

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:

<u>Dose</u>	<u>OC</u>	<u>LOCF</u>
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.

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.

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; $\alpha=0.10$). 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 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.

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. $\geq 3 \times \text{ULN}$). 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 _____ 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 _____. 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 $\leq 2,800/\text{cmm}$). 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 (DNNDP); this entailed using baseline measurements from the Phase II/III data set.³¹ Supplemental analyses provided data based on the DNNDP 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 QT_c 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 DNNDP 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 $QT_{CE} \geq 30$ 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).

³¹ See a July 9, 1999, memorandum from Greg Burkhart, DNNDP 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 \leq 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 \leq 160 mg/dl, the proportions of patients with a treatment-emergent glucose measurement \geq 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 $< \text{ULN}$, the incidence of elevated ($> \text{ULN}$) 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 .

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:

<u>Dose Cohort</u>	<u>% Reporting Somnolence</u>
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 xULN) 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 exposure-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 $\geq 7\%$ 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 ($\geq 7\%$ 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., \leq 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 (\leq 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

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 (\geq 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 $C_{ss,min}$, $C_{ss,av}$, $C_{ss,max}$, t_{max} , 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, DCPD) 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 (DCPD) 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