CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-436

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #21-436

Sponsor:	Otsuka/BMS
Drug:	Aripiprazole
Indication:	Schizophrenia
Material Submitted:	Response to 8-29-02 Approvable Letter
Correspondence Date:	September 18, 2002
Date Received:	September 19, 2002

I. Background

On 10-31-01, the sponsor submitted this NDA for the approval of aripiprazole in the treatment of schizophrenia.

The Office issued an approvable letter on 8-29-02. In summary, this letter indicated that, prior to approval, the sponsor would need to address several points, to include the following clinical issues:

1) follow-up laboratory data for 6 patients.
2) foreign regulatory update/foreign labeling.
3) world literature update.
4) submission of final printed labeling identical to that attached to the approvable letter.
5) safety update.
6) Phase 4 commitments to a) explore the efficacy of doses under 10 mg/day and b) provide data regarding longer-term efficacy (i.e., the results of study 138047).

This submission contains their response to the above.

II. Clinical Data

A. Follow-up Clinical Data on Six Patients

There were six patients who had abnormal laboratory findings at last visit with no follow-up:

1) 138001-33-102 (elevated SGOT).
2) 97201-36-18 (elevated SGOT).
3) 138001-7-458 (elevated CPK).

4) 97202-89-6 (low platelet count).
5) 138001-7-281 (low platelet count).
6) 97202-71-19 (low platelet count).

We had requested that the sponsor attempt to obtain follow-up data on these patients.

The sponsor re-contacted the involved investigator sites for these six patients. In most cases, there was no new information of consequence. Problems in data collection were mostly due to non-compliant patients, some of whom have been totally lost to follow-up (i.e., homeless). In one patient with an elevated CPK (138001-7-458), misplaced lab data was found and it showed diminishing CPK values at time of last measurement. In another case, the medical treatment facility had closed and no records were obtainable.

B. Foreign Regulatory Update/Foreign Labeling

Aripiprazole was approved in Mexico for the treatment of schizophrenia on 7-17-02. Marketing authorizations are pending in [redacted] The sponsor states that no negative regulatory actions have been taken in any country with respect to aripiprazole.

A review of the approved labeling from Mexico revealed no important clinical information that should be added to the U.S. labeling currently under consideration.

C. World Literature Update

The world's literature was updated by Julia Jui-mei Chuang from the sponsor's firm. Fifty-six articles were reviewed. No adverse safety findings were found. This fact was certified by Dr Joy Parris of Otsuka and Dr. Allan Safferman of BMS. A review of the three CV's of the above individuals was conducted and they are all satisfactory.

The databases searched with the appropriate search items included ADSI R&D Insight, MEDLINE, CAPLUS (Chemical Abstracts), EMBASE/EMBASE ALERTS, BIOSIS/Biological abstracts, SCISEARCH/Science Citation Index, DRUGU/Derwent Drug File, LIFESCI/Life Sciences Collection, TOXCENTER, IPA/International Pharmaceutical Abstracts, and

JICSTE/Japanese Information Center. The search interval was from January 1, 2002 to July 3, 2002.

Drs. Parris and Safferman each provided a warrant attesting to the above.

D. Product Labeling

The following comments are provided regarding the clinical sections of the sponsor's proposed labeling, found in volume 2 of this response:

CLINICAL PHARMACOLOGY/Clinical Studies
Efficacy information from the 52 week, active-controlled study should be removed since this trial, by design, cannot demonstrate the longer-term efficacy of aripiprazole in schizophrenia.

INDICATIONS AND USAGE
In accordance with the above comment, this section should indicate that the long-term efficacy of aripiprazole has not been established.

PRECAUTIONS/Use in Patients with Concomitant Illness
Placement of the statement regarding mortality in patients with psychosis associated with Alzheimer's dementia in this section (as opposed to WARNINGS) is not objectionable since the data do not clearly support a causal relationship between aripiprazole and these deaths.

ADVERSE REACTIONS/ECG Changes
The final paragraph, which describes QTc changes in study 99224, may be deleted as proposed by the sponsor given that the results in the 90mg dose group do appear to be driven by a single patient with highly variable QTc values. The small number of patients and high variability in ECG findings in this trial render these data difficult to interpret with reasonable certainty.

ADVERSE REACTIONS/Additional Findings Observed in Clinical Trials
The adverse event listing in this section was apparently constructed from a tabulation of ADR's, which excludes treatment-emergent events not deemed to be drug-related by investigators (Appendix 4.2.1 of this submission). The sponsor was requested to revise this table based on a

tabulation of all treatment-emergent adverse events (Appendix 4.2.2).[1]

DOSAGE AND ADMINISTRATION/Switching from Other Antipsychotics

The sponsor has added, as the first paragraph, some general guidance to prescribers regarding switching patients from other antipsychotics to aripiprazole. This language is very similar to that currently found in Seroquel labeling and is not objectionable.

However, they also propose to [redacted]

E. Safety Update

The sponsor has provided a Safety Update with a cut-off date of 6-30-02. The cut-off date for the 120-Day Safety Update, which was incorporated into the original clinical review, was 11-30-01.

Since the last update, 882 new patients received aripiprazole in non-Japanese Phase 2/3 studies as well as 59 new patients in non-Japanese Phase 1 trials and 55 new subjects in Japanese studies. As of 6-30-02, a total of 5,592 patients have been exposed to aripiprazole in non-Japanese Phase 2/3 studies.

There are no new safety data from short-term, placebo-controlled studies in patients with schizophrenia.

The review of this update focused on serious adverse events (SAE's), including deaths, in the non-Japanese Phase 2/3 studies. There were no new SAE's in the non-Japanese Phase 1 studies or in the Japanese studies.

1. Deaths

Among aripiprazole patients, there were 43 new deaths (39 in the Alzheimer's group) plus 2 deaths previously reported from studies that were still blinded as of the last update.

[1] In a 10-3-02 E-Mail to Charles Wolleben of BMS.

Deaths are enumerated by cause in Table 1 below. Line Listings and Narrative Summaries of new deaths were reviewed. The data were similar in every respect to those obtained from analysis of the prior studies and require no further comment.

TABLE 2:
ENUMERATION OF ARIPIPRAZOLE DEATHS BY CAUSE (N)
APPROVABLE RESPONSE SAFETY UPDATE

Cause of Death	Study Pool	
	Schizophrenia/ Bipolar	Dementia
Pneumonia (Aspiration)	-	1
Pneumonia (Other/Unspecified)	-	7
Myocardial Infarction	-	1
Heart Failure	1	4
Sepsis	-	6
Cachexia	-	2
Cardiac Arrest	1	8
Pulmonary Embolism	1	1
Cancer	2	-
Stroke	-	4
Respiratory Distress Syndrome	-	3
End-Stage Dementia	-	1
Intestinal Obstruction	-	1
Diabetes	-	1
TOTAL	**5**	**40**

Exposure-adjusted mortality rates (per 1000 PY's) for the cumulative database by diagnostic group are as follows and are similar to those observed in the previously reviewed safety database: 8.5 in the schizophrenia studies, 7.9 in the bipolar mania studies, and 220 in the dementia studies.

2. All Serious Adverse Events

There were 264 new SAE's in the non-Japanese Phase 2/3 studies. Line listings of all new SAE's were reviewed (Appendix 4.4A of the safety update). Narrative summaries of events that possibly represented clinically significant and previously unrecognized events were reviewed in detail.

Overall, the pattern of SAE's followed that of the previously reviewed database. No important, new SAE's were found.

F. Phase 4 Commitments

The sponsor agreed to all requested Phase 4 commitments, to include an exploration of the efficacy of doses under 10 mg/day and submission of data from study 138047 regarding the longer-term efficacy of aripiprazole in schizophrenia.

III. Conclusions and Recommendations

This submission is a full and adequate response to the clinical issues raised in our approvable letter. There is no clinical information in this submission that would change our previous conclusions about the approvability of aripiprazole.

From a clinical perspective, this application may be approved when agreement is reached on product labeling.

/S/

Gregory M. Dubitsky, M.D.
October 4, 2002

/S/

Robert Harris, M.D., Ph.D.
October 4, 2002

cc: NDA #21-436
HFD-120 (Div. File)
HFD-120/GDubitsky
/RHarris
/TLaughren
/SHardeman

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/s/

Greg Dubitsky
10/4/02 04:47:00 PM
MEDICAL OFFICER

Robert D. Harris
10/7/02 02:19:20 PM
MEDICAL OFFICER

Thomas Laughren
11/7/02 05:22:47 PM
MEDICAL OFFICER
We have reached agreement on final labeling as of 11-7-02, and I agree that we can now approve this NDA.--TPL

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ON ORIGINAL

Demographic Worksheet

lication Information *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21-436 **Submission Type:** N/A (pilot) **Serial Number:** N/A (pilot)

Populations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	699	All Females	227	Females >50	54
Age:	0-≤1 Mo.	0	>1 Mo.-≤2Year	0	>2-≤12	0
	12-16	0	17-64	918	≥65	8
Race:	White	506	Black	283	Asian	21
	Other	116				

Gender-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was gender-based analysis included in labeling? Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐

Is a dosing modification based on gender recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☐ FDA

Age-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was age-based analysis included in labeling? Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐

Is a dosing modification based on age recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☐ FDA

Race-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was race-based analysis included in labeling? Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐

Is a dosing modification based on race recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☐ FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

A PK study in 19 patients with hepatic impairment was done. A PK study in 6 patients with severe renal impairment was done. There were no modifications to the Dosage and Administration section of product labeling based on the results of these two studies.

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/s/

Greg Dubitsky
10/7/02 02:11:45 PM

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REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA#:	21-436
Sponsor:	Otsuka/Bristol-Myers Squibb
Due Date:	August 31, 2002

Drug Name:

Generic Name:	Aripiprazole (OPC-14597)
Trade Name:	[redacted]

Drug Categorization:

Pharmacological Class:	D_2 partial agonist
Proposed Indication:	Schizophrenia
Dosage Forms:	10mg, 15mg, 30mg tablets
Route:	Oral

Review Information

Clinical Reviewers:	Gregory M. Dubitsky, M.D. Robert Harris, M.D., Ph.D.
Completion Date:	June 12, 2002

NDA 21-436
ARIPIPRAZOLE TABLETS FOR SCHIZOPHRENIA
TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability

It is recommended that aripiprazole tablets be approved for the treatment of _____ adult patients with schizophrenia.

B. Recommendations for Phase 4 Studies

It is recommended that the following Phase 4 commitments be requested from the sponsor:

1) an adequate and well-controlled study of aripiprazole in the treatment of children and adolescents with schizophrenia.

2) a study to address the longer-term efficacy of aripiprazole in the treatment of adults with schizophrenia. The recently completed Study 138047 may be adequately designed to address longer-term efficacy (see section VI.C.4) and the study report may be submitted as an efficacy supplement to satisfy this commitment.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Program

The aripiprazole clinical program consisted of 35 Phase 1 and 36 Phase 2/3 studies conducted worldwide (excluding Japan) as of 11-30-01. The Phase 2/3 studies have been conducted in patients with schizophrenia and schizoaffective disorder, mania associated with bipolar disorder, and psychosis associated with Alzheimer's disease. A total of 4710 patients have received aripiprazole in the non-Japanese Phase 2/3 studies and, of these, 926 were patients with schizophrenia or schizoaffective disorder who received aripiprazole in short-term, placebo-controlled studies.

In addition, as of 10-31-01, 9 Phase 1 studies and 10 Phase 2/3 studies in schizophrenia have been conducted with aripiprazole in Japan. A total of 769 patients received aripiprazole in the Japanese Phase 2/3 trials. Japanese

studies are considered separately for reasons described in section IV.A. below.

B. Efficacy

The sponsor conducted five short-term, multicenter, randomized, double-blind, placebo-controlled trials in hospitalized patients to demonstrate efficacy in schizophrenia. The results of these studies are summarized below.[1]

Study 93202 was a 4-week trial in patients with DSM-III-R schizophrenia in acute relapse. Altogether, 103 patients were randomized to aripiprazole, haloperidol, or placebo. The active drugs were titrated to target doses of aripiprazole 30 mg/day or haloperidol 20 mg/day within the first 2 weeks of dosing. There were two primary efficacy variables: change from baseline in the BPRS total score and the percentage of patients with at least one point improvement on the CGI-severity scale. Aripiprazole demonstrated borderline statistical superiority on the latter variable only. Haloperidol was superior on both variables. This was a negative study for aripiprazole.

Study 94202 was a 4-week study in patients with DSM-IV schizophrenia in acute relapse. This study randomized 307 patients to one of three fixed doses of aripiprazole (2, 10, or 30 mg/day), haloperidol 10 mg/day, or placebo. One site was excluded from the efficacy analysis because of Agency disqualification of the investigator (Dr. Borison). All target doses were attained by day 3. There were two primary efficacy variables: change from baseline in the BPRS core score (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content items) and CGI rating of improvement at last visit. Aripiprazole 30mg was statistically superior to placebo only on the latter variable; the 2mg and 10mg doses showed no superiority. Haloperidol was superior only on the former variable. This was a failed study since neither aripiprazole nor the active comparator, haloperidol, demonstrated efficacy.

Study 97201 was a 4-week study in patients with DSM-IV schizophrenia or schizoaffective disorder. This trial randomized a total of 414 patients to fixed doses of

[1] The LOCF dataset was considered to be primary.

aripiprazole (15 or 30 mg/day), haloperidol 10 mg/day, or placebo. All study medication was given as a full fixed dose from the first day of treatment. There were three primary efficacy variables: changes from baseline in the PANSS total score, the PANSS positive subscale, and the CGI-severity score. After multiple comparison adjustment, both doses of aripiprazole were found to be statistically superior to placebo. There appeared to be no therapeutic advantage of the 30mg dose over the 15mg dose. The therapeutic response was similar for both the schizophrenia and schizoaffective subsets of the study population.

Study 97202 was a 4-week study in patients with DSM-IV schizophrenia or schizoaffective disorder. This trial randomized a total of 404 patients to fixed doses of aripiprazole (20 or 30 mg/day), risperidone 6 mg/day, or placebo. All study medication was given as a full fixed dose from the first day of treatment. There were three primary efficacy variables: changes from baseline in the PANSS total score, the PANSS positive subscale, and the CGI-severity score. After multiple comparison adjustment, both doses of aripiprazole were found to be statistically superior to placebo. There appeared to be no therapeutic advantage of the 30mg dose over the 15mg dose. The therapeutic response was similar for both the schizophrenia and schizoaffective subsets of the study population.

Study 138001 was a 6-week trial in patients with DSM-IV schizophrenia in acute relapse. A total of 420 patients were randomized to one of three fixed doses of aripiprazole (10, 15, or 20 mg/day) or placebo. Aripiprazole was given as a full fixed dose from the first day of treatment. There was one primary efficacy variable: mean change from baseline in the PANSS total score. A protocol amendment provided for two key secondary variables: mean changes from baseline in the PANSS-derived BPRS Core Score and the PANSS Negative Subscale score. All three aripiprazole doses were statistically superior to placebo on the primary variable and both key secondary variables. There was no apparent advantage of the 15 and 20mg doses over the 10mg dose.

In sum, three of the five short-term studies demonstrated the efficacy of aripiprazole over a dose range 10 to 30 mg/day. Of the two remaining studies, one was negative and one failed.

C. Safety

The primary aripiprazole safety database consisted of the pool of all non-Japanese Phase 2/3 studies. As of the cut-off date for the 120-Day Safety Update (11-30-01), 4710 patients had received aripiprazole in this pool of studies. This represents 2656.3 patient-years of exposure. Among these 4710 patients, 3561 participated in schizophrenia trials, 645 patients in bipolar mania studies, and 504 in dementia trials.

Other sources of safety data included Japanese Phase 2/3 studies, in which 769 patients received aripiprazole as of 10-31-01, and all Phase 1 studies. The sponsor also conducted a literature search to identify any other important safety findings.

Aripiprazole has not yet been marketed in any foreign country.

The major safety findings from the NDA safety review are summarized below.

In short-term, placebo-controlled schizophrenia trials, no adverse events met the commonly used criteria for common, drug-related events (≥5% incidence for drug and at least twice the placebo incidence). Somnolence did appear to be dose-related, occurring in 15.3% of patients treated with aripiprazole 30 mg/day. The incidence of extrapyramidal symptoms with aripiprazole approximated that with placebo except for akathisia (10.0% for aripiprazole vs. 6.8% for placebo).

The occurrence of orthostatic hypotension was not much higher than for placebo (14.0% vs. 11.9%).

At doses to 30 mg/day, there was no evidence of QT_c interval prolongation. However, in a special study that explored doses to 90 mg/day, there was substantial prolongation of QT_c at 75 and 90 mg/day (27 and 24 msec median changes from baseline to maximum value when QT was corrected by $QT_c = QT/RR^{0.37}$).

In a 26-week study designed to compare weight gain between aripiprazole and olanzapine, aripiprazole was associated with significant weight gain in 13% of patients compared to 33% of olanzapine-treated patients.

Special safety analyses did not suggest that aripiprazole treatment was associated with disturbance of glucose or lipid metabolism or elevated prolactin levels.

A finding of gallsand and gallstones in preclinical studies with monkeys prompted a concern that aripiprazole may be associated with gallbladder disease in humans. Another special safety analysis of Phase 2/3 data showed that the risk of gallbladder disease in patients who received aripiprazole was not higher than expected.

There were three safety findings among elderly patients with dementia who received aripiprazole which deserve special attention: mortality, pneumonia, and somnolence. Although this is not the target population for this NDA, aripiprazole is likely to be used off-label if approved and it would be prudent to advise prescribers of these findings, which are summarized in more detail in section VII.E of this review.

D. Dosing

The three positive efficacy trials utilized four fixed daily doses of aripiprazole: 10mg, 15mg, 20mg, and 30mg. Only one of these trials used a 10mg dose, study 138001. In this study, 10mg was efficacious. Thus, there is less evidence supporting the efficacy of the 10mg dose compared to each of the three higher doses, for which efficacy was shown in two studies.

In each of these three studies, there was no clear advantage of the higher dose(s) over the low dose.

In these studies, aripiprazole was administered as a full fixed dose once daily from the first day of treatment. In studies 97201 and 97202, aripiprazole was taken in the morning; in study 138001, aripiprazole was taken at about the same time each day but the time of day was not specified.

Steady-state blood levels are achieved within 14 days.

Based on the above considerations, it seems reasonable to recommend an adult starting dose of 15mg given once daily. If needed to achieve an acceptable therapeutic response,

the dose could be increased in increments of 5-10 mg/day at intervals of at least 2 weeks to a maximum of 30 mg/day.

Study 98215 examined three regimens for switching patients on other antipsychotics to aripiprazole (see section VII.B.9.d):

1) immediate initiation of 30 mg/day oral aripiprazole with simultaneous immediate discontinuation of the current antipsychotic (N=104),
2) immediate initiation of 30 mg/day oral aripiprazole while tapering off the current antipsychotic (over a 2-week period) (N=104), or
3) titrating up initiation of oral aripiprazole over a 2-week period (from 10 mg/day to 30 mg/day) while tapering off the current antipsychotic monotherapy over the same 2-week period, then maintaining 30 mg/day oral aripiprazole dosing (N=103).

This study showed that the overall efficacy, safety, and tolerability profiles were generally similar across the three treatment switching strategies.

E. Special Populations

The safety and efficacy of aripiprazole in pediatric patients have not been established.

Pharmacokinetic studies have demonstrated no major differences in the pharmacokinetics of aripiprazole based on age, gender, race, smoking status, hepatic or renal impairment, or CYP2D6 metabolizer status.[2]

[2] This information is based on the Application Summary. These studies are currently pending review by the FDA biopharmaceutics reviewer, Dr. Hong Zhao.

CLINICAL REVIEW

I. Introduction and Background

A. Role in the Treatment Armamentarium

Aripiprazole is an atypical antipsychotic developed for the treatment of psychosis in patients with schizophrenia. It differs from currently marketed atypical antipsychotics in that it is a partial agonist at dopamine D_2 receptors, i.e., it acts as an agonist in an animal model of dopaminergic hypoactivity and as an antagonist in animal models of dopaminergic hyperactivity. Thus, it belongs to a new class of antipsychotics called dopamine system stabilizers (or DSS's). The exact molecular mechanism for this partial agonism remains obscure. It is hypothesized that this action allows sufficient dopamine activity in the nigrostriatal pathways to prevent motor side effects while reducing dopamine sufficiently in mesolimbic pathways to produce antipsychotic effects.[3]

Additionally, aripiprazole possesses 5-HT_{1A} partial agonist activity and 5-$HT_{2A/2C}$ antagonist activity, which are thought to play some role in producing antipsychotic effects.

B. Safety Findings with Related Compounds

Aripiprazole is most closely related pharmacologically to the atypical antipsychotics, which have been associated with different safety issues to varying degrees. Atypical agents are listed in **Table I-1** along with the important safety concerns associated with each.

[3] Stahl SM. Dopamine System Stabilizers, Aripiprazole, and the Next Generation of Antipsychotics, Part 1. J Clin Psychiatry 2001;62:841-2.

TABLE I-1 MAJOR SAFETY CONCERNS WITH OTHER ATYPICAL ANTIPSYCHOTICS	
Clozapine	Agranulocytosis Seizures Myocarditis Orthostatic hypotension Hyperglycemia Weight gain
Risperidone	Prolactin elevation Orthostatic hypotension Weight gain
Olanzapine	Orthostatic hypotension Weight gain Hyperglycemia
Quetiapine	Orthostatic hypotension Weight gain ? Cataracts
Ziprasidone	QT interval prolongation
Sertindole (not marketed)	QT interval prolongation Sudden death

C. Administrative History

OPC-14597 (later named aripiprazole) was discovered by Otsuka Pharmaceutical Company in 1988 and was first administered to humans in 1990 in Japan. An IND application was submitted to the Agency on 6-10-93 to initiate studies in the U.S.

On 7-6-93, there was an internal meeting of the review team and, based on that discussion, Otsuka was informed that they could proceed with investigations under

Following completion of several studies under this IND, representatives of Otsuka met with the FDA review team on 2-19-97 for an End-of-Phase 2 meeting. Important clinical issues discussed at this meeting included the following:

- safety exposure should include 400-600 patients exposed for 6 months or longer.
- an evaluation of time to therapeutic effect would have to entail frequent measurements, examination of the distribution of times to onset, and a consensus on how to

define response, which could not be based on a total score of a number of diverse items.

- translation of Japanese CRF's would not be necessary but we would need English-based tabulated safety data and narrative summaries for serious adverse events.
- all studies capable of demonstrating the efficacy of aripiprazole would have to be submitted regardless of outcome.
- comparative safety claims would have to be based on either: 1) a comparison of the highest aripiprazole dose with the lowest dose of comparator after showing that the dose-response curve for aripiprazole was not inverted U-shaped OR 2) a trial with several fixed dose arms for each drug (e.g., a seven-arm study with 3 dose groups for each drug plus placebo).

A co-development agreement was signed between Otsuka and Bristol-Myers Squibb (BMS) in September 1999. As a result, it was decided to expand the development plan for aripiprazole to pursue additional indications beyond schizophrenia (see below).

Another meeting was held between the Division review team and representatives of Otsuka and Bristol-Myers Squibb on 2-2-00 to discuss the co-sponsors' expanded development program for aripiprazole. Specifically, the co-sponsors had elected to seek approval for the following indications: schizophrenia, [redacted]

- the program for [redacted] as described, was adequate in design to support approval.
- [redacted]
- the Division would require expert input before providing guidance on the indications of psychosis associated with [redacted] (This would be the subject of a 3-9-00 advisory committee meeting.)
- the indication of [redacted] is problematic since it is unclear whether this represents a psychiatric disease and outcome measures are ill-defined.

• the safety profile and proposed indications for aripiprazole do not qualify for priority review status.

A pre-NDA meeting was held with the sponsors on 7-2-01 to review plans for an NDA to be submitted in October 2001. This NDA would seek approval for the treatment of [redacted] schizophrenia and [redacted]. Important clinical issues discussed at this meeting included:

• data from fixed dose studies in schizophrenia suggested efficacy over a wide dose range (2-30 mg/day). After discussion of the data, it seemed most reasonable to recommend a target dose of 15 mg/day in labeling, while adding that doses to 30 mg/day are safe and effective but have not been shown to demonstrate an advantage over lower doses.

• probable labeling of the finding of gallsand and gallstones in monkeys given lack of an apparent signal in humans.

• potential problems with comparative safety claims in labeling.

• a precedent for describing effects on positive and negative symptoms of schizophrenia in labeling under Clinical Trials (but not Indications) even though such measures may not have been prespecified as primary variables.

• the schizophrenia studies would not support a second indication of [redacted] despite the fact that some of the patients in two of the trials were diagnosed with [redacted] (This fact might be mentioned under Clinical Trials, however.)

• pediatric PK data would not be incorporated into labeling until after approval in this population.

The two key studies in [redacted] were completed in July 2001. Subsequent to completion, it was discovered that one of these studies (138007) failed to demonstrate efficacy on the primary efficacy measure. Thus, the sponsor informed us on 9-24-01 that the upcoming NDA submission would not include the [redacted] but only the schizophrenia indication.

This NDA was submitted and received on 10-31-01. It was decided to file the NDA at a meeting on 12-18-01.

A 120-Day Safety Update to the NDA was submitted on 2-27-02.

D. Proposed Instructions for Use

Aripiprazole is proposed for use in the treatment of schizophrenia in adults.

The recommended starting dose is 15 mg/day administered once daily without regard to meals. Daily doses of 20 and 30 mg were also safe and efficacious in clinical trials but there appeared to be no therapeutic advantage, on average, of these doses over 15 mg/day. Safety and efficacy in pediatric patients has not been established.

Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment.

The efficacy of aripiprazole has not been evaluated in adequate, well-controlled studies beyond 6 weeks in duration. There is no body of evidence to suggest how long a patient should be treated with aripiprazole. Patients should be maintained on the dose to which they respond and should be periodically reassessed to determine the need for maintenance treatment.

Patients may be switched from other antipsychotics to aripiprazole by any of the following three methods: 1) immediate discontinuation of the current medication and immediate initiation of aripiprazole, 2) immediate initiation of aripiprazole while tapering the current medication over a two-week period, or 3) upward titration of aripiprazole over a two-week period while simultaneously tapering the current medication over the same two-week period.

E. Foreign Marketing

Aripiprazole has not been marketed in any foreign country.

II. Clinically Relevant Findings from Other Disciplines and from Consultants

A. Statistical Review and Evaluation

The Statistical Review and Evaluation is complete and is pending supervisory sign-off as of the date of this review.

Verbal consultation with the statistical reviewer, Dr. Yeh-Fong Chen, indicates agreement that studies 97201, 97202, and 138001 provide sufficient evidence of the efficacy of aripiprazole in the treatment of schizophrenia.

B. Biopharmaceutics

The biopharmaceutics review has not been completed as of the date of this review.

C. Pharmacology/Toxicology

The pharmacology/toxicology review has not been completed as of the date of this review.

D. Chemistry

The chemistry review was almost complete as of the date of this review. Verbal consultation with the chemistry reviewer, Dr. Sherita McLamore, indicated no major deficiencies or problems from a CMC standpoint.

E. DMETS Assessment of Tradename

The Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety evaluated the sponsor's initially proposed tradename for aripiprazole (Abilitat). They found it to be unacceptable because it could be mistaken with other marketed drugs (e.g., Adalat). In a 10-18-01 letter from the Division, the sponsor was notified of this finding and requested to propose an alternative tradename. Subsequently, the sponsor proposed the name ——— in a 4-24-02 submission. This proposal is currently under evaluation by DMETS.

F. DSI Clinical Site Inspections

The Division of Scientific Investigations (DSI) inspected a total of four clinical sites from studies 97201, 97202, and 138001. All inspections were classified as either NAI (no deviations from regulations) or VAI (minor deviations from regulations) according to a 5-28-02 report from DSI. All data were considered acceptable.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacodynamics

Aripiprazole is a partial agonist at dopamine D_2 receptors, that is, it acts as an agonist in an animal model of dopaminergic hypoactivity and as an antagonist in animal models of dopaminergic hyperactivity. It exhibits high to moderate affinity for dopamine D_3, histamine H_1, and alpha-1 adrenergic receptors as well as for multiple serotonin receptor subtypes (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7). It has low affinity for muscarinic receptors.

In a PET study (Study 94201) of aripiprazole binding to dopamine D_2 receptors in the brains of healthy male volunteers, it was demonstrated that aripiprazole binds to human D_2 receptors in a dose-related fashion up to 10 mg/day at steady-state. At 10 mg/day, binding was approximately 85%. At the next highest dose studied, 30 mg/day, receptor occupancy was in the range 80-95%.

B. Pharmacokinetics[4]

1. ADME

The absolute oral bioavailability of aripiprazole was 87% in healthy subjects. This indicates nearly complete absorption and little first-pass metabolism. Steady-state Cmax and AUC increase linearly and proportionally over the dose range 5-30 mg/day in healthy volunteers. In schizophrenic patients, aripiprazole pharmacokinetics appear to be linear at doses in the range 30-90 mg/day. Cmax occurs at 3-5 hours post-dose at steady-state. Administration of a high-fat meal had no effect on the pharmacokinetics of aripiprazole or its active metabolite. Activated charcoal decreased the concentrations of aripiprazole and its active metabolite by 54% each, suggesting that charcoal may be an effective intervention for overdose.

The steady-state volume of distribution after intravenous administration was 4.94 L/kg, suggesting extensive tissue distribution. Plasma protein binding was greater than 99%.

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[4] The data presented in this section are from section 7 (Clinical Pharmacology) of the Application Summary.

Aripiprazole is metabolized by three pathways: dehydrogenation, N-dealkylation, and hydroxylation. Dehydrogenation produces the active metabolite, OPC-14857, which is then further metabolized by N-dealkylation and hydroxylation. OPC-14857 has comparable binding affinity to D_2 and D_3 receptors and the AUC ratio of this metabolite to parent drug is 0.39. Thus, it likely contributes to the pharmacological activity of aripiprazole. The AUC ratios for all other metabolites to parent drug were very low (<0.002), making it unlikely that they contribute to the pharmacological effect of the drug.

The P450 isozymes responsible for aripiprazole metabolism are CYP3A4 (catalyzes all three pathways) and CYP2D6 (catalyzes dehydrogenation and hydroxylation). The isozymes CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2E1 do not appear to be involved in aripiprazole metabolism.

Aripiprazole is eliminated primarily via metabolism. Its metabolites are eliminated by both the renal and biliary routes in humans. The mean elimination half-life of aripiprazole is 75 hours (range 31-146 hours). With daily administration, steady-state concentrations of aripiprazole and its active metabolite OPC-14857 are achieved after approximately two weeks. Consistent with the long half-life, the steady-state accumulation index is 5.

2. Pharmacokinetics in Special Populations

Phase 1 trials and the results of a population pharmacokinetic analysis of Phase 2 and Phase 3 studies in adults showed no major differences in the pharmacokinetics of aripiprazole based on age, gender, race, or smoking status.

After administration of a single 15mg dose, there were no important differences in aripiprazole pharmacokinetics between healthy subjects and subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C).

Also, following a single 15mg dose in healthy subjects and in subjects with severe renal impairment (creatinine clearance <30mL/min), there were no differences in the pharmacokinetics of aripiprazole and OPC-14857 between the two groups.

After a single 10mg dose of aripiprazole in CYP2D6 poor metabolizers (PM) and extensive metabolizers (EM), plasma concentrations of the active metabolite OPC-14857 were decreased 37% in the PM vs. the EM subjects with an increase in parent drug concentrations that was complementary to the decrease in the metabolite. Since aripiprazole and OPC-14857 have comparable D_2 receptor affinities and similar protein binding, CYP2D6 genotype or phenotype is not expected to affect the safety or efficacy of aripiprazole.

3. Assessment of Drug-Drug Interactions

a. Effects of Other Drugs on Aripiprazole

Ketoconazole, a potent CYP3A4 inhibitor, decreased the clearance of a single 15mg dose of aripiprazole by 38% and increased plasma levels of OPC-14857 by 77%.

Quinidine, a potent CYP2D6 inhibitor, decreased the clearance of a single 10mg dose of aripiprazole by about 50% and decreased plasma levels of OPC-14857 by 34%.

Co-administration of carbamazepine 200mg BID with aripiprazole 30 mg/day in patients with schizophrenia or schizoaffective disorder increased the clearance of aripiprazole.

Co-administration of lithium (1200-1800 mg/day) for 21 days with aripiprazole 30 mg/day in patients with schizophrenia or schizoaffective disorder had no clinically significant effect on the pharmacokinetics of aripiprazole or OPC-14857. No effect of aripiprazole on lithium pharmacokinetics is expected.

Administration of valproate (350-1500 mg/day) for 21 days with aripiprazole 30 mg/day to patients with schizophrenia or schizoaffective disorder had no clinically significant effect on the pharmacokinetics of aripiprazole.

There was no evidence of EEG findings suggestive of epileptiform activity, encephalopathy, or other pathological EEG rhythms with co-administration of lithium, valproate, or carbamazepine with aripiprazole.

b. Effects of Aripiprazole on Other Drugs

Based on in vitro data, aripiprazole is not expected to significantly inhibit the in vivo activity of CYP1A2, 2C9, 2C19, 2D6, and 3A4 at clinically relevant concentrations.

Various studies examined the effect of aripiprazole at doses of 10-30 mg/day given for 14 days on substrates for CYP2D6 (dextromethorphan O-dealkylation), CYP3A4 (dextromethorphan N-demethylation), CYP2C9 (R and S warfarin), and CYP2C19 (omeprazole). No effects were observed in these studies.

IV. Description of Clinical Data Sources

Note: This review includes the clinical data contained in the 120-Day Safety Update to this NDA, which was submitted on 2-27-02.

A. Primary Development Program

Trials in the development program for aripiprazole were conducted in a number of locations worldwide, to include North America, Europe, and Japan. The Japanese studies were considered separately from trials conducted elsewhere for several reasons: 1) they were conducted on a narrow ethnic population, which limits generalizability; 2) there were differences in study drug tablet strength and formulation between the Japanese studies and other aripiprazole studies, 3) a different adverse event dictionary was used to code adverse events in the Japanese studies (J-ART versus modified COSTART in the other aripiprazole trials). Additionally, there was a difference in the cut-off dates for clinical safety data between the Japanese and non-Japanese study pools. Thus, for purposes of this review, the Japanese studies will constitute a separate study pool for safety data analysis.

A listing of all studies in the sponsor's development program is presented in **Appendix IV-1**.

1. Non-Japanese Studies

a. Patient Enumeration by Study Type

The cut-off date for safety data from the non-Japanese studies was 11-30-01.[5] At that timepoint, a total of 5634 subjects and patients had been exposed to aripiprazole tablets in non-Japanese studies.

Of these, 924 participated in 35 Phase 1 studies. These studies involved both healthy volunteers and patients with either schizophrenia or schizoaffective disorder.

Another 4710 patients participated in Phase 2/3 studies. The Phase 2/3 studies were of various designs in different indications: short-term placebo-controlled trials in schizophrenia, longer-term controlled studies in schizophrenia; short-term placebo-controlled trials in bipolar mania; a placebo-controlled study in Alzheimer's dementia; ongoing studies that remained blinded as of 11-30-01, and open-label studies or study phases that were ongoing as of 11-30-01; and completed special studies (2 high-dose pilot studies, 1 open-label treatment switching study, and 1 open-label pilot study in dementia).

Among the 4710 patients in Phase 2/3 trials, 3561 participated in schizophrenia trials, 645 patients in bipolar mania studies, and 504 in dementia trials.

A total of 926 patients received aripiprazole in 5 short-term, placebo-controlled schizophrenia studies within the non-Japanese Phase 2/3 study pool.

Subjects and patients in all non-Japanese trials are enumerated by study type in **Appendix IV-2**.

b. Demographic Characteristics

Demographic characteristics for aripiprazole-treated patients in the non-Japanese Phase 2/3 study pool are presented in **Appendix IV-3**. There were some noteworthy demographic differences between the patient groups studied for these indications:

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[5] Except for the Phase 1 study 138065, for which the cut-off date was 1-15-02.

- As expected, patients in dementia studies were considerably older than patients in the schizophrenia and bipolar studies (mean ages of 81.7, 38.7, and 40.1 years, respectively). Most dementia study patients (97%) were at least 65 years old.
- 75% of dementia patients and 56% of bipolar manic patients were female; only 33% of schizophrenia patients were female.
- 89% of dementia patients were white whereas only 74% of bipolar mania and 69% of schizophrenia patients were white.

Demographic features of control group (placebo, risperidone, olanzapine, and haloperidol) patients are presented in **Appendix IV-4**. In the placebo group, 116 patients were age 65 or older; in the other groups, there were very few elderly patients.

Demographic characteristics for patients in the 5 short-term placebo-controlled studies in schizophrenia are presented in **Appendix IV-5**. Aripiprazole patients were predominantly men (75%). The majority (85%) of the patients were between 18 and 50 years of age with the mean age ranging from 38.6 to 39.1 years, and approximately 1% of the patients were 65 years of age or older. Racially, 55% were white and 31% were black. Treatment groups were comparable with regard to age, gender, and race.

Two Phase III short-term placebo-controlled trials (31-97-201 and 31-97-202) included patients with a diagnosis of schizoaffective disorder; this population constituted approximately 30% of the overall patient population in each of these studies (132 of 414 randomized patients in 31-97-201 and 115 of 404 randomized patients in 31-97-202).

c. Extent of Exposure

Patient exposure by mean dose and duration of treatment with aripiprazole is summarized in **Appendix IV-6** for the non-Japanese Phase 2/3 study pool. A total of 1513 patients in this study pool received aripiprazole for 6 months or longer, 902 patients received aripiprazole for at least one year (≥360 days), and 421 patients continued aripiprazole treatment for at least 2 years (≥720 days). However, almost all of this longer-term use was in patients with schizophrenia; only 20 dementia patients and no

bipolar mania patients received aripiprazole for at least a year.

Overall, over half of these patients (N=2544) received a mean dose of aripiprazole in the range >25 and ≤32.5 mg/day.

For the non-Japanese Phase 2/3 study pool, exposure in patient-years by treatment was as follows:

Treatment	N	Patient-Years
Aripiprazole	4710	2656.3
Placebo	928	85.8
Haloperidol	673	207.3
Olanzapine	393	126.9
Risperidone	99	6.0

The 5 short-term placebo-controlled studies in schizophrenia were 4 or 6 weeks in duration. Three included a haloperidol control and one included a risperidone control. Patient exposure to aripiprazole in these short-term trials is summarized in **Appendix IV-7**. In the fixed dose studies, 892 patients received doses that ranged from 2-30 mg/day. In one flexible dose trial, 34 patients were dosed in the range 5-30 mg/day. At least 4 weeks of aripiprazole treatment was received by 181 patients in these trials.

In this short-term study pool, patient-years of exposure by treatment was as follows:

Treatment	N	Patient-Years
Aripiprazole	926	59.52
Placebo	413	24.19
Haloperidol	200	11.44
Risperidone	99	5.96

2. Japanese Studies

The cut-off date for clinical safety data from the Japanese studies was 10-31-01. As of that date, 132 subjects received aripiprazole in 9 Phase 1 trials and 769 patients received aripiprazole in 10 Phase 2/3 studies.

A much smaller number of patients received other study drugs in these studies: 131 received haloperidol, 121 received mosapramine, and only 8 received placebo.

Information regarding demographic characteristics and extent of aripiprazole exposure was not provided for these 19 trials.

B. Other Sources of Clinical Data

1. Non-IND Studies

No non-IND studies are reported.

2. Published Literature

The methodology for the literature search, which was conducted by both Otsuka and Bristol-Myers Squibb (BMS), was as follows:

Otsuka performed searches in Japan at Otsuka's Office of Scientific Information using these search terms: ARIPIPRAZOLE, OPC-14597, OPC141597, OPC-31, OPC31, ABILITAT, 156680-99-8 (CAS Registry #). Databases and dates searched for online bibliographic references available as of January 7, 2002 were: DERWENT DRUG FILE (1983-January 7, 2002), EMBASE/EMBASE Alert (1974 to January 7, 2002), MEDLINE (1966 to January 7, 2002), BIOSIS (1969 to January 7, 2002), CHEMICAL ABSTRACTS (1967 to January 7, 2002).

Bristol-Myers Squibb performed searches in the USA using these search terms: ARIPIPRAZOLE, OPC-14597, OPC14597, OPC-31, OPC31, 129722-12-9 (CAS Registry #), 156680-99-8 (CAS Registry #). The databases and dates searched for online bibliographic references available as of 2 January 2002 were: ADIS R&D Insight, MEDLINE (1958 TO January 2, 2002), CAPLUS/Chemical Abstracts (1907 TO January 2, 2002), EMBASE/EMBASE ALERTS (1974 TO January 2, 2002), BIOSIS/Biological abstracts (1969 TO January 2, 2002), SCISEARCH/Science Citation Index (1974 TO January 2, 2002), DRUGU/Derwent Drug File (1983 TO January 2, 2002), LIFESCI/Life Sciences Collection (1978 TO January 2, 2002), TOXCENTER (1947 TO January 2, 2002), IPA/International Pharmaceutical Abstracts (1970 to January 2, 2002), JICSTE/Japanese Information Center (1985 TO January 2, 2002).

In addition to these sources, abstracts and posters referring to aripiprazole presented at scientific meetings were included in the bibliography. A total of 161

literature references were submitted, including one article that has been submitted for publication.

Three physicians warranted that they had reviewed these articles in detail with respect to safety data relevant to aripiprazole and determined that this literature contains no findings that would adversely affect conclusions about safety contained in NDA 21-436.[6]

In addition, I reviewed the references by title only and found no titles suggesting significant adverse events associated with aripiprazole administration.

3. Postmarketing Experience

Aripiprazole has not been marketed.

V. Clinical Review Methods

A. Clinical Review Staff and Responsibilities

The clinical review of this NDA was a joint effort between two reviewers: Robert Harris, M.D., Ph.D., of the Neurology Group, and Gregory Dubitsky, M.D., of the Psychiatry Group.

Dr. Harris was responsible for reviewing the clinical safety data and writing sections IV and VII of this document. In addition, he reviewed and prepared comments on the clinical safety sections of the sponsor's proposed labeling (i.e., Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, and Dosage and Administration).

The remainder of the clinical review and this document was the responsibility of Dr. Dubitsky. Additionally, Dr. Dubitsky served as a mentor to Dr. Harris in carrying out his responsibilities for this NDA.

B. Items Utilized in the Review

The Division File for ——— was consulted in preparing this document.

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[6] These physicians were: Manabu Yamamura, M.D., Ph.D., and Joy Parris, M.D., both of Otsuka; and Allan Safferman, M.D., of Bristol-Myers Squibb.

Items from the NDA that were examined during the course of this review are depicted in **Appendix V-1**. This review was conducted primarily from documents located in the CDER Electronic Document Room (EDR) under NDA 21-436.

C. Specific Methods Used to Evaluate Data Quality

The Division of Scientific Investigations (DSI) inspected a total of 4 clinical sites from 3 of the key efficacy studies in this NDA. Results are described in section II.F of this review.

Dr. Harris conducted an audit of safety data by comparing Case Report Forms (CRF's), Narrative Summaries, and adverse event line listings for consistency of adverse event information across these three documents in a random sample of 39 patients. Also, Dr. Dubitsky audited the CRF's of 10 other randomly selected patients who dropped out for reasons other than adverse experiences to determine if any of these patients actually discontinued treatment for an adverse event. Results are described in section VII.D of this review.

D. Adherence to Accepted Ethical Standards

The sponsor indicates that all clinical studies followed Good Clinical Practices (GCP) guidelines.[7] Also, Otsuka certifies that, to the best of its knowledge, information, and belief, it had not and would not use the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

E. Evaluation of Financial Disclosure

For purposes of this NDA, there are three trials that are considered "covered clinical studies" in accordance with 21 CFR 54.2(e): 97201, 97202, and 138001.

Among the clinical investigators in these studies, two were identified by Otsuka and BMS as having financial arrangements that require disclosure:

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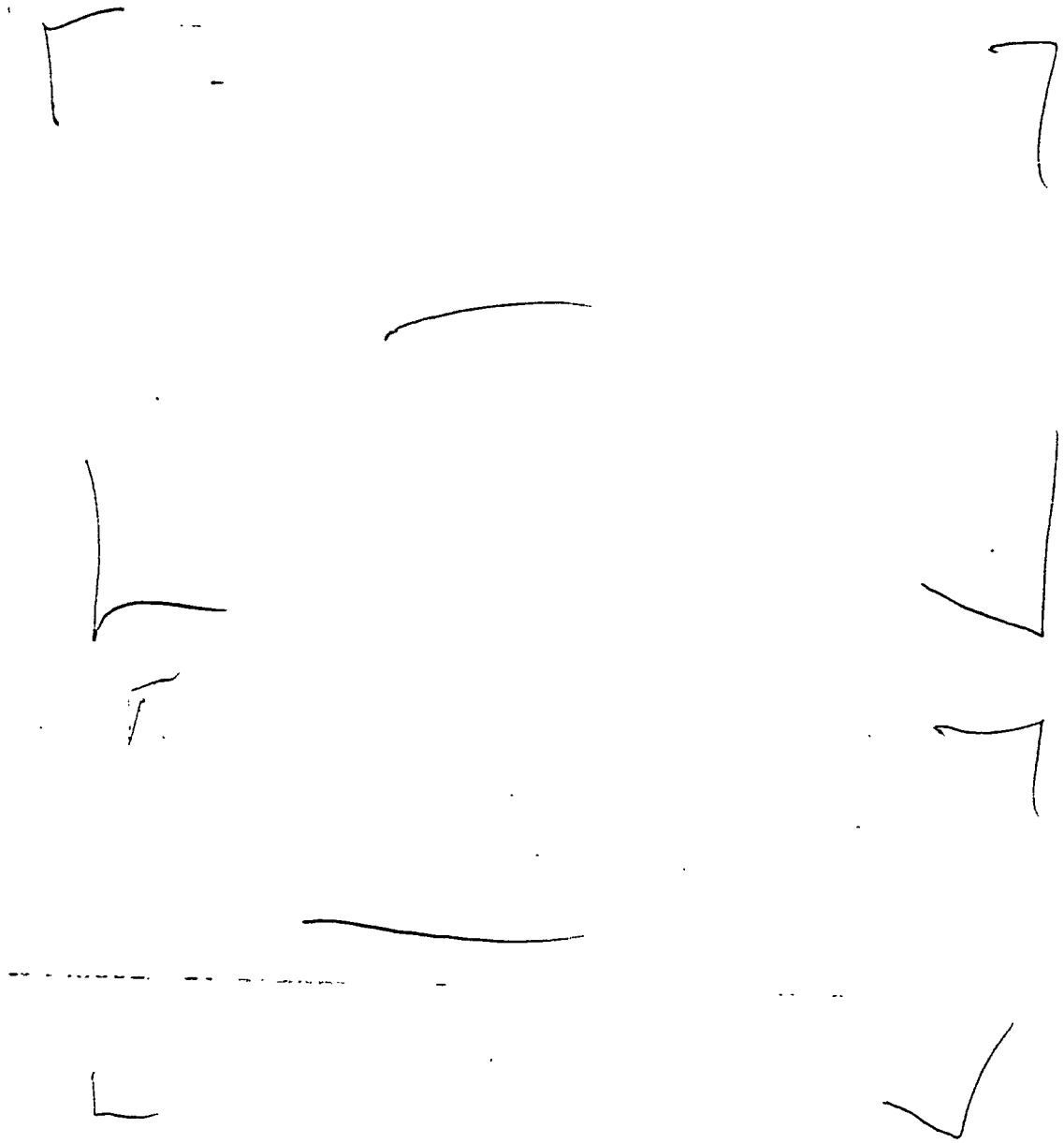
[7] See page 13 of the NDA Application Summary.



VI. Integrated Review of Efficacy

A. Overview of Studies Pertinent to Efficacy

The aripiprazole acute efficacy program consists of two Phase 2 trials (93202 and 94202) and three Phase 3 trials (97201, 97202, and 138001). The Phase 2 studies are considered supportive and the Phase 3 studies are considered pivotal by the sponsor.

All five trials were multicenter, randomized, double-blind, and placebo-controlled. Duration and dosing information for these studies is summarized in **Table VI-1** below.

TABLE VI-1:
ADEQUATE AND WELL-CONTROLLED EFFICACY TRIALS

Trial	Duration (weeks)	Dosing Regimen	Treatment:Dose(mg/day)
93202	4	Ascending	Aripiprazole: 30 Haloperidol: 20
94202	4	Fixed	Aripiprazole: 2/10/30 Haloperidol: 10
97201	4	Fixed	Aripiprazole: 15/30 Haloperidol: 10
97202	4	Fixed	Aripiprazole: 20/30 Risperidone: 6
138001	6	Fixed	Aripiprazole: 10/15/20

All were conducted in hospitalized patients. Four of the five were performed in the U.S.; the fifth trial (138001) was conducted in the U.S. and Canada.

Four longer-term trials were submitted in the original NDA submission (98217, 98304, 97301, and 98213). None were placebo-controlled or intended to show superiority over an active control agent. Thus, these studies are not capable of providing convincing evidence of efficacy and they will not be discussed further in this review.

B. Adequate and Well-Controlled Efficacy Trials

1. Study 93202

Investigators/Sites

This study was conducted at 10 centers. Investigators are listed in **Appendix VI-1**. There were two additional centers (01 and 03) that did not enroll any patients.

Objectives

The primary objective was to evaluate the efficacy and tolerability of OPC-14597 (a.k.a. aripiprazole) in the treatment of acute schizophrenia.

Secondary objectives were:

- evaluate the effective dose range.
- evaluate relative effect on positive versus negative symptoms.
- assess the pharmacokinetics of OPC-14597 in schizophrenic patients.
- compare the effects of OPC-14597 and haloperidol on serum prolactin in schizophrenic patients.

Patient Sample

Patients were male or female inpatients, between 18 and 65 years old, and had a DSM-III-R diagnosis of schizophrenia with an acute relapse. They must have had a BPRS total score of at least 30 with a score of at least 4 (moderately severe) on two of the four positive symptom items (i.e., conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content). Also, there must have been evidence of a previous response to antipsychotic medication. Patients with more than moderate motor symptoms, as measured by the Simpson-Angus Scale, Abnormal Involuntary Movements Scale, and Barnes Akathisia Scale, were excluded. Other exclusion criteria included:

- primary diagnosis other than schizophrenia.
- substance dependence within the past 2 months.
- cardiac patients for whom hypotension could be hazardous.
- acute or unstable medical condition.

Design

This was a 4-week, randomized, double-blind, placebo-controlled, parallel group, inpatient study. Patients underwent a 3-7 day placebo washout. Eligible patients were then randomized to either OPC-14597, placebo, or haloperidol.

This was the first placebo-controlled study with OPC-14597 in schizophrenia in the U.S. The protocol dosing schedule was amended several times based on information from Phase 1 PK studies. The final dosing schedule is depicted below.

TABLE VI-2: FINAL DOSING SCHEDULE STUDY 93202		
Study Days	**OPC-14597 (dose in mg/day)**	**Haloperidol (dose in mg/day)**
1,2	5	5
3,4	10	10
5,6	15	15
7-12	20	20
13-28	30	20

All study drugs were administered once daily after breakfast.

Analysis

Primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population at week 4 (for the last observation carried forward or LOCF dataset) and at each week (for the observed cases or OC dataset). The ITT for efficacy consisted of all patients who had a baseline and a post-baseline measurement of efficacy.

By protocol, there were two primary efficacy variables:

- change from baseline in the BPRS total score and
- the proportion of patients having improved by at least one point on the CGI-Severity scale.

The protocol indicated that changes from baseline in continuous variables and categorical outcomes would be analyzed using 1) Wilcoxon's test and 2) Fisher's exact test or chi-square test, respectively. After completion of the study, the sponsor had decided to utilize 1) ANCOVA and 2) the Cochran-Mantel-Haenszel test, respectively, for the primary analyses since these were considered the industry standards at that timepoint. Results using these latter methods were presented in the study report. Nonetheless, after this discrepancy was noted by both the FDA clinical and statistical reviewers, analyses using the protocol-specified methods were requested by the Agency. The results presented below are based on the protocol-specified analyses.

Another important issue in the review of this trial was the fact that neither the protocol nor any protocol amendments provided for multiplicity adjustment given that two efficacy variables had been designated as primary. Generally, in such a case, both variables must be positive at an alpha of 0.05 for the study to be considered positive. Again, the efficacy results are discussed below in light of this adjustment.

There was one interim analysis of the primary efficacy variables conducted when 50% of the patients had completed 4 weeks of treatment. Since there was no option for early termination of the trial and no change in the conduct of the study based on the interim results, no adjustment to the nominal p-values was made.

Baseline Demographics

Baseline demographic characteristics are summarized in **Appendix VI-2**. Most of the patients in each treatment group were male. Female patients were slightly older than the male patients in the OPC-14597 and placebo groups. Most patients were Caucasian or Black.

Baseline Severity of Illness

Baseline BPRS total scores and CGI-severity scores, shown in **Appendix VI-3**, were roughly comparable among the three treatment groups.

Patient Disposition

The enumeration of patients by disposition is displayed in **Appendix VI-4**.

Overall, slightly more than half (53/103 or 51.5%) of all randomized patients completed the trial. However, there were appreciable differences in completion rates between the active drug and the placebo groups: 61.8% of OPC-14597 patients, 58.8% of haloperidol patients, and only 34.3% of placebo patients completed the study.

The most common reasons for dropout in the active drug groups were withdrawn consent and lack of response to study drug. In the placebo group, withdrawn consent, marked deterioration in clinical status, and lack of response to study drug were most common.

An enumeration of patients by the number of study days completed is displayed in **Appendix VI-5**. At least 70% of the randomized patients in each treatment group completed 15-21 days in the study.

Concomitant Medications

Treatment with concomitant psychotropic medication was prohibited with the exception of lorazepam (up to 10 mg/day) for emergent anxiety or insomnia. There were no substantial differences across the three treatment groups in terms of the percentage of patients using lorazepam or the average dose (mg) used per day during double-blind treatment (see Table 7.4.9-1 in the study report). It is notable that four patients in the OPC-14597 group, one patient in the placebo group, and one patient in the haloperidol group took concomitant haloperidol. All but one of these patients took concomitant haloperidol for only one day. The remaining patient (93202-9-100) began haloperidol treatment on the final day of study drug.

Moderate to severe extrapyramidal symptoms, akathisia, or dystonia could be treated with benztropine at a dose up to 6 mg/day. The percentage of patients administered benztropine was considerably less in the OPC-14597 and placebo groups compared to the haloperidol group during double-blind therapy (17.6%, 28.6%, and 55.9%, respectively).

Efficacy Results

At our request, the sponsor analyzed the two primary efficacy variables utilizing the protocol-specified methods at the final visit (LOCF)(OC results were not reported). Analyses of secondary variables were not provided. Results were forwarded in a 3-17-02 E-Mail to the FDA Project Manager, Steve Hardeman.

Findings based on the mean change in the BPRS total score are summarized in **Appendix VI-6**. Baseline scores were compared using ANCOVA. Week 4 changes were compared using Wilcoxon's test.

OPC-14597 was numerically superior to placebo, demonstrating a decrease of 7.2 points in the BPRS total score compared to a decrease of 2.1 points in the placebo

group. However, the intergroup difference was not statistically significant (p=0.173). Haloperidol did demonstrate superiority over placebo, with a decrease of 8.1 points (p=0.010).

Results based on the proportion of patients with at least one point of improvement on the CGI-Severity scale are summarized in **Appendix VI-7**. The proportions meeting this criteria at weeks 4 were compared using the Chi-Square test as well as the Fisher's exact test.

In the OPC-14597 group, 42.4% of the LOCF population had at least one point improvement on the CGI-Severity scale; only 20% of the placebo group met this criteria. The difference between OPC-14597 and placebo was statistically significant using the Chi-Square test (p=0.045) but not using the Fisher's exact test (p=0.066). Haloperidol was statistically superior to placebo using both tests (p=0.003 and 0.005, respectively).

Conclusions

A finding of efficacy in this trial with two primary outcome variables requires statistical superiority over placebo for each variable at an alpha level of 0.05.

OPC-14597 failed to demonstrate statistical superiority over placebo on the BPRS total score. Efficacy results based on the percentage of patients with at least one point improvement on the CGI-Severity scale were analysis-dependent. Thus, this study failed to demonstrate the efficacy of OPC-14597.

On the other hand, haloperidol demonstrated clear evidence of efficacy.

In terms of OPC-14597, study 93202 must be considered negative.

2. Study 94202

Investigators/Sites

This study was conducted at the 22 centers listed in **Appendix VI-8**. The investigator at center 003 — was disqualified due to allegations of research misconduct and conviction on criminal charges. Therefore,

efficacy data from this center were excluded from analyses discussed below. An additional center (015) did not enroll any patients.

Objectives

The primary outcome of this study was to determine an optimal dose of OPC-14597 (a.k.a. aripiprazole) for the treatment of acute schizophrenia.

Patient Sample

Amendment #2 to the original protocol provided for the enrollment of 300 patients.

At screening, patients must have been in the age range 18-65 with a primary DSM-IV diagnosis of schizophrenia, in acute relapse, and hospitalized. Also required was a BPRS total score of at least 36 and a score of at least 4 ("moderate") on any two of the following four items: hallucinatory behavior, unusual thought content, conceptual disorganization, and suspiciousness. Antipsychotic medication must not have been taken for at least 72 hours prior to randomization (generally 4 weeks for a long-acting agent).

Patients experiencing their first episode of schizophrenia or with a history of being refractory to conventional antipsychotics were excluded at screening. Also, any of the following were exclusionary at this visit: moderate to severe EPS, dyskinesia, or akathisia; substance abuse or dependence, cardiac disease for whom hypotension could be hazardous, cardiac conduction defects, an acute or unstable medical condition, pregnant or lactating females, and females not using adequate contraception.

At baseline (randomization), patients were assessed again with respect to the above BPRS criteria, antipsychotic drug use, and motor symptoms.

Design

This was a 4-week, randomized, double-blind, placebo-controlled, parallel group, dose-ranging inpatient study.

Patients underwent a 3-7 day placebo washout period. Then, eligible patients were randomized to one of three fixed

doses of OPC-14597 (2, 10, or 30 mg/day), haloperidol (10 mg/day), or placebo. The dosing schedule is depicted in **Table VI-3** below. The dose of study drug could not be modified during the trial.

TABLE VI-3:
DOSING SCHEDULE
STUDY 94202

Study Days	OPC-14597			Halop.
	2 mg/day	10 mg/day	30 mg/day	
1	1	5	15	5
2	2	10	30	5
3-28	2	10	30	10

All study medication was administered once daily after breakfast. OPC-14597 was supplied a white tablets in dose levels of 1, 5, and 15mg. Haloperidol was supplied a overencapsulated 5mg tablets in brown opaque gelatin capsules in dose levels of 5 and 10mg. Placebo was provided as tablets that matched the OPC-14597 tablets and as capsules that matched the haloperidol capsules. Patients in all treatment groups received some combination of tablets and capsules.

Analysis

Primary and secondary efficacy analyses were performed on the efficacy intent-to-treat (ITT) population, defined in the study report as consisting of all patients who had a baseline and a post-baseline measurement of efficacy regardless of whether the patient received medication or had a protocol violation.[8]

By protocol, there were two primary efficacy variables:

- the change from baseline to last visit in the BPRS core score (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content) and
- the CGI rating of improvement at last visit.

The primary efficacy analysis was ANCOVA, with terms for treatment and center and, for the BPRS variable, baseline score as covariate. Amendment #2 to the protocol was

[8] The study protocol and amendments failed to specifically define an intent-to-treat population. Hence, the definition in the study report will be used for purposes of this review.

intended specify the use of Dunnett's procedure to adjust for multiplicity based on the pairwise comparison of each of the three dose groups to placebo.[9]

Neither the protocol nor any protocol amendments provided for multiplicity adjustment given that two efficacy variables had been designated as primary. In this case, it is presumed that, at each dose level, both variables must be positive at 0.017 for superiority over placebo to be declared at that dose. The efficacy results are discussed below in light of this adjustment.

Additionally, for reasons mentioned above, the discussion below will focus on analyses which excluded data from center 003.

Baseline Demographics

Appendix VI-9 displays the demographic characteristics of the patient sample at baseline. Most patients were male. Mean ages among the five treatment groups were in the late 30's to early 40's. Most patients were white except among males in the OPC-14597 30mg group, where Blacks outnumbered Whites. Overall, there were no notable demographic differences between treatment groups.

Baseline Severity of Illness

Appendix VI-10 depicts the mean BPRS core scores and CGI-severity scores at baseline. There were no major differences between treatment groups.

Patient Disposition

Appendix VI-11 displays the disposition of study patients by treatment group. Dropout rates ranged from 33% in the OPC-14597 30mg group to 55% in the placebo group. A few patients in the OPC-14597 2mg and 10mg and haloperidol groups dropped out due to a marked deterioration in clinical status. Several patients in each group (except the OPC-14597 10mg group) dropped out due to lack of response; this was the most common reason for dropout in

[9] The actual amendment indicates that pairwise comparisons would be performed using the Dunn test with an alpha of 0.017. A 3-14-02 E-Mail from the sponsor states that this was an error and that ANCOVA, followed by Dunnett's correction, was actually intended and used for the presented analyses.

the placebo group. About an equal percentage of patients dropped out due to adverse events in the low- and high-dose OPC-14597 and haloperidol groups. Four OPC-14597 patients dropped out for "other" reasons: under-treatment due to a date error, administrative reason, unauthorized absence from the hospital, and a departure from the inpatient unit.

An enumeration of patients by the number of study days completed is displayed in **Appendix VI-12**. At least 70% of the OPC-14597 patients completed 15-21 days in the study.

Concomitant Medications

Treatment with concomitant psychotropic medication was prohibited with the exception of lorazepam (up to 10 mg/day) for emergent anxiety or insomnia. Lorazepam was, in fact, the most commonly used concomitant medication: over 80% of patients in each treatment group took lorazepam at some time during double-blind treatment. There were no large differences between groups in the percentage of patients who took lorazepam. An appreciable impact of this usage on the core symptoms of psychosis seems unlikely but, to the extent that such an influence occurred, it would have blurred distinctions between the treatment groups.

During double-blind treatment, several patients received concomitant antipsychotic agents (fluphenazine, haloperidol, perphenazine, risperidone, thiothixene, and trifluoperazine).[10] This use occurred in small numbers of patients and was distributed among all treatment groups but most commonly in the placebo group. This may have biased results against the active drug groups.

Extrapyramidal symptoms, akathisia, or dystonia could be treated with benztropine at a dose up to 6 mg/day. The percentages of patients administered benztropine in the OPC-14597 groups were dose-related: 17%, 27%, and 34% in the 2, 10, and 30mg groups, respectively. In the haloperidol group, 44% received benztropine. In the placebo group, 30% did so.

[10] See Appendix 1B-1.2 of the study report.

Efficacy Results

Efficacy findings based on the change in the BPRS core score and the CGI-improvement item are displayed in **Appendix VI-13** and **Appendix VI-14**, respectively.

On the BPRS core score and prior to Dunnett's correction, OPC-14597 was not statistically superior to placebo at any dose at weeks 2, 3, or 4 using the observed cases dataset nor at week 4 with the LOCF dataset. Haloperidol was barely superior to placebo only at week 4 with the LOCF dataset ($p=0.0495$).

On the CGI-improvement item, OPC-14597 was not superior to placebo with the observed cases dataset at weeks 2, 3, or 4 prior to correction. With the LOCF dataset at week 4, superiority of OPC-14597 over placebo was demonstrated ($p=0.0055$). This significance was maintained following Dunnett's correction ($\alpha=0.017$). Haloperidol was not superior to placebo.

Conclusions

OPC-14597 demonstrated superiority over placebo for 30mg group on only one of the two primary efficacy variables (CGI-improvement item). Haloperidol was not superior to placebo.

Hence, study 94202 must be considered a failed study.

3. Study 97201

Investigators/Sites

This study involved 36 centers in the U.S. Principal investigators are listed in **Appendix VI-15**. (Gaps in the sequence of center numbering are due to centers that failed to enroll any patients.)

Objectives

The primary objective of this study was to compare the safety and efficacy of 15mg and 30mg aripiprazole doses to placebo in the treatment of acute psychosis in patients with schizophrenia or schizoaffective disorder.

Patient Sample

A total of 502 patients, age 18-65, with DSM-IV schizophrenia or schizoaffective disorder were screened. The following were important inclusion criteria:

- acute relapse of either schizophrenia or schizoaffective disorder at screening.
- generally, no treatment with a long-acting neuroleptic within one treatment cycle plus one week prior to randomization.
- at both screening and the end of placebo washout, PANSS total score of at least 60 and a score of at least 4 (moderate symptomatology) on any two of the four items of the PANSS psychotic subscale (hallucinatory behavior, delusions, conceptual disorganization, and suspiciousness).
- randomization within 4 weeks after starting treatment for the current episode.
- response to previously administered antipsychotic agents.
- females must not be pregnant or lactating; women of childbearing potential must agree to use acceptable contraception.

Exclusionary criteria included the following:

- first episode of schizophrenia or schizoaffective disorder.
- psychiatric diagnosis other than schizophrenia or schizoaffective disorder that required pharmacotherapy.
- a neurological condition.
- an acute or unstable medical condition requiring pharmacotherapy
- substance dependence within one month of the study.
- potential need for medications that could cause unwanted interactions or confound the analysis of efficacy, including carbamazepine, valproic acid, and lithium.
- potential need for any agent that is a potent inhibitor of CYP2D6.
- positive drug screen for drugs of abuse.

Design

This was a 4 week, randomized, double-blind, placebo- and haloperidol-controlled, parallel group, inpatient study.

After a minimum 5 day placebo washout, eligible patients were randomized to one of four treatment groups: aripiprazole 15mg/day, aripiprazole 30mg/day, haloperidol 10mg/day, or placebo. All study medication was given as a full fixed dose from the first day of treatment once daily in the morning. Patients who could not tolerate study medication were dropped out. Visual inspection was performed after dose administration to ensure ingestion.

Study medication was supplied as placebo capsules and tablets, aripiprazole 15mg tablets, and haloperidol 10mg capsules (each containing two 5mg tablets). All patients received 2 tablets and one capsule each morning. All tablets and all capsules were matched in appearance to maintain the blind.

Analysis

Primary efficacy analyses were performed on the intent-to-treat (ITT) population, defined in the study protocol as all patients having a baseline and a post-baseline observation regardless of whether the patient received medication.

By protocol, there were three primary efficacy variables:

- change from baseline in the PANSS total score.
- change from baseline in the PANSS positive subscale.
- change from baseline in the CGI-severity score.

The primary analysis was ANCOVA, with terms for treatment, center, and treatment-by-center interaction, with baseline score as covariate for the LOCF dataset. If the treatment-by-center interaction was non-significant at the 0.10 level, it was to be excluded from the model. All Observed-Cases analyses included only treatment and baseline values in the model; center effect was not included due to the large number of small centers in this trial.

By protocol, treatment comparisons would be done using a step-down procedure: aripiprazole 30mg vs. placebo would first be tested at a 2-tailed 0.05 level; then, if the null hypothesis was rejected, aripiprazole 15mg vs. placebo would be tested at a 2-tailed 0.05 level.

The protocol did not provide for multiplicity adjustment given that three efficacy variables had been designated as

primary. In such a case, generally all three variables must be positive at an alpha of 0.05 for the study to be considered positive. The efficacy results are discussed below in light of this adjustment.

An internal audit conducted by the sponsor revealed that data generated at centers 007 and 011 could not be validated. Thus, the sponsor conducted an additional analysis of the mean change from baseline in the PANSS total score which excluded the 16 patients randomized at center 007 and the 3 patients randomized at center 011.

Baseline Demographics

Appendix VI-16 displays the demographic characteristics of the randomized patient sample at baseline. Most patients were male. Mean ages were in the late 30's. Most patients were white; in the placebo group, almost half were non-white. Overall, there were no notable demographic differences between treatment groups.

Of the 401 patients in the efficacy ITT, 276 (69%) were diagnosed with schizophrenia; the remaining patients had a diagnosis of schizoaffective disorder. The two aripiprazole dose groups and the placebo groups had approximately the same percentage of schizophrenic patients (about 72%). The haloperidol group had a smaller proportion of schizophrenic patients (60%).

Baseline Severity of Illness

Appendix VI-17 depicts the mean PANSS total scores and CGI-severity scores at baseline. Differences between the groups were extremely small.

Patient Disposition

Appendix VI-18 enumerates the 414 randomized patients by disposition. Dropout rates ranged from 33% in the aripiprazole 15mg group to 45% in the placebo group. The percentage of dropouts due to adverse events was highest in the placebo group (16%). Dropout rates for adverse experiences for the two aripiprazole dose groups were almost identical (8-9%), despite a two-fold difference in dose. A relatively large proportion of patients (14% overall) dropped out after withdrawing consent. About 14% of all patients dropped out due to poor therapeutic

response, with the highest percentage in the aripiprazole 30mg group and the lowest in the 15mg group.

An enumeration of patients in-study by week is displayed in **Appendix VI-19**. At least 70% of the aripiprazole and haloperidol patients remained in-study at the week 3 visit.

Concomitant Medications

By protocol, lorazepam and other benzodiazepines were permitted during the study for any reason and at any dose deemed appropriate for the patient's management. If judged necessary, extrapyramidal symptoms could be treated with benztropine at doses not to exceed 6 mg/day. The severity of EPS was to be documented on the Simpson-Angus Scale and Barnes Akathisia Scale prior to first-time treatment with benztropine.

Anxiolytics were the most frequently used concomitant medication in this trial: approximately 80% of patients in each of the four treatment groups received a concomitant anxiolytic agent. Also, about 25% of patients in each group received a sedative/hypnotic agent.

A number of patients received a concomitant antipsychotic drug, most frequently in the placebo group (N=9) and haloperidol group (N=6). Five patients in the aripiprazole 15mg group and one aripiprazole 30mg patient received another antipsychotic. The degree to which this usage influenced the efficacy results is unknown. Based on the relatively larger number of placebo patients with such use, it seems more likely that this treatment would bias the results against aripiprazole rather than in favor of aripiprazole.

Efficacy Results

Efficacy results based on the changes from baseline in the PANSS total score, PANSS positive subscale, and CGI-severity of illness score are summarized in **Appendix VI-20**, **Appendix VI-21**, and **Appendix VI-22**, respectively.

With respect to the protocol-specified first step-down comparison (aripiprazole 30mg vs. placebo), aripiprazole

was superior to placebo at week 4 on all three variables in both OC and LOCF analyses at an alpha of 0.05.[11]

Similarly, regarding the second step-down comparison (aripiprazole 15mg vs. placebo), aripiprazole was superior to placebo at week 4 on all primary variables in both OC and LOCF analyses at an alpha of 0.05 (all p-values were ≤0.001).

An examination of OC results at earlier visits revealed less consistency: for both aripiprazole doses, week 2 results demonstrated superiority of drug over placebo. At week 3, however, most differences became non-significant; this appears to be due to large improvements in the placebo group at week 3, with smaller degrees of improvement from week 3 to week 4 in that group.

There is a pattern for dose-response that is consistent across all three primary efficacy variables: the mean changes from baseline at week 4 in the LOCF analyses are greater for the 15mg dose group than in the 30mg dose group. This is also true in the OC analyses. These data suggest that there is no therapeutic advantage of aripiprazole 30 mg/day over 15 mg/day.

Since this study enrolled both schizophrenic and schizoaffective patients, I examined the primary efficacy results (LOCF) based on the schizophrenia and schizoaffective subsets separately.[12] A comparison of the placebo-adjusted mean changes from baseline between the two diagnostic subsets revealed a similar degree of improvement on all three primary variables in both aripiprazole dose groups.

Efficacy analyses that excluded the centers where data could not be validated (centers 007 and 011) were provided by the sponsor for the change in the PANSS total score.[13] A comparison of the results with and without these two centers revealed no important differences. The FDA statistical reviewer, Dr. Yeh-Fong Chen, analyzed the other

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[11] For the comparison based on the CGI-severity score in the OC analysis at week 4, I consider the borderline p-value of 0.053 to be statistically significant.

[12] The results from the schizophrenia subset may be found on pages 107, 115, and 123 of the study report. Results from the schizoaffective subset may be found in a 5-15-02 submission from the sponsor.

[13] These results may be viewed on pages 207 and 208 of the study report.

two primary variables after excluding these two centers. She found the results to be consistent with those based on all centers.[14]

Changes in the PANSS negative subscale, one of the secondary variables in this study, demonstrated efficacy for the 15mg aripiprazole dose but not for the 30mg dose.[15] Although both doses were numerically superior to placebo, the mean drug/placebo difference for the lower dose was considerably larger than that for the higher dose (-2.4 vs. -1.1 in the LOCF analysis at week 4). To a small degree, this might be explained by slight worsening of Parkinsonian symptoms in the 30mg vs. the 15mg group as suggested by mean changes in Simpson-Angus Scale scores at endpoint: -0.3 for the 15mg patients and +0.2 for the 30mg patients.[16]

Conclusions

Study 97201 adequately demonstrates the efficacy of aripiprazole 15 mg/day and 30 mg/day in the treatment of psychosis among patients with schizophrenia. Data from this trial suggest no therapeutic advantage of the 30mg over the 15mg dose.

4. Study 97202

Investigators/Sites

This study was conducted at 40 centers in the U.S. Principal investigators are listed in **Appendix VI-23**.

Objectives

The objective of this study was to compare the safety and efficacy of aripiprazole 20mg and 30mg versus placebo in the treatment of acute psychosis in patients with schizophrenia or schizoaffective disorder.

Patient Sample

A total of 487 patients, age 18-65, with DSM-IV schizophrenia or schizoaffective disorder were screened. The following were important inclusion criteria:

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[14] Dr. Chen communicated her findings to me in a 4-22-02 E-Mail.
[15] Results are found on pages 126 and 127 of the study report.
[16] Negative change scores indicate improvement in Parkinsonism.

• acute relapse of either schizophrenia or schizoaffective disorder at screening.
• generally, no treatment with a long-acting neuroleptic within one treatment cycle plus one week prior to randomization.
• at both screening and the end of placebo washout, PANSS total score of at least 60 and a score of at least 4 (moderate symptomatology) on any two of the four items of the PANSS psychotic subscale (hallucinatory behavior, delusions, conceptual disorganization, and suspiciousness).
• randomization within 4 weeks after starting treatment for the current episode.
• response to previously administered antipsychotic agents.
• females must not be pregnant or lactating; women of childbearing potential must agree to use acceptable contraception.

Exclusionary criteria included the following:

• first episode of schizophrenia or schizoaffective disorder.
• psychiatric diagnosis other than schizophrenia or schizoaffective disorder that required pharmacotherapy.
• a neurological condition.
• an acute or unstable medical condition requiring pharmacotherapy.
• substance dependence within one month of the study.
• potential need for medications that could cause unwanted interactions or confound the analysis of efficacy, including carbamazepine, valproic acid, and lithium.
• potential need for any agent that is a potent inhibitor of CYP2D6.
• positive drug screen for drugs of abuse.

Design

This was a 4-week, randomized, double-blind, placebo- and risperidone-controlled, parallel group, inpatient study.

After a minimum 5 day placebo washout, eligible patients were randomized to one of four treatment groups: aripiprazole 20mg/day, aripiprazole 30mg/day, risperidone 6mg/day, or placebo.

Study medication was administered twice daily. Study medication was supplied as placebo tablets, encapsulated placebo tablets, aripiprazole 10mg and 15mg tablets, and encapsulated risperidone 1mg, 2mg, and 3mg tablets. All patients received two tablets and one capsule in the morning after breakfast and one capsule after the evening meal.

Aripiprazole was given as a full fixed dose once daily each morning from the first day of treatment; evening doses for aripiprazole group patients consisted of placebo.

Risperidone was titrated as follows: 1mg BID on day 1, 2mg BID on day 2, and 3mg BID on day 3 and thereafter. Dose modifications were not allowed and patients who could not tolerate study medication were dropped out. Visual inspection was performed after dose administration to ensure ingestion.

Analysis

Primary efficacy analyses were performed on the efficacy intent-to-treat sample, defined in the study protocol as all patients having a baseline and post-baseline observation regardless of whether study medication was received.

By protocol, there were three primary efficacy variables:

- change from baseline in the PANSS total score.
- change from baseline in the PANSS positive subscale.
- change from baseline in the CGI-severity score.

The primary analysis was ANCOVA, with terms for treatment, center, and treatment-by-center interaction, with baseline score as covariate. If the treatment-by-center interaction was non-significant at the 0.10 level, it was to be excluded from the model. All Observed-Cases analyses included only treatment and baseline values in the model; center effect was not included due to the large number of small centers in this trial.

By protocol, treatment comparisons were to be performed using a step-down procedure: aripiprazole 30mg vs. placebo would first be tested at a 2-tailed 0.05 level; then, if the null hypothesis was rejected, aripiprazole 20mg vs. placebo would be tested at a 2-tailed 0.05 level.

The protocol did not provide for multiplicity adjustment given that three efficacy variables had been designated as primary. Thus, all three variables must be positive at an alpha of 0.05 for the study to be considered positive. The efficacy results are discussed below in light of this adjustment.

Baseline Demographics

Appendix VI-24 displays the demographic characteristics of the randomized patient sample at baseline. Most patients were male. Mean ages were in the range of 38 to 40 years old and most patients were white. Overall, there were no major demographic differences among treatment groups.

Of the 392 patients in the efficacy ITT, 282 (72%) were diagnosed with schizophrenia; the remaining patients had a diagnosis of schizoaffective disorder. The two aripiprazole dose groups (20mg and 30mg) had a smaller percentage of patients diagnosed with schizophrenia than the placebo and risperidone groups: 66% and 71% versus 76% and 75%, respectively.

Baseline Severity of Illness

Appendix VI-25 depicts the mean PANSS total scores and CGI-severity scores at baseline. Mean PANSS total scores ranged from 92.6 to 95.7. Mean CGI-severity scores were essentially identical (4.8).

Patient Disposition

Appendix VI-26 enumerates the 404 randomized patients by disposition. Dropout rates ranged from 34% in the aripiprazole 30mg group to 50% in the placebo group. The percentage of dropouts due to adverse events was highest in the placebo group (17%). A relatively large proportion of patients (12% overall) dropped out after withdrawing consent. The highest percentage of dropouts due to poor clinical response occurred in the placebo group (21%); in the two aripiprazole groups, the percentages of patients dropping out for this reason were comparable.

An enumeration of patients in-study by week is displayed in **Appendix VI-27**. At least 70% of the aripiprazole and placebo patients were in-study at the week 2 visit. By the

week 3 visit, a considerably higher fraction of patients had dropped out of the placebo group compared to the three active drug groups.

Concomitant Medications

By protocol, lorazepam and other benzodiazepines were permitted during the study for any reason and at any dose deemed appropriate for the patient's management. If judged necessary, extrapyramidal symptoms could be treated with benztropine at doses not to exceed 6 mg/day. The severity of EPS was to be documented on the Simpson-Angus Scale and Barnes Akathisia Scale prior to first-time treatment with benztropine.

Anxiolytics were the most frequently used concomitant medication in this trial: about three-fourths of the patients in each of the four treatment groups received a concomitant anxiolytic agent. Also, 20-30% of patients in each group received a concomitant sedative/hypnotic agent.

A total of 10 efficacy ITT patients received a concomitant antipsychotic drug during study treatment and prior to or on the day of the final efficacy assessment (5 patients in the 20mg group, 1 in the 30mg group, 3 in the placebo group, and 1 in the risperidone group). Of the 6 aripiprazole patients, 2 took the concomitant antipsychotic one day prior to the final efficacy assessment; the remaining 4 did not receive the concomitant antipsychotic until the day of the final assessment.[17] Thus, while a significant confounding influence on efficacy cannot be absolutely ruled out, this seems unlikely.

Efficacy Results

Change from baseline data for the PANSS total score, PANSS positive subscale, and CGI-severity of illness score are summarized in **Appendix VI-28**, **Appendix VI-29**, and **Appendix VI-30**, respectively.

With respect to the protocol-specified first step-down comparison (aripiprazole 30mg vs. placebo), aripiprazole was superior to placebo at week 4 on all three variables in the LOCF analyses. However, aripiprazole 30mg was not statistically superior in the OC analyses for any of the

[17] This information is based on a 6-3-02 submission from BMS.

primary variables. It appears that a major contributor to the failure of the OC analyses to demonstrate superiority was the large change from baseline among placebo patients who remained in the study (e.g., -18.2 in the PANSS total score vs. -5.0 in the LOCF analysis). While there also was a larger mean change from baseline in the aripiprazole 30mg group for the OC vs. the LOCF analysis, the difference between the two analyses tended to be even larger in the placebo group. Thus, it seems that the dropout of poorly responding placebo patients biased the OC analyses against aripiprazole.

Similarly, with respect to the second step-down comparison (aripiprazole 20mg vs. placebo), aripiprazole was superior to placebo at week 4 on all primary variables in the LOCF analyses but was superior only for the PANSS positive subscale in the OC analyses. As with the 30mg OC results, the 20mg OC data appears to have been biased by the dropout of poorly responding placebo patients.

An examination of OC results at earlier visits revealed superiority of the 20mg dose over placebo at week 2 on all three primary variables as well as superiority of the 30mg dose on the CGI-severity score at week 2. At that visit, mean changes from baseline in the placebo groups were modest.

Examination of the risperidone vs. placebo comparisons at final visit revealed this same pattern of results: for two of the three primary variables (PANSS total score and positive subscale), the LOCF results were significant but the OC results were non-significant. For the CGI-severity score, both LOCF and OC results were significant but much more robust in the LOCF analysis.

An evaluation of dose-response revealed somewhat mixed results: aripiprazole 20mg was associated with slightly larger mean changes from baseline to week 4 for the PANSS total score and positive subscale (LOCF) compared to the 30mg dose; however, for the CGI-severity score, the 30mg dose was slightly better. None of the differences between the two doses for the three primary variables was large. These data suggest that there may be no therapeutic advantage of aripiprazole 30 mg/day over 20 mg/day.

Since this study enrolled both schizophrenic and schizoaffective patients, I examined the primary efficacy

results (LOCF) based on the schizophrenia and schizoaffective subsets separately.[18] A comparison of the placebo-adjusted mean changes from baseline between the two diagnostic subsets revealed a comparable degree of improvement on all three primary variables in both aripiprazole dose groups.

Changes in the PANSS negative subscale, one of the secondary variables in this study, demonstrated equivalent efficacy for the 20mg and 30mg aripiprazole doses (LOCF).

Conclusions

Study 97202 produced observed cases efficacy results that were biased by the early dropout of large numbers of poorly responding placebo patients. Thus, drug/placebo comparisons in this analysis tended to be non-significant.

On the other hand, the LOCF results clearly demonstrated the superiority of aripiprazole 20 mg/day and 30 mg/day over placebo on all three primary efficacy variables.

On the whole, this trial is felt to provide evidence of efficacy for both doses of aripiprazole studied in patients with schizophrenia. As with study 97201, data from this trial suggest no therapeutic advantage of the 30mg over the 20mg dose.

5. Study 138001

Investigators/Sites

This study was conducted at 57 centers, 53 in the U.S. and 4 in Canada. Principal investigators are listed in **Appendix VI-31**.

Objectives

This trial evaluated the efficacy of three fixed doses of aripiprazole versus placebo in the treatment of acutely relapsed schizophrenic patients. The secondary objective was to evaluate the safety of this treatment.

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[18] The results from the schizophrenia subset may be found on pages 104, 112, and 120 of the study report. Results from the schizoaffective subset may be found in a 5-15-02 submission from the sponsor.

Patient Sample

This study enrolled a total of 508 patients, age 18 and older, with DSM-IV schizophrenia who were in acute relapse and required hospitalization. The following were other important inclusion criteria:

- response to previously administered neuroleptics other than clozapine.
- treatment as an outpatient for at least one continuous 3 month period during the past year.
- females must not be pregnant or lactating; women of childbearing potential must be using acceptable contraception.
- at the baseline visit prior to randomization, PANSS total score of at least 60 (1-7 scale) and a score of at least 4 (moderate symptomatology) on any two of the following PANSS items: hallucinatory behavior, delusions, conceptual disorganization, and suspiciousness.

Exclusionary criteria included the following:

- DSM-IV diagnosis of schizoaffective disorder.
- history or clinical presentation consistent with delirium, dementia, amnesic or other cognitive disorder; or bipolar disorder.
- hospitalized for 14 or more days prior to screening for the current episode.
- substance dependence within 3 months of the study.
- at significant risk for suicide.
- unstable thyroid pathology within the past 6 months.
- a history of neuroleptic malignant syndrome.
- history of a medical condition that would place the patient at increased risk for a significant adverse event or interfere with the assessment of safety or efficacy.
- treatment with a long-acting antipsychotic within one treatment cycle plus one week prior to randomization.
- fluoxetine treatment within 4 weeks of randomization.
- regular use of benzodiazepines within 2 weeks of randomization.
- ECT within 2 months of randomization.

Design

This was a 6-week, randomized, double-blind, placebo-controlled, parallel group, inpatient study.

After a minimum 2 day neuroleptic washout period, eligible patients were randomized equally to one of four treatment groups: aripiprazole 10mg/day, 15mg/day, or 20mg/day; or placebo.

Aripiprazole was given as a full fixed dose from the first day of treatment. No modification of study medication dose was permitted during the 6-week trial. Patients unable to tolerate the study medication were dropped from the trial.

Study medication was supplied as placebo tablets and 10mg and 15mg aripiprazole tablets. Each patient received two tablets once daily at approximately the same time each day as follows:

- Aripiprazole 10mg dose= 1 10mg tablet + 1 placebo tablet
- Aripiprazole 15mg dose= 1 15mg tablet + 1 placebo tablet
- Aripiprazole 20mg dose= 2 10mg tablets
- Placebo dose= 2 placebo tablets

There was no requirement regarding the time of day dosing was to occur.

Patients displaying no improvement or a worsening of symptoms (CGI improvement score ≥4) at the end of week 3 were offered the option of open-label aripiprazole during weeks 4, 5, and 6.

Patients who completed this 6-week acute trial, including those receiving open-label aripiprazole, were eligible to enter a long-term, outpatient extension phase of this study.

Analysis

Efficacy analyses were performed on the Efficacy Sample, defined in the study protocol as all patients who were randomized, took at least one dose of study medication, and had at least one post-randomization efficacy assessment.

By protocol, there was one primary efficacy variable: mean change from baseline to week 6 in the PANSS total score.

The original protocol was amended on 2-8-01 to provide for two key secondary variables:

- mean change from baseline to week 6 in the PANSS-derived BPRS Core Score, defined as the sum of the following four PANSS Positive Subscale items - delusions (item 1), conceptual disorganization (item 2), hallucinatory behavior (item 3), and suspiciousness/persecution (item 6).
- mean change from baseline to week 6 in the PANSS Negative Subscale score.

This protocol amendment specified that primary and key secondary analyses were to be performed using ANCOVA, adjusting for baseline score and controlling for study center, for the LOCF datasets. For the OC datasets, ANCOVA controlling for treatment and baseline value was utilized.

The protocol specified that pairwise comparisons of each aripiprazole dose versus placebo on the primary efficacy variable were to be interpreted using a Hochberg's sequentially rejective procedure: superiority to placebo would be claimed if all three comparisons were significant at an alpha of 0.05; if two of the three were significant at 0.025; or if one of the three was significant at 0.0167.

The 2-8-01 protocol amendment indicated that for the key secondary analyses a hierarchical testing procedure would be used to maintain an overall experiment-wise Type I error rate of 0.05. First, only those treatment groups that were significant versus placebo in the primary variable analysis would be tested. Then, testing of the secondary variables would proceed sequentially. First, the BPRS Core score would be tested and, for those groups significantly different from placebo, the PANSS Negative Subscale score would be tested, each at an alpha of 0.05. Since there was no provision for multiplicity correction given the three dose groups, all three groups must be superior to placebo at an alpha of 0.05 to declare superiority on each key secondary variable.

For patients who received open-label aripiprazole after week 3, LOCF data reflected their last double-blind treatment assessment and OC data were considered missing for weeks 4, 5, and 6.

Baseline Demographics

Appendix VI-32 displays the demographic characteristics of the randomized patient sample at baseline. Most patients were male. Mean ages were in the range of 40 to 41 years old and about half of the patients were white. Overall, there were no major demographic differences among the four treatment groups.

Baseline Severity of Illness

Appendix VI-33 depicts the mean PANSS total scores and CGI-severity scores at baseline. Mean scores on both variables were comparable across treatment groups.

Patient Disposition

Appendix VI-34 enumerates the 420 randomized patients by disposition. Overall, 66% (278/420) of the randomized patients in this trial dropped out; dropout rates ranged from 59% in the aripiprazole 10mg group to 72% in the placebo group.

Altogether, 31% (131/420) of all patients dropped out to enter the open-label rescue phase due to lack of therapeutic effect (i.e., a CGI-improvement score of 4-7 at the end of week 3). This occurred most often in the placebo group (41% of placebo patients dropped out for this reason) although a substantial proportion (22-35%) of patients in the aripiprazole groups dropped out for this reason.

A more comprehensive measure of dropouts due to inadequate therapeutic response is derived by combining patients who entered open-label treatment due to lack of response with those who dropped out entirely due to lack of efficacy. This yields a total of 166 patients or 40% of all randomized patients. Slightly over half (51%) of placebo patients dropped out for one of these reasons with smaller but still large percentages in the aripiprazole groups: there was no clear dose relationship, with the highest percentage in the 15mg group (42%) and almost equal percentages in the 10mg and 20mg groups (31% and 33%, respectively) who dropped out for one of these reasons.

The percentage of dropouts due to adverse events was highest in the low dose aripiprazole group (10%) and lowest in the middle dose group (3%).

A relatively large proportion of patients (17% overall) dropped out after withdrawing consent, with the highest percentage in the middle aripiprazole dose group (23%).

An enumeration of patients in-study by week is displayed in **Appendix VI-35**. At least 70% of the patients in all treatment arms were in-study at the week 3 visit. However, the percentage of patients remaining fell dramatically thereafter, due mostly to the large numbers of patients who entered the open-label rescue phase after the week 3 visit. At week 6, well under half of all patients remained in-study, with only a third of the original number remaining in the mid-dose aripiprazole group.

Concomitant Medications

Lorazepam was permitted during the study for anxiety or insomnia. IM lorazepam could be used for emergent agitation if deemed absolutely necessary by the investigator. Daytime doses were not to exceed 4mg/day; an additional 1-2mg could be given at night as a sleep aid. No lorazepam doses were permitted within 4 hours of any safety or efficacy assessment.

Extrapyramidal symptoms could be treated, if necessary, with an anticholinergic agent at doses not to exceed the equivalent of 6 mg/day of benztropine. No such medication was to be given within 12 hours prior to any safety or efficacy assessment.

Neuroleptic agents were not to be taken during the study.

Anxiolytics were the most frequently used concomitant CNS medications used in this trial; these were used by 78-89% of patients across the four treatment groups. Also, a small percentage of patients in each group (2-5%) received a concomitant sedative/hypnotic agent.

A total of 18 ITT patients received a concomitant antipsychotic drug during study treatment and prior to or on the day of the final efficacy assessment (3 patients in the 10mg group, 5 in the 15mg group, 4 in the 20mg group, and 6 in the placebo group). Of the 12 aripiprazole

patients, 4 received prohibited antipsychotic treatment on the same day as the final efficacy assessment, 2 received a single dose of such treatment 1 day before the final assessment, 1 received a single dose of prohibited treatment 2 days before the final assessment, 1 received doses 1 day before and on the day of the final assessment, 2 received a concomitant antipsychotic over the first 2-3 days of a one month period of aripiprazole treatment, and, in the remaining 2 patients, the timing of the prohibited antipsychotic treatment relative to the final assessment was unknown.[19] Considering this information, the robust results of this study, and the 6 placebo patients who received an antipsychotic, it is unlikely that this usage among the aripiprazole patients biased the results in favor of drug.

Efficacy Results

Change from baseline data for the PANSS total score, PANSS-derived BPRS core score, and the PANSS Negative Subscale are summarized in **Appendix VI-36**, **Appendix VI-37**, and **Appendix VI-38**, respectively.

With respect to the primary efficacy variable (PANSS total score), the LOCF analysis at week 6 revealed statistical superiority of each aripiprazole dose over placebo at an alpha of 0.05. This was also observed at weeks 3, 4, and 5. The low and high dose groups were superior at weeks 1 and 2 (alpha=0.025).

The OC analysis of the change in the PANSS total score yielded weaker results. At weeks 4, 5, and 6, none of the three aripiprazole doses was superior to placebo and the middle dose (15mg) was superior at none of the weeks (alpha=0.05). Applying the Hochberg sequentially rejective procedure to the OC results at week 3, when at least 70% of patients in each arm remained in-study, the low and high dose (10mg and 20mg) were superior to placebo.

This difference between the LOCF and OC results after week 3 seems explainable by two factors: 1) marked improvement, on average, in the placebo patients who remained in the study after week 3 (change of -26.86 in the OC dataset versus -2.33 in the LOCF dataset at week 6) and 2) the large number of dropouts after week 3, with loss of

[19] This information is based on a 6-3-02 submission from BMS.

statistical power. Regarding the former, it is notable that the placebo-adjusted mean change from baseline in the PANSS total score at week 6 (95% CI) was substantially lower for all aripiprazole groups in the OC versus the LOCF analysis:

Dose	OC	LOCF
10mg	-6.6 (-14.7,+1.6)	-12.7 (-19.0,-6.4)
15mg	-5.1 (-13.6,+3.5)	-9.4 (-15.7,-3.1)
20mg	-2.1 (-10.3,+6.2)	-12.1 (-18.5,-5.7)

Also, among the aripiprazole patients who remained in-study, the unadjusted mean drops in the PANSS total score were considerably larger than those from the LOCF analysis for all three dose groups.

Thus, the OC results in this trial are felt to be less reliable than the LOCF results for ascertaining therapeutic response.

The sponsor conducted a linear trend test for response on the PANSS total score across the three aripiprazole doses using the LOCF analysis (excluding placebo). There were no linear trends at any visit.[20] Comparison of the mean changes from baseline in the PANSS total score across the three aripiprazole groups shows that improvement was generally slightly greater in the low dose group compared to the high dose group and substantially greater in the low dose group compared to the mid-dose group.

This study examined two key secondary variables: the PANSS-derived BPRS Core Score and the PANSS Negative Subscale. Since all three dose groups were deemed efficacious in the primary efficacy analysis, all three were considered in the analysis of key secondary variables. As mentioned above, since there was no provision in the study protocol for multiplicity correction given the three dose groups, all three doses must be superior to placebo at an alpha of 0.05 for a key secondary variable to be considered positive.

In accordance with the hierarchical testing procedure described in the amended protocol, the BPRS Core Score was considered first. At week 6 LOCF, all three doses were superior to placebo at an alpha of 0.05. This was also

[20] See Appendix 10.1.1F2 in the study report.

true at week 5. OC results were not considered positive at any visit.

The PANSS Negative Subscale was considered next. All three aripiprazole doses were superior to placebo at weeks 2 through 6 in the LOCF dataset with an alpha level of 0.05. OC results were not positive at any visit.

Conclusions

Study 138001 provides evidence of the efficacy of aripiprazole in 10mg, 15mg, and 20mg daily doses in the treatment of acutely relapsed schizophrenic patients.

The dropout of large numbers of poorly responding patients in this trial, in large part by design, renders the OC analysis much less reliable than the LOCF analysis. Based on the latter, all three aripiprazole doses (10mg, 15mg, and 20mg) were superior to placebo on the primary efficacy variable and on the two key secondary variables. These data do not suggest any therapeutic advantage of the 15mg and 20mg daily doses over the 10mg dose.

C. Other Data Pertinent to Important Clinical Issues

1. Predictors of Response

The sponsor evaluated the effect of demographic and baseline variables on efficacy by computing the model-based mean change from baseline in the PANSS total score (LOCF) for the following subgroups:

- gender (male and female).
- age (<50 and ≥50 years old).
- race (White, Black, Hispanic, and Asian).
- baseline PANSS total score (≤91 and >91).

Computations were based on the pool of the 5 short-term, placebo-controlled efficacy trials in schizophrenia. For age, the customary cut-off of 65 years would have yielded a very small sample in the older age group (1% of the total sample); hence, a cut-off of 50 was chosen. A cut-off of 91 for the baseline PANSS total score was chosen because this was the median score. Results are displayed in **Appendix VI-39**. Formal statistical testing was not performed on these findings.

Placebo-adjusted decreases in the PANSS total score were, on average, comparable between men and women treated with aripiprazole (-9.8 and -10.7, respectively).

There was a substantial difference between age groups in the mean placebo-adjusted PANSS score changes for aripiprazole: -11.5 in the younger patients and -1.0 in the older patients. This pattern also held true for the haloperidol-treated patients and, to a lesser extent, for the risperidone-treated patients. In fact, among the elderly patients, placebo treatment fared slightly better than haloperidol. These findings are attributable mainly to a large response in the placebo group among the older patients compared to the younger patients. The unadjusted changes from baseline were roughly comparable between the two age groups for each of the three active drug groups. Since the old and young subgroups do not represent randomized samples and, thus, factors other than age may be contributing to the subgroup differences. Additionally, an analysis of age on efficacy by each study was conducted by the statistical reviewer; this revealed findings that were not consistent across studies, suggesting that these studies should not have been pooled for this analysis. Overall, these observations cannot be interpreted with confidence.

Mean placebo-adjusted changes in the PANSS total score were similar between Whites and Blacks treated with aripiprazole (-10.7 and -11.3, respectively).

Substantial improvement in the Hispanic patients treated with placebo (mean PANSS change of -10.9) and considerable worsening in the Asian patients treated with placebo (+14.1) resulted in unusually small and large placebo-adjusted changes in these two racial groups treated with aripiprazole. Covariates other than race which might explain these findings are not known and the number of Asian patients was relatively small. Thus, as with age, it is difficult to interpret these results.

With respect to the baseline PANSS total score, patients above the median experienced more improvement than those at or below the median score: placebo-adjusted changes in the PANSS total score were -12.2 and -8.1, respectively, in the aripiprazole group. Likewise, in the other two drug groups as well as in the placebo group, patients with high scores at baseline experienced more improvement than those with

low scores. This pattern for patients more ill at baseline to experience a greater degree of improvement has been seen with other psychotropic agents.

In sum, there appears to be no effect of gender on response. With respect to race, Whites and Blacks seem to respond equally well to aripiprazole. Observed differences between age subgroups and Hispanic and Asian racial subgroups are hard to interpret. Patients with higher PANSS scores at baseline appear to manifest greater improvement than those with lower scores.

2. Size of Treatment Effect

The placebo-adjusted mean changes from baseline to endpoint (LOCF) in the PANSS total score for the three positive efficacy trials are displayed in **Table VI-4** below.[21]

TABLE VI-4
PLACEBO-ADJUSTED MEAN CHANGES FROM BASELINE TO ENDPOINT (LOCF) IN THE PANSS TOTAL SCORE

Study 97201		Study 97202		Study 138001	
Dose	**Mean Δ**	**Dose**	**Mean Δ**	**Dose**	**Mean Δ**
Ari 15mg	-12.6	Ari 20mg	-9.5	Ari 10mg	-12.7
Ari 30mg	-8.5	Ari 30mg	-8.9	Ari 15mg	-9.4
Hal 10mg	-10.9	Risp 6mg	-10.7	Ari 20mg	-12.1

The magnitude of the changes observed in the aripiprazole treatment arms were comparable to those observed in the haloperidol and risperidone treatment arms.

3. Choice of Dose

Altogether, the three positive efficacy trials utilized four fixed daily doses of aripiprazole: 10mg, 15mg, 20mg, and 30mg. Only one of these trials used a 10mg dose, study 138001. In this study, 10mg was efficacious. Study 94202, a failed study, also used a 10mg arm which did not demonstrate efficacy. However, since the haloperidol arm in that trial also did not show efficacy, study 94202 cannot support an inference that this dose is not effective. Nonetheless, there is less evidence supporting the efficacy of the 10mg dose compared to each of the three higher doses, for which efficacy was shown in two studies.

[21] Placebo adjusted change = (change on drug at endpoint) minus (change on placebo at endpoint). Negative scores imply improvement.

In each of these three studies, there was no clear advantage of the higher dose(s) over the low dose.

In these studies, aripiprazole was administered as a full fixed dose once daily from the first day of treatment. In studies 97201 and 97202, aripiprazole was taken in the morning; in study 138001, aripiprazole was taken at about the same time each day but the time of day was not specified.

Steady-state blood levels are achieved within 14 days.

Based on the experience summarized above, it seems reasonable to recommend an adult starting dose of 15mg given once daily. Recognizing that there may be a small subset of patients who require higher doses to attain an acceptable response, the dose could be increased in increments of 5-10 mg/day at intervals of at least 2 weeks to a maximum of 30 mg/day.

4. Duration of Treatment

None of the four longer-term studies reported in the original NDA submission are capable, by design, of providing convincing evidence of efficacy with longer-term use of aripiprazole.

The sponsor has completed one trial (study 138047) since the NDA submission that may be of adequate design to address longer-term efficacy. This study enrolled patients stabilized on their previous antipsychotic medication and randomized them to treatment with aripiprazole 15 mg/day or placebo (155 patients/arm) for 26 weeks of double-blind treatment. The primary efficacy measure was time to relapse. The sponsor may elect to submit an efficacy supplement based on this study in the future.

D. Conclusions Regarding Efficacy

Appendix VI-40 summarizes the efficacy results at endpoint from each of the five short-term, placebo-controlled studies of aripiprazole in schizophrenia for the primary variables and, for study 138001, the two key secondary variables. Since the methods for multiplicity adjustment in these trials tended to be complex and varied across the

five trials, these methods are summarized in **Appendix VI-41** for the reader's convenience.

Efficacy was demonstrated in three of the five studies (97201, 97202, and 138001) for fixed doses in the range of 10 to 30 mg/day using LOCF methods. Only study 97201 demonstrated efficacy for aripiprazole in the observed cases (OC) dataset. Failure to demonstrate superiority in the OC datasets in studies 97202 and 138001 is, in large part, attributable to the dropout of large numbers of poorly responding placebo patients, which biased the OC results against aripiprazole. Hence, the LOCF analyses are felt to be more reliable for those two trials.
None of the fixed dose studies substantiated an advantage of higher doses of aripiprazole over lower doses.

With respect to the two non-positive trials, study 93202 is negative. Assay sensitivity in that study was established by the superiority of the active control, haloperidol, over placebo. On the other hand, study 94202 is considered a failed study since assay sensitivity was not confirmed by haloperidol in that trial.

In summary, this NDA provides adequate evidence of the efficacy of aripiprazole in the treatment of psychosis in schizophrenia.

VII. Integrated Review of Safety

A. Methodology of the Safety Review

The evaluation of the safety of aripiprazole consisted of two general approaches:

- an assessment of the more serious adverse events, specifically deaths, non-fatal serious adverse events, and adverse events that led to premature termination, from the entire Japanese and non-Japanese study pools.

- an examination of the less serious adverse events within the pool of the 5 non-Japanese, short-term, placebo-controlled schizophrenia studies. This examination encompasses common adverse events, laboratory findings, vital sign data, and ECG findings associated with aripiprazole. Additionally, findings from special safety analyses and studies will be presented.

Some special analyses were performed by the sponsor prior to submission of the 120-Day Safety Update and, thus, do not include new data contained in the Update. For these analyses, the patient population of interest is designated as the "non-updated" Phase 2/3 database.

My assessment of non-fatal serious adverse events (SAE's) necessitated a special review method. There were a very large number of adverse events classified by the sponsor as serious in the non-Japanese Phase 2/3 database: of the 4710 patients in this database, 997 (21%) aripiprazole-treated patients experienced a treatment-emergent event considered by the sponsor to be serious. On my preliminary examination of line listings of these events, it seemed that numerous SAE's were not medically serious and unexpected in these study populations, e.g., 382 patients experienced psychosis that was classified as serious. Thus, I developed a special process for screening these events in order to focus only on those events that would generally be considered clinically significant in these patients.

This process involved a review of the line listing of all SAE's to identify those events that could, in my judgement, be considered medically serious in nature (for example, liver damage).[22] Overdoses and SAE's that resulted in death are examined in other sections of this review and, hence, were excluded from further consideration in my assessment of non-fatal SAE's. When there was doubt as to the nature or seriousness of a particular occurrence in the line listing, the Narrative Summary was examined and, if needed, additional information from the Case Report Form, Case Report Tabulations, or the sponsor was assessed. Identified events are discussed in section VII.B.2. below. For reference, a tabulation of the incidence of all sponsor-identified SAE's, including those with fatal outcome, is provided in **Appendix VII-1**.

B. Safety Findings

1. Deaths

For completed studies, the sponsor reported all deaths that occurred between: 1) the time of randomization or start of dosing and 30 days after the last dose of study drug (Otsuka studies) OR 2) between the time of informed consent

[22] This listing may be found in Appendix 4.7A of the 120-Day Safety Update.

and 30 days after the last dose of study drug (BMS studies). For ongoing studies, the sponsor reported all deaths that occurred as of the safety cut-off date regardless of timing relative to the last dose of study drug.

a. Non-Japanese Studies

1) Phase 1 Trials

There were no deaths in the non-Japanese Phase 1 studies.

2) Phase 2/3 Trials

a) Short-Term, Placebo-Controlled Schizophrenia Studies

In the pool of the 5 short-term, placebo-controlled Phase 2/3 trials (926 Aripiprazole-treated patients), there were no deaths.

b) All Phase 2/3 Studies

There were 76 deaths in the non-Japanese Phase 2/3 studies. Of these, 61 occurred in aripiprazole-treated patients, 2 in haloperidol-treated patients, and 13 in patients receiving blinded medication.[23]

I reviewed the Narrative Summaries for all 76 deaths; in some cases, relevant information from the Case Report Forms was also examined for clarification.

A line listing of all deaths in randomized patients is provided in **Appendix VII-2**. The individual causes of death indicated in this listing are based on my review of each case.[24]

All-cause mortality rates were computed for each treatment group and are presented below.

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[23] Another 10 deaths occurred in non-randomized patients who received no study drug; these deaths were not reviewed.
[24] Supplemental information provided by the sponsor was also reviewed for Patients 138005-43-96, 138005-12-49, 138006-8-98, and 138006-20-35.

TABLE VII-1: ALL-CAUSE MORTALITY RATES NON-JAPANESE PHASE 2/3 STUDY POOL				
	Aripiprazole	**Placebo**	**Haloperidol**	**Atypical Agents[25]**
# deaths	61	0	2	0
# patients	4710	928	673	492
Exposure(PY)	2656.3	85.8	207.3	132.9
Crude MR	1.3%	0.0%	0.3%	0.0%
Adjusted MR[26]	23.0	0.0	9.6	0.0

By comparison, the rates observed in the primary safety database of the Zyprexa (olanzapine) NDA (NDA 20-592) were 0.8% (crude rate) and 17.8/1000 PY's (exposure-adjusted rate) among olanzapine-treated patients.

Most of the aripiprazole deaths (39/61) occurred in trials of patients with Alzheimer's dementia. Thus, trials were subgrouped by the indication, i.e., trials in patients with Alzheimer's dementia (138004, 138005, and 138006) versus trials in patients with schizophrenia or bipolar disorder. Mortality rates were computed for each subgroup. These are presented in **Table VII-2** below.

TABLE VII-2 ALL-CAUSE MORTALITY RATES IN DEMENTIA STUDIES VS. SCHIZOPHRENIA/BIPOLAR DISORDER STUDIES NON-JAPANESE PHASE 2/3 STUDY POOL				
	Alzheimer Dementia Studies		**Schiz./Bipolar Studies**	
	Aripiprazole	**Placebo**	**Aripiprazole**	**Placebo**
#deaths	39	0	22	0
#patients	504	102	4206	826
Exposure(PY)	223.8	17.7	2432.5	68.1
Crude MR	7.7%	0.0%	0.5%	0.0%
Adjusted MR	174	0.0	9.0	0.0

The mortality rate in the pool of trials involving patients with Alzheimer's dementia was considerably higher than that in trials involving patients with schizophrenia or bipolar disorder. The crude and adjusted rates for the schizophrenia/bipolar pool approximate the rates for the

[25] Risperidone and olanzapine.
[26] Adjusted mortality rate = # deaths/1000 patient-years of exposure.

haloperidol control group shown in **Table VII-1** above; haloperidol was administered as a control only in schizophrenia trials.

Statistical comparison of the exposure-adjusted rates for drug and placebo in the Alzheimer's dementia study pool revealed a significant difference (p=0.05).[27] The corresponding comparison in the schizophrenia/bipolar study pool was non-significant (p=0.54).

A crude examination of the 39 aripiprazole-associated dementia study deaths by study day interval did not suggest any clustering of these events in time; see **Table VII-3** below.

TABLE VII-3:
DISTRIBUTION OF DEMENTIA STUDY DEATHS BY TIME INTERVAL

Time to Onset Study Day Interval	Ntotal (Start of Interval)	Number of Deaths in Interval	Crude Rate (%)
0-89	504	12	2.4%
90-179	337	16	4.7%
180-269	215	6	2.8%
270-359	103	5	4.9%

Additionally, an examination of these 39 deaths by last dose administered suggested no relationship to dose. For 4 of these patients, the last dose was unknown. Of the 35 patients with a known last dose, the range was 2-15 mg/day with most receiving either 2 mg/day (N=8), 5 mg/day (N=13), or 10 mg/day (N=11).

In the only completed placebo-controlled trial in Alzheimer's disease patients (study 138006), the acute phase (10 week) mortality rate in the aripiprazole group was 3.8% (4/105) versus 0.0% (0/102) in the placebo group. This difference approached significance (p=0.12, 2-tailed Fisher's exact test; α=0.10). Since exposures in the two groups were comparable, exposure-adjusted rates were not computed. The causes of death in the four aripiprazole-treated patients were pneumonia, heart failure, sepsis related to bronchitis, and, in the last case, unknown.

[27] Based on a comparison of incidence rate confidence intervals using the Poisson assumption; this was computed using Stata Software version 6.0 with the assistance of Andrew Mosholder, M.D., M.P.H.

Dysphagia was reported as an adverse experience in 1% of both aripiprazole and placebo patients.

An enumeration of all 61 aripiprazole deaths by cause and study pool is presented in **Table VII-4** below.

TABLE VII-4:
ENUMERATION OF DEATHS BY CAUSE (N)
ARIPIPRAZOLE-TREATED PATIENTS
NON-JAPANESE PHASE 2/3 STUDIES

Cause of Death	Study Pool	
	Schiz/Bip N=4206	Dementia N=504
Unknown	1	10
Suicide	10	-
Aspiration pneumonia	-	5
Pneumonia (other/unspecified)	-	5
Myocardial infarction	2	2
Heart failure	1	3
Sepsis	-	3
Respiratory infection(unspecified)	-	2
Overdose (non-aripiprazole)	2	-
Accidental injury	2	-
Cachexia (Alzheimer's disease)	-	2
Cardiac arrest	-	1
Pulmonary embolism	-	1
Asphyxia	1	-
Cancer	1	1
Stroke	-	1
Respiratory distress syndrome	1	-
Bronchitis	-	1
Renal failure	-	1
Volvulus	-	1
Murder	1	-
TOTAL	22	39

In 11 cases, the cause of death could not be determined with reasonable specificity and certainty. Most of these were in elderly patients (>80 years old) and many had underlying conditions that could predispose to death. One of these occurred in a 40 y.o female who was found to have cardiomegaly and coronary artery disease on autopsy (Patient 98304-440-63).

Suicides represented the most common specific cause of death. The exposure-adjusted suicide rate in the haloperidol group was over two-fold higher than that in the aripiprazole group in the schizophrenia/bipolar disorder (9.6 vs. 4.1 suicides/1000 PY's, respectively).

Five aripiprazole-treated patients died as a result of aspiration pneumonia. All five patients were elderly and suffered from Alzheimer's disease and two cases were the result of faulty feeding tube placement. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Nonetheless, esophageal dysmotility and aspiration have been associated with antipsychotic drug treatment (e.g., olanzapine) and a causative role for aripiprazole cannot be ruled out.[28]

Five aripiprazole patients died secondary to other or unspecified types of pneumonia. Again, all five were elderly patients with Alzheimer's disease. Conceivably, some of these may be secondary to unrecognized or unreported aspiration.

The frequencies of the remaining causes of death are not considered unexpected in these populations.

There were 1736 patients whose treatment remained blinded as of the safety data cut-off date. Given the 13 deaths from this group of patients, the crude mortality rate was 0.7%. A review of the causes of these deaths revealed no unusual pattern.

b. Japanese Studies

There were no deaths in the Japanese Phase I studies.

In the Japanese Phase 2/3 studies, there were 7 deaths among 769 patients treated with aripiprazole. These deaths are summarized in **Appendix VII-3**.

In this same pool of studies, there were 4 deaths among 131 patients treated with haloperidol. The crude mortality rates for aripiprazole and haloperidol were 0.9% and 3.1%, respectively. One additional death occurred in a patient treated with mosapramine, a foreign-marketed antipsychotic agent.

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[28] See PRECAUTIONS in Zyprexa labeling.

In these trials, there was one death of special interest: Patient #F0701 in study 95004 was a 64 y.o female who had non-insulin-dependent diabetes mellitus which was treated with an oral hypoglycemic agent at the start of the study. She had been treated with aripiprazole 6 mg/day for 80 days when she experienced diabetic ketoacidosis (DKA) with shock. There was no history of previous DKA. Three days later, she expired. Exacerbation of diabetes mellitus, to include DKA, has been reported with other atypical antipsychotics, such as clozapine.

2. Non-Fatal Serious Adverse Events

The sponsor defined a serious adverse event (SAE) by the following criteria:

- resulted in death.
- was immediately life-threatening.
- resulted in persistent or significant disability or incapacity.
- required hospitalization or prolonged existing hospitalization.
- was a congenital anomaly or birth defect.
- was a medically significant event that might jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed above.
- was a cancer.
- resulted in an overdose.
- resulted in drug dependency or drug abuse.

For completed studies, the sponsor reported all SAE's that occurred between: 1) the time of randomization or start of dosing and 30 days after the last dose of study drug (Otsuka studies) OR 2) between the time of informed consent and 30 days after the last dose of study drug (BMS studies). For ongoing studies, the sponsor reported all SAE's that occurred as of the safety cut-off date regardless of timing relative to the last dose of study drug.

a. Non-Japanese Studies

1) Phase 1

Among the 924 subjects and patients in the non-Japanese Phase 1 studies, there were three patients with adverse events classified as serious:

1) Patient 138021-1-2 experienced confusion and ataxia after receiving concomitant aripiprazole and lithium following aripiprazole monotherapy. The lithium level was within therapeutic range. These events resolved after treatment discontinuation and are attributable to lithium.

2) Patient 138030-1-17 was found unconscious after over 3 months of treatment with aripiprazole 30 mg/day. The patient admitted to the surreptitious use of alprazolam and methadone prior to the event.

3) Patient 138065-1-8 was hospitalized for injuries following a car accident.

2) Phase 2/3 Studies

a) Short-Term, Placebo-Controlled Schizophrenia Studies

Within the pool of the five short-term, placebo-controlled studies in schizophrenia (926 aripiprazole and 413 placebo patients), there were only three adverse events in the aripiprazole patients that I considered medically serious. The following events were experienced by one aripiprazole patient each: delirium associated with hyponatremia, syncope, and a grand mal seizure. No placebo patient in this study pool experienced any of these events.

b) All Phase 2/3 Studies

For the entire non-Japanese Phase 2/3 database, I identified a number of patients with non-fatal serious adverse events that I considered clinically important and possibly drug-related. I enumerated these patients in **Appendix VII-4** by specific adverse experience, treatment group (aripiprazole vs. placebo), and study pool (Alzheimer's dementia and schizophrenia/bipolar disorder). Within each study pool and for each event, I statistically compared the proportions of patients in the aripiprazole and placebo treatment groups with that event; p-values for

these comparisons are provided in this table. For no event was there a significantly higher proportion of patients in the aripiprazole group compared to placebo (alpha=0.10).

Additionally, I examined the line listing of SAE's among the 1736 patients whose treatment remained blinded as of the cut-off date. The objective of this search was to identify any medically significant events that were not seen among the unblinded aripiprazole-treated patients.

Only one such event was identified: Patient 138004-33-47 was a 83 female who discontinued study drug on day 20 due to an accidental head injury. Thirteen days later, she was hospitalized due to coffee ground loose stools. Endoscopy and colonoscopy revealed ischemic colitis and gastrointestinal bleeding. She was discharged 11 days later in stable condition.

b. Japanese Studies

There were four non-fatal serious adverse events that I considered medically important and possibly drug-related among the 901 subjects and patients who received aripiprazole in the Japanese trials:

1) Patient 91004-207-01 was a 43 y.o. female who experienced urinary retention beginning on day 14 of study drug administration. Fifteen days later, BUN and creatinine were markedly elevated (60 mg/dl and 9.0 mg/dl, respectively), suggesting severe renal impairment. Bilateral hydronephrosis and cystitis were confirmed on ultrasonography. Aripiprazole was discontinued on day 29; the last dose was 2 mg/day. Following treatment with catheterization, a cholinergic agent, and bladder training, symptoms gradually resolved.

2) Patient 91004-215-01 was a 44 y.o. male who experienced stupor, low grade fever, and hyponatremia (serum sodium=116 mEq/L) after two 1mg doses of aripiprazole. Water intoxication was diagnosed and medication was discontinued. The patient recovered after electrolyte replenishment. There was no previous history of polydipsia or hyponatremia.

3) Patient 93001-2511 was a 44 y.o. female who experienced muscle rigidity on day 19 of treatment at an aripiprazole dose of 20 mg/day (given bid). Four days later, fever

emerged followed by CPK elevation the next day. Aripiprazole was discontinued and intravenous dantrolene was started. Over the next week, symptoms resolved. The attending physician felt that this represented a possible case of neuroleptic malignant syndrome (NMS).

4) Patient 95004-F-08-02 was a 49 y.o. male who experienced a paralytic ileus on day 133 of aripiprazole treatment. Aripiprazole (9mg bid) was stopped and a tube was placed. Acute symptoms were alleviated and the ileus resolved over the next month.

In the absence of an adequate control group, it is difficult to assess causality of these events. The case of possible NMS is felt to be likely aripiprazole-related. The other three cases are possibly related to aripiprazole.

3. Dropouts

a. Non-Japanese Studies

1) Phase 1 Trials

The line listing of all aripiprazole-treated subjects in non-Japanese Phase 1 studies who discontinued study participation due to an adverse event was examined. Occurrences of adverse events that were considered to be potentially medically important and that were not previously reviewed (as a serious adverse event) were highlighted and the corresponding narrative summaries were reviewed to identify any clinically significant events possibly related to aripiprazole treatment. This review process revealed no adverse events that led to dropout which, in my judgement, were clinically important and possibly aripiprazole-related .

2) Phase 2/3 Trials

a) Short-Term, Placebo-Controlled Schizophrenia Studies

Appendix VII-5 displays the disposition of all dropouts for the pool of the 5 short-term placebo controlled trials in schizophrenia, which included a small percentage of patients with schizoaffective disorders. It is remarkable that the highest percentage of dropouts for adverse experiences occurred in the placebo group. A roughly equal percentage of dropouts due to lack of efficacy occurred in

the three active drug groups (12-14%) with the highest percentage of dropouts for this reason in the placebo group (20%). The large number of patients who withdrew consent in these studies (240 total, with 140 from the aripiprazole group) is also notable. Finally, it should be noted that 87 aripiprazole patients dropped out to begin open-label rescue medication, presumably due mainly to lack of therapeutic effect.

Appendix VII-6 displays the proportions of patients who discontinued treatment due to specific adverse experiences in the short-term, placebo-controlled schizophrenia studies. The only adverse event that led to dropout in more than 1% of the aripiprazole patients was psychosis: 3.6% of aripiprazole and 6.1% of placebo patients dropped out due to this adverse experience.

b) All Phase 2/3 Studies

The process that was used above to identify clinically important events in the Phase 1 studies was repeated for all aripiprazole-treated patients who dropped out due to an adverse experience in the entire non-Japanese Phase 2/3 database. This process revealed no new adverse events that led to dropout which, in my judgement, were clinically important and possibly aripiprazole-related .

b. Japanese Studies

The same process that was used for the non-Japanese studies above to identify clinically important events was repeated for all aripiprazole-treated patients who dropped out due to an adverse experience in the Japanese study pool. This revealed no new adverse events leading to dropout that, in my judgement, were clinically important and possibly aripiprazole-related.

4. Common Adverse Events

a. Categorization of Adverse Events

A treatment-emergent AE was defined as any new medical problem, or exacerbation of an existing problem, experienced by a patient during treatment, whether or not the problem was considered drug-related by the investigator. AE's discussed in this summary were obtained

from either reports of AEs volunteered by patients or investigator observation.

Reported adverse events were coded as COSTART terms. The accuracy of the translation of actual adverse event to COSTART terms was assessed by this reviewer by examining line listings of adverse events in the Modified COSTART Dictionary used in the NDA ISS. The coding process was found to be acceptable.

b. Study Pooling

I focused on adverse event information pooled from the 5 short-term, placebo-controlled schizophrenia trials.

This study pool consisted of:

- three 4-week studies with placebo and haloperidol control groups (93202, 94202, and 97201),
- one 4-week study with placebo and risperidone control groups (97202), and
- one 6-week study with a placebo control group (138001).

Four of the five short-term placebo-controlled studies had fixed-dose designs in which aripiprazole was administered at fixed daily doses and one had a flexible-dose design with aripiprazole being administered in varying doses. The four, fixed dose design studies were administered as follows:

- 2 mg, 10 mg, and 30 mg for 94202,
- 15 mg and 30 mg for 97201,
- 20 mg and 30 mg for 97202, and
- 10 mg, 15 mg, and 20 mg for 138001.

The fifth study, 93202, had a flexible-dose design in which aripiprazole was administered at daily doses ranging from 5 to 30 mg.

In the 138001 study, nonresponding patients were given an opportunity to receive open-label aripiprazole in a rescue phase after Week 3. For those patients who entered the rescue phase, only data obtained during the double-blind, placebo-controlled phase (i.e., first 3 weeks) were included in the analyses below.

c. Common, Drug-Related Adverse Events

The incidence of treatment-emergent adverse events was reviewed as presented in section 6.3 of the NDA ISS. This is summarized here.

The percentage of patients who had at least one AE was similar across treatment groups. In general, the AE profile for the aripiprazole group was comparable to that for the placebo group.

Treatment-emergent AEs for the short-term placebo-controlled studies in schizophrenia are presented in **Appendix VII-7**. An incidence of at least 1% in the aripiprazole group (prior to rounding the number) was used to identify AEs for this table.

There were noticeable differences between aripiprazole and placebo in the incidence of the following AEs:

- headache (31.7% in the aripiprazole group versus 24.5% in the placebo group),
- nausea (14.0% versus 9.7%),
- vomiting (12.0% versus 7.0%),
- insomnia (24.1% versus 18.6%),
- lightheadedness (11.4% versus 6.5%), and
- blurred vision (2.8% versus 1.0%).

However, the incidence of these AEs in the aripiprazole group was generally comparable to or lower than that in the haloperidol or risperidone group. Additionally, the incidence of somnolence and EPS-related AEs (extrapyramidal syndrome and akathisia) in the aripiprazole group was markedly lower than that in the haloperidol group.

Common, drug-related adverse events were considered to be those with an incidence of at least 5% in the aripiprazole group and at least twice the corresponding placebo incidence. No events met these criteria.

d. Dose-Relatedness

The sponsors evaluated dose-response for adverse event reporting rates using a Cochran-Mantel-Haenszel (CMH) test stratified by protocol. Stratification was employed to

take into account the different dose levels included among the four short-term placebo-controlled fixed-dose studies. AE reporting patterns appeared to vary among studies; for example, 7 of 11 reports of orthostatic hypotension at 30 mg came from one study (97201).

The results of the CMH test stratified by study identified somnolence as the only AE that showed a statistical trend (P-values =0.050, both including and excluding placebo).

e. Demographic Effects on Adverse Event Incidence

An assessment of the effect of demographic variables (age, gender, and race) on adverse event reporting rates was performed by comparing the drug:placebo odds ratios across demographic subgroups. Age subgroups were defined as 18-50 and >50 years old. Race subgroups were defined as White, Black, Hispanic and Other.

For each demographic subgroup, the drug:placebo ratio for a patient experiencing a particular event was computed from the pool of the 5 short-term, placebo-controlled trials in schizophrenia. Then the Breslow-Day Chi Square test for homogeneity of the odds ratios across the subgroups for each demographic variable was performed and the p values were reviewed. Alpha was arbitrarily set at 0.1.

The analysis showed the following statistically significant findings:

• Gender: for asthenia, the odds ratio was 3.25 for females versus 1.03 for males (p=0.085); for vomiting, the odds ratio was 2.46 for males versus 1.09 for females (p=0.068).

• Age: for nausea, the odds ratio in the younger age group was 1.73 versus 0.59 in the older patients (p=0.055)

5. Laboratory Data

a. Extent of Laboratory Testing

Routine assays of hematology, serum chemistry, and urinalysis variables were conducted during the 5 placebo controlled short-term schizophrenia studies. The tests used and their timing during each of the five trials are presented in **Appendix VII-8**.

b. Potentially Clinically Significant Laboratory Changes

The sponsor identified patients in the pool of the 5 short-term, placebo-controlled studies with normal pre-treatment lab values who had potentially clinically significant (PCS) laboratory changes using the criteria in **Appendix VII-9**. My analyses focused on a comparison of the aripiprazole and placebo treatment groups in terms of the proportions of these patients meeting those criteria during these studies.[29]

An examination of PCS laboratory values in aripiprazole-treated patients with abnormal pre-treatment values revealed no remarkable findings.

1) Serum Chemistry

A comparison between aripiprazole and placebo of the percentages of patients with PCS serum chemistry changes during treatment revealed no statistically significant differences with a higher aripiprazole percentage. See **Appendix VII-10**.

Seven aripiprazole patients in the study pool had PCS elevations in SGOT and/or SGPT. Increases in SGPT were to values in the range of 150-762 U/L and in SGPT to 124-485 U/L. Three patients had both SGOT and SGPT elevations. Patient 93202-5-158 had the most marked elevations: SGPT=762 U/L and SGOT=485 U/L. There was no associated elevated total bilirubin or jaundice in any of these patients. In five of the seven cases, the elevated transaminases returned to normal range with continued treatment. SGOT remained elevated in two patients at last assessment (Patient 138001-33-102 with a level of 150 U/L and Patient 97201-36-18 with a level of 86 U/L).

One additional patient had an elevation of total bilirubin to 2.3 mg/dL. There were no transaminase elevations or jaundice. Total bilirubin decreased to 1.7 mg/dL with continued aripiprazole treatment but there were no further values reported.

Twenty-three (3.3%) of the 694 aripiprazole-treated patients with a normal baseline CPK value had a potentially

[29] Specifically, the odds of having a PCS value were compared between drug and placebo using Fisher's exact or other appropriate test at an alpha of 0.05.

clinically significant CPK elevation during treatment (i.e. ≥3×ULN). This was slightly greater than the percentages of such patients in the placebo, haloperidol, and risperidone groups (2.2%, 2.3%, and 1.3%, respectively). The difference between aripiprazole and placebo (3.3% vs. 2.2%) was not statistically significant (p=0.4, Mantel-Haenszel chi-square). The reporting rates of related adverse events (e.g., myalgia) in this study pool were not significantly different from those in the placebo group. All but seven of the CPK abnormalities in aripiprazole patients resolved while the patients were still receiving drug. The highest CPK value [redacted] resolved spontaneously within 7 days while the patient remained on aripiprazole. Only one patient (138001-7-458) discontinued aripiprazole treatment due to an elevated CPK [redacted]. There were no follow-up values. This patient reported no muscle-related symptoms or symptoms related to possible neuroleptic malignant syndrome.

2) Hematology

A comparison of the percentages of patients with PCS hematology changes revealed only one statistically significant difference: for hematocrit, 1.1% of aripiprazole vs. 0.0% of placebo patients met PCS criteria for decreased hematocrit. The difference for hemoglobin values was not statistically significant. See **Appendix VII-11**.

Eight patients had a PCS decrease in hematocrit to values in the range of 20 to 37%. All were male. None of these patients reported any bleeding-related adverse events. In four of these cases, the hematocrit returned to normal range with continued aripiprazole treatment.

Among the remaining 4 cases, one patient had hematocrit values fluctuating in the range of 33.7% to 39.4% during treatment (baseline 44.8%). In two patients, hematocrits were improved but still abnormal (36.5% and 36.6% vs. 47.1% and 42.4% at baseline, respectively). The last patient (97202-81-17) had a markedly decreased hematocrit on day 3 of aripiprazole treatment (20.3% vs. 43.2% at baseline). He experienced a proportional drop in hemoglobin from 14.4 g/dL pre-treatment to 7.1 g/dL. There was no appreciable change in total serum bilirubin. On day 3, he withdrew consent and there are no follow-up values.

Clozapine, a drug pharmacologically related to aripiprazole, has been associated with significant leukopenia and neutropenia, with agranulocytosis in extreme cases. Five (0.6%) of the 851 aripiprazole-treated patients with a normal WBC at baseline had a PCS low WBC during treatment (defined as ≤ 2,800/cmm). Of these five patients, three had a one-time decrease in WBC that returned to normal within a week, one had a baseline WBC that was at the lower limit of normal and decreased slightly during the study (2,900/cmm to 2,660/cmm), and one had one-time recorded value of 10 cells/cmm, which is considered an error. None had an adverse event suggestive of an infectious process.

One (0.1%) of the 840 aripiprazole-treated patients with a normal baseline value had a low neutrophil count during treatment. The absolute neutrophil count for this patient decreased from borderline low at baseline to 663 cells/cmm (total WBC count was 3,900/cmm at that time). This value increased almost three-fold over the next week (to 1,795/cmm) and spontaneously returned to normal range over the next month, during which aripiprazole was continued. The patient had no physical findings of an adverse event such as infection secondary to this finding.

Seven (0.8%) of the 849 aripiprazole-treated patients with a normal platelet count at baseline had PCS low platelet counts during treatment. The baseline platelet counts for four of the seven patients were borderline low before treatment. In all four patients, platelet counts returned to normal range while on treatment; however, in one patient (97202-89-6), thrombocytopenia was found to have recurred at the last assessment (65,000/cmm) and there were no follow-up counts.

A fifth patient had one on-treatment abnormal value that returned to normal at the next study visit and remained in normal range thereafter. The other two patients (138001-7-281 and 97202-71-19) had normal pre-treatment platelet counts and only one on-drug count, which was abnormal in each patient (80,000/cmm and 81,000/cmm, respectively); in both cases, no further hematology data were reported.

None of these 7 patients with PCS low platelet counts had a physical manifestation of a bleeding disorder.

3) Urinalysis

A higher percentage of all patients on aripiprazole compared to placebo had PCS urine glucose elevations (1.7 vs. 0.3%, p=0.0475). However, when patients with a prior history of diabetes were excluded, there was no statistically significant difference between the two groups (0.5% vs. 0.3%, p = 1.000). See **Appendix VII-12**.

c. Median Change from Baseline in Laboratory Values

The median percentages of change from baseline were compared between aripiprazole and placebo for serum chemistry and hematology parameters. This comparison was based on visual inspection; no formal statistical testing was conducted by the sponsor.

1) Serum Chemistry

This examination revealed a 9.1% median change for ALT among aripiprazole patients compared to 0.0% median change for placebo. A median change of this magnitude is of questionable clinical significance.

For CPK, there was 22.1% median change for aripiprazole vs. 8.5% for placebo, 7.0% for haloperidol, and 8.2% for risperidone. The reason for the elevated median change in the aripiprazole group is not clear. However, several factors can be associated with CPK elevations (e.g., physical exertion and intramuscular injections) and conceivably the treatment groups were not balanced on one or more of these. Given that the proportion of patients with PCS elevations in CPK was not much higher for aripiprazole compared to placebo, the absence of related clinical signs or symptoms, and resolution of this abnormality in most patients while continuing aripiprazole, this finding is not deemed to be of major importance.

Finally, there was a 56.5% median decrease in serum prolactin levels in the aripiprazole group compared to 0.0% for placebo.

Data are displayed in **Appendix VII-13**.

2) Hematology

For neutrophil counts, there was a median 8.1% increase among aripiprazole patients vs. a 1.5% decrease among placebo patients. There were no other remarkable differences between these two treatment groups. See **Appendix VII-14**.

d. Dropouts due to Abnormal Laboratory Findings

A review of the incidence of treatment-emergent abnormal laboratory values that led to discontinuation of study therapy revealed only one such aripiprazole-treated patient, who dropped out due to an elevated CPK abnormal lab value (Patient 138001-7-458). This patient is discussed above.

6. Vital Sign Data

a. Vital Sign Assessments

In the short-term, placebo-controlled schizophrenia studies, vital sign measurements included blood pressure and radial pulse rates which were taken in the supine and standing positions at screening, baseline, and each follow-up visit. These measurements were made prior to any scheduled blood sampling. Blood pressure measurements were obtained after patients had been supine for 5 minutes and repeated 2 minutes after standing.

b. Potentially Clinically Significant Vital Sign Changes

The sponsor identified patients from the pool of placebo-controlled schizophrenia trials who experienced a potentially clinically significant (PCS) vital sign change by the criteria listed in **Appendix VII-15**.

The incidence of PCS vital sign abnormalities in the short-term placebo-controlled studies in schizophrenia is presented in **Appendix VII-16**. The incidence of PCS vital sign measurements for the short-term placebo-controlled studies differed little between the aripiprazole and placebo treatment groups. Statistical analysis of these data revealed only one statistically significant difference: standing heart rate was increased in 18.7% of aripiprazole patients vs. 13.1% of placebo patients ($p=0.0120$, Cochran-Mantel-Haenszel test). An increase in

standing heart rate may reflect a compensatory response to a lowering of blood pressure.

Displays of the incidence of PCS vital sign abnormalities by dose, age, gender and race were reviewed.[30] No differences in the occurrence of PCS vital sign abnormalities were found across dose and demographic subgroups although the limited sample size of patients 65 years and older precluded meaningful interpretation of their data compared to other age groups.

c. Mean Change from Baseline in Vital Sign Measures

Six vital sign variables were analyzed with respect to mean change from baseline in the short-term, placebo-controlled schizophrenia studies: diastolic BP (standing and supine), systolic BP (standing and supine), and pulse (standing and supine). **Appendix VII-17** displays the mean change from baseline to endpoint for these vital sign variables.

There were small mean increases in the aripiprazole group and small mean decreases in the placebo group for these six measures. No differences were considered clearly clinically significant.

d. Dropouts due to Vital Sign Abnormalities

One patient in the aripiprazole group (94202-6-112), a 42 year old heavy-smoking male, discontinued from the short-term placebo-controlled studies because of acute hypertension. Review of his narrative summary revealed he dropped out on day 7 of the study because of acute "severe" hypertension. The maximum elevation in supine systolic BP consisted of an increase from 130 mmHg at randomization, to 140 mm Hg on days 2, 7, 8, and 9 of the study. Maximal standing diastolic at termination was 100 mmHg (baseline=90 mmHg).

There were no dropouts in the placebo group for any vital sign abnormality.

[30] See Tables S.6.5.2, S.6.5.3, S.6.5.4, and S.6.5.5 in the NDA ISS.

7. Electrocardiographic (ECG) Data

a. ECG Assessments

The timing of 12-lead ECG's in the pool of the 5 short-term, placebo-controlled schizophrenia trials is presented by study in **Appendix VII-18**.

b. Potentially Clinically Significant ECG Changes

The criteria for identifying potentially clinically significant (PCS) ECG measurements are displayed in **Appendix VII-19**.

Visual inspection of the percentages of patients with PCS ECG abnormalities within the short-term, placebo-controlled schizophrenia studies revealed occurrences in the aripiprazole group for seven ECG variables: tachycardia, bradycardia, sinus tachycardia, sinus bradycardia, ventricular premature beats, first-degree AV block, and right bundle branch block. Data are displayed in **Appendix VII-20**.

A 2-tailed Fisher's exact test was performed to compare the odds of each abnormality in the aripiprazole vs. the placebo group for each of the seven variables. There were no statistically significant differences between aripiprazole and placebo (alpha=0.05).

QT interval data were analyzed separately by the sponsor and are discussed below.

c. Median Change from Baseline in ECG Values

The median change from baseline to minimum or maximum value for the PR interval, QRS interval, RR interval, and heart rate in the short-term placebo-controlled studies in schizophrenia is presented in **Appendix VII-21**.

The median changes from baseline for both the PR and QRS intervals were comparable between the aripiprazole and placebo groups. An increase in heart rate and decrease in RR interval were observed for aripiprazole relative to placebo. The median change from baseline to endpoint in heart rate was +4.0 bpm for aripiprazole compared with +1.0 bpm for placebo.

d. Special Analyses of the Corrected QT Interval

The sponsor presented QT interval data in the ISS using the fractional exponential correction method (QT_{cE}) recommended by the FDA Division of Neuropharmacological Drug Products (DNDP); this entailed using baseline measurements from the Phase II/III data set.[31] Supplemental analyses provided data based on the DNDP correction formula ($QT_{cN} = QT/RR^{0.37}$) and Bazett's formula ($QT_{cB} = QT/RR^{0.5}$).

Appendix VII-22 displays the results of QTc analyses using the QT_{cE} correction for the pool of the 5 short-term, placebo-controlled schizophrenia studies. Aripiprazole was comparable to placebo with respect to the mean changes in QT_c from baseline to study endpoint and to maximum reading. The percentages of patients with various degrees of QT_c prolongation were also comparable between aripiprazole and placebo. The results using Bazett's and DNDP correction formulae were similar.[32] Consistent with historical data, risperidone was associated with a small but statistically significant increase in QT_c regardless of the correction method employed. In addition, an increase in QT_c was also observed in the haloperidol group relative to placebo and was most apparent when the fractional exponential and QT_{cN} formulas were used.

A corresponding analysis by aripiprazole dose group over the range of 2 to 30 mg/day showed that mean changes in QT_{cE} at all doses were comparable to placebo.[33] For the group that received 30mg, the highest dose of aripiprazole administered in these studies, the mean change from baseline in QT_{cE} at study endpoint was -4.39 msec compared to -3.50 msec for placebo; the mean changes to maximal reading were +0.83 and +0.59 msec, respectively. The proportion of patients treated with 30mg who had a change in QT_{cE} ≥30 msec was 3.7% (9/241) compared to 6.0% (21/349) in the placebo group. No patient treated with 30mg of aripiprazole met any of the other criteria for QT_{cE} prolongation (change ≥60 msec or reading >450 msec).

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[31] See a July 9, 1999, memorandum from Greg Burkhart, DNDP Safety Team Leader, to Robert Temple, CDER Associate Director for Medical Policy, for a background discussion of this issue and information on this methodology.
[32] See ISS Supplemental Tables S.11.3.3.1A-1 and S.11.3.3.1A-2, respectively.
[33] See ISS Table 11.3.3.1B.

Study 99224, a special study that will be discussed in Section VII.B.9.c below, utilized doses up to 90 mg/day for 15 days. ECG's were assessed in this trial. This study suggested that at daily doses of 75mg and 90mg, there were sizeable median increases from baseline in the corrected QT interval: +27 and +24 msec, respectively, using the QT_{cN} correction. Thus, although QT_c prolongation is unlikely to be important at proposed doses (to 30 mg/day), the prolongation may become substantial in cases where aripiprazole is taken in overdose or when it's metabolism is significantly inhibited.

e. Dropouts due to ECG Abnormalities

There were no dropouts due to ECG abnormalities in the short-term, placebo-controlled studies in schizophrenia.

8. Special Safety Analyses

a. Orthostatic Hypotension

1) Orthostatic Blood Pressure Measurements

Supine and standing blood pressure measurements were obtained in all short-term placebo-controlled studies in schizophrenia. Orthostatic hypotension is defined as a decrease of ≥30 mmHg in supine to standing systolic blood pressure measurements. Blood pressure data from the short-term placebo-controlled database were analyzed to determine the incidence of ≥30-mmHg decreases.

There was a slightly higher incidence of orthostatic blood pressure measurements that met this criterion for patients in the aripiprazole group (14.0%) compared with the placebo group (11.9%), but the incidence with aripiprazole was less than with haloperidol (19.1%).

An examination of the incidence of ≥30 mmHg decreases in orthostatic systolic BP by dose in the pool of the short-term, fixed dose studies revealed no significant linear dose-response among the aripiprazole dose groups (range of doses was 2 to 30 mg/day).

2) Orthostatic-Related Adverse Events

A broad search was conducted using orthostatic hypotension and the related terms of syncope (includes faintness),

lightheadedness (includes dizziness), and orthostatic lightheadedness as search criteria.

In the short-term, placebo-controlled studies in schizophrenia, 13.6% of aripiprazole and 9.4% of placebo patients experienced an orthostatic-related AE. This was slightly higher than in the haloperidol group (11.5%) but less than in the risperidone group (17.2%). The incidences of orthostatic hypotension and orthostatic lightheadedness were similar between the aripiprazole and placebo groups (1-2%).

In the short-term placebo-controlled studies in schizophrenia, three (0.3%) of the 926 aripiprazole-treated patients discontinued due to orthostatic-related AE's of syncope, lightheadedness, and lightheadedness. No patients in the placebo group discontinued due to AEs related to orthostasis.

b. Glucose Metabolism

1) Adverse Events Related to Glucose Metabolism

A comprehensive search database was conducted to identify AE's that were potentially associated with glucose metabolism. The AE terms used for this search were diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, hyperglycemia, ketonuria, and glucose/carbohydrate intolerance.

a) Short-Term Study Pool

A total of four patients had an on-study AE of diabetes mellitus in the short-term placebo-controlled studies in schizophrenia: two (0.5%) of the 413 patients in the placebo group and two (0.2%) of the 926 patients in the aripiprazole group. The AE term of hyperglycemia was reported for 3 (0.3%) of 926 aripiprazole-treated patients and 1 (1.0%) of 99 risperidone-treated patients.

No patients in the short-term placebo-controlled studies in schizophrenia discontinued treatment due to an AE related to glucose metabolism.

b) Long-Term Studies

A similar comprehensive AE Database search was conducted for the long-term controlled studies. With extended exposure to aripiprazole, the incidence of treatment-emergent AEs related to glucose metabolism was low in the 52-week double-blind haloperidol-controlled studies (98217/98304). This finding was consistent with that in the short-term placebo-controlled studies in schizophrenia.

The incidence of hyperglycemia in the aripiprazole group was 0.2% (2/859) in the long-term double-blind haloperidol-controlled studies (98217/98304). No patients in the haloperidol group reported this event.

In the 26-week open-label olanzapine-controlled study (98213), diabetes mellitus was the only treatment-emergent AE related to glucose metabolism reported for patients in the aripiprazole group, and the incidence was equal to that in the olanzapine group (0.8%).

No other related AE's were reported in the aripiprazole groups in the long-term trials.

No aripiprazole-treated patients in the long-term controlled studies in schizophrenia discontinued treatment due to an AE related to glucose metabolism.

2) Laboratory Data Related to Glucose Metabolism

a) Glucose Levels

Blood samples for fasting glucose measurements were collected in just one of the short-term placebo-controlled studies in schizophrenia (study 138001). In study 138001, among patients with a baseline glucose measurement ≤ULN, the incidence of treatment-emergent glucose measurements >ULN was 5.5% (6/109) in aripiprazole and 10.3% (3/29) in placebo patients.

The other short-term and long-term controlled studies in schizophrenia collected only random blood samples for glucose levels. For the short-term studies, among the patients with a baseline glucose ≤160 mg/dl, the proportions of patients with a treatment-emergent glucose measurement ≥200 mg/dl were 1.4% for aripiprazole and 1.3% for placebo.

For the long-term haloperidol-controlled studies (98217/98304), among the patients with a baseline glucose ≤160 mg/dl, the proportions of patients with a treatment-emergent glucose measurement ≥200 mg/dl were 1.5% for aripiprazole and 1.2% for haloperidol. The corresponding figures for the long-term olanzapine-controlled study (98213) were 4.7% for aripiprazole and 4.5% for olanzapine).

b) Glycosylated Hemoglobin

Glycosylated hemoglobin is a measure of the degree of glucose elevation over time. This assay was collected in only in study 138001.

For patients who had a pretreatment glycosylated hemoglobin value < ULN, the incidence of elevated (> ULN) glycosylated hemoglobin was less for aripiprazole-treated patients compared with placebo-treated patients (9.2% vs. 15.7%). This difference was not statistically significant. In addition, the change from baseline to endpoint and change from baseline to maximum on-treatment evaluation (mean and median) were comparable between the aripiprazole and placebo groups.[34]

c. Lipid Metabolism

Fasting blood samples for the measurement of lipids were collected only for the short-term placebo-controlled study 138001; the other short-term and long-term studies required a random blood sample to be collected for the analysis of lipids. Variables measured included total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and the total cholesterol/HDL ratio.

Changes from baseline in fasting lipid results were small for both the aripiprazole and placebo groups in study 138001. For the aripiprazole group, small increases were noted for all lipid parameters, except triglycerides, which showed a small median decrease (-3.00 mg/dL vs. -4.50 mg/dL in the placebo group). HDL cholesterol analysis revealed a median % change for placebo of -7.76% and +2.53% for aripiprazole, which represents the only value found to be statistically significant .

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[34] See Supplemental Tables S.11.2.1.6B and S.11.2.1.6C in the NDA ISS.

Change from baseline in random lipids were analyzed in long-term controlled studies in schizophrenia (98217/98304/and 98213). The magnitude of the median changes in the random total cholesterol for the aripiprazole groups was small and less than that for the control agents (+5.0 vs. +8.0 mg/dL for haloperidol and -2.0 vs. +20.0 mg/dL for olanzapine in the haloperidol- and olanzapine-controlled trials, respectively).

Aripiprazole did not appear to adversely affect cholesterol metabolism in either the long-term nor the short-term trials.

d. Tolerance in the Elderly

Two studies that assess the safety and tolerability of aripiprazole in elderly patients have been completed: 98203 (a small pilot open-label ascending-dose cohort study in demented patients) and 138006 (a study that evaluated the safety and efficacy of aripiprazole in psychosis associated with Alzheimer's Dementia).

a) Study 98203

Study 98203 was an uncontrolled, ascending dose study in which 5 cohorts of elderly, demented patients received doses from 5 to 30 mg/day increased in step-wise fashion. The most frequently occurring AEs (occurring in =10% of patients) were somnolence (73%, 22/30), headache (40%, 12/30), agitation (27%, 8/30), constipation (23%, 7/30), and dyspepsia (23%, 7/30). Since no placebo arm was included in this study, the incidence of AEs occurring at the highest doses was evaluated in relation to incidence at lower doses. The following AEs were reported with increased frequency at the higher doses: somnolence, agitation, constipation, and orthostatic hypotension. In particular, the reporting rates for somnolence by dose cohort is notable:

Dose Cohort	% Reporting Somnolence
5-10 mg/day	0%
10-15 mg/day	60%
15-20 mg/day	80%
20-25 mg/day	100%
25-30 mg/day	100%

b) Study 138006

Study 138006 evaluated a flexible daily dose range of aripiprazole (2 mg to 15 mg) over a 10-week period. A total of 105 patients with psychosis associated with Alzheimer's disease between 56 and 95 years of age were treated with aripiprazole; of these, 104 were ≥65 years of age. Data from this study demonstrated that aripiprazole had reporting rates for two adverse events that notably exceeded the placebo reporting rates: accidental injury (8% vs. 4%) and somnolence (8% vs. 1%). The drug:placebo odds ratio for somnolence in this study was 7.8 compared to 1.4 in the pool of the short-term, placebo-controlled studies in patients with schizophrenia.

As discussed above, the mortality rate in the aripiprazole group in this trial was 3.8% (4/105) versus 0.0% (0/102) in the placebo group. This difference approached significance ($p=0.12$, 2-tailed Fisher's exact test; $\alpha=0.10$). Since exposures in the two groups were comparable, exposure-adjusted rates were not computed. The causes of death in the four aripiprazole-treated patients were pneumonia, heart failure, sepsis, and, in the last case, unknown.

Also, the incidence of all AE's classified by the sponsor as serious was higher in the aripiprazole group compared to the placebo group (15% vs. 9%); this difference approached statistical significance ($\alpha=0.10$). Except for accidental injuries (5% vs. 2% in placebo), there were no notable differences between aripiprazole and placebo in the proportion of patients with specific SAE's.

Elderly patients treated with aripiprazole may be at increased risk for accidental injury and somnolence compared to elderly patients treated with placebo. Otherwise, aripiprazole appeared safe and well-tolerated in the elderly patients.

e. Hepatobiliary Events

1) Preclinical Findings

In repeat-dose toxicity studies in monkeys, gallsand (the granular material in the gallbladder resembling mud) and an occasional stone (calculus) were observed at doses of 25

mg/kg/day or greater after 4 - 52 weeks of treatment. These doses were designed to achieve sustained plasma concentrations of aripiprazole at or above the plasma levels in humans achieved following administration of the highest expected clinical dose (30 mg/day). Neither gallsand nor gallstones were associated with elevated hepatic enzymes or histopathological changes in gallbladder mucosa. Two of 8 cases showed minimal histopathological changes consistent with focal hepatolithiasis were seen at 50 and 75 mg/kg/day after 39 weeks.

Monkey gallsand and gallstone chromatography from the 39 week study demonstrated that the major constituents were the sulfate conjugates of hydroxy aripiprazole and dehydrohydroxy aripiprazole. It was hypothesized that the formation of monkey gallsand and stones was consequent to precipitation of poorly soluble sulfate conjugates of aripiprazole metabolites in the bile of these monkeys. When *in vitro* hepatocyte data was analyzed in humans, monkey, rats, and mice hepatocytes, formation of hydroxy aripiprazole occurred across all 4 species, but only humans and monkeys had the sulfate and glucuronide conjugates of this metabolite.

2) Human Bile Study (138061)

A clinical pharmacology study (138061) was conducted to determine the concentration of these conjugates in human bile after aripiprazole oral doses of 15 to 30 mg/day for 7 days in healthy subjects. The highest concentrations of the conjugates in human bile at 30 mg/day were no more than 6% of the lowest bile concentrations found in monkeys in the 39 week study. Therefore, it appears that administration of aripiprazole 30 mg/day to humans will not produce concentrations expected to result in precipitation and subsequent gallstone formation.

Limitations of this study include the use of healthy volunteers in lieu of patients with schizophrenia and the fact that 7 days of treatment was likely insufficient to attain steady-state blood levels of aripiprazole and its active metabolite.

3) Occurrence of Hepatobiliary Adverse Events

In the non-updated Phase 2/3 database, there were 3823 unique patient exposures (representing 2063 patient-years of exposure) to aripiprazole in non-Japanese Phase 2/3 studies.

A comprehensive search of the AE database for aripiprazole Phase 2/3 studies was performed to identify patients who had a diagnosis or symptom suggestive of gallstones. In addition, the aripiprazole safety database was searched for medical history of gallstones, concomitant diagnostic procedures, or potential treatment of gallstones.

A broad group of search terms was used: any term including gallbladder or right upper quadrant pain, cholelithiasis, choledocholithiasis, cholecystitis, cholangitis, cholecystectomy, hepatobiliary, biliary, gallstones, jaundice, steatorrhea, fatty stools, clay-colored stools, colic (non-renal) cramping, and pancreatitis. Abdominal pain with the following qualifiers was also reviewed: middle of the upper abdomen, epigastric, epigastrium, recurrent, sharp or cramping or dull, radiating to back or below the right shoulder blade, interscapular, scapular, pain after ingestion of fatty or greasy foods, and abdominal pain that occurred within minutes following meals. The General Practice Research Database (GPRD) diagnostic and procedural codes related to gallbladder disorder were also added as search terms. In addition, any liver-related AEs including elevations (1.5 ×ULN) in alkaline phosphatase, bilirubin, AST, ALT, amylase, and lipase were identified. Case record results from this review were assessed and any cases clearly related to on-study onset or exacerbation of gallbladder disorder were identified.

Twelve patients (eight treated with aripiprazole, three treated with placebo, and one treated with haloperidol) with on-study events related to gallbladder disease were identified.

In the short-term placebo-controlled studies in schizophrenia, hepatobiliary-related AEs occurred in one (0.24%) of 413 patients in the placebo group (1/24.19 patient years) and none of 926 patients in the aripiprazole group (0/59.52 patient years).

In the short-term placebo-controlled studies in bipolar mania, two placebo-treated patients and one aripiprazole-treated patient had hepatobiliary AEs. These studies (138007 and 138009) remain blinded overall, but the treatment codes for these three patients were unblinded, and a denominator can be estimated from expected randomization. In these studies, two (1%) patients of an expected 200 placebo-treated patients and one (0.33%) patient of an expected 300 aripiprazole-treated patients had a hepatobiliary event that began during the 3-week short-term phase of the studies.

In long-term double-blind haloperidol-controlled studies (98217/98304), one (0.23%) of 431 haloperidol-treated patients and two (0.23%) of 859 aripiprazole-treated patients had a hepatobiliary-related AE. The expose-adjusted rates for hepatobiliary AE's were 4.2/1,000 PY's for aripiprazole and 5.2/1,000 PY's for haloperidol.

The remaining five cases among aripiprazole patients of events related to gallbladder disease occurred in the 2607 patients treated with aripiprazole during various open-label extension studies (or study phases), and no control group is available for comparison.

One patient (138001-68-275) discontinued study drug (aripiprazole) due to a hepatobiliary event, and this same patient was the only one in this group who died. The death occurred due to complications of adult respiratory distress syndrome, which developed 54 days after the initial event of pancreatitis associated with gallstones.

Seven of the eight aripiprazole-treated patients continued to receive aripiprazole despite a hepatobiliary-related AE. In one of the seven cases, the event (mild cholecystitis in 98217-277-6) continued and was unresolved at the time of last available data. In another case (00-7-0343), the initiating event of common duct stones resolved in 5 days; however, the secondary pancreatitis and liver inflammation was unresolved as of the last data available. In two cases (mild cholecystitis in 98304-447-63 and relapse of chronic mild cholecystitis in 98304-524-69), the events resolved after 5 to 152 days while the patients were still on study.

One patient in the placebo group (97201-20-5) and three patients in the aripiprazole group (138009-24-222, 98217-

286-5, and 97202-87-7) underwent cholecystectomy immediately or within 6 days of onset.

A secondary search of AE terms related to cholelithiasis and cholecystitis was conducted among 769 patients treated with aripiprazole in Japan. No cases were found.

4) Summary

Of 3823 patients exposed to aripiprazole in non-Japanese Phase 2/3 clinical studies, eight aripiprazole patients (0.2%) had on-study events related to gallbladder disease. Three (0.08%) of the 3823 patients had a resulting cholecystectomy. Using US NIH and Census Bureau data, an estimated 1,000,000 new cases of gallbladder disease (0.5%) and 600,000 cholecystectomies (0.3%) occurred in the adult United States population in 1991. In comparing the Phase 2/3 study data to these epidemiologic data, there is no evidence that patients treated with aripiprazole are at increased risk for the development of gallbladder disease.

In view of the lack of signal from the substantial clinical database together with these biliary metabolite concentration data, the sponsor concludes that the observation of biliary sludge and stones in one animal species, cynomolgus monkeys, has no known relevance to human dosing.

f. Weight Gain

To assess the relationship of aripiprazole to change in body weight, mean change from baseline weight (kg) and percentage of patients with significant weight gain, defined as a ≥7% increase from baseline, were analyzed. An additional study, 138002 submitted in the Safety Update, was also reviewed. This study was specifically planned to investigate weight gain associated with aripiprazole compared to olanzapine.

For the short-term placebo-controlled studies and long-term controlled studies in schizophrenia, change in body weight from baseline to a prespecified study time point and endpoint was analyzed using an ANCOVA model controlling for baseline weight, gender, and protocol.

a) Short-Term Study Pool

Body weight was measured at baseline, Week 2, and Week 4 for all short-term placebo-controlled studies in schizophrenia except for study CN138-001. For study 138001, weight was measured at baseline, Day 4, and then weekly up to Week 6. Weight change was evaluated at Week 4 using the observed cases (OC) and at Week 4 and endpoint using the LOCF observation.

On average, there was a minimal increase in weight (+0.7 kg) for patients in the aripiprazole group compared with a small decrease in the placebo group (-0.05 kg) at Week 4.

The percentage of patients with a significant weight gain (7% increase from baseline) at endpoint was greater by either measure (OC and LOCF) for patients in the aripiprazole group compared with the placebo group (8.1% vs. 3.2%, LOCF), but lower than that in the haloperidol and risperidone groups. Please see **Appendix VII-23**.

Very small mean increases from baseline in weight were noted for all dose levels of aripiprazole. There was no apparent relationship between weight gain and increase in dose.[35]

Summarizing, in short-term placebo-controlled studies in schizophrenia, patients who received aripiprazole showed an increase in body weight relative to patients who received placebo, based on the mean change from baseline in body weight and the percentage of patients with significant weight gain at endpoint. However, the magnitude of increase in body weight and the incidence of significant weight gain (≥7% increase from baseline) for the aripiprazole group were less than those for either the haloperidol or risperidone group.

b) Long-Term Studies

For the long-term double-blind haloperidol-controlled studies (98217/98304), body weight was measured at baseline, Weeks 1, 4, 8, 12, 26, 38, and 52 (endpoint). ANCOVA with adjustment for baseline weight, gender, and protocol was utilized to evaluate the weight change at

[35] See ISS Supplemental Table S.11.2.3.2 in the NDA ISS.

Weeks 8, 26, and 52 using the OC observation and at Week 52 using the LOCF observation.

Mean changes from baseline were slightly higher for the aripiprazole group compared with the haloperidol group for all data sets analyzed at all time points. The 52-week longitudinal analysis showed a +1.05 kg change for aripiprazole versus a +0.39 kg change for haloperidol at Week 52 (LOCF).

In the long-term double-blind haloperidol-controlled studies (98217/98304), 20% of the aripiprazole patients had a weight gain of at least 7% at week 52 compared to 13% of the haloperidol patients (LOCF).

In the 26-week olanzapine-controlled study, the LOCF analysis revealed a 0.91 kg mean decrease in the aripiprazole group vs. an increase of 3.62 kg in the olanzapine group. The proportion of patients with a weight gain of at least 7% was significantly less in the aripiprazole group compared to the olanzapine group (6% vs. 25%).

c) Study 138002

Study 138002 was a randomized, double-blind study that compared the safety and tolerability of aripiprazole versus olanzapine as evidenced by weight gain during treatment. The primary outcome measure was the percentage of patients showing significant weight gain (7% increase) from baseline to Week 26. The sponsor hypothesized that aripiprazole would be associated with less weight gain than olanzapine

This 26-week study demonstrated that aripiprazole 15-30 mg per day was associated with significant weight gain less frequently than olanzapine 10-20 mg per day in schizophrenic patients with an acute relapse (13% vs. 33%).

g. Prolactin Elevation

Phase 2/3 controlled studies were not designed for prolactin blood samples to be collected relative to dosing or time of day; only a random blood sample was collected for the analysis of prolactin.

The incidence of prolactin measurements > ULN was analyzed using Fisher's exact test. In addition, the median percent

change from baseline and the median percent change from baseline to highest on-treatment evaluation were analyzed using a two-sample Wilcoxon test.

Analyses of prolactin were conducted for the pool of the five short-term, placebo-controlled studies in schizophrenia and for one of the long-term double-blind haloperidol-controlled studies (98217). Prolactin samples were not collected for the other long-term double-blind haloperidol-controlled study (98304) or the olanzapine-controlled study (98213).

a) Short-Term Study Pool

For both baseline strata (i.e., ≤ULN and >ULN), the incidence of increases in prolactin levels >ULN was significantly less for the aripiprazole group compared with the placebo group. Please see **Appendix VII-24**. Conversely, the incidence for the haloperidol and risperidone groups was greater when compared with aripiprazole in both baseline strata.

b) Long-Term Study (98217)

For both baseline strata (≤ULN, >ULN), the incidence of prolactin level > ULN was significantly lower in the aripiprazole group compared with the haloperidol group. Please see **Appendix VII-25**.

For the long-term double-blind haloperidol-controlled study 98217, analysis of median percent change from baseline in serum prolactin showed decreases for the aripiprazole group that were significantly different from the increases seen in the haloperidol group at weeks 8, 26, and 52. At week 52 (LOCF), there was a median 40% decrease in serum prolactin in the aripiprazole group compared to a 177% increase in the haloperidol group.

h. Seizures

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

In the short-term, placebo-controlled studies, one of the 926 aripiprazole patients (138001-21-262) had a seizure (0.11%) and none of the 413 placebo patients had a seizure.

The incidence of seizure-related AEs in the long-term double-blind haloperidol-controlled studies (98217/98304) was low. None of the haloperidol-treated patients and only 0.46% (3/859) of the aripiprazole-treated patients had a seizure-related AE. In the open-label olanzapine-controlled study (98213), none of the aripiprazole-treated patients and 0.81% (1/123) of the olanzapine-treated patients had a seizure-related AE.

i. Treatment-Emergent Suicidality

a) Suicide-Related Events in the Short-Term Study Pool

In the short-term, placebo-controlled study pool, the incidence rate of suicide attempt in the aripiprazole group was low and comparable to that in the placebo group (0.2% each). Please see **Appendix VII-26**. No patients died as a result of a suicide attempt during the short-term placebo-controlled studies in schizophrenia.

The incidence rate of suicide-related AEs (suicidal ideation, intentional injury, and suicide attempt [includes patients who died as a result of the suicide attempt]) was very low and was similar across all treatment groups (1.1% in the aripiprazole group, 0.7% in the placebo group, 0.5% in the haloperidol group, and 0% in the risperidone group).

b) Suicide-Related Events in Long-Term Studies

In the long-term double-blind haloperidol-controlled studies in schizophrenia (98217/98304), the incidence rate of suicide attempt was low and similar between the aripiprazole (0.4%) and haloperidol (0.5%) groups. Please see **Appendix VII-27**. Three (0.3%) of the 859 aripiprazole-treated patients (98304-439-60, 98304-509-50, and 98304-558-58) and one (0.2%) of the 431 haloperidol-treated patients (98304-447-55) died as a result of a suicide attempt.

There was only one suicide-related AE (suicidal thought in an aripiprazole-treated patient) in the open-label olanzapine-controlled study (98213).

c) Suicidality as Measured by the MADRS

As an additional measure of treatment-emergent suicidality, changes in item 10 of the Montgomery-Asberg Depression Rating Scale (MADRS) were examined. Item 10 specifically addresses suicidal thoughts and is rated from 0 to 6, with low scores (0 to 2) indicating rare or fleeting suicidal thoughts and higher scores (5 or 6) indicating explicit plans or active preparation for suicide. MADRS testing was performed throughout studies 98217/98304.

The results of Item 10 show that for patients with baseline MADRS scores of 0 to 2, the incidence of MADRS scores of 5 or 6 at any time during the study was slightly lower in the aripiprazole group (4/842 or 0.5%) than in the haloperidol group (5/420 or 1.2%).

j. Extrapyramidal Symptoms (EPS)

1) EPS-Related Adverse Events

The analysis of EPS-related AEs was based on data from the non-Japanese Phase 2/3 database in the non-updated NDA database. EPS-related AEs were grouped into six categories according to their modified COSTART term:

- **Dystonic Events** included dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, or torticollis;
- **Parkinsonian Events** included akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, or tremor;
- **Akathisia Events** included akathisia or hyperkinesia;
- **Dyskinetic Events** included buccoglossal syndrome, choreoathetosis, dyskinesia, or tardive dyskinesia;
- **Residual Events** included movement disorder, myoclonus, or twitching;
- **Any Extrapyramidal Event** included any of the modified COSTART terms identified above.

The above categories were examined for both short-term and long-term studies.

a) Short-Term Study Pool

Appendix VII-28 presents the incidence of EPS-related AEs for the short-term placebo-controlled studies in schizophrenia.

For the pool of the short-term placebo-controlled studies in schizophrenia, the percentage of patients who had at least one EPS-related AE in the aripiprazole group (21.1%) was comparable to that in the placebo group (19.4%) and substantially lower than that in the haloperidol (43.5%) and risperidone (30.3%) groups. For individual AEs, rates were similar between the aripiprazole and placebo groups, except for akathisia, which had a slightly higher rate in the aripiprazole group (aripiprazole 10.0% versus placebo 6.8%). No differences were found when the reporting rates of EPS-related AEs were evaluated by dose, age, gender and race subgroups in the short-term placebo-controlled studies in schizophrenia.

Tardive dyskinesia was rarely reported in the short-term placebo-controlled studies: two (0.2%) of the 926 aripiprazole-treated patients and one (0.2%) of the 413 placebo-treated patients reported tardive dyskinesia in these studies. There were no reports of tardive dyskinesia in the haloperidol and risperidone groups.

Appendix VII-29 displays the percentages of patients who dropped out due to an EPS-related adverse event in the short-term, placebo-controlled schizophrenia studies. The proportion of patients who discontinued treatment due to EPS-related AEs for the aripiprazole group (7/926 or 0.8%) was slightly higher than that for the placebo group (0%). No patients discontinued treatment due to tardive dyskinesia.

b) Long-Term Studies

This review focuses only on the dyskinetic events in the long-term active-controlled studies. Aripiprazole was compared only to haloperidol in studies 98217 and 98304, which were 52 week double-blind trials. Four out of 431 haloperidol patients (0.9%) developed tardive dyskinesia compared to 5/859 aripiprazole patients (0.6%). This is not statistically significant. Dyskinesia differences between aripiprazole and haloperidol were more striking. Seven of 431 haloperidol (1.6%) patients developed the

dyskinesia while 1/859 (0.1%) aripiprazole patients developed this symptom. This was statistically significant on the 2-tailed Fisher's exact test (p = 0.0025).

A much smaller 26 week open-label study (98213) compared aripiprazole to olanzapine (123 patients in the olanzapine arm and 127 in the aripiprazole arm) showed no dyskinetic events at all.

In the long-term double-blind haloperidol-controlled studies, 1/431 haloperidol patients (0.2%) and no aripiprazole patients discontinued due to dyskinesia.

2) EPS Rating Scale Data

Standard rating scales (Simpson-Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale) were completed at baseline and specified study weeks in the short-term, placebo-controlled and long-term active-controlled schizophrenia trials.

For the pool of short-term studies, the change from baseline in the SAS Total Score, AIMS Total Score (first seven items), and Barnes Akathisia Scale Global Clinical Assessment was analyzed by the analysis of covariance (ANCOVA) approach, controlling for the baseline score and study center. The score at endpoint and the highest total score on treatment were both used for these evaluations. Endpoint was the patient's last evaluation in the defined study interval that was within 7 days of the last dose of medication. A similar analysis was performed for the long-term active-controlled studies.

a) Short-Term Study Pool

Appendix VII-30 displays the mean changes from baseline to endpoint and highest score for the three EPS rating scales in the short-term, placebo-controlled schizophrenia studies. There were no significant differences in the mean change from baseline to endpoint and highest on-treatment evaluations between the aripiprazole and placebo groups in the SAS Total Score.

The mean change from baseline to endpoint in the AIMS Total Score showed a significantly greater decrease for the aripiprazole group compared with the placebo group. The

difference between the aripiprazole and placebo groups in the mean change from baseline to highest AIMS Total Score also reached statistical significance with aripiprazole having a lower mean change from baseline.

By ANCOVA (controlling for baseline and study center), there were statistically significant increases in the mean change from baseline to endpoint and highest scores in the Barnes Akathisia Global Clinical Assessment in the aripiprazole compared to the placebo group.

When examined by aripiprazole dose, there was no apparent relationship between increasing dose level and mean change at endpoint for any of the EPS scales.[36]

A potential confounder in the evaluation of these data is the use of anticholinergic medication for EPS-related adverse events. In this pool of studies, such medication was used by 18.7% of aripiprazole patients, which was comparable to use in the placebo group (14.8%) and the risperidone group (20.2%) but much lower than in the haloperidol group (42.0%).

b) Long-Term Studies

In the pool of long-term controlled studies, I focused on the AIMS Total Score Data, where the AIMS Total Score ranges from 0-28, and a negative change score denotes improvement.

In the pool of the haloperidol-controlled studies, the mean changes from baseline to week 6, week 26, week 52, and to the highest score were significantly less in the aripiprazole group compared to the haloperidol group ($p<0.001$). Anticholinergic medication for potential EPS was used by 23.5% of aripiprazole and 56.8% of haloperidol patients.

In the open-label olanzapine-controlled study, the mean changes from baseline at weeks 8 and 26 and to the highest on-treatment score, there were no statistically significant differences between aripiprazole and olanzapine. In this study, about equal percentages of patients in the two treatment groups used anticholinergic medication for

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[36] See Table 11.2.4.1B in the NDA ISS.

potential EPS (28.4% of aripiprazole and 25.2% of olanzapine patients).

k. Neuroleptic Malignant Syndrome (NMS)

All medications associated with NMS have dopamine D2-receptor antagonist properties. NMS has also been associated with the withdrawal of anti-Parkinson therapy, leading to the hypothesis that the syndrome is the result of decreased dopamine activity in the CNS. Preclinical data suggest aripiprazole acts both as a dopamine antagonist and an agonist, so the sponsor hypothesizes that aripiprazole may cause less NMS occurrences.

a) Reports of NMS

The sponsor's comprehensive search of the Phase 2/3 clinical database was completed to identify aripiprazole-treated patients who had NMS reported as an AE. Of the 3823 patients treated with aripiprazole in the non-updated non-Japanese Phase 2/3 database, there was only one patient (98304-534-54) with reported NMS that was reasonably attributable to aripiprazole. The incidence of reported NMS during aripiprazole exposure in the Phase 2/3 studies was 0.03% (1/3823 patients), which is at the lower end of the range documented in the literature (0.07 to 0.2%).

One patient (138007-19-133) experienced NMS following treatment for a week with aripiprazole. The NMS developed 17 days after the last dose and after he already initiated treatment with other two drugs, risperidone and haloperidol. It is difficult to attribute this case to aripiprazole given the length of time since the last dose and use of other antipsychotics in the interim.

Of the 769 patients exposed to aripiprazole in the original Japanese Phase II/III database, one patient (95003-5002) was reported to have NMS. The incidence of reported NMS for aripiprazole-treated patients in the Japanese studies was 0.13% (1/769 patients). NMS was also reported in 0.8% (1/120 patients) of the haloperidol-treated patients in Japan.

b) Search for NMS

Phase 2/3 clinical databases were searched for a cluster of concurrent symptoms that are potential markers of NMS: any fever, muscle rigidity, and abnormal CPK elevation (≥ULN).

In the database searches, no aripiprazole-treated patients were identified as having reported all three of the primary features of potential NMS either simultaneously or separately while on aripiprazole in Phase 2/3 clinical studies.

All safety narratives from the Japanese studies were reviewed for potential NMS. Three additional patients were identified with symptoms suggestive of NMS. None were diagnosed with NMS by an attending physician.

A single aripiprazole patient (98304-508-52) was diagnosed with rhabdomyolysis, associated with elevated CPK values. But this conclusion is confounded by the fact no confirmatory urine myoglobin measurements were obtained and by the fact that the patient had received both aripiprazole and haloperidol for two months preceding the event.

A comprehensive search of the Phase 2/3 database retrieved no new reports of NMS during the reporting period for the 120-Day Safety Update.

There were no new reports of NMS in the Japanese clinical studies during the reporting period for the 120-Day Safety Update.

9. Special Studies Relevant to Safety

a. Ethanol Interaction (Study 00230)

The objective of this study was to assess the potential for pharmacodynamic interactions between orally co-administered low dose (10mg) aripiprazole and ethanol. A secondary study objective investigated the effect of orally co-administered ethanol on the pharmacokinetics of orally administered aripiprazole. The study had a randomized, double-blind, placebo-controlled, parallel group, multiple-dose design.

On Day 1, all subjects received a single oral dose of a placebo tablet at 2 hours after breakfast (i.e., placebo dosing at 8:00 AM). On Days 2 through 15, subjects received

a single oral dose of 10 mg of aripiprazole (Group 1) or matching placebo (Group 2) at 2 hours after breakfast (i.e., at 8:00 AM). On Day 15, the subjects in both groups were administered the aripiprazole or placebo dose in combination with a 0.8 g/kg ethanol dose, 2 hours after breakfast (i.e., at 8:00 AM). A rigid meal schedule was followed from enrollment until the end of the study, 16 days later.

Pharmacodynamic assessments were performed prior to dosing and at 1, 2, 3, 4, 5, 6 and 8 h after the dose on Day 1 and on Day 15.

A total of 26 healthy male and female subjects were randomized to treatment, 19 (73%) completed the study and 7 (27%) discontinued from the study early.

Three pharmacodynamic outcome variables were investigated:

- Digit Symbol Substitution Test (DSST), a measure of psychomotor speed;
- Simple Reaction Time (SRT), and
- Photoelectric Rotary Movement test (PRM), a measure of gross motor skills.

There were no deaths or serious adverse events during this study.

Seven subjects discontinued on Day 15 due to adverse events. Five of these subjects began vomiting following the administration of ethanol (4 subjects in placebo group and 1 subject in the aripiprazole group).

Steady-state was confirmed prior to the fourteenth day of aripiprazole dosing.

In terms of the key pharmacodynamic outcome measures, the DSST showed a statistically significant degradation in performance in patients co-administered aripiprazole and alcohol (EtOH) compared to placebo and alcohol. The sponsor discounted this difference since there was an unexpected marked improvement in test scores for alcohol and placebo. The maximum change from baseline in the percent of symbols correctly reported was -12% for aripiprazole + alcohol versus +12% for placebo + alcohol (p=0.0090, Wilcoxon rank-sum test).

The SRT revealed longer reflex times in the aripiprazole group compared to placebo, but not significantly so.

The PRM essentially showed no difference between the placebo and aripiprazole groups following EtOH ingestion.

In terms of pharmacokinetics, when aripiprazole was given with ethanol, the mean aripiprazole Css,min, Css,av, Css,max, tmax, AUC , and CL/F did not differ significantly from those following administration of aripiprazole alone. In addition, no significant differences in pharmacokinetics between aripiprazole given alone and aripiprazole given with ethanol were found for the major active metabolite OPC-14857.

Blood ethanol concentrations were not significantly different between the subjects co-administered ethanol with placebo and those given ethanol with aripiprazole.

In conclusion, alcohol seemed to have little effect on gross motor skill testing and reaction time. However, the co-administration of aripiprazole and alcohol was associated with a marked degradation in psychomotor speed compared to alcohol alone.

A limitation of this study was that only low dose aripiprazole (10mg/day) was used; the possibility of a greater interactive effect may exist at the higher doses likely to be used in clinical practice.

b. Dose Escalation (Study 98202)

This study was found to have significant deviations from GCP Standards during an internal company audit conducted by Otsuka at the clinical site. The audit raised questions about the integrity of the data and the company decided not to use any of the data generated by this trial in developing conclusions about aripiprazole use. The sponsor elected to repeat the entire study as protocol 98224 (see below) at a different study site and using different investigators. The findings of the audit were reported to the Agency, which later inspected the site but did not issue a notice of adverse findings.

Since the data from this trial were deemed to be unreliable, this study will not be reviewed in detail here.

c. Dose Escalation (Study 99224)

The primary objective was to investigate the tolerability and safety of aripiprazole at doses higher than 30 mg/day.

This was a randomized, double-blind, inpatient, pilot study. It addressed the safety and tolerability of aripiprazole 30 (control), 45, 60, 75, and 90 mg/day over a 15-day treatment period for each dose. Male or female patients, aged 18 - 59 years, with a diagnosis of schizophrenia or schizoaffective disorder on stable treatment with an oral antipsychotic medication prior to the start of aripiprazole dosing, were studied. Patients were genotyped to exclude poor metabolizers via CYP2D6 pathway.

Cohorts consisting of 10 patients entered the double-blind therapy with three patients in each cohort randomized to the 30 mg (control) dose and the other seven patients randomized to aripiprazole at a dose escalated by 15 mg from the maximum dose received by the previous cohort. These seven patients received the dose most recently tolerated in the study for one day and the escalated dose for the next 14 days (e.g., at Treatment Step 1: three patients received 30 mg/day for 15 days; seven patients received 30 mg/day on Day 1 and 45 mg/day for the next 14 days).

For each patient, the study consisted of 5 days of placebo washout and 15 days of treatment followed by at least 6 days of washout. A Data Safety Monitoring Committee (DSMC) performed a clinical assessment of available safety data at the conclusion of each Treatment Step. Patients in the subsequent Treatment Step were randomized only after a majority of the DSMC members came to a consensus on the safety and tolerability of the current dose. The DSMC reviewed data in a blinded fashion. Safety and efficacy assessments were performed at baseline (Day 0, last day of placebo washout), at Days 8 and 15 (treatment period), and at Day 21 (last day of placebo washout).

Measures of safety were:

- EPS-Related Safety Profiles
- Adverse events
- Laboratory Tests (days 8, 15, and 21)
- Vital Signs (days 8, 15, and 21)

- ECG's (days 1, 8, 15, and 21)
- Physical Examinations
- Body-Weight

Thirty-two men and 8 women, between the ages of 26 and 53 years, received at least one dose of aripiprazole. Twelve patients received 30 mg/day, 7 patients received 45 mg/day, 7 patients received 60 mg/day, 7 patients received 75 mg/day, and 7 patients received 90 mg/day of aripiprazole.

Thirty-two (80%) of the 40 randomized patients completed the study.

No deaths were reported during the study. Only one patient (45 mg dose group), had a serious adverse event during the study; this adverse event (paranoid reaction), however, occurred 10 days after the final study dose was taken and is probably unrelated to study drug.

Four (10%) of the 40 patients discontinued from the study because of an adverse event: 2 of the 12 patients in the 30 mg group for anxiety and psychosis, respectively, and 2 of the 7 patients in the 60 mg group for agitation and vomiting, respectively.

Certain adverse events were reported at substantially higher rates in the high dose groups (75 and 90mg) compared to the lower dose groups: akathisia, dysarthria, dyspepsia, impaired concentration, and tachycardia.

Twenty-two (55%) of the 40 patients reported an EPS-related adverse event during the study, with the highest incidence occurring in the 90 mg treatment group (6 patients; 86%). The most frequently reported EPS-related adverse event was akathisia: 6 (50%) patients in the 30 mg group, 2 (29%) patients in the 45 mg group, 2 (29%) patients in the 60 mg group, 3 (43%) patients in the 75 mg group, and 6 (86%) patients in the 90 mg group.

The only remarkable vital sign finding was a higher incidence of pulse rates ≥120 bpm and ≥15 bpm higher than baseline in the high dose groups compared to the low dose groups: 71% and 86% of patients in the 75mg and 90mg groups, respectively, met these criteria compared to 29-43% of patients in the lower dose groups. The median change from baseline to maximum supine heart rate was +37 bpm in the 90mg group vs. +20 to +27 in the other dose groups.

There were a few remarkable ECG findings. The incidence of premature ventricular beats was highest in the 90mg group (2/7 patients) with only one other patient with this abnormality in the other dose groups (1 patient in the 45mg group).

Only one patient had a QTc interval (Bazett's correction) ≥450 msec and at least 10% above baseline: Patient 99224-620-40 in the 90mg group had a QTc of 451 msec on day 8 (395 msec at baseline). The median change from baseline to maximum value in QTcN ($QT/RR^{0.37}$) was higher in the higher vs. the lower dose groups:

30mg (N=12)	+15.6 msec
45mg (N=7)	+ 3.4 msec
60mg (N=7)	+ 7.7 msec
75mg (N=7)	+26.7 msec
90mg (N=7)	+24.0 msec

These data suggest that QTc prolongation may become significant in cases of overdose or inhibition of aripiprazole metabolism. Although a moderate degree of QTc prolongation was observed at 30mg, this is likely an aberrancy since 1) QTc was minimally increased in the next two higher doses and 2) the mean change was only +1.29 msec at 30mg in the short-term, placebo-controlled schizophrenia trials with a much larger sample size (N=241).

Median changes from baseline to maximum value for ECG-measured heart rate were consistent with the data for pulse rate discussed above: +27.0 bpm for the 75 and 90mg groups vs. +14.0 to +17.0 bpm in the lower dose groups.

Plasma concentrations of aripiprazole and its metabolites (OPC-14587, OPC-3373, DM-1451, DCPP) were assessed following treatment. A noncompartmental pharmacokinetic analysis was performed. The results indicated that:

- Aripiprazole pharmacokinetics appear to be linear following multiple doses in the range of 30 - 90 mg.
- Plasma concentrations of aripiprazole and its metabolites increased proportionately with the dose.
- Dichlorophenylpiperazine (DCPP) concentrations are consistently low (< 10 ng/mL) but present in most patients following doses ≥60 mg.

d. Drug Switching (Study 98215)

The primary objective was to assess the relative safety and tolerability of three alternative dosing schemes for switching patients from prior antipsychotic monotherapy to aripiprazole monotherapy.

This was a multicenter, randomized, open-label, parallel-group, 8-week outpatient study.

Approximately 306 eligible patients were to be randomized to one of three dosing schemes:

Treatment Group 1-immediate initiation of 30 mg/day oral aripiprazole with simultaneous immediate discontinuation of current antipsychotic monotherapy,
Treatment Group 2-immediate initiation of 30 mg/day oral aripiprazole while tapering off the current antipsychotic monotherapy (over a 2-week period), and
Treatment Group 3-titrating up initiation of oral aripiprazole over a 2-week period (from 10 mg/day to 30 mg/day) while tapering off the current antipsychotic monotherapy over the same 2-week period, then maintaining 30 mg/day oral aripiprazole dosing.

Doses of study medication were not modified during the study. Patients who could not tolerate study drug were withdrawn from the study. During the treatment period, rating scales were completed weekly to evaluate clinical response and extrapyramidal symptoms (EPS). Blood samples were collected on specified study days for the determination of plasma concentration of aripiprazole.

Three hundred fifty-five patients were enrolled in the study; 311 of these patients were randomized to treatment with aripiprazole: 104 were randomized to Treatment Group 1, 104 were randomized to Treatment Group 2, and 103 were randomized to Treatment Group 3.

Two hundred ten patients were diagnosed with schizophrenia and 101 were diagnosed with schizoaffective disorder. Two hundred eighty seven patients were on atypical antipsychotic medications at the time of study entry and 24 were on typical antipsychotic medications. Three hundred nine patients were included in the Safety Sample (defined as all patients in the Randomized Sample who took at least

one dose of study medication) and 305 in the Efficacy Sample (defined as all patients in the Randomized Sample who had a baseline and at least one post-baseline efficacy evaluation).

Outcome variables measured included 1) Efficacy Results (Positive and Negative Syndrome Scale, Clinical Global Impression scale, and Rating of Medication Influences), 2) Pharmacokinetic Results, and 3) Safety Evaluations (Adverse Events, Deaths, Vital Signs and Physical Findings, and Laboratory Data).

In terms of efficacy, numerical changes in the direction of improvement were seen in all three treatment groups for each of the efficacy variables examined in this study. For the PANSS-Total and PANSS-Positive Subscale Scores, the numerical decrease was greatest for Treatment Group 3, followed by Treatment Group 2, and then Treatment Group 1. For the other efficacy parameters, similar improvements in scores were seen across the three treatment groups.

Two hundred sixty-eight (87%) of the 309 patients in the Safety Sample reported at least one adverse event during the study; 92 (89%) of the patients in Treatment Group 1, 93 (89%) of the patients in Treatment Group 2, and 83 (81%) of the patients in Treatment Group 3.

No deaths were reported during the study.

Twenty-three patients had at least one serious adverse event during the study: nine in Treatment Group 1, seven in Treatment Group 2, and seven in Treatment Group 3. The most commonly reported SAE was hospitalization for psychosis (7, 4, and 5 patients in Groups 1, 2, and 3, respectively). Other SAE's (vaginal prolapse, overdose, pregnancy, suicide attempt, agitation, drug dependence, and chest pain/hypertension) were not deemed to be drug-related by me.

Fifty (16%) of the 309 patients in the Safety Sample discontinued from the study because of an adverse event; 16 (16%) of the patients in Treatment Group 1, 20 (19%) of the patients in Treatment Group 2, and 14 (14%) of the patients in Treatment Group 3. Psychosis was the adverse event most commonly leading to dropout. An examination of dropout rates by specific adverse events revealed no major differences across the three treatment groups.

Among the most frequently occurring adverse events (10% incidence in any treatment group), reporting rates were comparable across the three groups.

The aripiprazole plasma concentrations observed in this study were within the range of plasma concentrations observed from other Phase II/III studies which were analyzed using a population pharmacokinetic approach (00233).

In conclusion, the overall safety and tolerability profiles were generally similar across the three treatment switching strategies. Based on the results of this trial, all three methods can be used safely for switching patients to aripiprazole from another antipsychotic monotherapy.

e. Neurocognitive Effects (Study 98213)

The primary objective of this study was to characterize and compare the neurocognitive effects of aripiprazole (30 mg) with olanzapine (10 mg to 15 mg) in adult outpatients with stable schizophrenia or schizoaffective disorder who had been on a stable dose of an oral typical antipsychotic agent, risperidone, or quetiapine, for at least one month.

This was a multicenter, randomized, open-label, parallel-group study lasting 26 weeks.

Randomization was stratified by prior treatment.

A total of 255 patients were randomized: 127 to the olanzapine group and 128 to the aripiprazole group. One hundred nine (43%) of the 255 randomized patients completed the study and 146 (57%) discontinued early.

Neurocognitive effects were assessed based on the California Verbal Learning Test (CVLT), Benton Visual Retention Test (BVRT), Wisconsin Card Sorting Test (WCST), Trail Making Test, Continuous Performance Test, Verbal Fluency, Letter-Number Sequencing, and the Grooved Pegboard.

A principal components factors analysis was conducted to reduce the large amount of neurocognitive data to a small number of factors for purposes of analysis. This analysis yielded three factors:

• Factor 1 (general cognitive factor) based primarily on the BVRT, Letter-Number Sequencing, Grooved Pegboard, CVLT, verbal fluency, and Trailmaking A and B.

• Factor 2 (executive functioning) based primarily on the WCST-categories, WCST-percent perseverative errors, and WCST-percent conceptual level responses.

• Factor 3 (secondary verbal memory) based primarily on CVLT total recall trials 1-5 and semantic clustering ratio.

Continuous Performance Test (CPT) data were analyzed separately.

Examination of changes from baseline to last visit (> 14 days LOCF) revealed the aripiprazole and olanzapine groups to be very comparable on Factor 1 (general cognitive functioning). Both groups showed modest, non-significant, improvements from baseline.

Neither treatment group showed a significant improvement from baseline to last visit or a differential treatment effect on Factor 2(executive functioning) or the CPT.

However, a differential treatment effect favoring aripiprazole was noted on Factor 3 (secondary verbal memory). The aripiprazole group showed a highly significant improvement from baseline on this factor, whereas the olanzapine group did not.

10. Overdose Experience

The sponsor provided a comprehensive review of the non-updated non-Japanese Phase 2/3 database to identify patients taking an overdose of aripiprazole. The sponsor searched the dosing records to identify patients who ingested a single dose > 90 mg. The safety profile of aripiprazole in the identified patients was reviewed.

Only 3 patients reportedly had overdoses > 90mg:

Patient 98204-357-2, reported to have taken 140 mg of aripiprazole, was alert and oriented when seen in the emergency room (ER) but complained of somnolence. The patient was treated with 50 g of charcoal orally and was discharged the same day.

Patient 97203-13-4 reported having taken 440 mg of aripiprazole, although there were no data to confirm this event. He was an asymptomatic outpatient, evaluated at his doctor's clinic, and never went to the hospital ER. Study medication was interrupted for 3 days, but no medical intervention was used to treat the event. The patient remained asymptomatic and continued participation in the study.

Patient 138002-61-250 was reported to have taken 180 mg of aripiprazole as well as detergent. The patient presented in the ER with mild somnolence and was treated with gastric lavage, activated charcoal, intravenous fluids, and laxatives. The patient was hospitalized 1 day for this event and transferred to another hospital for observation.

One other patient (138001-74-368) attempted suicide by ingesting four double-blind study tablets (equivalent to either 20 mg or 40 mg of aripiprazole) in addition to his daily dose of study medication. He simultaneously consumed two pills of lorazepam and six pills of acetaminophen. Seen in the ER, complaining of somnolence and nausea, he was treated with 50 g of charcoal and sorbitol and recovered. He was discharged to a psychiatric hospital that same day.

Finally the sponsors report an 18-month-old male child, weighing 10 kg, who reportedly took 15 mg of aripiprazole (equivalent of 1.5 mg/kg) and 2 mg of Ativan. Circumstances of this incident are not reported. The child presented to a hospital ER with stable vital signs. In the ER, the child was somnolent but was easily aroused. Treatment included administration of charcoal and oral alimentation. One day later the child was discharged from the hospital with no residual effects. Pediatric follow-up confirmed a complete recovery.

Although aripiprazole appears to have a wide therapeutic index there is potential for patients to overdose intentionally or inadvertently. Activated charcoal has been used in the emergency treatment of drug overdose. Administration of activated charcoal at 1 hour after aripiprazole dosing reduced plasma concentrations of aripiprazole and its active metabolite OPC-14857 to about one-half of those expected for an aripiprazole dose given alone. In the event of accidental or intentional overdose

with aripiprazole, activated charcoal may be useful as a rescue treatment. Single doses of activated charcoal have the greatest benefit when given within 1 hour after overdose ingestion. Aripiprazole is highly protein bound and, therefore, dialysis is unlikely to reduce plasma concentration.

Study 99224 studied doses of aripiprazole up to 90 mg/day for 15 continuous days. As discussed above, data from this trial suggested that doses of 75 and 90 mg/day are associated with greater elevations in heart rate and with greater prolongation of the QTc interval than those observed at lower doses.

11. Human Reproductive Data

A comprehensive search of the non-Japanese Phase 2/3 database was completed to identify aripiprazole-treated patients who became pregnant during participation in a clinical study. The search retrieved the AE terms of pregnancy and positive pregnancy test, and pregnancy listed as the reason for discontinuation of study medication on the end-of-study case report form. Patients with reported positive pregnancy tests who, on further evaluation by follow-up pregnancy tests, ultrasound examination, or data clarification, were confirmed not to be pregnant were not reviewed and were not recorded as "pregnancies."

A total of nine aripiprazole-treated patients were reported to have become pregnant. Of these, seven were reported in the original NDA submission and two were new reports during the reporting period for the 120-Day Safety Update. Narratives for all nine patients were reviewed.

A total of 5 elective abortions were performed in the series. There was one ectopic pregnancy reported. Two remaining women delivered healthy infants, following an uncomplicated course. One was completely lost to follow-up and no one knows the outcome of her pregnancy.

This number of pregnancies is too small to generate meaningful conclusions. Absent well-controlled studies evaluating the safety of aripiprazole in pregnant women, and with limited clinical experience, it is not known whether aripiprazole causes fetal harm when administered to a pregnant woman. Reproductive capacity assessment similarly cannot be determined. Therefore, aripiprazole

should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

12. Withdrawal Phenomena/Abuse Potential

There were no human studies that adequately assessed withdrawal phenomena associated with the discontinuation of aripiprazole or the abuse liability of this drug.

Three preclinical studies (one in rats and two in rhesus monkeys) examined abuse potential and withdrawal effects. The sponsor reported no evidence of significant physical dependence, withdrawal signs, or abuse liability in these studies. These trials will be reviewed in detail by the pharmacology/toxicology reviewer.

C. Adequacy of Patient Exposure and Safety Assessments

The aripiprazole NDA database is quite large and more than adequate to evaluate safety.

ICH guidelines suggest that at least 100 patients be exposed up to one year, 300-600 for 6 months, and about 1500 total in an NDA safety database. These guidelines have been met: in the non-Japanese Phase 2/3 database, 902 patients received aripiprazole for at least one year, 1513 for at least 6 months, and 4710 received aripiprazole regardless of duration.

In proposed labeling, the sponsor has recommended a dose range of 15 to 30 mg/day for aripiprazole. Exposure to doses in this range was adequate in the safety studies (see **Appendix IV-6**).

The safety assessments performed in the Phase 2/3 clinical trials are adequate.

D. Assessment of Data Quality and Completeness

Data contained in this NDA generally appeared to be reasonably reliable and complete. The only notable deficiency was the apparent lack of follow-up on abnormal laboratory values observed in some patients, making it impossible to determine the outcomes of these abnormalities. Given that this shortcoming was noted in a relatively small number of patients, it does not unduly impede the overall assessment of safety in this NDA.

An audit of safety data was conducted by comparing Case Report Forms (CRF's), Narrative Summaries, and adverse event line listings for consistency of adverse event information across the three documents. This audit was performed on a randomly selected sample of 39 patients with CRF's (i.e., patients who died, had a non-fatal serious adverse event, or had an adverse experience that led to treatment discontinuation). Consistency of adverse event information across the three documents was found to be acceptable.

Additionally, the CRF's of 10 other randomly selected patients who dropped out for reasons other than adverse experiences were requested from the sponsor. These were audited by Dr. Dubitsky to determine if any of these patients actually discontinued treatment for an adverse event and, hence, were misclassified by the sponsor. The reasons for dropout were consistent with their classification as dropouts for reasons other than adverse events.

A listing of the 49 audited patients is presented in **Appendix VII-31.**

E. Summary of Important Drug-Related Safety Findings

This review of the aripiprazole safety database, to include the special safety analyses and special safety studies, revealed few significant safety concerns. I feel that three findings, all from the trials in elderly patients with dementia, merit special attention: mortality, pneumonia, and somnolence.

1. Mortality in Patients with Dementia

There was a relatively high death rate among the aripiprazole-treated patients in the dementia trials (studies 138004, 138005, and 138006).

The crude mortality rate (MR) in the dementia study pool was 7.7% (39/504). The exposure-adjusted MR was 174 per 1,000 patient-years of exposure (39/223.8 patient-years). Among the 102 placebo patients in this pool, there were 17.7 patient-years of exposure and no deaths. The difference in exposure-adjusted mortality between

aripiprazole and placebo in this study pool was statistically significant (p=0.05).

An examination of the dementia study deaths by time to occurrence and last aripiprazole dose revealed no clustering in time nor any relationship to dose.

The double-blind acute phase of Study 138006 is the only completed placebo-controlled trial of aripiprazole in Alzheimer's disease. In this 10-week study, the crude MR was 3.8% (4/105) vs. 0% (0/102) in the placebo group. The 4 aripiprazole deaths were due to pneumonia, heart failure, sepsis related to bronchitis, and one case in which the cause could not be determined.

By comparison, among the younger patients in the schizophrenia/bipolar study pool, the crude MR was only 0.5% (22/4206) and the exposure-adjusted MR was 9.0 per 1,000 patient-years (22/2432.5 patient-years). Among the 826 placebo patients in this pool, there were 68.1 patient-years of exposure and no deaths.

Thus, there were striking differences between the all-cause mortality rates among the elderly, demented patients treated with aripiprazole versus placebo and, not unexpectedly, among aripiprazole-treated patients who were elderly with dementia compared to younger patients with schizophrenia and bipolar disorder.

Examination of the causes of death in the 39 deaths among the 504 aripiprazole-treated elderly patients with dementia revealed that the causes for 10 of the deaths were unexplained. Another 10 deaths were due to pneumonia (5 due to aspiration pneumonia and 5 from other unspecified cases of pneumonia). These were the largest categories for the known causes of death in these patients. Heart failure, sepsis and yet additional non-clarified respiratory infections occurred less frequently. Pneumonia, to include aspiration pneumonia, will be discussed further in the next section.

In conclusion, it is difficult to discern with reasonable certainty whether the observed mortality rate in the elderly, demented patients treated with aripiprazole is significantly higher than expected for this patient population. Mortality rates in patients with Alzheimer's disease vary with the severity of the illness and there is

insufficient knowledge about dementia severity in these studies to adjust for this factor. The number of deaths that would have been observed in an adequate control group is unknowable. However, the absence of deaths among the placebo patients in study 138006 suggests that aripiprazole may confer an elevated risk of death in elderly patients with dementia.

Although psychosis in dementia is not the target indication for this NDA, if approved, aripiprazole is likely to be used in a variety of patients. Therefore, it would be prudent to warn prescribers of this finding and advise them to use caution when aripiprazole is used in elderly, demented patients.

2. Pneumonia in Patients with Dementia

Fatal aspiration pneumonia was deemed to be the cause of death in 5 of the 504 aripiprazole-treated patients in the pool of studies in patients with Alzheimer's dementia (studies 138004, 138005, and 138006). Also, there were 5 fatal cases of unspecified pneumonia and 2 fatal cases of unspecified respiratory infection among these patients. There were no deaths from any cause among the 102 placebo-treated patients in this pool of studies.

The dementia study pool was searched for all cases (fatal plus non-fatal) of aspiration pneumonia.[37] In all, 7 cases of aspiration pneumonia were identified in the aripiprazole patients and none in the placebo patients. Thus, the crude incidence rates of aspiration pneumonia were 1.4% for aripiprazole and 0.0% for placebo. The exposure-adjusted rates for aspiration pneumonia (per 1,000 patient-years) were 31.3 for aripiprazole and 0.0 for placebo. For all events coded as pneumonia in this study pool, the crude rates were 3.0% for aripiprazole and 0.0% for placebo; exposure-adjusted rates were 67.0 for aripiprazole and 0.0 for placebo.[38]

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[37] This search was conducted on the JMP file in the 120-Day Safety Update that contains the cumulative adverse event data listing for this study pool. The parameter AETXT (description of AE on the CRF) was searched for events containing any of the following words: aspiration, inhalation, Mendelson's, and Mendelhson's.

[38] By comparison, the reporting rate for all events coded as pneumonia in the schizophrenia/bipolar disorder study pool (N=4206) was 0.5% or 8.2 per 1,000 patient-years of exposure.

In the only completed placebo-controlled dementia study (the double blind, 10 week phase of study 138006), no patients in either the aripiprazole or the placebo treatment groups were reported to experience aspiration pneumonia. With respect to all cases of pneumonia, 1.9% (2/105) aripiprazole patients and 1.0% (1/102) placebo patients developed pneumonia in this study.[39]

These data are summarized in **Table VII-5** below for the convenience of the reader.

TABLE VII-5
REPORTING RATES FOR PNEUMONIA IN DEMENTIA STUDIES[40]

	Aripiprazole Rate	Placebo Rate
Aspiration Pneumonia		
Dementia Study Pool		
Crude Rate	1.4%	0.0%
Exposure-Adj. Rate	31.3	0.0
Study 138006		
Crude Rate	0.0%	0.0%
All Pneumonia		
Dementia Study Pool		
Crude Rate	3.0%	0.0%
Exposure-Adj. Rate	67.0	0.0
Study 138006		
Crude Rate	1.9%	1.0%

There are several possible explanations for aspiration pneumonia in elderly, demented patients. First, a mechanical cause did exist in 2 of the 5 aspiration fatalities in the dementia trials, namely faulty NG tube placement. Second, advanced Alzheimer's disease itself is associated with appreciable morbidity and mortality secondary to aspiration pneumonia. Third, it is also well-known that esophageal dysmotility and aspiration can occur with anti-psychotic drug treatment, so an etiologic role for aripiprazole is not ruled out. Fourth, a known risk of somnolence and obtundation is aspiration and

[39] This includes events for which the verbatim term was "pneumopathie" or "pneumopathy."
[40] The study pool consists of studies 138004, 138005, and 138006. "Aspiration pneumonia" includes all events identified through the search described above. "All pneumonia" includes all events coded to the preferred term "pneumonia." Exposure-adjusted rates are per 1,000 patient-years.

subsequent pneumonia. Somnolence, in turn, may be related to aripiprazole treatment in these patients (see below).

Three factors make interpretation of these data difficult: 1) the absence of an adequate control group for comparison with the aripiprazole rate in the dementia study pool, 2) a number of fatalities attributed to unspecified pneumonia or unknown causes of death in this pool, and 3) the appreciable background rate for aspiration pneumonia in elderly patients with Alzheimer's disease. Hence, the above data cannot definitively demonstrate that aripiprazole confers an increased risk of aspiration pneumonia, although that possibility is suggested. This should be an important focus for postmarketing surveillance if and when aripiprazole is approved for marketing.

3. Somnolence in Patients with Dementia

In study 138006, which examined aripiprazole tolerability in elderly demented patients, the aripiprazole:placebo odds ratio for somnolence was 7.8 compared to 1.4 for the pool of the short-term, placebo-controlled studies in younger patients with schizophrenia.

Study 98203 was an uncontrolled ascending dose study in which 5 cohorts of elderly demented patients received doses from 5 to 30 mg/day increased in step-wise fashion. This trial revealed that the occurrence of somnolence appeared to be dose-related, reported in 0% of patients in the 5-10 mg/day cohort and in 100% of patients in the 20-25 mg/day and 25-30 mg/day cohorts.

The rate of accidental injury in study 98203 was 8% for aripiprazole and 4% for placebo. Possibly somnolence contributed to this finding.

Thus, somnolence appears to be especially prevalent and dose-related among elderly, demented patients who receive aripiprazole. This may place such patients at risk for accidents, such as falls, and, if substantial, at risk for aspiration and pneumonia (see above).

VIII. Dosing, Regimen, and Administration Issues

Based on a consideration of the above safety and efficacy findings, the following dosage and administration

instructions are recommended for most patients with schizophrenia:

Adult patients with schizophrenia can be started at a dose of 15mg given once daily without regard to the time of day or meals. In patients who do not achieve an acceptable response, the dose may be increased in increments of 5-10 mg/day at intervals of at least 2 weeks to a maximum of 30 mg/day.

IX. Use in Special Populations

The safety and efficacy of aripiprazole in pediatric patients has not been established.

The following factors do not appear to require adjustment of aripiprazole dosing: age, gender, race, smoking status, hepatic or renal impairment, and CYP2D6 status.[41]

Aripiprazole is likely to be used off-label for various indications, to include psychosis associated with dementia in elderly patients. Prescribers should be aware of the high mortality rate, incidence of pneumonia, particularly aspiration pneumonia, and susceptibility to somnolence observed in clinical trials when aripiprazole was used in this population.

X. Review of Proposed Labeling

The following comments are based on a review of the clinical sections of sponsor's proposed labeling as presented in their 10-31-01 submission.

Clinical information in the following sections was reviewed by Dr. Harris: Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, and Dosage & Administration/Switching from Other Antipsychotics.

Dr. Dubitsky reviewed clinical information in the following sections: Clinical Pharmacology/Clinical Studies, Indications & Usage, and Dosage & Administration.

Throughout the proposed labeling, the formerly proposed tradename for aripiprazole (Abilitat) should be replaced with the recently proposed [redacted]

[41] This conclusion is tentative pending completion of the biopharmaceutics review of relevant studies.

Number of Pages Redacted 7

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Draft Labeling
(not releasable

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June 12, 2002

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June 12, 2002

cc: NDA 21-436
HFD-120/Division File
HFD-120/GDubitsky
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NDA 21-436
ARIPIPRAZOLE

SECTION XII:
APPENDICES TO THE
REVIEW AND EVALUATION OF CLINICAL DATA

NDA DATA SOURCES

APPENDIX IV-1: TABLE OF STUDIES	
NON-JAPANESE STUDIES	
Phase 1 (Clinical Pharmacology Studies)	
Single-Dose	
96201	Open-label study to assess the absorption, distribution, metabolism, and excretion of a single oral 20 mg dose of [^{14}C]-aripiprazole in 12 healthy subjects aged 21 - 45 years. Open-label study to assess the absorption, distribution, metabolism, and excretion of a single oral 20 mg dose of [^{14}C]-aripiprazole in 12 healthy subjects aged 21 - 45 years.
96203	Open-label, two-phase, study to evaluate the safety of aripiprazole given in ethanol solution, and assess the relative bioavailability of aripiprazole in solution, capsule, and tablet form in a total of 15 healthy subjects aged 21 - 45 years who each participated in either the sequential, ascending, single-dose study of aripiprazole (1, 5, 10, or 20 mg) in ethanol solution or the randomized, single-dose, two-way crossover study of aripiprazole 20 mg in either capsule or tablet form.
98201	Open-label, single-dose, parallel group study to evaluate the influence of diurnal variation on the pharmacokinetics of aripiprazole 20 mg in 32 healthy subjects aged 18 to 45 years.
98205	Open-label, single-dose study to evaluate the pharmacokinetics of aripiprazole 15 mg in normal subjects matched to subjects with varying degrees of hepatic impairment (based on creatinine clearance) in 25 total subjects aged 39 to 71 years.
98206	Double-blind, parallel group, placebo-controlled study of two doses of aripiprazole 15 mg to determine whether inhibition of CYP3A4

APPENDIX IV-1: TABLE OF STUDIES	
	alters the pharmacokinetic characteristics of aripiprazole in 29 healthy subjects aged 18 to 45 years with a study duration of 28 days.
98207	Open-label, parallel group study using a single dose of aripiprazole 10 mg to assess the effect of CYP2D6 inhibition on aripiprazole pharmacokinetics in 3 groups of a total of 29 healthy subjects aged 18 to 45 years grouped as CYP2D6 extensive metabolizers, or poor metabolizers.
98208	Open-label study of the pharmacokinetics of a single 15mg dose of aripiprazole in 6 volunteers with normal renal function and 6 patients with renal impairment.
00225	Open label, two-center, single-dose, 3-by-2 factorial design study to assess the pharmacokinetic effects of age and gender on aripiprazole 15 mg on 60 healthy subjects, 10 of each gender per age group: 18 to 40 years, 41 to 64 years, and ≥ 65 years.
00226	Open label, two-period, randomized, complete block, crossover study to assess the effect of famotidine 40 mg co-administration on aripiprazole 15 mg pharmacokinetics, each given separately and together as single doses in 17 healthy subjects aged 18 to 45 years.
00227	Single-dose, open-label, historic-control study of the effects of activated charcoal on aripiprazole pharmacokinetics in 9 healthy male subjects aged 18 to 45 years treated with aripiprazole 15 mg followed 1 hour later by 50 g dose of activated charcoal.
138015	Open-label, randomized, 3-period, 3 treatment, crossover bioequivalence study to assess the effects aripiprazole monohydrate content on the pharmacokinetics of aripiprazole in 46 healthy subjects receiving single doses of 15 mg aripiprazole as reference (100% anhydrous), prototype #1 (20% monohydrate) or prototype #2

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	(100% monohydrate). Study was terminated early at end of Period 1.
138016	Open-label, randomized, 3-period, 3-treatment crossover study to assess absolute bioavailability using single doses of the 5 mg aripiprazole tablet formulation and 5 mg aripiprazole IM formulation with reference to 2 mg aripiprazole IV infusion in 18 healthy subjects.
138018	Open-label, randomized, 3-period, 2-treatment crossover study to assess the effect of a high fat meal and intrasubject variability on the pharmacokinetics of a single dose of aripiprazole 15 mg in 45 healthy subjects.
138019	Open-label, single-dose, bioavailability study comparing aripiprazole 3mg liquid versus 5mg tablet in 16 subjects.
138028	Open-label, single dose study to assess the pharmacokinetics, metabolism, and routes and extent of elimination of a single oral 5 mg dose of [^{14} C]- aripiprazole in 9 healthy subjects.
138034	Open-label, randomized, 3-period, 3 treatment, crossover study to determine whether 2 prototype forms of a single dose of aripiprazole 10 mg containing differing fractions of the monohydrate form (20% monohydrate or 100% monohydrate) were bioequivalent to a reference product (100% anhydrous) prepared by a commercial process in 66 healthy subjects.
138035	Open-label, randomized, 2-period, 2-treatment crossover study to demonstrate bioequivalence of a single 15 mg dose of aripiprazole (commercial tablet formulation) when administered as 1 x 15 mg tablet compared to 3 x 5 mg tablets in 60 healthy subjects receiving both treatments in randomly assigned sequences.
138052	Open-label, single-dose, bioavailability study of aripiprazole 5mg flashmelt tablets in 40 subjects.

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138054	Open-label, two-way crossover, single-dose bioequivalence study of aripiprazole 15mg commercial tablets versus clinical trial tablets. Study was terminated (80 enrolled, 0 completers).
138063	Open-label, single-dose, bioavailability study comparing aripiprazole 5, 10, and 15mg commercial tablets versus liquid in 60 subjects.
138065	Single-dose bioequivalence study of aripiprazole 30mg tablets versus 3x10mg in 48 subjects.
Multiple-Dose	
93201	Randomized, double-blind, placebo-controlled, single-center, multiple-dose, ascending dose 14 day study to assess the tolerability and pharmacokinetics of aripiprazole (5, 10, 15, 20 mg/day) in 39 healthy male subjects aged 21 to 45 years.
93204	Randomized, double-blind, placebo-controlled, single-center, multiple-dose 14 day study to assess the tolerability and pharmacokinetics of aripiprazole titrated from 10 to 30 mg/day in 11 healthy male subjects aged 18 to 40 years.
94201	Open-label, multiple dose 14 day study of aripiprazole to determine the degree of D_2 receptor binding by aripiprazole measured by PET scan in 17 healthy male subjects aged 21 to 45 years assessed by treatments with 10 mg/day on Day 1, 20 mg/day on Day 2, 30 mg/day for Days 3 - 14, or 10, 2, 1, or 0.5 mg/day on Days 1 - 14 followed by IV ^{11}C raclopride for PET scanning.
97205	Open label study to assess the influence of multiple doses of aripiprazole 10, 20, 30 mg on the metabolism of dextromethorphan (DM) received pre and post aripiprazole dosing in 22 healthy male subjects aged 18 to 45 years for 14 days.
00230	Double-blind, placebo-controlled, randomized, parallel group, multiple-dose, sequential crossover 15 day study to assess the

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	potential pharmacodynamic interactions between co-administered aripiprazole 10 mg with ethanol in 26 healthy subjects aged 21 to 45 years and who met criteria for cytochrome P450 extensive metabolizer genotypes.
00231	Open label, multiple dose sequential, crossover study to assess the pharmacokinetic effect aripiprazole on dextromethorphan (DM) metabolism via cytochrome P450 2D6 in 25 healthy subjects aged 18 to 45 years genotyped as CYP2D6 extensive metabolizers treated with a single dose of 30 mg DM, followed by Days 4 - 17 single oral dose of aripiprazole 10 mg with a Day 18 single oral dose of aripiprazole 10 mg and subsequent 30 mg DM two hours later.
00232	Open-label, sequential-crossover, multiple-dose, 18 day study to determine the effect of co-administered aripiprazole on the pharmacokinetics of omeprazole in 25 healthy subjects aged 18 to 45 years treated with 20 mg oral dose of omeprazole followed on Days 4 - 17 with single oral dose of 10 mg aripiprazole and Day 18 treatment with aripiprazole 10 mg followed 2 hours later with 20 mg omeprazole.
138014	Flexible-dose study of the pharmacokinetics of aripiprazole 1-15mg in 30 pediatric subjects; 2 week acute study with optional 18 month extension for safety evaluation.
138021	Open label, sequential treatment design study to assess the safety of aripiprazole 30 mg and lithium (dose titrated to achieve therapeutic concentrations) coadministration in 12 chronically institutionalized patients with schizophrenia or schizoaffective disorder.
138022	Open-label, single group, PK interaction study of aripiprazole and carbamazepine in 4 schizophrenic patients.
138023	Open-label, sequential treatment design study to assess the safety profile of aripiprazole 30 mg and divalproex sodium (dose titrated up

APPENDIX IV-1: TABLE OF STUDIES	
	to therapeutic levels) coadministration in 10 chronically institutionalized patients with schizophrenia or schizoaffective disorder who required divalproex for management of symptoms.
138030	Open-label, 6 month safety study of aripiprazole 5-30 mg/day in 9 schizophrenic patients.
138043	Open-label, sequential 2-period study to demonstrate a lack of effect of concomitant aripiprazole administration of 10 mg once daily for 18 days on the pharmacokinetics and pharmacodynamics of a single 30 mg dose of warfarin in 12 healthy subjects.
138061	Open-label, single group, one-week study of the hepatobiliary metabolism of aripiprazole 15 and 30mg in 16 subjects. This study was conducted pursuant to the finding of gallstones and gallsand in animal studies to assess for the presence of the animal gall compounds in humans after treatment with aripiprazole.
Completed Phase 2/3 Studies	
Schizophrenia, Short-Term, Placebo-Controlled Studies	
93202	Randomized, double-blind, placebo-controlled, parallel group, inpatient, 4 week ascending dose study to assess efficacy and tolerability of aripiprazole 5 - 30 mg vs. haloperidol 5 - 20 mg in 103 adults aged 18 to 65 years with schizophrenia (DSM-III-R) in acute schizophrenic relapse and history of response to antipsychotic drugs.
94202	Randomized, double-blind, placebo-controlled, parallel group, inpatient, 4 week dose ranging study to assess efficacy and tolerability of aripiprazole (3 fixed doses: 2, 10, 30 mg) vs. haloperidol 10 mg in 307 adults aged 18 to 65 years with schizophrenia (DSM-IV) in acute relapse and history of response to antipsychotic drugs.

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97201	Randomized, double-blind, placebo-controlled, parallel group, inpatient, fixed-dose 4 week study to compare safety and efficacy of aripiprazole (15 mg or 30 mg) vs. haloperidol 10 mg in 414 adults aged 18 to 68 years with psychosis [schizophrenia (282 patients) and schizoaffective disorder (132 patients)] (DSM-IV) in acute relapse and history of response to antipsychotic drugs.
97202	Randomized, double-blind, placebo-controlled, parallel group, in-patient, fixed-dose 4 week study to compare the safety and efficacy of aripiprazole (20 mg or 30 mg) vs. risperidone 6 mg in 404 adults aged 18 to 65 years with psychosis [schizophrenia (289 patients) and schizoaffective disorder (115 patients)] (DSM-IV) in acute relapse and history of response to antipsychotic drugs.
138001	Randomized, double-blind, placebo-controlled, fixed-dose 6 week study of aripiprazole (10, 15, 20 mg) in 420 adults ≥ 18 years of age, hospitalized for schizophrenia (DSM-IV) in acute relapse, previously responded to antipsychotic medication, previously treated as an outpatient for at least one continuous 3-month period during the past 12 months.
Schizophrenia, Long-Term Studies	
98217/98304	Randomized, double-blind, active-control 52 week study to evaluate the safety and long-term maintenance effects of aripiprazole 30 mg (20 - 30 mg) vs. haloperidol 10 mg (7 - 10 mg) in 1,294 adults aged 18 to 65 years with schizophrenia (DSM-IV) in acute relapse and history of response to antipsychotic drugs.
97301	Double-blind, haloperidol-controlled, 52 week study of flexible dose aripiprazole (2-30 mg/day) in 130 patients with schizophrenia.
98213	Randomized, open-label, outpatient 26 week study to compare the neurocognitive effects of aripiprazole 30 mg (20 - 30 mg) vs.

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	olanzapine 15 mg (10 - 15 mg) in 255 adults aged 18 to 65 years with schizophrenia or schizoaffective disorder (DSM-IV), on a stable dose of a typical or atypical antipsychotic agent, for at one least month prior to randomization and not hospitalized for an exacerbation for at least 2 months prior to randomization.
138002	Double-blind, olanzapine-controlled, 26 week study of flexible dose aripiprazole (15-30 mg/day) in 317 patients with schizophrenia.
138047	Double-blind, placebo-controlled, 26 week study of fixed dose aripiprazole (15 mg/day) in 310 patients with schizophrenia.
Schizophrenia, Special Studies	
98202	Randomized, double-blind, in-patient, escalating dose, 15 day pilot study to assess the tolerability and safety of higher doses of aripiprazole (45 mg, 60 mg, 75 mg, 90 mg) compared to 30 mg in 20 adults aged 18 to 45 years with schizophrenia or schizoaffective disorder (DSM-IV) receiving a stable dose of an oral antipsychotic drug (used as monotherapy) for at least one month prior to study screening.
98203	Open-label, inpatient 3 week pilot study to assess the safety and tolerability of aripiprazole (5 mg to 30 mg increased in a stepwise manner) in 30 elderly adults aged 64 to 95 years with dementia of the Alzheimer's type (DSM-IV) that met the BPRS Core and AMME criteria.
98215	Randomized, open-label, parallel group, outpatient 8 week study to assess the safety and tolerability of three alternative dosing schemes for switching patients from prior antipsychotic monotherapy to aripiprazole 30 mg monotherapy in 311 adults aged 18 to 65 years with schizophrenia or schizoaffective disorder (DSM-IV).
99224	Randomized, double-blind, inpatient, escalating dose, 15 day pilot study (repeat of 98-202) to assess the safety and tolerability of

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	higher doses of aripiprazole (45, 60, 75 and 90 mg/day) compared to 30 mg/day in 40 adults aged 18 to 59 years with schizophrenia or schizoaffective disorder (DSM-IV), on a stable dose of an oral antipsychotic agent used as monotherapy for at least one month prior to screening.
Bipolar Mania Studies	
138007	Placebo-controlled, fixed dose, 3-week study of aripiprazole (15 and 30mg/day) in 401 patients with bipolar mania.
138009	Placebo-controlled, flexible dose, 3-week study of aripiprazole (15-30mg/day) in 262 patients with bipolar mania.
Dementia Studies	
138006	Placebo-controlled, flexible dose, 10 week study of aripiprazole (2-15 mg/day) in 208 patients with psychosis associated with Alzheimer's disease.
Ongoing Phase 2/3 Studies	
Schizophrenia Studies	
138001 extension	Randomized, double-blind, outpatient, flexible-dose, extended-dosing study of aripiprazole (10 - 15 mg or 20 - 30 mg) in adults ≥ 18 years of age with schizophrenia who have completed the 6-week Acute Phase of Study CN138-001 and for whom continued treatment is indicated. Dosing will continue until aripiprazole is available as a marketed product, or until December 2002, whichever is sooner.
138002 extension	Double-blind, flexible-dose, extended-dosing study of aripiprazole (15, 20, or 30 mg) vs. olanzapine (10, 15, or 20 mg) in adults ≥ 18 years of age with schizophrenia who have completed the 12-week Acute Phase Study CN138-002 and have responded to treatment. After May 2002, dosing will continue in an open-label fashion until

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	aripiprazole is available as a marketed product, or until December 2002, whichever is sooner.
138003	Randomized, double-blind, 26-week study to assess the efficacy and safety of aripiprazole (15, 20, or 30 mg) vs. olanzapine (10, 15, or 20 mg) in 704 adults 18 - 65 years of age with acute schizophrenia (DSM-IV) in acute relapse with a history of response to a neuroleptic treatment other than clozapine. An optional Extension Phase allows for 26 weeks of continued double-blind dosing.
138032	Randomized, double-blind, active-controlled, flexible-dose, 124-week (maximum) switch study to assess the efficacy and safety of aripiprazole (15 or 30 mg per day) versus perphenazine (8 - 64 mg per day) in 300 adults ≥ 18 years of age with treatment-resistant schizophrenia aripiprazole (DSM-IV). Treatment phases were as follows: a 2- to 14-day Screening Phase, with a 48-hour washout, a 6-week, open-label (olanzapine or risperidone) neuroleptic treatment phase to verify that patients were resistant to neuroleptic treatment, followed by a 2- to 10-day, single-blind placebo phase, followed by randomization to the 6-week, double-blind (aripiprazole vs. perphenazine) treatment phase, followed by an optional, 109-week, open-label aripiprazole phase.
138047 extension	Randomized, open-label, flexible-dose, 52-week, extended-dosing study of aripiprazole (15 - 30 mg) or olanzapine (10 - 20 mg) in adults ≥ 18 years of age with schizophrenia who have completed the 26-week Acute Phase of Study CN138-047 or who relapsed after a minimum of 2 weeks of dosing on Study CN138-047.
95201	Multi-center, inpatient and outpatient, long-term study to determine the tolerability and safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) in schizophrenic adults (DSM-III-R or DSM-IV) aged 18

APPENDIX IV-1: TABLE OF STUDIES	
	to 65 years who participated in protocol 31-93-202 or 31-94-202. As part of the NDA submission, 143 patients have been enrolled.
97203	Multi-center, inpatient and outpatient, long-term study to determine the safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) as maintenance therapy in adults aged 18 to 65 years with schizophrenia or schizoaffective disorder (DSM-IV) who participated in protocol 31-97-201 or 31-97-202. As part of the NDA submission, 541 patients have been enrolled.
97303	Multi-center, outpatient, long-term study to determine the safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) as maintenance therapy in adults aged 18 years and over with schizophrenia (DSM-IV) who participated in protocol 31-97-301 or 31-98-304-01. As part of the NDA submission, 631 patients have been enrolled.
98204	Multi-center, 28-day, inpatient and outpatient study to determine the tolerability of aripiprazole (20 mg and 15 mg) in patients aged 15 to 35 years with first episode schizophrenia or schizoaffective disorder (DSM-IV) occurring not more than one year prior to study entry. As part of the NDA submission, 8 patients have been enrolled in the study.
98218	Multi-center, outpatient, long-term study to determine the safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) as maintenance therapy in adults aged 18 years and over with chronic schizophrenia (DSM-IV) who participated in protocol 31-98-217. As part of the NDA submission, 93 patients have been enrolled.
98220	Multi-center, outpatient, long-term study to determine the safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) as maintenance therapy in adults aged 18 to 65 years with chronic schizophrenia or schizoaffective disorder (DSM-IV) who participated in protocol 31-98-

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	213. As part of the NDA submission, 104 patients have been enrolled.
98222	Multi-center, outpatient, long-term study to determine the safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) as maintenance therapy in patients aged 15 years and over with psychotic disorders or psychotic behaviors of dementia (DSM-IV) who participated in protocol 31-98-215 or 31-98-204. As part of the NDA submission, 207 patients have been enrolled.
Bipolar Mania Studies	
138008	Randomized, double-blind, 12-week study to assess the efficacy and safety of aripiprazole (15 or 30 mg) vs. haloperidol (10 or 15 mg) in the maintained response to treatment in 347 adults 18-65 years of age with bipolar I disorder (DSM-IV), manic or mixed, in acute relapse. An optional Extension Phase allows for an additional 14 weeks of continued double-blind dosing of aripiprazole (15 or 30 mg) vs. haloperidol (10 or 15 mg).
138010	Randomized, double-blind, placebo-controlled study to assess the efficacy and safety of aripiprazole (15 or 30 mg) in the maintenance treatment of patients with bipolar I disorder (DSM-IV). Treatment phases are as follows: a 6- to 18-week Stabilization Phase, followed by a 26-week Maintenance Phase, followed by a 74 week (maximum) Extension Phase.
138037	Open-label, long-term study to assess the safety and efficacy of aripiprazole (15 or 30 mg) in the treatment of patients with bipolar I disorder (DSM-IV) who have completed a previous acute aripiprazole mania study. Treatment phases are as follows: acute 6- to 18-week, open-label (aripiprazole) Stabilization Phase, followed by an open-label, 26-week Maintenance Phase, followed by an Extension Phase of up to 50 additional weeks of dosing. Dosing will continue until

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	aripiprazole is available as a marketed product, or until December 2002, whichever is sooner.
Psychosis in Alzheimer's Disease Studies	
138004	Randomized, double-blind, placebo-controlled, 10-week acute phase study of three fixed doses to assess the efficacy and safety of aripiprazole (2, 5, or 10 mg) in institutionalized patients 55 - 95 years of age with psychosis (delusions or hallucinations) associated with dementia of the Alzheimer's type (DSM-IV) present at least intermittently for one month or longer. An optional Extension Phase is a 130-week flexible-dose, open-label study of aripiprazole (2, 5, 10, or 15 mg) for patients who have completed the Acute Phase and for whom continued treatment is indicated.
138005	Randomized, double-blind, placebo-controlled, flexible-dose 10-week acute phase study to assess the efficacy and safety of aripiprazole (2, 5, 10, or 15 mg) in institutionalized patients 55 - 95 years of age with psychosis (delusions or hallucinations) associated with dementia of the Alzheimer's type (DSM-IV) present at least intermittently for one month or longer. An optional Extension Phase is a 130-week flexible-dose, open-label study of aripiprazole (2, 5, 10, or 15 mg) for patients who have completed the Acute phase and for whom continued treatment is indicated.
138006 extension	An optional extension Phase to a flexible-dose, 10-week randomized, double-blind, placebo-controlled study in institutionalized patients 55 - 95 years of age with psychosis (delusions or hallucinations) associated with dementia of the Alzheimer's type (DSM-IV). This extension phase is a 130-week flexible-dose, open-label study of aripiprazole (2, 5, 10, or 15 mg) for patients who have completed the Acute Phase and for whom continued treatment is indicated.

APPENDIX IV-1: TABLE OF STUDIES	
JAPANESE-STUDIES	
Phase 1	
91001a	Phase I clinical study to evaluate the safety and pharmacokinetics of OPC-14597 by single oral administration at 0.25, 0.5, 1, 2, 4, and 6 mg in comparison with haloperidol at 3 mg in 14 healthy adult male volunteers.
91001	Phase I clinical study to evaluate the safety and pharmacokinetics of OPC-14597 by 3-day repeated oral administration at 4 mg/day in 6 healthy adult male volunteers in comparison with haloperidol at 2 mg/day in 2 healthy adult male volunteers.
93003	Bioavailability study of non-deteriorated and deteriorated OPC-14597 tablets in healthy adult male volunteers. Twelve subjects were allocated to 2 groups of 6 subjects each. The study was conducted in a 2-treatment, 2-period, crossover manner with a washout period of at least 4 weeks between the 2 periods. In each period, the subjects received a single oral dose of either 1 non-deteriorated or 1 deteriorated OPC-14597 4-mg tablet. Because 1 subject dropped out after receiving treatment only in period 1, 1 additional subject was enrolled.
94002	Single-blind, placebo-controlled, parallel-group study of OPC-14597 at 1, 2, and 4 mg and haloperidol at 2 mg by single oral administration in 40 healthy adult male volunteers (8 on placebo) to investigate the characteristics and potency of OPC-14597 by quantitative pharmaco-EEG analysis.
94003	Bioavailability study (2) of non-deteriorated and deteriorated OPC-14597 tablets in healthy adult male volunteers with low gastric acidity. Six subjects were allocated to 2 groups of 3 subjects each.

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	The study was conducted in a 2-treatment, 2-period, crossover manner with a washout period of at least 4 weeks between the 2 periods. In each period, the subjects received a single oral dose of either 1 non-deteriorated or 1 deteriorated OPC-14597 4-mg tablet in a fasted state in the morning.
99001	Open-label crossover bioequivalence study of OPC-14597 3-mg and 6-mg tablets in healthy adult male volunteers under a fasting condition. The objective of the study was to examine the bioequivalence between single oral administration of 2 OPC-14597 3-mg tablets and 1 OPC-14597 6-mg tablet in 26 healthy adult male volunteers under a fasting condition by measuring the plasma concentration of OPC-14597. The study was conducted in a 2-treatment, 2-period, crossover manner with a washout period of 28 days between the 2 periods. In each period (period I or II), the subjects received a single oral dose of either 2 3-mg tablets or 1 6-mg tablet under a fasting condition.
99002	Open-label pharmacokinetic study of OPC-14597 to investigate pharmacokinetics in the plasma, urinary excretion of OPC-14597 and its metabolites, and safety by 14-day repeated oral administration at 3 mg to 15 healthy adult male volunteers.
00001	Open-label crossover bioequivalence study of OPC-14597 to examine the bioequivalence between single oral administration of OPC-14597 1% powder (300 mg) and one OPC-14597 3-mg tablet in 14 healthy adult male volunteers under a fasting condition by measuring the plasma concentration of OPC-14597.
00002	Open-label crossover bioequivalence study of OPC-14597 to examine the bioequivalence between single oral administration of 3 OPC-14597 1-mg tablets and 1 OPC-14597 3-mg tablet in 14 healthy adult male volunteers under a fasting condition by measuring the plasma

APPENDIX IV-1: TABLE OF STUDIES	
	concentration of OPC-14597.
Phase 2/3	
91003	Multicenter, open-label study to investigate the efficacy and safety of OPC-14597 at 1-16 mg administered orally once daily for 4 weeks (up to 8 weeks if possible) in 26 patients aged 20-66 years hospitalized for the treatment of schizophrenia.
91004	Multicenter, open-label study to investigate the efficacy and safety of OPC-14597 at 1-10 mg administered orally once or twice daily for 4 weeks (up to 8 weeks if possible) in 30 patients aged 17-59 years hospitalized for the treatment of schizophrenia.
93001	Multicenter, open-label study to investigate the efficacy, safety, and optimum dose of OPC-14597 by oral administration at 4-30 mg (dose titration) in 138 schizophrenic patients aged 18-67 years.
93002	Late phase II, multicenter, open-label, follow-on study of the long-term (up to 12 months) effect of OPC-14597at 4-30 mg/day administered orally in 57 schizophrenic patients aged 18-63 years.
94001	Late phase II, multicenter, open-label, follow-on study of the long-term (up to 24 months) effect of OPC-14597at 4-30 mg/day administered orally in 8 schizophrenic patients aged 18-60 years.
95002	Multicenter, double-blind study of OPC-14597 at 6-24 mg/day and haloperidol at 3-12 mg/day administered orally for 8 weeks in 243 schizophrenic patients aged 17-65 years to determine the therapeutic efficacy and safety of OPC-14597 in schizophrenia in comparison with haloperidol.
95003	Multicenter, double-blind study of OPC-14597 at 6-24 mg/day and mosapramine hydrochloride (mosapramine) at 45-180 mg/day administered orally for 8 weeks in 245 schizophrenic patients aged 19-70 years to determine the therapeutic efficacy and safety of OPC-14597 in

APPENDIX IV-1: TABLE OF STUDIES	
	schizophrenia in comparison with mosapramine.
95004	Multicenter, open-label, long-term study of OPC-14597 at 6-24 mg/day administered orally for 24 and 52 weeks in 97 schizophrenic patients aged 18-72 years in the ~~~~ area to evaluate the long-term safety, as well as efficacy and usefulness, of OPC-14597.
95005	Multicenter, open-label, long-term study of OPC-14597 at 6-24 mg/day administered orally for 24 and 52 weeks in 116 schizophrenic patients aged 19-68 years in the area to evaluate the long-term safety, as well as efficacy and usefulness, of OPC-14597.
95006	Multicenter, open-label, long-term study of OPC-14597 at 6-24 mg/day administered orally for 24 and 52 weeks in 116 schizophrenic patients aged 22-70 years in the ~~~~ areas to evaluate the long-term safety, as well as efficacy and usefulness, of OPC-14597.

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APPENDIX IV-2: ENUMERATION OF SUBJECTS IN ALL NON-JAPANESE TRIALS BY TREATMENT AND STUDY TYPE[42]				
Study Type	Aripiprazole	Placebo	Haloperidol	Atypical[43]
Phase 1	924[44]	40[45]	0	0
Phase 2/3				
Short-Term, Placebo-Controlled				
Schizophrenia				
Fixed Dose	892	378	166	99
Flexible Dose	34	35	34	0
Bipolar Mania	393	260	0	0
Dementia	105	102	0	0
Long-Term Controlled				
Schizophrenia				
Flexible Dose	1141	0	431	282
Fixed Dose	153	153	0	0
Other Special Studies[46]	739	0	42	0
Ongoing (uncontrolled or OL)	2936	0	0	111
Total Phase 2/3	4710[47]	928	673	492
TOTAL PHASE 1/2/3	5634	968	673	492

[42] This table excludes an enumeration of patients in studies that were blinded as of 11-30-01.
[43] Includes olanzapine and risperidone.
[44] Includes 68 subjects who received an oral liquid formulation and 36 subjects who received a flashmelt formulation.
[45] Includes placebo and other protocol-specified drugs.
[46] Includes patients from four uncontrolled special studies, the open-label rescue phase of three trials (CN138-001, CN138-007, and CN138-009), and one discontinued trial (31-97-301).
[47] Patients who participated in more than one type of study (N=1683) are counted only once in this total.

APPENDIX IV-3: DEMOGRAPHIC CHARACTERISTICS OF PATIENTS TREATED WITH ARIPIPRAZOLE NON-JAPANESE PHASE 2/3 STUDIES				
	Schizophrenia N=3561	**Bipolar Mania N=645**	**Dementia N=504**	**TOTAL N=4710**
AGE				
Mean (years)	38.7	40.1	81.7	43.5
Range (years)	17.0-80.0	18.0-74.0	56.0-99.0	17.0-99.0
N by age range(yrs)				
<18	4	0	0	4
18-50	3045	526	0	3571
51-64	474	103	14	591
≥65	38	16	490	544
GENDER (N(%))				
Male	2398(67%)	285(44%)	127(25%)	2810(60%)
Female	1163(33%)	360(56%)	377(75%)	1900(40%)
RACE (N(%))				
White	2463(69%)	475(74%)	448(89%)	3386(72%)
Black	729(20%)	72(11%)	31(6%)	832(18%)
Hispanic	222(6%)	81(13%)	16(3%)	319(7%)
Asian	66(2%)	11(2%)	7(1%)	84(2%)
Other	81(2%)	6(1%)	2(0%)	89(2%)

APPENDIX IV-4:
DEMOGRAPHIC CHARACTERISTICS OF CONTROL GROUP PATIENTS
NON-JAPANESE PHASE 2/3 STUDIES

	Placebo N=928	Risperidone N=99	Olanzapine N=393	Haloperidol N=673
AGE				
Mean (years)	44.6	38.6	39.5	37.4
Range (years)	18-99	18-64	18-77	18-65
N by age range(yrs)				
18-50	689	91	326	593
51-64	123	8	59	79
≥65	116	0	8	1
GENDER (N(%))				
Male	540(58%)	71(72%)	254(65%)	420(62%)
Female	388(42%)	28(28%)	139(35%)	253(38%)
RACE (N(%))				
White	640(69%)	54(55%)	269(68%)	537(80%)
Black	195(21%)	38(38%)	86(22%)	101(15%)
Hispanic	66(7%)	4(4%)	33(8%)	17(3%)
Asian	14(2%)	2(2%)	3(1%)	3(0%)
Other	13(1%)	1(1%)	2(1%)	15(2%)

APPENDIX IV-5: DEMOGRAPHIC CHARACTERISTICS OF PATIENTS BY TREATMENT GROUP NON-JAPANESE, SHORT-TERM, PLACEBO-CONTROLLED, PHASE 2/3 STUDIES IN SCHIZOPHRENIA				
	Aripiprazole N=926	**Placebo N=413**	**Haloperidol N=200**	**Risperidone N=99**
AGE				
Mean (years)	39.1	39.1	38.8	38.6
Range (years)	18.0-73.0	18.0-76.0	18.0-65.0	18.0-64.0
N by age range(yrs)				
18-50	791	367	179	91
51-64	127	40	20	8
≥65	8	6	1	0
GENDER (N(%))				
Male	699(75%)	309(75%)	149(75%)	71(72%)
Female	227(25%)	104(25%)	51(26%)	28(28%)
RACE (N(%))				
White	506(55%)	209(51%)	122(61%)	54(55%)
Black	283(31%)	144(35%)	58(29%)	38(38%)
Hispanic	93(10%)	42(10%)	14(7%)	4(4%)
Asian	21(2%)	10(2%)	1(1%)	2(2%)
Other	23(2%)	8(2%)	5(3%)	1(1%)

APPENDIX IV-6: ENUMERATION OF ARIPIPRAZOLE-TREATED PATIENTS BY DOSE AND DURATION OF TREATMENT NON-JAPANESE PHASE 2/3 STUDIES							
TX Duration (days)	Overall Mean Dose (mg/day)						
	Unknown/ Blinded	≤12.5	>12.5 ≤17.5	>17.5 ≤25	>25 ≤32.5	>32.5	Total
1-20	13	106	205	139	546	41	1050
21-41	11	84	116	182	352	0	745
42-89	12	95	82	162	439	1	791
90-119	2	42	23	43	130	0	240
120-149	0	41	16	31	112	0	200
150-179	1	45	39	14	72	0	171
180-269	2	115	62	37	140	1	357
270-359	2	81	25	38	108	0	254
360-719	4	41	25	78	333	0	481
≥720	0	8	17	84	312	0	421
Total	47	658	610	808	2544	43	4710

APPENDIX IV-7:
ENUMERATION OF ARIPIPRAZOLE-TREATED PATIENTS BY DOSE AND DURATION OF TREATMENT
NON-JAPANESE, SHORT-TERM, PLACEBO-CONTROLLED, PHASE 2/3 STUDIES IN SCHIZOPHRENIA

TX Duration (Days)	Fixed Dose Studies[48]					Flexible Dose		Total
	Dose (mg/day)					N	Mean Dose (mg/day)[49]	
	2	10	15	20	30			
1-7	59	165	207	199	262	34	8.8	926
8-14	55	136	182	170	233	30	20.3	806
15-21	45	124	165	146	205	24	28.0	709
22-28	39	101	125	116	176	21	28.3	578
29-35	0	48	48	60	24	1	30.0	181
36-42	0	46	35	40	0	0	0	121
>42	0	13	6	12	0	0	0	31
Total	59	165	207	199	262	34	20.0	926

[48] For the fixed dose studies, the number in each cell represents the number of patients who received treatment during that study day interval by the dose received.
[49] The dose range for the flexible dose study was 5-30 mg/day. The mean dose represents the mean for all patients treated during each study day interval.

ITEMS UTILIZED IN THE REVIEW

APPENDIX V-1 ITEMS UTILIZED IN THE REVIEW[50]	
Submission Date	**Items Reviewed**
31-OCT-2001	Sponsor's Proposed Labeling NDA Application Summary Debarment Certification Financial Disclosure Certification Integrated Summary of Efficacy Integrated Summary of Safety Case Report Tabulations Case Report Forms Study Reports: 00230, 93202, 94201, 94202, 97201, 97202, 98202, 98203, 98213, 98215, 99224, and 138001.
17-JAN-2002*	Supplemental Vital Sign Data
12-FEB-2002	Table of Studies
27-FEB-2002	120-Day Safety Update Integrated Summary of Safety Case Report Tabulations Case Report Forms Study Reports: 138002 and 138006.
15-MAR-2002*	Literature Search
17-MAR-2002*	Reanalysis of Efficacy Data for Study 93202
22-MAR-2002	Case Report Forms for Non-Adverse Dropouts (for auditing)
29-MAR-2002*	CT Scan Report (Patient 91003-107-02)
10-APR-2002	Information on 4 Deaths

[50] * designates items submitted in hardcopy only. Other items were reviewed from electronic files in the CDER Electronic Document Room.

APPENDIX V-1 ITEMS UTILIZED IN THE REVIEW[50]	
Submission Date	**Items Reviewed**
15-APR-2002	Amended Table of Studies
16-APR-2002	Narrative Summaries for 3 Deaths
24-APR-2002	Alternate Tradename Proposal
29-APR-2002	Lab Data (3 patients), SAE Data (3 patients)
30-APR-2002	Narrative Summaries (3 patients)
8-MAY-2002	Lab Data (2 patients)
10-MAY-2002	Lab Data (2 patients)
15-MAY-2002	Efficacy Data in Schizoaffective Patients Supplemental Lab Data Demographic/Adverse Event Analysis Information on Adverse Event Classification
3-JUN-2002	Concomitant Antipsychotic Usage (97202 and 138001)

EFFICACY

APPENDIX VI-1: STUDY 93202 PRINCIPAL INVESTIGATORS			
Center	Investigator	Center	Investigator
02	John Csernansky, M.D.	08	Craig Karson, M.D.
04	James Garbutt, M.D.	09	Joseph P. McEvoy, M.D.
05	Donald C. Goff, M.D.	10	Mauricio Tohen, M.D.
06	Alan I. Green, M.D.	11	Robert Litman, M.D.
07	Dilip V. Jeste, M.D.	12	Thomas N. Posever, M.D.

APPENDIX VI-2
STUDY 93202
BASELINE DEMOGRAPHICS (ALL RANDOMIZED PATIENTS)

TX Group	Gender	N	Age (years)		Race (N)		
			Mean	Range	White	Black	Other
OPC-14597	Male	32	32.4	18-57	18	13	1
	Female	2	42.5	37-48	1	1	0
Haloperidol	Male	30	38.6	21-65	15	13	2
	Female	4	38.8	26-46	2	2	0
Placebo	Male	29	36.9	21-52	15	12	2
	Female	6	42.5	31-59	3	3	0

APPENDIX VI-3
STUDY 93202
BASELINE SEVERITY OF ILLNESS (EFFICACY ITT)

TX Group	N	Mean BPRS Total Score	Mean CGI-Severity Score
OPC-14597	33	53.0	4.8
Haloperidol	33	50.3	4.7
Placebo	35	50.0	4.5

APPENDIX VI-4 STUDY 93202 ENUMERATION OF PATIENTS BY DISPOSITION			
	Treatment Group		
	OPC-14597	Haloperidol	Placebo
Randomized	34	34	35
Completed	21	20	12
Dropouts by Reason			
-screening criteria not met	0	0	1
-withdrawn consent	4	6	6
-non-compliance	1	0	0
-marked deterioration	2	1	7
-lack of response	6	4	8
-adverse event	0	2	0
-other	0	1[51]	1[52]

APPENDIX VI-5 STUDY 93202 PATIENT ENUMERATION BY NUMBER OF STUDY DAYS COMPLETED (N(% OF TOTAL RANDOMIZED))			
Days Completed	OPC-14597	Haloperidol	Placebo
1-7	34 (100%)	34 (100%)	35 (100%)
8-14	30 (88%)	30 (88%)	31 (89%)
15-21	24 (71%)	25 (74%)	26 (74%)
22 or more	21 (62%)	20 (59%)	15 (43%)

[51] Escaped from the hospital.
[52] Death in the family.

APPENDIX VI-6 STUDY 93202 MEAN CHANGE FROM BASELINE IN THE BPRS TOTAL SCORE (LOCF)				
	Baseline		Week 4	
	N	Mean BPRS	N	Δ
OPC-14597	33	53.0	33	-7.2
Placebo	35	50.0	35	-2.1
Haloperidol	33	50.3	33	-8.1
p-values (Wilcoxon Rank-Sum Test)				
OPC v. Plac	0.1732		0.173	
Hal v. Plac	0.8939		0.010	

APPENDIX VI-7
STUDY 93202
NUMBER AND PERCENTAGE OF PATIENTS WITH ≥1 POINT IMPROVEMENT ON THE CGI-SEVERITY SCALE (LOCF)

	Baseline		Week 4	
	N	Mean CGI-S	n	%
OPC-14597	33	4.8	14	42.4%
Placebo	35	4.5	7	20.0%
Haloperidol	33	4.7	18	54.5%
p-values (Chi-Square)				
OPC v. Plac	-		0.045	
Hal v. Plac	-		0.003	
p-values (2-tailed Fisher's Exact Test)				
OPC v. Plac	-		0.066	
Hal v. Plac	-		0.005	

APPENDIX VI-8: STUDY 94202 PRINCIPAL INVESTIGATORS			
Center	Investigator	Center	Investigator
001	Joseph P. McEvoy, M.D.	012	Norman C. Moore, M.D. Samuel Shillcut, Pharm.D., Ph.D.
002	Bernard Beitman, M.D.	013	Peter Powchik, M.D.
003	Richard Borison, M.D., Ph.D.	014	Frederick W. Reimherr, M.D.
004	David Brown, M.D.	016	Neil M. Richtand, M.D., Ph.D.
005	Jose M. Canive, M.D. John Lauriello, M.D.	017	Murray H. Rosenthal, D.O.
006	James C.-Y. Chou, M.D.	018	Joyce G. Small, M.D.
007	David G. Daniel, M.D.	019	Manuel E. Tancer, M.D.
008	Arnold J. Friedhoff, M.D.	020	William C. Wirshing, M.D.
009	Donald C. Goff, M.D.	022	James C. Garbutt, M.D.
010	Mark Hamner, M.D.	023	Alan Green, M.D.
011	Gunnar Lawrence Larson, M.D.	025	Robert Litman, M.D.

APPENDIX VI-9
STUDY 94202
BASELINE DEMOGRAPHICS (ALL RANDOMIZED PATIENTS)

TX Group	Gender	N	Age (years)		Race (N)		
			Mean	Range	White	Black	Other
OPC 2mg	Male	47	40.1	22-65	22	19	6
	Female	12	38.8	19-51	11	1	0
OPC 10mg	Male	49	37.2	18-64	20	19	10
	Female	11	40.6	23-56	6	5	0
OPC 30mg	Male	46	38.8	18-61	19	23	4
	Female	15	38.9	24-57	11	3	1
Haloperidol	Male	52	38.0	19-60	28	19	5
	Female	11	43.2	25-63	9	2	0
Placebo	Male	53	37.5	19-57	28	20	5
	Female	11	40.5	28-55	5	4	2

APPENDIX VI-10
STUDY 94202
BASELINE SEVERITY OF ILLNESS (EFFICACY ITT)

TX Group	N	Mean BPRS Core Score	Mean CGI-Severity Score
OPC 2mg	58	16.2	4.7
OPC 10mg	57	16.8	4.8
OPC 30mg	60	16.2	4.7
Haloperidol	61	16.6	4.8
Placebo	64	16.0	4.7

APPENDIX VI-11
STUDY 94202
ENUMERATION OF PATIENTS BY DISPOSITION

	Treatment Group				
	OPC 2mg	OPC 10mg	OPC 30mg	Hal	Plac
Randomized	59	60	61	63	64
Completed	37	35	41	34	29
Dropouts by Reason					
-screening criteria not met					
-withdrawn consent	7	12	9	13	10
-non-compliance	0	0	1	0	0
-marked deterioration	3	4	0	4	8
-lack of response	8	3	6	8	12
-adverse event	4	2	4	4	1
-other	0	4	0	0	4

APPENDIX VI-12
STUDY 94202
PATIENT ENUMERATION BY NUMBER OF STUDY DAYS COMPLETED
(N(% OF TOTAL RANDOMIZED))

Days Completed	OPC 2mg	OPC 10mg	OPC 30mg	Hal	Plac
1-7	59(100%)	60(100%)	61(100%)	63(100%)	64(100%)
8-14	55(93%)	49(82%)	57(93%)	55(87%)	57(89%)
15-21	46(78%)	43(72%)	50(82%)	43(68%)	41(64%)
22 or more	39(66%)	39(65%)	42(69%)	35(56%)	32(50%)

APPENDIX VI-13
STUDY 94202 (EXCLUDING CENTER 003)
MEAN CHANGE FROM BASELINE IN THE BPRS CORE SCORE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
OPC 2mg	51	16.1	45	-1.7	36	-3.5	32	-4.8	51	-2.5
OPC 10mg	51	17.0	43	-2.7	39	-3.3	32	-3.6	51	-2.4
OPC 30mg	54	16.2	51	-2.6	41	-3.6	37	-4.4	54	-3.3
Haloperidol	54	16.6	45	-3.6	37	-4.4	31	-4.7	54	-3.8
Placebo	57	16.1	46	-2.2	34	-3.3	27	-5.1	57	-2.0
2-sided p-values										
2mg vs. Plac	0.7332		0.5806		0.7781		0.8521		0.7034	
10mg vs. Plac	0.1320		0.8103		0.6557		0.0881		0.8939	
30mg vs. Plac	0.9946		0.6317		0.7824		0.4901		0.1165	
Hal vs. Plac	0.4750		0.0897		0.2765		0.7817		0.0495	

APPENDIX VI-14
STUDY 94202 (EXCLUDING CENTER 003)
CGI-IMPROVEMENT SCORE

	Observed Cases						LOCF	
	Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Mean	N	Mean	N	Mean
OPC 2mg	46	3.7	36	3.1	32	2.9	51	3.7
OPC 10mg	43	3.4	39	3.2	32	3.1	51	3.5
OPC 30mg	51	3.3	41	2.9	37	2.7	54	3.1
Haloperidol	45	3.3	37	3.2	31	2.9	54	3.4
Placebo	45	3.6	34	3.2	27	2.9	57	3.9
2-sided p-values								
2mg vs. Plac	0.7029		0.6750		0.9639		0.5860	
10mg vs. Plac	0.2813		0.7792		0.4416		0.2260	
30mg vs. Plac	0.1275		0.2144		0.4731		0.0055	
Hal vs. Plac	0.1552		0.8036		0.9537		0.0811	

APPENDIX VI-15: STUDY 97201 PRINCIPAL INVESTIGATORS			
Center	**Investigator**	**Center**	**Investigator**
001	Faruk Abuzzahab, M.D., Ph.D.	023	Michael Lesem, M.D.
002	Bijan Bastani, M.D.	024	Robert Levine, M.D.
003	Robert Bielski, M.D.	025	Robert Litman, M.D.
004	Arthur Freeman, III, M.D. J. Gary Booker, M.D.	026	Michael McLarnon, M.D.
006	John Carmen, M.D.	027	Charles Merideth, M.D.
007	Stanley Cheren, M.D.	028	Alexander Miller, M.D. Larry Ereshefsky, Pharm.D.
008	Cal Cohn, M.D.	029	Richard Pearlman, M.D.
009	David Daniel, M.D.	030	Steven Potkin, M.D.
011	Ronald Centric, D.O.	031	Neil Richtand, M.D., Ph.D.
013	Jay Feierman, M.D.	032	Samuel Risch, M.D.
014	James Ferguson, M.D.	034	J. J. Rodos, D.O.
015	Arnold Friedhoff, M.D.	035	Anthony Rothschild, M.D.
016	Hal Goldberg, M.D.	036	David Sack, M.D.
018	Mahlon Hale, M.D.	037	Joyce Small, M.D.
019	James Hartford, M.D.	038	Kenneth Sokolski, M.D.
020	Mary Ann Knesevich, M.D.	039	Tram Tran-Johnson, Pharm. D.
021	Irving Kolin, M.D.	041	Scott West, M.D.
022	William Lawson, M.D.	043	Dan Zimbroff, M.D.

APPENDIX VI-16: DEMOGRAPHIC CHARACTERISTICS STUDY 97201 (ALL RANDOMIZED PATIENTS)							
	Age (years)		Gender (%)		Race (%)		
	Mean	Range	Male	Female	White	Black	Other
Ari 15mg	37.8	19-61	75%	25%	60%	25%	15%
Ari 30mg	39.3	19-65	69%	31%	59%	26%	15%
Placebo	38.5	19-68	70%	30%	51%	32%	17%
Hal 10mg	38.9	18-59	65%	35%	67%	23%	10%

APPENDIX VI-17 STUDY 97201 BASELINE SEVERITY OF ILLNESS (ALL RANDOMIZED PATIENTS)			
TX Group	N	Mean PANSS Total Score	Mean CGI-Severity Score
Ari 15mg	102	98.5	4.9
Ari 30mg	102	99.0	4.8
Placebo	106	100.2	4.9
Haloperidol	104	99.3	4.8

APPENDIX VI-18 STUDY 97201 ENUMERATION OF ALL PATIENTS BY DISPOSITION				
	Treatment Group			
	Ari 15mg	Ari 30mg	Plac	Hal
Randomized	102	102	106	104
Completed	68	60	58	62
Dropouts by Reason				
-adverse event	9	8	17	11
-lost to follow-up	0	1	1	0
-withdrew consent	15	10	12	20
-administrative reasons	1	1	1	0
-noncompliance	0	1	1	1
-poor clinical response	9	21	16	10

APPENDIX VI-19 STUDY 97201 ENUMERATION OF ITT PATIENTS IN-STUDY BY WEEK[53] (N(% OF ITT))				
Week	Ari 15mg	Ari 30mg	Placebo	Haloperidol
Baseline (ITT)	99	100	102	99
1	97(98%)	100(100%)	102(100%)	97(98%)
2	84(85%)	87(87%)	89(87%)	82(83%)
3	77(78%)	73(73%)	69(68%)	70(71%)
4	68(69%)	61(61%)	60(59%)	61(62%)

[53] Based on patients with PANSS total score data.

APPENDIX VI-20
STUDY 97201
MEAN CHANGE FROM BASELINE IN THE PANSS TOTAL SCORE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 15mg	99	97.9	84	-13.3	77	-14.8	68	-24.3	99	-15.5
Ari 30mg	100	98.5	87	-10.3	73	-14.0	61	-19.1	100	-11.4
Haloperidol	99	99.6	82	-12.0	70	-14.9	61	-16.6	99	-13.8
Placebo	102	100.2	89	-2.6	69	-9.4	60	-11.4	102	-2.9
2-sided p-values										
15mg vs. Plac	0.355		<0.001		0.120		<0.001		<0.001	
30mg vs. Plac	0.508		0.010		0.193		0.040		0.009	
Hal vs. Plac	0.804		0.002		0.124		0.163		0.001	

APPENDIX VI-21
STUDY 97201
MEAN CHANGE FROM BASELINE IN THE PANSS POSITIVE SUBSCALE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 15mg	99	24.6	84	-4.1	77	-4.5	68	-6.4	99	-4.2
Ari 30mg	100	24.4	87	-3.1	73	-4.5	61	-6.2	100	-3.8
Haloperidol	99	25.1	82	-3.7	70	-4.7	61	-5.0	99	-4.4
Placebo	103	24.9	89	-0.7	69	-2.8	60	-2.6	103	-0.6
2-sided p-values										
15mg vs. Plac	0.716		<0.001		0.088		<0.001		<0.001	
30mg vs. Plac	0.511		0.008		0.091		0.001		0.001	
Hal vs. Plac	0.707		0.001		0.072		0.023		<0.001	

APPENDIX VI-22
STUDY 97201
MEAN CHANGE FROM BASELINE IN THE CGI-SEVERITY OF ILLNESS SCORE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 15mg	99	4.9	84	-0.5	77	-0.7	68	-0.9	99	-0.6
Ari 30mg	100	4.8	87	-0.3	73	-0.5	60	-0.7	100	-0.4
Haloperidol	99	4.9	82	-0.4	70	-0.6	61	-0.6	99	-0.5
Placebo	103	4.9	89	-0.1	69	-0.3	60	-0.4	103	-0.1
2-sided p-values										
15mg vs. Plac	0.766		<0.001		0.007		0.001		<0.001	
30mg vs. Plac	0.230		0.017		0.132		0.053		0.019	
Hal vs. Plac	0.397		0.004		0.091		0.147		0.002	

APPENDIX VI-23: STUDY 97202 PRINCIPAL INVESTIGATORS			
Center	**Investigator**	**Center**	**Investigator**
050	David Brown, M.D.	073	Denis Mee-Lee, M.D.
051	Jose Canive, M.D.	074	Herbert Y. Meltzer, M.D.
052	Aly Ahmed, M.D.	076	B. Rhett Myers, M.D.
053	James Chou, M.D.	078	Stephen Peterson, M.D.
054	Emmett Cooper, M.D.	079	Debra Brescan, M.D. Luis Ramirez, M.D.
055	John W. Crayton, M.D.	080	Christine Grissom, M.D. Timothy Reid, M.D.
056	David Daniel, M.D.	081	Robert Riesenberg, M.D.
057	Lawrence Adler, M.D.	082	Fred Schaerf, M.D., Ph.D.
058	Mohsain Essa, M.D.	083	Herbert Y. Meltzer, M.D.
059	Louis Fabre, M.D., Ph.D.	084	Philip Seibel, M.D.
060	Ira Glick, M.D.	086	Samuel Shillcutt, Pharm.D., Ph.D.
062	Alan Green, M.D.	087	Jeff Simon, M.D.
063	Barry Guze, M.D.	088	Thomas Smith, M.D.
064	Mark Hamner, M.D.	089	Vicky Spratlin, M.D.
066	Richard Josiassen, Ph.D.	090	Stephen Strakowski, M.D.
067	Steven Potkin, M.D.	091	Steven Targum, M.D.
068	Gunnar Larson, M.D.	092	Marshall Thomas, M.D.
069	Mark Lerman, M.D.	093	Cherian Verghese, M.D.
071	Robert Litman, M.D.	094	Kenneth Weiss, M.D.
072	Joseph McEvoy, M.D.	095	William Wirshing, M.D. Stephen Marder, M.D.

APPENDIX VI-24: DEMOGRAPHIC CHARACTERISTICS STUDY 97202 (ALL RANDOMIZED PATIENTS)							
	Age (years)		Gender (%)		Race (%)		
	Mean	Range	Male	Female	White	Black	Other
Ari 20mg	38.1	18-57	72%	28%	60%	32%	8%
Ari 30mg	40.2	20-65	65%	35%	61%	34%	5%
Placebo	38.8	18-62	71%	29%	58%	35%	7%
Risp 6mg	38.6	18-64	72%	28%	55%	39%	6%

APPENDIX VI-25 STUDY 97202 BASELINE SEVERITY OF ILLNESS (ALL RANDOMIZED PATIENTS)			
TX Group	N	Mean PANSS Total Score	Mean CGI-Severity Score
Ari 20mg	101	94.4	4.8
Ari 30mg	101	92.6	4.8
Placebo	103	95.7	4.8
Risperidone	99	94.9	4.8

APPENDIX VI-26 STUDY 97202 ENUMERATION OF ALL PATIENTS BY DISPOSITION				
	Treatment Group			
	Ari 20mg	Ari 30mg	Plac	Risp
Randomized	101	101	103	99
Completed	61	67	52	62
Dropouts by Reason				
-adverse event	11	8	17	8
-lost to follow-up	0	2	0	2
-withdrew consent	18	9	11	12
-protocol violation	0	1	1	1
-noncompliance	1	2	0	1
-poor clinical response	10	12	22	13

APPENDIX VI-27 STUDY 97202 ENUMERATION OF ITT PATIENTS IN-STUDY BY WEEK[54] (N(% OF ITT))				
Week	Ari 20mg	Ari 30mg	Placebo	Risperidone
Baseline (ITT)	98	96	103	95
1	96(98%)	95(99%)	102(99%)	95(100%)
2	77(79%)	79(82%)	77(75%)	84(88%)
3	68(69%)	73(76%)	56(54%)	68(72%)
4	61(62%)	68(71%)	52(50%)	61(64%)

[54] Based on patients with PANSS total score data.

APPENDIX VI-28
STUDY 97202
MEAN CHANGE FROM BASELINE IN THE PANSS TOTAL SCORE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 20mg	98	94.0	77	-15.5	68	-18.6	61	-23.4	98	-14.5
Ari 30mg	96	92.3	79	-13.8	73	-19.0	68	-20.2	96	-13.9
Risperidone	95	93.6	84	-14.2	68	-18.3	61	-22.7	95	-15.7
Placebo	103	95.0	77	-8.9	56	-15.4	52	-18.2	103	-5.0
2-sided p-values										
20mg vs. Plac	0.670		0.023		0.348		0.132		0.001	
30mg vs. Plac	0.270		0.089		0.288		0.552		0.003	
Risp vs. Plac	0.557		0.062		0.394		0.191		<0.001	

APPENDIX VI-29
STUDY 97202
MEAN CHANGE FROM BASELINE IN THE PANSS POSITIVE SUBSCALE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 20mg	98	24.8	77	-5.1	68	-6.2	61	-7.5	98	-4.9
Ari 30mg	96	24.0	79	-3.9	73	-5.1	68	-5.7	96	-3.9
Risperidone	95	23.9	84	-5.0	68	-5.8	61	-7.3	95	-5.2
Placebo	103	24.5	77	-2.5	56	-4.7	52	-5.3	103	-1.8
2-sided p-values										
20mg vs. Plac	0.710		0.002		0.167		0.045		0.001	
30mg vs. Plac	0.433		0.111		0.721		0.700		0.018	
Risp vs. Plac	0.401		0.003		0.277		0.073		<0.001	

APPENDIX VI-30
STUDY 97202
MEAN CHANGE FROM BASELINE IN THE CGI-SEVERITY OF ILLNESS SCORE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 20mg	98	4.8	77	-0.6	69	-0.8	61	-1.0	98	-0.5
Ari 30mg	96	4.7	79	-0.6	73	-0.8	68	-0.9	96	-0.6
Risperidone	95	4.8	84	-0.7	68	-0.8	61	-1.1	95	-0.7
Placebo	103	4.8	77	-0.3	56	-0.6	52	-0.7	103	-0.2
2-sided p-values										
20mg vs. Plac	0.926		0.003		0.200		0.165		0.030	
30mg vs. Plac	0.538		0.011		0.328		0.335		0.006	
Risp vs. Plac	0.737		0.001		0.167		0.043		<0.001	

APPENDIX VI-31: STUDY 138001 PRINCIPAL INVESTIGATORS			
Center	Investigator	Center	Investigator
001	David Adson, M.D.	033	David Daniel, M.D.
002	Mohammed Bari, M.D.	035	Marshall R. Thomas, M.D.
003	Joseph Bona, M.D., Ph.D.	037	Adam Lowy, M.D.
004	David L. Garner, M.D.	038	Bijan Bastani, M.D.
005	Hisham Hafez, M.D.	040	Jose Canive, M.D.
007	Philip G. Janicak, M.D.	041	Andrew Cutler, M.D.
008	Richard P. Johnson, M.D.	043	Alan I. Green, M.D.
009	Richard Josiassen, Ph.D.	045	Eduardo Dunayevich, M.D.
010	Mary Ann Knesevich, M.D.	046	Joseph Fanelli, M.D.
011	Gunnar Larson, M.D.	047	Mark R. Bloch, M.D.
012	Mark Lerman, M.D.	050	Naveed Iqbal, M.D.
013	Joseph P. McEvoy, M.D.	051	Jeffrey A. Lieberman, M.D.
014	Richard Pearlman, M.D.	054	Rudra Prakash, M.D.
015	William Petrie, M.D.	055	Jeffrey L. Rausch, M.D.
016	Robert Moreines, M.D.	056	Neil Richtand, M.D., Ph.D.
017	Valerie Smith-Gamble, M.D.	057	Adam Wolkins, M.D.
020	Seeth Vivek, M.D.	062	Craig Wronski, D.O.
021	Jesse Carr, M.D.	064	Osvaldo Caro, M.D.
022	Louise Beckett, M.D.	066	S. Craig Risch, M.D.
023	Harold Harsch, M.D.	068	Michael Woodbury, M.D.
024	Patricia Solbach, Ph.D.	069	Evagelos Coskinas, M.D.
025	Samuel Shillcutt, Pharm.D., Ph.D.	070	Kathleen Degen, M.D.
026	Richard Jaffe, M.D.	072	Roberto Gill, M.D.
027	Cherian Verghese, M.D.	073	Sean Flynn, M.D.
028	Tram K. Tran-Johnson, Pharm.D., Psy.D.	074	Alain Labelle, M.D.
029	Alexander L. Miller, M.D.	075	Wilson Lit, M.D.
030	Harold D. Udelman, M.D.	076	Bill Macewan, M.D.
031	David W. Brown, M.D.	082	Carlos Figueroa, M.D.
032	Timothy Reid, M.D.		

APPENDIX VI-32: DEMOGRAPHIC CHARACTERISTICS STUDY 138001 (ALL RANDOMIZED PATIENTS)							
	Age (years)		Gender (%)		Race (%)		
	Mean	Range	Male	Female	White	Black	Other
Ari 10mg	40.0	18-73	77%	23%	50%	27%	23%
Ari 15mg	40.0	19-68	75%	25%	54%	26%	20%
Ari 20mg	40.4	19-69	82%	18%	52%	29%	19%
Placebo	41.2	19-76	77%	23%	45%	34%	21%

APPENDIX VI-33 STUDY 138001 BASELINE SEVERITY OF ILLNESS (ALL RANDOMIZED PATIENTS)			
TX Group	N	Mean PANSS Total Score	Mean CGI-Severity Score
Ari 10mg	106	92.7	4.8
Ari 15mg	106	93.2	4.8
Ari 20mg	100	92.5	4.7
Placebo	108	92.3	4.6

APPENDIX VI-34 STUDY 138001 ENUMERATION OF ALL PATIENTS BY DISPOSITION				
	Treatment Group			
	Ari 10mg	Ari 15mg	Ari 20mg	Plac
Randomized	106	106	100	108
Completed DB Treatment	43	32	37	30
Dropouts from DB TX by Reason				
-entered OL rescue after wk 3	28	37	22	44
-lack of efficacy	5	8	11	11
-adverse event	11	3	5	6
-withdrew consent	18	24	18	13
-patient unreliability	1	1	1	0
-lost to follow-up	0	0	4	0
-other cause	0	1	2	4

APPENDIX VI-35 STUDY 138001 ENUMERATION OF ITT PATIENTS IN-STUDY BY WEEK[55] (N(% OF EFFICACY SAMPLE))				
Week	**Ari 10mg**	**Ari 15mg**	**Ari 20mg**	**Plac**
N-Efficacy Sample	103	103	97	107
1	89(86%)	95(92%)	87(90%)	100(93%)
2	86(83%)	89(86%)	81(84%)	88(82%)
3	78(76%)	82(80%)	68(70%)	82(77%)
4	51(50%)	41(40%)	49(51%)	42(39%)
5	45(44%)	37(36%)	40(41%)	31(29%)
6	42(41%)	34(33%)	39(40%)	30(28%)

[55] Based on patients with PANSS total score data.

APPENDIX VI-36
STUDY 138001
MEAN CHANGE FROM BASELINE IN THE PANSS TOTAL SCORE

	Observed Cases								LOCF	
	Baseline		Week 3		Week 4		Week 6		Week 6	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 10mg	103	92.76	78	-15.69	51	-23.69	42	-33.42	103	-15.04
Ari 15mg	103	93.27	82	-10.59	41	-22.51	34	-31.92	103	-11.73
Ari 20mg	97	92.29	68	-14.99	49	-20.86	39	-28.91	97	-14.44
Placebo	107	92.40	82	-7.45	42	-18.96	30	-26.86	107	-2.33
2-sided p-values										
10mg vs. Plac	0.902		0.008		0.212		0.113		<0.001	
15mg vs. Plac	0.763		0.300		0.373		0.242		0.004	
20mg vs. Plac	0.969		0.018		0.619		0.624		<0.001	

APPENDIX VI-37
STUDY 138001
MEAN CHANGE FROM BASELINE IN THE PANSS-DERIVED BPRS CORE SCORE

	Observed Cases								LOCF	
	Baseline		Week 3		Week 4		Week 6		Week 6	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 10mg	103	16.87	78	-4.04	51	-5.56	42	-7.53	103	-3.91
Ari 15mg	103	16.78	82	-2.49	41	-5.28	34	-7.18	103	-2.88
Ari 20mg	97	16.69	68	-3.65	49	-4.63	39	-6.40	97	-3.56
Placebo	107	16.78	82	-2.21	42	-4.56	30	-5.77	107	-1.37
2-sided p-values										
10mg vs. Plac	0.825		0.003		0.183		0.037		<0.001	
15mg vs. Plac	0.998		0.648		0.366		0.110		0.014	
20mg vs. Plac	0.851		0.025		0.924		0.465		<0.001	

APPENDIX VI-38
STUDY 138001
MEAN CHANGE FROM BASELINE IN THE PANSS NEGATIVE SUBSCALE

	Observed Cases								LOCF	
	Baseline		Week 3		Week 4		Week 6		Week 6	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 10mg	103	23.39	78	-3.58	51	-5.29	42	-7.37	103	-3.52
Ari 15mg	103	23.37	82	-2.06	41	-4.91	34	-7.28	103	-2.65
Ari 20mg	97	23.31	68	-3.53	49	-5.02	39	-6.89	97	-3.33
Placebo	107	22.65	82	-1.13	42	-3.99	30	-5.21	107	+0.08
2-sided p-values										
10mg vs. Plac	0.455		0.006		0.247		0.075		<0.001	
15mg vs. Plac	0.467		0.287		0.437		0.102		0.002	
20mg vs. Plac	0.511		0.010		0.362		0.170		<0.001	

APPENDIX VI-39

MODEL-BASED MEAN CHANGE FROM BASELINE IN THE PANSS TOTAL SCORE (LOCF) FOR DEMOGRAPHIC AND BASELINE SCORE SUBGROUPS

POOL OF FIVE SHORT-TERM, PLACEBO-CONTROLLED STUDIES IN SCHIZOPHRENIA

		PANSS Total Score at Endpoint							
Subgroup		N	Placebo	N	Haloperidol	N	Risperidone	N	Aripiprazole
Gender	Men	301	-2.8	137	-13.4	67	-14.1	661	-12.6
	Women	103	-3.2	49	-14.1	28	-15.3	224	-13.9
Age (years)	< 50	351	-1.8	162	-14.2	87	-14.2	743	-13.3
	≥ 50	53	-9.8	24	-9.4	8	-17.6	142	-10.8
Race	White	204	-2.0	115	-14.4	53	-15.0	492	-12.7
	Black	140	-2.4	51	-11.5	36	-15.8	260	-13.7
	Hispanic	42	-10.9	14	-14.1	4	-1.8	91	-9.0
	Asian	10	14.1	1	-14.0	1	11.4	21	-22.5
Baseline PANSS Total	Above Median (> 91)	196	-5.7	105	-18.1	49	-17.1	433	-17.9
	Below Median (≤ 91)	208	0.1	81	-9.4	46	-11.4	452	-8.0

APPENDIX VI-40 SUMMARY OF EFFICACY RESULTS AT STUDY ENDPOINT						
Study	Treatment	Variable	Observed Cases		LOCF	
			p-value	Superiority[56]	p-value	Superiority
93202	Aripiprazole	BPRS Total	Not Reported by Sponsor		0.173	ns
		CGI-severity			0.045	
	Haloperidol	BPRS Total			0.010	*
		CGI-severity			0.003	
94202	Ari 2mg	BPRS Core	0.8521	ns	0.7034	ns
		CGI-improvement	0.9639		0.5860	
	Ari 10mg	BPRS Core	0.0881	ns	0.8939	ns
		CGI-improvement	0.4416		0.2260	
	Ari 30mg	BPRS Core	0.4901	ns	0.1165	ns
		CGI-improvement	0.4731		0.0055	
	Haloperidol	BPRS Core	0.7817	ns	0.0495	ns
		CGI-improvement	0.9537		0.0811	
97201	Ari 15mg	PANSS total	<0.001	*	<0.001	*
		PANSS positive	<0.001		<0.001	
		CGI-severity	0.001		<0.001	
	Ari 30mg	PANSS total	0.040	*	0.009	*
		PANSS positive	0.001		0.001	
		CGI-severity	0.053		0.019	
	Haloperidol	PANSS total	0.163	ns	0.001	*
		PANSS positive	0.023		<0.001	
		CGI-severity	0.147		0.002	

[56] *=treatment is statistically superior to placebo after multiplicity adjustment; ns=not superior.

APPENDIX VI-40 SUMMARY OF EFFICACY RESULTS AT STUDY ENDPOINT						
Study	Treatment	Variable	Observed Cases		LOCF	
			p-value	Superiority[56]	p-value	Superiority
97202	Ari 20mg	PANSS total	0.132	ns	0.001	*
		PANSS positive	0.045		0.001	
		CGI-severity	0.165		0.030	
	Ari 30mg	PANSS total	0.552	ns	0.003	*
		PANSS positive	0.700		0.018	
		CGI-severity	0.335		0.006	
	Risperidone	PANSS total	0.191	ns	<0.001	*
		PANSS positive	0.073		<0.001	
		CGI-severity	0.043		<0.001	
138001	Ari 10mg	PANSS total	0.113	ns	<0.001	*
	Ari 15mg	PANSS total	0.242		0.004	
	Ari 20mg	PANSS total	0.624		<0.001	
	Ari 10mg	PANSS/BPRS core	0.037	*	<0.001	*
		PANSS negative	0.075		<0.001	
	Ari 15mg	PANSS/BPRS core	0.110	ns	0.014	*
		PANSS negative	0.102		0.002	
	Ari 20mg	PANSS/BPRS core	0.465	ns	<0.001	*
		PANSS negative	0.170		<0.001	

APPENDIX VI-41 SUMMARY OF MULTIPLICITY ADJUSTMENT METHODOLOGIES FOR P-VALUE INTERPRETATION		
Study	**TX Arm**	**Criteria for Statistical Superiority over Placebo**
93202	Aripiprazole	p≤0.05 on BOTH primary variables
	Haloperidol	p≤0.05 on BOTH primary variables
94202	Ari 2mg	p≤0.017 on BOTH primary variables
	Ari 10mg	p≤0.017 on BOTH primary variables
	Ari 30mg	p≤0.017 on BOTH primary variables
	Haloperidol	p≤0.05 on BOTH primary variables
97201	Ari 15mg	If 30mg superior, p≤0.05 on ALL 3 primary variables. If 30mg not superior, 15mg not tested.
	Ari 30mg	p≤0.05 on ALL 3 primary variables
	Haloperidol	p≤0.05 on ALL 3 primary variables
97202	Ari 20mg	If 30mg superior, p≤0.05 on ALL 3 primary variables. If 30mg not superior, 15mg not tested.
	Ari 30mg	p≤0.05 on ALL 3 primary variables
	Risperidone	p≤0.05 on ALL 3 primary variables
138001 (1°variable)	Ari 10/15/20	p≤0.05 for all 3 doses OR p≤0.025 for any 2 doses OR p≤0.0167 for any 1 dose.
138001 (2°variables)	Ari 10mg	For BPRS core score, p≤0.05. For PANSS negative subscale, p≤0.05 AND p≤0.05 for BPRS core.
	Ari 15mg	For BPRS core score, p≤0.05. For PANSS negative subscale, p≤0.05 AND p≤0.05 for BPRS core.
	Ari 20mg	For BPRS core score, p≤0.05. For PANSS negative subscale, p≤0.05 AND p≤0.05 for BPRS core.

SAFETY

APPENDIX VII-1: INCIDENCE OF ALL SPONSOR-IDENTIFIED SERIOUS AE's[57] NON-JAPANESE PHASE 2/3 STUDIES (N=4710)	
Body System/Adverse Event	**N(%)**
Body as a Whole	
Psychosocial support	48(1.02%)
Accidental injury	37(0.79%)
Suicide attempt	26(0.55%)
Overdose	23(0.49%)
Chest pain	18(0.38%)
Asthenia	8(0.17%)
Fever	7(0.15%)
Sepsis	7(0.15%)
Hernia	6(0.13%)

[57] Events are listed by preferred (coded) term. The incidence is corrected for gender as approporiate. In addition, the following events were reported as SAE's in only one patient each: abscess, AIDS, allergic reaction, craving alcohol, adjustment disorder, food poisoning, hyperplastic polyp, multisystem failure, back pain, rigidity, arrhythmia, arteriosclerosis, dissecting artery, AV block, bigeminy, bradycardia, congestive heart failure, coronary artery disorder, peripheral vascular disorder, ventricular extrasystoles, orthostatic hypotension, palpitation, phlebitis, tachycardia, supraventricular tachycardia, thrombosis, varicose vein, anorexia, appendicitis, gastrointestinal carcinoma, gastrointestinal disorder, dysphagia, hepatitis, fecal impaction, jaundice, nausea and vomiting, esophgeal stenosis, hypothyroidism, macrocytic anemia, coagulation time decreased, leukocytosis, thrombocytopenic purpura, thrombocythemia, electrolyte abnormality, hypokalemia, hyponatremia, LDH increased, malnourished, hypoglycemic reaction, arthritis, bone disorder, rhabdomyolysis, abnormal gait, coma, dysarthria, dyskinesia, dystonia, hypertonia, cerebral ischemia, CNS neoplasm, nervousness, neuralgia, salivation increased, somnolence, stress, subdural hematoma, tremor, asphyxia, lung carcinoma, cough increased, respiratory disorder, pulmonary embolism, hemoptysis, pleural effusion, basal cell carcinoma, psoriasis, rash, cataract, retinal disorder, vestibular disorder, eardrum rupture, hip fracture, menstrual disorder, ovarian disorder, vaginal disorder, dysmenorrhea, uterine hemorrhage, menorrhagia, prostate carcinoma, prostatic disorder, abnormal kidney function, urinary tract infection, pyelonephritis, and urinary retention.

APPENDIX VII-1: INCIDENCE OF ALL SPONSOR-IDENTIFIED SERIOUS AE's[57] NON-JAPANESE PHASE 2/3 STUDIES (N=4710)	
Body System/Adverse Event	**N(%)**
Abdominal pain	6(0.13%)
Cellulitis	5(0.11%)
Infection	5(0.11%)
Carcinoma	3(0.06%)
Gangrene	3(0.06%)
Neoplasm	3(0.06%)
Intentional injury	2(0.04%)
Mendelson's syndrome	2(0.04%)
Neuroleptic malignant syndrome	2(0.04%)
Cardiovascular	
Myocardial infarction	10(0.21%)
Syncope	8(0.17%)
Cardiac arrest	5(0.11%)
Hypertension	4(0.08%)
Abnormal ECG	3(0.06%)
Heart failure	3(0.06%)
Deep vein thrombosis	3(0.06%)
Hypotension	2(0.04%)
Myocardial ischemia	2(0.04%)
Shock	2(0.04%)
Digestive	
Vomiting	7(0.15%)
Cholecystitis	5(0.11%)
Cholelithiasis	3(0.06%)
Gastritis	3(0.06%)

APPENDIX VII-1: INCIDENCE OF ALL SPONSOR-IDENTIFIED SERIOUS AE's[57] NON-JAPANESE PHASE 2/3 STUDIES (N=4710)	
Body System/Adverse Event	**N(%)**
Gastroenteritis	3(0.06%)
Nausea	3(0.06%)
Intestinal obstruction	3(0.06%)
Pancreatitis	3(0.06%)
Abnormal liver function tests	2(0.04%)
Diarrhea	2(0.04%)
Rectal disorder	2(0.04%)
Dyspepsia	2(0.04%)
Gastrointestinal hemorrhage	2(0.04%)
Liver damage	2(0.04%)
Hematologic	
Anemia	5(0.11%)
Leukopenia	3(0.06%)
Metabolic/Nutritional	
Dehydration	8(0.17%)
CPK increased	5(0.11%)
Diabetes mellitus	4(0.08%)
Alcohol intolerance	3(0.06%)
Hyperglycemia	3(0.06%)
Cachexia	2(0.04%)
Hypoglycemia	2(0.04%)
Weight loss	2(0.04%)
Musculoskeletal	
Myasthenia	2(0.04%)
Nervous	

APPENDIX VII-1: INCIDENCE OF ALL SPONSOR-IDENTIFIED SERIOUS AE's[57] NON-JAPANESE PHASE 2/3 STUDIES (N=4710)	
Body System/Adverse Event	**N(%)**
Psychosis	382(8.11%)
Schizophrenic reaction	130(2.76%)
Suicidal thoughts	58(1.23%)
Depression	41(0.87%)
Agitation	24(0.51%)
Hallucination	24(0.51%)
Manic reaction	23(0.49%)
Paranoid reaction	22(0.47%)
Anxiety	21(0.45%)
Hostility	18(0.38%)
Psychiatric decompensation	15(0.32%)
Seizure	13(0.28%)
Manic depressive reaction	12(0.25%)
Delusions	10(0.21%)
Drug dependence	10(0.21%)
Confusion	7(0.15%)
Insomnia	7(0.15%)
Abnormal behavior	6(0.13%)
Mental disorder	5(0.11%)
Extrapyramidal syndrome	5(0.11%)
Akathisia	4(0.08%)
Abnormal thinking	3(0.06%)
Cerebrovascular accident	3(0.06%)
Grand mal seizure	3(0.06%)
Withdrawal syndrome	3(0.06%)

APPENDIX VII-1: INCIDENCE OF ALL SPONSOR-IDENTIFIED SERIOUS AE's[57] NON-JAPANESE PHASE 2/3 STUDIES (N=4710)	
Body System/Adverse Event	**N(%)**
Delirium	2(0.04%)
Personality disorder	2(0.04%)
Lightheadedness	2(0.04%)
Respiratory	
Pneumonia	22(0.47%)
Lung disorder	10(0.21%)
Dyspnea	6(0.13%)
Asthma	4(0.08%)
Bronchitis	3(0.06%)
Pulmonary edema	2(0.04%)
Aspiration pneumonia	2(0.04%)
Respiratory failure	2(0.04%)
Skin	
Skin Ulcer	3(0.06%)
Skin melanoma	2(0.04%)
Urogenital	
Pregnancy	3(0.16%)
Breast carcinoma	2(0.04%)
Kidney failure	2(0.04%)

APPENDIX VII-2: DEATH LINE LISTING NON-JAPANESE PHASE 2/3 STUDIES[58]					
Patient Unique ID Number	Age	Sex	Day of Onset/ Day of Last Dose	Last Dose (mg/day)	Cause of Death (as determined from Narrative Summary review)
TREATMENT=ARIPIPRAZOLE					
97201-7-8	38	M	96/83	30	Overdose (EtOH/fluoxetine)
97201-8-11	47	M	36/35	30	Asphyxia (house fire)
97201-18-10	68	F	54/53	5	Suicide (hanging)
97201-22-4	47	M	57/57	30	Myocardial infarction
97301-120-1	60	F	11/11	30	Suicide (hanging)
98213-602-5	60	M	313/312	15	Myocardial infarction
98304-437-59	59	F	553/553	15	Suicide (stabbing)
98304-438-57	30	M	129/128	30	Heart failure (congenital defect)
98304-439-60	45	F	126/126	30	Suicide (drowning)
98304-440-63	40	F	45/44	30	Unknown (underlying cardiomegaly/CAD)
98304-485-66	27	M	18/18	30	Suicide (hanging)
98304-509-50	28	M	10/4	30	Suicide (hanging)
98304-558-58	27	M	7/7	30	Suicide (hanging)
98304-559-50	30	M	525/616	30	Metastatic melanoma
98304-568-53	28	F	44/43	20	Suicide (jumping)

[58] Days were counted relative to the start of dosing with the designated treatment. Onset refers to the start of the adverse event deemed to be causally related to death when such a premorbid event was identified; otherwise, it is the day of death. Dose at onset equals zero when the designated treatment was discontinued prior to onset.

APPENDIX VII-2: DEATH LINE LISTING NON-JAPANESE PHASE 2/3 STUDIES[58]					
Patient Unique ID Number	**Age**	**Sex**	**Day of Onset/ Day of Last Dose**	**Last Dose (mg/day)**	**Cause of Death (as determined from Narrative Summary review)**
138001-12-492	54	M	95/52	20	Suicide (wrist laceration)
138001-13-151	41	M	57/54	Unknown	Suicide
138001-68-275	62	F	107/103	20	Respiratory distress synd. assoc. w/pancreatitis
138001-68-454	57	F	95/93	10	Skull fracture assoc. w/seizure
138002-75-339	46	M	61/60	Unknown	Murder (strangulation)
138004-3-25	86	F	271/270	15	Unknown (H/O CHF)
138004-11-31	80	M	163/163	10	Cerebrovascular accident
138004-11-211	85	M	69/68	10	Unknown (unspecified complication of surgery)
138004-11-213	82	F	3/3	2	Unknown
138004-20-17	87	F	332/332	10	Unknown
138004-20-208	89	F	151/151	5	Sepsis
138004-42-119	84	F	215/201	2	Volvulus
138004-59-135	90	F	76/75	2	Respiratory infection
138004-83-125	78	M	19/18	5	Pneumonia
138004-84-107	80	F	104/104	10	Cancer (colon)
138004-98-196	74	M	175/169	2	Aspiration pneumonia
138004-105-195	69	M	37/13	2	Cachexia assoc. with Alzheimer's disease
138005-3-16	76	M	92/86	15	Pneumonia, H/O GERD
138005-9-42	78	F	176/140	10	Cachexia assoc. with Alzheimer's disease

APPENDIX VII-2: DEATH LINE LISTING NON-JAPANESE PHASE 2/3 STUDIES[58]					
Patient Unique ID Number	**Age**	**Sex**	**Day of Onset/ Day of Last Dose**	**Last Dose (mg/day)**	**Cause of Death (as determined from Narrative Summary review)**
138005-11-22	88	M	182/162	10	Aspiration pneumonia
138005-12-49	93	F	244/242	5	Unspecified respiratory infection
138005-20-65	89	F	136/137	5	Pneumonia
138005-43-96	86	F	220/214	5	Unknown (underlying arteriosclerosis)
138005-43-103	82	M	127/126	Unknown	Heart failure
138006-8-18	79	M	145/142	10	Heart failure
138006-8-36	86	F	122/119	5	Renal failure
138006-8-71	84	M	41/42	2	Aspiration pneumonia D/T incorrect alimentation
138006-8-98	83	F	138/138	2	Pulmonary embolism
138006-8-138	92	F	48/42	Unknown	Pneumonia
138006-8-139	91	F	72/67	Unknown	Heart failure
138006-8-167	87	F	84/84	2	Unknown
138006-20-30	77	M	241/241	5	Aspiration pneumonia
138006-20-34	86	M	324/324	5	Aspiration pneumonia D/T incorrect alimentation
138006-20-35	94	M	307/297	Unknown	Pneumonia
138006-20-75	87	F	61/61	10	Sepsis
138006-20-78	97	M	178/178	5	Cardiac arrest
138006-20-79	96	F	149/147	5	Unknown
138006-20-221	78	F	50/50	10	Unknown
138006-21-7	89	F	163/162	5	Unknown (sudden death)

APPENDIX VII-2: DEATH LINE LISTING NON-JAPANESE PHASE 2/3 STUDIES[58]					
Patient Unique ID Number	**Age**	**Sex**	**Day of Onset/ Day of Last Dose**	**Last Dose (mg/day)**	**Cause of Death (as determined from Narrative Summary review)**
138006-21-176	96	M	79/76	5	Myocardial infarction
138006-36-66	76	F	272/271	10	Myocardial infarction
138006-71-120	82	F	202/204	10	Bronchitis
138006-71-159	82	F	113/110	5	Unknown
138006-73-188	93	F	109/109	7	Sepsis
138007-108-470	39	M	42/41	30	Overdose (heroin)
138047-7-117	30	M	1/1	15	Accident (struck by cars)
TREATMENT=HALOPERIDOL					
97301-130-1	43	M	43/42	7	Suicide (hanging)
98304-447-55	34	M	156/155	10	Suicide (jumping)
TREATMENT=BLINDED					
138003-26-411	62	M	95/92	Unknown	Asphyxia (self-induced)
138003-45-475	24	M	5/4	Unknown	Asphyxia (aspirated vomit)
138004-11-10	89	F	56/48	Unknown	Shock (probable UGI bleed)
138004-28-35	83	F	11/10	Unknown	Aortic aneurysm
138004-28-114	91	M	22/15	Unknown	Pneumonia
138004-42-87	79	F	38/36	Unknown	Unknown
138004-75-161	78	F	36/35	Unknown	Cerebral hemorrhage
138004-76-223	92	F	48/47	Unknown	Myocardial infarction
138004-83-231	85	F	70/70	Unknown	Heart failure
138004-102-248	82	M	6/6	Unknown	Unknown
138005-15-56	92	F	15/4	Unknown	Cardiopulmonary arrest
138005-46-141	95	F	20/8	Unknown	Pneumonia
138007-47-103	52	M	341/280	Unknown	Unknown

APPENDIX VII-3: DEATH LINE LISTING FOR ARIPIPRAZOLE-TREATED PATIENTS JAPANESE PHASE 2/3 STUDIES					
Protocol/Patient ID	**Age**	**Sex**	**Days on Drug (Post D/C)[59]**	**Last Dose (mg/day)**	**Cause of Death (as determined from Narrative Summary review)**
31-91-003/10702	51	M	30(1)	10	Unknown (sudden death)
31-95-003/06701	49	M	56(157)	6	Suicide (hanging)
31-95-003/08603	29	M	34(0)	9	Suicide (jumping)
31-95-004/F0701	64	F	80(2)	6	Diabetic ketoacidosis
31-95-005/H0202	36	M	260(0)	12	Suicide (jumping)
31-95-006/T1606	62	M	364(3)	3	Metastatic colon cancer
31-95-006/T1902	46	M	169(116)	6	Choking (misswallowing)

[59] The number of days between discontinuation of aripiprazole and death is provided in parentheses.

APPENDIX VII-4 ENUMERATION OF PATIENTS WITH SPECIFIC NON-FATAL SERIOUS ADVERSE EVENTS (N) NON-JAPANESE PHASE 2/3 STUDY POOL						
Body System/SAE	**Alzheimer's Dementia**			**Schizophrenia/Bipolar**		
	Ari N=504	**Placebo N=102**	**p-value[60]**	**Ari N=4206**	**Placebo N=826**	**p-value**
Body as a Whole						
Neoplasm	0	1	-	4	0	1.00
Carcinoma	4	0	1.00	8	0	0.37
AIDS	0	0	-	1	0	1.00
Sepsis	3	0	1.00	2	0	1.00
Cardiovascular						
Myocardial Infarction	1	0	1.00	5	0	1.00
Syncope	1	0	1.00	7	1	1.00
Deep Vein Thrombosis	1	0	1.00	2	0	1.00
Gangrene	1	0	1.00	3	0	1.00
Hypotension	0	0	-	1	0	1.00
Pulmonary Embolism	0	0	-	1	0	1.00
Digestive						
Cholelithiasis	1	0	1.00	3	1	0.51
Cholecystitis	1	0	1.00	2	0	1.00
Pancreatitis	0	0	-	3	0	1.00
UGI Bleed	1	0	1.00	1	1	0.30
Gastritis	0	0	-	2	0	1.00

[60] P-values are based on a 2-tailed Fisher's exact comparison of aripiprazole vs. placebo. Where no aripiprazole patients experienced an event, testing was not performed.

APPENDIX VII-4 ENUMERATION OF PATIENTS WITH SPECIFIC NON-FATAL SERIOUS ADVERSE EVENTS (N) NON-JAPANESE PHASE 2/3 STUDY POOL						
Body System/SAE	**Alzheimer's Dementia**			**Schizophrenia/Bipolar**		
	Ari N=504	**Placebo N=102**	**p-value[60]**	**Ari N=4206**	**Placebo N=826**	**p-value**
Appendicitis	0	0	-	1	0	1.00
Hepatitis	0	0	-	2	0	1.00
Esophageal Stenosis	0	0	-	1	0	1.00
Endocrine						
Diabetes Mellitus	0	0	-	3	0	1.00
Hematologic						
Leukopenia	1	0	1.00	0	0	-
Anemia	2	0	1.00	2	0	1.00
Thrombocytopenic Purpura	0	0	-	1	0	1.00
Metabolic/Nutritional						
Hyperglycemia	1	0	1.00	1	0	1.00
Hyponatremia	0	0	-	2	0	1.00
Hypoglycemia	1	0	1.00	1	0	1.00
Musculoskeletal						
Rhabdomyolysis	0	0	-	1	0	1.00
Nervous						
Seizure	6	1	1.00	12	0	0.24
Delirium	0	0	-	1	0	1.00
TIA	0	1	-	1	0	1.00
NMS	0	0	-	2	0	1.00
CVA	1	0	1.00	1	0	1.00
Subdural Hematoma	1	0	1.00	0	0	-
Respiratory						

APPENDIX VII-4 ENUMERATION OF PATIENTS WITH SPECIFIC NON-FATAL SERIOUS ADVERSE EVENTS (N) NON-JAPANESE PHASE 2/3 STUDY POOL						
Body System/SAE	**Alzheimer's Dementia**			**Schizophrenia/Bipolar**		
	Ari N=504	**Placebo N=102**	**p-value[60]**	**Ari N=4206**	**Placebo N=826**	**p-value**
Pneumonia (unspecified)	5	0	0.60	12	1	0.71
Respiratory Failure	0	0	-	1	0	1.00
Aspiration pneumonia	1	0	1.00	0	0	-
Pulmonary Edema	2	0	1.00	0	0	-
Hemoptysis	1	0	1.00	0	0	-
Special Senses						
Ruptured Eardrum	0	0	-	1	0	1.00
Cataract	1	1	0.31	0	0	-
Urogenital						
Kidney Failure	0	0	-	1	0	1.00

APPENDIX VII-5:
ENUMERATION OF ALL DROPOUTS
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Number (%) of Patients			
	Placebo	Haloperidol	Risperidone	Aripiprazole
	N = 413	N = 200	N = 99	N = 926
Discontinued	232 (56)	84 (42)	37 (37)	424 (46)
AE[a]	41 (10)	17 (9)	8 (8)	65 (7)
Lack of efficacy	84 (20)	27 (14)	13 (13)	108 (12)
Lost to follow-up	1 (< 1)	0	2 (2)	6 (1)
Patient withdrew consent	50 (12)	38 (19)	12 (12)	140 (15)
Noncompliance	1 (< 1)	1 (1)	1 (1)	9 (1)
Other[b]	11 (3)	1 (1)	1 (1)	9 (1)
Entered open-label rescue[c]	44 (11)	n/a	n/a	87 (9)
Completed Study	181 (44)	116 (58)	62 (63)	502 (54)

[a] As recorded on the end-of-study status form.

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

[c] Includes patients from Study CN138-001 who received open-label aripiprazole rescue treatment after Week 3 because of lack of response to double-blind treatment (lack of efficacy). Not applicable in studies involving haloperidol or risperidone controls.

APPENDIX VII-6
ENUMERATION OF DROPOUTS DUE TO ADVERSE EVENTS
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Body System/ Primary Term[a]	Number (%) of Patients							
	Placebo		Haloperidol		Risperidone		Aripiprazole	
	N = 413		N = 200		N = 99		N = 926	
Any Treatment-Emergent AE Leading to Discontinuation of Study Therapy[b]	39	(9.4)	16	(8.0)	8	(8.1)	68	(7.3)
Body As A Whole								
Accidental Injury[c]	0		0		0		1	(0.1)
Intentional Injury	0		0		0		1	(0.1)
Pain Chest[d]	0		0		0		1	(0.1)
Suicide Attempt	0		0		0		1	(0.1)
Cardiovascular System								
Hemorrhage[e]	0		0		0		1	(0.1)
Hypertension	0		0		0		1	(0.1)
Syncope[f]	0		0		0		1	(0.1)
Tachycardia	0		0		1	(1.0)	0	
Digestive System								
Nausea	1	(0.2)	1	(0.5)	0		3	(0.3)
Nausea And Vomiting	0		0		0		1	(0.1)
Vomiting	0		1	(0.5)	0		1	(0.1)
Abnormal Liver Function Test	0		1	(0.5)	1	(1.0)	0	
Diarrhea	1	(0.2)	0		0		0	
Metabolic/Nutritional System								
Creatine Phosphokinase Increased[g]	0		0		0		1	(0.1)
Musculoskeletal System								
Cramp Muscle	0		0		0		1	(0.1)

APPENDIX VII-6
ENUMERATION OF DROPOUTS DUE TO ADVERSE EVENTS
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Body System/ Primary Term[a]	Number (%) of Patients							
	Placebo		Haloperidol		Risperidone		Aripiprazole	
	N = 413		N = 200		N = 99		N = 926	
Nervous System								
Psychosis	25	(6.1)	3	(1.5)	5	(5.1)	33	(3.6)
Agitation	8	(1.9)	0		0		6	(0.6)
Akathisia	0		3	(1.5)	0		6	(0.6)
Anxiety	1	(0.2)	0		0		5	(0.5)
Reaction Schizophrenic	2	(0.5)	0		0		3	(0.3)
Hostility	2	(0.5)	0		0		2	(0.2)
Insomnia	0		0		0		2	(0.2)
Lightheadedness	0		0		0		2	(0.2)
Depression	0		0		0		1	(0.1)
Dystonia	0		1	(0.5)	0		1	(0.1)
Extrapyramidal Syndrome	0		0		0		1	(0.1)
Paranoid Reaction	2	(0.5)	0		0		1	(0.1)
Seizure Grand Mal	0		0		0		1	(0.1)
Somnolence	1	(0.2)	1	(0.5)	0		1	(0.1)
Hyperactivity	1	(0.2)	0		0		0	
Hypertonia	0		1	(0.5)	1	(1.0)	0	
Libido Decreased	0		1	(0.5)	0		0	
Rigidity Cogwheel	0		1	(0.5)	0		0	
Seizure	0		1	(0.5)	0		0	
Tremor Extremity	0		1	(0.5)	0		0	
Respiratory System								
Hiccup	0		0		0		1	(0.1)

APPENDIX VII-6
ENUMERATION OF DROPOUTS DUE TO ADVERSE EVENTS
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Body System/ Primary Term[a]	Number (%) of Patients			
	Placebo	Haloperidol	Risperidone	Aripiprazole
	N = 413	N = 200	N = 99	N = 926
Skin/Appendages				
Rash	0	0	0	1 (0.1)
Rash Maculopapular	1 (0.2)	0	0	0
Urogenital System				
Urinary Retention	0	1 (0.5)	0	0

[a] Modified COSTART term.

[b] AEs for which the "action taken" column on the AE form was marked "discontinue medication."

[c] Reported term was superficial laceration to left wrist as a result of suicide attempt.

[d] Myocardial infarction ruled out by cardiologist.

[e] Reported term was hematoma on the right occipital side of skull resulting from a fall during grand mal seizure.

[f] Syncope was reported to be mild and not related to aripiprazole.

[g] The event started at the end of Week 3, at which time the patient entered the open-label rescue phase. The CPK value remained elevated, which resulted in discontinuation of open-label treatment. (This patient is also noted in Section 6.4.1.)

APPENDIX VII-7
PRPORTIONS OF PATIENTS REPORTING ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 1% IN THE ARIPIPRAZOLE GROUP SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Number (%) of Patients							
Body System/	**Placebo**		**Haloperidol**		**Risperidone**		**Aripiprazole**	
Primary Term[a]	N = 413		N = 200		N = 99		N = 926	
Any Treatment-Emergent AE	362	(87.7)	183	(91.5)	92	(92.9)	844	(91.1)
Body As A Whole								
Headache	101	(24.5)	58	(29.0)	31	(31.3)	294	(31.7)
Asthenia	22	(5.3)	19	(9.5)	6	(6.1)	64	(6.9)
Pain Extremity	19	(4.6)	9	(4.5)	5	(5.1)	62	(6.7)
Pain Abdomen	20	(4.8)	8	(4.0)	4	(4.0)	48	(5.2)
Pain	13	(3.1)	10	(5.0)	2	(2.0)	46	(5.0)
Infection	13	(3.1)	4	(2.0)	2	(2.0)	40	(4.3)
Accidental Injury[b]	18	(4.4)	8	(4.0)	1	(1.0)	39	(4.2)
Pain Back	25	(6.1)	6	(3.0)	7	(7.1)	36	(3.9)
Fever	5	(1.2)	4	(2.0)	2	(2.0)	20	(2.2)
Edema Peripheral	2	(0.5)	4	(2.0)	0		17	(1.8)
Pain Chest	11	(2.7)	6	(3.0)	2	(2.0)	16	(1.7)
Rigidity Neck	6	(1.5)	3	(1.5)	4	(4.0)	15	(1.6)
Pain Neck	6	(1.5)	4	(2.0)	2	(2.0)	14	(1.5)
Stiffness	5	(1.2)	5	(2.5)	0		11	(1.2)
Cardiovascular System								
Hypotension Orthostatic	4	(1.0)	1	(0.5)	3	(3.0)	18	(1.9)
Tachycardia	4	(1.0)	0		15	(15.2)	18	(1.9)
Hypertension	4	(1.0)	2	(1.0)	1	(1.0)	17	(1.8)
Hypotension	4	(1.0)	1	(0.5)	0		10	(1.1)

APPENDIX VII-7
PRPORTIONS OF PATIENTS REPORTING ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 1% IN THE ARIPIPRAZOLE GROUP SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Body System/ Primary Term[a]	Number (%) of Patients							
	Placebo		Haloperidol		Risperidone		Aripiprazole	
	N = 413		N = 200		N = 99		N = 926	
Digestive System								
Dyspepsia	64	(15.5)	21	(10.5)	12	(12.1)	137	(14.8)
Nausea	40	(9.7)	22	(11.0)	11	(11.1)	130	(14.0)
Vomiting	29	(7.0)	23	(11.5)	7	(7.1)	111	(12.0)
Constipation	32	(7.7)	20	(10.0)	11	(11.1)	95	(10.3)
Diarrhea	27	(6.5)	9	(4.5)	8	(8.1)	55	(5.9)
Dry Mouth	17	(4.1)	7	(3.5)	7	(7.1)	40	(4.3)
Disorder Dental	13	(3.1)	3	(1.5)	7	(7.1)	28	(3.0)
Anorexia	13	(3.1)	2	(1.0)	2	(2.0)	15	(1.6)
Nausea And Vomiting	4	(1.0)	2	(1.0)	1	(1.0)	13	(1.4)
Musculoskeletal System								
Myalgia	15	(3.6)	5	(2.5)	2	(2.0)	39	(4.2)
Cramp Muscle	6	(1.5)	0		0		13	(1.4)
Disorder Joint	3	(0.7)	1	(0.5)	5	(5.1)	13	(1.4)
Nervous System								
Agitation	143	(34.6)	72	(36.0)	21	(21.2)	287	(31.0)
Anxiety	99	(24.0)	66	(33.0)	18	(18.2)	232	(25.1)
Insomnia	77	(18.6)	48	(24.0)	20	(20.2)	223	(24.1)
Lightheadedness	27	(6.5)	18	(9.0)	11	(11.1)	106	(11.4)
Somnolence	33	(8.0)	41	(20.5)	14	(14.1)	102	(11.0)
Akathisia	28	(6.8)	36	(18.0)	14	(14.1)	93	(10.0)
Psychosis	35	(8.5)	7	(3.5)	11	(11.1)	61	(6.6)
Extrapyramidal Syndrome	24	(5.8)	39	(19.5)	0		56	(6.0)
Tremor	8	(1.9)	7	(3.5)	2	(2.0)	28	(3.0)
Hypertonia	12	(2.9)	4	(2.0)	8	(8.1)	21	(2.3)
Salivation Increased	5	(1.2)	2	(1.0)	3	(3.0)	17	(1.8)

APPENDIX VII-7
PRPORTIONS OF PATIENTS REPORTING ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 1% IN THE ARIPIPRAZOLE GROUP SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Number (%) of Patients			
Body System/	**Placebo**	**Haloperidol**	**Risperidone**	**Aripiprazole**
Primary Term[a]	N = 413	N = 200	N = 99	N = 926
Nervous System (continued)				
Depression	10 (2.4)	3 (1.5)	2 (2.0)	16 (1.7)
Abnormal Dream	4 (1.0)	2 (1.0)	4 (4.0)	13 (1.4)
Hallucination	3 (0.7)	0	0	12 (1.3)
Nervousness	3 (0.7)	2 (1.0)	4 (4.0)	12 (1.3)
Respiratory System				
Rhinitis	14 (3.4)	10 (5.0)	11 (11.1)	40 (4.3)
Pharyngitis	15 (3.6)	9 (4.5)	2 (2.0)	39 (4.2)
URI	12 (2.9)	6 (3.0)	7 (7.1)	31 (3.3)
Coughing	9 (2.2)	5 (2.5)	2 (2.0)	27 (2.9)
Sinusitis	5 (1.2)	5 (2.5)	1 (1.0)	16 (1.7)
Dyspnea	3 (0.7)	3 (1.5)	3 (3.0)	10 (1.1)
Skin/Appendages				
Rash	20 (4.8)	11 (5.5)	8 (8.1)	54 (5.8)
Pruritus	10 (2.4)	1 (0.5)	0	18 (1.9)
Dry Skin	2 (0.5)	1 (0.5)	2 (2.0)	16 (1.7)
Sweating	8 (1.9)	3 (1.5)	0	11 (1.2)
Special Senses				
Blurred Vision	4 (1.0)	12 (6.0)	4 (4.0)	26 (2.8)
Pain Ear	7 (1.7)	1 (0.5)	1 (1.0)	13 (1.4)
Urogenital System				
Dysmenorrhea[c]	6 (5.8)	3 (5.9)	0	14 (6.2)
Vaginitis[c]	5 (4.8)	1 (2.0)	1 (3.6)	7 (3.1)

[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, contusions, sprains, fracture, and other minor injuries.

[c] Incidence rate adjusted for gender (women): placebo N = 104, haloperidol N = 51, risperidone N = 28, and aripiprazole N = 227.

APPENDIX VII-8:
LABORATORY ASSESSMENTS IN SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Study	Tests	Schedule of Assessments
93-202	Hematology, Chemistry, U/A, and Prolactin Tests...	Pre-study and weeks 1,2, 3, 4
	Stool Analysis	Pre-study and week 4
	Serum Pregnancy Test	Screening
94-202	Hematology, Chemistry.....	Screening and days 7, 14, 21, 28
	U/A	Screening and day 28
	Serum Pregnancy.....	Screening
	Prolactin Tests	Baseline, days 7,14, 21, 28
	Urine Drug Abuse Screen	Screening and upon readmission to unit
97-201	Hematology, Chemistry, U/A	Screening, baseline, days 14, 28
	Serum Pregnancy	Screening and day 28
	Urine Drug Screen, Serum Alcohol Test	Screening and upon readmission to unit
97-202	Hematology, Chemistry	Screening, baseline, days 14, 28
	Prolactin	Baseline, days 14, 28
	U/A.....	Baseline, days 14, 28
	Serum Pregnancy Test	Screening
	Urine Drug Screens, Serum Alcohol Tests	Screening and upon readmission to unit
138-001	Hematology, Chemistry, Urine	Screening, End of Weeks 3, 6
	Prolactin, Pregnancy Test.....	Screening, Week 6
	Drug Screen, Alcohol Test.....	Screening

APPENDIX VII-9
CRITERIA FOR 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
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
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units

APPENDIX VII-10
INCIDENCE OF PCS CHEMISTRY VALUES
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

		Number of Patients with Potentially Clinically Significant Abnormality[a]/Number Assessed[b] (%)			
Laboratory Test	**On-Study Value**	**Placebo**	**Haloperidol**	**Risperidone**	**Aripiprazole**
AST(SGOT)	≥ 3 x ULN	1/372 (0.3)	0/172 (0.0)	1/88 (1.1)	5/810 (0.6)
ALT(SGPT)	≥ 3 x ULN	2/341 (0.6)	0/159 (0.0)	1/74 (1.4)	5/763 (0.7)
Alkaline Phosphatase	≥ 3 x ULN	0/371 (0.0)	0/183 (0.0)	0/93 (0.0)	0/807 (0.0)
LDH	≥ 3 x ULN	0/371 (0.0)	0/188 (0.0)	0/92 (0.0)	0/822 (0.0)
BUN	≥ 30 mg/dL	1/388 (0.3)	0/189 (0.0)	0/94 (0.0)	0/852 (0.0)
Creatinine	≥ 2.0 mg/dL	0/389 (0.0)	0/188 (0.0)	0/93 (0.0)	0/847 (0.0)
Uric Acid	Abnormal[c]	4/385 (1.0)	0/188 (0.0)	0/94 (0.0)	0/836 (0.0)
Bilirubin (Total)	≥ 2.0 mg/dL	2/384 (0.5)	0/189 (0.0)	1/91 (1.1)	1/857 (0.1)
CPK	≥ 3 x ULN	6/274 (2.2)	3/133 (2.3)	1/79 (1.3)	23/694 (3.3)
Prolactin	> ULN	20/286 (7.0)	80/148 (54.1)	75/84 (89.3)	11/609 (1.8)

[a] Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (Table 5.2.3.2A).

[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).

APPENDIX VII-11
INCIDENCE OF PCS HEMATOLOGY VALUES
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

		Number of Patients with Potentially Clinically Significant Abnormality[a]/Number Assessed[b] (%)							
Laboratory Test	**On-Study Lab**	**Placebo**		**Haloperidol**		**Risperidone**		**Aripiprazole**	
Hematocrit	Abnormal[c]	0/316	(0.0)	1/134	(0.7)	2/83	(2.4)	8/760	(1.1)
Hemoglobin	Abnormal[d]	0/350	(0.0)	0/160	(0.0)	0/79	(0.0)	4/783	(0.5)
WBC	$\leq 2,800/mm^3$	1/391	(0.3)	2/188	(1.1)	0/94	(0.0)	5/851	(0.6)
Eosinophils	$\geq 10\%$	10/361	(2.8)	3/176	(1.7)	2/87	(2.3)	9/788	(1.1)
Neutrophils	$< 1,000/mm^3$	1/391	(0.3)	1/188	(0.5)	0/95	(0.0)	1/840	(0.1)
Platelet Count	$< 100,000/mm^3$	0/389	(0.0)	1/186	(0.5)	1/93	(1.1)	7/849	(0.8)

[a] Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (Table 5.2.3.2A).

[b] Includes only patients with a baseline value within normal limits.

[c] Hematocrit: Abnormal: $\leq 37\%$ (men)/32% (women) and a $\geq 3\%$ decrease from baseline.

[d] Hemoglobin: Abnormal: ≤ 11.5 g/dL (men)/≤ 9.5 g/dL (women).

APPENDIX VII-12
INCIDENCE OF PCS URINALYSIS VALUES
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

Laboratory Test		Number of Patients with Potentially Clinically Significant Abnormality[a]/Number Assessed (%)			
All Patients[b] Baseline Level	On-Study Value	Placebo	Haloperidol	Risperidone	Aripiprazole
Protein					
All Patients	≥ 2-unit increase	0/366 (0.0)	0/175 (0.0)	0/94 (0.0)	3/824 (0.4)
= 0	≥ 2-unit increase	0/356 (0.0)	0/169 (0.0)	0/93 (0.0)	3/805 (0.4)
> 0	≥ 2-unit increase	0/6 (0.0)	0/3 (0.0)	0/0 (–)	0/11 (0.0)
Glucose					
All Patients	≥ 2-unit increase	1/366 (0.3)	4/175 (2.3)	1/94 (1.1)	14/824 (1.7)
= 0	≥ 2-unit increase	1/351 (0.3)	3/170 (1.8)	1/88 (1.1)	9/793 (1.1)
> 0	≥ 2-unit increase	0/11 (0.0)	1/2 (50.0)	0/5 (0.0)	5/23 (21.7)

[a] Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (Table 5.2.3.2A).

[b] Includes patients with a missing baseline value. The number of patients assessed for each of the baseline strata may not add up to the total number indicated for "all patients."

APPENDIX VII-13
MEDIAN PERCENT CHANGE FROM BASELINE TO ENDPOINT IN SERUM CHEMISTRY VARIABLES SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES[61]

Lab Measure	Placebo		Aripiprazole	
	N	Median % Change	N	Median % Change
AST (SGOT)	391	0.0	858	0.0
ALT (SGPT)	391	0.0	858	9.1
Alk. Phos	390	0.0	858	-2.2
LDH	391	1.9	857	0.0
BUN	391	0.0	858	0.0
Creatinine	391	0.0	858	0.0
Uric Acid	391	0.0	857	0.0
Tot. Bilirubin	390	0.0	858	0.0
CPK	353	8.5	816	22.1
Prolactin	338	0.0	729	-56.5
Total Protein	391	0.0	857	0.0
Calcium	390	0.0	858	0.0
Sodium	391	0.0	858	0.0
Potassium	390	0.0	858	-2.1
Chloride	391	0.0	857	0.0
Total Cholesterol	34	-4.4	111	-1.4
Glucose (Fasting)	34	-1.0	112	0.0

[61] Changes in total cholesterol and fasting glucose are based on the results of study 138001 only. The other studies did not obtain blood specimens under fasting conditions.

APPENDIX VII-14
MEDIAN-PERCENT CHANGE FROM BASELINE TO ENDPOINT IN HEMATOLOGY VARIABLES

Laboratory Test	Placebo		Aripiprazole	
	N	Median % Change	N	Median % Change
Hematocrit	358	0.9	818	-0.2
Hemoglobin	391	0.7	850	0.0
WBC	391	1.8	850	3.3
Eosinophils	392	-3.4	845	-4.0
Neutrophils	392	-1.5	844	8.1
Platelets	391	1.1	850	3.1

APPENDIX VII-15
CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS

Vital Sign	Criterion Value[a]	Change from Baseline[a]
Heart rate	120 bpm 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic blood pressure	180 mmHg 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic blood pressure	105 mmHg 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Temperature[b]	≥ 37.8°C	Change of ≥ 1.1°C
Weight[b]	–	Change of ≥ 7% of body weight

APPENDIX VII-16
INCIDENCE OF PCS VITAL SIGN CHANGES IN SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

		Number of Patients with Potentially Clinically Significant Abnormality[a] / Number Assessed (%)							
Vital Sign Measurement		Placebo		Haloperidol		Risperidone		Aripiprazole	
Systolic Blood Pressure									
Supine	Increase[b]	6/412	(1.5)	4/199	(2.0)	0/99	(0.0)	9/913	(1.0)
	Decrease[c]	36/412	(8.7)	19/199	(9.6)	6/99	(6.1)	54/913	(5.9)
Standing	Increase[b]	4/413	(1.0)	2/199	(1.0)	1/99	(1.0)	9/915	(1.0)
	Decrease[c]	46/413	(11.1)	34/199	(17.1)	15/99	(15.2)	104/915	(11.4)
Diastolic Blood Pressure									
Supine	Increase[d]	15/412	(3.6)	7/199	(3.5)	4/99	(4.0)	29/913	(3.2)
	Decrease[e]	31/412	(7.5)	17/199	(8.5)	9/99	(9.1)	50/913	(5.5)
Standing	Increase[d]	21/413	(5.1)	8/199	(4.0)	7/99	(7.1)	60/915	(6.6)
	Decrease[e]	20/413	(4.8)	14/199	(7.0)	9/99	(9.1)	45/915	(4.9)
Heart Rate	–								
Supine	Increase[f]	6/408	(1.5)	6/199	(3.0)	10/99	(10.1)	23/905	(2.5)
	Decrease[g]	2/408	(0.5)	6/199	(3.0)	1/99	(1.0)	9/905	(1.0)
Standing	Increase[f]	54/413	(13.1)	43/199	(21.6)	38/99	(38.4)	170/911	(18.7)
	Decrease[g]	0/413	(0.0)	0/199	(0.0)	0/99	(0.0)	3/911	(0.3)

APPENDIX VII-17 MEAN CHANGE FROM BASELINE TO ENDPOINT IN VITAL SIGN VARIABLES				
Vital Sign Measure	Aripiprazole		Placebo	
	N	Mean Δ	N	Mean Δ
Standing diastolic BP	909	+0.9	412	-0.3
Supine diastolic BP	904	+0.8	409	-0.6
Standing systolic BP	909	+2.2	412	-1.1
Supine systolic BP	904	+1.7	409	-0.9
Heart rate standing	898	+3.9	409	-0.8
Heart rate supine	891	+2.5	403	-1.2

APPENDIX VII-18 SCHEDULE FOR 12-LEAD ECG TRACINGS SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRNEIA STUDIES		
Study	Duration	Schedule of ECG's
93202	4 weeks	Baseline, weeks 2, 4
94202	4 weeks	Baseline, weeks 2, 4
97201	4 weeks	Baseline, weeks 2, 4
97202	4 weeks	Baseline, weeks 2, 4
138001	6 weeks	Baseline, weeks 3, 6

APPENDIX VII-19
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

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.

APPENDIX VII-20
PERCENTAGE OF PATIENTS MEETING CRITERIA FOR A POTENTIALLY CLINICALLY SIGNIFICANT ECG MEASUREMENT

	Number of Patients with Potentially Clinically Significant Abnormality[a] (%)			
	Placebo	Haloperidol	Risperidone	Aripiprazole
ECG Parameter	N = 382	N = 185	N = 95	N = 841
Rate				
Tachycardia	5 (1.31)	0 (0.00)	0 (0.00)	2 (0.24)
Bradycardia	4 (1.05)	1 (0.54)	2 (2.11)	3 (0.36)
Rhythm				
Sinus tachycardia	5 (1.31)	0 (0.00)	0 (0.00)	2 (0.24)
Sinus bradycardia	4 (1.05)	1 (0.54)	2 (2.11)	3 (0.36)
Supraventricular premature beat	0 (0.00)	0 (0.00)	1 (1.05)	0 (0.00)
Ventricular premature beat	5 (1.31)	0 (0.00)	1 (1.05)	9 (1.07)
Supraventricular tachycardia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ventricular tachycardia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Atrial fibrillation	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Atrial fibrillation with rapid ventricular response	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Atrial flutter	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Conduction				
1° atrioventricular block	0 (0.00)	1 (0.54)	0 (0.00)	1 (0.12)
2° atrioventricular block	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
3° atrioventricular block	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Left bundle branch block	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Right bundle branch block	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Pre-excitation syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Other intraventricular conduction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Infarction				
Acute infarction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Subacute (recent) infarction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Old infarction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
ST/T Morphological				
Myocardial ischemia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Symmetrical T-wave inversions	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

APPENDIX VII-21
MEDIAN CHANGE FROM BASELINE TO THE MINIMUM OR MAXIMUM ON-TREATMENT ECG VALUE
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Placebo		Haloperidol		Risperidone		Aripiprazole	
ECG Parameter	N	Median Change	N	Median Change	N	Median Change	N	Median Change
PR Maximum (msec)	380	2.00	180	3.00	95	5.00	831	2.00
QRS Maximum (msec)	380	1.00	180	0.50	95	2.00	831	2.00
RR								
Maximum (msec)	380	18.00	180	21.00	95	-24.00	831	-11.00
Minimum (msec)	380	-22.50	180	-29.50	95	-90.00	831	-64.00
Heart Rate								
Maximum (bpm)	380	2.00	180	3.00	95	12.00	831	7.00
Minimum (bpm)	380	-1.00	180	-2.00	95	3.00	831	1.00

APPENDIX VII-22
ANALYSES OF THE QTc INTERVAL
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA STUDIES

	Placebo	Haloperidol	Risperidone	Aripiprazole
Sample Size[a]	379	180	95	828
Baseline QT_{cE} (msec)	390.8	387.0	392.6	389.1
Mean Change at Endpoint (msec)	-3.56	-0.62 *	2.44 **	-4.16
Mean Change at Max QT_{cE} (msec)	0.35	4.07 **	8.10 **	0.12
	Number of Patients/Number Assessed (%)			
> 450 msec[b]	1/382 (0.3)	2/185 (1.1)	0/95 (0.0)	2/841 (0.2)
> 500 msec[b]	0/382 (0.0)	0/185 (0.0)	0/95 (0.0)	0/841 (0.0)
≥ 30 msec increase[c]	21/380 (5.5)	14/180 (7.8)	10/95 (10.5)	36/831 (4.3)
≥ 60 msec increase[c]	0/380 (0.0)	1/180 (0.6)	0/95 (0.0)	0/831 (0.0)

** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$) 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} = Aripiprazole 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 on-study measurement.

APPENDIX VII-23
PERCENTAGE OF PATIENTS WITH ≥7% WEIGHT GAIN
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

	Number of Patients with Significant Weight Gain[a]/ Number Assessed (%)							
Study Week	**Placebo**		**Haloperidol**		**Risperidone**		**Aripiprazole**	
Endpoint (OC)[b]	9/173	(5.2)	15/105	(14.3)*	10/63	(15.9)*	56/479	(11.7)*
Endpoint (LOCF)[b]	12/379	(3.2)	16/164	(9.8)**	10/94	(10.6)**	69/852	(8.1)**

** ($P \leq 0.01$), *($0.01 < P \leq 0.05$). Significantly different from placebo (Fisher's exact test).

a ≥ 7% increase from baseline.

b Endpoint for studies 31-93-202, 31-94-202, 31-97-201, 31-97-202 was Week 4 (OC and LOCF) and for study CN138-001 was Week 6 (OC and LOCF).

APPENDIX VII-24
PERCENTAGE OF PATIENTS WITH >ULN PROLACTIN LEVELS
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

		Number of Patients with Abnormality/ Number Assessed (%)			
Baseline Level	**On-Study Level**	**Placebo**	**Haloperidol**	**Risperidone**	**Aripiprazole**
≤ ULN	> ULN	20/286 (7.0)	80/148 (54.1)**	75/84 (89.3)**	11/609 (1.8)**L
> ULN	> ULN	24/53 (45.3)	32/37 (86.5)**	7/7 (100.0)*	14/123 (11.4)**L

** ($P \leq 0.01$), *($0.01 < P \leq 0.05$), significantly different from placebo (Fisher's exact test).

**L indicates significantly less than placebo.

APPENDIX VII-25
PERCENTAGE OF PATIENTS WITH >ULN PROLACTIN LEVELS
STUDY 98217

Prolactin[a]		Number of Patients with Abnormality/ Number Assessed (%)			
Baseline Level	On-Study Level	Haloperidol		Aripiprazole	
≤ ULN	> ULN	27/44	(61.4)	3/87	(3.4) **
> ULN	> ULN	2/2	(100.0)	0/9	(0.0) *

**(P ≤ 0.01), *(0.01 < P ≤ 0.05), significantly different from haloperidol (Fisher's exact test).

[a] Prolactin was not collected for study 31-98-304-01.

APPENDIX VII-26
PERCENTAGE OF PATIENTS WITH A SUICIDE-RELATED AE
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

	Number (%) of Patients			
	Placebo	Haloperidol	Risperidone	Aripiprazole
Primary Term[a]	N = 413	N = 200	N = 99	N = 926
Any Event	3 (0.7)	1 (0.5)	0 (0)	10 (1.1)
Thought Suicidal	1 (0.2)	1 (0.5)	0 (0)	5 (0.5)
Intentional Injury	1 (0.2)	0 (0)	0 (0)	3 (0.3)
Suicide Attempt[b]	1 (0.2)	0 (0)	0 (0)	2 (0.2)

[a] Modified COSTART term.

[b] None resulted in death during the short-term placebo-controlled studies.

APPENDIX VII-27
PERCENTAGE OF PATIENTS WITH A SUICIDE-RELATED AE LONG-TERM, HALOPERIDOL-CONTROLLED SCHIZOPHRENIA TRIALS

	Number (%) of Patients	
	Haloperidol	Aripiprazole
Primary Term[a]	N = 431	N = 859
Any Suicide-Related Event	6 (1.4)	12 (1.4)
Thought Suicidal	4 (0.9)	7 (0.8)
Intentional Injury	0 (0)	1 (0.1)
Suicide Attempt[b]	2 (0.5)	4 (0.4)

[a] Modified COSTART term.

[b] Three (0.3%) of the aripiprazole-treated patients (98304-439-60, 98304-509-50, and 98304-558-58) and one (0.2%) of the haloperidol-treated patients (98304-447-55) died as a result of a suicide attempt.

APPENDIX VII-28
PERCENTAGE OF PATIENTS WITH AN EPS-RELATED EVENT SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

	Number (%) of Patients			
EPS Category/ Primary Term[a]	**Placebo** N = 413	**Haloperidol** N = 200	**Risperidone** N = 99	**Aripiprazole** N = 926
Any Treatment-Emergent EPS-Related AE	80 (19.4)	87 (43.5)	30 (30.3)	195 (21.1)
Dystonic Events	9 (2.2)	13 (6.5)	9 (9.1)	21 (2.3)
Rigidity Neck	6 (1.5)	3 (1.5)	4 (4.0)	15 (1.6)
Dystonia	2 (0.5)	9 (4.5)	5 (5.1)	5 (0.5)
Oculogyric Crisis	1 (0.2)	1 (0.5)	0	1 (0.1)
Parkinsonian Events	44 (10.6)	52 (26.0)	10 (10.1)	105 (11.3)
Extrapyramidal Syndrome	24 (5.8)	39 (19.5)	0	56 (6.0)
Tremor	8 (1.9)	7 (3.5)	2 (2.0)	28 (3.0)
Hypertonia	12 (2.9)	4 (2.0)	8 (8.1)	21 (2.3)
Rigidity Cogwheel	2 (0.5)	4 (2.0)	2 (2.0)	8 (0.9)
Akathisia Events	30 (7.3)	36 (18.0)	15 (15.1)	95 (10.3)
Akathisia	28 (6.8)	36 (18.0)	14 (14.1)	93 (10.0)
Hyperkinesia	2 (0.5)	0	1 (1.0)	2 (0.2)
Dyskinetic Events	6 (1.5)	1 (0.5)	2 (2.0)	6 (0.7)
Dyskinesia	4 (1.0)	0	1 (1.0)	2 (0.2)
Dyskinesia Tardive	1 (0.2)	0	0	2 (0.2)
Syndrome Buccoglossal	0	0	1 (1.0)	0
Residual Events	9 (2.2)	3 (1.5)	0	11 (1.2)
Disorder Movement	5 (1.2)	3 (1.5)	0	5 (0.5)
Twitch	2 (0.5)	0	0	5 (0.5)
Myoclonus	2 (0.5)	0	0	1 (0.1)

[a] Modified COSTART term.

APPENDIX VII-29
PERCENTAGE OF DROPOUTS DUE TO AN EPS-RELATED EVENT SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

	Number (%) of Patients			
EPS Category/ Primary Term[a]	**Placebo** N = 413	**Haloperidol** N = 200	**Risperidone** N = 99	**Aripiprazole** N = 926
Any Treatment-Emergent EPS-Related AE Leading to Discontinuation of Study Therapy[b]	0	6 (3.0)	1 (1.0)	7 (0.8)
Dystonic Events	0	1 (0.5)	0	1 (0.1)
Dystonia	0	1 (0.5)	0	1 (0.1)
Parkinsonian Events	0	2 (1.0)	1 (1.0)	1 (0.1)
Extrapyramidal Syndrome	0	0	0	1 (0.1)
Hypertonia	0	1 (0.5)	1 (1.0)	0
Rigidity Cogwheel	0	1 (0.5)	0	0
Akathisia Events	0	3 (1.5)	0	6 (0.6)
Akathisia	0	3 (1.5)	0	6 (0.6)

[a] Modified COSTART term.

[b] EPS-related AE for which the "action taken" column on the AE form was marked "discontinue medication".

APPENDIX VII-30
MEAN CHANGE FROM BASELINE IN EPS-RATING SCALES
SHORT-TERM, PLACEBO-CONTROLLED SCHIZOPHRENIA TRIALS

EPS Scale	Placebo	Haloperidol	Risperidone	Aripiprazole
SAS Total Score[a]	**N = 402**	**N = 183**	**N = 94**	**N = 886**
Mean Baseline (SE)	12.39 (0.14)	12.49 (0.22)	11.74 (0.31)	12.38 (0.10)
Change at Endpoint (SE)	-0.08 (0.13)	1.23 (0.20)**	-0.47 (0.29)	-0.06 (0.09)
Change at Highest Score (SE)	0.78 (0.15)	2.95 (0.23)**	0.40 (0.32)	0.96 (0.10)
Barnes Akathisia[b]	**N = 411**	**N = 192**	**N = 95**	**N = 903**
Mean Baseline (SE)	0.60 (0.04)	0.72 (0.07)	0.39 (0.10)	0.55 (0.03)
Change at Endpoint (SE)	-0.05 (0.04)	0.40 (0.07)**	-0.06 (0.09)	0.08 (0.03)*
Change at Highest Score (SE)	0.25 (0.05)	0.92 (0.07)**	0.20 (0.10)	0.40 (0.03)**
AIMS Total Score[c]	**N = 407**	**N = 192**	**N = 94**	**N = 891**
Mean Baseline (SE)	1.97 (0.16)	2.16 (0.24)	1.82 (0.35)	1.66 (0.11)
Change at Endpoint (SE)	-0.02 (0.10)	-0.37 (0.16)	-0.64 (0.22)*	-0.44 (0.07)**
Change at Highest Score (SE)	0.38 (0.10)	0.22 (0.16)	-0.16 (0.23)*	0.06 (0.07)*

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

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

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

c AIMS Total Score ranges from 0 to 28. A negative change score indicates imrovement.

APPENDIX VII-31
LISTING OF PATIENTS AUDITED
(Study-Center-Patient Number)

PATIENTS AUDITED FOR ADVERSE EVENT INFORMATION	
138001-8-167	97203-73-4
138001-50-350	97203-66-7
138001-31-501	93202-8-38
138001-15-21	98304-451-51
138001-25-438	98304-440-63
97201-16-1	98304-506-52
00230-1-13	98215-384-37
98217-297-2	98203-353-31
98217-309-1	97301-216-2
99224-620-15	98203-2-13
93201-31-131	97202-90-8
98217-294-12	98304-481-50
98217-277-17	98304-445-54
138003-36-328	138001-57-146
138003-140-453	138001-76-452
138035-1-54	138004-49-33
97202-84-5	97202-90-8
97202-55-3	98217-306-14
94201-1-15	98213-600-1
97203-67-19	
PATIENTS AUDITED FOR REASON FOR DROPOUT	
93202-9-116	138001-12-427
94202-1-244	138001-13-180
97202-76-8	98217-306-4
97201-39-15	98217-309-1
97201-30-19	98304-416-55

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

/s/

Greg Dubitsky
6/12/02 09:16:59 AM
MEDICAL OFFICER

Robert D. Harris
6/12/02 04:37:08 PM
MEDICAL OFFICER

Thomas Laughren
7/21/02 01:37:11 PM
MEDICAL OFFICER
I agree that, from a clinical standpoint, this NDA is approvable; see memo to file for more detailed comments.--TPL

APPEARS THIS WAY
ON ORIGINAL

Safety Update Review: N/A

APPEARS THIS WAY
ON ORIGINAL