see the appendix for the sponsor provided list) were found in all treatment groups at low frequencies, appeared balanced across treatment groups, and were not considered to have affected the conduct or analysis.

- Protocol violations, the reviewer: With respect to the efficacy section of this review, Appendix 7.3A was reviewed with specific attention to events which could confound results, such as missing lithium and valproic acid levels (aripiprazole ~10, placebo~14), lithium and valproic acid at or near randomization, psychotropic drugs at or near randomization (aripiprazole~25 and placebo ~28), and prohibited or excessive concomitant medications (aripiprazole ~6 and placebo~4).
- I asked Dr. Chen to re-analyze the data dropping certain patients (or doing a worse case scenario). This analysis did not change the results of the primary efficacy analysis. However, formal reanalysis by the sponsor should be performed as this was a preliminary analysis and on further review, my selection of patients may not have been optimal.

**2. Scales used for discontinuation at week 2 versus YMRS scores:**

Patients who were considered as not responding at week 2 (as indicated by CGI-BP Change from Preceding Phase (mania) score of ≥ 4) were discontinued from the blinded treatment phase and given the option to enter open-label for week 3. (A copy of this scale is included in the appendix of this document). As this criteria was different from the primary efficacy scale, YMRS, the concordance between the two scales was examined. It was difficult for me to tell from the disposition table who discontinued at the end of week 2 secondary to the criteria versus who discontinued and entered open-label secondary to the criteria. The length of time patients remained in the double blind phase was examined in the file FDA.dem.xpt.

CCHMAN is the JMP variable that captures the change from preceding phase (mania) score. This Change from Preceding Phase was to be judged with respect to the patient's baseline condition at day 4 through week 3 (p. 326 of study report). When searched for visit 2 CCHMAN ≥ 4 (in FDA.eff.xpt), 36 placebo and 22 aripiprazole patients were found.

**Aripiprazole**: Of the 22 patients identified as having CCHMAN ≥ 4 at week 2 , some seemed by YMRS to be improving, and yet would meet criteria for discontinuation. The table below shows some of these patients as an example. These patients were chosen because YMRS total scores at visit 2 were considerably lower than baseline YMRS total scores. The last two columns indicate the days in double blind and whether the patient entered open-label treatment or the date of entry into open-label if the patient did go into this phase.


CCHCCHMAN=change from preceding phase, mania variable in the JMP table, BYdate=baseline YMRS total date, BY=baseline YMRS total score, Ydate=YMRS date, Y=YMRS score, BMdate=baseline MADRS date, BM=baseline MADRS, DB=days in double-blind from FDA.dem.xpt, OL=date patient entered open-label from FDA.dem.xpt or Appendix 8.3. There were no MADRS dates or scores for these patients at visit 2.

With respect to disposition as seen in the JMP tables, patient 36-290 is coded as withdrawal of consent. All others are coded as completed study.

The duration in days of all acute dosing column (DURAT) in the dataset FDA.dem.xpt was examined for the above patients. For all except patient 29-119, the duration in double-blind (DURACDB) = to duration of all acute dosing. For patient 29-119, the duration of all acute dosing was 20 days.

**Placebo:** 36 placebo patients were identified as having CCHMAN ≥ 4 at week 2. Of these, six seemed to have YMRS scores that were improved considerably. This data is captured in the table below.


CCH=CCHMAN=change from preceding phase, mania variable in the JMP table, BYdate=baseline YMRS total date, BY=baseline YMRS total score, Ydate=YMRS date, Y=YMRS score, BMdate=baseline MADRS date, BM=baseline MADRS, DB=days in double-blind from FDA.dem.xpt, OL=date patient entered open-label from FDA.dem.xpt or Appendix 8.3. There were no MADRS dates or scores for these patients at visit 2.

With regard to disposition as seen in the JMP tables, patients 4-233, 30-269, 42-120, 59-287, 42-37 are coded as completed study. Patient 57-307 is coded as treatment failure/lack of efficacy.

For all of the above patients, the duration in days of acute dosing was compared to the time in double-blind (DURAT to DURACDB). In all cases, the duration of acute dosing was longer than the time in double blind by about 6-8 days, possibly indicating the open label phase.

I have discussed with Dr. Chen whether people who met the CCHMAN criteria were discontinued. It appears this was the case for most patients meeting criteria although it looks like some possibly were not dropped out (for example, 11-122, 23-48, 31-218, 45-136). With regard to both of these issues, Dr. Chen dropped or used a worse-case scenario to informally assess the impact of each of these. This analysis did not cause the study to lose significance. Additionally, it is noted that this type of scale discrepancy is not necessarily unexpected.

**3. WEEK # Versus Visit #:**

I discussed with Dr. Chen what appeared to be discrepancies in the Visit column and the week columns. For the most part, it appears that this is not a significant problem and the sponsor has provided variables which demarcate which data were used.

**4. Subgroup analysis:**

The following information is based on the sponsor's table, Table 6.1.8, "YMRS Total Score: Mean Change from Baseline to Week 3 by Population Subsets; 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, CN1380740, LOCF Data Set, Efficacy Sample" and includes demographic data. Discussion of this table occurs later in this review, however the psychiatric variables and YMRS information are below.

**Psychiatric Variables:** With regard to "type of episode" and "rapid cycling", there was some difference between patients with a baseline manic episode and those with a baseline mixed episode with decreases of almost 4 in the manic group and only about 2.3 in the mixed group. Both rapid cycling and non rapid cycling patients showed statistically significant differences between aripiprazole and placebo.

**Mean YMRS total scores at baseline:** Mean YMRS total scores were divided by the sponsor into two groups: patients with ≤ median of 27 and patients with ≥ median of 27. The aripiprazole patients ≤ to the median did only slightly better than placebo (p=0.043, decrease of about 2 points) while the patients ≥ to the median did almost 4.8 points better (p=0.001).

5. **Length of time in the current manic episode and the presence or absence of psychotic features at baseline-**

This information was not submitted from the sponsor and should be requested to help better characterize the patient population and evaluate any differential treatment effect, specifically with respect to the presence or absence of psychotic features at baseline.

**Conclusions:**

I recommend the Division make any final action contingent upon the results obtained after re-analysis regarding protocol violations, and YMRS (subgrouping relative to the median) and after baseline summary information for the presence or absence of psychotic features and the mean time in the current episode have been seen, reviewed and determined to be noncontributory to the efficacy results.

In my opinion, the data can be considered supportive of some utility of aripiprazole in the treatment of acutely manic or mixed Bipolar I patients for two weeks in the acute phase IF the re-analyses (as outlined below) support the current p-values. I question consideration of secondary variables called "key" in this submission as they were not specified or agreed to in advance of this submission. My opinion regarding primary efficacy is based on the following.

If after re-analyses the primary efficacy measure is still significant, it would indicate that acutely manic or mixed Bipolar I patients become less manic with aripiprazole treatment (YMRS from about 28 to about 20) than with placebo treatment (YMRS from about 30 to about 27) at weeks 2 and 3 by LOCF analysis. This difference is statistically significant at both time points.

However, there is a large attrition rate in both groups with 29% of the placebo group and 42% of the treatment group completing. Although not directly comparable, the disposition tables for the

other trials provide the following: Trial CN138074 about 52% of the placebo group and 55% of the aripiprazole patients completed 3 weeks; Trial CN138008, the active control study, about 77% of the aripiprazole patients and 55% of the haloperidol patients completed 3 weeks; Trial CN138007, the fixed-dose trial, about 40% of all of the groups completed 3 weeks. From table 10.1B, Mean Change from Baseline in YMRS, OC data set, it appears that much of the drop-out may be due to the forced discontinuation at week 2 (placebo, 72 at week 2 and 29 at week 3 versus aripiprazole, 83 at week 2 and 56 at week 3).

Due to the large number of dropouts between weeks 2 and 3, which may be in part attributed to the forced discontinuation, I believe that the period of this trial should be considered to be two weeks and not 3. Additionally, the OC data numerically, not statistically, favor placebo at week three.

With regard to re-analyses, protocol violations to consider are: patients who did not have baseline labs to check therapeutic levels or who were therapeutic on one, patients with benzodiazepine use within 4 hours of rating scales or patients with excessive amounts within 1 day of scales, perhaps patients with anticholinergics within 12 hours of scales, patients with positive drug tests at randomization or during the study, and patients who started the study on medications such as flouxetine. The breakdown by median YMRS ≥ provided above was for the pooled studies. It might be helpful to see if this is seen in this study in terms of possible information for labeling.

**CN 138074:** " A Multicenter, Randomized, Double-Blind Study of Aripiprazole Versus Placebo in the Treatment of Acutely Manic Patients With Bipolar Disorder."

Sites: 29 U.S. Investigators representing 29 sites (Investigators are listed in the appendix of this document)

**Subjects:** 353 enrolled with 272 randomized to either placebo (n=135) or aripiprazole (n=137). Inclusion criteria included: Adult DSM-IV Bipolar I acute manic or mixed patients requiring hospitalization with a YMRS ≥ 20.

**Exclusion criteria included**: Overall, the exclusion criteria essentially were the same as those of Study CN138009 except carbamazepine levels as well as lithium and valproate levels were to be below certain levels, the use of psychotropic medications was banned for 2 days before randomization in CN138074 (versus 1 day in CN138009) and the use of other antidepressants within one week of the baseline visit was reassessed by protocol in CN138074.

**Demographics at baseline:**

In general, the groups were similar with the aripiprazole group slightly younger in mean and median ages and more white patients were randomized to aripiprazole than to placebo. The male-female ratio was about the same between groups with slightly more females than males in the placebo group versus the aripiprazole group. Sponsor-provided tables are duplicated below.

Baseline summary information regarding the presence or absence of psychotic symptoms and the time in current episode was not provided.

**Table 8.3: Demographic Characteristics, Randomized Sample**

| Variable | | Placebo N = 135 | Aripiprazole N = 137 | Total N = 272 |
|---|---|---|---|---|
| Age (years) | Mean | 40.4 | 37.3 | 38.8 |
| | Median | 42 | 38 | 40 |
| | Range | 18.0 - 64.0 | 18.0 - 72.0 | 18.0 - 72.0 |
| | S.E. | 0.9 | 0.9 | 0.7 |
| Gender N (%) | Male | 63 (47) | 69 (50) | 132 (49) |
| | Female | 72 (53) | 68 (50) | 140 (51) |
| Race N (%) | White | 92 (68) | 104 (76) | 196 (72) |
| | Black | 30 (22) | 26 (19) | 56 (21) |
| | Asian/Pacific Islander | 1 (1) | 1 (1) | 2 (1) |
| | Hispanic/Latino | 11 (8) | 3 (2) | 14 (5) |
| | American/Alaskan Native | 0 | 1 (1) | 1 (0) |
| | Other | 1 (1) | 2 (1) | 3 (1) |
| Weight (kg) | Mean | 85 | 87.5 | 86.3 |
| | Median | 84 | 83.3 | 83.3 |
| | Min-Max | 45.5 - 145.4 | 47.3 - 168.8 | 45.5 - 168.8 |
| | S.E. | 1.8 | 2 | 1.3 |
| | Missing | 3 | 3 | 6 |

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**Table 8.4A: Psychiatric History of Bipolar Disorder, Randomized Sample**

| Variable | | Placebo N = 135 | Aripiprazole N = 137 | Total N = 272 |
|---|---|---|---|---|
| Age Current Episode Began | Mean | 40.3 | 37.2 | 38.8 |
| | Median | 42.0 | 38.0 | 40.0 |
| | Min - Max | 18.0 - 64.0 | 17.0 - 72.0 | 17.0 - 72.0 |
| | S.E. | 0.9 | 0.9 | 0.7 |
| Current Episode N (%) | Manic | 81 (60) | 78 (57) | 159 (58) |
| | Mixed | 54 (40) | 59 (43) | 113 (42) |
| Rapid Cycling N (%) | Yes | 22 (16) | 26 (19) | 48 (18) |
| | No | 113 (84) | 111 (81) | 224 (82) |

Protocol CN138074

**Design:** The design of Study CN138074 is similar to CN138009 in that it is a flexible dose study and different in that there is no forced discontinuation at week 2.

Screening: 1-7 days screening, up to 14 days with permission from BMS.
Randomized: Qualified patients were randomized to either aripiprazole 30 mg, which could be decreased to 15mg if not tolerated, or placebo for 3 weeks. (Amendment #3, September 08, 2002, clarified that if a dose was reduced secondary to intolerance and clinical response, the dose could be increased subsequently at the discretion of the Investigator.) All patients were hospitalized for 2 weeks and given the option to become outpatients and continue double-blind therapy at week 2 if they met the following criteria: CGI-BP Severity of Illness Score $\leq 3$ and CGI-BP Change from Preceding Phase Score of $\leq 2$ at the end of week 2.

**Use of concomitant medications:** Antipsychotic agents including recent treatment with long acting agents, antidepressants, lithium, carbamazepine, valproic acid, and all other psychotropics were not allowed between baseline and end of study. Lorazepam was not allowed after day 10 and was allowed until day 10 in the same fashion as trial CN138009: up to 6mg/day on days 1-4, up to 4 mg/day on days 5-7, and up to 2 mg/day on days 8-10. Anticholinergic use was permitted after randomization in the double-blind period for the treatment of EPS symptoms.

**Primary Efficacy Variable:** The primary efficacy measure was the same as that in study CN138009 and was the mean change in YMRS total score from baseline to end of week 3. The YMRS was given at screening, at baseline, and at visits day 2, 4, week 1, day 10, week 2 and week 3 or early discontinuation.

**Secondary Efficacy:** Rating scales for secondary measures were the CGI-BP, PANSS, and the MADRS. The CGI-BP was administered at baseline, day 4, week1, day 10, week 2, and week 3 or early discontinuation. The MADRS was administered at baseline, at week 1, week 2, and week 3 or early discontinuation. The PANSS was administered at baseline, week 1, week 2, and week 3 or early discontinuation.

**Key** secondary endpoints were discussed in Administrative letter #1, dated November 21, 2002. KEY secondary efficacy measures were: response rate defined as a 50% improvement from baseline in the YMRS total, the mean change from baseline in the CGI-BP Severity of Illness Score (mania), the mean change from baseline in the PANSS Hostility Subscale Score, and the mean CGI-BP Change from Preceding Phase Score (mania). A more detailed discussion may be found in Dr. Chen's review of this submission.

**Study Conduct:**

- Changes to the protocol: Three amendments and one administrative letter were submitted to the protocol. Amendment #1 allowed for pharmacogenomic blood sampling. Amendment #2 included an addition of a urine or serum pregnancy test at day 4. Amendment #3 included an additional drug and alcohol screen for outpatients at week 3.

- **Unblinding** occurred in one placebo patient: The site left the label on her medication bottle and she withdrew consent on day one after learning she had been randomized to receive placebo.

- Use of Concomitant Medications: 84% of the placebo group and 86% of the aripiprazole group used concomitant anxiolytic medications. 67% of the placebo group and 63% of the aripiprazole group used concomitant analgesic or antipyretics. 9% of the aripiprazole group and 11% of the placebo group used hypnotics & sedatives. 7% of the placebo group and 21% of the aripiprazole group used concomitant anticholinergic medications.

- Protocol violations: These are discussed later in this section.

- Dosing: At endpoint, the mean dose of aripiprazole was 27.68mg. 21 of the aripiprazole patients were taking 15mg instead of 30mg at endpoint. The mean placebo use at endpoint was 1.88 tablets.

- Compliance: Although this data are available in an appendix upon request, no summary information regarding compliance was provided.

**RESULTS:**

**DISPOSITION:** The sponsor-provided disposition table is below and indicates that > 50% of each group completed three weeks of treatment (52% placebo and 55% aripiprazole) and that more placebo patients left double-blind treatment secondary to lack of efficacy while more aripiprazole patients left secondary to withdrawal of consent.

The sponsor was asked to submit more information regarding the patients coded as withdrawal of consent. In the response to this request, dated December 16, 2003, the sponsor compiled CRF text comments. In study CN138074, 35 aripiprazole patients and 24 placebo patients were reported as discontinuation due to withdrawal of consent. This included two patients who withdrew prior to receiving study medication.

Fourteen of the aripiprazole patients had additional text information. Patients coded as withdrawal of consent left for a variety of reasons including; personal problems (1), wanting to be home for Christmas (1), sick relative (1), non-specific (7), using alcohol and beginning quetiapine on the day of dropping out (1), and starting a non-allowed concomitant shortly after leaving (2) .

The sponsor-provided disposition table follows.

The disposition of all patients randomized to treatment is presented in Table 8.1.

**Table 8.1: Disposition of Patients**

| | Number of Patients (%)[a] | | |
|---|---|---|---|
| **Patient Status** | **Placebo** | **Aripiprazole** | **Total** |
| **Enrolled** | n/a | n/a | 353 |
| Baseline failures | n/a | n/a | 81 |
| **Randomized** | 135 | 137 | 272 |
| **Discontinued Double-Blind Treatment** | | | |
| Adverse Experience | 10(7) | 12(9) | 22(8) |
| Lack of Efficacy | 28(21) | 12(9) | 40(15) |
| Subject Withdrew Consent | 25(19) | 35(25) | 59(22) |
| Subject Unreliable | 1(1) | 2(1) | 3(1) |
| Lost to Follow-Up | 0 | 1(1) | 1(< 1) |
| Other Known Cause[b] | 1(1) | 1(1) | 2(1) |
| **Completed Double-Blind Treatment** | 71(52) | 75(55) | 145(53) |

Protocol CN138074

Source: Appendix 8.1.1

[a] Percentages based on number of randomized patients.

[b] Other reasons for discontinuation included: placebo patient discharged due to incarceration; aripiprazole patient discharged due to patient recovery.

**Primary Efficacy:** Overall, about 52% of the placebo and 55% of the aripiprazole patients completed 3 weeks of double-blind treatment. The LOCF analysis favored aripiprazole at week 3, the primary efficacy measure, and at all time points after day 2. For the aripiprazole group, the mean baseline YMRS was about 29 and was about 16 at trial completion. For the placebo group, the mean baseline YMRS was about 28 and was about 21 at completion. OC data analysis was statistically significant in favor of aripiprazole at all time points after day 2. Sponsor provided tables of the LOCF data are below.

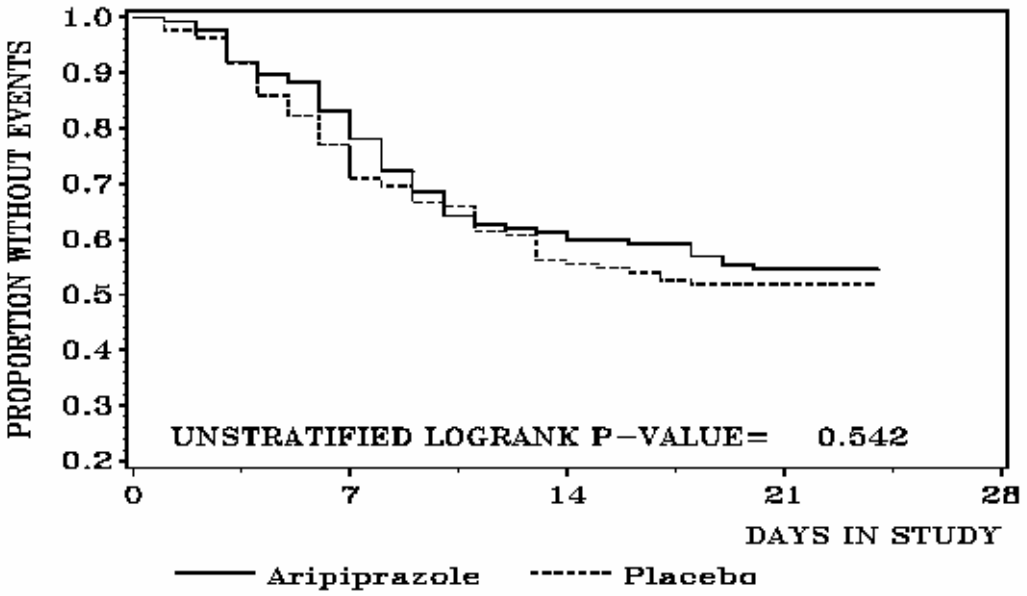
**Table 10: Summary of Efficacy Results at Endpoint, Efficacy Sample, LOCF Data Set**

| | Treatment Group | |
|---|---|---|
| **Variable** | **Placebo** | **Aripiprazole** |
| **PRIMARY EFFICACY ENDPOINT** | | |
| Y-MRS Total Score | N = 132 | N = 136 |
| Mean Baseline | 28.45 | 28.80 |
| (95% CI) | (27.47, 29.42) | (27.85, 29.76) |
| Mean Change at Week 3 | -7.19 | -12.52** |
| (95% CI) | (-9.30, -5.08) | (-14.59, -10.45) |
| **KEY SECONDARY ENDPOINTS** | | |
| Response Rate at Week 3[a] | N = 132 | N = 136 |
| N (%) | 42 (32%) | 72 (53%)** |
| (S.E.%) | (4.1%) | (4.3%) |

**Table 10.1A: Mean Change from Baseline in Y-MRS Total Score, Efficacy Sample, LOCF Data Set**

| | Mean Change from Baseline in Y-MRS[a] | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|
| Day/Week | Placebo[c] N = 132 | Aripiprazole[d] N = 136 | Aripiprazole vs Placebo |
| Mean Baseline | 28.45 | 28.80 | 0.557 |
| **Double-Blind Treatment** | | | |
| Day 2 | -3.89 | -5.01 | 0.123 |
| Day 4 | -5.37 | -8.17 | 0.002 |
| Week 1 | -6.59 | -9.73 | 0.004 |
| Day 10 | -7.62 | -11.55 | 0.001 |
| Week 2 | -7.80 | -12.37 | < 0.001 |
| Week 3 | -7.19 | -12.52 | < 0.001 |
| Week 3: 95% CI for treatment difference (Aripiprazole - Placebo): -5.33 (-7.90, -2.76) | | | |

Figure 8.1: Time to Discontinuation Due to All Reasons, Randomized Sample




HAZARD RATIO Aripiprazole OVER Placebo : 0.90 (95% CI= 0.64- 1.27)

Protocol CN138074
Source: Appendix 8.1.1

**Secondary Efficacy:**

The sponsor specified four key secondary variables; response rate, mean change from baseline in the CGI-BP Severity of Illness Score (mania), mean change from baseline in the PANSS Hostility Scale, and mean change from preceding phase score (mania). A hierarchical testing procedure was used for the analysis of key secondary variables and followed in sequence, as listed above, after the primary efficacy measure analysis was found statistically significant at $p \leq 0.05$. Analysis was to stop with the first comparison that failed to reach statistical significance.

The analysis of these variables demonstrated a statistically significant difference in favor of aripiprazole on all key secondary variables. The sponsor-provided tables representing this data are below. The reader is deferred to Dr. Chen's review for a more complete discussion.

**Table 10.2.1A: Response Rate for the Y-MRS Total Score, Efficacy Sample, LOCF Data Set**

| | Number Responding [a]/Number Assessed (%) | | | | Pair-wise Comparisons P-values [b] |
|---|---|---|---|---|---|
| Day/Week | Placebo | | Aripiprazole | | Aripiprazole vs Placebo |
| Day 2 | 7/124 | (6) | 12/131 | (9) | 0.425 |
| Day 4 | 19/132 | (14) | 29/135 | (21) | 0.184 |
| Week 1 | 35/132 | (27) | 53/136 | (39) | 0.036 |
| Day 10 | 41/132 | (31) | 65/136 | (48) | 0.006 |
| Week 2 | 41/132 | (31) | 69/136 | (51) | 0.001 |
| Week 3 | 42/132 | (32) | 72/136 | (53) | 0.001 |
| Week 3: 95% CI for response ratio (Aripiprazole vs Placebo)[c]: | | | | | 1.66 (1.24, 2.22) |

Protocol CN138074

Source: Appendix 10.1A

[a] A responder is a patient with a decrease of ≥ 50% from baseline on the Y-MRS Total Score.

[b] CMH General Association Test, controlling for study center.

[c] Values greater than 1 favor aripiprazole.

**Table 10.2.2A: Mean Change from Baseline in the CGI-BP Severity of Illness Score (mania), Efficacy Sample, LOCF Data Set**

| | Mean Change from Baseline in CGI-BP Severity of Illness Score (mania) [a] | | Pair-wise Comparisons P-values [b] |
|---|---|---|---|
| Day/Week | Placebo [c] N = 129 | Aripiprazole [d] N = 135 | Aripiprazole vs Placebo |
| Mean Baseline | 4.71 | 4.69 | 0.850 |
| **Double-Blind Treatment** | | | |
| Day 4 | -0.52 | -0.62 | 0.319 |
| Week 1 | -0.73 | -1.01 | 0.025 |
| Day 10 | -1.00 | -1.26 | 0.075 |
| Week 2 | -1.10 | -1.51 | 0.015 |
| Week 3 | -1.12 | -1.59 | 0.009 |
| Week 3: 95% CI for treatment difference (Aripiprazole - Placebo): | | | -0.47 (-0.82, -0.12) |

Protocol CN138074

Source: Appendix 10.2.2A

[a] CGI-BP Severity of Illness Score (mania) is from 1 (normal) to 7 (very severely ill). A negative change score signifies improvement.

[b] ANCOVA, controlling for treatment, study center, and baseline value. LS-Means P-values for comparisons.

[c] Day 4 N = 125, Week 1 N = 128

[d] Day 4 N = 131

**Table 10.2.3A: Mean Change from Baseline in the PANSS Hostility Subscale Score, Efficacy Sample, LOCF Data Set**

| | Mean Change from Baseline in PANSS Hostility Subscale Score[a] | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|
| Week | Placebo N = 122 | Aripiprazole N = 124 | Aripiprazole vs Placebo |
| Baseline | 10.74 | 10.60 | 0.709 |
| **Double-Blind Treatment** | | | |
| Week 3 | -0.82 | -2.21 | 0.002 |
| Week 3: 95% CI for treatment difference (Aripiprazole - Placebo): | | | -1.39 (-2.27, -0.51) |

Protocol CN138074

Source: Appendix 10.2.3

[a] PANSS Hostility Subscale Score is from 4 to 28. A negative change score signifies improvement.

[b] ANCOVA, controlling for treatment, study center, and baseline value. LS Means P-values for comparisons.

**Table 10.2.4A: Mean CGI-BP Change from Preceding Phase Score (mania), Efficacy Sample, LOCF Data Set**

| | Mean CGI-BP Change from Preceding Phase Score (mania)[a] | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|
| Day/Week | Placebo[c] N = 129 | Aripiprazole[d] N = 135 | Aripiprazole vs Placebo |
| Day 4 | 3.34 | 3.27 | 0.626 |
| Week 1 | 3.34 | 2.95 | 0.006 |
| Day 10 | 3.14 | 2.81 | 0.037 |
| Week 2 | 3.17 | 2.71 | 0.006 |
| Week 3 | 3.22 | 2.63 | 0.001 |

Protocol CN138074

Source: Appendix 10.2.2A

[a] CGI-BP Change from Preceding Phase (mania): 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse; unadjusted means are displayed.

[b] CMH Row Means Test, controlling for study center.

[c] Day 4 N = 125

[d] Day 4 N = 131

**Depression Scales:**

These scales are not part of the primary analysis but were viewed as bipolar disorder has multiple states. Overall, it does not appear that the aripiprazole patients became more depressed.

**MADRS:** The mean change from baseline in the MADRS total score for patients with a baseline MADRS > 20 in the efficacy sample by LOCF analysis numerically favors aripiprazole at weeks 1, 2, and 3, although the differences are not statistically significant. At baseline, the placebo group was 26.41 and the aripiprazole group was 25.53 (p=0.394). OC analysis of the group with a baseline MADRS >20 also shows aripiprazole group improving numerically more at all time points than placebo. This is significant at week 2 only (p=0.015) and the aripiprazole group at week 2 is doing better than at week 3 with mean changes of -17.18 at week 2 and -14.48 at week 3. (These data may be found in the study report on pages 170 and 171, Tables S.10.3.8.A and S.10.3.8B.)

**CGI-BP Change from Preceding Phase Score (depression):** When looking at the LOCF analysis, the aripiprazole group is numerically better at all measures including baseline. These differences generally are minimal and not significant. At week 3, the aripiprazole group is 3.18 and the placebo group is 3.36 (3=minimally improved, 4=no change). The OC analysis does not show statistical differences between the groups and at week 3, both groups are at about 2.9. (This data may be found in the study report page 109, Tables 10.3.4A and 10.3.4B)

**Areas of potential concern regarding the Efficacy results:**

**1. Protocol deviations:**

The sponsor provided a list of protocol deviations they considered to be of clinical relevance and an appendix (7.3) presenting a listing of patients with protocol deviations. The types of violations the sponsor considered of clinical relevance included: fluoxetine treatment within 4 weeks of initiating the study (1 aripiprazole patient), psychotropic drugs within 48 hours of randomization (4 aripiprazole and 6 placebo), lithium, valproic acid, or carbamazepine out of range before randomization (7 aripiprazole and 6 placebo), missing these levels (aripiprazole 5 and placebo 7), prohibited concomitant medication taken prior to discontinuation or end of study assessment (9 aripiprazole versus 7 placebo) and lorazepam exceeding the limit (2 aripiprazole, 0 placebo).

Appendix 7.3 of the study report contains the patient listings of protocol violations. There are roughly 75 patients over 16 sites (about 37 aripiprazole and 38 placebo) with positive stimulant or drugs of abuse screens. It appears that a number of these were in the few days preceding randomization, some after (about 3 aripiprazole and 8 placebo) and several patients either tested positive for more than one substance or had more than one occasion of a positive test result. 16 patients became outpatients at week 2 without meeting the CGI criteria. There are about 28 patients who used either another atypical, haloperidol, chlorpromazine, or lithium, or fluoxetine (1 aripiprazole) within a few days before randomization.

The sponsor notes that “There were no apparent elements of the conduct of the study or any changes in the conduct (including protocol deviations) that affected the validity of this trial.”

Dr. Chen performed a re-analysis to examine the effects of the protocol violations on the primary efficacy analysis based on patients whom I chose. The data were still significant. However, with further examination, I am unsure this analysis included the correct patients and believe the sponsor should perform additional re-analyses.

2. **Unblinding** This occurred only in one patient.

3. **Psychotic features at baseline-** No baseline summary was provided and no subgroup analysis was performed with regard to the efficacy measures. Given the class of this drug, this information has relevance.

4. **The length of the current manic episode**- No baseline summary was provided.

5. **Subgroup analysis:** efficacy by baseline YMRS score median ≥ 27 or ≤ 27:

The following information is based on the sponsor's table, Table 6.1.8, "YMRS Total Score: Mean Change from Baseline to Week 3 by Population Subsets; 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, CN1380740, LOCF Data Set, Efficacy Sample" and includes demographic data. Discussion of this table occurs later in this review, however the psychiatric variables and YMRS information are below.

**Psychiatric Variables:** With regard to "type of episode" and "rapid cycling", there was some difference between patients with a baseline manic episode and those with a baseline mixed episode with decreases of almost 4 in the manic group and only about 2.3 in the mixed group. Both rapid cycling and non rapid cycling patients showed statistically significant differences between aripiprazole and placebo.

**Mean YMRS total scores at baseline:** Mean YMRS total scores were divided by the sponsor into two groups: ≤ median of 27 and ≥ median of 27. The aripiprazole patients ≤ to the median did only slightly better than placebo (p=0.043, decrease of about 2 points) while the patients ≥ to the median did almost 4.8 points better (p=0.001).

**Conclusions:**

I recommend the Division make any final action contingent upon the results obtained after re-analysis regarding protocol violations, and YMRS (subgroups relative to the median) and after baseline summary information for the presence or absence of psychotic features and the mean time in the current episode have been seen, reviewed and determined to be noncontributory to the efficacy results.

Otherwise, the data from this study support the use of aripiprazole in acute mania for the period of three weeks as per pre-agreed criteria between the Division and the sponsor. (b) (4)

The similar rates of completion for the placebo and aripiprazole groups at the end of the 3 week double blind period (52%placebo, 55%aripiprazole) may reflect the difficulty in treating this population, the actual robustness of the drug, or some combination thereof. At the end of weeks 2 and 3, the aripiprazole treated patients showed by, LOCF data, a statistically significant reduction in mean YMRS total scores over the placebo patients. At week 3, this means that aripiprazole patients decreased from 29 at baseline → 16.5 and the placebo group from 28 → 21. The OC data analysis also was statistically significantly positive at weeks 2 and 3 in favor of aripiprazole. These data indicate that at week 3, aripiprazole patients have gone from a baseline YMRS of almost 29 →12 and placebo from about 29 →16.

A similar caveat about data reanalysis(ses) is made for this trial as was made for study CN138009 with regard to protocol violations, the presence or absence of psychotic features, and the length of the current manic episode at baseline for the groups. Additionally, the YMRS data indicating that aripiprazole patients with a median baseline score of ≥ 27 have statistically significant mean changes from baseline to week 3 whereas the aripiprazole treated patients with a median baseline score of ≤ 27 do not are from the pooled studies. It might be helpful to see if this is seen in this study in terms of possible information for labeling.

## EFFICACY: SUBGROUP ANALYSIS BY POPULATION SUBSETS:

The sponsor provided a table, Table 6.1.8, that displays YMRS total score, mean change from baseline to week 3 by population subsets in studies CN138007, CN138009, and CN138074 by LOCF analysis. Table 6.1.8 is duplicated in Appendix B of this document.

**Race:** Patients coded as "black" and "other" showed no statistical difference between aripiprazole and placebo groups while the patients coded as "white" did. There are about 4x as many "white" patients as "black" and about 7x as many "white" patients as "other" which may account for this. However, looking at absolute changes in the mean scores on YMRS, the white patients sustained about a 3.9 point decrease while the black and other patients experienced only a 2.2-2.3 decrease.

**Age:** Age ≤ 50 versus age ≥ 50 showed statistically significant changes between aripiprazole and placebo although the changes in the two age groups are similar with both achieving about a 3.2 point change. There are 4.4x more patients in the younger group than the older.

**Psychiatric Variables:** With regard to "type of episode" and "rapid cycling", there was some difference between patients with a baseline manic episode and those with a baseline mixed episode with decreases of almost 4 in the manic group and only about 2.3 in the mixed group. Both rapid cycling and non rapid cycling patients showed statistically significant differences between aripiprazole and placebo.

**Mean YMRS total scores at baseline:** Mean YMRS total scores were divided by the sponsor into two groups: ≤ median of 27 and ≥ median of 27. The aripiprazole patients ≤ to the median did only slightly better than placebo (p=0.043, decrease of about 2 points) while the patients ≥ to the median did almost 4.8 points better (p=0.001).

Overall, these studies are not powered adequately to make definitive conclusions with regard to this issue and generally, I am uncertain what the significance of the findings is.

### D. Efficacy Conclusions

(b) (4)

[redacted]

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**S002:** Contingent upon statistically significant results after the requested re-analyses, the primary efficacy data from trial CN138009 and CN138074 meet the pre-agreed criteria for efficacy and the results indicate that aripiprazole offers some utility over placebo in the treatment of acutely manic or mixed Bipolar I patients.

The low retention seen in CN138009, a three week trial, is somewhat bothersome and patients are not "well" upon study termination. However, those in the study and taking aripiprazole are doing better than the placebo patients and the difference likely is clinically meaningful. These results may reflect the difficulty in treating this population the robustness of the drug or some combination thereof. For these reasons, I believe the data can be viewed as supportive of some utility in the acute treatment of bipolar patients, again pending the results of reanalysis. (b) (4)

[redacted]

In study CN138074, the retention rates are about equal (by LOCF) between groups and just over 50%. Again, this may reflect the difficulty in treating these patients or it may reflect the actual robustness of the drug or some combination thereof. However, this study demonstrated efficacy at both weeks 2 and 3 by LOCF and OC analysis on the primary endpoint. Additionally, the four key secondary efficacy measures were all statistically significant in favor of aripiprazole.

Study CN138007, the only fixed dose study the sponsor completed is negative. The mean changes at week three are higher in all groups than those seen in CN138009 and CN138074.

## VII. Integrated Review of Safety

### A. Brief Statement of Conclusions

There were two deaths in the acute bipolar mania trials. One of these patients had not taken study medication. One patient died 5 days after his last dose of medication from an overdose of hydrocodone on day 8. This death is not likely directly attributable to aripiprazole although it is possible continuing akathisia, which possibly was drug related versus his illness, could have contributed to this event.

The incidences of treatment emergent serious adverse events in the four pooled studies were similar for placebo and aripiprazole patients at 5.6% to 5.8%. Reaction manic occurred in slightly more aripiprazole patients (2.6% versus 2.2%) than the placebo patients. One "risk of suicide attempt" and two overdoses (anti insomnia medication, hydrocodone) occurred in the aripiprazole patient group. None occurred in the placebo group.

In the four pooled studies, the percentages of patients discontinuing secondary to a treatment emergent adverse event were 10.9% of the aripiprazole patients and 9.5% of the placebo patients. Two of these events occurred at ≥ 2% in the aripiprazole group; reaction manic (2.5% versus 0.7%) and akathisia (2.3% versus 0.5 %).

In the four pooled placebo controlled trials, common and drug related adverse events as defined as occurring in at least 5% of the aripiprazole treated patients and at least 2x the incidence of the placebo group, were akathisia (15% versus 3.4%), accidental injury (5.8% versus 2.7%), and extrapyramidal syndrome(5.1% versus 2.2 %). Constipation, somnolence, and vomiting occurred at almost this level. Hyper-tension occurred in 3.0% of the aripiprazole patients versus 1.2% of the placebo patients.

More aripiprazole treated patients than placebo treated patients experienced a PCS increase in creatine phosphokinase with the median percent change higher in the placebo group by > 2 fold (15.7% versus 6.1%). Two aripiprazole treated patient discontinued a study secondary to either hypotension or orthostatic hypotension. No aripiprazole treated patient in this study pool experienced a QTcE >450msec. No patients in the acute trials discontinued secondary to EKG abnormalities.

Post marketing data suggest that anaphylaxis, laryngospasm, and torticollis have been reasonably associated with the use of aripiprazole and may be drug related. Future reporting of events such as DVT/PE , pancreatitis, and overdose should be followed closely by the sponsor. A case of hyperammonemia and severe encephalopathy is inconclusive and cannot reasonably be attributed directly to drug. Further information regarding the workup for an amino acid disorder might be helpful as would further detail on a case described in the PSUR reviews.

### B. Description of Patient Exposure

The studies for acute mania were conducted in North America, South America, Europe, and Africa. The ISS-ISE submitted for supplements 002 (b) (4) contains safety data, with a cutoff date of February 07, 2003, for completed studies (CN138007, CN138008, CN138009, CN138037, (b) (4), CN 138074) and ongoing studies (CN138010 and (b) (4)); November 30, 2002 for all non-bipolar studies, and March 13, 2003 and April 30, 2003 for post-marketing safety surveillance information. The 120-day update presents data available as of June 30, 2003 for Phase II/II studies and June 7,2003 for Phase I studies.

- This ISS-ISE contains a total of 6554 patients who were exposed to aripiprazole with 4142.8 patient exposure years. 1975 of these patients were exposed for ≥ 180 days, 1323 for ≥ 360 days. The mean doses were in the range of 25-32.5 mg.

- As per the ISS submitted with supplement 002, a total of 1141 patients with 151.2 exposure years were treated with aripiprazole in all bipolar mania clinical studies; 568 in 3-week placebo-controlled trials, 175 in 26 week active controlled trials, 571 in ongoing uncontrolled/open label trials, and 128 in "other" bipolar mania trials. The safety sample for the 3-week placebo-controlled studies is comprised of 977 patients who received at least one dose of study medication; 568 aripiprazole- treated patients and 409 placebo-treated patients. 305 patients received fixed doses of aripiprazole (150 received 15 mg day and 155 received 30 mg/day) and 185 of these patients were exposed to aripiprazole for ≥ 90 days. For the majority (58.8%), the overall mean dose was between 25 and 32.5 mg.

- The Safety Update contains data on 7487 patients treated with aripiprazole representing 4731 patient-exposure years. This is an increase of 933 patients exposed to aripiprazole contributing 588 patient-exposure years. (b) (4) The data in the table below are taken from the sponsor's table, Table 2, of the Update and show the breakdown of the bipolar mania patients by trial design.

Pools

| **Bipolar Mania** | Aripiprazole N | Haloperidol N | Placebo N |
|---|---|---|---|
| 3-week placebo-controlled- | 597 | n/a | 436 |
| • Fixed dose | • 305 | n/a | • 149 |
| • Flexible dose | • 292 | n/a | • 287 |
| 26 week haloperidol controlled | 175 | 169 | 0 |
| Other | 128 (63)* | n/a | n/a |
| Ongoing un-controlled/open label | 576 (243)* | n/a | n/a |
| Blinded ongoing | n/a | n/a | n/a |
| Total | 1170 | 169 | 436 |

* the numbers in the parentheses represent patients who were in open-label extensions but were already counted in the aripiprazole column under other study groups

The ISS submitted with supplement 005 in January of 2004 has composite safety tables for all the bipolar studies. From this ISS, it is seen that there are 208.7 patient years of exposure to aripiprazole in bipolar mania patients. 19.5% (228) were exposed to aripiprazole for ≥ 90 days. For all patients exposed to aripiprazole in all Phase 2 and 3 studies, there were 4786.5 patient years of exposure with 28.2% (2114) exposed for ≥ 180 days and 13.9%(1043) for ≥ 540 days.

From the ISS submitted in supplement 005, it is seen that 58.9% of bipolar mania patients received overall mean doses of 25 mg and 32.5mg, while 43.5% of all aripiprazole treated patients in all Phase 2 and 3 studies received overall mean doses between 25 and 32.5 mg. This data may be found in the appendix and is provided as information for the Team Leader and the Division Director. Otherwise, unless specified, this safety review was conducted on the ISS and the 120 day Safety Update submitted with supplements 002 (b) (4)

Exposure data as per sponsor-provided tables:

Aripiprazole
BMS-337039/OPC-14597 Integrated Summary of Efficacy and Safety

**Table 7.3.2B: Number and Percentage of Patients Who Received Aripiprazole by Overall Mean Dose Category and Duration of Therapy: Bipolar Mania, Safety Sample**

| Total Duration of Treatment | Number (%) of Aripiprazole Patients (N = 1141) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Overall Mean Dose (mg) | | | | | | |
| | Unavailable[a] | ≤ 12.5 | > 12.5 - ≤ 17.5 | > 17.5 - ≤ 25 | > 25 - ≤ 32.5 | > 32.5 | Total |
| 1 - 20 days | 8 (0.7) | 1 (0.1) | 120 (10.5) | 48 (4.2) | 274 (24.0) | 0 | 451 (39.5) |
| 21 - 41 days | 0 | 2 (0.2) | 25 (2.2) | 46 (4.0) | 135 (11.8) | 0 | 208 (18.2) |
| 42 - 89 days | 0 | 0 | 67 (5.9) | 67 (5.9) | 163 (14.3) | 0 | 297 (26.0) |
| 90 - 119 days | 0 | 0 | 15 (1.3) | 19 (1.7) | 37 (3.2) | 0 | 71 (6.2) |
| 120 - 149 days | 0 | 0 | 10 (0.9) | 12 (1.1) | 46 (4.0) | 0 | 68 (6.0) |
| 150 - 179 days | 0 | 0 | 3 (0.3) | 6 (0.5) | 5 (0.4) | 0 | 14 (1.2) |
| 180 - 269 days | 0 | 0 | 11 (1.0) | 7 (0.6) | 9 (0.8) | 0 | 27 (2.4) |
| 270 - 359 days | 0 | 0 | 1 (0.1) | 2 (0.2) | 0 | 0 | 3 (0.3) |
| 360 - 719 days | 0 | 0 | 1 (0.1) | 0 | 1 (0.1) | 0 | 2 (0.2) |
| Total | 8 (0.7) | 3 (0.3) | 253 (22.2) | 207 (18.1) | 670 (58.8) | 0 | 1141 (100.0) |

[a] Dosage data were not available at time of database cut-off.

Aripiprazole
OPC-14597/BMS-337039 CN138
120 Day Safety Update - Bipolar Mania

**Table 4.1.2C: Number and Percentage of Patients Who Received Aripiprazole by Overall Mean Dose Category and Duration of Therapy for Bipolar Mania Patients: Bipolar Mania 120-Day Safety Update, Safety Sample**

| Total Duration of Treatment | Number (%) of Aripiprazole Patients (N = 1170) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Overall Mean Dose (mg) | | | | | | |
| | Unavailable[a] | ≤ 12.5 | > 12.5 - ≤ 17.5 | > 17.5 - ≤ 25 | > 25 - ≤ 32.5 | > 32.5 | Total |
| 1 - 20 days | 7 (0.6) | 1 (0.1) | 120 (10.3) | 52 (4.4) | 287 (24.5) | 0 | 467 (39.9) |
| 21 - 41 days | 0 | 2 (0.2) | 25 (2.1) | 47 (4.0) | 144 (12.3) | 0 | 218 (18.6) |
| 42 - 89 days | 0 | 0 | 68 (5.8) | 67 (5.7) | 161 (13.8) | 0 | 296 (25.3) |
| 90 - 119 days | 0 | 0 | 14 (1.2) | 18 (1.5) | 39 (3.3) | 0 | 71 (6.1) |
| 120 - 149 days | 0 | 0 | 11 (0.9) | 13 (1.1) | 47 (4.0) | 0 | 71 (6.1) |
| 150 - 179 days | 0 | 0 | 3 (0.3) | 6 (0.5) | 6 (0.5) | 0 | 15 (1.3) |
| 180 - 269 days | 0 | 0 | 11 (0.9) | 7 (0.6) | 9 (0.8) | 0 | 27 (2.3) |
| 270 - 359 days | 0 | 0 | 1 (0.1) | 2 (0.2) | 0 | 0 | 3 (0.3) |
| 360 - 719 days | 0 | 0 | 1 (0.1) | 0 | 1 (0.1) | 0 | 2 (0.2) |
| Total | 7 (0.6) | 3 (0.3) | 254 (21.7) | 212 (18.1) | 694 (59.3) | 0 | 1170 (100.0) |

[a] Dosage data were not available at time of data cut-off date.

## C. Methods and Specific Findings of Safety Review

The evidence of the safety of aripiprazole in the treatment of acute mania is based on four three-week placebo-controlled trials conducted in bipolar I patients with an acute manic or mixed episode. The two fixed dose studies (one completed, one terminated early) contributed safety data on 149 placebo patients, 150 aripiprazole 15mg patients, and 155 aripiprazole 30 mg patients. The safety data from both fixed and flexible dose studies, completed and not-completed (terminated) were pooled and provided as well as that from the haloperidol-aripiprazole study.

(b) (4)

Tables with integrated placebo controlled safety data to include this study are in the ISS for supplement 005. These tables were not reviewed extensively in this review. As the haloperidol-aripiprazole study had no placebo group, this type of comparative analysis was not possible. However, deaths and serious adverse event data did offer indirect supportive data of the safety of aripiprazole in this patient population. Errata with additional safety information for trials CN138007 and CN138009 were reviewed.

Line listings of spontaneously reported adverse events, as provided in two PSURs were reviewed, for deaths and non fatal serious adverse events. Selected reports were reviewed and are discussed in the appropriate section of this review.

### D. Adequacy of Safety Testing

The acute controlled trials included a placebo group allowing comparisons between aripiprazole treated and placebo treated patients. The 12-week active controlled trial had no placebo group. Therefore, comparative conclusions to placebo cannot be made. Generally, the methods used to assess safety, although not identical in each trial, were adequate in design. Adverse events were monitored at each visit.

### E. Assessment of Data Quality and Completeness

**Trial Conduct** :The are protocol violations for missing information such as labs, vital sign, pregnancy tests, and EKGs in all of the placebo controlled trials. In some tables the denominators are somewhat lower than the entire number of patients in a group. For example, Table 7.1.7.aA-1 on page 195 of the ISS, displays the incidence of treatment emergent serum chemistry measures of potential clinical significance in the 3 week placebo controlled trial. There are 333-451 aripiprazole patients and 228-314 placebo patients are in the denominators when these combined trials have about 568 aripiprazole patients and 409 placebo patients. The denominators generally represent patients with baseline normal values, which could mean the others were abnormal versus missing.

The DSI inspection report indicates that site 23 in study CN138009 failed to report four subjects who experienced adverse events.

**Pooling:** The pooled studies for ISS were CN138007, CN138009, (b) (4), and CN138074. This group includes both completed and terminated studies and may not have been optimal for data analysis.

**Technical:** Navigation of the PSUR information was difficult at times as some of the pages are not amenable to searching with the search function for words in the text. For example, with a search for the word "fatal" in the 1st PSUR, I did not locate it until page 6092 when the word actually occurs on several earlier pages including 5668, 5673 (also numbered as page 4), and page 5684 (also numbered page 15). Within this document the second set of page numbers on the page do match the page numbers in the table of contents.

Within the 2nd PSUR, there are page numbers in the table of contents that do not seem to be related to the page numbers on the bottom of the page, of which, there are two on many pages. For example, the table of contents (on page 233 =page 2905) notes that Late Breaking Information is section 8.2 on page 70. Section 8.2, the Late Breaking Information section is on page 2977, which has no second page number. Multiple pages (29944-2970) also have the other page number as 232. While this type of page numbering may have some internal use to the sponsor, it made reviewing these documents more difficult.

## F. Summary of Critical Safety Findings and Limitations of Data

### F1) Deaths:

Incidence by exposure year in all aripiprazole trials is displayed as per the sponsor-provided table below. More aripiprazole treated patients have died in the dementia trials than in the other trials. Placebo deaths are not displayed so a comparison to this in the elderly population is not possible from this table. Although the higher death rate among aripiprazole patients in dementia trials likely reflects the underlying patient population and the illness, placebo-controlled data from study CN138005 should assist in interpretation of this information.

**Table 4.5A: Incidence of Deaths by Patient-Exposure Years; All Aripiprazole Data Set by Indication and Overall: Bipolar Mania ISE/ISS and Bipolar Mania 120-Day Safety Update**

| | Bipolar Mania | Dementia | Schizophrenia | All Aripiprazole |
|---|---|---|---|---|
| **ISE/ISS[a]** | **N = 1141** | **N = 696** | **N = 4717** | **N = 6554** |
| Patient Exposure Years | 151.2 | 442.1 | 3549.5 | 4142.8 |
| N (%) of Deaths | 2 (0.2) | 105 (15.1) | 34 (0.7) | 141 (2.1) |
| Per Patient-Exposure Years | 0.013 | 0.238 | 0.010 | 0.034 |
| **120-Day Safety Update[b]** | **N = 1170** | **N = 788** | **N = 5529** | **N = 7487** |
| Patient Exposure Years | 153.5 | 640.2 | 3937.6 | 4731.3 |
| N (%) of Deaths | 2 (0.2) | 139 (17.6) | 38 (0.7) | 179 (2.4) |
| Per Patient-Exposure Years | 0.013 | 0.217 | 0.010 | 0.038 |

[a] Data cut-off date of November 30, 2002 for non-bipolar studies and February 7, 2003 for bipolar studies.

[b] Data cut-off date of June 30, 2003.

**Deaths in the Bipolar Mania Trials:** There were three deaths in the bipolar mania trials (n=1170).

These are displayed below in a table and discussed after the table.

| Study | Demographics | Study day | Dose date relative | Cause of Death |
|---|---|---|---|---|
| 138008-84-159 | 50 y.o. male | (b) (6) | Pre-randomization | Cardiac arrest |
| 138074-18-252 | 37 y.o. male | | 3 | Hydrocodone Intoxication |
| 138010-134-131 | 39 y.o. male | | 41 (in open label) | Heroin intoxication |

Patient 18-252:. This 37 year old male patient experienced anxiety and akathisia on (b) (6) of treatment with aripiprazole resulting in medication discontinuation. The patient was discontinued

from the study on (b) (6) and discharged from the hospital on (b) (6) On (b) (6), he was found dead at home. The cause of death was determined to be hydrocodone intoxication. At the time of his death, moderate anxiety and mild akathisia were ongoing. This death is not likely to be directly attributable to aripiprazole although it is possible his akathisia was drug related versus part of his illness and perhaps could have been continuing at the time due to the long half life of aripiprazole.

Patient 138010-134-341 was a 39 year old male taking 30 mg of aripiprazole. On (b) (6) of combined participation), the patient was taken to the E.R. secondary to low blood pressure and poor respiratory rate. He was discharged later that day. On (b) (6) of combined study participation, the patient returned to the ER unresponsive, in severe distress, and ultimately died. The autopsy report indicated that this patient died due to severe heroin intoxication. Toxicology reports, presumably during the study, indicated the presence of alprazolam. It is unclear what role aripiprazole, if any, may have contributed although I do not believe this death is directly attributable to aripiprazole as the patient overdosed on heroin.

Patient 138008-84-159- This was a 50 year old man enrolled from (b) (6), who suffered fatal cardiac arrest. This patient experienced severe worsening of his mania starting on (b) (6) and was hospitalized. Secondary to this deterioration and the requirement for a higher dose of medication, the randomization was postponed for 1 week. The patient died on (b) (6).The CRF notes concomitant medication of haloperidol 15 mg and that he had not received any study medication. The role, if any, of worsening mania in his death is not clear, however he had taken no study medication.

**Blinded study CN138010:** There were no deaths among patients receiving study treatment.

**F2) Treatment Emergent Serious Adverse Events ( TE SAE):** For the completed placebo controlled studies in acute bipolar mania, treatment emergent SAEs that resulted between consent date and 30 days after the last dose were captured in summary tables. There are four additional patients who experienced SAEs after the database was locked in study CN138007. All four patients experienced prolonged hospitalization for the treatment of underlying mania.

A total of 1170 patients were exposed to aripiprazole in all acute bipolar mania studies. Of these, 10.7% experienced at least one TE SAE.

Table 7.1.5A, as per the sponsor, displays the incidence of TE SAEs occurring in studies CN138007, CN138009, (b) (4), and CN138074, and may be found in the safety section of Appendix B of this document. In the acute bipolar mania studies, 5.8 % of the aripiprazole treated and 5.6% of the placebo treated patients experienced a treatment emergent SAE. Reaction manic occurred in 2.6% (15) of the aripiprazole patients and 2.2% (9) of the placebo patients. One suicide attempt occurred in the aripiprazole patient group and none in the placebo group. Over dose occurred in 2 aripiprazole patients and no placebo patients.

(b) (4) 0/27 placebo and 3/29 aripiprazole patients experienced a serious adverse event. These events were psychosis, reaction manic, reaction manic-depressive, thought suicidal.

The fixed dose studies, CN138007 (b) (4) indicate that 6.7% of the 15mg aripiprazole group, 4.5% of the 30 mg group, and 5.4% of the placebo group experienced a treatment emergent SAE. Two of 150 patients in the aripiprazole 15 mg group experienced seizures as a TE SAE versus 0/155 and 0/149 in the aripiprazole 30mg and placebo groups respectively.

For study CN138008, 17 patients (12 haloperidol, 5 aripiprazole) experienced a SAE in the 12 week acute phase study or within 30days of discontinuation from the study. One aripiprazole patient (CN138008-101-216) experienced a SAE while in the 14 week extension phase which overlapped with the 30 day post 12 week reporting period. The SAEs (total of 6) reported for the aripiprazole patients occurred on days 26-115 of dosing and were listed as: reaction manic in 3 patients, depression in one patient, hernia in one patient, and psychosocial support in one patient. The incidence of aripiprazole and haloperidol patients coded as experiencing reaction manic and depression were the same.

**Blinded Trial CN 138010:** This section was reviewed and written by Dr. Greg Dubitsky.

The sponsor submitted line listings of serious adverse events among patients receiving study medication that remained blinded in the original submission of this supplement and in the safety update. These listings were examined for patients from study CN138010 and only two of these events were considered unexpected and clinically significant:

• Patient 138010-93-154 was a 23 year old female who, after 307 days of blinded treatment, was involved in a car accident and experienced a paralysis of cranial nerve IV (coded as "paralysis"), with ptosis and double-vision in her right eye. The patient continued in the study and this event resolved about 3 weeks later.
• Patient 138010-21-409 was a 32 year old female who received blinded study medication for (b) (6) days. (b) (6) days after discontinuing this treatment, the patient was hospitalized for a moderate blood clot (coded as "thrombosis"), which resolved a week later.

Neither event is considered to be reasonably attributable to the study treatment.

**F3) Dropouts Secondary to Adverse Events:**

**All bipolar mania trials :**Table 4.3B in the Update provides the incidences of treatment emergent adverse events that led to discontinuation by study therapy and includes longer term trials, trials still blinded, and open label data as well as the acute mania placebo and haloperidol controlled trial data. This table is not included within this document but may be found on page 61 of the 120 day safety update. As seen in this table, 20.3% of aripiprazole patients in bipolar mania trial (n=1170) experienced a treatment emergent adverse event which led to study discontinuation.

2.6% of the bipolar patients discontinued secondary to treatment emergent akathisia, 1.5% secondary to treatment emergent agitation, 1.5% secondary to treatment emergent anxiety, 2.8 % secondary to reaction manic, and 1.3% secondary to reaction manic depressive. These numbers are higher than those reported for the schizophrenic population in which 1.0% dropped out secondary to treatment emergent agitation, 1.0 % secondary to akathisia, and 1.1% secondary to

anxiety. Dystonia and EPS are both reported as treatment emergent adverse events leading to discontinuation in slightly more bipolar patients than schizophrenic patients (0.1% versus 0.2% and 0.3% versus 0.9% , respectively). These differences may reflect the differences in the underlying illnesses, some differential treatment effect or the differences in the two populations in previous drug exposure.

Among patients in **study CN138010,** who dropped out secondary to adverse events while receiving blinded medication, none of the events were considered clinically significant and unexpected.

**Pooled Acute Studies : Table 7.1.4A** of the ISS presents the incidence of discontinuation secondary to an adverse event for the pooled studies CN 138007, CN138009, (b) (4), and CN138074 and may be found in the safety section of appendix B of this document. 39/409 placebo patients and 62/568 aripiprazole patients discontinued secondary to a treatment emergent adverse event. Two events leading to discontinuation occurred at ≥ 2% in the aripiprazole group. These were reaction manic (0.7% placebo, 2.5% aripiprazole) and akathisia (0.5 % placebo; 2.3% aripiprazole).

With respect to dosing, in the fixed dose studies, the incidence of discontinuation secondary to an adverse event was higher in the 15 mg aripiprazole group (14.7%) than in either the 30 mg aripiprazole group (8.4%) or the placebo group (8.7%). The sponsor-provided table of this data, Table 7.1.4B, may be found in the safety section of the appendix of this document.

The study report for (b) (4) indicates that 3/27 placebo and 0/29 aripiprazole patients discontinued secondary to an adverse event. One of these began before dosing. The events associated with discontinuation in the placebo patients who were dosed were anxiety and hematuria.

In **study 138008**, dropouts secondary to adverse events were higher in the haloperidol group (49.1%) than in the aripiprazole group (18.9%). (The sponsor-provided table, Table 12.4 has not been included in this document but may be found on page 153 of the study report). About 39% of the haloperidol group discontinued for EPS type side effects. The most common adverse events causing discontinuation in the haloperidol group were "EPS" (18.9% versus 2.9% aripiprazole) and akathisia (14.2% versus 5.1% aripiprazole). The most common adverse events causing discontinuation in the aripiprazole group were depression (6.3% aripiprazole versus 4.1% haloperidol) and akathisia (5.1%).

**F4) Common Adverse Events:**

**Classification of Adverse Events:** Across all studies, treatment emergent adverse events were defined as any new medical problem or exacerbation of an existing condition or symptom, experienced by a patient after randomization and receipt of at least one dose of study medication regardless of whether the investigator considered the event drug-related. The adverse events were obtained from either reports volunteered by patients or investigator observation.

The original investigator terms were coded into COSTART terms. Appendix 5.3.4.2B of the ISS (not provided in this review) contains a listing of those patients for whom the preferred term was re-classified and displays the previous term and the adverse event text. Overall, these re-classifications do not appear likely to impact adversely on the safety profile.

**COMMON ADVERSE EVENTS:** In the pooled studies CN138007, CN138009, (b) (4) and CN138074, 329/409 placebo and 493/568 aripiprazole patients experienced an adverse event.

**Common and drug related adverse events:** The table displaying these data, Table 7.1.3.1A, is in the safety section of Appendix B of this document.

Adverse events reported in at least 5% of the aripiprazole treated patients and at least twice the incidence of the placebo group, are accidental injury (5.8% aripiprazole and 2.7% placebo), akathisia (15% aripiprazole and 3.4% placebo), and extrapyramidal syndrome (5.1% aripiprazole and 2.2 % placebo). Agitation occurred in only slightly more aripiprazole patients (15.7% versus 15.2%).

Events occurring in at least 5% in the drug group and almost 2x the incidence of the placebo group are constipation, vomiting, and somnolence. Other noticeable events occurring at higher incidences in the aripiprazole treated patients than the placebo patients are:

- Hypertension (3.0% versus 1.2%)
- Peripheral edema (3.3% versus 1.2%)
- Increased salivation (4.0% versus 0.7%)

**DEMOGRAPHIC EFFECTS ON ADVERSE EVENTS:** The demographic data for the dataset "all bipolar mania trials" (open label, placebo-controlled, active-controlled; n=1170) and for the dataset "3 week placebo-controlled trials" (CN 138007, CN 138009, (b) (4) CN138074;n=409 placebo, 568 aripiprazole) are displayed below for age, gender and race. The data in this table are derived from the sponsor's tables (Table 4.1.1, page 26 of the Safety Update and Table 7.1.1, page 132 of the ISS-ISE). It is noted that the total number of patients listed under the age categories in the table for the all bipolar is 1172.

All Bipolar 3-week placebo controlled trials

| Aripiprazole | | BLANK COLUMN | Placebo | | Aripiprazole | |
|---|---|---|---|---|---|---|
| **Variable** | **N(%)** | | **Variable** | **N(%)** | **Variable** | **N(%)** |
| **AGE** | | | **AGE** | | **AGE** | |
| <18 | 0 | | | | | |
| 18-50 | 941(80) | | 18-50 | 333(81) | 18-50 | 469(83) |
| 51-64 | 207(18) | | 51-64 | 71(17) | 51-64 | 89(16) |
| ≥65 | 22(2) | | ≥65 | 5(1) | ≥65 | 10(2) |
| ≥ 75 | 2 (<1) | | | | | |
| **GENDER** | | | **GENDER** | | **GENDER** | |
| Female | 660 (56) | | Female | 227(56) | Female | 296(52) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Male | 510 (44) | | Male | 182(44) | Male | 272(48) |
| **RACE** | | | **RACE** | | **RACE** | |
| White | 884(76) | | White | 297(73) | White | 421(74) |
| Black | 138(12) | | Black | 71(17) | Black | 89(16) |
| Hispanic | 118(10) | | Hispanic | 32(8) | Hispanic | 42(7) |
| Asian | 18 (2) | | Asian | 2(0) | Asian | 11(2) |
| Other | 12 (1) | | Other | 7(2) | Other | 5(1) |

**Subgroup analysis :** The sponsor performed subgroup analysis for the demographic subgroups of age, gender, and race on the reporting rates of the adverse events occurring in ≥ 1% of the pooled aripiprazole group in the 3-week placebo-controlled acute mania studies CN138007, CN138009, (b) (4), and CN138074. The data are displayed in Tables S.7.1.3.4, S.7.1.3.5, S7.1.3.6A and B as found in the ISS. These tables are not reproduced within this document. For each adverse event primary term, an odds ratio for aripiprazole: placebo was computed for each subgroup and the Breslow-Day Chi-Square test for homogeneity across subgroups was performed.

There was a significant difference in reporting rates based on age 18-50 years old versus ≥ 51years old for four adverse events. Insomnia (p=0.008; OR 1.49 = younger group and OR 0.34 older group), diarrhea (p=0.002; OR=1.26 younger group, OR=0.22 older group), akathisia (p=0.024; OR= 6.85 younger, OR=1.6 older), and accidental injury (p=0.038; OR=3.18 younger group, OR= 0.56 older group) occurred more often in the younger patients.

There was a significant difference in reporting rates based on gender for only one adverse event; accidental injury was reported more frequently among women than men (OR=14.63 women, OR=1 men, p=0.004). A second adverse event, akathisia occurred more frequently in men (OR=14.62) than in women (OR=3.38) although the p-value missed statistical significance (0.052).

The sponsor denoted race as “white”, “black”, or “other” for purposes of this analysis. There was a significant difference in reporting rates based on race (white, black, other) for the adverse event vomiting; (white OR=2.97, black OR=0.62, other OR=0.5; p=0.016). The number of white patients on either placebo or aripiprazole is about 4-5x that of the number of black patients and about 7x the number of other patients.

**Dose and Adverse Events:** With respect to dosing, the sponsor provided a table (Table S.7.1.3.3 of the ISS*) listing the incidences of treatment emergent adverse events by dose in trials CN138007 (b) (4) A CMH test stratified by dose was used to evaluate this with and without placebo for individual adverse events occurring in at least 1% of the pooled group. Data from the without placebo column were reviewed. No individual adverse event was reported at a statistically significantly higher rate between the two doses. Percentage-wise, vomiting occurred in almost twice as many aripiprazole 15 mg patients as aripiprazole 30 mg patients (11.3% versus 5.8%; placebo 4.7%). Numerically, more aripiprazole patients on 15 mg doses experienced any adverse event than either aripiprazole 30 mg patients or placebo patients (86.7%, 81.9%, and 77.9% respectively). (*Table S.7.1.3.3. cannot be found in this document but is in the ISS-ISE, pages 447-452).

**F5) Laboratory Measures:**

Routine hematology, chemistry, and urinalysis testing were performed in all studies, although not identically so in timing. In general, this assessment included adequate measures of liver function, basic electrolytes, and general hematologic indices. Additionally, effort was made to obtain fasting chemistries and glycosylated hemoglobin (Hemoglobin A1C) was measured. Although a fasting total cholesterol was measured, no information regarding HDL/LDL was reported.

Studies CN138007, CN138009 (b) (4) performed routine chemistry, hematology, and urine tests at week 2 as well as at screening, week 3/early discontinuation. In studies CN 138074 (b) (4). CN 138008, a study designed to run longer, incorporated testing to accommodate this additional time. All studies were to include pre-dosing pregnancy testing for WOCBP. All studies included as entrance criteria an assessment of lithium, valproic acid, or carbamazepine levels. Protocol violations regarding some of these issues were discussed in the efficacy sections of the reviews of the trials earlier in this document.

**Criteria for Potentially Clinically Significant Laboratory Changes (PCS) :**

**Chemistry and Electrolytes:** The criteria for PCS laboratory tests results, as provided by the sponsor, are displayed in the safety section of Appendix B. There were no criteria for electrolytes or cholesterol or incidences of PCS electrolyte displayed in the submission. The sponsor submitted the information for electrolytes, upon request, via an email dated April 01, 2004. It appears they did not measure bicarbonate levels.

The proportions of patients in studies CN138007, CN138009, (b) (4), and CN138074 meeting these criteria can be found in Tables 7.1.7.1A-1 and 7.1.7.1B-1 of the ISS-ISE which are included in the safety section of Appendix B of this document.

The proportions of patients experiencing PCS laboratory abnormalities were similar with the exception of prolactin, in which PCS increases were seen in 7.0% of the placebo versus 3.3% of the aripiprazole group.

One aripiprazole treated patient developed potentially clinically significant treatment emergent increase in potassium (from 4.0 mEq/L to 6.6 mEq/L with the ULN at 5.2 mEq/L) after 9 days on aripiprazole.

One aripiprazole treated patient developed a potentially clinically significant treatment emergent decrease in chloride (from a baseline chloride of 103 mEq/L to 89 mEq/L with the LLN = 97 mEq/L) after 13 days on aripiprazole. There were no other chloride measures for this patient.

**Hematology:** With regard to hematology measures, 2/437 (0.5%) aripiprazole treated patients and 0/305 placebo treated patients experienced PCS hematocrit levels and 1/380 aripiprazole and

0/280 placebo patients experienced eosinophilia. Leucocytosis occurred in 1/278 placebo patients and 0/393 aripiprazole patients.

**Median Change From Baseline In Laboratory Tests:**

The median change from baseline to end of treatment was performed for serum chemistries on the four placebo-controlled studies. Aripiprazole treated patients experienced higher median percent changes from baseline in ALT (9.5% versus 4.5%) than placebo-treated patients although the percent experiencing PCS values were lower for the drug group (0.3%) than for the placebo group (0.4%). The median change differences are unlikely to have clinical significance.

Prolactin levels sustained a larger decrease in the aripiprazole group than the placebo group showing a median % change of -50 versus -18.2% respectively.

More aripiprazole treated patients than placebo treated patients experienced a PCS increase in creatine phosphokinase (CPK) with the median percent change higher in the placebo group by > 2 fold (15.7% versus 6.1%). I looked at the line listings for the patients with elevated CPK values who started with baselines under the upper limit of normal for CPK values. The most extreme elevation occurred in a 47 year old male patient who started with a baseline of 128, was randomized to aripiprazole 30mg, and on day 22 had a CPK of 4153. This was apparently without serious clinical correlation.

Generally, the other elevations were in the range of 4-13 fold over baseline. The corresponding information for the placebo group shows a highest CK of 1506 about 2 weeks into the study after a baseline of 61. There were four other patients who experienced a treatment emergent PCS CPK value. These ranged from 6.7-12 fold over baseline. Two of the placebo patients discontinued secondary to increased CPKs. CPK increases are included in current labeling as "Frequent" in the "Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole" section.

**Hematology:** The median percent change from baseline to endpoint in hematology measurements may be found in the safety section of Appendix B of this document (sponsor provided table 7.1.7.1.B-2). These changes are fairly similar between groups with the exception of WBC counts (7.7% placebo versus 4.6% aripiprazole) and platelet counts (1.4% placebo versus 3.0% aripiprazole). Differences in these median % changes of platelet counts are unlikely to be clinically significant.

**Dropouts due to Laboratory Abnormalities:**

No aripiprazole-treated patients in the four placebo-controlled acute mania studies (CN 138007, CN138009, (b) (4) CN138074) discontinued secondary to a laboratory abnormality. Two placebo-treated patients from these studies discontinued secondary to increased CPK. There were no discontinuations of aripiprazole treated patients in the acute mania placebo controlled studies (CN 1380078, CN138009, (b) (4), CN138074) secondary to abnormal hematology laboratory values.

**F6) Vital Signs Data**

**Vital Signs Assessments:**

In the four placebo-controlled studies and the active-comparator study, supine and standing systolic and diastolic blood pressure and radial artery pulse rates were measured at screening, baseline, day 4, day 10, and weeks 1, 2, and 3/early termination. Orthostatic measures were taken after the patient had been supine for 5 minutes, was instructed to stand, and repeated after 2 minutes standing. Study CN 138008 incorporated an additional 12-week randomized phase during which vital signs were measured at the end of weeks 4, 5, 6,8.10, and 12/study discontinuation.

**Potentially Clinically Significant Vital Sign Changes:** The criteria for PCS vital sign measures are duplicated from the sponsor as inclusions in the safety appendix. The proportions of patients who met these criteria in the pooled placebo-controlled studies of acute mania are presented in safety section of Appendix B and are briefly discussed below.

More aripiprazole patients experienced higher PCS standing (4.50% versus 1.60%) and supine heart rate increases (1.32% versus 0.80%) than placebo. No patients discontinued because of increases in standing heart rate. One person with an elevated standing pulse experienced a decrease of ≥ 30 mmHg in supine-standing systolic blood pressure measurement. More placebo patients experienced supine heart rate decreases than aripiprazole patients (1.06% versus 0%; p~.03). One aripiprazole treated patient discontinued a study secondary to hypotension and one secondary to orthostatic hypotension (both in study CN138007).

Potentially significant diastolic blood pressure increases and decreases were seen in fewer aripiprazole treated patients with supine position than placebo (0.36% to 0.54% in the aripiprazole group versus 1.02% and 1.7% in the placebo group). More aripiprazole patients experienced both PCS increases and decreases (2.88% each) in weight than placebo patients (2.37% increases and 1.69% decreases).

**By dose:** The sponsor provided table from the ISS is below. One aripiprazole 15 mg patient discontinued from study CN138007 secondary to severe orthostatic hypotension.

**Table 12.8.1A: Number of Patients with Potentially Clinically Significant Vital Sign Abnormalities Occurring During Double-Blind Treatment, Safety Sample**

| Vital Sign Measurement | Number of Patients with Potentially Clinically Significant Vital Sign Abnormalities[a]/Number Assessed (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Placebo | | Aripiprazole 15 mg | | Aripiprazole 30 mg | | Total |
| **Any Event** | 12/133 | (9%) | 10/131 | (8%) | 16/135 | (12%) | 38 |
| **Systolic blood pressure, standing** | | | | | | | |
| Increase | 0/128 | (0%) | 0/127 | (0%) | 2/129 | (2%) | 2 |
| Decrease | 6/128 | (5%) | 2/127 | (2%) | 5/129 | (4%) | 13 |
| **Systolic blood pressure, supine** | | | | | | | |
| Increase | 0/128 | (0%) | 0/127 | (0%) | 2/129 | (2%) | 2 |
| Decrease | 5/128 | (4%) | 2/127 | (2%) | 3/129 | (2%) | 10 |
| **Diastolic blood pressure, standing** | | | | | | | |
| Increase | 0/128 | (0%) | 2/127 | (2%) | 0/129 | (0%) | 2 |
| Decrease | 4/128 | (3%) | 2/127 | (2%) | 1/129 | (1%) | 7 |
| **Diastolic blood pressure, supine** | | | | | | | |
| Increase | 1/128 | (1%) | 1/127 | (1%) | 0/129 | (0%) | 2 |
| Decrease | 2/128 | (2%) | 0/127 | (0%) | 2/129 | (2%) | 4 |
| **Heart Rate, standing** | | | | | | | |
| Increase | 2/121 | (2%) | 4/122 | (3%) | 4/126 | (3%) | 10 |
| Decrease | 0/121 | (0%) | 0/122 | (0%) | 0/126 | (0%) | 0 |
| **Heart Rate, supine** | | | | | | | |
| Increase | 2/121 | (2%) | 1/120 | (1%) | 3/127 | (2%) | 6 |
| Decrease | 3/121 | (3%) | 0/120 | (0%) | 0/127 | (0%) | 3 |
| **Weight** | | | | | | | |
| Increase | 2/86 | (2%) | 3/91 | (3%) | 3/91 | (3%) | 8 |
| Decrease | 0/86 | (0%) | 2/91 | (2%) | 3/91 | (3%) | 5 |

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Source: Appendix 12.8.1A

[a] Criteria for identifying potentially clinically significant vital sign measurements are based on the guidelines suggested by the FDA Division of Neuropharmacological Drug Products (Supplemental Table 6.3.4.3).

**Mean Change from Baseline to Endpoint in Vital Sign Measures:**

Mean and median changes from baseline to endpoint in the 3-week placebo controlled trials were presented by the sponsor in Table 7.1.8.1B, page 202 of the ISS. The median changes are all 0.

Both standing and supine mean heart rates (bpm) increased slightly in the aripiprazole-treated patients when compared to placebo-treated patients in whom both standing and supine heart rates declined slightly.

Mean systolic blood pressure (mmHg) changes for both standing and supine measures were minimally lower in the aripiprazole group than in the placebo group. Mean diastolic blood pressure changes for both standing and supine measures show the placebo group experiencing

slight mean decreases in both while the aripiprazole group had no mean change in standing diastolic blood pressure and a very small mean change in supine blood pressure.

Mean weight (kg) change in the aripiprazole group was 0 versus a slight decrease in the weight of placebo-treated patients. More people on aripiprazole experienced weight loss (2.88% aripiprazole, 1.69% placebo) and weight gain (2.88 % aripiprazole, 2.37% placebo).

**Discontinuations due to Vital Sign Abnormalities:**

In the acute mania placebo-controlled trials (CN138007, CN138009, (b) (4) ,CN138074), adverse events directly or potentially related to vital signs which lead to discontinuation, occurred for the adverse events of syncope (0.4%), hypotension (0.2%), orthostatic hypotension (0.2%), and palpitation (0.2%) and no placebo patients. Lightheadedness leading to discontinuation occurred in 2 aripiprazole patients (0.4%) and one placebo patient (0.2%)

- Dosing: In the fixed dose studies (CN 138007, (b) (4) )- the only discontinuation secondary to orthostatic hypotension with syncope occurred in the 15 mg aripiprazole group.

**F7) EKG DATA**

**EKG Assessments:** In the acute mania placebo-controlled trials (CN 138007, CN138009, (b) (4) , CN138074), 12 lead EKGs were collected, in general at screening and at week 3 or discontinuation. EKGs were also collected on patients who switched to open label treatment at week 2 in trials CN 138007, CN138009, (b) (4) . As trial CN 138074 did not have the forced discontinuation based on CGI criteria at week 2, routine EKGs were not performed at this time period.

**Potentially Clinically Significant EKG Changes:** The criteria used to determine PCS EKG changes in the acute mania placebo-controlled trials (CN 138007, CN138009, (b) (4) CN138074) and the incidences of these events, as provided by the sponsor, are provided in the safety section of Appendix B of this document, Table 7.1.9.1.

No patients discontinued from an acute placebo controlled bipolar trial secondary to an EKG abnormality. Sinus tachycardia/ tachycardia as a PCS event occurred in 1/447 aripiprazole patients and no placebo patients. Conduction disorders as PCS events occurred in 4/447 aripiprazole treated and 0/314 placebo treated patients; two of the 4 aripiprazole events were right bundle branch block (RBB).

**Median Change from Baseline in EKG values:** A table (sponsor provided table 7.1.9.6) displaying the mean and median changes from baseline to final on-treatment readings in the placebo-controlled acute mania studies (CN138007, CN 138009, (b) (4) , and CN138074) is provided in the safety section of Appendix B of this document.

The mean change in heart rate among aripiprazole treated patients was +2.51 bpm, median 2.0 compared to a mean change of -0.38 bpm, median -1.0 in placebo treated patients. This is

consistent with the directions of the respective vital sign data. A decrease in the RR interval is seen which likely corresponds to the increase in heart rates.

QT data is discussed in the section "Special Safety Issues" F3.

**G) SPECIAL SAFETY ISSUES:**

**G1) Extrapyramidal symptoms (EPS):**

Assessment of EPS in the bipolar mania program included the incidence of AEs such as dystonic events, parkinsonism, akathisia, and dyskinesia, the incidence of the use of concomitant anticholinergic medication for EPS, and changes from baseline on EPS rating scales (SAS, AIMS, Barnes Akathisia). Additionally, an integrated review of the combined endpoint of reported EPS-related adverse events or use of concomitant anticholinergic medications was performed.

- **Adverse events:** The table detailing the incidence of treatment emergent EPS-related adverse events in the 3-week placebo controlled trials CN 138007, CN 138009, (b) (4) CN 138074, is included in the safety section of the appendix of this document (Table 9.1.1.1.A). 28.9% of the aripiprazole group and 14.2% of the placebo group experienced at least one EPS- related adverse event. Akathisia was the primary adverse event driving this difference with 15% of the aripiprazole group and 3.4% of the placebo group experiencing this.

- EPS and tremor occurred in 5.1% and 5.8% of the aripiprazole patients respectively and 2.2% and 3.4% of the placebo patients respectively. The sponsor notes there were no clinically relevant differences when evaluated by dose, age, gender, or race. From the fixed dose studies, akathisia leading to discontinuation occurred slightly more frequently in the 15 mg group (2.7%) than in the 30 mg group (1.9%) and placebo group (1.3%). The only EPS event leading to discontinuation occurred in the 30 mg group.

- 3.3% of the aripiprazole-treated patients and 1.0% of the placebo-treated patients discontinued because of EPS-related adverse events, primarily secondary to akathisia (2.3% aripiprazole versus 0.5% placebo).

- In study CN 138008, during the 12 week period 62.7% of the haloperidol treated patients and 24% of the aripiprazole-treated patients experienced at least one EPS event (Table 12.5.4 in the safety appendix of this document). The number one reason for discontinuation due to an adverse event for the haloperidol group was "EPS"(18.9% of the haloperidol patients versus 2.9 % of the aripiprazole patient) followed by akathisia (14.2% of haloperidol patients versus 5.1% of aripiprazole patients). The number one and two reasons in the aripiprazole group were depression (6.3% aripiprazole versus 4.1% haloperidol) and akathisia. More aripiprazole patients discontinued secondary to nausea (1.7% versus 0.6%) and lightheadedness (1.7% versus 0%) than haloperidol patients.

- **Anticholinergic Use:** In the three week placebo-controlled trials (CN 138007, CN138009, (b) (4) CN138074) 34/409 (8.3%) placebo treated patients and 118/568 (20.8%) aripiprazole treated patients used anticholinergic medications for the treatment of potential EPS-related adverse events. In both groups, about 94% of the use was of benztropine with trihexyphenidyl and biperiden used otherwise.

- In study CN 138008, it was prohibited by the protocol to use anticholinergic medications to treat the symptoms of EPS. However, 16.6% (28 patients) of the haloperidol patients and 2.9% (5 patients) of the aripiprazole patients did receive anticholinergic treatment. Biperiden was used in about 60-70% of these patients.

- **Composite EPS: Data taken from sponsor tables 9.1.3.1 and 9.1.3.2**

**3-week studies** **CN 138008**

| | **Placebo (n=409)** | **Aripiprazole (n=568)** | **Haloperidol N=169** | **Aripiprazole N=175** |
|---|---|---|---|---|
| **Any EPS-Related AE** | **58 (14.2%)** | **164 (28.9%)** | **112 (66.3%)** | **42 (24.0%)** |
| **Any Anticholinergic Use for EPS** | **34 (8.3%)** | **118 (20.8%)** | **28 (16.6%)** | **5 (2.9%)** |
| **Any EPS related AE or Med Use** | **68 (16.6%)** | **189 (33.3%)** | **112 (66.3%)** | **42 (24%)** |

- **Scales:** The Simpson-Angus scale (SAS), the Abnormal Involuntary Movements Scale (AIMS) and the Barnes Akathisia Rating Scale (Barnes) were completed to assess parkinsonism, dyskinesia, and akathisia respectively.
- In the three week acute mania placebo-controlled studies, there were statistically significant differences in favor of placebo on both the SAS and the Barnes in mean changes from baseline to endpoint and from baseline to highest on-treatment evaluation. The AIMS assessment indicated similar mean changes to endpoint and highest on-treatment evaluation for placebo and aripiprazole groups. These changes are shown below in the sponsor-provided table.
- By dose information (from studies CN138007, (b) (4) can be found in the ISS, page 342, Table 9.1.4.1B. With the exception of the AIMS change at endpoint, aripiprazole 30 mg dosing, generally resulted in less worsening when compared to aripiprazole 15 mg, although the differences between the two are slight and unlikely to be clinically meaningful.

**Table 9.1.4.1A: Mean Change from Baseline to Endpoint and Highest Score, SAS and AIMS Total Score, and Barnes Akathisia Global Clinical Assessment, LOCF Data Set: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| EPS Scale | Placebo | Aripiprazole |
|---|---|---|
| **SAS Total Score**[a] | **N = 394** | **N = 554** |
| Mean Baseline (SE) | 11.33 (0.10) | 11.36 (0.09) |
| Change from Baseline at Endpoint (SE) | 0.03 (0.12) | 0.61 (0.10)** |
| Change from Baseline at Highest Score (SE) | 0.58 (0.13) | 1.45 (0.12)** |
| **AIMS Total Score**[b] | **N = 306** | **N = 455** |
| Mean Baseline (SE) | 0.74 (0.10) | 0.78 (0.08) |
| Change from Baseline at Endpoint (SE)[c] | -0.18 (0.08) | -0.16 (0.07) |
| **Barnes Akathisia**[d] | **N = 395** | **N = 553** |
| Mean Baseline (SE) | 0.52 (0.04) | 0.57 (0.04) |
| Change from Baseline at Endpoint (SE) | -0.06 (0.05) | 0.25 (0.05)** |
| Change from Baseline at Highest Score (SE) | 0.23 (0.06) | 0.67 (0.05)** |

Note: For each analysis, patients in the Safety Sample were required to have both a baseline and an on-treatment assessment for the rating scale that was analyzed.

**($P \leq 0.01$), * ($0.01 < P \leq 0.05$) significantly different from placebo by ANCOVA, controlling for baseline and study center. Means and SEs are model-based (least squares) estimates.

[a] SAS Total Score ranges from 10 to 50. A negative change score indicates improvement.

[b] AIMS Total Score ranges from 0 to 28. A negative change score indicates improvement.

[c] AIMS Total Score was assessed only at endpoint, therefore, change at highest score is equal to change at endpoint.

[d] Global Clinical Assessment Score ranges from 0 (absent) to 5 (severe akathisia). A negative change score indicates improvement.

In study CN138008, the haloperidol group showed worsening on all three scales that was statistically significantly different than the aripiprazole treated patients. These data were discussed in the efficacy section of the review of Trial CN138008.

### G2). Metabolic Analyses

**Glucose metabolism:** The sponsor conducted a search of the adverse event database to assess treatment-emergent adverse events potentially related to glucose dysregulation. The search terms used included diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, hyperglycemia, ketonuria, and glucose/carbohydrate intolerance. Terms referencing "diabetic" and "glucose" were reviewed for potential inclusion. In the 3-week acute mania placebo controlled trials, CN138007, CN138009, (b) (4) and CN138074 2/409, 0.5% of the placebo patients and 0.2% of the aripiprazole treated patients experienced "Any Glucose-Related AE". The aripiprazole event was diabetes mellitus. The placebo events were diabetes mellitus and hyperglycemia. There were 2 cases of any glucose related adverse event in all of bipolar mania trials (n=1170). One was diabetes mellitus and one was a hypoglycemic reaction.

In the four acute mania trials listed above, the incidence of treatment-emergent high glucose measures (baseline ≤ ULN to >ULN, fasting values) was higher in the aripiprazole group (14/158 or 8.9%) than in the placebo group (5/91 or 5.5%). Median changes from baseline to maximum value in fasting glucose measurements were 3.0mg/dL(n=170) in the aripiprazole group and 0.0 mg/dL in the placebo group (n=102). The sponsor performed a Wilcoxon test and notes there was not statistical difference between these changes.

Recently, new labeling language regarding diabetes and glucose related issues has been issued.

**Lipids:** Analysis of change(s) from baseline to maximum value in fasting cholesterol for aripiprazole and placebo patients in the acute mania placebo-controlled trials was performed by the sponsor and indicated a median decrease of 2 mg/dL in the aripiprazole patients (n=199, median baseline 190mg/dL) versus a median increase of 1.0 mg/dL in the placebo patients (n=135, median baseline of 183 mg/dL). This difference was not statistically significant.

The cholesterol changes in study CN138008 were more dramatic than those seen in the studies above. The aripiprazole group in study CN138008 had a median change of 20 mg/dL (9.7%) from a baseline of 189 mg/dL versus the haloperidol group who experienced a median change of 7.5mg/dL from a baseline of 194.0 mg/dL (3.9%). Both studies attempted to use fasting measures.

I did not see a similar analysis of triglyceride data.

**G3) QT assessment: (Dr. Greg Dubitsky performed much of the review of this section.)**

The sponsor utilized three formulae for adjusting the QT interval for heart rate: QTcN=QT/ $RR^{0.37,}$ which has been recommended by the FDA Division of Neuropharmacologoical Drug Products (DNDP) in the past; 2) $QTcE=QT/RR^{0.35}$, the fractional exponent correction formula derived from baseline measurements in the Phase 3 schizophrenia and bipolar mania trails, a procedure recommended previously by DNDP and 3) Bazett's ($QTcB=QT/RR^{0.5}$)[1]. Since the correction using the QTcE formula is based on baseline data from aripiprazole trials and has been advocated by DNDP, this review focuses on this correction.

The following sponsor- provided table displays the information for QTcE data for the pool of 4 short-term, placebo-controlled studies in bipolar mania:

[1] The process of determining the QTcE correction formula is described in detail in a 7-9-99 Memorandum from Dr. Greg Burkhart, former Safety Team Leader, to Dr. Robert Temple, Associate Director for Medical Policy

**Table 9.3.3.1: Analysis of $QT_{cE}$ (Fractional Exponent Correction): 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| | Placebo | Aripiprazole |
|---|---|---|
| Sample Size[a] | 310 | 440 |
| Baseline $QT_{cE}$ (msec) | 391.2 | 390.7 |
| Mean Change at Endpoint (msec) | -2.81 | -1.42 |
| Mean Change at Max $QT_{cE}$ (msec) | -2.35 | -1.03 |
| | **Number of Patients/Number Assessed (%)** | |
| > 450 msec[b] | 1/314 (0.3) | 0/448 (0.0) |
| > 500 msec[b] | 0/314 (0.0) | 0/448 (0.0) |
| ≥ 30 msec increase[c] | 9/312 (2.9) | 29/444 (6.5)* |
| ≥ 60 msec increase[c] | 1/312 (0.3) | 2/444 (0.5) |

** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$) significantly different from placebo. Comparisons of means were done by ANCOVA, controlling for baseline $QT_{cE}$. Comparisons of proportions were done by Fisher's exact test. $QT_{cE}$ = Fractional Exponent Correction Formula ($QT/RR^{0.35}$).

[a] Includes all patients with both a baseline and an endpoint measurement.

[b] Includes all patients with an on-study measurement.

[c] Includes all patients with both a baseline and an on-study measurement.

There were mean decreases in QTcE in both treatment groups, both in terms of mean change to endpoint and mean change to maximum value.

No aripiprazole treated patient in this study pool experienced a QTcE >450msec. However, a significantly higher proportion of patients in the aripiprazole group experienced a prolongation of QTcE of at least 30 msec compared to the placebo group (6.5% vs. 2.9%). About an equal proportion in both groups experienced a prolongation of at least 60msec (0.5% vs 0.3%).

Of the 14 aripiprazole treated patients with a reported adverse event term of QT prolongation, none are from the acute mania placebo controlled trials.

**Deaths Possibly Secondary to Sudden Cardiac Death:** The sponsor performed a review to identify patients who may have died because of sudden cardiac death potentially related to conduction abnormalities (QT). None were from the acute bipolar mania trials.

**G4) Neuroleptic Malignant Syndrome (NMS):** The sponsor searched the adverse events database for all phase II/III completed studies to identify aripiprazole treated patients with NMS as a reported adverse event. Two patients (of 6554) met the sponsor's criteria. One patient was in a schizophrenia trial and one was in the acute bipolar mania trial 138007-19-133. The sponsor notes both of these were reported in the ISS for the NDA. For the bipolar patient, the last dose of aripiprazole 15mg was on day 7 and the event onset was on day 24. The narrative indicates this patient was receiving both haloperidol and risperidone at the time of the NMS."

The sponsor indicates that one new case of possible NMS occurred subsequent to the September 2002 update in a blinded phase of an Alzheimer's trial. Patient 138004-105-429, a 91 year old male, discontinued study medication and was hospitalized on (b) (6) with fever and a urinary tract

infection. The sponsor notes there were no additional symptoms suggestive of NMS and the patient's symptoms resolved on (b) (6)

The sponsor searched for cases of potential NMS was conducted with the symptoms/signs of any fever, muscle rigidity, and abnormal CPK (≥ 3 x ULN) and that no aripiprazole-treated patients were identified as having all of these three features while in clinical studies of aripiprazole.

The Update notes there were no new reports of NMS as an adverse event in the reporting period of the update and no aripiprazole treated patients meeting the three criteria stated above for potential NMS while participating in clinical trials of aripiprazole.

**G5) Seizures:** The incidence of seizure-related adverse events in the three-week placebo controlled trials (CN 138007, CN138009, (b) (4) CN138074) was 1/409 (0.2%) in the placebo group and 2/568 (0.4%) in the aripiprazole group.

**G6) Orthostatic Blood Pressure Changes: (Dr. Greg Dubitsky performed the review of this section.)**

Within the pool of 4 short-term, placebo-controlled studies in patients with bipolar mania (CN138007, CN138009, (b) (4) and CN138074), 3.1% (17/550) of aripiprazole patients and 2.3% (9/391) of placebo patients experienced a decrease in systolic blood pressure of at least 30 mmHg with supine to standing postural change. This difference is not statistically significant.[1] These changes were first observed at day 3 to day 23 of dosing in the aripiprazole group.

In the fixed dose study CN138007, the incidence of an orthostatic blood pressure change, as defined above, was higher in the aripiprazole 30mg group compared to the 15mg group (4.7% vs. 1.6%); the placebo incidence was intermediate (2.3%).

The sponsor performed a search for adverse event terms within this study pool that suggested the occurrence of orthostatic hypotension.[2] The fractions of patients reporting at least one of these events was similar for aripiprazole and placebo (12.3% and 11.2%, respectively). Among the aripiprazole patients, 0.7% dropped out due to an orthostasis-related adverse event compared to 0.2% of placebo patients. One patient in each group had such an event that was classified as serious (syncope in both cases).

Few patients in either group experienced both a 30 mmHg drop in systolic blood pressure along with an orthostasis-related adverse event (0.4% in aripiprazole and 0.3% in placebo).

**G7) Pregnancy-** The sponsor searched the all Phase 2/3 database to identify aripiprazole-treated patients who became pregnant during participation in a clinical study. The following table was created from the sponsor's table, Table S.9.4.4. and displays all pregnancies in the aripiprazole bipolar studies in patients who received aripiprazole. Table S.9.4.4. is not included otherwise within this document but may be found on page 734 of the ISS.

[1] Mantel-Haenszel Chi-Square p-value = 0.5.

[2] Orthostatic hypotension, syncope (including faintness), lightheadedness (including dizziness), and orthostatic lightheadedness.

| Study-Patient # | Study-Patient# | Age | | |
|---|---|---|---|---|
| 138009-42-120 | = 138010-100-116 (maintenance trial) | 26 y | 131 days of exposure to drug in the study with gestational exposure of about 5-6 weeks | Normal delivery of healthy infant (jaundice for 24 hours and shoulder left dislocation) |
| 138010-10-509 | | 44 y | Stopped study day 113 due increase depression, pregnancy test negative. Day 138 follow-up visit, patient thought she was pregnant, positive test at day 141, spontaneous abortion day 151 | Spontaneous abortion |
| 138010-141-266 | | 18y | | Elective abortion |
| 138074-16-98 | = 138037-19-23 (open label) | 27 y | Study day 77 of combined Estimated gestational age 2 weeks-narrative notes she was on oral contraception | Elective abortion |

**G8) Suicidality**

The sponsor searched the all aripiprazole Phase 2/3 studies to identify patients who expressed suicidal ideation, attempted suicide, self-inflicted an injury, or completed suicide.

- For the placebo-controlled studies in Bipolar mania, CN138007, CN138009, (b) (4) and CN138074, 7/568 aripiprazole patients and 6/409 placebo patients experienced any suicide-related event. For the placebo group, all six events were suicidal thought. For the aripiprazole patients, one event was an attempt and the other six were suicidal thought.

- No patient in study CN138008 had a suicide related adverse event.

- In all of the bipolar trials, 25/1141 (2.2%) experienced any suicide-related event. This is comprised of 3 attempts and 22 "thought suicidal".

- MADRS Item 10 analysis: Item 10 specifically addresses suicidal thoughts and is rated 0-6, with a score of 0-2 indicating absence or fleeting suicidal thoughts and 5-6 indicating explicit plans or active preparation. In studies CN138007, CN138009, and (b) (4) the MADRS was administered at baseline and at the end of week 3. In study CN138074, the MADRS was administered weekly during the 3 week study. Among patients with a baseline of 0-2, treatment emergent suicidality, as based on this analysis, was 0.5% (2/448) for aripiprazole-treated patients and 0% (0/293) for placebo treated patients. In study CN138008, the same type of analysis revealed that 1/173 aripiprazole treated patients and 0/162 haloperidol treated patients experienced a change from 0-2 to 5-6.

**G9) Drug Abuse Potential and Overdose –** Aripiprazole has not been studied systematically in humans for either abuse potential, tolerance, or dependence.

The sponsor searched the all Phase 2/3 database to identify patients who took >60 mg of aripiprazole and identified seven patients, all of whom are included in the data found in the package insert. None were from bipolar mania studies.

**G10) Dosing Recommendations:** The only completed fixed dose study did not demonstrate the efficacy of either dose of aripiprazole over placebo. The sponsor provided a table, Table 10 (p 366 ISS) displaying mean change in YMRS from baseline in the two, on face, positive studies, CN138009 and CN138074 and the haloperidol study, CN138008, based on endpoint doses. The data in Table 10 will not be discussed further as the studies they are based upon are flexible dose studies. Otherwise, dosing recommendations may be found in section **VIII. Dosing, Regimen, and Administration Issues** and section **X.C. Labeling**.

**H) Post Marketing- PSUR**

The sponsor provided two post marketing surveillance reports (PSUR) as part of this submission; one in the original ISS for this submission and one in the 120-day update. The sponsor notes that the PSURs contain both clinical and spontaneous reporting databases. The first 6 month PSUR for aripiprazole was issued on March 13, 2003 and covers the interval of July 17, 2002 to January 16, 2003. There is an update for late reports in the spontaneous database which covers eight deaths. These were reviewed. The 2nd PSUR is included in the120 day update and covers the period from January 17, 2003 to July 16, 2003. The Late Breaking Information for this PSUR notes, "No important information was identified after the data-lock point."

PSUR #1: July 17, 2002 - January 16, 2003- The sponsor noted that sales figure from Global Services for the 4th quarter of 2002 were not available prior to this report period. There were no spontaneously reported cases of death and eleven of serious adverse events.

PSUR #2: January 17, 2003 – July 16, 2003 - Drug Exposure for this period was derived by the sponsor from sales and does not include the total amount distributed in all countries. The sponsor estimated that a total of (b) (4) unique patients were exposed between October 1, 2002 and March 31, 2003 based on sales of (b) (4) milligrams and each patient receiving (b) (4). 132 spontaneous reports classified as serious and 14 spontaneous reports of death meeting PSUR criteria were received in this reporting period. The sponsor concluded that "There were no new major findings that have bearing on the established overall safety profile of aripiprazole."

**Blinded data**: The only trial with blinded data when the 120 day update was submitted was from trial CN138010. The blinded data from study CN138010 were reviewed by Dr. Greg Dubitsky for deaths and serious adverse events. This information has been incorporated into previous sections of this review as appropriate.

## Reports Reviewed from the PSURs:

Only the spontaneously reported cases were reviewed as part of the review of the PSURs. Line listings for the spontaneous reports were reviewed for deaths and serious, rare non-fatal events. Reports were read as indicated by this review. (Dr. Greg Dubitsky assisted in the selection of cases for review in both of the PSURs listed below.) Some report synopses may be found in the safety appendix of this document. Others are included below.

**ENCEPHALOPATHY:**

**Hyperammonemic Encephalopathy:** This case was discussed internally at a meeting. Further information is included in the synopsis of the case, which follows.

**MFR # 12152492:** This report presents a 25 year old male bipolar patient with a history of a generalized seizure at the age of three who experienced hyperammonemia, encephalopathy, and unresponsiveness resulting in ICU hospitalization from (b) (6) and treatment with lactulose.

The patient was taking 15 mg aripiprazole daily with no listed concomitant medications. Previous drug history included Depakoate until July, topiramate from July 2002 to November 2002, and olanzapine, which he discontinued one month before the event. Aripiprazole was started in November at 15 mg per day and was discontinued at the time of the event.

Admitting hospital laboratory values showed a high ammonia at 77 umol/l (normal 11-32 umol/l), low glucose (31), INR low at 1 (2.0-3.5 normal), AST was low at 4 (11-35 normal) on admission but within normal in about 2 days, BUN, creatinine, ALP, total bilirubin, and prothrombin times were within normal. Urine toxicology indicated the presence of olanzapine, although he reportedly stopped taking this one month earlier. The ammonia increased to 148 umol/l by the day after hospitalization, 149 umol/l the next day, and reduced to 25 umol/l two days before discharge.

Upon discharge, he had no residual sequelae and follow-up information indicates he has fully recovered. The patient was restarted on olanzapine on January 07, 2003. Subsequent to discharge, the patient received a workup for a urea cycle disorder, which was negative. However, it was thought he could have a potential amino acid disorder. His primary care physician assessed the hyperammonemia as a drug reaction to aripiprazole.

I cannot rule out some contributory role of aripiprazole although the case may be confounded by recent use of other medications and possibly concurrent use of olanzapine (as per an admission toxicology screen) and the possibility of a potential amino acid disorder.

**Anoxic encephalopathy: MFR#12151007:** This case was reported by a physician regarding a 25 year old male patient with a history of insulin dependent diabetes mellitus, suicide attempt, and depression who was found unarousable in his apartment on (b) (6), twenty two days after starting aripiprazole 15 mg, His blood glucose was 82. He was admitted to the ICU in an unexplained coma with a low grade fever and was treated with antibiotics, antivirals, and bromocriptine. His CK was 500-800 but he was suspected to have been in coma for 8-10 hours before being discovered. Serum toxicology was negative and urine toxicology was positive for

tricyclics. The patient was taking amitriptyline for increased back pain. There is a long list of concomitant medications including risperidone, cyclobenzaprine, venlafaxine, amitriptyline, insulin, an unspecified ACE inhibitor, lorazepam, escitalopram, zolpidem, tramadol, quetiapine, ramipril, celecoxib, ranitidine, and fexofenadine although the report notes that the psychiatrist stopped all other psychotropic medications (not specified) three weeks prior to this. The patient was given two sample packs of aripiprazole 15mg dose for symptoms such as auditory and visual hallucinations and anhedonia. The provisional diagnosis is neuroglycopenia hypoglycemia. The patient has received a tracheostomy and was breathing independently with an unchanged neurological status at the time of the Update. This is a complicated case and I am not able to determine what role, if any, aripiprazole contributed.

**OVERDOSE:**

**MFR#122875646**: This case is a 21 year old female who overdosed on aripiprazole (assumed to be between 180-270 mg) and possibly venlafaxine as both bottles were found empty, as a suicide attempt. She experienced coma, status epilepticus, respiratory arrest, atrial fibrillation, bradycardia, QT and QRS prolongation, hypotension, acidosis, and increased CPK as sequelae to this event. Concomitant medications include venlafaxine, escitalopram, and ranitidine. She presented to the ER unresponsive to verbal or tactile stimuli and was given naloxone. She remained unresponsive, experienced seizures and respiratory arrest requiring intubation. During intubation, she experienced atrial fibrillation, bradycardia, prolonged QT and hypotension. She was also acidotic. She eventually recovered without neurologic sequelae and was discharged. In my opinion, this case is too confounded and the details too uncertain to reasonably attribute the chain of events to aripiprazole, however, it is noted that the dose of aripiprazole was not high.

**DEATH:**

Synopses of eight deaths are included in the safety appendix of this document. In general, these cases are confounded by concomitant medications or medical history or paucity of details or unknown causes of death. Therefore, in my opinion, it appears causality cannot be reasonably attributed to aripiprazole in these cases.

**ANAPHYLAXIS**:

**MFR# 12290995:** This is a report from a physician of a 49 year old female patient with schizophrenia on several concomitant medications including benztropine, temazepam, and sertraline, who experienced an anaphylactic reaction on the fifth day of oral aripiprazole treatment of 5 mg daily. She contacted the physician via phone complaining of respiratory difficulties, periorbital swelling, and severe hives. She was advised to go to the ER. In the ER, she was treated with IV diphenhydramine and observed overnight. At the time of the report, all symptoms were resolved. Although the report is not detailed, it is consistent with an anaphylactic drug reaction in presentation symptoms and signs, the time of onset, and the resolution. In my opinion, based on this report, it is reasonable to conclude that aripiprazole is causal or contributory in this event.

**VAGINAL HEMORRHAGE:**

**MFR#12315826:** I was not able to locate this report in either of the PSURs. It appears to be ISR 4191795 from the AERs Database.

This is a case of a female in her 40's who developed vaginal bleeding, easy bruising, and rash while taking aripiprazole. The patient took aripiprazole for two weeks in December, developed a rash, and the medication was discontinued. Aripiprazole was restarted in March. In mid June, the patient developed severe vaginal bleeding, easy bruising, and was hospitalized in late June, secondary to severe thrombocytopenia and anemia which were symptomatic. She was treated with iron, prednisone, and a transfusions of platelets and whole blood. Admission labs showed a platelet count of 3000, hemoglobin of 3.5, and white count of 4.0. Aripiprazole was discontinued the day after admission. Four days after admission, the hemoglobin was 8.0, hematocrit 24.4, white count 3.4 and platelet count 51, 000. A spleen ultrasound was normal. It was noted she ultimately had a splenectomy as treatment for the ITP. The patient was discharged about two weeks after admission with a platelet count of 70,000. Aripiprazole was not restarted. Discharge medications included fluphenazine and benztropine mesylate, medications she had taken for 20 years previous and that were discontinued about 7-10 days before the June hospital admission.

The narrative notes that the patient "had idiopathic thrombocytopenic purpura". I am unsure whether this is being referenced as a chronic condition which was known, an acute development of ITP, which I believe is not common in adults, or whether the diagnosis was made in the hospital. If this patient did not have pre-existing ITP, this case conceivably could represent a drug induced state. I recommend we ask the sponsor to clarify the details if possible and confirm that this is MFR#12315826.

**THROMBOCYTOPENIA:**

**MFR#12257010:** A report from a physician through a BMS sales representative notes a patient was hospitalized after developing thrombocytopenia while taking aripiprazole. The report states no bleeding was noted. The patient required a hematology evaluation. Aripiprazole was discontinued and the platelet count improved. This report is scant in detail but the report as given does not allow me to exclude a possible association to aripiprazole given the dechallenge information reported.

**NEUTROPENIA:**

**MFR#12224267:** This patient experienced several low ANCs, lowest of 1000, while on aripiprazole. Aripiprazole was started on December 19, 2002 and increased on January 10$^{th}$, 2003. Quetiapine was tapered off beginning January 27, 2003 and discontinued on February 14, 2003. She was also on vitamin E. An ANC preceding aripiprazole in November, 2000 was 1677. On February 1$^{st}$, 2003 it was 1100 and by February 11$^{th}$, 2003, it was 1000. ANC was noted "okay" on February 17$^{th}$, 2003, 1300 on February 20$^{th}$, 2003, and 1100 on February 24$^{th}$, 2003. Aripiprazole was discontinued on February 24, 2003. ANC is reported as "okay" on February 27$^{th}$ and 1700 on March 03, 2003. It is possible that aripiprazole treatment enhanced or

contributed to this, however, the "okay" on treatment may make this less likely depending on the value and she may fluctuate around this level.

**PANCREATITIS:**

**MFR#12291886:** This case was reported via a BMS sales representative from a physician of an 18 year old male patient with Asperger's and obsessive-compulsive symptoms who was placed on aripiprazole 15 mg daily. Shortly after initiation, the patient experienced excessive sweating, which was not reported to the M.D. Four weeks later, the patient developed pancreatitis and was diagnosed with gallstones and scheduled for a cholecystectomy. Concomitant medications are listed as Wellbutrin and Celexa. This patient was on a citalopram and had gallstones however, he is young and in my opinion, a contributory role of aripiprazole cannot be completely excluded.

**MFR#12215745:** This report is very scant and states that a health professional reported that a patient developed pancreatitis while on aripiprazole which was medically significant. There is not enough information in this report to make any conclusion.

**HYPONATREMIA:**

**MFR#12186342:** This report is from a pharmacy student who was notified by a physician of a 66 year old male who experienced hyponatremia while taking aripiprazole for approximately one week at 7.5mg/day. Past medical history includes alcohol abuse, hypertension, and COPD and this patient was on concomitant medications which included hytrin, lanoxin, and zestril. If for no other reasons, the concomitant medications make it difficult to reasonably conclude aripiprazole is causative and there are no baseline laboratories given nor are actual laboratories reported.

**MFR#12321139:** This is a pharmacist-reported case that was told by a clinical nurse specialist about a 75 year old patient with history that included diabetes, cardiac failure, triple vessel bypass graft and hypertension who was being treated as an inpatient for major depression. She was on both aripiprazole and hydrochlorothiazide with a reported sodium of 139 prior to initiation of aripiprazole. At some point she fell, was taken to the ER on (b) (6) where she was admitted with a change in mental status. Laboratories that day showed a sodium of 102 and glucose of 152. She was admitted to the ICU. Both aripiprazole and hydrochlorothiazide were stopped and 3% IV sodium chloride was initiated. Her sodium level was 121 the next day. The patient was still hospitalized 6 weeks later. It is possible aripiprazole was involved in this decrease in sodium, perhaps through an interaction with the other medication, in this elderly patient with multiple medical problems although as the patient was on hydrochlorothiazide, this seems a more likely suspect.

**Hyponatremia and Seizures: MFR#12153813:** This report is scant and states only that a physician reported low sodium levels and seizures in a patient using both aripiprazole and escitalopram. The report is not detailed enough to reasonably determine causality.

**PULMONARY EMBOLISM:**

**MFR#12208708:** This is a report of a 36 year old male who reportedly was on aripiprazole 15mg day for about 10 days when he developed back and left side pain and breathing problems. He was hospitalized due to pneumonia and bilateral pulmonary emboli (b) (6). It appears from the report the emboli diagnosis was made on a hospital CT. Chest x-ray indicated pneumonia. The patient was treated with IV heparin and discharged on enoxaparin sodium and warfarin and was asymptomatic on discharge. The report does not list previous medical history. Aripiprazole was discontinued at some point. This patient's pneumonia may have been the precipitating event. It is reasonably not attributed directly to aripiprazole.

**MFR#12254819:** This report contains virtually no information other than a report was made in May of 2003 to a BMS sales representative by a physician that one of his patients on aripiprazole for one week developed a pulmonary embolism. The lack of details makes it difficult to reasonably conclude that aripiprazole was directly attributable but more information would be helpful.

**DVT and Pulmonary Embolism: MFR #12306668:** This is a 45 year old male with a history of alcoholism in recovery for 10 years, diabetes insipidus, and paranoid schizophrenia who developed a pulmonary embolism and deep vein thrombosis after receiving aripiprazole 15 mg daily for 31/2 weeks. Concomitant medications include haloperidol, divalproex sodium, gabapentin, lorazepam, and escitalopram. He was treated with warfarin. The patient continued on aripiprazole and was reportedly doing well at the time of the report. This cannot reasonably be directly attributed to aripiprazole. The history is not detailed and the patient had a risk factor, deep vein thrombosis, was on concomitant medications, and had a history of diabetes insipidus and schizophrenia.

**SYNCOPE AND/OR QT PROLONGATION:**

**MFR #12169926:** This is a 20 year old female with a history including depression and polysubstance abuse who experienced syncope, orthostatic hypotension, and QT prolongation while taking aripiprazole 15 mg. The QTc was 453- 455 (uncorrected 480). Aripiprazole was withheld for one day and the events resolved overnight. She was on concomitant medications including trazodone, venlafaxine, topiramate, and albuterol. The concomitant use of venlafaxine and the overnight resolution make it difficult to determine causality although some interaction between the two drugs is possible. Additionally, the QT intervals can vary considerably throughout the day.

**MFR#12257242:** This is a physician report via a BMS sales representative of a 40 year old hospitalized male who fainted a few hours after taking one dose of aripiprazole and who apparently had cardiac surgery two months prior to this which, per the report, caused him to develop an arrhythmia. He continued on aripiprazole with no further events. The physician who evaluated the syncope felt the arrhythmia was secondary to the coronary artery bypass. It seems reasonably likely, that as presented in this narrative, aripiprazole was not causal.

**LARYNGOSPASM:**

**MFR# 12297453:** This is a report from a physician regarding a 32 year old male with a history of dystonic reactions and drug sensitivity to haloperidol, fluphenazine, and risperidone and cocaine addiction with reported last use within 24 hours to a few days of the event taking aripiprazole 15 mg daily. During the morning after his first dose, he developed a dystonic reaction, drooling, uncontrolled tongue movement, and laryngospasm, was treated with IV diphenhydramine and benztropine and transferred for possible intubation. Apparently, his symptoms subsided and he was returned to the psychiatric unit. Aripiprazole was not re-started.

Not within the narrative of this case but later, the sponsor notes that "the ingestion of aripiprazole prior to the event was questionable." From the narrative, it was not clear to me that ingestion was in question. If this patient took aripiprazole, then it seems reasonable to conclude that this episode of laryngospasm can be considered to be possibly drug induced in a patient with a history of previous dystonic reactions.

**MFR #12301636:** This case is reported by a mother of a 16 year old patient with a history of hypercholesterolemia, mycotic allergy and dust allergy, and similar reaction to this one with risperidone in the past, who experienced throat tightness, laryngospasm, dyspnea, muscle spasms, and trismus while taking 20 mg aripiprazole daily. Trismus developed the day after hospitalization on an inpatient adolescent unit and initiation of aripiprazole. Benztropine was started and aripiprazole continued. The patient was discharged after one week. Three days later, she experienced symptoms of throat swelling and was taken to the ER where she received treatment with IV diphenhydramine and benztropine. Her symptoms subsided and she continued aripiprazole and benztropine. From this narrative, the role of aripiprazole cannot be excluded, again in a patient with a reported past history of a similar reaction to another atypical.

**MFR# 12286795:** This report is from a nurse practitioner of a 36 year old male with a history of schizoaffective disorder who experienced priapism, tongue edema, headache, and acneiform dermatitis while taking aripiprazole. From the narrative, it appears that the tongue edema started very soon after an increase in aripiprazole from 15mg daily, which he had been taking for 2 weeks, to 30 mg. This edema was not considered severe and later decreased. One month after starting aripiprazole, he experienced the rash and later the priaprism. The priaprism resolved with discontinuation of the aripiprazole. This narrative was coded under "Tongue Oedema" , which was apparently not severe enough to stop the medication. This tongue edema possibly was a dystonic reaction, although it is not possible to make a definite conclusion as there are details missing that could aid in this assessment. The priapism, however, does seem drug related and has been reported with aripiprazole treatment. Priapism is in the current label.

**TORTICOLLIS:** These cases appear to be drug related although the "immediate" resolution in third case, if literal, is somewhat unusual.

**MFR#12141842:** This physician report indicates that a 39 year old female with a history of schizophrenia developed a "severe torticollis" on day 10 of 15 mg daily aripiprazole treatment which was treated with a single 3mg dose of cogentin and resolved within one hour.

**MFR#12145025:** This case was reported to a BMS sales representative by a physician. The patient is a 12 year old male with schizophrenia and autism who developed flu-like symptoms,

rash, fever, headache, torticollis, and opisthotonus starting 48 hours after beginning aripiprazole 15 mg daily treatment. He was taken to the ER, hospitalized, and treated with Benadryl. The aripiprazole was discontinued and the events resolved fully.

**MFR#12263398:** This case was reported by a nurse practitioner regarding a 16 year old female patient who was on venlafaxine for depression and was started on aripiprazole for psychotic symptoms. About 2 hours after taking the 2nd dose of aripiprazole 15mg, she a stiff jaw, swollen tongue, and torticollis and was seen at primary care by a physician's assistant who treated with methocarbamol. The patient returned home. One and one half hours later the patient's mother called the nurse practitioner and stated that her daughter was having difficulty swallowing. The patient was sent to an ER where it is reported she developed opisthotonus, which was treated with IV diphenhydramine, with immediate resolution of the symptoms. The ER notes reflect that the patient was having no trouble breathing or swallowing and was having involuntary spasms of her face, neck, and shoulders. She was observed for less than 3 hours after these events in the ER and was discharged with a prescription for diphenhydramine 50 mg every 8 hours. The patient was seen by the nurse practitioner two days later and was reportedly stable. Aripiprazole was not restarted.

**RHABDOMYOLOSIS OR ELEVATED CPK WITHOUT OBVIOUS NMS:**

**MFR #12158440:** This patient is a 17 year old male with a history of schizophrenia, mental retardation and fetal alcohol syndrome, and peanut allergy who experienced neck pain, muscle pain, tooth ache, and headache after receiving aripiprazole orally for approximately one week. Concomitant medications reported were sodium valproate 1500 mg daily and buproprion 100 mg twice a day. Other recent medication use is quetiapine one week prior to starting aripiprazole and acetaminophen use (6-7 doses) over six to eight hours for the neck pain. On admission to the hospital, CPK was 7890 (ULN 300), LDH was 1548 and AST 35. TSH, ALT, and ALP were normal, toxicology screen negative, EKG normal. Three days post admission, his CPK was 10,680. He was treated with IV bicarbonate and reportedly did not develop NMS. This case is confounded by concomitant use of valproate, although the details of how long this patient had been treated with valproate preceding this event are not known. No conclusive role of aripiprazole can be made at this time but some role of aripiprazole in facilitating these events cannot be completely ruled out.

**MFR# 10550994**: This is a 37 year old male schizophrenic patient enrolled in clinical study who developed a CPK elevation (19,800 with baseline 101) 26 days after starting aripiprazole. Aripiprazole was discontinued the day before hospitalization. The patient was asymptomatic and with normal kidney function. His CPK peaked at 25, 531 and declined over 20 days to 427. No medical history or concomitant medication use were reported. The investigator judged the event to be related to study drug. There is a paucity of information to allow one to reasonably attribute this to aripiprazole. However given the data presented as it is, one cannot completely exclude a contributory role of aripiprazole in this event.

**MFR#12225686:** This report is of a 35 year old female on multiple medications including lamictal, ambien, benzodiazepines, vistaril, neurontin, limbitrol, prednisone, vioxx, hydrochlorothiazide, and aripiprazole who developed elevated CPK. She was started on

aripiprazole in mid-December, 2003. At some time, she developed pain in her right shoulder for which she sought medical care. The dates are unclear. The first reported CPK is March 20, 2003 and was 3262. The next CPK, March 26, 2003 was 8779 with BUN slightly low at 7 (8-20 normal) and normal creatinine. The final CPK level reported was March 28, 2003 at 5292. Originally, she was thought possibly to have a rotator cuff tear but the MRI was negative. The MRI did show muscle swelling consistent with rhabdomyolysis and aripiprazole was discontinued although lamictal was not. The patient was not restarted on aripiprazole. Causality is difficult to conclude given the lack of details and multiple concomitant medications a contributory role of aripiprazole cannot be ruled out. It appears the December date is an error as it would precede the event.

**ASTHMA:**

**MFR#12316980**: This is a report from a mother of the patient via a pharmacist about reported increased asthma symptoms and itching in her 12 year old son. The patient had been on aripiprazole for about 18 days and was also on Paxil, Trileptal, xopenex, and Pulmicort. The patient apparently saw a different M.D. than the prescribing one for these concerns and was given pimecrolimus and flucinolone cream. There are not enough details to adequately evaluate this case but it does not appear he required emergent care for the asthma.

**JAUNDICE OR LIVER FUNCTION RELATED:**

**MFR#12291282**: Physician report of a patient who developed jaundice and elevated liver enzymes while on aripiprazole. The patient was on no concomitant medications. The paucity of details does not allow meaningful interpretation.

**MFR#12311239:** This is a physician reported case of a 34 year old female with a history that includes cognitive disorder, hypertension, diabetes, hypothyroidism, and schizophrenia who experienced hepatitis . She was on multiple concomitant medications including olanzapine, lorazepam, rosiglitazone, enalapril, atorvastatin, and niacin. A few days after she began aripiprazole, she began experiencing nausea and vomiting resulting in hospitalization for three days.
Two months before starting aripiprazole, her liver function tests are reported as normal. After 35 days of aripiprazole treatment, laboratory tests showed an INR at 2x the ULN, prothrombin time of 2x the ULN, AST of 1703 (15-46), ALT 2960 (11-66), and slightly low albumin at 3.2 (3.5-5.2). At 52 days after aripiprazole administration, the AST was 50, ALT was 129, and albumin was 3.7. At some point, she was hospitalized for 3 days. A viral hepatitis panel was negative and ultrasound unremarkable. The AST and ALT had returned to normal 22 days after aripiprazole was discontinued. The report notes that one week prior to the hepatitis, she took approximately one month's worth of multivitamins. Although she was on other medications, from the report, it is reasonable to conclude that aripiprazole possibly contributed to this event as the AST and ALT were normal before and after aripiprazole treatment.

**MFR#12161477:** This is a 34 year old male schizophrenic patient who experienced high LFTs (AST and ALT) while taking aripiprazole 15 mg/day for about 28 days. These lab abnormalities were detected during an admission for symptoms of schizophrenia. Other tests including

toxicology, ALP, hepatitis, protein, albumin, CBC, and electrolytes were normal. The physician reporting noted no risk factors for these elevations and no concomitant medications. The AST and ALT levels were normalizing as of the time of the report. The data taken as it is given do not allow one to rule out a role of aripiprazole in the elevations of these liver enzymes.

**VENTRICULAR TACHYCARDIA:**

**MFR#12274122:** This physician report via a BMS sales representative concerns a patient with a medical history of irregular heartbeart who experience ventricular tachycardia on the day aripiprazole 15 mg was started for treatment of psychosis leading to discontinuation of the drug. The event resolved. The paucity of details and previous medical history do not allow definitive conclusions.

**MFR#12280178:** This is a physician report of an 82 year old patient who experienced ventricular tachycardia 7 days after starting aripiprazole 10 mg while being treated for post operative agitation after a triple heart valve repair. She had a medical history that includes congestive heart failure and atrial fibrillation and recently had a stroke. This case of ventricular tachycardia could reasonably be attributed to other factors and is confounded.

## VIII. Dosing, Regimen, and Administration Issues

Contingent upon the primary efficacy measures remaining positive for trials CN138009 and CN138074, dosing recommendations would be a starting dose of 15mg daily, titrated up to 30 mg per clinical response.

The majority of patients in studies CN138009 and CN138074 who remained in double blind treatment at the end of week three (86% and 85% respectively) were on 30 mg. Patients were started and could titrate down as indicated for tolerability. The incidence of dose reduction from 30 mg to 15 mg was 14% in trial CN138009 and 15% in CN138074.

Serious adverse events and adverse events were not significantly worse with the 30 mg group in the fixed dose study and in fact, in the fixed dose study CN138007, more adverse events were seen in the 15 mg group than the 30 mg group although this may be somewhat biased as people were started and could decrease the dose secondary to tolerance issues.

## IX. Use in Special Populations

### A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

These analyses were not powered to detect statistically significant differences with respects to the subgroups age, race, and gender.

**B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

The information below is excerpted from the safety and efficacy sections of this review.

**Safety:** Adverse Events: There was a significant difference in reporting rates based on age 18-50 years old versus ≥ 51years old for four adverse events. Insomnia (p=0.008; OR 1.49 = younger group and OR 0.34 older group), diarrhea (p=0.002; OR=1.26 younger group, OR=0.22 older group), akathisia (p=0.024; OR= 6.85 younger, OR=1.6 older), and accidental injury (p=0.038; OR=3.18 younger group, OR= 0.56 older group) occurred more often in the younger patients.

There was a significant difference in reporting rates based on gender for only one adverse event; accidental injury was reported more frequently among women than men (OR=14.63 women, OR=1 men, p=0.004). A second adverse event, akathisia occurred more frequently in men (OR=14.62) than in women (OR=3.38) although the p-value missed statistical significance (0.052).

The sponsor denoted race as "white", "black", or "other" for purposes of this analysis. There was a significant difference in reporting rates based on race (white, black, other) for the adverse event vomiting; (white OR=2.97, black OR=0.62, other OR=0.5; p=0.016). The number of white patients on either placebo or aripiprazole is about 4-5x that of the number of black patients and about 7x the number of other patients.

**Dose and Adverse Events:** With respect to dosing, the sponsor provided a table (Table S.7.1.3.3 of the ISS) listing the incidences of treatment emergent adverse events by dose in trials CN138007 and (b) (4) A CMH test stratified by dose was used to evaluate this with and without placebo for individual adverse events occurring in at least 1% of the pooled group. Data from the without placebo column were reviewed. No individual adverse event was reported at a statistically significantly higher rate between the two doses. Percentage-wise, vomiting occurred in almost twice as many aripiprazole 15 mg patients as aripiprazole 30 mg patients (11.3% versus 5.8%; placebo 4.7%). Numerically, more aripiprazole patients on 15 mg doses experienced any adverse event than either aripiprazole 30 mg patients or placebo patients (86.7%, 81.9%, and 77.9% respectively). (Table S.7.1.3.3. cannot be found in this document but is in the ISS-ISE, pages 447-452).

**Efficacy :** (As displayed in Table 6.1.8, which is duplicated in the appendix of this document.)

**Race:** Patients coded as "black" and "other" showed no statistical difference between aripiprazole and placebo groups while the patients coded as "white" did. There are about 4x as many "white" patients as "black" and about 7x as many "white" patients as "other" which may account for this. However, looking at absolute changes in the mean scores on YMRS, the white patients sustained about a 3.9 point decrease while the black and other patients experienced only a 2.2-2.3 decrease.

**Age:** Age ≤ 50 versus age ≥ 50 showed statistically significant changes between aripiprazole and placebo although the changes in the two age groups are similar with both achieving about a 3.2 point change. There are 4.4x more patients in the younger group than the older.

**Psychiatric Variables:** With regard to "type of episode" and "rapid cycling", there was some difference between patients with a baseline manic episode and those with a baseline mixed episode with decreases of almost 4 in the manic group and only about 2.3 in the mixed group. Both rapid cycling and non rapid cycling patients showed statistically significant differences between aripiprazole and placebo.

**Mean YMRS total scores at baseline:** Mean YMRS total scores were divided by the sponsor into two groups: ≤ median of 27 and ≥ median of 27. The aripiprazole patients ≤ to the median did only slightly better than placebo (p=0.043, decrease of about 2 points) while the patients ≥ to the median did almost 4.8 points better (p=0.001).

Overall, these studies are not powered adequately to make definitive conclusions with regard to this issue and generally, I am uncertain what the significance of the findings is.

### C. Evaluation of Pediatric Program

The sponsor has been issued a Pediatric Written Request.

### D. Comments on Data Available or Needed in Other Populations

It might be helpful to have fixed dose studies to better understand dose to safety and efficacy relationships. These were not provided with the negative fixed dose study and the second fixed dose study was terminated.

## X. Conclusions and Recommendations

### A. Conclusions

(b) (4)

**S002:** Contingent upon statistically significant results after the requested re-analyses, the primary efficacy data from trial CN138009 and CN138074 meet the pre-agreed criteria for efficacy and the results indicate that aripiprazole offers some utility over placebo in the treatment of acutely manic or mixed Bipolar I patients.

The low retention seen in CN138009, a three week trial, is somewhat bothersome and patients are not "well" upon study termination. However, those in the study and taking aripiprazole are doing better than the placebo patients and the difference likely is clinically meaningful. These results may reflect the difficulty in treating this population the robustness of the drug or some combination thereof. For these reasons, I believe the data can be viewed as supportive of some utility in the acute treatment of bipolar patients, again pending the results of reanalysis. (b) (4)

In study CN138074, the retention rates are about equal (by LOCF) between groups and just over 50%. Again, this may reflect the difficulty in treating these patients or it may reflect the actual robustness of the drug or some combination thereof. However, this study demonstrated efficacy at both weeks 2 and 3 by LOCF and OC analysis on the primary endpoint. Additionally, the four key secondary efficacy measures were all statistically significant in favor of aripiprazole.

Study CN138007, the only fixed dose study the sponsor completed is negative. The mean changes at week three are higher in all groups than those seen in CN138009 and CN138074The sponsor submitted 3 trials with supplemental NDA 21436 002. Of these three trials, the fixed dose study is negative and pending a change in result after re-analyses requested, the two flexible dose studies indicate some utility of aripiprazole in the treatment of acutely manic or mixed Bipolar I patients.

### B. Recommendations

I recommend that the Division consider an approvable action on supplemental NDA 21436/S002. This recommendation is contingent upon data re-analyses of both pivotal trials yielding significant results as outlined in the body of this review. With this said, it is my opinion that the data of study CN138009 provide support for two weeks of efficacy in acutely manic patients and that the data of study CN138074 provide support for both two and three weeks. (b) (4)

(b) (4)

(b) (4)

Specific labeling recommendations and requests are outlined or discussed in the next section of this review.

Further follow up by the sponsor of events of DVT /PE, pancreatitis, and a description of what occurs in overdose is requested. Additionally, several cases in the PSUR may have further information that would aid in the evaluation of these events. These are discussed in the safety review section of this document under H. Post Marketing.

## C. Proposed Labeling

The following are based on a review of the labeling sent with supplement 002 on June 23, 2003. All conclusions regarding efficacy are contingent upon maintaining positive results after the re-analyses as discussed elsewhere in this review. Otherwise, the following are my labeling recommendations to the Division Director and Team Leader.

CLINCAL PHARMACOLOGY
Clinical Studies :

(b) (4)

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(b) (4)

# XI. Appendix

## A. Individual More Detailed Study Reviews (If performed)

(b) (4)

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**APPENDIX B. Other Relevant Materials**
CRF audit:

| Trial | Patient I.D. |
|---|---|
| **CN138007** | 23-479 |
| | 44-273 |
| **CN138008** | 7-229 |
| | 32-57 |
| | 43-5 |
| | 61-61 |
| | 122-314 |
| | 133-330 |
| **CN138009** | 6-71 |
| | 8-83 |
| | 9-335 |
| | 26-197 |
| | 8-83 |
| | 9-335 |
| | 26-197 |
| | 36-270 |
| | 44-164 |
| | 52-238 |
| **CN138010** | 1-365 (=CN138007-37-514) |
| | 32-35 (=CN138007-55-27) |
| | 58-326 (=CN138009-29-309) |
| | (b) (4) |
| | (b) (4) |
| | 100-42 (=CN138009-42-37) |
| | 146-503 |
| | 3-3 |
| | 34-95 |

**COSTART AUDIT**

| Preferred Term | Investigator Term |
|---|---|
| Abnormal behavior | Intermittent nonpurposeful lip puckering |
| Exfoliative dermatitis | Peeling feet |
| | Dry scaly feet |
| Infection | Toe infection |
| | Athlete's foot |
| | Cold symptoms |
| URI | cold |
| Inflammation | Inflammed S1 nerve |
| | Inflammed posterior cervix with whitish |
| photosensitivity | Sunburn, skin sensitive |

| | |
|---|---|
| | Eyes sensitive to light |
| asthenia | Body aches, fatigue |
| myalgia | Body aches, fatigue |
| | Chest pain (non cardiac) muscle |
| myopathy | Restless quivering muscle |
| depression | Depressed with suicidal thoughts |
| | Relapse of depression with suicidal thoughts |
| Thought suicidal | Depressed with suicidal thoughts |
| Reaction manic depressive | Bipolar Disorder with suicidal ideation |
| Decompensation psychiatric | Exacerbation of mania |
| confusion | Flight of ideas |
| Liver damage | Mild toxic exposure |
| Creatine phosphokinase increased | Elevated creatinine kinase/CK-MB728/25 |
| Urinary retention | Urinary hesitancy |
| twitch | Facial tic |
| | EPS-mouth twitching |
| Cramp muscle | |
| salivation | Drooling EPS |
| Disorder of joint | Stiff & resist of elbows |
| Pain abdomen | Diarrhea and GI cramping |
| Neurosis | Intermittent PTSD nightmares |
| Movement disorder | Pill rolling hand movement |
| Disorder peripheral vascular | Raynaud's phenomenon |
| Abnormal urine | RBC in urine |
| flatulence | Satiety (fullness in her stomach) |
| URI | Tickle in throat |
| anxiety | Throat blockage |

**Study Principal Investigators: CN138007**

| | |
|---|---|
| 002 | Mohammed Bari, M.D. |
| 008 | Rif S. El-Mallakh, M.D. |
| 011 | Mark B. Hamner, M.D. |
| 012 | Radwan Haykal., M.D |
| 013 | Gunnar L. Larson, M.D. |
| 014 | Joseph P. McEvoy, M.D. |
| 017 | Richard Pearlman, M.D. |
| 018 | Joachim Raese, M.D. |
| 019 | Samuel Craig Risch, M.D. |
| 021 | Norman Sussman, M.D. |
| 022 | Alan Swann, M.D. |
| 023 | Kathleen Toups, M.D. |
| 024 | Harold D. Udelman, M.D. |
| 025 | Richard Wang, M.D. |
| 026 | David Brown, M.D. |
| 034 | Dan Anderson, M.D. (PI as of 9-09-01), Craig Wronski, DO |

| | |
|---|---|
| 036 | Asaf Aleem, M.D. |
| 037 | Brendan T. Carroll, M.D. |
| 038 | Lori L. Davis, M.D. |
| 039 | G. Michael Dempsey, M.D. |
| 040 | Jose M. Canive, M.D. |
| 042 | Joseph F. Goldberg, M.D. |
| 044 | Mahlon S. Hale, M.D. |
| 047 | Michael Lambert, M.D. (PI as of 6-27-01), Frederick Petty, M.D., PhD |
| 048 | Neil M. Richtand, MD, PhD |
| 049 | Judy S. Rivenbark, M.D. |
| 050 | Tram K. Tran-Johnson, PharMD, PsyD |
| 053 | Laszlo Gyulai, M.D. |
| 055 | Robert C. Jamieson, M.D. |
| 056 | Gregory Bishop, M.D. (PI as of 3-01-01), Christopher Kelsey,M.D. |
| 058 | Rakesh Ranjan, M.D. |
| 059 | Jeffrey L. Rausch, M.D. |
| 060 | Mark . Townsend, M.D. |
| 061 | David Morin, M.D., Carlos A. Zarate, Jr. M.D. (PI as of 12-28-00) |
| 075 (non IND) | Eduardo Kalina, M.D. |
| 076 | Kenneth N. Sokolski, M.D. |
| 077 (non IND) | Ignacio Rosales, M.D. |
| 078 | Marilyn J. Vache, M.D. (PI as of 10-18-00), J. Charlene Trascy, DO |
| 081 | Rahim Shafa, M.D. |
| 088 (non IND) | Roxana B. Galeno, M.D. |
| 090 | Seeth Vivek, M.D. |
| 093 (non IND) | Miguel Herrera Estrella, M.D. |
| 096 | Kathleen Degen, M.D. |
| 099 | Richard Douyon, M.D. |
| 102 | Leon Rubenfaer, M.D. |
| 103 | Lawrence D. Ginsberg, M.D. |
| 105 | Mary Ann Knesevich, M.D. |
| 106 | Jasbir Kang, M.D. |
| 107 | Adam Lowy, M.D. (PI as of 1-11-01), Teresa Pigott, M.D. |
| 108 | Sohail Punjwani, M.D. |
| 110 | Azfar Malik, MD, MBA |
| 112 | Michael G. Plopper, M.D. |
| 116 | Michael Banov, M.D. |
| 117 (non IND) | Jose de Jesus Castillo, M.D. |
| **STUDY CN 138009** | |
| 003 | Raj Shiwach, M.D, M.R.C., Psych. |
| 004 | Tram K. Tran-Johnson, PharmD, PsyD |
| 005 | Barry R. Rittberg, M.D. |
| 006 | Steven Brannan, M.D., Charles Bowden, M.D. (PI as of 6-26-01) |
| 007 | Ronald Brenner, M.D. |

| | |
|---|---|
| 008 | Franca Centorrino, M.D. |
| 009 | Andrew J. Cutler, M.D. |
| 010 | Anita Kablinger, M.D. |
| 011 | Philip G. Janicak, M.D. |
| 012 | Terence Ketter, M.D. |
| 017 | Eduardo Dunayevich, M.D. |
| 018 | Denis Mee-Lee, M.D. |
| 020 | Cherian Verghese, M.D. |
| 021 | Richard H. Weisler, M.D. |
| 022 | Andrew Winokur, M.D., PhD |
| 023 | Evagelos Coskinas, M.D., PhD, Himasiri DeSilva, M.D. (PI as of 9-18-01) |
| 024 | David Daniel, M.D. |
| 025 | John Downs, M.D. |
| 026 | James Russell, M.D., Anne Andorn, M.D. (PI as of 9-19-00) |
| 027 | Paul Markovitz, M.D., PhD. |
| 028 | Frederick Schaerf, M.D., PhD. |
| 029 | Anantha Shekhar, M.D., PhD. |
| 030 | Bijan Bastani, M.D. |
| 031 | Christopher Chung, M.D. |
| 034 | Patricia Suppes, M.D., PhD |
| 036 | Howard Keith Mason, M.D. |
| 040 | Richard James Farrer, M.D. |
| 041 | Donald Hilty, M.D. |
| 042 | Scott Hoopes, M.D. |
| 043 | Robert Taylor Segraves, M.D., PhD. |
| 044 | Bradley C. Diner, M.D. |
| 045 | Robert Lynn Horne, M.D. |
| 051 | Joachim D. Raese, M.D. |
| 052 | Michael T. Levy, M.D. |
| 053 | Louise Beckett, M.D. |
| 057 | Natalie Gershman, M.D. |
| 058 | A. Ari Albala, M.D. (PI as of 4-27-01) |
| 059 | Dennis M. Pavlinac, M.D. |
| **STUDY CN138074** | |
| 001 | Lawrence D. Ginsberg, M.D. |
| 002 | Laszlo Gyulai, M.D. |
| 003 | Leon Rubenfaer, M.D. |
| 004 | Rakesh Ranjan, M.D. |
| 005 | Joachim Raese, M.D. |
| 007 | Philip G. Janicak, M.D. |
| 008 | Anantha Shekhar, M.D. |
| 009 | Paul E. Keck, Jr., M.D. |
| 010 | Ramanath Gopalan, M.D. |
| 011 | Joseph . McEvoy, M.D. |

| | |
|---|---|
| 012 | Tram K. Tran-Johnson, PharmD, PsyD |
| 013 | A. Ari Albala, M.D. |
| 014 | Bradley C. Diner, M.D. |
| 015 | Denis Mee-Lee, M.D. |
| 016 | Michael Plopper, M.D. |
| 017 | Adam Lowy, M.D. |
| 018 | Andrew J. Cutler, M.D. |
| 021 | Rif S. El-Mallakh, M.D. |
| 022 | Alan Swann, M.D. |
| 023 | David Brown, M.D. |
| 024 | Bijan Bastani, M.D. |
| 025 | Neil M. Richtand, M.D., PhD. |
| 026 | Natalie Gershman, M.D. |
| 027 | Franca Centorrino, M.D. |
| 028 | Himasiri DeSilva, M.D. |
| 029 | Lori L. Davis, M.D. |
| 030 | Sohail Punjwani, M.D. |
| 031 | Ronald Brenner, M.D. |
| 034 | Arifulla Khan, M.D. |
| **STUDY CN 138008-NON IND STUDY** | |
| 002 | Prof. Jaromir Svestka |
| 006 | Dr. G.A.D. Hart |
| 007 | Dr. Rykie Marlet Libenberg |
| 010 | Dr. Joerg Walden |
| 018 | Dr. Wolfgang Maier |
| 022 | Dr. Jaroslaw Strzelec |
| 023 | Dr. Janusz Bukowski |
| 024 | Prof . Aleksandeer Araszkiewicz |
| 027 | Dr. Wojciech Stankiewicz |
| 028 | Dr. Izabela Niewiadomska |
| 030 | Dr. Mieczyslaw Janiszewski |
| 032 | Dr. Dominika Dudek |
| 034 | Prof. Anna Grzywa |
| 035 | Prof. Eugenio Aguglia |
| 036 | Dr. Alessandro Lenzi |
| 037 | Dr. Carlo Andrea Robotti |
| 038 | Prof. Giovanni-Battista |
| 039 | Prof. Giancarlo Nivoli |
| 040 | Dr. Giampaolo Minnai |
| 042 | Dr. Franco Garonna |
| 043 | Dr. Horacio Firmino |
| 048 | Dr. Andre De Nayer |
| 049 | Dr. Jos Bollen |
| 051 | Dr. Peeter Jaanson |

| | |
|---|---|
| 052 | Dr. Katrin Eino |
| 053 | Dr. Ljudmilla Väre |
| 054 | Prof. Raisa Andrezina |
| 055 | Dr. Paulis Revelis |
| 056 | Prof. Benjaminas Burba |
| 057 | Prof. Algirdas Dembinskas |
| 060 | Prof. Jean-Michel Azorin |
| 061 | Dr. Georges Pierre Badet |
| 067 | Dr. Pierre Goron-Parry |
| 070 | Dr. Patricia Parry-Pousse |
| 071 | Dr. Gerard Pupeschi |
| 074 | Dr. Georges Zaykine |
| 075 | Dr. Daniel Dassa |
| 080 | Prof. Fabrizio Ciappi |
| 083 | Dr. Eleni Palazidou |
| 084 | Dr. Sophia Frangou |
| 085 | Dr. Enric Alvarez |
| 086 | Dr. Eduard Vieta |
| 087 | Dr. Wolfgang Gaebel |
| 088 | Dr. Christiane Hornstein |
| 091 | Dr. Michael T. Theodores |
| 098 | Dr. Rainer Danzinger |
| 099 | Dr. Siegfried Kasper |
| 101 | Prof. Vera Folnegovic-Smalc |
| 102 | Prof. Ljiljana Moro |
| 103 | Prof. Miro Jakovljevic |
| 104 | Prof. Nikola Mandic |
| 106 | Dr. Jiri Pisvejc |
| 107 | Dr. Patrick Briant |
| 108 | Dr. Claude Emile Pages |
| 113 | Prof. Manuel Franco |
| 115 | Dr. Mocrane Abbar |
| 122 | Dr./Prof. Marcio Versiani |
| 123 | Dr. Arthur Guerra De Andrade |
| 126 | Dr. Jef Hulselmans |
| 128 | Dr. Jose de Jesus Castillo Ruiz |
| 129 | Dr. Miguel herrera |
| 130 | Dr. Juan Ignacio Rosales Barrera |
| 133 | Dr. Jose Alfonso Ontiveros |
| 134 | Prof. Sergey N. Mosolov |
| 135 | Dr. Margarita A. Morozova |
| 137 | Prof. Sveltana I. Bogoslovskaya |
| 138 | Prof.  Yuri Alexandrovsky |
| 139 | Prof. Mikolay G. Neznanov |

Clinical Review Section

| | |
|---|---|
| 142 | Prof. Kausar K. Yakhin |
| 144 | Prof. Denis L. Shapovalov |
| 145 | Dr. Sergey I. Dmitrenkov |
| 146 | Prof. Anatoly B. Smulevich |
| 147 | Prof. Mikhail S. Sheifer |
| 149 | Prof. Galina P. Panteleeva |
| 152 | Prof. Victor A. Kontsevoy |

Study Schedule for Trial CN138008

1.1 Flow Chart/Time and Events Schedule

| | *STUDY VISITS* | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | DAY | | | | | | | END OF WEEK | | | | | |
| | Screening 1 - 7 days | Baseline (Randomization) 1 | 4 | 7 | 10 | 14 | 21[g] | 4 | 5 | 6 | 8 | 10 | 12[a] |
| **PROCEDURE** | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | |
| Demographic Data | X | | | | | | | | | | | | |
| Entrance Criteria | X | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | |
| Psychiatric History | X | | | | | | | | | | | | |
| Previous medications | X | | | | | | | | | | | | |
| **EFFICACY** | | | | | | | | | | | | | |
| Y-MRS | X | X[b] | X | X | X | X | X | X | X | X | X | X | X |
| CGI - BP | | X[b] | X | X | X | X | X | X | X | X | X | X | X |
| PANSS | | X[b] | | | | | X | | | X | | | X |
| MADRS | | X[b] | X | X | X | X | X | X | X | X | X | X | X |
| **SAFETY** | | | | | | | | | | | | | |
| Physical Exam | X | | | | | | X | | | | | | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Weight | X | | | | | | X | | | | X | | X |
| ECG Lead | X | | | | | | X | | | | X | | X |
| Clinical Laboratory Tests[c] (serum, hematology, urine) | X | | | | | | X | | | | X | | X |
| Lithium and Divalproex levels | X[d] | | | | | | | | | | | | |
| Pregnancy test (WOCBP) | X[e] | | | | | | X | | | | X | | X |
| Blood alcohol test | X | | | | | | | | | | | | |
| SAS | | X[b] | | X | | X | X | | | X | | | X |
| AIMS | | X[b] | | | | X | X | | | X | | | X |
| Barnes Akathisia | | X[b] | | X | | X | X | | | X | | | X |
| Adverse events | | X | X | X | X | X | X | X | X | X | X | X | X |
| **PHARMACOECONOMICS/QUALITY OF LIFE** | | | | | | | | | | | | | |
| Pharmacoeconomic Measures | | X | | X | | X | X | X | X | X | X | X | X |
| PFSR | | | | X | | | | X | | X | | | X |
| MAS | | X | | X | | | | X | | X | | | X |
| Q-LES-Q[f] | | X | | | | | | X | | X | | | X |
| **OTHER** | | | | | | | | | | | | | |
| Concomitant Therapy Form | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Study Therapy Form | | | X | X | X | X | X | X | X | X | X | X | X |
| Drug Accountability Form | | X | | X | | X | X | X | X | X | X | X | X |
| Baseline Visit Form | | X | | | | | | | | | | | |
| End of Study Form | | | | | | | X | | | | | | X |

[a] End of study or at the time of earlier discontinuation.

[b] Evaluations should be done prior to administration of first dose of study medication.

[c] Including prolactin level.

[d] May be reassessed at baseline, if necessary.

[e] Serum or urine pregnancy test should be performed within 72 hours of the first administration of randomized study medication.

[f] Abbreviated version.

[g] End of Week 3 study or at the time of earlier discontinuation.

**Table 8.4B: End of Baseline Ratings, Randomized Sample**

| Characteristic | | Haloperidol N = 172 | Aripiprazole N = 175 | Total N = 347 |
|---|---|---|---|---|
| Y-MRS Total Score | Mean | 31.5 | 31.1 | 31.3 |
| | Median | 30.0 | 30.0 | 30.0 |
| | Minimum - Maximum | 20.0 - 54.0 | 20.0 - 54.0 | 20.0 - 54.0 |
| | SE | 0.6 | 0.5 | 0.4 |
| CGI-BP Severity Score – Mania | Mean | 4.9 | 5.0 | 5.0 |
| | Median | 5.0 | 5.0 | 5.0 |
| | Minimum - Maximum | 3.0 - 7.0 | 3.0 - 7.0 | 3.0 - 7.0 |
| | SE | 0.1 | 0.1 | 0.0 |
| | Missing | 1 | 1 | 2 |
| CGI-BP Severity Score – Depression | Mean | 1.4 | 1.3 | 1.3 |
| | Median | 1.0 | 1.0 | 1.0 |
| | Minimum - Maximum | 1.0 - 5.0 | 1.0 - 6.0 | 1.0 - 6.0 |
| | SE | 0.1 | 0.1 | 0.0 |
| | Missing | 1 | 1 | 2 |
| CGI-BP Severity Score - Overall | Mean | 4.5 | 4.5 | 4.5 |
| | Median | 5.0 | 5.0 | 5.0 |
| | Minimum - Maximum | 1.0 - 7.0 | 1.0 - 7.0 | 1.0 - 7.0 |
| | SE | 0.1 | 0.1 | 0.1 |
| | Missing | 1 | 1 | 2 |
| PANSS Total Score | Mean | 62.6 | 61.8 | 62.2 |
| | Median | 60.0 | 59.0 | 60.0 |
| | Minimum - Maximum | 35.0 - 130.0 | 36.0 - 131.0 | 35.0 - 131.0 |
| | SE | 1.3 | 1.2 | 0.9 |
| | Missing | 2 | 1 | 3 |

2

2) Patient Disposition trial 138008-Acute Phase: Table 8.1

**Table 8.1: Disposition of Patients**

| | Number of Patients (%)[a] | | |
|---|---|---|---|
| **Patient Status** | **Haloperidol** | **Aripiprazole** | **Total** |
| Enrolled | -- | -- | 372 |
| Baseline failure | -- | -- | 25 |
| **Randomized** | 172 | 175 | 347 |
| **Completed First 3 Weeks**[b] | 95 (55.2) | 134 (76.6) | 229 (66.0) |
| **Discontinued First 3 Weeks** | 77 (44.8) | 41 (23.4) | 118 (34.0) |
| AE | 53 (30.8) | 17 (9.7) | 70 (20.2) |
| Lack of efficacy | 6 (3.5) | 12 (6.9) | 18 (5.2) |
| Patient withdrew consent | 12 (7.0) | 9 (5.1) | 21 (6.1) |
| Patient unreliability | 0 | 1 (0.6) | 1 (0.3) |
| Lost to follow-up | 4 (2.3) | 0 | 4 (1.2) |
| Other known cause[c] | 2 (1.2) | 2 (1.1) | 4 (1.2) |
| **Did not enter Weeks 4 - 12** | 8 (4.7) | 5 (2.9) | 13 (3.7) |
| Lack of efficacy | 2 (1.2) | 5 (2.9) | 7 (2.0) |
| AE | 6 (3.5) | 0 | 6 (1.7) |
| **Entered Weeks 4 - 12** | 87 (50.6) | 129 (73.7) | 216 (62.2) |
| **Completed 12 Weeks** | 50 (29.1) | 89 (50.9) | 139 (40.1) |

TABLE 8.2A

**Table 8.2A: Number of Patients in Samples**

| Sample | Haloperidol | Aripiprazole | Total |
|---|---|---|---|
| Randomized[a] | 172 | 175 | 347 |
| Safety[b] | 169 | 175 | 344 |
| Efficacy[b] | 164 | 174 | 338 |
| Patients who completed Week 3, with a CGI-BP (mania) Score < 4 and a MADRS Total Score < 18 at Week 3 | 77 | 112 | 189 |

Protocol CN138008

Source: Appendices 8.1.1, 9.1, 10.1A, 10.6, 10.7

[a] Three patients were randomized but never treated. Patients 138008-35-369 and 138008-84-34 were randomized to haloperidol but withdrew consent. Patient 138008-27-54 was randomized to aripiprazole but was discontinued because of having taken prohibited anti-hypertensive medication.

[b] Patient 138008-85-88 was randomized to haloperidol but treated with aripiprazole.

3) Incidence of Treatment Emergent Adverse Events by time period in study CN138008:

**Table 7.2.2.1: Incidence of Treatment-Emergent AEs by Time of First Onset (at Least 1% Incidence in the Aripiprazole Group during Any Time Interval): 26-Week Active-Controlled Study in Acute Bipolar Mania (CN138008), Safety Sample**

| | Number of Patients | | | | | |
|---|---|---|---|---|---|---|
| **Day of First Onset** | **≤ 3 Weeks (≤ 21 Days)** | | **4 - 12 Weeks (22 - 84 Days)** | | **> 12 Weeks (≥ 85 Days)** | |
| **Body System/ Primary Term[a]** | **Haloperidol** | **Aripiprazole** | **Haloperidol** | **Aripiprazole** | **Haloperidol** | **Aripiprazole** |
| **Number Entering Interval** | **N = 169** | **N = 175** | **N = 90** | **N = 135** | **N = 34** | **N = 55** |
| Disorder Joint | 2 (1.2) | 0 | 0 | 0 | 0 | 1 (1.8) |
| **Nervous System** | | | | | | |
| Insomnia | 11 (6.5) | 21 (12.0) | 1 (1.1) | 3 (2.2) | 0 | 1 (1.8) |
| Akathisia | 35 (20.7) | 18 (10.3) | 3 (3.3) | 2 (1.5) | 0 | 0 |
| Extrapyramidal Syndrome | 52 (30.8) | 12 (6.9) | 6 (6.7) | 3 (2.2) | 0 | 0 |
| Lightheadedness | 4 (2.4) | 11 (6.3) | 1 (1.1) | 2 (1.5) | 0 | 0 |
| Agitation | 7 (4.1) | 9 (5.1) | 1 (1.1) | 3 (2.2) | 0 | 0 |
| Somnolence | 9 (5.3) | 9 (5.1) | 2 (2.2) | 7 (5.2) | 0 | 0 |
| Tremor | 11 (6.5) | 8 (4.6) | 5 (5.6) | 4 (3.0) | 0 | 0 |
| Anxiety | 9 (5.3) | 4 (2.3) | 1 (1.1) | 3 (2.2) | 0 | 0 |
| Depression | 11 (6.5) | 4 (2.3) | 10 (11.1) | 14 (10.4) | 0 | 2 (3.6) |
| Dystonia | 13 (7.7) | 2 (1.1) | 0 | 0 | 0 | 0 |

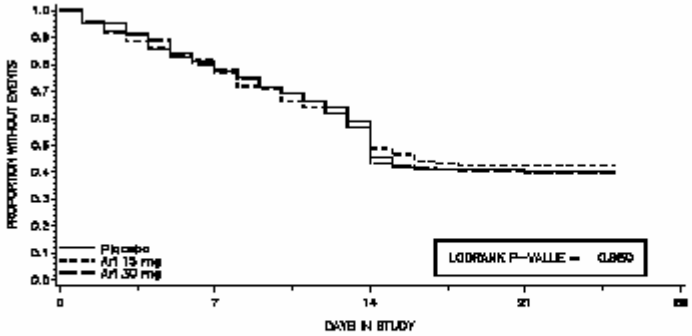
**Table S.7.3: Protocol Deviations of Clinical Relevance**

| Protocol Deviation | Treatment Group | Patient Number |
|---|---|---|
| Used prohibited concomitant medications[e] | aripiprazole | 138008-2-225 (oxazepam) |
| | aripiprazole | 138008-7-15 (lorazepam) |
| | haloperidol | 138008-7-17 (lorazepam) |
| | aripiprazole | 138008-7-110 (alprazolam) |
| | haloperidol | 138008-7-128 (lorazepam) |
| | aripiprazole | 138008-35-311 (lorazepam) |
| | aripiprazole | 138008-36-247 (lorazepam) |
| | aripiprazole | 138008-38-166 (lorazepam) |
| | haloperidol | 138008-40-29 (lorazepam) |
| | aripiprazole | 138008-40-87 (haloperidol) |
| | haloperidol | 138008-42-90 (lorazepam) |
| | aripiprazole | 138008-42-97 (lorazepam) |
| | aripiprazole | 138008-42-226 (lorazepam) |
| | aripiprazole | 138008-42-237 (lorazepam) |
| | haloperidol | 138008-42-258 (alprazolam & delorazepam) |
| | haloperidol | 138008-48-164 (procyclidine) |
| | haloperidol | 138008-54-60 (clonazepam) |
| | aripiprazole | 138008-60-254 (oxazepam) |
| | aripiprazole | 138008-61-61 (lorazepam) |
| | aripiprazole | 138008-71-185 (lorazepam) |
| | aripiprazole | 138008-74-101 (oxazepam) |
| | haloperidol | 138008-75-3 (lorazepam) |
| | aripiprazole | 138008-75-23 (oxazepam) |
| | aripiprazole | 138008-75-67 (oxazepam) |
| | aripiprazole | 138008-75-220 (lorazepam) |
| | aripiprazole | 138008-88-20 (lorazepam) |
| | aripiprazole | 138008-95-138 (lorazepam) |
| | aripiprazole | 138008-101-125 (lorazepam) |
| | aripiprazole | 138008-101-215 (lorazepam) |
| | aripiprazole | 138008-103-353 (lorazepam) |
| | aripiprazole | 138008-106-104 (oxazepam) |
| | aripiprazole | 138008-108-107 (oxazepam) |
| | haloperidol | 138008-113-172 (clorazepate) |
| | aripiprazole | 138008-115-109 (lorazepam) |
| | haloperidol | 138008-115-132 (lorazepam) |
| | aripiprazole | 138008-115-134 (lorazepam) |
| | aripiprazole | 138008-115-140 (lorazepam) |
| | aripiprazole | 138008-115-153 (lorazepam) |
| | aripiprazole | 138008-115-242 (lorazepam) |
| | haloperidol | 138008-122-160 (lorazepam) |
| | haloperidol | 138008-122-173 (lorazepam) |
| | haloperidol | 138008-122-175 (lorazepam) |
| | aripiprazole | 138008-122-189 (lorazepam) |
| | haloperidol | 138008-122-207 (lorazepam) |
| | haloperidol | 138008-123-335 (lorazepam) |

**TRIAL CN138007**



**Figure 8.1: Time to Discontinuation Due to All Reasons or Entry in Open-Label, Randomized Sample**




Protocol CN138-007

**Table 10.1A: Mean Change from Baseline in Y-MRS, LOCF Data Set, Efficacy Sample**

| | Mean Change from Baseline in Y-MRS[a] | | | Pairwise Comparisons P-values[b] | | |
|---|---|---|---|---|---|---|
| | Placebo N = 130[c] | Aripiprazole 15 mg N = 127[c] | Aripiprazole 30 mg N = 129[c] | Aripiprazole 15 mg vs. placebo | Aripiprazole 30 mg vs. placebo | Overall test P-value |
| Mean Baseline | 28.27 | 27.94 | 27.83 | 0.600 | 0.488 | 0.769 |
| Double-Blind Treatment | | | | | | |
| Day 4 | -5.58 | -6.37 | -6.23 | 0.303 | 0.400 | 0.547 |
| Week 1 | -7.99 | -8.78 | -8.65 | 0.434 | 0.510 | 0.701 |
| Day 10 | -8.97 | -9.69 | -9.19 | 0.530 | 0.849 | 0.813 |
| Week 2 | -9.95 | -10.11 | -10.27 | 0.899 | 0.798 | 0.968 |
| Week 3 | -10.12 | -10.01 | -10.80 | 0.928 | 0.599 | 0.802 |
| Week 3: 95% confidence interval for treatment differences (aripiprazole - placebo) | | | | | | |
| | | 0.12 | -0.68 | | | |
| | | (-2.43, 2.66) | (-3.22, 1.86) | | | |

Protocol CN138-007

**Table 10.1B: Mean Change from Baseline in Y-MRS, OC Data Set, Efficacy Sample**

| | Mean Change from Baseline in Y-MRS[a] | | | | | | Pairwise Comparisons P-values[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo | | Aripiprazole 15 mg | | Aripiprazole 30 mg | | Aripiprazole 15 mg vs. placebo | Aripiprazole 30 mg vs. placebo | Overall test P-value |
| | N | Mean | N | Mean | N | Mean | | | |
| Mean Baseline | 130 | 28.20 | 127 | 27.89 | 129 | 27.64 | 0.649 | 0.406 | 0.707 |
| Double-Blind Treatment | | | | | | | | | |
| Day 4 | 126 | -5.25 | 123 | -5.88 | 124 | -5.84 | 0.450 | 0.482 | 0.699 |
| Week 1 | 108 | -8.27 | 105 | -9.30 | 111 | -8.79 | 0.383 | 0.654 | 0.683 |
| Day 10 | 92 | -10.10 | 87 | -11.03 | 94 | -10.12 | 0.500 | 0.986 | 0.745 |
| Week 2 | 94 | -11.37 | 85 | -13.35 | 89 | -11.82 | 0.147 | 0.736 | 0.320 |
| Week 3 | 55 | -15.50 | 56 | -17.79 | 55 | -17.27 | 0.109 | 0.217 | 0.245 |
| Week 3: 95% confidence interval for treatment differences (aripiprazole - placebo) | | | | | | | | | |
| | | | | -2.29 (-5.10. 0.52) | | -1.77 (-4.59, 1.05) | | | |

Protocol CN138-007

**TABLES for Study CN138009:**

**End of Baseline Ratings:**



**Table 8.4B: End of Baseline Ratings, Randomized Sample**

| Characteristic | | Placebo N = 132 | Aripiprazole N = 130 | Total N = 262 |
|---|---|---|---|---|
| Y-MRS Total Score | Mean | 29.1 | 27.8 | 28.4 |
| | Median | 27.0 | 26.0 | 27.0 |
| | Min-Max | 21.0 - 52.0 | 20.0 - 44.0 | 20.0 - 52.0 |
| | S.E. | 0.6 | 0.5 | 0.4 |
| CGI-BP Severity | Mean | 4.7 | 4.5 | 4.6 |
| Score - Mania | Median | 5.0 | 4.0 | 4.0 |
| | Min-Max | 3.0 - 7.0 | 3.0 - 6.0 | 3.0 - 7.0 |
| | S.E. | 0.1 | 0.1 | 0.0 |
| | Missing | 1 | 0 | 1 |
| CGI-BP Severity | Mean | 2.5 | 2.2 | 2.3 |
| Score - Depression | Median | 2.0 | 2.0 | 2.0 |
| | Min-Max | 1.0 - 6.0 | 1.0 - 5.0 | 1.0 - 6.0 |
| | S.E. | 0.1 | 0.1 | 0.1 |
| | Missing | 1 | 0 | 1 |
| CGI-BP Severity | Mean | 4.7 | 4.4 | 4.6 |
| Score - Overall | Median | 5.0 | 4.0 | 4.0 |
| | Min-Max | 3.0 - 7.0 | 3.0 - 7.0 | 3.0 - 7.0 |
| | S.E. | 0.1 | 0.1 | 0.0 |
| | Missing | 1 | 0 | 1 |
| PANSS Total Score | Mean | 66.5 | 63.8 | 65.2 |
| | Median | 64.5 | 59.0 | 60.0 |
| | Min-Max | 32.0 - 153.0 | 38.0 - 144.0 | 32.0 - 153.0 |
| | S.E. | 1.7 | 1.7 | 1.2 |
| PANSS Cognitive | Mean | 16.5 | 15.8 | 16.2 |
| Subscale | Median | 15.0 | 15.5 | 15.0 |


**Table 8.4B: End of Baseline Ratings, Randomized Sample**

| Characteristic | | Placebo N = 132 | Aripiprazole N = 130 | Total N = 262 |
|---|---|---|---|---|
| | Min-Max | 8.0 - 36.0 | 8.0 - 35.0 | 8.0 - 36.0 |
| | S.E. | 0.5 | 0.5 | 0.3 |
| PANSS Hostility Subscale | Mean | 11.1 | 10.3 | 10.7 |
| | Median | 10.0 | 9.0 | 10.0 |
| | Min-Max | 4.0 - 23.0 | 4.0 - 25.0 | 4.0 - 25.0 |
| | S.E. | 0.4 | 0.3 | 0.2 |
| MADRS Total Score | Mean | 14.5 | 14.1 | 14.3 |
| | Median | 13.0 | 12.0 | 12.0 |
| | Min-Max | 0.0 - 39.0 | 0.0 - 36.0 | 0.0 - 39.0 |
| | S.E. | 0.7 | 0.6 | 0.5 |

Protocol CN138-009

**Table S.10.3.11A: Percentage of Patients With a Lack of Clinical Response at Week 2, LOCF Data Set, Efficacy Sample**

| | Lack of Clinical Response[a]/Number Assessed (%) | | | | Pairwise Comparisons P-values[b] |
|---|---|---|---|---|---|
| | Placebo | | Aripiprazole | | Aripiprazole vs Placebo |
| Week 2 | 66/122 | (54) | 87/123 | (71) | 0.016 |
| Week 3: 95% confidence interval for ratio versus placebo | | | | | 1.27 (1.05, 1.54) |

Protocol CN138-009
Source: Appendix 10.1.1A

[a] Lack of clinical response is defined as less than a 5% decrease from baseline on the Y-MRS.

[b] CMH General Association Test.

**Table S.10.3.11B: Percentage of Patients With a Lack of Clinical Response at Week 2, OC Data Set, Efficacy Sample**

| | Lack of Clinical Response[a]/Number Assessed (%) | | | | Pairwise Comparisons P-values[b] |
|---|---|---|---|---|---|
| | Placebo | | Aripiprazole | | Aripiprazole vs Placebo |
| Week 2 | 48/72 | (67) | 65/83 | (78) | 0.105 |
| Week 3: 95% confidence interval for ratio versus placebo | | | | | 1.17 (0.97, 1.43) |

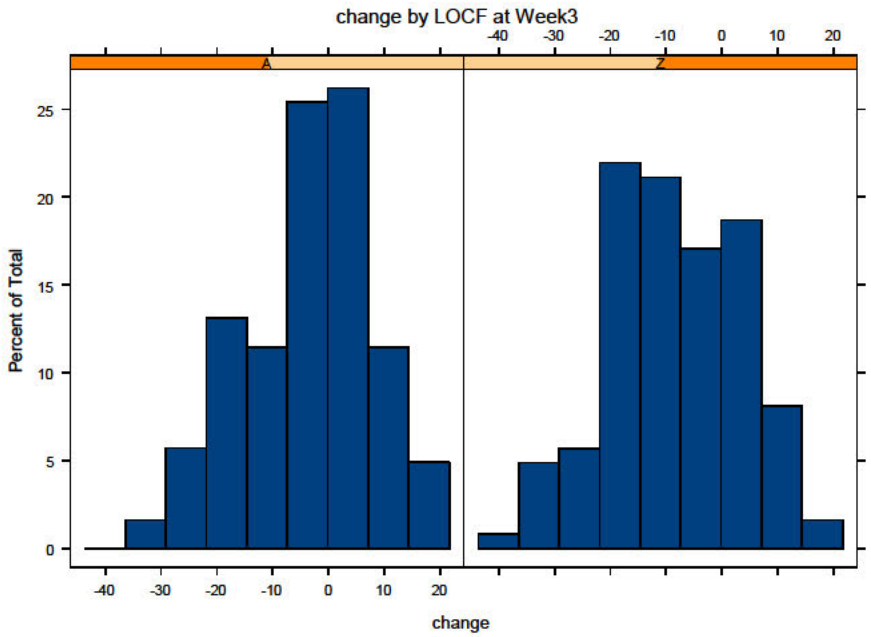
Protocol CN138-009
Source: Appendix 10.1.1A

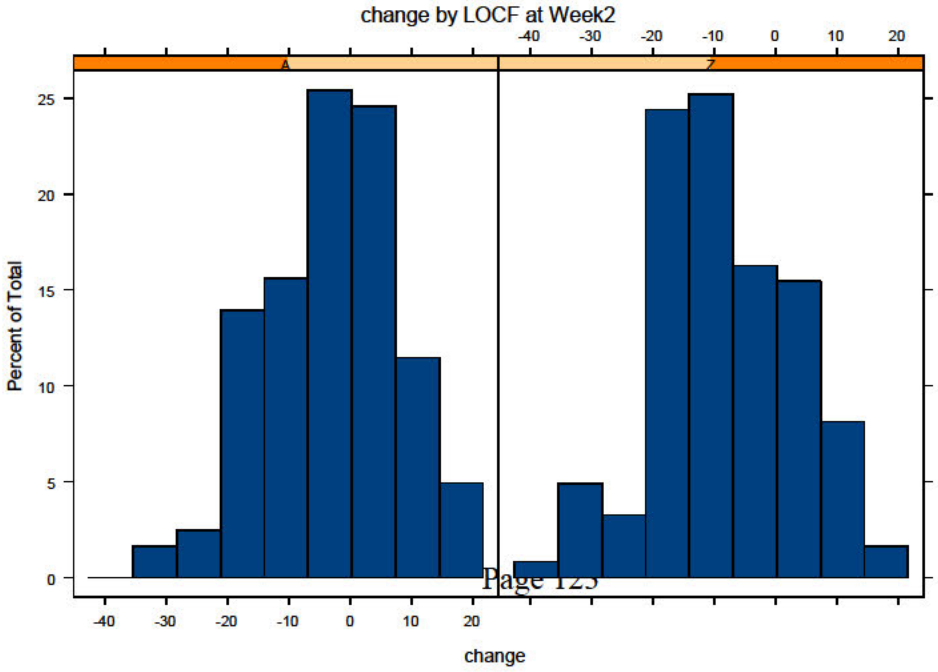
[a] Lack of clinical response is defined as less than a 5% decrease from baseline on the Y-MRS.

[b] CMH General Association Test.

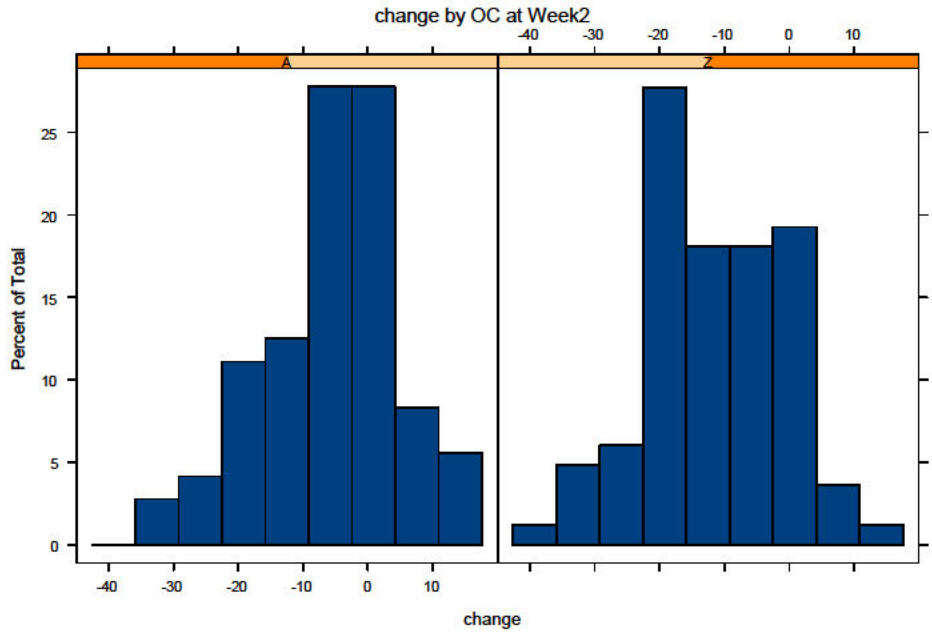
Clinical Review Section

**TRIAL CN138009: Histogram of proportion of patients per group and mean change in YMRS-LOCF**



**TRIAL CN138009: Histogram of proportion of patients per group and mean change in YMRS-OC**



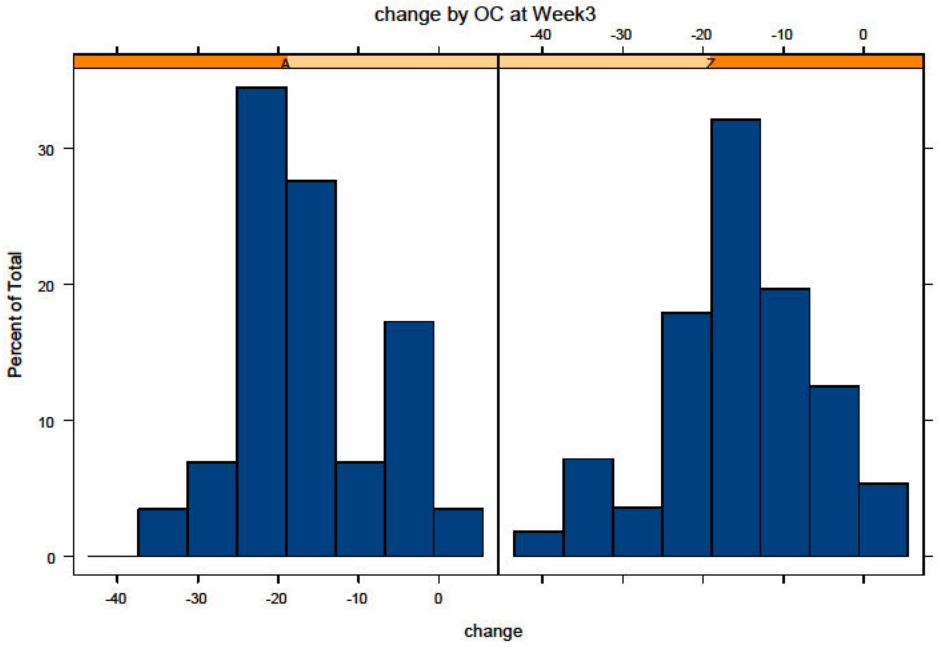



**Table 6.1.8: Y-MRS Total Score: Mean Change from Baseline to Week 3 by Population Subsets; 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, CN138074), LOCF Data Set, Efficacy Sample**

| Subgroup | Value | N | Placebo | N | Aripiprazole | Aripiprazole vs. Placebo P-value |
|---|---|---|---|---|---|---|
| **Gender** | Men | 178 | -6.9 | 244 | -9.6 | 0.019 |
| | Women | 206 | -6.9 | 271 | -10.5 | < 0.001 |
| **Age Group** | ≤ 50 | 313 | -7.1 | 424 | -10.3 | < 0.001 |
| | > 50 | 71 | -5.9 | 91 | -9.1 | 0.092 |
| **Race** | White | 279 | -6.7 | 386 | -10.3 | < 0.001 |
| | Black | 66 | -5.5 | 75 | -7.8 | 0.244 |
| | Other[a] | 39 | -8.8 | 54 | -11.0 | 0.407 |
| **Type of Episode** | Manic | 240 | -6.5 | 321 | -10.4 | < 0.001 |
| | Mixed | 144 | -7.4 | 194 | -9.7 | 0.044 |
| **Rapid Cycling** | No | 305 | -7.3 | 415 | -9.9 | 0.002 |
| | Yes | 79 | -5.5 | 100 | -10.6 | 0.001 |
| **Baseline Y-MRS Total Score** | ≤ median | 197 | -6.9 | 272 | -8.8 | 0.043 |
| **(Median = 27)** | > median | 187 | -6.8 | 243 | -11.6 | < 0.001 |
| **Baseline CGI-BP Severity of Illness (Mania) Score** | At most moderately ill | 158 | -6.3 | 219 | -9.2 | 0.009 |
| | At least markedly ill | 226 | -7.2 | 296 | -10.7 | 0.001 |
| **Baseline CGI-BP Severity of Illness (Depression) Score** | At most mildly ill | 270 | -7.0 | 383 | -10.2 | 0.001 |
| | At least moderately ill | 114 | -6.5 | 132 | -9.7 | 0.019 |
| **Baseline MADRS Total Score** | ≤ median | 207 | -6.6 | 283 | -10.2 | 0.001 |
| **(Median = 14)** | > median | 177 | -7.1 | 232 | -9.9 | 0.008 |

Note: Analyses were model-based, controlling for treatment, study, and baseline score-based means.

[a] Includes Hispanic, Asian, and Other race groups.

SAFETY

APPEARS THIS WAY ON ORIGINAL

**Table 6.4.2A: Cumulative Number of Patients Who Received Aripiprazole, by Duration of Exposure: All Aripiprazole Data Set by Indication and Overall, Safety Sample**

| | Number (%) of Patients | | | |
|---|---|---|---|---|
| | Bipolar Mania N = 1170 | Dementia N = 788 | Schizophrenia N = 5529 | All Aripiprazole N = 7487 |
| **Patient-exposure years** | **208.7** | **640.2** | **3937.6** | **4786.5** |
| **Duration of Exposure** | | | | |
| ≥ 1 day | 1170 (100.0) | 788 (100.0) | 5529 (100.0) | 7487 (100.0) |
| ≥ 21 days | 703 (60.1) | 734 (93.1) | 4492 (81.2) | 5929 (79.2) |
| ≥ 42 days | 486 (41.5) | 668 (84.8) | 3673 (66.4) | 4827 (64.5) |
| ≥ 90 days | 228 (19.5) | 570 (72.3) | 2278 (41.2) | 3076 (41.1) |
| ≥ 180 days | 79 (6.8) | 449 (57.0) | 1586 (28.7) | 2114 (28.2) |
| ≥ 270 days | 48 (4.1) | 366 (46.4) | 1343 (24.3) | 1757 (23.5) |
| ≥ 360 days | 34 (2.9) | 255 (32.4) | 1168 (21.1) | 1457 (19.5) |
| ≥ 540 days | 18 (1.5) | 158 (20.1) | 867 (15.7) | 1043 (13.9) |
| ≥ 720 days | 9 (0.8) | 91 (11.5) | 724 (13.1) | 824 (11.0) |



**Table 6.4.2B: Number and Percentage of Patients Who Received Aripiprazole by Overall Mean Dose Category and Duration of Therapy: Bipolar Mania, Safety Sample**

| Total Duration of Treatment | Number (%) of Aripiprazole Patients (N = 1170) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Overall Mean Dose (mg) | | | | | | |
| | Unavailable[a] | ≤ 12.5 | > 12.5 - ≤ 17.5 | > 17.5 - ≤ 25 | > 25 - ≤ 32.5 | > 32.5 | Total |
| 1 - 20 days | 7 (0.6) | 1 (0.1) | 120 (10.3) | 52 (4.4) | 287 (24.5) | 0 | 467 (39.9) |
| 21 - 41 days | 0 | 2 (0.2) | 25 (2.1) | 47 (4.0) | 143 (12.2) | 0 | 217 (18.5) |
| 42 - 89 days | 0 | 0 | 65 (5.6) | 59 (5.0) | 134 (11.5) | 0 | 258 (22.1) |
| 90 - 119 days | 0 | 0 | 10 (0.9) | 17 (1.5) | 39 (3.3) | 0 | 66 (5.6) |
| 120 - 149 days | 0 | 0 | 10 (0.9) | 12 (1.0) | 39 (3.3) | 0 | 61 (5.2) |
| 150 - 179 days | 0 | 0 | 4 (0.3) | 9 (0.8) | 9 (0.8) | 0 | 22 (1.9) |
| 180 - 269 days | 0 | 0 | 12 (1.0) | 6 (0.5) | 13 (1.1) | 0 | 31 (2.6) |
| 270 - 359 days | 0 | 0 | 3 (0.3) | 3 (0.3) | 8 (0.7) | 0 | 14 (1.2) |
| 360 - 719 days | 0 | 0 | 9 (0.8) | 4 (0.3) | 12 (1.0) | 0 | 25 (2.1) |
| ≥ 720 days | 0 | 0 | 2 (0.2) | 2 (0.2) | 5 (0.4) | 0 | 9 (0.8) |
| Total | 7 (0.6) | 3 (0.3) | 260 (22.2) | 211 (18.0) | 689 (58.9) | 0 | 1170 (100) |

[a] Patients were lost to follow up; therefore, dosage data were not available.

**Table 7.1.5A: Incidence of Treatment-Emergent SAEs: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| Body System/ Primary Term[a] | Number (%) of Patients | |
|---|---|---|
| | Placebo N = 409 | Aripiprazole N = 568 |
| **Any Treatment-Emergent SAE** | 23 (5.6) | 33 (5.8) |
| **Body As A Whole** | | |
| Overdose[b] | 0 | 2 (0.4) |
| Pain Chest[c] | 1 (0.2) | 2 (0.4) |
| Pain Abdomen | 1 (0.2) | 1 (0.2) |
| Pain Extremity | 0 | 1 (0.2) |
| Pain Jaw | 0 | 1 (0.2) |
| Suicide Attempt[d] | 0 | 1 (0.2) |
| Syndrome Neuroleptic Malignant[e] | 0 | 1 (0.2) |
| Accidental Injury | 1 (0.2) | 0 |
| Discomfort Chest | 1 (0.2) | 0 |
| **Cardiovascular System** | | |
| Hypertension | 0 | 1 (0.2) |
| Hypotension[f] | 0 | 1 (0.2) |
| Syncope[g] | 1 (0.2) | 1 (0.2) |
| **Digestive System** | | |
| Obstruction Intestinal | 1 (0.2) | 0 |
| **Nervous System** | | |
| Reaction Manic | 9 (2.2) | 15 (2.6) |
| Anxiety | 0 | 2 (0.4) |
| Depression | 2 (0.5) | 2 (0.4) |
| Psychosis | 0 | 2 (0.4) |
| Reaction Manic Depressive | 2 (0.5) | 2 (0.4) |
| Seizure[h] | 1 (0.2) | 2 (0.4) |
| Thought Suicidal | 3 (0.7) | 2 (0.4) |

**Table 7.1.5A: Incidence of Treatment-Emergent SAEs: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| Body System/ Primary Term[a] | Number (%) of Patients | |
|---|---|---|
| | Placebo N = 409 | Aripiprazole N = 568 |
| Abnormal Thinking | 0 | 1 (0.2) |
| Decompensation Psychiatric | 0 | 1 (0.2) |
| Disorder Personality | 0 | 1 (0.2) |
| Drug Dependence[i] | 0 | 1 (0.2) |
| Extrapyramidal Syndrome | 0 | 1 (0.2) |
| Insomnia | 0 | 1 (0.2) |
| Agitation | 2 (0.5) | 0 |
| **Skin/Appendages** | | |
| Urticaria | 1 (0.2) | 0 |

Footnotes refer to aripiprazole-treated patients.

[a] Modified COSTART term.

[b] One patient took an overdose of anti-insomnia medication. The event resolved 2 days after overdose and was considered unrelated to study medication. The second patient died of hydrocodone intoxication, 5 days after study drug discontinuation.

[c] One patient experienced moderate chest pain (ECG normal) with same-day resolution that was not related to study medication. The second patient was hospitalized for severe chest pain 1 day after study discontinuation. This event was considered unrelated to study medication and resolved 1 day later.

[d] The reported term was risk of suicide attempt, but no suicidal gesture or suicide attempt was reported. The event was considered unrelated to study medication.

[e] The onset of symptoms of NMS (fever and increased CPK) was reported 17 days after the last dose of aripiprazole. The investigator considered the event to be not likely related to aripiprazole and related to post-study treatment with risperidone and haloperidol.

[f] The patient experienced a single episode of very severe hypotension, considered possibly related to study medication.

[g] The patient received the last dose of 30-mg aripiprazole on Day 7 and experienced a syncopal event of moderate intensity on Day 8. The event resolved the same day and was considered possibly related to study medication.

[h] One aripiprazole patient discontinued on Day 13 and then experienced a very severe seizure later that day. The event resolved that same day and was designated as possibly related to study medication. The other aripiprazole patient experienced two seizures, severe in nature and 2 days apart, that were considered not likely related to study medication.

[i] The patient was hospitalized 5 days after study discontinuation for mild cocaine use, which resolved the same day. The event was considered unrelated to study medication.

**Table 7.1.5B: Incidence of Treatment-Emergent SAEs by Dose: 3-Week Placebo-Controlled Fixed-Dose Studies in Acute Bipolar Mania (CN138007, (b) (4) Safety Sample**

| Body System/ Primary Term[a] | Number (%) of Patients | | |
|---|---|---|---|
| | | Aripiprazole | |
| | Placebo N = 149 | 15 mg N = 150 | 30 mg N = 155 |
| **Any Treatment-Emergent SAE** | 8 (5.4) | 10 (6.7) | 7 (4.5) |
| **Body As A Whole** | | | |
| Pain Chest[b] | 0 | 0 | 1 (0.6) |
| Suicide Attempt[c] | 0 | 0 | 1 (0.6) |
| Syndrome Neuroleptic Malignant[d] | 0 | 1 (0.7) | 0 |
| **Cardiovascular System** | | | |
| Hypotension[e] | 0 | 1 (0.7) | 0 |
| **Nervous System** | | | |
| Reaction Manic | 3 (2.0) | 2 (1.3) | 3 (1.9) |
| Anxiety | 0 | 1 (0.7) | 1 (0.6) |
| Depression | 2 (1.3) | 1 (0.7) | 1 (0.6) |
| Drug Dependence[f] | 0 | 0 | 1 (0.6) |
| Extrapyramidal Syndrome | 0 | 0 | 1 (0.6) |
| Abnormal Thinking | 0 | 1 (0.7) | 0 |
| Agitation | 1 (0.7) | 0 | 0 |
| Disorder Personality | 0 | 1 (0.7) | 0 |
| Psychosis | 0 | 1 (0.7) | 0 |
| Reaction Manic Depressive | 2 (1.3) | 0 | 0 |
| Seizure[g] | 0 | 2 (1.3) | 0 |
| Thought Suicidal | 2 (1.3) | 0 | 0 |

Footnotes refer to aripiprazole-treated patients.

[a] Modified COSTART term.

[b] The patient was hospitalized for severe chest pain 1 day after study discontinuation. This event was considered unrelated to study medication and resolved 1 day later.

[c] The reported term was risk of suicide attempt, but no suicidal gesture or suicide attempt was reported. The event was considered unrelated to study medication.

[d] The onset of symptoms of NMS (fever and increased CPK) was reported 17 days after the last dose of aripiprazole. The investigator considered the event to be not likely related to aripiprazole and related to post-study treatment with risperidone and haloperidol.

[e] The patient experienced a single episode of very severe hypotension, considered possibly related to study medication.

[f] The patient was hospitalized 5 days after study discontinuation for mild cocaine use that resolved the same day. The event was considered unrelated to study medication.

[g] One patient discontinued on Day 13 and then experienced a very severe seizure later that day. The event resolved that same day and was designated as possibly related to study medication. The other patient experienced two seizures, severe in nature and 2 days apart, that were considered not likely related to study medication.

**Table 7.1.4A: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Therapy: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| Body System/ Primary Term[a] | Number (%) of Patients | |
|---|---|---|
| | Placebo N = 409 | Aripiprazole N = 568 |
| **Any Treatment-Emergent AE Leading to Discontinuation of Study Therapy**[b] | 39 (9.5) | 62 (10.9) |
| **Body As A Whole** | | |
| Asthenia | 0 | 1 (0.2) |
| Pain Back | 0 | 1 (0.2) |
| Rigidity Neck | 2 (0.5) | 1 (0.2) |
| Stiffness | 1 (0.2) | 1 (0.2) |
| Suicide Attempt[c] | 0 | 1 (0.2) |
| Discomfort Chest | 1 (0.2) | 0 |
| Headache | 2 (0.5) | 0 |
| Pain Abdomen | 1 (0.2) | 0 |
| Pain Chest | 1 (0.2) | 0 |
| **Cardiovascular System** | | |
| Syncope[d] | 0 | 2 (0.4) |
| Hypotension[e] | 0 | 1 (0.2) |
| Hypotension Orthostatic[f] | 0 | 1 (0.2) |
| Palpitation | 0 | 1 (0.2) |
| **Digestive System** | | |
| Nausea | 2 (0.5) | 5 (0.9) |
| Vomiting | 1 (0.2) | 2 (0.4) |
| Diarrhea | 1 (0.2) | 1 (0.2) |
| Nausea And Vomiting | 0 | 1 (0.2) |
| Obstruction Intestinal | 1 (0.2) | 0 |
| **Metabolic/Nutritional System** | | |
| CPK Increased | 2 (0.5) | 0 |

**Table 7.1.4A: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Therapy: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| Body System/ Primary Term[a] | Number (%) of Patients | |
|---|---|---|
| | Placebo N = 409 | Aripiprazole N = 568 |
| SGOT Increased | 1 (0.2) | 0 |
| SGPT Increased | 1 (0.2) | 0 |
| **Musculoskeletal System** | | |
| Disorder Joint | 1 (0.2) | 0 |
| **Nervous System** | | |
| Reaction Manic[g] | 3 (0.7) | 14 (2.5) |
| Akathisia | 2 (0.5) | 13 (2.3) |
| Agitation | 10 (2.4) | 8 (1.4) |
| Anxiety | 1 (0.2) | 6 (1.1) |
| Depression | 3 (0.7) | 2 (0.4) |
| Extrapyramidal Syndrome | 0 | 2 (0.4) |
| Hostility | 1 (0.2) | 2 (0.4) |
| Insomnia | 2 (0.5) | 2 (0.4) |
| Lightheadedness | 1 (0.2) | 2 (0.4) |
| Nervousness | 3 (0.7) | 2 (0.4) |
| Psychosis | 3 (0.7) | 2 (0.4) |
| Reaction Manic Depressive[h] | 6 (1.5) | 2 (0.4) |
| Tremor | 0 | 2 (0.4) |
| Abnormal Dream | 0 | 1 (0.2) |
| Abnormal Thinking | 0 | 1 (0.2) |
| Concentration Impaired | 0 | 1 (0.2) |
| Delusions | 2 (0.5) | 1 (0.2) |
| Disorder Personality | 3 (0.7) | 1 (0.2) |
| Hypertonia | 0 | 1 (0.2) |
| Impulsive | 0 | 1 (0.2) |
| Paranoid Reaction | 2 (0.5) | 1 (0.2) |

**Table 7.1.4A: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Therapy: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| Body System/ Primary Term[a] | Number (%) of Patients | |
|---|---|---|
| | Placebo N = 409 | Aripiprazole N = 568 |
| Seizure[i] | 1 (0.2) | 1 (0.2) |
| Thinking Slowed | 0 | 1 (0.2) |
| Confusion | 1 (0.2) | 0 |
| Dystonia | 1 (0.2) | 0 |
| Hypesthesia | 1 (0.2) | 0 |
| Somnolence | 1 (0.2) | 0 |
| **Skin/Appendages** | | |
| Rash | 1 (0.2) | 1 (0.2) |
| Urticaria | 1 (0.2) | 0 |
| **Special Senses** | | |
| Abnormal Vision | 0 | 1 (0.2) |

Footnotes refer to aripiprazole-treated patients.

[a] Modified COSTART term.

[b] AEs for which the "action taken" column on the AE form was marked "discontinue medication."

[c] The reported term was risk of suicide attempt, but no suicidal gesture or suicide attempt was reported.

[d] One patient experienced an episode of severe orthostatic hypotension that resolved the same day and was considered probably related to study medication. The second patient experienced a syncopal event of moderate intensity that resolved the same day and was considered possibly related to study medication.

[e] One patient experienced a single episode of very severe hypotension, considered possibly related to study medication.

[f] One patient (included in footnote d above) experienced an episode of severe orthostatic hypotension that resolved the same day and was considered probably related to study medication.

[g] Reported terms included increased or exacerbation of manic symptoms.

[h] Reported terms included a worsening of bipolar symptoms.

[i] The aripiprazole-treated patient experienced two seizures, severe in nature and 2 days apart, that were considered not likely related to study medication.

**Table 7.1.4B: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Therapy by Dose: 3-Week Placebo-Controlled Fixed-Dose Studies in Acute Bipolar Mania (CN138007, (b) (4) Safety Sample**

| Body System/ Primary Term[a] | Number (%) of Patients | | |
|---|---|---|---|
| | | Aripiprazole | |
| | Placebo | 15 mg | 30 mg |
| | N = 149 | N = 150 | N = 155 |
| **Any Treatment-Emergent AE Leading to Discontinuation of Study Therapy[b]** | 13 (8.7) | 22 (14.7) | 13 (8.4) |
| **Body As A Whole** | | | |
| Suicide Attempt[c] | 0 | 0 | 1 (0.6) |
| Headache | 1 (0.7) | 0 | 0 |
| Pain Abdomen | 1 (0.7) | 0 | 0 |
| Pain Back | 0 | 1 (0.7) | 0 |
| Rigidity Neck | 1 (0.7) | 0 | 0 |
| Stiffness | 1 (0.7) | 1 (0.7) | 0 |
| **Cardiovascular System** | | | |
| Hypotension[d] | 0 | 1 (0.7) | 0 |
| Hypotension Orthostatic[e] | 0 | 1 (0.7) | 0 |
| Palpitation | 0 | 1 (0.7) | 0 |
| Syncope[e] | 0 | 1 (0.7) | 0 |
| **Digestive System** | | | |
| Nausea | 2 (1.3) | 2 (1.3) | 1 (0.6) |
| Vomiting | 0 | 1 (0.7) | 1 (0.6) |
| Diarrhea | 1 (0.7) | 1 (0.7) | 0 |
| Nausea And Vomiting | 0 | 1 (0.7) | 0 |
| **Musculoskeletal System** | | | |
| Disorder Joint | 1 (0.7) | 0 | 0 |
| **Nervous System** | | | |
| Reaction Manic[f] | 1 (0.7) | 5 (3.3) | 4 (2.6) |

**Table 7.1.4B: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Therapy by Dose: 3-Week Placebo-Controlled Fixed-Dose Studies in Acute Bipolar Mania (CN138007, (b) (4) Safety Sample**

| | Number (%) of Patients | | |
|---|---|---|---|
| | | Aripiprazole | |
| Body System/ Primary Term[a] | Placebo N = 149 | 15 mg N = 150 | 30 mg N = 155 |
| Akathisia | 2 (1.3) | 4 (2.7) | 3 (1.9) |
| Agitation | 1 (0.7) | 2 (1.3) | 2 (1.3) |
| Concentration Impaired | 0 | 0 | 1 (0.6) |
| Delusions | 0 | 0 | 1 (0.6) |
| Depression | 3 (2.0) | 1 (0.7) | 1 (0.6) |
| Extrapyramidal Syndrome | 0 | 0 | 1 (0.6) |
| Impulsive | 0 | 0 | 1 (0.6) |
| Psychosis | 2 (1.3) | 1 (0.7) | 1 (0.6) |
| Abnormal Dream | 0 | 1 (0.7) | 0 |
| Abnormal Thinking | 0 | 1 (0.7) | 0 |
| Anxiety | 0 | 2 (1.3) | 0 |
| Dystonia | 1 (0.7) | 0 | 0 |
| Insomnia | 1 (0.7) | 0 | 0 |
| Lightheadedness | 0 | 1 (0.7) | 0 |
| Nervousness | 0 | 1 (0.7) | 0 |
| Paranoid Reaction | 1 (0.7) | 1 (0.7) | 0 |
| Reaction Manic Depressive[f] | 2 (1.3) | 1 (0.7) | 0 |
| Seizure[h] | 0 | 1 (0.7) | 0 |
| Thinking Slowed | 0 | 1 (0.7) | 0 |
| Tremor | 0 | 1 (0.7) | 0 |
| **Skin/Appendages** | | | |
| Rash | 1 (0.7) | 0 | 0 |
| **Special Senses** | | | |
| Abnormal Vision | 0 | 1 (0.7) | 0 |

Footnotes refer to aripiprazole-treated patients.



[a] Modified COSTART term.

[b] AEs for which the "action taken" column on the AE form was marked "discontinue medication."

[c] The reported term was risk of suicide attempt, but no suicidal gesture or suicide attempt was reported.

[d] One patient experienced a single episode of very severe hypotension, considered possibly related to study medication.

[e] One patient experienced an episode of severe orthostatic hypotension that resolved the same day and was considered probably related to study medication.

[f] Reported terms included increased or exacerbation of manic symptoms.

[g] Reported terms included a worsening of bipolar symptoms.

[h] The aripiprazole-treated patient experienced two seizures, severe in nature and 2 days apart, that were considered not likely related to study medication.

**Table 7.1.3.1A: Incidence of Treatment-Emergent AEs That Occurred in at Least 1% of Patients in the Aripiprazole Group: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| Body System Primary Term[a] | Number (%) of Patients | | | |
|---|---|---|---|---|
| | Placebo N = 409 | | Aripiprazole N = 568 | |
| **Any AE** | **329** | **(80.4)** | **493** | **(86.8)** |
| **Body As A Whole** | | | | |
| Headache | 115 | (28.1) | 165 | (29.0) |
| Asthenia | 38 | (9.3) | 52 | (9.2) |
| Pain Extremity | 22 | (5.4) | 49 | (8.6) |
| Accidental Injury[b] | 11 | (2.7) | 33 | (5.8) |
| Pain Abdomen | 29 | (7.1) | 28 | (4.9) |
| Pain Back | 18 | (4.4) | 28 | (4.9) |
| Edema Peripheral | 5 | (1.2) | 19 | (3.3) |
| Infection | 7 | (1.7) | 19 | (3.3) |
| Stiffness | 5 | (1.2) | 16 | (2.8) |
| Pain | 14 | (3.4) | 14 | (2.5) |
| Pain Dental | 9 | (2.2) | 13 | (2.3) |
| Pain Chest | 6 | (1.5) | 11 | (1.9) |
| Rigidity Neck | 6 | (1.5) | 10 | (1.8) |
| Pain Neck | 9 | (2.2) | 8 | (1.4) |
| Migraine | 1 | (0.2) | 6 | (1.1) |
| Pain Pelvic | 4 | (1.0) | 6 | (1.1) |
| **Cardiovascular System** | | | | |
| Hypertension | 5 | (1.2) | 17 | (3.0) |
| Tachycardia | 3 | (0.7) | 6 | (1.1) |
| **Digestive System** | | | | |
| Nausea | 57 | (13.9) | 108 | (19.0) |
| Dyspepsia | 47 | (11.5) | 91 | (16.0) |
| Constipation | 27 | (6.6) | 74 | (13.0) |
| Vomiting | 23 | (5.6) | 61 | (10.7) |

**Table 7.1.3.1A: Incidence of Treatment-Emergent AEs That Occurred in at Least 1% of Patients in the Aripiprazole Group: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| Body System Primary Term[a] | Number (%) of Patients: Placebo N = 409 | Aripiprazole N = 568 |
|---|---|---|
| Diarrhea | 42 (10.3) | 52 (9.2) |
| Dry Mouth | 22 (5.4) | 34 (6.0) |
| Anorexia | 17 (4.2) | 19 (3.3) |
| Flatulence | 3 (0.7) | 8 (1.4) |
| Nausea And Vomiting | 3 (0.7) | 6 (1.1) |
| **Musculoskeletal System** | | |
| Myalgia | 14 (3.4) | 27 (4.8) |
| Cramp Muscle | 7 (1.7) | 14 (2.5) |
| Disorder Joint | 6 (1.5) | 10 (1.8) |
| **Nervous System** | | |
| Agitation | 62 (15.2) | 89 (15.7) |
| Akathisia | 14 (3.4) | 85 (15.0) |
| Somnolence | 33 (8.1) | 81 (14.3) |
| Anxiety | 43 (10.5) | 72 (12.7) |
| Insomnia | 45 (11.0) | 72 (12.7) |
| Lightheadedness | 38 (9.3) | 59 (10.4) |
| Tremor | 14 (3.4) | 33 (5.8) |
| Extrapyramidal Syndrome | 9 (2.2) | 29 (5.1) |
| Reaction Manic | 20 (4.9) | 25 (4.4) |
| Salivation Increased | 3 (0.7) | 23 (4.0) |
| Nervousness | 15 (3.7) | 16 (2.8) |
| Abnormal Dream | 13 (3.2) | 15 (2.6) |
| Hypertonia | 13 (3.2) | 15 (2.6) |
| Depression | 11 (2.7) | 10 (1.8) |
| Paresthesia | 5 (1.2) | 9 (1.6) |
| Disorder Speech | 1 (0.2) | 7 (1.2) |

**Table 7.1.3.1A: Incidence of Treatment-Emergent AEs That Occurred in at Least 1% of Patients in the Aripiprazole Group: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| Body System<br>Primary Term[a] | Number (%) of Patients<br>Placebo<br>N = 409 | <br>Aripiprazole<br>N = 568 |
|---|---|---|
| Hostility | 3 (0.7) | 7 (1.2) |
| Dystonia | 1 (0.2) | 6 (1.1) |
| Thought Suicidal | 6 (1.5) | 6 (1.1) |
| Vasodilation | 6 (1.5) | 6 (1.1) |
| **Respiratory System** | | |
| Pharyngitis | 9 (2.2) | 18 (3.2) |
| Rhinitis | 11 (2.7) | 16 (2.8) |
| URI | 18 (4.4) | 16 (2.8) |
| Coughing | 8 (2.0) | 15 (2.6) |
| Sinusitis | 5 (1.2) | 14 (2.5) |
| Dyspnea | 2 (0.5) | 10 (1.8) |
| **Skin/Appendages** | | |
| Rash | 20 (4.9) | 26 (4.6) |
| Pruritus | 17 (4.2) | 11 (1.9) |
| Sweating | 3 (0.7) | 8 (1.4) |
| Dry Skin | 5 (1.2) | 6 (1.1) |
| **Special Senses** | | |
| Blurred Vision | 8 (2.0) | 20 (3.5) |
| Conjunctivitis | 3 (0.7) | 7 (1.2) |
| Abnormal Vision | 2 (0.5) | 6 (1.1) |
| Pain Ear | 3 (0.7) | 6 (1.1) |
| **Urogenital System** | | |
| Dysmenorrhea[c] | 6 (2.6) | 10 (3.4) |
| Vaginitis[c] | 5 (2.2) | 6 (2.0) |
| Infection Urinary Tract | 8 (2.0) | 8 (1.4) |

[a] Modified COSTART term.



[b] Reported terms mapped to accidental injury were reviewed to confirm the appropriateness of the mapping. Reported terms included lacerations, burns, abrasions, falls, sprains, cuts, and insect bites.

[c] Incidence rate adjusted for gender (women): placebo N = 227; aripiprazole = 296.

**Table 5.3.4.2A: Criteria for Identifying Potentially Clinically Significant Laboratory Values**

| Laboratory Tests | Criteria[a] |
|---|---|
| **Chemistry**[b] | |
| AST (SGOT) | ≥ 3 x upper limit of normal |
| ALT (SGPT) | ≥ 3 x upper limit of normal |
| Alkaline phosphatase | ≥ 3 x upper limit of normal |
| LDH | ≥ 3 x upper limit of normal |
| BUN | ≥ 30 mg/dL |
| Urea[c] | ≥ 10.1 mmol/L |
| Creatinine | ≥ 2.0 mg/dL |
| Uric acid | |
| Men | ≥ 10.5 mg/dL |
| Women | ≥ 8.5 mg/dL |
| Bilirubin (total) | ≥ 2.0 mg/dL |
| **Hematology** | |
| 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 | Absolute count < 1,000/mm$^3$ |
| Platelet count | ≤ 100,000/mm$^3$ or ≥ 700,000/mm$^3$ |

**Table 5.3.4.2A: Criteria for Identifying Potentially Clinically Significant Laboratory Values**

| Laboratory Tests | Criteria[a] |
|---|---|
| **Urinalysis** | |
| Protein | Increase of ≥ 2 units |
| Glucose | Increase of ≥ 2 units |
| Casts | Increase of ≥ 2 units |

[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 (27 Feb 87).[38]

[b] In addition to the above-listed laboratory tests, the following tests were evaluated for the Phase III aripiprazole program: prolactin > upper limit of normal; CPK ≥ 3 x upper limit of normal.

[c] May have been analyzed in other studies, but only presented for CN138008.

**Table 5.3.4.2B: Criteria for Identifying Potentially Clinically Significant Vital Sign Measurements**

| Vital Sign | Criterion Value[a] | Change from Baseline[a] |
|---|---|---|
| Heart rate | 120 bpm<br>50 bpm | ≥ 15 bpm increase<br>≥ 15 bpm decrease |
| Systolic blood pressure | 180 mmHg<br>90 mmHg | ≥ 20 mmHg increase<br>≥ 20 mmHg decrease |
| Diastolic blood pressure | 105 mmHg<br>50 mmHg | ≥ 15 mmHg increase<br>≥ 15 mmHg decrease |

[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 (27 Feb 87).[38]

**Table 5.3.4.2C: Criteria for Identifying Potentially Clinically Significant ECG Measurements**

| 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 fibrillation with rapid ventricular response | ≥ 100 bpm | increase of ≥ 15 bpm |
| 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 |

**Table 5.3.4.2C: Criteria for Identifying Potentially Clinically Significant ECG Measurements**

| Variable | Criterion Value[a] | Change Relative to Baseline[a] |
|---|---|---|
| **ST/T Morphological** | | |
| Myocardial ischemia | all | not present → present |
| Symmetrical T-wave inversions | all | not present → present |
| Increase in $QT_c$ | $QT_c \geq 450$ millisecond | ≥ 10% increase |

[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.

**Table 7.1.7.1A-1: Incidence of Treatment-Emergent Serum Chemistry Measurements of Potential Clinical Significance: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| | | Number of Patients with Potentially Clinically Significant Abnormality[a]/Number Assessed (%)[b] | | | |
|---|---|---|---|---|---|
| **Laboratory Test** | **Criterion** | **Placebo** | | **Aripiprazole** | |
| AST (SGOT) | ≥ 3 x ULN | 0/292 | (0.0) | 0/425 | (0.0) |
| ALT (SGPT) | ≥ 3 x ULN | 1/277 | (0.4) | 1/392 | (0.3) |
| Alkaline Phosphastase | ≥ 3 x ULN | 0/294 | (0.0) | 0/414 | (0.0) |
| LDH | ≥ 3 x ULN | 0/273 | (0.0) | 0/400 | (0.0) |
| Blood Urea Nitrogen | ≥ 30 mg/dL | 0/305 | (0.0) | 0/430 | (0.0) |
| Creatinine | ≥ 2.0 mg/dL | 0/314 | (0.0) | 0/450 | (0.0) |
| Uric Acid | Abnormal[c] | 0/285 | (0.0) | 1/407 | (0.2) |
| Bilirubin, Total | ≥ 2.0 mg/dL | 0/313 | (0.0) | 0/451 | (0.0) |
| CPK | ≥ 3 x ULN | 5/245 | (2.0) | 10/368 | (2.7) |
| Prolactin | > ULN | 16/228 | (7.0) | 11/333 | (3.3) |

[a] Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (Table 5.3.4.2A).

[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).

**Table 7.1.7.1A-2: Median Percent Change from Baseline to Endpoint; Serum Chemistry Measurements: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| | Placebo | | Aripiprazole | |
|---|---|---|---|---|
| **Laboratory Test** | **N** | **Median % Change** | **N** | **Median % Change** |
| AST (SGOT) | 315 | 0.0 | 451 | 0.0 |
| ALT (SGPT) | 315 | 4.5 | 451 | 9.5 |
| Alkaline Phosphatase | 314 | 0.0 | 451 | 0.0 |
| LDH | 310 | -1.3 | 449 | -2.5 |
| Total Protein | 314 | 1.4 | 451 | 1.2 |
| Blood Urea Nitrogen | 315 | 0.0 | 445 | 0.0 |
| Creatinine | 316 | 0.0 | 450 | 0.0 |
| Uric Acid | 311 | -1.4 | 449 | 1.7 |
| Bilirubin (Total) | 315 | 0.0 | 451 | 0.0 |
| CPK | 309 | 6.1 | 447 | 15.7 |
| Prolactin | 308 | -18.2 | 447 | -50.0 |

**Table S.7.1.7.1A-2: Median Percent Change from Baseline to Endpoint; Serum Chemistry Measurements (Electrolytes): 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| | Placebo | | Aripiprazole | |
|---|---|---|---|---|
| Laboratory Test | N | Median % Change | N | Median % Change |
| Calcium | 315 | 1.0 | 450 | 1.1 |
| Sodium | 316 | 0.0 | 451 | 0.0 |
| Potassium | 314 | 0.0 | 450 | -2.1 |
| Chloride | 316 | 0.0 | 450 | 0.0 |

**Table 7.1.7.1B-2: Median Percent Change from Baseline to Endpoint, Hematology Measurements: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| | Placebo | | Aripiprazole | |
|---|---|---|---|---|
| **Laboratory Test** | **N** | **Median % Change** | **N** | **Median % Change** |
| Hematocrit | 307 | 0.9 | 437 | 0.8 |
| Hemoglobin | 307 | 0.8 | 437 | 0.6 |
| WBC | 307 | 7.7 | 437 | 4.6 |
| Eosinophils (relative) | 304 | -10.6 | 429 | -11.8 |
| Neutrophils (absolute) | 289 | 9.1 | 393 | 8.0 |
| Platelet Count | 307 | 1.4 | 436 | 3.0 |

**Table 7.1.8.1A: Incidence of Potentially Clinically Significant Vital Sign Abnormalities: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| | Number of Patients with Potentially Clinically Significant Abnormality[a]/Number Assessed (%) | |
|---|---|---|
| **Vital Sign Measurement** | **Placebo** | **Aripiprazole** |
| **Systolic Blood Pressure** | | |
| Standing increase[b] | 3/ 392 (0.77) | 5/ 550 (0.91) |
| Standing decrease[c] | 13/ 392 (3.32) | 13/ 550 (2.36) |
| Supine increase[b] | 3/ 393 (0.76) | 4/ 551 (0.73) |
| Supine decrease[c] | 9/ 393 (2.29) | 6/ 551 (1.09) |
| **Diastolic Blood Pressure** | | |
| Standing increase[d] | 6/ 392 (1.53) | 6/ 550 (1.09) |
| Standing decrease[e] | 6/ 392 (1.53) | 7/ 550 (1.27) |
| Supine increase[d] | 4/ 393 (1.02) | 2/ 551 (0.36) |
| Supine decrease[e] | 5/ 393 (1.27) | 3/ 551 (0.54) |
| **Heart Rate** | | |
| Standing increase[f] | 6/ 374 (1.60) | 24/ 533 (4.50) |
| Standing decrease[g] | 1/ 374 (0.27) | 1/ 533 (0.19) |
| Supine increase[f] | 3/ 376 (0.80) | 7/ 530 (1.32) |
| Supine decrease[g] | 4/ 376 (1.06) | 0/ 530 (0.00) |
| **Weight** | | |
| Increase | 7/ 295 (2.37) | 12/ 417 (2.88) |
| Decrease | 5/ 295 (1.69) | 12/ 417 (2.88) |

[a] Criteria for identifying potentially clinically significant vital sign measurements are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (Table 5.3.4.2B).

[b] ≥ 180 mmHG and a ≥ 20 mmHg from baseline.

[c] ≤ 90 mmHg and a ≥ 10 mmHg decrease from baseline.

[d] ≥ 105 mmHg and a ≥ 15 mmHg increase from baseline.

[e] ≤ 50 mmHg and a ≥ 15 mmHg decrease from baseline.

[f] ≥ 120 bpm and ≥ 15 bpm increase from baseline.

[g] ≤ 50 bpm and a ≥ 15 bpm decrease from baseline.

**Table 7.1.8.1B: Mean and Median Change from Baseline to Endpoint, Vital Sign Measurements: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| | | Placebo | | | Aripiprazole | | |
|---|---|---|---|---|---|---|---|
| **Vital Sign Measurement** | | **N** | **Mean (SE)** | **Median** | **N** | **Mean (SE)** | **Median** |
| **Heart Rate** | (bpm) | | | | | | |
| Standing | | 370 | -0.3 (0.7) | 0.0 | 520 | 0.9 (0.6) | 0.0 |
| Supine | | 371 | -0.7 (0.7) | 0.0 | 519 | 1.1 (0.5) | 0.0 |
| **Diastolic Blood Pressure** | (mmHg) | | | | | | |
| Standing | | 389 | -0.6 (0.5) | 0.0 | 546 | 0.0 (0.5) | 0.0 |
| Supine | | 391 | -0.5 (0.5) | 0.0 | 547 | -0.1 (0.5) | 0.0 |
| **Systolic Blood Pressure** | (mmHg) | | | | | | |
| Standing | | 389 | -0.1 (0.7) | 0.0 | 546 | -0.4 (0.6) | 0.0 |
| Supine | | 391 | -0.1 (0.7) | 0.0 | 547 | -0.3 (0.6) | 0.0 |
| **Weight** | (kg) | 294 | -0.2 (0.2) | 0.0 | 410 | 0.0 (0.1) | 0.0 |

**Table 7.1.9.6: Mean and Median Change from Baseline for the Minimum, Maximum, and Endpoint On-Treatment ECG Value: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| | | Placebo | | | Aripiprazole | | |
|---|---|---|---|---|---|---|---|
| **ECG Parameter** | | **N** | **Mean (SE)** | **Median** | **N** | **Mean (SE)** | **Median** |
| PR | | | | | | | |
| Maximum | (msec) | 312 | 0.76 (0.85) | 0.50 | 443 | -0.04 (0.80) | 0 |
| Endpoint | (msec) | 310 | 0.65 (0.85) | 0 | 439 | -0.16 (0.80) | 0 |
| QRS | | | | | | | |
| Maximum | (msec) | 312 | -0.23 (0.37) | 0 | 444 | -0.37 (0.37) | 0 |
| Endpoint | (msec) | 310 | -0.31 (0.38) | -0.50 | 440 | -0.48 (0.37) | -1.00 |
| RR | | | | | | | |
| Maximum | (msec) | 312 | 7.01 (8.41) | 4.50 | 444 | -25.37 (7.11) | -23 |
| Minimum | (msec) | 312 | 3.50 (8.08) | 2.00 | 444 | -29.39 (7.18) | -27 |
| Endpoint | (msec) | 310 | 7.30 (8.46) | 7.50 | 440 | -25.91 (7.18) | -23.5 |
| Heart Rate | | | | | | | |
| Maximum | (bpm) | 312 | -0.09 (0.76) | 0 | 444 | 2.93 (0.68) | 2.00 |
| Minimum | (bpm) | 312 | -0.35 (0.77) | -0.50 | 444 | 2.49 (0.67) | 2.00 |
| Endpoint | (bpm) | 310 | -0.38 (0.77) | -1.00 | 440 | 2.51 (0.67) | 2.00 |

**Table 7.1.9.1: Incidence of Treatment-Emergent ECG Abnormalities of Potential Clinical Significance: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| | Number of Patients with Potentially Clinically Significant Abnormality[a] (%) | |
|---|---|---|
| **ECG Measurement** | **Placebo** | **Aripiprazole** |
| **Rate** | | |
| Tachycardia | 0/ 314 (0.0) | 1/ 447 (0.2) |
| Bradycardia | 4/ 314 (1.3) | 4/ 447 (0.9) |
| **Rhythm** | | |
| Sinus tachycardia | 0/ 314 (0.0) | 1/ 447 (0.2) |
| Sinus bradycardia | 4/ 314 (1.3) | 4/ 447 (0.9) |
| Supraventricular premature beat | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Ventricular premature beat | 4/ 314 (1.3) | 4/ 447 (0.9) |
| Supraventricular tachycardia | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Ventricular tachycardia | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Atrial fibrillation | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Atrial fibrillation with rapid ventricular response | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Atrial flutter | 0/ 314 (0.0) | 0/ 447 (0.0) |
| **Conduction** | | |
| 1° atrioventricular block | 0/ 314 (0.0) | 1/ 446 (0.2) |
| 2° atrioventricular block | 0/ 314 (0.0) | 0/ 447 (0.0) |
| 3° atrioventricular block | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Left bundle branch block | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Right bundle branch block | 0/ 314 (0.0) | 2/ 447 (0.4) |
| Pre-excitation syndrome | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Other intraventricular conduction | 0/ 314 (0.0) | 1/ 447(0.2) |
| **Infarction** | | |
| Acute infarction | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Subacute (recent) infarct | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Old infarction | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Myocardial ischemia | 0/ 314 (0.0) | 0/ 447 (0.0) |
| Symmetrical T-wave inversion | 1/ 314 (0.3) | 2/ 447 (0.4) |

**Table 12.5.4: Incidence of EPS-Related AEs, Safety Sample**

| EPS Category/ Primary Term[a] | Number (%) of Patients | |
|---|---|---|
| | Haloperidol N = 169 | Aripiprazole N = 175 |
| **Any EPS Event[b]** | **106 (62.7)** | **42 (24.0)** |
| **Dystonic Events** | | |
| Dystonia | 13 (7.7) | 2 (1.1) |
| Rigidity Neck | 0 | 1 (0.6) |
| Oculogyric Crisis | 1 (0.6) | 0 |
| **Parkinsonism Events** | | |
| Extrapyramidal Syndrome | 60 (35.5) | 16 (9.1) |
| Tremor | 17 (10.1) | 12 (6.9) |
| Hypertonia | 7 (4.1) | 1 (0.6) |
| Hypokinesia | 2 (1.2) | 0 |
| **Akathisia Events** | | |
| Akathisia | 39 (23.1) | 20 (11.4) |
| Hyperkinesia | 2 (1.2) | 0 |
| **Dyskinetic Events** | | |
| Dyskinesia | 5 (3.0) | 2 (1.1) |
| **Residual Events** | | |
| Twitch | 0 | 1 (0.6) |
| Disorder Movement | 2 (1.2) | 0 |
| Myoclonus | 1 (0.6) | 0 |

Protocol CN138008

**Table 9.1.1.1A: Incidence of Treatment-Emergent EPS-Related AEs: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| EPS Category<br>Primary Term[a] | Number (%) of Patients<br>Placebo<br>N= 409 | | Aripiprazole<br>N= 568 | |
|---|---|---|---|---|
| **Any EPS-Related Event** | 58 | (14.2) | 164 | (28.9) |
| **Akathisia Events** | | | | |
| Akathisia | 14 | (3.4) | 85 | (15.0) |
| Hyperkinesia | 0 | | 2 | (0.4) |
| **Dyskinetic Events** | | | | |
| Dyskinesia | 0 | | 2 | (0.4) |
| Syndrome Buccoglossal | 0 | | 1 | (0.2) |
| Dyskinesia Tardive | 1 | (0.2) | 0 | |
| **Dystonic Events** | | | | |
| Rigidity Neck | 6 | (1.5) | 10 | (1.8) |
| Dystonia | 1 | (0.2) | 6 | (1.1) |
| **Parkinsonism Events** | | | | |
| Tremor | 14 | (3.4) | 33 | (5.8) |
| EPS | 9 | (2.2) | 29 | (5.1) |
| Hypertonia | 13 | (3.2) | 15 | (2.6) |
| Rigidity Cogwheel | 4 | (1.0) | 5 | (0.9) |
| Tremor Extremity | 1 | (0.2) | 4 | (0.7) |
| Akinesia | 0 | | 1 | (0.2) |
| Hypokinesia | 1 | (0.2) | 0 | |
| **Residual Events** | | | | |
| Twitch | 8 | (2.0) | 4 | (0.7) |
| Disorder Movement | 0 | | 2 | (0.4) |
| Myoclonus | 0 | | 2 | (0.4) |

[a] Modified COSTART term.

**Table 9.1.1.1B: Incidence of Treatment-Emergent EPS-Related AEs That Led to Discontinuation: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| EPS Category | Number (%) of Patients | | | |
|---|---|---|---|---|
| | Placebo | | Aripiprazole | |
| Primary Term[a] | N = 409 | | N = 568 | |
| **Any EPS-Related Event** | 4 | (1.0) | 19 | (3.3) |
| **Akathisia Events** | | | | |
| Akathisia | 2 | (0.5) | 13 | (2.3) |
| **Dystonic Events** | | | | |
| Rigidity Neck | 2 | (0.5) | 1 | (0.2) |
| Dystonia | 1 | (0.2) | 0 | |
| **Parkinsonism Events** | | | | |
| EPS | 0 | | 2 | (0.4) |
| Tremor | 0 | | 2 | (0.4) |
| Hypertonia | 0 | | 1 | (0.2) |

[a] Modified COSTART term.

**Table 9.1.4.1A: Mean Change from Baseline to Endpoint and Highest Score, SAS and AIMS Total Score, and Barnes Akathisia Global Clinical Assessment, LOCF Data Set: 3-Week Placebo-Controlled Studies in Acute Bipolar Mania (CN138007, CN138009, (b) (4) CN138074), Safety Sample**

| EPS Scale | Placebo | Aripiprazole |
|---|---|---|
| **SAS Total Score**[a] | **N = 394** | **N = 554** |
| Mean Baseline (SE) | 11.33 (0.10) | 11.36 (0.09) |
| Change from Baseline at Endpoint (SE) | 0.03 (0.12) | 0.61 (0.10)** |
| Change from Baseline at Highest Score (SE) | 0.58 (0.13) | 1.45 (0.12)** |
| **AIMS Total Score**[b] | **N = 306** | **N = 455** |
| Mean Baseline (SE) | 0.74 (0.10) | 0.78 (0.08) |
| Change from Baseline at Endpoint (SE)[c] | -0.18 (0.08) | -0.16 (0.07) |
| **Barnes Akathisia**[d] | **N = 395** | **N = 553** |
| Mean Baseline (SE) | 0.52 (0.04) | 0.57 (0.04) |
| Change from Baseline at Endpoint (SE) | -0.06 (0.05) | 0.25 (0.05)** |
| Change from Baseline at Highest Score (SE) | 0.23 (0.06) | 0.67 (0.05)** |

Note: For each analysis, patients in the Safety Sample were required to have both a baseline and an on-treatment assessment for the rating scale that was analyzed.

**($P \leq 0.01$), * ($0.01 < P \leq 0.05$) significantly different from placebo by ANCOVA, controlling for baseline and study center. Means and SEs are model-based (least squares) estimates.

[a] SAS Total Score ranges from 10 to 50. A negative change score indicates improvement.

[b] AIMS Total Score ranges from 0 to 28. A negative change score indicates improvement.

[c] AIMS Total Score was assessed only at endpoint, therefore, change at highest score is equal to change at endpoint.

[d] Global Clinical Assessment Score ranges from 0 (absent) to 5 (severe akathisia). A negative change score indicates improvement.

**Table 9.1.4.1B: Mean Change from Baseline to Endpoint and Highest Score, SAS and AIMS Total Score, and Barnes Akathisia Global Clinical Assessment, LOCF Data Set: 3-Week Placebo-Controlled Fixed-Dose Studies in Acute Bipolar Mania (CN138007, (b) (4), Safety Sample**

| | | Aripiprazole | | P-Value[a] | |
|---|---|---|---|---|---|
| **EPS Scale** | **Placebo** | **15 mg** | **30 mg** | **Aripiprazole 15 mg vs Placebo** | **Aripiprazole 30 mg vs Placebo** |
| **SAS Total Score[b]** | **N = 146** | **N = 146** | **N = 149** | | |
| Mean Baseline (SE) | 11.73 (0.17) | 11.81 (0.17) | 11.55 (0.17) | 0.734 | 0.431 |
| Change at Endpoint (SE) | -0.06 (0.21) | 0.87 (0.21) | 0.68 (0.21) | 0.001 | 0.010 |
| Change at Highest Score (SE) | 0.65 (0.23) | 1.65 (0.23) | 1.45 (0.23) | 0.001 | 0.009 |
| **AIMS Total Score[c]** | **N = 105** | **N = 119** | **N = 115** | | |
| Mean Baseline (SE) | 1.00 (0.18) | 0.95 (0.17) | 0.84 (0.17) | 0.820 | 0.484 |
| Change at Endpoint (SE)[d] | -0.27 (0.16) | -0.40 (0.15) | -0.35 (0.16) | 0.544 | 0.739 |
| **Barnes Akathisia[e]** | **N = 146** | **N = 146** | **N = 149** | | |
| Mean Baseline (SE) | 0.60 (0.08) | 0.71 (0.08) | 0.62 (0.08) | 0.297 | 0.866 |
| Change at Endpoint (SE) | -0.09 (0.09) | 0.27 (0.09) | 0.11 (0.09) | 0.003 | 0.101 |
| Change at Highest Score (SE) | 0.26 (0.09) | 0.65 (0.09) | 0.65 (0.09) | 0.002 | 0.001 |

Note: For each analysis, patients in the Safety Sample were required to have both a baseline and an on-treatment assessment for the rating scale that was analyzed.

[a] Comparison of model-based means (aripiprazole vs. placebo) from ANCOVA with baseline as covariate, controlling for study center. Means and SEs presented in this table are model-based (least squares) estimates.

[b] SAS Total Score ranges from 10 to 50. A negative change score indicates improvement.

[c] AIMS Total Score ranges from 0 to 28. A negative change score indicates improvement.

[d] AIMS Total Score was assessed only at endpoint, therefore, change at highest score is equal to change at endpoint.

[e] Global Clinical Assessment Score ranges from 0 (absent) to 5 (severe akathisia). A negative change score indicates improvement.

## PSUR Reports or Reviewer written synopses of reports:

**MFR# 12176566:** This case is of a 46 year old male bipolar patient with a history of obesity, mild mental retardation, hypertension, penicillin allergy, and smoking who experienced cardio-respiratory arrest about 18 days after admission to a psychiatric facility for increasing aggression. At admission to the facility, he was apparently started on aripiprazole 15mg per day. Within a few days, this was increased to 30 mg and oxcarbazepine was added. Divalproex sodium was added 13 days after admission.

The day before the arrest, the patient tripped and sustained a small laceration and lip contusion. At the time he was found, he was oriented and denied a loss of consciousness. His blood pressure was high at 180/105. He was taken to the ER and was described as alert and without focal neurologic findings. Early the next morning, around 1:30, he was given oral clonidine and noted to be asleep and snoring. Two hours later he was discharged back to the psychiatric facility, however, en route, he coded and CPR was initiated. On return to the ER, he was in asystole and without respirations and was intubated and coded. During the second set of defibrillations, the patient developed supraventricular tachycardia. He was transferred to the ICU and maintained on life support for 3 days. The patient's family refused autopsy.

The hospital intensivist reported the patient was hemodynamically stable after the resuscitation and the cause of death was listed as coronary artery disease. CT of the head was non-contributory.

**MFR#12181277:** This was a 22 year old female with a history of schizoaffective disorder, hypothyroidism, obesity, and mental retardation who lived in respite care facility who died in her sleep. Medications included aripiprazole for about 25 days, olanzapine, divalproex sodium, and citalopram. She had no history of cardiac, hepatic, renal, or neurological disorders. This case is confounded by concomitant medications and a paucity of details which do not allow for meaningful interpretation.

**MFR#12178216:** This was a 52 year old non-smoking male with a history of hypertension who died while hospitalized in a psychiatric facility secondary to being unmanageable at home and afraid he would hurt himself. About 3 weeks into the hospitalization, he collapsed and became unresponsive. He was noted as having bizarre behavior and confusion earlier that day. This patient was on multiple medications, the history is complicated, and he had risk factors for cardiovascular disease. Autopsy results are pending.

**MFR#12184008:** This was a 51 year old male schizophrenic or schizoaffective patient on aripiprazole for about 2 months before he was found dead. The date of his death is not known so it is difficult to construct a timeline and make reasonable conclusions. Apparently, he developed a high WBC count with 95% segmented cells and 3% lymphocytes, which may have preceded treatment with aripiprazole as it was "recalled" that he had had a high percent of segmented cells the October before this report was filed (February). On the day of his death, he complained of fatigue and coughed a lot. He was on several medications, including clozapine, and one to prevent seizures on clozapine. The information is inadequate to interpret definitively.

**MFR# 12194536:** This was 40-45 year old male smoker, overweight, who died in his sleep about 6 weeks after starting aripiprazole 10 mg per day. He was taking concomitant olanzapine and risperidone. It is not possible to reasonably attribute this death directly to aripiprazole given the concomitant medication and unknown cause of death.

**MFR#12206215**: This was coded as a brain death but the case has no identifiable patient and the reporter apparently had no direct knowledge of a patient.

**MFR# 12173894:** This is a physician report of a 27 year old female patient who **arrested**, was coded for a prolonged time without return of a rhythm or pulse and was pronounced dead. At the time of her death, it appears she was on several medications including aripiprazole, oxcarbazepine, clozapine, furosemide, and haloperidol. Her medical conditions included hypercholesterolemia, mild hypertension, seizure disorder, nephrotic syndrome, bronchial asthma, and morbid obesity. She resided in a nursing home however had been transferred to a psychiatric facility secondary to delusions, paranoia, physical aggression and agitation. While in the hospital, she was noted to have increased blood pressure of 190-200/100-120 and was treated with clonidine. Her blood pressure decreased to 120/70 and she developed drooling, drowsiness, emesis, fever, and difficulty breathing and was transferred to the ER for evaluation. In the ER, respirations were 26, BP 138/45 and pulse oximetry, 94%. Wheezing, crackles, and mild respiratory distress were noted and albuterol and atrovent nebulizers were initiated. She was given haloperidol for agitation. She was discharged back to the psychiatric facility the next day with a blood pressure of 122/88, pulse 88, respirations of 24, and temperature of 97.6F.

The day after this, she was reportedly agitated and her blood pressure was high at 150/100. Amlodipine was started and the patient was "put to bed" around 10 that night. About an hour later, she was found lying on the floor face down near her bed and was unable to be awakened by staff. Her pulse was strong but she was noted to have shallow respirations. Blood sugar was 135mg/dl. About 30 minutes later, the patient arrested. An autopsy was performed.

This is the case of a death of unknown cause in a young female. There are several medical conditions in her history, such as her seizure disorder and the asthma, which could have contributed to this chain of events. Additionally, she was on several medications. It is difficult to determine how or whether aripiprazole contributed to this.

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/s/
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Teresa Podruchny
4/14/04 06:34:37 PM
MEDICAL OFFICER

Paul Andreason
4/15/04 10:48:47 PM
MEDICAL OFFICER
I agree that supplement 002 is potentially approvable (b) (4) [redacted] See my memo to the file dated April 15, 2004.

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-436/S-002

# CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. **ORGANIZATION**: HFD-120
2. **NDA** **21-436**
3. **SUPPLEMENT NUMBER AND DATES**: SE1-002 (b) (4)

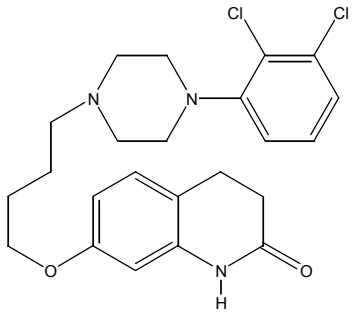
LETTER DATE: 06-23-03
STAMP DATE: 06-25-03

4. **AMENDMENT/REPORTS/DATES**
5. **RECEIVED BY CHEMIST**: 07-01-03

6. **APPLICANT NAME & ADDRESS**: Outsuka America Pharmaceuticals, Inc.
2440 Research Boulevard
Rockville, MD 20850 ® Tablets

8. **NONPROPRIETARY NAME**: Aripiprazole

9. **CHEMICAL NAME and STRUCTURE**:
7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone




10. **DOSAGE FORMS**: Tablets
11. **POTENCY:** 10 mg; 15 mg, and 30 mg
12. **PHARMACOLOGICAL CATEGORY**: Schizophrenia
13. **HOW DISPENSED**: ___X___ R(x) _____(OTC)
14. **RECORD and REPORTS CURRENT**: ___X___ Yes _____No
15. RELATED IND/NDA/DMF:

16. **SUPPLEMENT PROVIDES FOR:** This supplement provides for the use of Abilify™ in the treatment of acute manic episodes in patients with Bipolar I Disorder

17. **ADDITIONAL COMMENTS**: The applicant was telephoned on Wednesday, July 16, 2003 and indicated that all Chemistry, Manufacturing and Control information pertaining to the drug substance and the drug product remain unchanged

18. **CONCLUSIONS & RECOMMENDATIONS:** The sponsor has submitted adequate information to support this change. It is the recommendation of the CMC reviewer that this supplement be APPROVED.

cc:
Division File NDA 21-436
HFD-120/TOliver
HFD-120/SMcLamore
HFD-120/SHardeman

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Thomas Oliver
7/17/03 09:44:35 AM
CHEMIST

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-436/S-002

# STATISTICAL REVIEW(S)


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

# STATISTICAL REVIEW AND EVALUATION
## Clinical Studies

| | |
|---|---|
| NDA/Serial Number: | 21-436/SE1-002 |
| Drug Name: | ABILIFY(aripiprazole) Tablets |
| Indication: | Acute Mania in Bipolar I Disorder |
| Applicant: | Bristol-Myers Squibb |
| Dates: | Date of Document: 6/24/03 |
| | PDUFA Due Date: 4/25/04 |
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| Biometrics Division: | Biometrics I, HFD-710 |
| Statistical Reviewer: | Yeh-Fong Chen, Ph.D. |
| Concurring Reviewers: | Kun Jin, Ph.D. |
| | Kooros Mahjoob, Ph.D. |
| Medical Division: | Division of Neuropharmacological Drug Products, HFD-120 |
| Clinical Team: | Teresa Podruchny, M.D., Medical Reviewer |
| | Paul Andreason, M.D., Medical Team Leader |
| Project Manager: | Doris Bates, Ph.D. |

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# 1. EXECUTIVE SUMMARY

## 1.1 CONCLUSIONS AND RECOMMENDATIONS

After reviewing three pivotal studies, CN138007, CN138009 and CN138074, this reviewer determined that Study CN138007 was a failed study. Study CN138009 had significant results shown on the primary endpoint by the primary analysis (LOCF). The interpretation of significant findings, however, should be carefully considered due to large number and unbalanced dropouts at the end of visits, which then resulted OC analysis results numerically favored placebo. Study CN138074 clearly demonstrated the aripiprazole's efficacy for the treatment of acute manic or mixed episodes in patients with a diagnosis of Bipolar I Disorder.

The sponsor described four key secondary endpoints (b) (4); however these endpoints were not prospectively specified in the original protocol or any amendments for Study CN138009 as the KEY secondary endpoints, (b) (4)

## 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Abilify (aripiprazole) is a recently marketed product approved for the treatment of schizophrenia and is currently being developed for additional indications. In this submission, the sponsor seeks the approval for the treatment of acute manic or mixed episodes in patients with a diagnosis of Bipolar I Disorder.

The sponsor's bipolar mania program consists of five 3-week placebo-controlled studies (CN138007, CN138009, (b) (4) CN138074 and (b) (4) one 26 week active-controlled study with a 12-week acute phase and a 14-week extension phase (CN138008), and two long-term studies: one open-label maintenance study (CN138037) and one double-blind maintenance placebo-substitution study (CN138010).

Among these studies, Studies CN138007, CN138009 and CN138074 were completed. (b) (4) (b) (4) Study CN138010 was still ongoing when the application was sent in and Study 138037 was an open-labeled study. So, this review only focuses on the review and evaluation of three pivotal studies: Study CN138007, CN138009 and CN138074.

The duration of treatment for these three studies was 3 weeks. The patient population included men and women aged 18 years and older who were in acute relapse with a diagnosis of Bipolar I Disorder, manic or mixed type, and who required hospitalization. The primary efficacy measure for these 3-week placebo-controlled was the mean change from baseline to Week 3 in the Y-MRS Total Score. Study

CN138007 was designed with fixed doses of 15 mg/day and 30 mg/day of aripiprazole. Study CN138009 and Study CN138074 were, however, designed with not fixed doses. Patients randomized to aripiprazole were started at a dose of 30 mg/day, with the option to decrease to 15 mg/day based on tolerability, and to subsequently increase to 30 mg/day based on clinical response at any time during the study. According to the sponsor's submission, they concluded that Study CN138009 and CN138074 provide evidence that aripiprazole is effective in the treatment of acute mania in Bipolar I Disorder using a dose regimen of 15 mg/day or 30 mg/day. Study CN138007, evaluating fixed doses of 15 mg/day and 30 mg/day of aripiprazole, resulted in a negative outcome due to a high placebo response, although the level of improvement for patients on aripiprazole was consistent with other studies.

## 1.3 STATISTICAL ISSUES AND FINDINGS

For all three pivotal studies, the statistical reviewer confirmed the entire sponsor's efficacy analysis results. Except of 2 patients in Study CN138007 and 2 patients in Study CN138074 that the sponsor analyzed them by the treatment they received instead of the treatments they were randomized, no major inconsistency was found between the sponsor's and this reviewer's analyses results. After reviewing three pivotal studies, this reviewer determined that Study CN138007 was a failed study. Although Study CN138009 had significant results shown on the primary endpoint by the primary analysis (LOCF), the interpretability of the study's significant findings should be carefully considered due to large number and unbalanced dropouts happened at the end of visits, which then resulted OC analysis results favored the placebo. Study CN138074 clearly demonstrated the aripiprzole's efficacy for the treatment of acute manic or mixed episodes in patients with a diagnosis of Bipolar I Disorder.

For both studies CN138009 and CN138074, in addition to the primary endpoint, the significant results were also shown on the secondary endpoints. (b) (4)

This reviewer noticed that first of all, for Study CN138009, although the sponsor stated in the study reports' final discussion that two secondary endpoints (i.e., the mean change from baseline to Week 3 in the CGI-BP Severity of Illness on mania score and the percentage of patients with discontinuation due to lack of efficacy or entry into the open-label aripiprazole phase at Week 2) were two key secondary criteria, these were not prospectively planned in the original study protocol or any amendments. Secondly, although the sponsor had significant results shown on all four secondary endpoints (analysis of responders, CGI-BP Severity of Illness Score on mania, PANSS Hostility Subscale and CGI-BP change from Preceding Phase Score on mania) for both Studies CN138009 and CN138074, due to not prospectively specified key

secondary endpoints for Study 138009, (b) (4)

# 2. INTRODUCTION

## 2.1 OVERVIEW

Abilify (aripiprazole) is a recently marketed product approved for the treatment of schizophrenia and is currently being developed for additional indications. In this submission, the sponsor seeks the approval for the treatment of acute manic or mixed episodes in patients with a diagnosis of Bipolar I Disorder.

The sponsor's bipolar mania program consists of five 3-week placebo-controlled studies (CN138007, CN138009, (b) (4) CN138074 (b) (4)), one 26-week active-controlled study with a 12-week acute phase and a 14-week extension phase (CN138008), and two long-term studies; one open-label maintenance study (CN138037) and one double-blind maintenance placebo-substitution study (CN138010).

Three of five 3-week placebo-controlled studies were completed. They are Studies CN138007, CN138009 and CN138074. (b) (4) (b) (4) another long-term double-blind maintenance placebo-substitution Study CN138010 was still ongoing when this application was sent in, this review only focuses on evaluating the efficacy of three 3-week placebo controlled studies: CN138007, CN138009 and CN138074 (b) (4)

The duration of treatment for these three studies was 3 weeks. The patient population included men and women aged 18 years and older who were in acute relapse with a diagnosis of Bipolar I Disorder, manic or mixed type, and who required hospitalization. The primary efficacy measure for these 3-week placebo-controlled was the mean change from baseline to Week 3 in the Y-MRS Total Score. Study CN138007 was designed with fixed doses of 15 mg/day and 30 mg/day of aripiprazole. Study CN138009 and Study CN138074 were, however, designed with not fixed doses. Patients randomized to aripiprazole were started at a dose of 30 mg/day, with the option to decrease to 15 mg/day based on tolerability, and to subsequently increase to 30 mg/day based on clinical response at any time during the study.

According to the sponsor's submission, they concluded that the efficacy of aripiprazole in the treatment of acute manic or mixed episodes in patients with a diagnosis of Bipolar I Disorder was demonstrated in two 3-week placebo-controlled studies (CN138009 and CN138074) (b) (4)

## 2.2 DATA SOURCES

The submission can be accessed by the following link in EDR:
"\\Cdsesub1\n21436\S_002\2003-06-23"

# 3. STATISTICAL EVALUATION

## 3.1 EVALUATION OF EFFICACY

The following study descriptions are based on the sponsor's study reports.

3.1.1. Description of Study CN138007

This study was titled as "A Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Two Fixed Doses of Aripiprazole in the Treatment of Hospitalized Patients with Acute Mania." There were sixty investigators from 56 study centers (51 in the United States, three in Mexico, and two in Argentina) participated in the conduct of the study.

3.1.1.1 Study Objectives

The primary objective of this study was to compare the efficacy of two fixed doses of aripiprazole with placebo on the Young-Mania Rating Scale (Y-MRS) in the treatment of acutely relapsed patients with a diagnosis of Bipolar I Disorder, manic or mixed. The secondary objective of this study was to compare the safety of two fixed doses of aripiprazole to placebo in the treatment of acutely relapsed patients with a diagnosis of Bipolar I Disorder, manic or mixed.

3.1.1.2 Study Design

This study was a multicenter, multinational, 3-week, randomized, double-blind, fixed-dose, placebo controlled trial with three parallel groups of hospitalized patients. The patients in this trial met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for Bipolar I Disorder and were in acute relapse of manic or mixed symptoms that required hospitalization. This diagnosis was confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) or the Mini International Neurological Interview (MINI). After a 1- to 7-day screening period (screening may have been extended up to 14 days with permission from BMS), and after a minimum 24-hour psychotropic washout, patients fulfilling all entrance criteria, including a Y-MRS score of $\geq 20$ at the baseline visit were randomized into the 3-week treatment phase. Patients received blinded fixed doses of 15 mg or 30 mg of aripiprazole or placebo, once daily. Patients unable to tolerate study medication were discontinued from the study. Patients remained hospitalized for a minimum of 2 weeks during the treatment period.

Patients meeting the following Clinical Global Impression-Bipolar Version (CGI-BP) criteria at the end of Week 2 were allowed to be discharged:

- CGI-BP Severity of Illness (mania) score of 3 or less (mildly ill, minimal ill, not ill), and

- CGI-BP Change from Preceding Phase (mania) score of 2 or less (much improved, very much improved).

Patients not meeting these criteria remained hospitalized for the duration of the 3-week treatment period. Day passes were allowed as of Day 10, based on the judgment of the investigator. Drug and Alcohol screens were performed for any patient returning to the hospital from a day pass. Overnight passes were not allowed.

Patients showing no improvement or a worsening of symptoms (i.e., CGI-BP Change from Preceding Phase (mania) $\geq$ 4) at Week 2, were offered the option of open-label aripiprazole during Week 3. Treatment with open-label aripiprazole was initiated at 30 mg per day with the option of decreasing to 15 mg based on tolerability.
Patients who completed the 3-week study were eligible for entry into one of two separate long-term, outpatient studies, CN138-010 (double-blind maintenance) or CN138-037 (open-label maintenance).

3.1.1.3 Efficacy Variables

Primary Efficacy Variable

The primary efficacy variable for this study was the mean change from baseline to Week 3 on the Y-MRS Total Score. This scale consisted of 11 items assessing the core symptoms of mania (elevated mood, increased motor activity-energy, sexual interest, sleep, irritability, speech, language-thought disorder, content, disruptive-aggressive behavior, appearance, and insight). Each item had five defined grades of severity.

Secondary Efficacy Variables

The secondary efficacy variables for this study were the mean change from baseline to Week 3 in the CGI-BP Severity of Illness (mania) score and the percentage of patients with discontinuation due to lack of efficacy or entry into the open-label aripiprazole phase at Week 2 with a CGI-BP Change from Preceding Phase (mania) score of 4 to 7. The CGI-BP Severity of Illness (mania) score is a 7-point scale which rated the severity of mania (normal, not ill to very severely ill) and change from preceding phase (very much improved to very much worse). Change from Preceding Phase was judged with respect to the patients' condition at baseline.

3.1.1.4 Statistical Methods

The planned sample size for this study was 375 evaluable patients (125 per treatment group). The Randomized Sample included all patients who were randomized to treatment. The Efficacy Sample included all patients who were randomized to treatment, took at least one dose of study medication and had at least one post-randomization efficacy evaluation.

The Last Observation Carried Forward (LOCF) data set was considered primary and The analyses of the OC data set were considered secondary and were performed to corroborate those on the LOCF data set.

Primary Efficacy Analysis

The primary efficacy variable, the mean change from baseline in the Y-MRS to Week 3 was analyzed by the Analysis of Covariance (ANCOVA) with baseline Y-MRS as the covariate and study center and treatment as main effects. The primary presentations of results were the model-based estimates and 95% confidence intervals (CI) for the treatment difference (aripiprazole minus placebo), which were derived from the estimation (ESTIMATE) of the treatment contrasts.

Secondary Efficacy Analyses

Secondary efficacy analyses for this study included:

- Mean change from baseline to Week 3 in the CGI-BP Severity of Illness (mania) Score, analyzed by ANCOVA for each specified visit. The LOCF and OC data sets were used;

- The rate of discontinuation due to lack of efficacy at any time during the study or entry into the open-label aripiprazole phase at Week 2 with a CGI-BP Change from Preceding Phase (mania) Score of 4 to 7, shown by treatment group and evaluated by the CMH test controlling for study center.

3.1.2 Efficacy Analysis Results for Study CN138007

3.1.2.1 Data Sets

The distribution of all randomized patients within each of the patient samples is presented by treatment group in Table 3.1.2.1.

Table 3.1.2.1 Number of Patients in Samples for Study CN138007

| | Placebo | Aripiprazole 15 mg | Aripiprazole 30 mg | Total |
|---|---|---|---|---|
| Randomized[a] | 134 | 131 | 136 | 401 |
| Safety[a] | 133 | 131 | 135 | 399 |
| Efficacy[a] | 130 | 127 | 129 | 386 |

[a] Patient 138007-56-94 was randomized to placebo but received aripiprazole 15 mg. This patient is tabulated in the aripiprazole 15 mg group in Efficacy and Randomized Samples and is tabulated in the placebo group in the Safety Sample. Patient 138007-56-181 was randomized to aripiprazole 15 mg but received placebo. This patient is tabulated in the placebo group in Efficacy and Randomized Samples and is tabulated in the aripiprazole 15 mg group in the Safety Sample.

3.1.2.2 Disposition of Patients

Five hundred thirty four patients were enrolled in the study. Of these, 401 were randomized to receive double-blind treatment; 134 to the placebo group, 131 to the 15-mg aripiprazole group, and 136 to the 30-mg aripiprazole group. Of the 401 randomized patients, 164 (41%) completed double-blind treatment period and 237 (59%) discontinued from the study early.

The percentage of patients who completed study on double-blind treatment was similar across the three treatment groups. The disposition of all patients randomized to treatment is presented by treatment group in Table 3.1.2.2.

Table 3.1.2.2 Disposition of Patients for Study CN138007

| | Number (%) of Patients | | | |
|---|---|---|---|---|
| **Patient Status** | **Placebo** | **Aripiprazole 15 mg** | **Aripiprazole 30 mg** | **Total** |
| **Enrolled Sample** | n/a | n/a | n/a | 534 |
| Baseline failures | n/a | n/a | n/a | 133 |
| **Randomized** | 134 | 131 | 136 | 401 |
| **Discontinued from Double-Blind Treatment** | 80(60) | 75(57) | 82(60) | 237(59) |
| Due to lack of response entered open-label aripiprazole[a] | 27(20) | 14(11) | 26(19) | 67(17) |
| Adverse Event | 9(7) | 20(15) | 9(7) | 38(9) |
| Lack of efficacy | 10(7) | 9(7) | 12(9) | 31(8) |
| Patient withdrew consent | 22(16) | 28(21) | 29(21) | 79(20) |
| Patient unreliability | 1(1) | 0 | 1(1) | 2(< 1) |
| Lost to follow-up | 3(2) | 3(2) | 4(3) | 10(2) |
| Other known cause[b] | 8(6) | 1(1) | 1(1) | 10(2) |
| **Completed Double-Blind Treatment** | 54(40) | 56(43) | 54(40) | 164(41) |

[a] Patients not responding at Week 2, as indicated by CGI-BP Change from Preceding Phase (mania) score of four to seven, were placed on open-label aripiprazole.
[b] Other reasons for discontinuation may have included: pregnancy, other known cause (other), study terminated by sponsor, protocol violation, patient met withdrawal criteria, patient did not satisfy one or more screening criteria, or general inability to continue.

### 3.1.2.3 Demography and Patient Characteristics

Treatment groups were comparable with respect to age, gender, race and body weight. Demographic characteristics for the Randomized Sample are presented by treatment group in Table 3.1.2.3.

Table 3.1.2.3 Demographic Characteristics by Randomized Sample for Study CN138007

| Variable | | Placebo N = 134 | Aripiprazole 15 mg N = 131 | Aripiprazole 30 mg N = 136 | Total N = 401 |
|---|---|---|---|---|---|
| Age | Mean | 40.6 | 39.3 | 41.4 | 40.5 |
| (years) | Median | 40.5 | 39.0 | 42.0 | 40.0 |
| | Min - Max | 18.0 - 71.0 | 18.0 - 68.0 | 19.0 - 74.0 | 18.0 - 74.0 |
| | S. E. | 1.0 | 1.0 | 1.0 | 0.6 |
| Gender | Male | 65 (49) | 65 (50) | 62 (46) | 192 (48) |
| N (%) | Female | 69 (51) | 66 (50) | 74 (54) | 209 (52) |
| Race | White | 96 (72) | 99 (76) | 98 (72) | 293 (73) |
| N (%) | Black | 19 (14) | 19 (15) | 19 (14) | 57 (14) |
| | Asian/Pacific Islander | 0 | 1 (1) | 3 (2) | 4 (1) |
| | Hispanic/Latino | 17 (13) | 12 (9) | 16 (12) | 45 (11) |
| | Other | 2 (1) | 0 | 0 | 2 (< 1) |
| Weight (kg) | Mean | 84.8 | 88.8 | 84.8 | 86.1 |
| | Median | 80.6 | 85.1 | 81.3 | 81.9 |
| | Min-Max | 47.7 - 168.8 | 49.5 - 165.6 | 50.4 - 156.6 | 47.7 - 168.8 |
| | S.E. | 1.9 | 1.9 | 1.7 | 1.1 |
| | Missing | 5 | 4 | 2 | 11 |

### 3.1.2.4 Sponsor's Efficacy Analysis Results

#### 3.1.2.4.1 Primary Efficacy Measure: Mean Change from Baseline in Y-MRS Total Score

Change in Y-MRS Total Scores were derived by subtracting baseline Y-MRS Total Scores from the Y-MRS Total Scores at each study week. Negative change Scores indicated improvement. The mean change from baseline to Week 3 in the Y-MRS

Total Score was the primary efficacy measure. The analysis of the change in the Y-MRS Total Score for the LOCF data set at Week 3 showed no statistically significant difference between placebo and any of the aripiprazole treatment groups at any time point.

The analysis of the mean change from baseline for the OC data set showed that the aripiprazole treatment groups were not statistically significantly different from placebo at any visit. Sample sizes decreased substantially between Week 2 and Week 3 and the mean change from baseline Y-MRS Total Scores for all treatment groups showed improvement when the option to switch to open-label aripiprazole could be exercised.

Results of the analysis of the mean change in the Y-MRS Total Score are shown by treatment group and study week in Table 3.1.2.4 for the LOCF data set and in Table 3.1.2.5 for the OC data set.

Table 3.1.2.4 Mean Change from Baseline in Y-MRS by LOCF Data Set in Efficacy Sample for Study CN138007

| | Mean Change from Baseline in Y-MRS[a] | | | Pairwise Comparisons P-values[b] | | |
|---|---|---|---|---|---|---|
| | Placebo N = 130[c] | Aripiprazole 15 mg N = 127[c] | Aripiprazole 30 mg N = 129[c] | Aripiprazole 15 mg vs. placebo | Aripiprazole 30 mg vs. placebo | Overall test P-value |
| Mean Baseline | 28.27 | 27.94 | 27.83 | 0.600 | 0.488 | 0.769 |
| Double-Blind Treatment | | | | | | |
| Day 4 | -5.58 | -6.37 | -6.23 | 0.303 | 0.400 | 0.547 |
| Week 1 | -7.99 | -8.78 | -8.65 | 0.434 | 0.510 | 0.701 |
| Day 10 | -8.97 | -9.69 | -9.19 | 0.530 | 0.849 | 0.813 |
| Week 2 | -9.95 | -10.11 | -10.27 | 0.899 | 0.798 | 0.968 |
| Week 3 | -10.12 | -10.01 | -10.80 | 0.928 | 0.599 | 0.802 |
| Week 3: 95% confidence interval for treatment differences (aripiprazole - placebo) | | | | | | |
| | | 0.12 | -0.68 | | | |
| | | (-2.43, 2.66) | (-3.22, 1.86) | | | |

[a] Y-MRS total score is from 0 to 60. A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment, center and baseline value. LS Means P-values for comparisons. Superiority of each fixed dose of aripiprazole is claimed if overall comparison and pairwise comparison are statistically significant at 5% level.
[c] At Day 4, N = 126 for placebo, N = 123 for aripiprazole 15 mg, N = 124 for aripiprazole 30 mg.

Table 3.1.2.5 Mean Change from Baseline in Y-MRS by OC Data Set in Efficacy Sample for Study CN138007

| | Mean Change from Baseline in Y-MRS[a] | | | | | | Pairwise Comparisons P-values[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo | | Aripiprazole 15 mg | | Aripiprazole 30 mg | | Aripiprazole 15 mg vs. placebo | Aripiprazole 30 mg vs. placebo | Overall test P-value |
| | N | Mean | N | Mean | N | Mean | | | |
| Mean Baseline | 130 | 28.20 | 127 | 27.89 | 129 | 27.64 | 0.649 | 0.406 | 0.707 |
| Double-Blind Treatment | | | | | | | | | |
| Day 4 | 126 | -5.25 | 123 | -5.88 | 124 | -5.84 | 0.450 | 0.482 | 0.699 |
| Week 1 | 108 | -8.27 | 105 | -9.30 | 111 | -8.79 | 0.383 | 0.654 | 0.683 |
| Day 10 | 92 | -10.10 | 87 | -11.03 | 94 | -10.12 | 0.500 | 0.986 | 0.745 |
| Week 2 | 94 | -11.37 | 85 | -13.35 | 89 | -11.82 | 0.147 | 0.736 | 0.320 |
| Week 3 | 55 | -15.50 | 56 | -17.79 | 55 | -17.27 | 0.109 | 0.217 | 0.245 |
| Week 3: 95% confidence interval for treatment differences (aripiprazole - placebo) | | | | | | | | | |
| | | | | -2.29 (-5.10. 0.52) | | -1.77 (-4.59, 1.05) | | | |

[a] Y-MRS total score is from 0 to 60. A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment and baseline value. LS Means P-values for comparisons. Superiority of each fixed dose of aripiprazole is claimed if overall comparison and pairwise comparison are statistically significant at 5% level.

3.1.2.4.2 Secondary Analyses

Mean Change from Baseline in the CGI-BP Severity of Illness (Mania) Score

The mean change from baseline to Week 3 in the CGI-BP Severity of Illness (mania) score was the first of the two secondary outcome measures. The results of the analysis of the change from baseline in the CGI-BP Severity of Illness (mania) score by LOCF data set are shown in Table 3.1.2.7. The analysis shows no statistically significant difference between placebo and any aripiprazole treatment group at any visit.

The results of the analysis of the mean change from baseline for the OC data set are shown in Table 3.1.2.8. The aripiprazole treatment groups were not statistically significantly different from placebo at any visit. As expected, Week 3 sample sizes decreased substantially and the mean change from baseline CGI-BP Severity of Illness (mania) score improved for both treatment groups when the option to switch to open-label aripiprazole cold be exercised.

Table 3.1.2.7 Mean Change from Baseline in the CGI-BP Severity of Illness (Mania) Score by LOCF Data Set in Efficacy Sample for Study CN138007

| | Mean Change from Baseline in CGI-BP Severity of Illness (Mania) Score[a] | | | Pairwise Comparisons P-values[b] | |
|---|---|---|---|---|---|
| | Placebo N = 129 | Aripiprazole 15 mg N = 125 | Aripiprazole 30 mg N = 128 | Aripiprazole 15 mg vs. placebo | Aripiprazole 30 mg vs. placebo |
| Mean Baseline | 4.68 | 4.66 | 4.70 | 0.819 | 0.856 |
| Double-Blind Treatment | | | | | |
| Day 4 | -0.50 | -0.61 | -0.55 | 0.251 | 0.580 |
| Week 1 | -0.88 | -0.99 | -0.90 | 0.364 | 0.865 |
| Day 10 | -1.01 | -1.11 | -1.01 | 0.462 | 0.984 |
| Week 2 | -1.20 | -1.25 | -1.21 | 0.748 | 0.930 |
| Week 3 | -1.17 | -1.29 | -1.33 | 0.497 | 0.365 |
| Week 3: 95% confidence interval for treatment differences (aripiprazole-placebo) | | | | | |
| | | -0.12 | -0.15 | | |
| | | (-0.45, 0.22) | (-0.48, 0.18) | | |

[a] CGI-BP Severity of Illness (mania) score is from 1 (normal) to 7 (very severely ill). A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment, center and baseline value. LS Means P-values for comparisons.

Table 3.1.2.8 Mean Change from Baseline in the CGI-BP Severity of Illness (Mania) Score by OC Data Set in Efficacy Sample for Study CN138007

| | Mean Change from Baseline in CGI-BP Severity of Illness (Mania) Score[a] | | | | | | Pairwise Comparisons P-values[b] | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | Aripiprazole 15 mg | | Aripiprazole 30 mg | | Aripiprazole 15 mg vs. placebo | Aripiprazole 30 mg vs. placebo |
| | N | Mean | N | Mean | N | Mean | | |
| Mean Baseline | 129 | 4.71 | 125 | 4.71 | 128 | 4.73 | 0.989 | 0.878 |
| Double-Blind Treatment | | | | | | | | |
| Day 4 | 124 | -0.47 | 121 | -0.56 | 123 | -0.52 | 0.377 | 0.654 |
| Week 1 | 108 | -0.89 | 104 | -1.00 | 110 | -0.90 | 0.434 | 0.951 |
| Day 10 | 91 | -1.11 | 87 | -1.21 | 94 | -1.03 | 0.567 | 0.619 |
| Week 2 | 93 | -1.39 | 84 | -1.59 | 89 | -1.28 | 0.268 | 0.572 |
| Week 3 | 55 | -2.08 | 55 | -2.27 | 55 | -2.13 | 0.312 | 0.797 |
| Week 3: 95% confidence interval for treatment differences (aripiprazole-placebo) | | | | | | | | |
| | | | | -0.20 | | -0.05 | | |
| | | | | (-0.58, 0.18) | | (-0.43, 0.33) | | |

[a] CGI-BP Severity of Illness (mania) score is from 1 (normal) to 7 (very severely ill). A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment, baseline value. LS Means P-values for comparisons.

Rate of Discontinuation

The rate of discontinuation due to lack of efficacy or entry into open-label aripiprazole dosing at Week 2 with a CGI-BP Change from Preceding Phase (mania) score of 4 to 7 was the additional secondary outcome measure. The results of the analysis for this secondary endpoint are displayed in Table 3.1.2.9. Neither aripiprazole treatment group showed a statistically significantly lower rate of discontinuation than the placebo treatment group.

Table 3.1.2.9 Rate of Discontinuation Due to Lack of Efficacy or Entry into Open-Label Aripiprazole at Week 2 with a CGI-BP Change from Preceding Phase (Mania) Score of 4 to 7 by OC Data Set in Efficacy Sample for CN138007

| Number Discontinuing/Number Assessed[a](%) | | | Pairwise Comparisons P-values[b] | |
|---|---|---|---|---|
| Placebo | Aripiprazole 15 mg | Aripiprazole 30 mg | Aripiprazole 15 mg vs. placebo | Aripiprazole 30 mg vs. placebo |
| 35/130 (27) | 23/127 (18) | 32/129 (25) | 0.091 | 0.816 |
| 95% confidence interval for ratio vs. placebo | | | | |
| | | | 0.67 | 0.95 |
| | | | (0.43, 1.07) | (0.63, 1.45) |

[a] The number discontinuing is the number of patients who drop due to lack of efficacy at any time or who complete Week 2 and then switch to the open-label phase.
[b] CMH General Association test.

3.1.2.4 The Sponsor's Final Discussion for Efficacy Analysis Results

In this Phase III trial, aripiprazole did not separate from placebo at any time point on the prospectively defined primary and key secondary efficacy criteria (Y-MRS Total Score, CGI-BP Severity of Illness (mania) score, and the rate of discontinuation due to lack of efficacy or entry into the open-label aripiprazole treatment). In addition, aripiprazole did not separate from placebo on the other prospectively-defined secondary efficacy endpoints.

The sponsor's explanation about the failure of the aripiprazole arms to distinguish themselves from placebo with respect to efficacy evaluations was due to a higher-than expected placebo response rate. Published reviews by Keck et al of placebo response rates in controlled clinical trials of similar design in acute mania have shown that the placebo response rate averages 23%. At 38%, the overall response rate in Study CN138-007 was substantially higher than this averaged historical control and is twice the response rate (19%) seen in another recent BMS-sponsored Phase III trial (CN138 009), which used identical patient selection criteria. The high placebo response rate was particularly evident in the Y-MRS change at Week 3 analysis, with a score of –10.12 in CN138007 versus a score of -3.35 in CN138009.

3.1.2.5 Statistical Reviewer's Findings and Comments

1. The statistical reviewer confirmed all of the sponsor's efficacy analysis results for this study. This study is a negative study, where the placebo group patients' LOCF least square mean change from baseline of Y-MRS total score at Week 3 (the primary endpoint) were even higher than aripiprazole 15 mg group patients'. Although the aripiprazole 30mg group of patients performed numerically better than the placebo group of patients for the primary endpoint, the difference is not statistically significant.

2. Although the sponsor mentioned in their final discussion that two efficacy endpoints, i.e., CGI-BP Severity of Illness (mania) score and the rate of discontinuation due to lack of efficacy or entry into the open-label aripiprazole treatment are key secondary efficacy criteria, they did not designate them in original protocol or amendments as key secondary endpoints (b) (4)

3.1.3 Description of Study CN138009

This study was titled as "A Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Flexible Doses of Aripiprazle in the Treatment of Hospitalized Patients with Acute Mania." There were forty investigators from 38 study centers in the United States of America participated in the conduct of the study.

3.1.3.1 Study Objectives

The primary objective of this study was to compare the efficacy of a flexible dosing regimen of aripiprazole to placebo on the Young-Mania Rating Scale (Y-MRS) in the treatment of acutely relapsed patients with a diagnosis of Bipolar I Disorder, manic or mixed. The secondary objective of this study was to compare the safety of flexible doses of aripiprazole to placebo in the same population.

3.1.3.2 Study Design

This study was a 3-week, multicenter, randomized, double-blind, placebo controlled trial with two parallel groups of hospitalized patients. The patients in this trial met Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV) criteria for Bipolar I Disorder and were in acute relapse of manic or mixed symptoms that required hospitalization. This diagnosis was confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) or the Mini International Neurological Interview (MINI). After a 1- to 7-day screening period (screening may have been extended to14 days with permission from BMS), and after a minimum 24-hour psychotropic medication washout, patients fulfilling the entrance criteria at baseline (including Y-MRS Score of $\geq$ 20) were evenly randomized to aripiprazole or placebo for the 3-week treatment phase. Patients assigned to aripiprazole started at a dose of 30 mg (two tablets) once daily. Blinded dose

reductions were allowed if 30 mg (i.e., two tablets of aripiprazole or placebo) was not tolerated. Following dose reductions, patients took one tablet (15 mg aripiprazole or placebo) per day. Patients unable to tolerate study medication were discontinued from the study. Patients remained hospitalized for a minimum of 2 weeks during the treatment period.

Patients meeting the following Clinical Global Impressions – Bipolar Version (CGI-BP) criteria at the end of Week 2 were allowed to be discharged:

- CGI-BP Severity of Illness (mania) score of 3 or less (mildly ill, minimally ill, not ill); and

- CGI-BP Change from Preceding Phase (mania) score of 2 or less (much improved, very much improved).

Patients not meeting these criteria remained hospitalized for the duration of the 3-week treatment period. Day passes were allowed on or after Day 10 based on the judgment of the investigator. A drug screen and an alcohol test were to be performed for any patient returning to the hospital from a day pass. Overnight passes were not allowed.

Patients showing no improvement or a worsening of symptoms (i.e., CGI-BP Change from Preceding Phase (mania) score $\geq 4$) at Week 2 were allowed to be dropped from the blinded treatment phase and enter into an open-label aripiprazole treatment group for Week 3. Treatment with open-label aripiprazole was initiated at 30 mg per day with the option of decreasing to 15 mg per day based on tolerability.

Patients who completed the 3-week study were eligible for entry into one of two separate, long-term, outpatient studies (CN138-010 [double-blind maintenance] or CN138-037 [open-label maintenance]). Results of these studies will be presented in separate study reports.

3.1.3.3 Efficacy Variables

The efficacy variables are the same as those described in Section 3.1.1.3 for Study CN138007.

3.1.3.4 Statistical Methods

The planned sample size for this study was 250 evaluable patients (approximately 125 per treatment group).

The data set descriptions and analysis methods for all efficacy endpoints are the same as those described in Section 3.1.1.4 for Study CN138007.

### 3.1.4 Efficacy Analysis Results for Study CN138009

#### 3.1.4.1 Data Sets

The distribution of all randomized patients within each of the patient samples is presented by treatment group in Table 3.1.4.1.

Table 3.1.4.1 Number of Patients in Samples for Study CN138009

| | Placebo | Aripiprazole | Total |
|---|---|---|---|
| Randomized | 132 | 130 | 262 |
| Safety | 127 | 127 | 254 |
| Efficacy | 123 | 125 | 248 |

#### 3.1.4.2 Disposition of Patients

A total of 358 patients were enrolled in the study. Of these, 262 were randomized to receive double-blind treatment. Of the 262 randomized patients, 82 (31%) completed double-blind treatment period and 180 (69%) discontinued from the study early.

The percentage of aripiprazole-treated patients who completed study on double-blind treatment was twice than that of patients who received placebo. The percentage of patients who switched from double-blind treatment to open-label treatment at Week 2 was lower in the aripiprazole group than in the placebo group. The disposition of all patients randomized to treatment is presented by treatment group in Table 3.1.4.2.

Table 3.1.4.2 Disposition of Patients for Study CN138009

| | Number of Patients (%) | | | | | |
|---|---|---|---|---|---|---|
| **Patient Status** | **Placebo** | | **Aripiprazole** | | **Total** | |
| **Enrolled** | n/a | | n/a | | 358 | |
| Baseline failures | n/a | | n/a | | 96 | |
| **Randomized** | 132 | | 130 | | 262 | |
| **Discontinued from Double-Blind Treatment** | 104 | (79) | 76 | (58) | 180 | (69) |
| Entered open-label treatment phase due to lack of response[a] | 37 | (28) | 17 | (13) | 54 | (21) |
| Adverse event | 13 | (10) | 14 | (11) | 27 | (10) |
| Lack of Efficacy | 16 | (12) | 13 | (10) | 29 | (11) |
| Patient withdrew consent | 30 | (23) | 28 | (22) | 58 | (22) |
| Patient unreliability | 0 | | 3 | (2) | 3 | (1) |
| Lost to follow-up | 2 | (2) | 1 | (1) | 3 | (1) |
| Pregnancy | 0 | | 0 | | 0 | |
| Death | 0 | | 0 | | 0 | |
| Other known cause[b] | 6 | (5) | 0 | | 6 | (2) |
| **Completed Double-Blind Treatment** | 28 | (21) | 54 | (42) | 82 | (31) |

[a] Patients not responding at Week 2, as indicated by CGI-BP Change from Preceding Phase (mania)

score of 4 to 7, were offered open-label aripiprazole treatment.

[b] Other reasons for discontinuation may have included: pregnancy, other known cause (other), study terminated by sponsor, protocol violation, patient met withdrawal criteria, patient did not satisfy one or more screening criteria, or general inability to continue.

### 3.1.4.3 Demography and Patient Characteristics

Treatment groups were comparable with respect to age, gender, race and body weight. Demographic characteristics for the Randomized Sample are presented by treatment group in Table 3.1.4.3.

Table 3.1.4.3 Demographic Characteristics in Randomized Sample for Study CN138009

| | | Placebo | Aripiprazole | Total |
|---|---|---|---|---|
| **Variable** | | **N = 132** | **N = 130** | **N = 262** |
| Age | Mean | 40.5 | 40.5 | 40.5 |
| (years) | Median | 41.0 | 40.0 | 40.5 |
| | Range | 18.0 - 70.0 | 18.0 - 74.0 | 18.0 - 74.0 |
| | S. E. | 1.0 | 1.1 | 0.8 |
| Gender | Male | 55 (42) | 59 (45) | 114 (44) |
| N (%) | Female | 77 (58) | 71 (55) | 148 (56) |
| Race | White | 103 (78) | 95 (73) | 198 (76) |
| N (%) | Black | 20 (15) | 16 (12) | 36 (14) |
| | Asian/Pacific Islander | 1 (1) | 6 (5) | 7 (3) |
| | Hispanic/Latino | 5 (4) | 11 (8) | 16 (6) |
| | American/Alaskan Native | 1 (1) | 0 | 1 (0) |
| | Other | 2 (2) | 2 (2) | 4 (2) |
| Weight (kg) | Mean | 86.3 | 85.2 | 85.8 |
| | Median | 81.5 | 83.7 | 82.8 |
| | Min-Max | 46.8 - 184.5 | 47.7 - 147.1 | 46.8 - 184.5 |
| | S.E. | 2.1 | 1.8 | 1.4 |
| | Missing | 4 | 5 | 9 |

### 3.1.4.4 Sponsor's Efficacy Analysis Results

#### 3.1.4.4.1 Primary Efficacy Measure: Mean Change from Baseline in Y-MRS Total Score

The primary efficacy measure was the mean change from baseline to Week 3 in the Y-MRS Total Score. The analysis of the change in Y-MRS Total Score for the LOCF data set at Week 3 showed that the patients in the aripiprazole treatment group had statistically significantly greater improvement compared to patients in the placebo treatment group. Actually, for the LOCF analysis of the change scores the statistically significant results were shown from Day 4 through Week 3 for the comparisons

between the aripiprazole treatment group and the placebo group. The detailed LOCF and OC analysis results of mean change from baseline for Y-MRS Total Score are shown in Table 3.1.4.4 and Table 3.1.4.5, respectively.

Table 3.1.4.4 Mean Change from Baseline in Y-MRS by LOCF Data Set in Efficacy Sample for Study CN138009

| | LOCF Data Set | | |
|---|---|---|---|
| | Mean Change from Baseline in Y-MRS[a] | | Pairwise Comparisons P-values[b] |
| Phase/ Variable | Placebo N = 122[c] | Aripiprazole N = 123[c] | Aripiprazole versus Placebo |
| Mean Baseline | 29.68 | 28.16 | .019 |
| **Double-Blind Treatment Phase** | | | |
| Day 4 | -2.80 | -5.66 | 0.004 |
| Week 1 | -3.56 | -7.44 | 0.002 |
| Day 10 | -3.71 | -8.24 | 0.001 |
| Week 2 | -3.13 | -8.32 | < 0.001 |
| Week 3 | -3.35 | -8.15 | 0.002 |
| Week 3: 95% confidence interval for treatment differences (Aripiprazole - Placebo) | -4.80 (-7.80, -1.80) | | |

[a] Y-MRS Total Score is from 0 to 60. A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment, center, and baseline value. LS Means P-values for comparisons.
[C] At Day 4, N=118 for Placebo, N=118 for Aripiprazole; At Week 1, N=121 for Placebo.

Table 3.1.4.5 Mean Change from Baseline in Y-MRS Total Score by OC Data Set in Efficacy Sample for Study CN138009

| | OC Data Set | | | | |
|---|---|---|---|---|---|
| | Mean Change from Baseline in Y-MRS[a] | | | | Pairwise Comparisons P-values[b] |
| | Placebo | | Aripiprazole | | Aripiprazole vs Placebo |
| | N | Mean | N | Mean | |
| Mean Baseline | 122 | 29.11 | 123 | 27.93 | 0.129 |
| **Double-Blind Treatment Phase** | | | | | |
| Day 4 | 118 | -2.89 | 118 | -5.64 | 0.006 |
| Week 1 | 95 | -5.15 | 107 | -8.27 | 0.025 |
| Day 10 | 82 | -6.88 | 91 | -10.60 | 0.024 |
| Week 2 | 72 | -5.74 | 83 | -11.54 | 0.001 |
| Week 3 | 29 | -16.17 | 56 | -15.43 | 0.700 |
| Week 3: 95% confidence interval for treatment differences (Aripiprazole - Placebo) | | | | | 0.74 (-3.07, 4.56) |

[a] Y-MRS Total Score is from 0 to 60. A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment and baseline value. LS Means P-values for comparisons.

The analysis of the mean change from baseline for the OC data showed that the aripiprazole treatment group of patients had statistically significant greater improvement than the placebo group of patients from Day 4 through Week 2. As expected, at Week 3 sample sizes decreased substantially and the mean change from baseline Y-MRS Total Score showed improvement for both treatment groups when the option to move to open-label aripiprazole could be exercised. These changes were most notable in the placebo group of patients, which had a higher incidence of switches at Week 2. It was also noticed that at Week 3, the OC analysis results showed that the placebo group of patients had better improvement than the aripiprazole treatment group of patients.

3.1.4.4.2 Secondary Analyses

Mean Change from Baseline in the CGI-BP Severity of Illness (Mania) Score

The results of the analysis of the change from baseline in the CGI-BP Severity of Illness (mania) score for LOCF data set are shown in Table 3.1.4.6. The analysis shows significantly greater improvement for the aripiprazole treatment group compared to the placebo treatment group, from Day 4 through Week 3.

Table 3.1.4.6 Mean Change from Baseline in the CGI-BP Severity of Illness (Mania) Score by LOCF Data Set in Efficacy Sample for Study CN138009

| | **Mean Change from Baseline in CGI-BP Severity of Illness (Mania) Score[a]** | | **Pairwise Comparisons P-values[b]** |
|---|---|---|---|
| **Phase/Variable** | **Placebo N = 122[c]** | **Aripiprazole N = 124[c]** | **Aripiprazole vs Placebo** |
| Mean Baseline | 4.74 | 4.56 | 0.051 |
| **Double-Blind Treatment Phase** | | | |
| Day 4 | -0.22 | -0.53 | 0.005 |
| Week 1 | -0.30 | -0.71 | 0.002 |
| Day 10 | -0.31 | -0.85 | 0.001 |
| Week 2 | -0.32 | -1.02 | < 0.001 |
| Week 3 | -0.39 | -1.00 | 0.001 |
| Week 3: 95% confidence interval for treatment differences (Aripiprazole - Placebo) | | | -0.61 (-0.98, -0.24) |

[a] CGI-BP Severity of Illness (mania) score is from 1 (normal) to 7 (very severely ill). A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment, center, and baseline value. LS Means P-values for comparisons.
[c] At Day 4, N = 119 for placebo, N = 119 for aripiprazole.

The results of the analysis of the mean change from baseline for the OC data set are shown in Table 3.1.4.7. The aripiprazole treatment group showed significantly greater improvement compared with the placebo group at Day 4, Day 10, and Week 2. As expected, Week 3 sample sizes decreased substantially. The mean change from baseline CGI-BP Severity of Illness (mania) score improved for both treatment groups when the option to move to open-label aripiprazole could be exercised. These differences are more apparent in the placebo group, which had a higher incidence of switching to open-label at Week 2 and also notice that, like the primary endpoint, at Week 3, the OC analysis results showed that the placebo group of patients had better improvement than the aripiprazole treatment group of patients.

Table 3.1.4.7 Mean Change from Baseline in the CGI-BP Severity of Illness (Mania) Score by OC Data Set in Efficacy Sample for Study CN138009

| | OC Data Set | | | | |
|---|---|---|---|---|---|
| | Mean Change from Baseline in CGI-BP Severity of Illness (Mania) Score[a] | | | | Pairwise Comparisons P-values[b] |
| | Placebo | | Aripiprazole | | Aripiprazole vs Placebo |
| | N | Mean | N | Mean | |
| Mean Baseline | 122 | 4.68 | 124 | 4.52 | 0.099 |
| **Double-Blind Treatment Phase** | | | | | |
| Day 4 | 119 | -0.27 | 119 | -0.56 | 0.015 |
| Week 1 | 95 | -0.55 | 107 | -0.83 | 0.094 |
| Day 10 | 80 | -0.75 | 91 | -1.14 | 0.048 |
| Week 2 | 72 | -0.68 | 83 | -1.47 | < 0.001 |
| Week 3 | 29 | -2.18 | 56 | -1.92 | 0.378 |
| Week 3: 95% confidence interval for treatment differences (Aripiprazole - Placebo) | | | | | 0.26 (-0.26, 0.77) |

[a] CGI-BP Severity of Illness (mania) score is from 1 (normal) to 7 (very severely ill). A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment, and baseline value. LS Means P-values for comparisons.

Rate of Discontinuation

The rate of discontinuation due to lack of efficacy or entry into open-label aripiprazole dosing at Week 2 with a CGI-BP Change from Preceding Phase (mania) score of 4 to 7 was the additional secondary outcome measure. The results of the analysis of the rate of discontinuation due to above two reasons are displayed in Table 3.1.4.8. The analysis shows that the aripiprazole treatment group had a statistically significantly lower rate of discontinuation for these reasons than the placebo treatment group.

Table 3.1.4.8 Rate of Discontinuation Due to Lack of Efficacy or Entry into the Open-Label Aripiprazole Phase at Week 2 with a CGI-BP Change from Preceding Phase (Mania) Score of 4 to 7 by OC Data Set in Efficacy Sample for Study CN138009

| Number Discontinuing/Number Assessed(%)[a] | | Pairwise Comparisons P-values[b] |
|---|---|---|
| Placebo | Aripiprazole | Aripiprazole vs Placebo |
| 50/123 (41) | 28/124 (23) | 0.003 |
| 95% confidence interval for ratio vs placebo | | 0.55 (0.37, 0.87) |

[a] The number discontinuing is the number of patients who dropped due to lack of efficacy at any time or who completed Week 2 and then switched to open-label treatment.
[b] CMH General Association Test.

3.1.4.5 The Sponsor's Final Discussion for Efficacy Analysis Results

In this Phase III trial, aripiprazole separated from placebo at Week 3 on the prospectively defined primary endpoint and secondary efficacy endpoints. Specifically, on the primary efficacy criteria (Y-MRS Total Score) patients in the aripiprazole treatment group had statistically significantly greater improvement compared to patients in the placebo treatment group from Day 4 through Week 3. On the first of the key secondary efficacy criteria, the CGI-BP Severity of Illness (mania) score, analysis showed significantly greater improvement for the aripiprazole treatment group compared to the placebo treatment group, from Day 4 through Week 3. On the second of the key secondary efficacy criteria, the rate of discontinuation due to lack of efficacy or entry into open-label aripiprazole treatment, analysis showed that the aripiprazole treatment group had a statistically significantly lower rate of discontinuation than the placebo treatment group. (**Note**: Although the sponsor mentioned key secondary endpoints in this discussion, this does not agree with what was described in the protocol, where not any key secondary endpoint was prospectively specified.)

There were often notable differences between the LOCF and OC endpoint analyses. The LOCF data set analyses generally demonstrated the superiority of aripiprazole over placebo. However, when OC data sets were analyzed, efficacy endpoints were generally similar between placebo and aripiprazole. This finding is likely explained by the predefined protocol design, which allowed for discontinuation of blinded therapy at Week 2 (with an optional switch to open-label aripiprazole dosing). A large number of study patients took advantage of this option. At endpoint (Week 3), OC data set analyses primarily included only patients who were responding well to treatment. Therefore, the OC results are not valid after Week 2.

3.1.4.6 Statistical Reviewer's Findings and Comments

1. The statistical reviewer confirmed all of the sponsor's efficacy analysis results. Since the sponsor had significant results on the primary endpoint and also secondary

endpoints, the sponsor determined it to be a positive study. However, it was noticed that although at Week 3 the analysis of LOCF data showed significant differences between the aripiprazole and the placebo on the primary endpoint and one of two secondary endpoints (i.e. change from baseline in Y-MARS total and CGI-BP Severity of Illness on mania scores), the analysis of OC data showed that not only insignificant results, but results were favor to the placebo. It raised a concern about the bias of the LOCF analysis results at Week 3.

About the insignificant OC analysis results at Week 3, clearly one reason could be due to the high dropouts happened after Week 2 when patients, who showed no improvement or a worsening of symptoms, discontinued from the treatment phase and entered the open-label aripiprazole during Week 3. About the placebo patients performed better than the aripiprazole patients at Week 3, it was noticed that there are only 29 patients in the placebo group at Week 3 but 56 patients in aripiprazole treatment group. So, the OC analysis results at Week 3 were clearly seriously biased. On the other hand, since the differences between two treatment groups were significant at Week 2 on both LOCF and OC analysis results when there were comparable numbers of patients existing in both groups (72 in Placebo and 83 in Aripiprazole), the bias of LOCF analysis results at Week 3 may not be a concern. Therefore, the LOCF analysis results at Week 3 should be interpreted with caution.

2. Like Study CN138007, although the sponsor mentioned in their final discussion that two efficacy endpoints, the CGI-BP Severity of Illness (mania) score and the rate of discontinuation due to lack of efficacy or entry into open-label aripiprazole treatment are key secondary efficacy criteria, they were not designated in the original protocol or any amendments as key secondary endpoints (b) (4)

3.1.5 Description of Study CN138074

This study was titled as "A Multicenter, Randomized, Double-Blind Study of Aripiprazole versus Placebo in the Treatment of Acutely Manic Patients with Bipolar Disorder". There were twenty-nine study centers in the United States of American participated in this study.

3.1.5.1 Study Objectives

Same as what was described in Section 3.1.3.1 for Study CN138009.

3.1.5.2 Study Design

The whole study design was similar to what was designed for Study CN138009 (described in Section 3.1.3.2), but this study did not have the step to allow patients who were not responding at Week 2 (as indicated by a CGI-BP change from preceding phase (mania) score $\geq 4$) to discontinue from the blinded treatment phase into the open-label aripiprazole treatment group for Week 3.

3.1.5.3 Efficacy Variables

Except that four secondary efficacy outcome measures (response rate, CGI Secerity Score (mania), PANSS Hostility sub-scale and CGI-BP Change from Preceding phase (mania)) were amended as KEY secondary measures in the sponsor's protocol administrative letter, others were the same as what was described in Section 3.1.3.3 for Study CN138009.

3.1.5.4 Statistical Methods

The planned sample size for this study was 250 evaluable patients (125 per treatment group).

Primary Efficacy Analysis

Same as what was described in Section 3.1.1.4 for Study CN138007.

Key Secondary Analyses

Per the sponsor's Administrative Letter 1, a hierarchical testing procedure was used for the analysis of these variables in order to keep the overall experimentwise Type I error rate at 0.05. If the difference between placebo and aripiprazole in the primary analysis was statistically significant, then testing of the key secondary endpoints could proceed sequentially in the following order: (1) analysis of responders; (2) CGI-BP Severity of Illness Score (mania); (3) PANSS Hostility Subscale; and (4) CGI-BP Change from Preceding Phase Score (mania). Analysis was to stop with the first treatment comparison that failed to reach statistical significance.

All analyses of key secondary efficacy variables were performed using the LOCF and OC data sets. For ANCOVA models, analyses of the LOCF data set, controlling for baseline, study center and treatment were primary; analyses of the OC data set, controlling for baseline and treatment were considered corroborative.

3.1.6 Efficacy Analysis Results for Study CN138074

3.1.6.1 Data Sets

The distribution of randomized patients within each of the patient samples is presented by treatment group in Table 3.1.6.1. Three of the 272 randomized patients were excluded from the Safety Sample because they did not receive study medication according to the dosing record.

Table 3.1.6.1 Number of Patients in Samples for Study CN138074

| Sample[a] | Placebo | Aripiprazole | Total |
|---|---|---|---|
| Randomized | 135 | 137 | 272 |
| Safety | 133 | 136 | 269 |
| Efficacy | 132 | 136 | 268 |

[a] Patient 138074-22-269 was randomized to aripiprazole, but received placebo; this patient is tabulated in the placebo group in the Efficacy and Randomized Samples, and is tabulated in the aripiprazole group in the Safety Sample. Patient 138074-22-271 was randomized to placebo, but received aripiprazole; this patient was tabulated in the aripiprazole group in the Efficacy and Randomized Samples, and is tabulated in the placebo group in the Safety Sample.

3.1.6.2 Disposition of Patients

The disposition of all patients randomized to treatment is presented in Table 3.1.6.2.

Table 3.1.6.2 Disposition of Patients for Study CN138074

| | Number of Patients (%)[a] | | |
|---|---|---|---|
| **Patient Status** | **Placebo** | **Aripiprazole** | **Total** |
| **Enrolled** | n/a | n/a | 353 |
| Baseline failures | n/a | n/a | 81 |
| **Randomized** | 135 | 137 | 272 |
| **Discontinued Double-Blind Treatment** | | | |
| Adverse Experience | 10(7) | 12(9) | 22(8) |
| Lack of Efficacy | 28(21) | 12(9) | 40(15) |
| Subject Withdrew Consent | 25(19) | 35(25) | 59(22) |
| Subject Unreliable | 1(1) | 2(1) | 3(1) |
| Lost to Follow-Up | 0 | 1(1) | 1(< 1) |
| Other Known Cause[b] | 1(1) | 1(1) | 2(1) |
| **Completed Double-Blind Treatment** | 71(52) | 75(55) | 145(53) |

[a] Percentages based on number of randomized patients.
[b] Other reasons for discontinuation included: placebo patient discharged due to incarceration; aripiprazole patient discharged due to patient recovery.

As we can observe from the table, a total of 353 patients were enrolled in this study. Of these, 272 patients were randomized to double-blind treatment. Of the 272 randomized

patients, 145 (53%) completed 3 weeks of treatment and 127 (47%) discontinued early. While the percentage of patients completing treatment was similar across the two treatment groups (52% for placebo and 55% for aripiprazole), the incidence of discontinuation due to lack of efficacy was twice as high in the placebo group (21%) as in the aripiprazole group (9%).

3.1.6.3 Demography and Patient Characteristics

Table 3.1.6.3 shows the Demographic characteristics for the Randomized Sample. As we can observe from the table, the treatment groups were comparable with respect to age, gender and weight; however, there was a slightly greater number of white patients randomized to the aripiprazole group and a greater number of hispanic/latino patients randomized to the placebo group.

Table 3.1.6.3 Demographic Characteristics in Randomized Sample for Study CN138074

| | | Placebo | Aripiprazole | Total |
|---|---|---|---|---|
| **Variable** | | **N = 135** | **N = 137** | **N = 272** |
| Age (years) | Mean | 40.4 | 37.3 | 38.8 |
| | Median | 42 | 38 | 40 |
| | Range | 18.0 - 64.0 | 18.0 - 72.0 | 18.0 - 72.0 |
| | S.E. | 0.9 | 0.9 | 0.7 |
| Gender N (%) | Male | 63 (47) | 69 (50) | 132 (49) |
| | Female | 72 (53) | 68 (50) | 140 (51) |
| Race N (%) | White | 92 (68) | 104 (76) | 196 (72) |
| | Black | 30 (22) | 26 (19) | 56 (21) |
| | Asian/Pacific Islander | 1 (1) | 1 (1) | 2 (1) |
| | Hispanic/Latino | 11 (8) | 3 (2) | 14 (5) |
| | American/Alaskan Native | 0 | 1 (1) | 1 (0) |
| | Other | 1 (1) | 2 (1) | 3 (1) |
| Weight (kg) | Mean | 85 | 87.5 | 86.3 |
| | Median | 84 | 83.3 | 83.3 |
| | Min-Max | 45.5 - 145.4 | 47.3 - 168.8 | 45.5 - 168.8 |
| | S.E. | 1.8 | 2 | 1.3 |
| | Missing | 3 | 3 | 6 |

3.1.6.4 Sponsor's Efficacy Analysis Results

3.1.6.4.1 Primary Efficacy Analysis: Mean Change from Baseline in Y-MRS Total Score

Tables 3.1.6.4 and 3.1.6.5 show the sponsor's LOCF and OC analysis results for the mean change from baseline in Y-MRS Total Score.

Table 3.1.6.4 Mean Change from Baseline in Y-MRS Total Score in Efficacy Sample by the LOCF Data Set for Study CN138074

| | Mean Change from Baseline in Y-MRS[a] | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|
| Day/Week | Placebo[c] N = 132 | Aripiprazole[d] N = 136 | Aripiprazole vs Placebo |
| Mean Baseline | 28.45 | 28.80 | 0.557 |
| **Double-Blind Treatment** | | | |
| Day 2 | -3.89 | -5.01 | 0.123 |
| Day 4 | -5.37 | -8.17 | 0.002 |
| Week 1 | -6.59 | -9.73 | 0.004 |
| Day 10 | -7.62 | -11.55 | 0.001 |
| Week 2 | -7.80 | -12.37 | < 0.001 |
| Week 3 | -7.19 | -12.52 | < 0.001 |
| Week 3: 95% CI for treatment difference (Aripiprazole - Placebo): -5.33 (-7.90, -2.76) | | | |

[a] Y-MRS Total Score is from 0 to 60. A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment, study center, and baseline value. LS-Means P-values for comparisons. [c] Day 2 N = 124. [d] Day 2 N = 131, Day 4 N = 135.

Table 3.1.6.5 Mean Change from Baseline in Y-MRS Total Score in Efficacy Sample by the OC Data Set for Study CN138074

| | Mean Change from Baseline in Y-MRS[a] | | | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|---|---|
| | Placebo | | Aripiprazole | | |
| Day/Week | N | Mean | N | Mean | Aripiprazole vs Placebo |
| Mean Baseline | 132 | 28.60 | 136 | 28.96 | 0.576 |
| **Double-Blind Treatment** | | | | | |
| Day 2 | 124 | -4.11 | 131 | -5.43 | 0.080 |
| Day 4 | 127 | -5.85 | 131 | -8.85 | 0.002 |
| Week 1 | 114 | -7.78 | 122 | -10.40 | 0.023 |
| Day 10 | 97 | -10.66 | 100 | -14.30 | 0.003 |
| Week 2 | 87 | -11.65 | 88 | -15.90 | 0.002 |
| Week 3 | 72 | -12.80 | 81 | -17.22 | 0.004 |
| Week 3: 95% CI for treatment difference (Aripiprazole - Placebo): | | | | | -4.42 (-7.41, -1.43) |

[a] Y-MRS Total Score is from 0 to 60. A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment and baseline value. LS Means P-values for comparisons.

As we can observe from the first table, the LOCF results revealed significantly greater improvement in bipolar symptoms in the aripiprazole group than the placebo group beginning on Day 4 and continuing through Endpoint Week 3. These results were supported by analysis of the OC data set. which also revealed significantly greater improvement in the aripiprazole group than the placebo group from Day 4 through Week 3.

3.1.6.4.2 Key Secondary Efficacy Analyses

Response Rate

The analysis of response rates for the Y-MRS Total Score by the LOCF data set and OC data set are shown in Table 3.1.6.6 and 3.1.6.7.

Table 3.1.6.6 Response Rate for the Y-MRS Total Score in Efficacy Sample for the LOCF Data Set for Study CN138074

| | Number Responding [a]/Number Assessed (%) | | | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|---|---|
| Day/Week | Placebo | | Aripiprazole | | Aripiprazole vs Placebo |
| Day 2 | 7/124 | (6) | 12/131 | (9) | 0.425 |
| Day 4 | 19/132 | (14) | 29/135 | (21) | 0.184 |
| Week 1 | 35/132 | (27) | 53/136 | (39) | 0.036 |
| Day 10 | 41/132 | (31) | 65/136 | (48) | 0.006 |
| Week 2 | 41/132 | (31) | 69/136 | (51) | 0.001 |
| Week 3 | 42/132 | (32) | 72/136 | (53) | 0.001 |
| Week 3: 95% CI for response ratio (Aripiprazole vs Placebo)[c]: | | | | | 1.66 (1.24, 2.22) |

[a] A responder is a patient with a decrease of ≥ 50% from baseline on the Y-MRS Total Score.
[b] CMH General Association Test, controlling for study center.
[c] Values greater than 1 favor aripiprazole.

Table 3.1.6.7 Response Rate on the Y-MRS Total Score in Efficacy Sample for the OC Data Set for Study CN138074

| | Number Responding[a]/Number Assessed (%) | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|
| Day/Week | Placebo | Aripiprazole | Aripiprazole vs Placebo |
| Day 2 | 7/124 (6) | 12/131 (9) | 0.286 |
| Day 4 | 18/127 (14) | 29/131 (22) | 0.098 |
| Week 1 | 34/114 (30) | 49/122 (40) | 0.097 |
| Day 10 | 40/97 (41) | 59/100 (59) | 0.013 |
| Week 2 | 38/87 (44) | 57/88 (65) | 0.005 |
| Week 3 | 37/72 (51) | 57/81 (70) | 0.016 |
| Week 3: 95% CI for response ratio (Aripiprazole vs Placebo)[c]: | | | 1.37 (1.06, 1.77) |

[a] A responder is a patient with a decrease of ≥ 50% from baseline on the Y-MRS Total Score.
[b] CMH General Association Test.
[c] Values greater than 1 favor aripiprazole.

As presented in Table 3.1.6.6, statistical analysis of the LOCF data set revealed that significantly more patients responded to aripiprazole than placebo from Week 1 through Week 3. These results were generally supported by analysis of the OC data set shown in Table 3.1.6.7, which revealed that significantly more patients responded to aripiprzole from Day 10 through Week 3.

Mean Change from Baseline in the CGI-BP Severity of Illness Score (mania)

Tables 3.1.6.8 and 3.1.6.9 show the analysis results of the LOCF data and OC data for this endpoint, respectively. Both LOCF and OC analysis results revealed greater numerical improvement in the aripiprazole treatment group than the placebo group at all time points. The LOCF analysis results showed statistically significant differences between the two groups (in favor of aripiprazole) at Weeks 1, 2 and 3 but the OC analysis results only showed statistically significant difference between the two groups at Week 2 and Week 3.

Table 3.1.6.8 Mean Change from Baseline in the CGI-BP Severity of Illness Score (mania) in Efficacy Sample by the LOCF Data set for Study CN138074

| | Mean Change from Baseline in CGI-BP Severity of Illness Score (mania) [a] | | Pair-wise Comparisons P-values [b] |
|---|---|---|---|
| Day/Week | Placebo [c] N = 129 | Aripiprazole [d] N = 135 | Aripiprazole vs Placebo |
| Mean Baseline | 4.71 | 4.69 | 0.850 |
| **Double-Blind Treatment** | | | |
| Day 4 | -0.52 | -0.62 | 0.319 |
| Week 1 | -0.73 | -1.01 | 0.025 |
| Day 10 | -1.00 | -1.26 | 0.075 |
| Week 2 | -1.10 | -1.51 | 0.015 |
| Week 3 | -1.12 | -1.59 | 0.009 |
| Week 3: 95% CI for treatment difference (Aripiprazole - Placebo): | | | -0.47 (-0.82, -0.12) |

[a] CGI-BP Severity of Illness Score (mania) is from 1 (normal) to 7 (very severely ill). A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment, study center, and baseline value. LS-Means P-values for comparisons.
[c] Day 4 N = 125, Week 1 N = 128
[d] Day 4 N = 131

Table 3.1.6.9 Mean Change from Baseline in the CGI-BP Severity of Illness Score (mania) in Efficacy Sample by the OC Data Set for Study CN138074

| | Mean Change from Baseline in CGI-BP Severity of Illness Score (mania)[a] | | | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|---|---|
| | Placebo | | Aripiprazole | | |
| Day/Week | N | Mean | N | Mean | Aripiprazole vs Placebo |
| Mean Baseline | 129 | 4.75 | 135 | 4.73 | 0.832 |
| **Double-Blind Treatment** | | | | | |
| Day 4 | 125 | -0.54 | 131 | -0.64 | 0.3 |
| Week 1 | 114 | -0.85 | 121 | -1.1 | 0.067 |
| Day 10 | 97 | -1.34 | 100 | -1.56 | 0.167 |
| Week 2 | 88 | -1.52 | 88 | -1.94 | 0.025 |
| Week 3 | 72 | -1.88 | 81 | -2.3 | 0.041 |
| Week 3: 95% CI for treatment difference (Aripiprazole - Placebo): | | | | | -0.42 (-0.82, -0.02) |

[a] CGI-BP Severity of Illness Score (mania) is from 1 (normal) to 7 (very severely ill). A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment and baseline value. LS-Means P-values for comparisons.

Mean Change from Baseline in the PANSS Hostility Subscale Score

The LOCF analysis results for this endpoint are shown in Table 3.1.6.10. As presented in the table, the results revealed significantly greater improvement in the aripiprazole treatment group than the placebo group at Week 3. This result was also supported by statistical analysis of the OC data set shown in Table 3.1.6.11.

Table 3.1.6.10 Mean Change from Baseline in the PANSS Hostility Subscale Score in Efficacy Sample by the LOCF Data Set for Study CN138074

| | Mean Change from Baseline in PANSS Hostility Subscale Score[a] | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|
| Week | Placebo N = 122 | Aripiprazole N = 124 | Aripiprazole vs Placebo |
| Baseline | 10.74 | 10.60 | 0.709 |
| **Double-Blind Treatment** | | | |
| Week 3 | -0.82 | -2.21 | 0.002 |
| Week 3: 95% CI for treatment difference (Aripiprazole - Placebo): | | | -1.39 (-2.27, -0.51) |

[a] PANSS Hostility Subscale Score is from 4 to 28. A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment, study center, and baseline value. LS Means P-values for comparisons.

Table 3.1.6.11 Mean Change from Baseline in the PANSS Hostility Subscale Score in Efficacy Sample by the OC Data Set for Study CN138074

| | Mean Change from Baseline in PANSS Hostility Subscale Score[a] | | | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|---|---|
| | Placebo | | Aripiprazole | | |
| Week | N | Mean | N | Mean | Aripiprazole vs Placebo |
| Mean Baseline | 122 | 10.61 | 124 | 10.40 | 0.632 |
| **Double-Blind Treatment** | | | | | |
| Week 3 | 72 | -2.76 | 81 | -3.76 | 0.028 |
| Week 3: 95% CI for treatment difference (Aripiprazole - Placebo): | | | | | -1.00 (-1.89, -0.11) |

[a] PANSS Hostility Subscale Score is from 4 to 28. A negative change score signifies improvement.
[b] ANCOVA, controlling for treatment and baseline value. LS Means P-values for comparisons.

Mean CGI-BP Change from Preceding Phase Score (Mania)

The results of the analysis of the mean CGI-BP Change from Preceding Phase Score (mania) for the LOCF and OC data sets are shown in Table 3.1.6.12 and 3.1.6.13, respectively. Both LOCF and OC analysis results for this endpoint revealed greater numerical improvement in the aripiprazole treatment group than the placebo group at all time points. The LOCF analysis results showed statistically significant differences between the two groups (in favor of aripiprazole) from Week 1 through Week 3 but the OC analysis results only showed statistically significant differences between the two groups at Week 1 and Week 3.

Table 3.1.6.12 Mean CGI-BP Change from Preceding Phase Score (mania) in Efficacy Sample by the LOCF Data Set for Study CN138074

| | Mean CGI-BP Change from Preceding Phase Score (mania)[a] | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|
| Day/Week | Placebo[c] N = 129 | Aripiprazole[d] N = 135 | Aripiprazole vs Placebo |
| Day 4 | 3.34 | 3.27 | 0.626 |
| Week 1 | 3.34 | 2.95 | 0.006 |
| Day 10 | 3.14 | 2.81 | 0.037 |
| Week 2 | 3.17 | 2.71 | 0.006 |
| Week 3 | 3.22 | 2.63 | 0.001 |

[a] CGI-BP Change from Preceding Phase (mania): 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse; unadjusted means are displayed.
[b] CMH Row Means Test, controlling for study center.

Table 3.1.6.13 Mean CGI-BP Change from Preceding Phase Score (mania) in Efficacy Sample by the OC Data Set for Study CN138074

| | Mean CGI-BP Change from Preceding Phase Score (mania)[a] | | | | Pair-wise Comparisons P-values[b] |
|---|---|---|---|---|---|
| | Placebo | | Aripiprazole | | |
| Day/Week | N | Mean | N | Mean | Aripiprazole vs Placebo |
| Day 4 | 125 | 3.34 | 131 | 3.27 | 0.567 |
| Week 1 | 114 | 3.28 | 121 | 2.91 | 0.019 |
| Day 10 | 97 | 2.77 | 100 | 2.50 | 0.110 |
| Week 2 | 88 | 2.66 | 88 | 2.33 | 0.072 |
| Week 3 | 72 | 2.51 | 81 | 2.12 | 0.050 |

[a] CGI-BP Change from Preceding Phase (mania): 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse; unadjusted means are displayed.
[b] CMH Row Means Test.

3.1.6.5 The Sponsor's Final Discussion of Efficacy Analysis Results

Aripiprazole was robustly and consistently effective in the treatment of patients with acute mania. On the primary efficacy measure, the Y-MRS, aripiprazole-treated patients exhibited statistically significant greater improvement in bipolar symptoms than placebo-treated patients as early as Study Day 4 and throughout the duration of the 3 Weeks of double-blind treatment (P-values from Day 4 through Week 3 were $\leq$ 0.004).

In order to keep the overall experimentwise Type I Error at 0.05, a hierarchical testing procedure was used for the analysis of key secondary efficacy variables. The aripiprazole group was statistically superior to placebo at endpoint on every one of the key secondary efficacy measures including: response rate (53% responders in the aripiprazole group compared with 32% in the placebo group); the CGI-BP Severity of Illness Score (mania); the PANSS Hostility Subscale Score, and the CGI-BP Change from Preceding Phase (mania).

Aripiprazole-treated patients were also statistically superior to placebo on five of the eight additional efficacy measures at endpoint including: rate of discontinuation due to lack of efficacy (only 9% of aripiprazole patients discontinued due to lack of efficacy vs. 21% of placebo patients); the CGI-BP Severity of Illness Score (for depression and overall bipolar illness); the CGI-BP Change from Preceding Phase (for overall bipolar illness only); and the PANSS Total Score.

3.1.6.6 Statistical Reviewer's Findings and Comments

1. The statistical reviewer confirmed all of the sponsor's efficacy analysis results. This study is positive with significant analysis results shown for the primary endpoint and all four key secondary endpoints. Without any concern, this reviewer agrees with the sponsor that this study demonstrated the aripiprazole's efficacy in the treatment of patients with bipolar disorder.

## 3.2 EVALUATION OF SAFETY

The safety evaluation was not performed in this review.

# 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor presented in the Integrated Summary of Efficacy and Safety (ISE-ISS) of the submission the subgroup analysis for gender, age, race, psychiatric characteristics (type of episode and rapid cycling) and baseline psychiatric status by analyzing the combined data of Studies CN138-007, CN138-009 and CN138-074. The results were confirmed by this reviewer.

The efficacy of aripiprazole was found to be similar across all these subsets. For nearly every subset results were statistically significant in favor of aripiprazole. Exceptions were > 50 age group, blacks and race "other" groups. Even though these subsets had small sample sizes, numerical differences favoring aripiprazole were observed.

## 4.1 GENDER, RACE AND AGE

The sponsor's LOCF subgroup analysis results on the Y-MRS Total Score mean change from baseline to Week 3 for gender, race and age are shown in Table 4.1.1.

Table 4.1.1 Subgroup Analysis Results for Gender, Race and Age by Combined data from Studies CN138-007, CN138-009 and CN138-074

| Subgroup | Value | N | Placebo | N | Aripiprazole | Aripiprazole vs. Placebo P-value |
|---|---|---|---|---|---|---|
| Gender | Men | 178 | -6.9 | 244 | -9.6 | 0.019 |
| | Women | 206 | -6.9 | 271 | -10.5 | <0.001 |
| Age Group | ≤50 | 313 | -7.1 | 424 | -10.3 | <0.001 |
| | >50 | 71 | -5.9 | 91 | -9.1 | 0.092 |
| Race | White | 279 | -6.7 | 386 | -10.3 | <0.001 |
| | Black | 66 | -5.5 | 75 | -7.8 | 0.244 |
| | other[a] | 39 | -8.8 | 54 | -11.0 | 0.407 |

Note: Analyses were model-based, controlling for treatment, study, and baseline score-based means.
[a] "other" includes Hispanic, Asian, and other race groups.

## 4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Table 4.1.2 shows the sponsor's subgroup analysis results by LOCF on the Y-MRS Total Score mean change from baseline to Week 3 for type of episode, rapid cycling and baseline psychiatric status evaluated by the Y-MRS Total Score, CGI-BP Severity of Illness mania and depression Scores, and MADRS Total Score.

Table 4.1.2 Subgroup Analysis Results for Psychiatric Characteristics and Baseline Psychiatric Status by Combined data from Studies CN138007, CN138 009 and CN138074

| Subgroup | Value | N | Placebo | N | Aripiprazole | Aripiprazole vs. Placebo P-value |
|---|---|---|---|---|---|---|
| Type of Episode | Manic | 240 | -6.5 | 321 | -10.4 | <0.001 |
| | Mixed | 144 | -7.4 | 194 | -9.7 | 0.044 |
| Rapid Cycling | No | 305 | -7.3 | 415 | -9.9 | 0.002 |
| | Yes | 79 | -5.5 | 100 | -10.6 | 0.001 |
| Baseline Y-MRS Total Score (median=27) | ≤median | 197 | -6.9 | 272 | -8.8 | 0.043 |
| | >median | 187 | -6.8 | 243 | -11.6 | <0.001 |
| Baseline CGI-BP Severity of Illness (Mania) Score | At most moderately ill | 158 | -6.3 | 219 | -9.2 | 0.009 |
| | At least markedly ill | 226 | -7.2 | 296 | -10.7 | 0.001 |
| Baseline CGI-BP Severity of Illness (Depression) Score | At most mildly ill | 270 | -7.0 | 383 | -10.2 | 0.001 |
| | At least moderately ill | 114 | -6.5 | 132 | -9.7 | 0.019 |
| Baseline MADRS Total Score (median=14) | ≤median | 207 | -6.6 | 283 | -10.2 | 0.001 |
| | >median | 177 | -7.1 | 232 | -9.9 | 0.008 |

Note: Analyses were model-based, controlling for treatment, study, and baseline score-based means.

# 5. SUMMARY AND CONCLUSIONS

## 5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

For all three pivotal studies, the statistical reviewer confirmed the entire sponsor's efficacy analysis results. Except of 2 patients in Study CN138007 and 2 patients in Study CN138074 that the sponsor analyzed them by the treatment they received instead of the treatments they were randomized, no major inconsistency was found between the sponsor's and this reviewer's analyses results. After reviewing three pivotal studies, this reviewer determined that Study CN138007 was a failed study. Study CN138009 had significant results shown on the primary endpoint by the primary analysis (LOCF), however the interpretability of the study's significant findings should be carefully considered due to large number and unbalanced dropouts at the end of visits, which then resulted OC analysis results favored the placebo. Study CN138074 clearly demonstrated the aripiprazole's efficacy for the treatment of acute manic or mixed episodes in patients with a diagnosis of Bipolar I Disorder.

For both studies CN138009 and CN138074, in addition to the primary endpoint, the significant results were also shown on the secondary endpoints. (b) (4) [redacted]

This reviewer noticed that first of all, for Study CN138009, although the sponsor stated in the study reports' final discussion that two secondary endpoints (i.e., the mean change from baseline to Week 3 in the CGI-BP Severity of Illness on mania score and the percentage of patients with discontinuation due to lack of efficacy or entry into the open-label aripiprazole phase at Week 2) were two key secondary criteria, these were not prospectively planned in the original study protocol or any amendments. Secondly, although the sponsor had significant results shown on all four secondary endpoints (analysis of responders, CGI-BP Severity of Illness Score on mania, PANSS Hostility Subscale and CGI-BP change from Preceding Phase Score on mania) for both Studies CN138009 and CN138074, due to not prospectively specified key secondary endpoints for Study 138009, (b) (4) [redacted]

## 5.2 CONCLUSIONS AND RECOMMENDATIONS

After reviewing three pivotal studies, CN138007, CN138009 and CN138074, this reviewer determined that Study CN138007 was a failed study. Study CN138009 had significant results shown on the primary endpoint by the primary analysis (LOCF). The interpretation of significant findings, however, should be carefully considered due to large number and unbalanced dropouts at the end of visits, which then resulted OC analysis results numerically favored placebo. Study CN138074 clearly demonstrated the aripiprazole's efficacy for the treatment of acute manic or mixed episodes in patients with a diagnosis of Bipolar I Disorder.

(b) (4) [redacted]

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

Concurrence:

Dr. Jin

Dr. Mahjoob

cc: NDA 21-436/SE1-002
HFD-120/Dr. Katz
HFD-120/Dr. Andreason
HFD-120/Dr. Podruchny
HFD-120/Dr. Bates
HFD-700/Dr. Anello
HFD-710/Dr. Mahjoob
HFD-710/Dr. Jin
This review consists of 36 pages. MS Word: C:/yfchen/NDA21436/Bipolar/review.doc

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/s/
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Yeh-Fong Chen
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Kun Jin
3/24/04 04:28:39 PM
BIOMETRICS

Kooros Mahjoob
3/24/04 05:05:37 PM
BIOMETRICS

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-436/S-002

# OTHER REVIEW(S)

**DEPARTMENT OF HEALTH & HUMAN SERVICES** **Public Health Service**

**Division of Scientific Investigations**
**Office of Medical Policy**
**Center for Drug Evaluation and Research**
**Food and Drug Administration**
**Rockville MD 20857**

# CLINICAL INSPECTION SUMMARY

DATE: March 22, 2004

TO: Doris Bates, Ph.D, Regulatory Project Manager
Teresa A. Podruchny, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-436/SE1-002

APPLICANT: Bristol-Myers Squibb/Otsuka Pharmaceuticals

DRUG: Abilify (aripiprazole)

THERAPEUTIC CLASSIFICATION: Type S

PROPOSED INDICATION: Bipolar Disorder, Acute Mania

CONSULTATION REQUEST DATE: August 14, 2003

ACTION GOAL DATE: April 25, 2004

## I. BACKGROUND:

Abilify (aripiprazole) is an atypical antipsychotic agent. It is approved for use in treatment of schizophrenia. In this application, the sponsor has requested the use of aripiprazole in treatment of acute mania in Bipolar I Disorder. The application included the results of protocols CN138-009 entitled "a multicenter, randomized, double-blind, placebo-controlled study of flexible doses of aripiprazole in the treatment of hospitalized patients with acute mania" and protocols CN138-074 entitled "a multicenter, randomized, double-blind study of aripiprazole versus placebo in the treatment of acutely manic patients with Bipolar Disorder."

Protocol CN138-009

This study was a multi-center, randomized, double-blind, placebo-controlled study. Subjects would undergo screening evaluations to determine eligibility prior to study enrollment. During the screening phase, patients would undergo psychiatric evaluation including the DSM-IV diagnosis of Bipolar I Disorder displaying an acute manic or mixed episode requiring hospitalization. After 1-7 days screening phase (may be up to 14 days), each subject was randomly assigned to receive placebo or aripiprazole. Subjects who were assigned to aripiprazole received a starting dose of 30 mg and allowed to be decreased to 15 mg if 30 mg was intolerable. Original protocol stated that subjects would remain hospitalized for the duration of the three weeks of the treatment phase. Amended protocol changed to the fact that subjects remained hospitalized for a minimum of two weeks of the treatment period. Subjects must meet the following criteria after the end of week 2 in order to be discharged: 1) CGI-BP Severity (mania) score of 3 or less (mildly ill, minimally ill or not ill; and 2) CGI-BP change from preceding phase (mania) score of 2 or less (much improved, very much improved). The primary efficacy measure was mean change from randomization to week 3 in the Young Mania Rating Scale (Y-MRS) scores. Reduction of $\geq$50% in Y-MRS was used as evidence of therapeutic response in an individual patient.

Protocol CN138-074

This study was a multi-center, randomized, double-blind, parallel, placebo-controlled study. Subjects would undergo screening evaluations to determine eligibility prior to study enrollment. During the screening phase, patients would undergo psychiatric evaluation including the DSM-IV diagnosis of Bipolar I Disorder displaying an acute manic or mixed episode requiring hospitalization. After 1-7 days screening phase (up to 14 days), each subject was randomly assigned to one of the two groups to receive placebo or aripiprazole. Subjects who were assigned to aripiprazole received a starting dose of 30 mg and allowed to be decreased to 15 mg if 30 mg was intolerable. Subjects would remain hospitalized for a minimum of the first two weeks of the treatment phase. The primary efficacy measure was mean change from randomization to week 3 in the Y-MRS scores.

As per the request of the Review Division (HFD-120), inspection assignments were issued in October 2003 for three domestic sites: Drs. Cutler, Rubenfaer and Coskinas/DeSilva. These clinical investigators were chosen for the sample size and/or their involvement with multiple studies.

II. RESULTS (by site):

| NAME | Protocol | Location | ASSIGNED DATE | DATE EIR RECEIVED | CLASSIFICATION |
|---|---|---|---|---|---|
| Andrew Cultler, M.D. | CN138-009<br>CN138-074 | Winter Park, FL | 10/7/2003 | 12/3/2003 | VAI |
| E. Coskinas, MD, PhD<br>H. DeSilva, M.D. | CN138-009<br>CN138-074 | Orange and Santa Ana, CA | 10/7/2003 | 1/28/2004 | VAI |
| Leon Rubenfaer, MD | CN138-074 | New Baltimore, MI | 10/7/2003 | 3/2/2004 | VAI-RR |

**1. Andrew Cutler, M.D. (Protocol CN 138-009: site 009; Protocol CN 138-074: site 018)**

a. What was inspected:

For protocol CN138-009, 20 subjects were enrolled and study records were reviewed for 8 of 10 completed subjects. For protocol CN 138-074, 29 subjects were enrolled and an audit of 15 subjects' records was conducted during the inspection.

b. Limitations of inspection: N/A

c. General observations/commentary:


d. Recommendation: Overall, data appear acceptable.

**2. Leon Rubenfaer, M.D. (Protocol CN 138-074: site 003)**

a. What was inspected:

Dr. Rubenfaer is the Medical Director and Clinical Investigator of Pioneer Pharmaceutical Research, a research arm of Pioneer Behavioral Health. For protocol CN138-074, 25 subjects were enrolled for protocol CN138-074 and 7 subjects completed the study. Reasons for discontinuation included withdrawal of consent (6 subjects), lack of efficacy (8 subjects) and other reasons (4 subjects). An audit of all subjects' records was conducted.

b. Limitations of inspection: N/A

c. General observations/commentary:

The original Structured Clinical Interview for DSM-IV Axis I Disorders score sheets used to confirm Bipolar Disorder were not available for 8 subjects: subjects 060, 091, 186, 230, 245, 270, 288 and 327.

The protocol required that serum levels of lithium and valproic acid be performed during the screening period. The protocol also specified that lithium must be <0.6 mmol/L and divalproex must be <50 ug/ml, prior to randomization. The site did not perform lithium levels for subject 35 and 122.

The protocol specified that a drug screen to be performed at screening and all subjects with a positive result must be discussed with the sponsor to discuss prior to randomization. The following subjects were noted to have positive drug screen results, yet the site enrolled these subjects in the study without obtaining approval from the sponsor.

Subject 023 and 179: Opiates
Subject 060: Amphetamines
Subject 184: Amphetamines and Cannabis
Subject 270: Opiates and Cannabis
Subject 288: Barbiturates
Subject 021, 124 and 240: Cannabis

The protocol required that a drug or alcohol screen be performed upon returning to the hospital from a day pass. The investigator did not perform a drug/alcohol test for subject 288 and an alcohol screen for subject 186. Subject 186 was positive for amphetamine on the drug screen for day passes on (b) (6) and continued enrollment of the subject in the study.

The pregnancy test for subject 327 at day 3 visit was not obtained as required by the protocol.

d. Recommendation: The inspection revealed multiple protocol violations at this site. DSI suggests the Review Division should consider excluding data from the above subjects who did not fulfill all eligibility criteria for enrollment in the study and reanalyze the data to see if there is any impact on study outcome.

**3. Evagelos Coskinas, M.D, Ph.D./Himasiri DeSilva, M.D. (Protocol CN 138-009: site 023; Protocol CN 138-074: site 028)**

a. What was inspected:

For protocol CN138-009, 18 subjects were screened, 17 were randomized. 11 subjects discontinued and 6 completed the study. An audit of 6 subjects' records was conducted.

10 subjects were screened, 9 were randomized as specified in protocol CN138-074. Two subjects discontinued and 7 subjects completed the study. An audit of 4 subjects' records was conducted.

b. Limitations of inspection:

(b) (4) He has left Affiliated Research Institute (currently Clinical Innovation, Inc.), a site management organization, upon the completion of last study subject's treatment for protocol CN138-009 in September 2001. Dr. DeSilva, subinvestigator of the study, then assumed the role as the

clinical investigator.

c. General observations/commentary:

Protocol CN 138-009

The inspectional observations included:

1) Serum lithium levels were not done for five subjects (# 29, 40, 49, 56, 65) and divalproex level for subject 114.
2) Subject 29 was documented as a high risk for suicide, yet the subject was enrolled in the study.
3) No physical examinations were performed on three subjects (#29, 56, 114).
4) The site did not obtain a pregnancy test for subject 56.
5) The protocol-required end of study evaluations for subject 40 and 49 were not done.
6) There was a delay in reporting the SAE of prolonged hospital stay for subject 114.
7) The site failed to report the following adverse events (AE) experienced by subjects during the study:
   Subject 40: headache and diarrhea
   Subject 49: headache
   Subject 56: headache
   Subject 65: headache

Protocol CN 138-009 and Protocol CN 138-074

Both protocols suggested that records be kept for the amount of drug currently in storage area, dates and initials of each person responsible for each drug product inventoried or moved, and the amount being transferred to another area for dispensing or storage. The FDA investigator noted that drug accountability records were not maintained for holding, transport and dispensing of drug while at the clinical investigator's office. It appears that the subjects received the study medication as prescribed and complied with the study drug. In such case, this record keeping deficiency may not have any clinical significance, and data from those subjects' records could be used to support an approval decision for the NDA.

d. Recommendation: The inspection revealed protocol violations and a few instances of non-reporting of adverse events at this site. DSI suggests the Review Division should consider excluding data from the above subjects who did not fulfill all eligibility criteria for enrollment in the study to see if there is any impact on study outcome. The Review Division should include the non-reported AEs of four subjects in safety database.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, multiple instances of protocol violations noted in two out of three study sites inspected. The protocol required that serum levels of lithium and valproic acid be performed during the screening period. The protocol also specified that lithium must be <0.6 mmol/L and divalproex must be <50 ug/ml, prior to randomization. Drs. Coskinas/DeSilva and Dr. Rubenfaer did not obtain serum levels of lithium and valproate levels in certain study subjects who participated in protocol CN 138-009 and CN 138-074 respectively. Given the common use of mood stabilizers like lithium and valproate in treatment of Bipolar Disorder patients, the sites should have ensured that these levels were below the range as specified prior to study drug treatment.

The protocol specified that a drug screen to be performed at screening and all subjects with a positive result must be discussed with the sponsor to discuss prior to randomization. Six subjects were noted to have positive drug screen results, yet Dr. Rubenfaer enrolled these subjects in the protocol CN 138-074. The protocol also specified that a drug or alcohol screen be performed upon returning to the hospital from a day pass. For example, the site did not perform a drug/alcohol test for subject 288 previously tested positive for barbiturates. The site did not perform an alcohol screen for subject 186. Subject 186 was positive for amphetamine on the drug screen for day passes on (b) (6) and continued enrollment of the subject in the study.

DSI suggests the Review Division should consider excluding the subjects who did not meet all eligibility criteria and reanalyze the data to see any impact on study outcome. I have conveyed the Review Division Medical Officer to re-examine the data submitted in the NDA application regarding the extent of such protocol violations at sites other than those inspected. Otherwise, data from these centers that had been inspected appear acceptable for use in support of this NDA.

_____

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAI-RR= Deviation(s) form regulations, response received and reviewed. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

cc:
NDA 21-487
HFD-45/Division File / Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/U
HFD-46/Khin
HFD-46/George GCPB1 Files

rd:NK:3/22-23/04

*O:\NK\CIS\NDA21436SE1002 arip Bipolar Mania CIS.doc*

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/s/
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Ni Aye Khin
3/24/04 03:32:52 PM
MEDICAL OFFICER

Khin U
3/24/04 03:36:28 PM
MEDICAL OFFICER

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-436/S-002

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # __21436_____ SUPPL #__002__

Trade Name _ABILIFY_____ Generic Name _aripiprazole___

Applicant Name _Otsuka_____ HFD # _120_____

Approval Date If Known _see electronic signature page_

**CLAIM: The use of aripiprazole in the treatment of acute manic or mixed episodes associated with Bipolar Disorder.**

**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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_✓__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

__SE1_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_✓__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change

or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_✓__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

__Three (3)_____

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?

_____

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# _21-436_____ __Abilify Tablets___

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.) NOT APPLICABLE

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 NDA'S 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:

__CN138009 _(Investigation 1)_____

__CN138074 _(Investigation 2)_____

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"):

_ CN138009 (Investigation 1) _____

_ CN138074 (Investigation 2) _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _42776____ YES /_✓__/ ! NO /___/ Explain: _____

!

!

Investigation #2 !

!

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 /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ 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: _____

_____

See electronic signature page
Signature Date
Title:

See electronic signature page
Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

cc:
Archival NDA
HFD-   /Division File
HFD-   /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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/s/
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Doris Bates
9/29/04 10:15:32 AM

Russell Katz
9/29/04 12:54:23 PM

# PEDIATRIC PAGE

**NDA/BLA # :** 21-436 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 002

**Stamp Date:** July 29, 2004 **Action Date:** September 29, 2004

**HFD** 120 **Trade and generic names/dosage form:** ABILIFY (aripiprazole)

**Applicant:** Otsuka Pharmaceuticals, Ltd. **Therapeutic Class:** Antimanic

**Indication(s) previously approved:** schizophrenia, longer-term treatment of schizophrenia.

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

**Number of indications for this application(s):** 1

**Indication #1:** monotherapy in treatment of acute manic or mixed episodes associated with bipolar disorder

**Is there a full waiver for this indication (check one)?**

- ☐ **Yes: Please proceed to Section A.**

☑ **No: Please check all that apply:** ✓ **Partial Waiver** ✓ **Deferred** ____ **Completed**
**NOTE: More than one may apply**
**Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason(s) for full waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

**Min** _____ **kg** _____ **mo.** _____ **yr.** 0 **Tanner Stage** _____
**Max** _____ **kg** _____ **mo.** _____ **yr.** 10 **Tanner Stage** _____

**Reason(s) for partial waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

☑ **Other:** Disease/condition not known to exist in this age group

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

**Min** _____ **kg**_____ **mo.**_____ **yr.** 10 **Tanner Stage**_____
**Max**_____ **kg**_____ **mo.**_____ **yr.** 17 **Tanner Stage**_____

**Reason(s) for deferral:**

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ☑ **Adult studies ready for approval**
- ❑ **Formulation needed**

**Other:**_____

**Date studies are due (mm/dd/yy):** September 30, 2008

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

**Min** _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
**Max**_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

**Comments:**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

***{See appended electronic signature page}***
*Doris J. Bates, Ph.D.*
**Regulatory Project Manager**

**cc: NDA**
**HFD-960/ Grace Carmouze**
**(revised 12-22-03)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

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/s/

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Doris Bates
9/28/04 05:43:08 PM

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | | |
|---|---|---|---|
| NDA 21-436 | Efficacy Supplement Type SE-1 | Supplement Number 002 | |
| Drug: Abilify (aripiprazole) Tablets | | Applicant: Otsuka Pharmaceutical Company, Ltd. | |
| RPM: Doris J. Bates, Ph.D. | | HFD-120 | Phone # 301.594.2850 |

| | |
|---|---|
| Application Type: (✓) 505(b)(1) ( ) 505(b)(2)<br>(This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)<br><br>**If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.**<br><br>( ) Confirmed and/or corrected | Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): |

| | |
|---|---|
| ❖ Application Classifications: | |
| • Review priority | (✓) Standard ( ) Priority |
| • Chem class (NDAs only) | Not Applicable |
| • Other (e.g., orphan, OTC) | Not Applicable |
| ❖ User Fee Goal Dates | September 29, 2004 |
| ❖ Special programs (indicate all that apply) | (✓) None<br>Subpart H<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review<br>( ) CMA Pilot 1<br>( ) CMA Pilot 2 |
| ❖ User Fee Information | |
| • User Fee | (✓) Paid UF ID number 4544 |
| • User Fee waiver | ( ) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other (specify) _____ |
| • User Fee exception | ( ) Orphan designation<br>( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions)<br>( ) Other (specify) _____ |
| ❖ Application Integrity Policy (AIP) | |
| • Applicant is on the AIP | ( ) Yes (✓) No |

| | |
|---|---|
| • This application is on the AIP | ( ) Yes (✓) No |
| • Exception for review (Center Director's memo) | Not Applicable |
| • OC clearance for approval | Not Applicable |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent. | (✓) Verified |
| ❖ Patent | |
| • Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | Patent Information Submitted |
| • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | Not Applicable 21 CFR 314.50(i)(1)(*i*)(A)<br>( ) Verified<br><br>21 CFR 314.50(i)(1)<br>( ) (ii) ( ) (iii) |
| • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | Not Applicable |
| • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).* | Not Applicable<br>( ) N/A (no paragraph IV certification)<br>( ) Verified |
| • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.<br><br>Answer the following questions for each paragraph IV certification:<br><br>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?<br><br>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).<br><br>*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*<br><br>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?<br><br>*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*<br><br>*If "**No**," continue with question (3).*<br><br>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? | ( ) Yes ( ) No<br><br>( ) Yes ( ) No<br><br>( ) Yes ( ) No |

| | |
|---|---|
| (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).<br><br>*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*<br><br>(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?<br><br>*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*<br><br>*If "**No**," continue with question (5).*<br><br>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?<br><br>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).<br><br>*If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*<br><br>*If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.* | ( ) Yes ( ) No<br><br>( ) Yes ( ) No |
| ❖ Exclusivity (approvals only) | ✓ |
| • Exclusivity summary<br>• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) | Yes |
| • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.* | ( ) Yes, Application #_____<br>(✓) No |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | Not Applicable |

| General Information | |
|---|---|
| ❖ Actions | |
| • Proposed action | (✓) AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | Approvable, 4-23-04 |
| • Status of advertising (approvals only) | (✓) Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | (✓) Yes ( ) Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated<br>*To be determined by Press Office.* | ( ) None<br>( ) Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | ✓ final agreed upon with firm |
| • Most recent applicant-proposed labeling | Not Applicable |
| • Original applicant-proposed labeling | Not Applicable |
| • Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | Not Applicable |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | Not Applicable |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | Not Applicable |
| • Applicant proposed | Not Applicable |
| • Reviews | Not Applicable |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | YES, see AP letter |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | See AP letter |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | ✓ |
| ❖ Memoranda and Telecons | Not Applicable |
| ❖ Minutes of Meetings | |
| • EOP2 meeting | Not Applicable |
| • Pre-sNDA meeting | 05-09-2003 |
| • Pre-Approval Safety Conference | Not Applicable |
| • Other | Suppl. Filing Meeting 08-14-2003 |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | Not Applicable |
| • 48-hour alert | Not Applicable |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) | Not Applicable |

| | |
|---|---|
| **Summary Application Review** | |
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader)) | ✓ |
| **Clinical Information** | |
| ❖ Clinical review(s) | ✓ (both review cycles) |
| ❖ Microbiology (efficacy) review(s) | Not Applicable |
| ❖ Safety Update review(s) | Not Applicable |
| ❖ Risk Management Plan review(s) | Not Applicable |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | ✓ |
| ❖ Demographic Worksheet *(NME approvals only)* | Not Applicable |
| ❖ Statistical review(s) | ✓ (from prior review cycle) |
| ❖ Biopharmaceutical review(s) | ✓ (from prior review cycle) |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling | Not Applicable |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | ✓(from prior review cycle) |
| • Bioequivalence studies | Not Applicable |
| **CMC Information** | |
| ❖ CMC review(s) | See below |
| ❖ Environmental Assessment | |
| • Categorical Exclusion | ✓(from prior review cycle) |
| • Review & FONSI | Not Applicable |
| • Review & Environmental Impact Statement | Not Applicable |
| ❖ Microbiology (validation of sterilization & product sterility) review(s) | Not Applicable |
| ❖ Facilities inspection (provide EER report) | Not Applicable<br>Date completed:<br>( ) Acceptable<br>( ) Withhold recommendation |
| ❖ Methods validation | Not Applicable<br>( ) Completed<br>( ) Requested<br>( ) Not yet requested |
| **Nonclinical Pharm/Tox Information** | |
| ❖ Pharm/tox review(s), including referenced IND reviews | (b) (4) |
| ❖ Nonclinical inspection review summary | Not Applicable |
| ❖ Statistical review(s) of carcinogenicity studies | Not Applicable |
| ❖ CAC/ECAC report | Not Applicable |

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/s/

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Doris Bates
9/29/04 10:18:18 AM

## Bates, Doris J

**From:** Susan H Behling [Susan.Behling@bms.com]
**Sent:** Tuesday, September 21, 2004 8:43 AM
**To:** Podruchny, Teresa
**Cc:** Andreason, Paul J; Bates, Doris J
**Subject:** Re: 5-26-04 submission looking for medwatch reports

We'll get these to you this morning.

Podruchny, Teresa wrote:

> Hi,
>
> I guess I should tell you where I am in the document. I am in appendices 6.1A,B,and C of the 5/26/04 submission Safety Update. In addition to having
> difficulty locating some MedWatch reports, I can't seem to find some of the
> narratives. There may be a simple explanation.
>
> For example, for case 12331583 with the preferred term "Gastrointestinal Haemorrhage", looking in the TOC for Appendix 6.1A, under PRESENTATION OF
> CASES, I don't see GI listed and was unable to find the narrative searching
> by the case number.
>
> I may ask for a few MedWatch forms tomorrow as I continue, but for now, here
> is a list of case numbers of which, mostly, I can't locate the narratives.
>
> 12315826-narrative
> 12331583-narrative
> 12330379-narrative
> 12351698-narrative and Medwatch
>
> Please feel free to contact me as needed.
>
> Thanks so much,
> Teresa
>
> -----Original Message-----
> From: Susan H Behling [mailto:Susan.Behling@bms.com]
> Sent: Monday, September 20, 2004 4:58 PM
> To: Podruchny, Teresa
> Cc: Bates, Doris J; Andreason, Paul J
> Subject: Re: 5-26-04 submission looking for medwatch reports
>
> Hi Teresa: I received your call and I am looking into the matter. At first glance I do not see MedWatch forms associated with the PSUR in the safety update. If you provide me with the case numbers, I'll get them to you ASAP. If they are in the response, I'll find out if there is

some way for you to search (other than using the pdf search which I guess you are having no luck with?). I doubt there is an index within the PSUR since the PSURs are generated for the purposes of international filings and do not include the Medwatch forms as a matter of routine.

I'll get back to you.

Sue

Podruchny, Teresa wrote:

> Hi Ms. Behling,
>
> Regarding sNDA 21436-002, as I noted in my voice mail, I am trying to
>
> locate
>
> specific medwatch reports and am finding this difficult
> to do.
>
> Searching is
>
> very slow and does not seem to work. Is there an index
> that
> cross-references on what page I may find the MedWatch Report for a
>
> specific
>
> case I have located in the PSUR?
>
> Thanks for your assistance in this matter.
>
> Regards,
> Teresa A. Podruchny

"MMS <cder.fda.gov>" made the following annotations.
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This message was sent from Bristol-Myers Squibb, Co. across the Internet
in
encrypted format and was successfully decrypted, unless otherwise noted.
Bristol-Myers Squibb
==========
==

"MMS <cder.fda.gov>" made the following annotations.
---
This message was sent from Bristol-Myers Squibb, Co. across the Internet in encrypted format and was successfully decrypted, unless otherwise noted. Bristol-Myers Squibb
==========

**Bates, Doris J**

**From:** Susan H Behling [Susan.Behling@bms.com]
**Sent:** Tuesday, September 21, 2004 9:30 AM
**To:** Podruchny, Teresa
**Cc:** Batesd@cder.fda.gov
**Subject:** PSUR Cases

MedWatch
_Sep212004.p

Hi Teresa: It turns out that narratives were not written in PSUR 7460.3
for the four cases you identified. For PSURs, all cases are reviewed; however, only certain clinically relevant / special interest cases are summarized in narrative format and discussed within Section 6, Individual Case History Analysis section. In place of the narrative, I have attached the MedWatch forms for those four cases. I hope this is of help to you. I'll be here if you need any others,

Best regards,

Sue

"MMS <cder.fda.gov>" made the following annotations.
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This message was sent from Bristol-Myers Squibb, Co. across the Internet in encrypted format and was successfully decrypted, unless otherwise noted. Bristol-Myers Squibb
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/s/

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Doris Bates
9/21/04 02:30:37 PM
CSO
see emails for dates of transmission and receipt

## Bates, Doris J

**From:** Susan H Behling [Susan.Behling@bms.com]

**Sent:** Friday, September 17, 2004 5:09 PM

**To:** Andreason, Paul J

**Cc:** Bates, Doris J; kusuma mallikaarjun; Charles D Wolleben

**Subject:** S-002 Status: S-005 Question Response

Hi Paul: It's been awhile and I understand you've been knee deep (in hurricane waters, and other things) so to speak, of late. At the same time we are anxiously awaiting some momentum towards closure on the acute mania SNDA. As I understand it from Doris, there are no known remaining issues, so I'm assuming we should be seeing some labeling from you soon. If there is anything you need from us to help bring this to closure, I hope you'll be in touch and please know that we will make ourselves available to do whatever possible to support a final action on this SNDA by the 29th. If there are any remaining concerns, can you please let me know about this early next week?

The response to Dr. Podruchny's question on the CN138010 study report tables is provided below, and we conclude there was no impact on the efficacy or safety outcomes nor on the tables or figures. I hope I'm not out of place by saying this, but please use your discretion if you feel this might distract Dr. Podruchny from her activities on S-002. S-002 is our top priority if there is any question in the Division.

Hope to hear from you soon!

Sue

Response to FDA questions about amendment 1 to the CN138010 CSR

**Question 1**: Do the changes in the appendices change any of the summary tables or figures in the CSR or ISS? **Response:** Amendment 1 to the CSR for CN138010 with changes to the Protocol Deviations Appendix did not impact any of the summary tables or figures in the CSR or ISS.

**Question 2**: Do these changes impact the analyses with respect to the efficacy or safety outcomes? **Response**: Amendment 1 to the CSR with corrections to the Protocol Deviations Appendix does not impact the analyses with respect to the safety or efficacy outcomes.

In order to assist you in your review and avoid any unnecessary confusion, please note that patients who received lorazepam or most anticholinergics were not considered protocol deviations unless dosing was above a protocol-specified threshold. As a result, such patients would not appear in the Protocol Deviations Appendix. However, all patients with these concomitant medications, regardless of dose, were included in the concomitant medications incidence tables. In addition, small differences in the programming specifications for prohibited or excessive concomitant medications were applied to generate the Protocol Deviations Appendix vs the tabulation of concomitant medications for the incidence tables in the CSR. Specifically, the CSR concomitant medication tables were produced using a programming algorithm that assumed the medication was concomitant unless it could be clearly ruled out. However, one patient (Patient ID =138010-32-516) with an end date missing the year is included in the Concomitant Medication Table 9.5A-1 for receiving an antipsychotic (per the standardized programming rule) but was not listed as a protocol deviation for the Stabilization Phase since a detailed review of this patient's data indicated it was very likely that the medication was stopped prior to entry into the study. Finally, for those cases when the same medication was recorded on two records with the same start date but different end dates (one with an end date=continuing and one with an end date specified), the concomitant medication tables in the CSR were produced based on the determination of concomitant use using the record with the end date specified, while the determination of a protocol deviation for the Protocol Deviations Appendix was made based on the record with end date of continuing. This resulted in the following 6 patients classified as

protocol deviations who were not included in the concomitant medication table: 138-010-93-495, 138010-118-148 (classified as maintenance phase protocol deviations), 138010-49-197, 138010-118-390 (classified as Maintenance and Extension phase protocol deviations), 138010-3-367, 138010-118-246 (classified as Extension phase protocol deviations).

This being said, we would reiterate that Amendment 1 to the CSR for CN138010 did not impact any of the summary tables or figures in the CSR or ISS or the analyses with respect to the safety or efficacy outcomes.

"MMS <cder.fda.gov>" made the following annotations.

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/s/

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Doris Bates
9/21/04 02:20:43 PM
CSO
received from firm on date of email.

## Bates, Doris J

**From:** Bates, Doris J
**Sent:** Friday, July 23, 2004 1:27 PM
**To:** 'Susan H Behling'; kusuma mallikaarjun
**Cc:** Bates, Doris J
**Subject:** RE: S-002, NDA-21436-Acute Mania: Submission of July 19: Incomplete Response -- Letter Attached

Incomplete
ter 2 DFS.pdf (:

Good afternoon Susan, Kusuma,

Attached to this email is a .pdf file of our signed letter confirming that your July 19, 2004 submission is not a complete response. The review clock will start for the resubmission on the date that the information necessary to complete the response is received by the Agency; the letter explains this procedure and also explains in more detail what is needed to complete the response.

I noted that we have previously referred to the prior incomplete response, submitted May 26, 2004 and received May 28, 2004 by its May 28 receipt date. This letter refers to it by the May 26 submission date, for greater consistency.

Please feel free to contact me if there is any difficulty opening or printing the attached file.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Doris Bates
9/10/04 04:26:13 PM
CSO
Sent to firm on date shown in email

**Bates, Doris J**

**From:** Bates, Doris J
**Sent:** Monday, August 16, 2004 5:15 PM
**To:** Bates, Doris J; 'Susan H Behling'; 'kusuma mallikaarjun'
**Cc:** 'Charles.Wolleben@bms.com'; Andreason, Paul J; Podruchny, Teresa
**Subject:** RE: NDA 21-436 S-002

Apologies for the typo in prior message header.

-----Original Message-----
From: Bates, Doris J
Sent: Monday, August 16, 2004 5:14 PM
To: 'Susan H Behling'; 'kusuma mallikaarjun'
Cc: 'Charles.Wolleben@bms.com'; Andreason, Paul J; Podruchny, Teresa; Bates, Doris J
Subject: RE: NDA 21-436 S-002

Good afternoon Susan, Kusuma, and Chuck,

This email confirms that your July 28, 2004 submission, received July 29, 2004, constitutes a complete Class One response to our April 23, 2004 action letter. The goal date for our next action on this submission is therefore two months from the receipt date: September 29, 2004.

We will be sending you a formal letter to this effect. In the meantime, please feel free to refer to this email.

I have also added Drs. Podruchny and Andreason as CC recipients. Given the relatively short time frame from now until this action will be due, you should feel free to include them as direct recipients on responses to clinical questions, if any arise. This will prevent delays in communication that might otherwise arise if I am absent or unavailable for a period of time.

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Doris Bates
9/10/04 04:17:53 PM
CSO
sent to firm on date shown on email.

**Bates, Doris J**

**From:** Andreason, Paul J
**Sent:** Tuesday, July 20, 2004 9:48 AM
**To:** 'Susan H Behling'
**Cc:** Bates, Doris J; kusuma mallikaarjun; Podruchny, Teresa; Katz, Russell G
**Subject:** RE: July 2 Letter on S-002, NDA-21436-Acute Mania

Susan-

I returned from being away yesterday and before I was able to respond to your request for a teleconference with me, I received your July 19, 2004 letter stating that your submission had been electronically submitted. It appears that a teleconference with me on the subject of your pending response is therefore of little value; however, I note that this July 19, 2004 cover letter states that a corrected appendix is not included and that we would have to ask for it if we wanted to see it. We do need this appendix.

It is impossible for us to check your re-analysis for internal consistency without this appendix. As you recall, it was by comparing the appendices that included the list of patients that were protocol violators to the re-analysis that we originally found the inconsistencies in the May 28th submission that lead us to conclude that the May 28 response was incomplete. Therefore, in my opinion, I do not see how we could likewise consider this July 19 submission a complete response unless we have what we need to perform the review, which in this case at least includes the corrected appendices and the explanations for the corrections that were made. Had I the opportunity to speak with you on this subject before the submission was sent, this would have been my advice.

Sincerely,
Paul A.
Paul J. Andreason, MD
Psychopharmacology Team Leader
DNDP HFD-120
CDR USPHS

-----Original Message-----
From: Susan H Behling [mailto:Susan.Behling@bms.com]
Sent: Wednesday, July 14, 2004 4:53 PM
To: andreasonp@cder.fda.gov; kusuma mallikaarjun; Batesd@cder.fda.gov
Subject: Re: July 2 Letter on S-002, NDA-21436-Acute Mania
Importance: High

Dr. Andreason: We have completed an exhaustive review of the response issue that the Division identified in the July 2 letter and we are in the final processing stages of the response. Kusuma and I would like to provide you with a top level overview of our findings if it is possible to have your ear for a few minutes. Would it be possible to call you

tomorrow or Friday to discuss?

Thanks in advance for your consideration of this request.  We know how buy you are but we would really like an opportunity to talk.

Sue

"MMS <cder.fda.gov>" made the following annotations.

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Doris Bates
9/10/04 04:14:18 PM
CSO
Sent to firm on date shown on email.

**Bates, Doris J**

**From:** Bates, Doris J
**Sent:** Tuesday, June 15, 2004 5:28 PM
**To:** Bates, Doris J; 'Susan H Behling'
**Cc:** 'kusuma mallikaarjun'
**Subject:** RE: NDA 21-436, S-002, Response to Action Letter

I omitted to revise the message header, for which I apologize. I have revised it below, so that it can be distributed if need be without causing confusion.

-----Original Message-----
From: Bates, Doris J
Sent: Tuesday, June 15, 2004 5:25 PM
To: 'Susan H Behling'
Cc: kusuma mallikaarjun; Bates, Doris J
Subject: RE: NDA 21-436, S-002, May 26, 2004 Response to Action Letter

Good afternoon Susan and Kusuma,

I wanted to let you know that Drs. Andreason and Podruchny have completed their assessment of your May 26, 2004 resubmission to NDA 21-436, S-002. They have determined that the submission is not a complete response.

The review clock will not start until the response is completed, which can be accomplished by submitting the additional information needed. Information we already have on hand can be cross-referenced rather than submitted again.

I am in the process of obtaining further details and it is my intention to assure that you receive an official letter, with further explanation as to where the response is incomplete, by the end of this week. In the meantime, however, I did want you to have this important information as soon as possible.

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Doris Bates
9/10/04 04:11:41 PM
CSO
Sent to firm on date shown in email.

## Bates, Doris J

**From:** Bates, Doris J

**Sent:** Tuesday, August 31, 2004 10:13 AM

**To:** Bates, Doris J

**Subject:** FW: FW: NDA 21-436 S-002 and S-005: Urgent Question from Clinical Rev iewer iewer

Includes complete thread for two questions sent to BMS, and the response to the first one.

-----Original Message-----
**From:** Bates, Doris J
**Sent:** Tuesday, August 31, 2004 10:10 AM
**To:** 'Charles D Wolleben'; Bates, Doris J; Podruchny, Teresa
**Cc:** Andreason, Paul J; Susan Behling; Mallikaarjun, Kusuma
**Subject:** RE: FW: NDA 21-436 S-002 and S-005: Urgent Question from Clinical Rev iewer

Good morning Susan, Chuck, and Kusuma

I received the following request from Dr. Podruchny last week and, although I was virtually certain that I had sent it to you, I have been unable to find any evidence for this in my email account or in the Division archives. (We have had server problems recently.) I am therefore sending it immediately, with profound apologies if this is in fact the first time you have seen it. As previously, a reply by secure email is perfectly fine.
**********

Please provide responses to the following questions. If this information is in the submission, please reference the pages.

1) In general, what is the average time spent in the open label stabilization phase before randomization in the patients who comprised the primary efficacy population? Please answer this in days (mean, median, standard deviation, mode, range) and provide this for placebo versus aripiprazole.
2) Also, since the earliest a patient could have been randomized is 6 weeks and after meeting the YMRS and MADRS criteria for 4 consecutive weeks, please subgroup the average time in open label stabilization as 0-14 days, 15-28 days, 29-42 days, etc and provide the number of patients who were stabilized for these time periods before randomization for the patients comprising the primary efficacy population. Please further stratify this in two ways: (see the rough examples of the type of tables I am requesting below).

- placebo versus aripiprazole
- IND sites placebo versus aripiprazole versus non-IND sites placebo versus aripiprazole

For example, the tables would look something like this:

| Mean Time in stab before random | Placebo (total n) | Aripiprazole (total n) |
|---|---|---|
| 0-14 days | # of patients | # of patients |
| 15-28 days | etc | etc |
| 29-42 days | | |
| 43- 56 days | | |
| Etc…. | | |

| | IND sites | | Non-IND sites | |
|---|---|---|---|---|
| Mean Time in stab before random | Placebo (n) | Ari (n) | Placebo (n) | Ari (n) |
| 0-14 days | | | | |
| 15-28 days | | | | |
| 29-42 days | | | | |
| 43- 56 days | | | | |
| Etc…. | | | | |

Thank you.

**********

Please feel free to respond to Dr. Podruchny directly as well as to Drs. Andreason and myself.

Many thanks,

*Doris J. Bates, Ph.D.*
*Regulatory Project Manager*
*Division of Neuropharmacological Drug Products*
*Office of Drug Evaluation I*
*Center for Drug Evaluation and Research*

-----Original Message-----
**From:** Charles D Wolleben [mailto:Charles.Wolleben@bms.com]
**Sent:** Tuesday, August 24, 2004 2:33 PM
**To:** Bates, Doris J; Podruchny, Teresa
**Cc:** Andreason, Paul J; Susan Behling; Mallikaarjun, Kusuma
**Subject:** Re: FW: NDA 21-436 S-002 and S-005: Urgent Question from Clinical Rev iewer

Doris/Dr Podruchny:

There were no Non-IND sites in -009 and -074 (all US).

Regarding -010, the following 5 sites were non-IND:
089 (Argentina)
091 (Argentina)
093 (Mexico)
111 (Argentina)
118 (Mexico).

Hope this helps. Call or email if this does not address your questions.

Chuck

Bates, Doris J wrote:

Hello Chuck, I received Susan's out of office email right after sending this, so am copying it to you as well.

Sincerely,

*Doris J. Bates, Ph.D.*
*Regulatory Project Manager*
*Division of Neuropharmacological Drug Products*
*Office of Drug Evaluation I*
*Center for Drug Evaluation and Research*

-----Original Message-----
**From:** Bates, Doris J
**Sent:** Tuesday, August 24, 2004 1:38 PM
**To:** 'Susan H Behling'; 'kusuma mallikaarjun'
**Cc:** Andreason, Paul J; Podruchny, Teresa; Bates, Doris J
**Subject:** RE: NDA 21-436 S-002 and S-005: Urgent Question from Clinical Reviewer

Dear Susan and Kusuma,

Our clinical reviewer has identified an urgent question related to both S-002 and S-005.

In the case of S-002, we will need a response as soon as possible because of the very limited time remaining in the review cycle for this submission; please respond by COB a week from today. (Secure email is fine for this response.)

For S-005, we can wait a bit longer for your reply but would like the information by mid-September if possible. (Secure email is again fine.)

**********
Please identify, by number, all of the non-IND sites

- in studies 009 and 074 for supplement 002

- in study 010 for supplement 005.
**********

Thank you in advance; for S-002 especially, it will help if you can include Drs. Podruchny and Andreason as CC recipients on any e-mail responses (to minimize routing delays).

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Doris Bates
8/31/04 10:17:48 AM
CSO

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436, S-002

Otsuka Maryland Research Institute
Attn: Dr. Kusuma Mallikaarjun
Director, Regulatory Affairs
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Mallikaarjun:

We acknowledge receipt on July 29, 2004 of your July 28, 2004 submission to the above referenced supplemental new drug application for ABILIFY (aripiprazole) Tablets.

As you were informed by secure e-mail on August 16, 2004, we consider this submission, in conjunction with your earlier submissions dated May 26, 2004 and July 19, 2004, to be a complete, class 1 response to our April 23, 2004 action letter. Therefore, the primary user fee goal date is September 29, 2004 and the secondary user fee goal date is January 28, 2005.

As you are also aware, under the Pediatric Research Equity Act (PREA), 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. In connection with this requirement, we reference:

1. The existing Pediatric Written Request for aripiprazole in pediatric mania; note that the requirements for PREA may need to be addressed separately from those for exclusivity, depending upon study design.
2. The partial waiver (ages 0 to 10) and partial deferral (ages 10 to 17) already granted for this indication on February 11, 2003 and May 9, 2003. The partial waiver applies to both PREA-related studies and your Written Request; with respect to the partial deferral, FDA may choose to defer the submission of your PREA-related study reports to a later date than those required for your Written Request (February 11, 2008).
3. The pharmacology/toxicology comment in our action letter of April 23, 2004, with respect to preclinical studies (juvenile animals) which will be required to support pediatric studies of this drug;



If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Russell Katz
8/30/04 07:30:20 AM

Full thread attached.

-----Original Message-----
**From:** Charles D Wolleben [mailto:Charles.Wolleben@bms.com]
**Sent:** Tuesday, August 24, 2004 2:33 PM
**To:** Bates, Doris J; Podruchny, Teresa
**Cc:** Andreason, Paul J; Susan Behling; Mallikaarjun, Kusuma
**Subject:** Re: FW: NDA 21-436 S-002 and S-005: Urgent Question from Clinical Rev iewer

Doris/Dr Podruchny:

There were no Non-IND sites in -009 and -074 (all US).

Regarding -010, the following 5 sites were non-IND:
089 (Argentina)
091 (Argentina)
093 (Mexico)
111 (Argentina)
118 (Mexico).

Hope this helps. Call or email if this does not address your questions.

Chuck

Bates, Doris J wrote:

Hello Chuck, I received Susan's out of office email right after sending this, so am copying it to you as well.

Sincerely,

*Doris J. Bates, Ph.D.*
*Regulatory Project Manager*
*Division of Neuropharmacological Drug Products*
*Office of Drug Evaluation I*
*Center for Drug Evaluation and Research*

-----Original Message-----
**From:** Bates, Doris J
**Sent:** Tuesday, August 24, 2004 1:38 PM
**To:** 'Susan H Behling'; 'kusuma mallikaarjun'
**Cc:** Andreason, Paul J; Podruchny, Teresa; Bates, Doris J
**Subject:** RE: NDA 21-436 S-002 and S-005: Urgent Question from Clinical Reviewer

Dear Susan and Kusuma,

Our clinical reviewer has identified an urgent question related to both S-002 and S-005.

In the case of S-002, we will need a response as soon as possible because of the very limited time remaining in the review cycle for this

submission; please respond by COB a week from today. (Secure email is fine for this response.)

For S-005, we can wait a bit longer for your reply but would like the information by mid-September if possible. (Secure email is again fine.)

**********
Please identify, by number, all of the non-IND sites

- in studies 009 and 074 for supplement 002

- in study 010 for supplement 005.
**********

Thank you in advance; for S-002 especially, it will help if you can include Drs. Podruchny and Andreason as CC recipients on any e-mail responses (to minimize routing delays).

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Doris Bates
8/24/04 04:16:54 PM
CSO

**Bates, Doris J**

**From:** Bates, Doris J
**Sent:** Tuesday, August 24, 2004 1:38 PM
**To:** 'Susan H Behling'; 'kusuma mallikaarjun'
**Cc:** Andreason, Paul J; Podruchny, Teresa; Bates, Doris J
**Subject:** RE: NDA 21-436 S-002 and S-005: Urgent Question from Clinical Reviewer

Dear Susan and Kusuma,

Our clinical reviewer has identified an urgent question related to both S-002 and S-005.

In the case of S-002, we will need a response as soon as possible because of the very limited time remaining in the review cycle for this submission; please respond by COB a week from today. (Secure email is fine for this response.)

For S-005, we can wait a bit longer for your reply but would like the information by mid-September if possible. (Secure email is again fine.)

**********
Please identify, by number, all of the non-IND sites

- in studies 009 and 074 for supplement 002

- in study 010 for supplement 005.
**********

Thank you in advance; for S-002 especially, it will help if you can include Drs. Podruchny and Andreason as CC recipients on any e-mail responses (to minimize routing delays).

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Doris Bates
8/24/04 01:52:28 PM
CSO
sent on date signed in. See email for transmission time

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436, S-002

Otsuka Maryland Research Institute
Attn: Dr. Kusuma Mallikaarjun
Director, Regulatory Affairs
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Mallikaarjun:

Reference is made to your supplemental New Drug Application for ABILIFY (aripiprazole) Tablets, submitted June 23, 2003, received June 25, 2003. Reference is also made to our action letter of April 23, 2004, and to your submission of May 26, 2004, which was received by this Agency on May 28, 2004. This submission did not constitute a complete response to our action letter.

We acknowledge receipt on July 20, 2004 of your July 19, 2004 submission to this supplemental application.

As you were informed by secure e-mail on July 20, 2004, we do not consider your July 19, 2004 submission to be a complete response to our action letter. The review clock cannot be started until we have received a complete response.

Please note that you may complete the response by submitting the additional information that we describe as still being necessary, and cross-referencing your submissions of May 26, 2004 and July 19, 2004. Once this additional information has been assessed and we determine that the response is now complete, the review clock will restart on the date that the final item(s) of information is/are received by the Agency.

The following deficiency from our action letter still needs to be addressed:

> Your July 19, 2004 cover letter states that this submission includes an evaluation of discrepancies between your May 26 submission and the CSR Protocol Deviations Appendices in your original submission of June 25, 2003. Your submission also includes, per our request, a revised sensitivity analysis for your response to Question 3 in our April 23, 2004 action letter.
>
> However, although your letter also states that you found and corrected errors in the original CSR Protocol Deviations Appendices, the corrected appendices are not included in this submission, and you indicate that the the Division should request these corrected appendices in order to receive them.

The Division does need these corrected appendices, and in general should routinely receive all such appendices in which data and/or analyses of data are presented. In this case, it will be impossible for us to check the re-analysis of protocol violators which you have performed, to assure its internal consistency and completeness, without these corrected appendices. It was by comparing the original appendices that included the list of patients who were protocol violators to your May 26 re-analysis that we were able to identify inconsistencies in the May 26th submission that led us to conclude that the response was incomplete.

We consider the July 19 submission an incomplete response, therefore, because essential information is missing from it that is necessary for us to perform a full review of the submission.

Please submit the corrected appendices as soon as possible. Within 14 days of receipt of this information, we will inform you whether your response is now complete. If it is incomplete, we will explain what further information is needed to complete it; if it is complete, we will inform you of the action due date.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Russell Katz

7/23/04 12:48:55 PM

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436, S-002

Otsuka Maryland Research Institute
Attn: Dr. Kusuma Mallikaarjun
Director, Regulatory Affairs
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Mallikaarjun:

We acknowledge receipt on May 28, 2004 of your May 26, 2004 submission to the above referenced supplemental new drug application for ABILIFY (aripiprazole) Tablets.

As you were informed by secure e-mail on June 15, 2004, we do not consider this submission to be a complete response to our action letter. We will not start the review clock until we have received a complete response. Please note that you may complete the response by submitting only the additional information that we list below as still being necessary, and cross-referencing your submission of May 28, 2004.

The following deficiencies from our action letter still need to be addressed:

> "We note that you have included, according to the intent-to-treat principle, patients with various protocol violations in your analyses. We are particularly interested in the effects on your primary analysis of including patients who did not have baseline valproate or lithium levels, patients with benzodiazepine use within 1 day of a rating having been done, patients with positive drug screens at anytime during the study, and patients who began the study within 30 days of taking fluoxetine or within 14 days of other antidepressants."

While you have submitted a response to this point, it is incomplete in the following respect: some subjects identified by either our clinical reviewer or our field investigator (Division of Scientific Investigations) as protocol violators, within the constraints outlined above, have not been included in your reanalysis. Some of these subjects apparently are listed in the study report appendices, but cannot be found on the lists provided with your response.

You should be aware that our assessment is a preliminary one. We did not perform an exhaustive audit of these data once we were aware that the submission was incomplete in this respect. Therefore, we do not have an exhaustive list of protocol violators which we have identified but which you have not included in the resubmission. Please reexamine the study data thoroughly and submit a reanalysis that includes all protocol violators meeting the above cited conditions.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Russell Katz
7/2/04 07:08:17 AM

Memo to File
NDA 21-436: ABILIFY (aripiprazole)
Otsuka America / Bristol-Myers Squibb
Bipolar Disorder: S-002 (3 week studies) (b) (4)
Filing Meeting

**DATE:** August 14, 2003
**ATTENDING:** R. Katz, P. Andreason, T. Podruchny, N. Khin, Y.-F. Chen, R. Baweja, K. Kumi, S. Tabacova, D. Bates
**INPUT RECEIVED FROM:** K. Jin, T. Oliver, S. McLamore, L. Freed

**Background:**

- A pre-sNDA meeting was held with representatives of both firms on May 9, 2003. Please see minutes of this meeting for more details.
- The firms were informed that the three-week (b) (4)
- (b) (4)

**Summary:**

- The action due date (b) (4) is **April 23, 2004** (April 25 is a Sunday).
- **The submission is fileable for all disciplines.**
- Disciplines conducting reviews of the resubmission are Clinical, Statistics, (b) (4), and CMC.
- OCPB review is not necessary; interaction studies with lithium, carbamazepine, and valproate have already been performed and labeling is satisfactory. A short memo will be provided by OCPB to that effect, *in lieu* of a full review.
- (b) (4) .
- The clinical reviewer noted a total absence of hyperlinking in the document, which is an all-electronic submission.
- DSI inspection will be performed. Appropriate domestic sites will be inspected.
- Reviews are anticipated to be complete by March 1, 2004. **CMC review is complete as of this meeting, with approval actions recommended for both supplements.**

**Post Meeting Notes:**

- Following the meeting, Ms. Susan Behling at BMS was contacted by phone and informed that the submissions have been filed.
- (b) (4)

Please see electronic signature page

Doris J. Bates, Ph.D.
Regulatory Project Manager
*For the attendees*

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/s/

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Doris Bates
4/15/04 10:37:03 AM

## Bates, Doris J

**From:** Bates, Doris J
**Sent:** Tuesday, April 13, 2004 2:43 PM
**To:** Bates, Doris J
**Subject:** FW: Aripiprazole NDA 21-436 S-002 (b) (4): Comments from OCPB

The attached email from OCPB indicates that no review activities were needed for the supplements in question.

OCPB was notified of the supplement submission and included in the filing review meeting because of language in the submission labeling addressing the concomitant use of aripiprazole with lithium, valproate, and carbamazepine. This language was developed prior to the submission of the mania efficacy supplements and remains satisfactory according to OCPB.

Therefore, no further OCPB review was required beyond provision of this feedback at the time of submission filing.

*Doris J. Bates, Ph.D.*
*Regulatory Project Manager*
*Division of Neuropharmacological Drug Products*
*Office of Drug Evaluation I*
*Center for Drug Evaluation and Research*

-----Original Message-----
**From:** Kumi, Kofi A
**Sent:** Monday, April 05, 2004 9:58 AM
**To:** Bates, Doris J
**Cc:** Podruchny, Teresa; Andreason, Paul J; Baweja, Raman K; Kumi, Kofi A
**Subject:** FW: Aripiprazole

-----Original Message-----
**From:** Kumi, Kofi A
**Sent:** Friday, April 02, 2004 6:24 PM
**To:** Baweja, Raman K
**Cc:** Kumi, Kofi A
**Subject:** Aripiprazole

Hello Doris: This is OCPB comments on the following NDAs for Aripiprazole.

NDA: 21-436 S- 002 (b) (4)
Drug: Aripiprazole
Trade Name: Abilify
Indications: Treatment of Bipolar Disorder
Submission Date: 6/23/03
Review Date: 4/2/04
Reviewer: Kofi A. Kumi, Ph.D.
Team Leader: Raman Baweja, Ph.D.

Comments

This NDA submission did not contain pharmacokinetics/biopharmaceutics information to be reviewed. The sponsor is not proposing any changes in the clinical pharmacology and biopharmaceutic sections of the approved label. Therefore, this e-mail serves as OCPB's review for the above submissions.

thanks,
Kofi

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/s/
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Doris Bates
4/13/04 02:43:10 PM
CSO
Decision approved by Team Leader, OCPB, and by Team Leader, Psychiatric Drugs; information placed in DFS for the record by CSO.

## Bates, Doris J

**From:** Bates, Doris J

**Sent:** Monday, November 24, 2003 1:52 PM

**To:** 'Mallikaarjun, Kusuma'

**Cc:** 'Susan H Behling'; Bates, Doris J

**Subject:** RE: NDA Supplements, aripiprazole

Good afternoon Dr. Mallikaarjun, this is Doris Bates. I am copying Ms. Behling on this email for ease of reference.

I have received a question from the clinical review team on Supplements 002 (b) (4) to NDA 21-436, which follows:

1. For study 138009, appendix 8.1.1 is the by-patient listing of final disposition and it noted this appendix is available by request. Our clinical reviewer would like to receive it; she would also like to receive all other such lists for the other pivotal trials (and only for the other pivotal trials – she does not need them for any non-pivotal, e.g. supportive, trials.)
2. The above request applies to all pivotal trials for both supplements, S-002 (b) (4).
3. Also, the reviewer would like all available information about why patients left this and all other pivotal studies for s-002 (b) (4), specifically for headings such as "patient withdrew consent" and "other known cause".

An initial reply via secure e-mail is fine, but must be followed up with an official submission to the EDR for our records.

Please let me know if there are any questions about this request; and thanks in advance for your help.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Doris Bates
11/24/03 03:23:36 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**SUPPLEMENTAL NDA ACKNOWLEDGED/FILED:**
**FILING REVIEW ISSUES IDENTIFIED**
**(PHARMACOLOGY/TOXICOLOGY, STATISTICS)**

NDA 21-436 / S-002, (b) (4)

Otsuka America Pharmaceutical Inc.
Attn: Dr. Kusuma Mallikaarjun
Director, Regulatory Affairs / Abilify™
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Mallikaarjun:

Please refer to your supplemental new drug applications (sNDAs), referenced above, which were submitted on June 23, 2003 and received on June 25, 2003 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ABILIFY (aripiprazole) Tablets.

These supplemental applications provide for the use of aripiprazole monotherapy in the acute treatment of Bipolar Disorder. S-002 provides for clinical trials of three weeks' duration, (b) (4)

We have completed our filing review for these supplemental applications and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 14, 2003 in accordance with 21 CFR 314.101(a). Our goal date for acting on these submissions is April 25, 2004.

In our filing review, we have identified the following review issues:

**Pharmacology / Toxicology**
Please submit the following reports, which were marked as "not submitted / available upon request" in the initial submissions:

- (b) (4)
- (b) (4)
- (b) (4)

**Statistics**

- Please provide a missing variabl (b) (4)

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 call Doris J. Bates, Regulatory Project Manager, at (301) 594-2850.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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Russell Katz
9/3/03 04:38:32 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# REQUEST FOR CONSULTATION

| | | | | |
|---|---|---|---|---|
| TO *(Division/Office)*: HFD-860 / Dr. Baweja, Dr. Kumi | | | FROM: Doris J. Bates | |
| DATE June 27, 2003 | IND NO. | NDA NO. 22436, SE1-002 (b) (4) | TYPE OF DOCUMENT Efficacy supplement | DATE OF DOCUMENT June 24 2003 |
| NAME OF DRUG Abilify (aripiprazole) | PRIORITY CONSIDERATION Standard SE1, 10 month April 25, 2004 | | CLASSIFICATION OF DRUG: Bipolar Disorder S-002: 3 week studies (b) (4) | DESIRED COMPLETION DATE: August 14, 2003 filing meeting |

NAME OF FIRM: Bristol-Myers Squibb

**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<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ 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 – S-002 is for the acute 3 week claim (b) (4) EDR hotlinks are below. Note data are most likely all in S-002: \\CDSESUB1\N21436\S_002\2003-06-23

(b) (4)

Should have very little OCPB content.

| 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/

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Doris Bates
6/27/03 06:29:26 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# REQUEST FOR CONSULTATION

| | | | | |
|---|---|---|---|---|
| TO *(Division/Office)*: HFD-710 (Dr. Jin) | | | FROM: HFD-120 (Dr. Bates for Dr. Laughren) | |
| DATE 6/27/03 | IND NO. | NDA NO. 21436, SE1-002 (b) (4) | TYPE OF DOCUMENT Efficacy supplements | DATE OF DOCUMENT 6/24/03 |
| NAME OF DRUG ABILIFY (aripiprazole) | PRIORITY CONSIDERATION Ten month, due April 25, 2004 | | CLASSIFICATION OF DRUG Bipolar disorder S-002: 3 week studies (b) (4) | DESIRED COMPLETION DATE: August 14, 2003 filing meeting |

NAME OF FIRM: Bristol-Myers Squibb

**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
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- ☐ 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<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☒ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ 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 – S-002 is for the acute 3 week claim (b) (4) EDR hotlinks are below. Note data are most likely all in S-002: \\CDSESUB1\N21436\S_002\2003-06-23 (b) (4)

| | |
|---|---|
| SIGNATURE OF REQUESTER see electronic signature | METHOD OF DELIVERY (Check one)<br>☐ MAIL ☒ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

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/s/

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Doris Bates
6/27/03 06:16:57 PM