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

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

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

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

No deaths were reported during the study.

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

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

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

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

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

e. Neurocognitive Effects (Study 98213)

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

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

Randomization was stratified by prior treatment.

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

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

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

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

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

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

Continuous Performance Test (CPT) data were analyzed separately.

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

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

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

10. Overdose Experience

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

Only 3 patients reportedly had overdoses > 90mg:

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

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

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

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

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

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

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

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

11. Human Reproductive Data

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

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

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

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

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

12. Withdrawal Phenomena/Abuse Potential

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

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

C. Adequacy of Patient Exposure and Safety Assessments

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

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

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

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

D. Assessment of Data Quality and Completeness

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

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

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

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

E. Summary of Important Drug-Related Safety Findings

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

1. Mortality in Patients with Dementia

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

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

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

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

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

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

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

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

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

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

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

2. Pneumonia in Patients with Dementia

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

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

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

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

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

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

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

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

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

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

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

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

3. Somnolence in Patients with Dementia

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

Study 98203 was an uncontrolled ascending dose study in which 5 cohorts of elderly demented patients received doses from 5 to 30 mg/day increased in step-wise fashion. This trial revealed that the occurrence of somnolence appeared to be dose-related, reported in 0% of patients in the 5-10 mg/day cohort and in 100% of patients in the 20-25 mg/day and 25-30 mg/day cohorts.

The rate of accidental injury in study 98203 was 8% for aripiprazole and 4% for placebo. Possibly somnolence contributed to this finding.

Thus, somnolence appears to be especially prevalent and dose-related among elderly, demented patients who receive aripiprazole. This may place such patients at risk for accidents, such as falls, and, if substantial, at risk for aspiration and pneumonia (see above).

VIII. Dosing, Regimen, and Administration Issues

Based on a consideration of the above safety and efficacy findings, the following dosage and administration

instructions are recommended for most patients with schizophrenia:

Adult patients with schizophrenia can be started at a dose of 15mg given once daily without regard to the time of day or meals. In patients who do not achieve an acceptable response, the dose may be increased in increments of 5-10 mg/day at intervals of at least 2 weeks to a maximum of 30 mg/day.

IX. Use in Special Populations

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

The following factors do not appear to require adjustment of aripiprazole dosing: age, gender, race, smoking status, hepatic or renal impairment, and CYP2D6 status.[41]

Aripiprazole is likely to be used off-label for various indications, to include psychosis associated with dementia in elderly patients. Prescribers should be aware of the high mortality rate, incidence of pneumonia, particularly aspiration pneumonia, and susceptibility to somnolence observed in clinical trials when aripiprazole was used in this population.

X. Review of Proposed Labeling

The following comments are based on a review of the clinical sections of sponsor's proposed labeling as presented in their 10-31-01 submission.

Clinical information in the following sections was reviewed by Dr. Harris: Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, and Dosage & Administration/Switching from Other Antipsychotics.

Dr. Dubitsky reviewed clinical information in the following sections: Clinical Pharmacology/Clinical Studies, Indications & Usage, and Dosage & Administration.

Throughout the proposed labeling, the formerly proposed tradename for aripiprazole (Abilitat) should be replaced with the recently proposed [redacted]

[41] This conclusion is tentative pending completion of the biopharmaceutics review of relevant studies.

Number of Pages Redacted 7

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Draft Labeling
(not releasable

Gregory M. Dubitsky, M.D.
June 12, 2002

Robert Harris, M.D., Ph.D.
June 12, 2002

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 21-436
HFD-120/Division File
HFD-120/GDubitsky
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NDA 21-436
ARIPIPRAZOLE

SECTION XII:
APPENDICES TO THE
REVIEW AND EVALUATION OF CLINICAL DATA

NDA DATA SOURCES

APPENDIX IV-1: TABLE OF STUDIES	
NON-JAPANESE STUDIES	
Phase 1 (Clinical Pharmacology Studies)	
Single-Dose	
96201	Open-label study to assess the absorption, distribution, metabolism, and excretion of a single oral 20 mg dose of [^{14}C]-aripiprazole in 12 healthy subjects aged 21 - 45 years. Open-label study to assess the absorption, distribution, metabolism, and excretion of a single oral 20 mg dose of [^{14}C]-aripiprazole in 12 healthy subjects aged 21 - 45 years.
96203	Open-label, two-phase, study to evaluate the safety of aripiprazole given in ethanol solution, and assess the relative bioavailability of aripiprazole in solution, capsule, and tablet form in a total of 15 healthy subjects aged 21 - 45 years who each participated in either the sequential, ascending, single-dose study of aripiprazole (1, 5, 10, or 20 mg) in ethanol solution or the randomized, single-dose, two-way crossover study of aripiprazole 20 mg in either capsule or tablet form.
98201	Open-label, single-dose, parallel group study to evaluate the influence of diurnal variation on the pharmacokinetics of aripiprazole 20 mg in 32 healthy subjects aged 18 to 45 years.
98205	Open-label, single-dose study to evaluate the pharmacokinetics of aripiprazole 15 mg in normal subjects matched to subjects with varying degrees of hepatic impairment (based on creatinine clearance) in 25 total subjects aged 39 to 71 years.
98206	Double-blind, parallel group, placebo-controlled study of two doses of aripiprazole 15 mg to determine whether inhibition of CYP3A4

APPENDIX IV-1: TABLE OF STUDIES	
	alters the pharmacokinetic characteristics of aripiprazole in 29 healthy subjects aged 18 to 45 years with a study duration of 28 days.
98207	Open-label, parallel group study using a single dose of aripiprazole 10 mg to assess the effect of CYP2D6 inhibition on aripiprazole pharmacokinetics in 3 groups of a total of 29 healthy subjects aged 18 to 45 years grouped as CYP2D6 extensive metabolizers, or poor metabolizers.
98208	Open-label study of the pharmacokinetics of a single 15mg dose of aripiprazole in 6 volunteers with normal renal function and 6 patients with renal impairment.
00225	Open label, two-center, single-dose, 3-by-2 factorial design study to assess the pharmacokinetic effects of age and gender on aripiprazole 15 mg on 60 healthy subjects, 10 of each gender per age group: 18 to 40 years, 41 to 64 years, and ≥ 65 years.
00226	Open label, two-period, randomized, complete block, crossover study to assess the effect of famotidine 40 mg co-administration on aripiprazole 15 mg pharmacokinetics, each given separately and together as single doses in 17 healthy subjects aged 18 to 45 years.
00227	Single-dose, open-label, historic-control study of the effects of activated charcoal on aripiprazole pharmacokinetics in 9 healthy male subjects aged 18 to 45 years treated with aripiprazole 15 mg followed 1 hour later by 50 g dose of activated charcoal.
138015	Open-label, randomized, 3-period, 3 treatment, crossover bioequivalence study to assess the effects aripiprazole monohydrate content on the pharmacokinetics of aripiprazole in 46 healthy subjects receiving single doses of 15 mg aripiprazole as reference (100% anhydrous), prototype #1 (20% monohydrate) or prototype #2

APPENDIX IV-1: TABLE OF STUDIES	
	(100% monohydrate). Study was terminated early at end of Period 1.
138016	Open-label, randomized, 3-period, 3-treatment crossover study to assess absolute bioavailability using single doses of the 5 mg aripiprazole tablet formulation and 5 mg aripiprazole IM formulation with reference to 2 mg aripiprazole IV infusion in 18 healthy subjects.
138018	Open-label, randomized, 3-period, 2-treatment crossover study to assess the effect of a high fat meal and intrasubject variability on the pharmacokinetics of a single dose of aripiprazole 15 mg in 45 healthy subjects.
138019	Open-label, single-dose, bioavailability study comparing aripiprazole 3mg liquid versus 5mg tablet in 16 subjects.
138028	Open-label, single dose study to assess the pharmacokinetics, metabolism, and routes and extent of elimination of a single oral 5 mg dose of [^{14} C]- aripiprazole in 9 healthy subjects.
138034	Open-label, randomized, 3-period, 3 treatment, crossover study to determine whether 2 prototype forms of a single dose of aripiprazole 10 mg containing differing fractions of the monohydrate form (20% monohydrate or 100% monohydrate) were bioequivalent to a reference product (100% anhydrous) prepared by a commercial process in 66 healthy subjects.
138035	Open-label, randomized, 2-period, 2-treatment crossover study to demonstrate bioequivalence of a single 15 mg dose of aripiprazole (commercial tablet formulation) when administered as 1 x 15 mg tablet compared to 3 x 5 mg tablets in 60 healthy subjects receiving both treatments in randomly assigned sequences.
138052	Open-label, single-dose, bioavailability study of aripiprazole 5mg flashmelt tablets in 40 subjects.

APPENDIX IV-1: TABLE OF STUDIES	
138054	Open-label, two-way crossover, single-dose bioequivalence study of aripiprazole 15mg commercial tablets versus clinical trial tablets. Study was terminated (80 enrolled, 0 completers).
138063	Open-label, single-dose, bioavailability study comparing aripiprazole 5, 10, and 15mg commercial tablets versus liquid in 60 subjects.
138065	Single-dose bioequivalence study of aripiprazole 30mg tablets versus 3x10mg in 48 subjects.
Multiple-Dose	
93201	Randomized, double-blind, placebo-controlled, single-center, multiple-dose, ascending dose 14 day study to assess the tolerability and pharmacokinetics of aripiprazole (5, 10, 15, 20 mg/day) in 39 healthy male subjects aged 21 to 45 years.
93204	Randomized, double-blind, placebo-controlled, single-center, multiple-dose 14 day study to assess the tolerability and pharmacokinetics of aripiprazole titrated from 10 to 30 mg/day in 11 healthy male subjects aged 18 to 40 years.
94201	Open-label, multiple dose 14 day study of aripiprazole to determine the degree of D_2 receptor binding by aripiprazole measured by PET scan in 17 healthy male subjects aged 21 to 45 years assessed by treatments with 10 mg/day on Day 1, 20 mg/day on Day 2, 30 mg/day for Days 3 - 14, or 10, 2, 1, or 0.5 mg/day on Days 1 - 14 followed by IV ^{11}C raclopride for PET scanning.
97205	Open label study to assess the influence of multiple doses of aripiprazole 10, 20, 30 mg on the metabolism of dextromethorphan (DM) received pre and post aripiprazole dosing in 22 healthy male subjects aged 18 to 45 years for 14 days.
00230	Double-blind, placebo-controlled, randomized, parallel group, multiple-dose, sequential crossover 15 day study to assess the

APPENDIX IV-1: TABLE OF STUDIES	
	potential pharmacodynamic interactions between co-administered aripiprazole 10 mg with ethanol in 26 healthy subjects aged 21 to 45 years and who met criteria for cytochrome P450 extensive metabolizer genotypes.
00231	Open label, multiple dose sequential, crossover study to assess the pharmacokinetic effect aripiprazole on dextromethorphan (DM) metabolism via cytochrome P450 2D6 in 25 healthy subjects aged 18 to 45 years genotyped as CYP2D6 extensive metabolizers treated with a single dose of 30 mg DM, followed by Days 4 - 17 single oral dose of aripiprazole 10 mg with a Day 18 single oral dose of aripiprazole 10 mg and subsequent 30 mg DM two hours later.
00232	Open-label, sequential-crossover, multiple-dose, 18 day study to determine the effect of co-administered aripiprazole on the pharmacokinetics of omeprazole in 25 healthy subjects aged 18 to 45 years treated with 20 mg oral dose of omeprazole followed on Days 4 - 17 with single oral dose of 10 mg aripiprazole and Day 18 treatment with aripiprazole 10 mg followed 2 hours later with 20 mg omeprazole.
138014	Flexible-dose study of the pharmacokinetics of aripiprazole 1-15mg in 30 pediatric subjects; 2 week acute study with optional 18 month extension for safety evaluation.
138021	Open label, sequential treatment design study to assess the safety of aripiprazole 30 mg and lithium (dose titrated to achieve therapeutic concentrations) coadministration in 12 chronically institutionalized patients with schizophrenia or schizoaffective disorder.
138022	Open-label, single group, PK interaction study of aripiprazole and carbamazepine in 4 schizophrenic patients.
138023	Open-label, sequential treatment design study to assess the safety profile of aripiprazole 30 mg and divalproex sodium (dose titrated up

APPENDIX IV-1: TABLE OF STUDIES	
	to therapeutic levels) coadministration in 10 chronically institutionalized patients with schizophrenia or schizoaffective disorder who required divalproex for management of symptoms.
138030	Open-label, 6 month safety study of aripiprazole 5-30 mg/day in 9 schizophrenic patients.
138043	Open-label, sequential 2-period study to demonstrate a lack of effect of concomitant aripiprazole administration of 10 mg once daily for 18 days on the pharmacokinetics and pharmacodynamics of a single 30 mg dose of warfarin in 12 healthy subjects.
138061	Open-label, single group, one-week study of the hepatobiliary metabolism of aripiprazole 15 and 30mg in 16 subjects. This study was conducted pursuant to the finding of gallstones and gallsand in animal studies to assess for the presence of the animal gall compounds in humans after treatment with aripiprazole.
Completed Phase 2/3 Studies	
Schizophrenia, Short-Term, Placebo-Controlled Studies	
93202	Randomized, double-blind, placebo-controlled, parallel group, inpatient, 4 week ascending dose study to assess efficacy and tolerability of aripiprazole 5 - 30 mg vs. haloperidol 5 - 20 mg in 103 adults aged 18 to 65 years with schizophrenia (DSM-III-R) in acute schizophrenic relapse and history of response to antipsychotic drugs.
94202	Randomized, double-blind, placebo-controlled, parallel group, inpatient, 4 week dose ranging study to assess efficacy and tolerability of aripiprazole (3 fixed doses: 2, 10, 30 mg) vs. haloperidol 10 mg in 307 adults aged 18 to 65 years with schizophrenia (DSM-IV) in acute relapse and history of response to antipsychotic drugs.

APPENDIX IV-1: TABLE OF STUDIES	
97201	Randomized, double-blind, placebo-controlled, parallel group, inpatient, fixed-dose 4 week study to compare safety and efficacy of aripiprazole (15 mg or 30 mg) vs. haloperidol 10 mg in 414 adults aged 18 to 68 years with psychosis [schizophrenia (282 patients) and schizoaffective disorder (132 patients)] (DSM-IV) in acute relapse and history of response to antipsychotic drugs.
97202	Randomized, double-blind, placebo-controlled, parallel group, in-patient, fixed-dose 4 week study to compare the safety and efficacy of aripiprazole (20 mg or 30 mg) vs. risperidone 6 mg in 404 adults aged 18 to 65 years with psychosis [schizophrenia (289 patients) and schizoaffective disorder (115 patients)] (DSM-IV) in acute relapse and history of response to antipsychotic drugs.
138001	Randomized, double-blind, placebo-controlled, fixed-dose 6 week study of aripiprazole (10, 15, 20 mg) in 420 adults ≥ 18 years of age, hospitalized for schizophrenia (DSM-IV) in acute relapse, previously responded to antipsychotic medication, previously treated as an outpatient for at least one continuous 3-month period during the past 12 months.
Schizophrenia, Long-Term Studies	
98217/98304	Randomized, double-blind, active-control 52 week study to evaluate the safety and long-term maintenance effects of aripiprazole 30 mg (20 - 30 mg) vs. haloperidol 10 mg (7 - 10 mg) in 1,294 adults aged 18 to 65 years with schizophrenia (DSM-IV) in acute relapse and history of response to antipsychotic drugs.
97301	Double-blind, haloperidol-controlled, 52 week study of flexible dose aripiprazole (2-30 mg/day) in 130 patients with schizophrenia.
98213	Randomized, open-label, outpatient 26 week study to compare the neurocognitive effects of aripiprazole 30 mg (20 - 30 mg) vs.

APPENDIX IV-1: TABLE OF STUDIES	
	olanzapine 15 mg (10 - 15 mg) in 255 adults aged 18 to 65 years with schizophrenia or schizoaffective disorder (DSM-IV), on a stable dose of a typical or atypical antipsychotic agent, for at one least month prior to randomization and not hospitalized for an exacerbation for at least 2 months prior to randomization.
138002	Double-blind, olanzapine-controlled, 26 week study of flexible dose aripiprazole (15-30 mg/day) in 317 patients with schizophrenia.
138047	Double-blind, placebo-controlled, 26 week study of fixed dose aripiprazole (15 mg/day) in 310 patients with schizophrenia.
Schizophrenia, Special Studies	
98202	Randomized, double-blind, in-patient, escalating dose, 15 day pilot study to assess the tolerability and safety of higher doses of aripiprazole (45 mg, 60 mg, 75 mg, 90 mg) compared to 30 mg in 20 adults aged 18 to 45 years with schizophrenia or schizoaffective disorder (DSM-IV) receiving a stable dose of an oral antipsychotic drug (used as monotherapy) for at least one month prior to study screening.
98203	Open-label, inpatient 3 week pilot study to assess the safety and tolerability of aripiprazole (5 mg to 30 mg increased in a stepwise manner) in 30 elderly adults aged 64 to 95 years with dementia of the Alzheimer's type (DSM-IV) that met the BPRS Core and AMME criteria.
98215	Randomized, open-label, parallel group, outpatient 8 week study to assess the safety and tolerability of three alternative dosing schemes for switching patients from prior antipsychotic monotherapy to aripiprazole 30 mg monotherapy in 311 adults aged 18 to 65 years with schizophrenia or schizoaffective disorder (DSM-IV).
99224	Randomized, double-blind, inpatient, escalating dose, 15 day pilot study (repeat of 98-202) to assess the safety and tolerability of

APPENDIX IV-1: TABLE OF STUDIES	
	higher doses of aripiprazole (45, 60, 75 and 90 mg/day) compared to 30 mg/day in 40 adults aged 18 to 59 years with schizophrenia or schizoaffective disorder (DSM-IV), on a stable dose of an oral antipsychotic agent used as monotherapy for at least one month prior to screening.
Bipolar Mania Studies	
138007	Placebo-controlled, fixed dose, 3-week study of aripiprazole (15 and 30mg/day) in 401 patients with bipolar mania.
138009	Placebo-controlled, flexible dose, 3-week study of aripiprazole (15-30mg/day) in 262 patients with bipolar mania.
Dementia Studies	
138006	Placebo-controlled, flexible dose, 10 week study of aripiprazole (2-15 mg/day) in 208 patients with psychosis associated with Alzheimer's disease.
Ongoing Phase 2/3 Studies	
Schizophrenia Studies	
138001 extension	Randomized, double-blind, outpatient, flexible-dose, extended-dosing study of aripiprazole (10 - 15 mg or 20 - 30 mg) in adults ≥ 18 years of age with schizophrenia who have completed the 6-week Acute Phase of Study CN138-001 and for whom continued treatment is indicated. Dosing will continue until aripiprazole is available as a marketed product, or until December 2002, whichever is sooner.
138002 extension	Double-blind, flexible-dose, extended-dosing study of aripiprazole (15, 20, or 30 mg) vs. olanzapine (10, 15, or 20 mg) in adults ≥ 18 years of age with schizophrenia who have completed the 12-week Acute Phase Study CN138-002 and have responded to treatment. After May 2002, dosing will continue in an open-label fashion until

APPENDIX IV-1: TABLE OF STUDIES	
	aripiprazole is available as a marketed product, or until December 2002, whichever is sooner.
138003	Randomized, double-blind, 26-week study to assess the efficacy and safety of aripiprazole (15, 20, or 30 mg) vs. olanzapine (10, 15, or 20 mg) in 704 adults 18 - 65 years of age with acute schizophrenia (DSM-IV) in acute relapse with a history of response to a neuroleptic treatment other than clozapine. An optional Extension Phase allows for 26 weeks of continued double-blind dosing.
138032	Randomized, double-blind, active-controlled, flexible-dose, 124-week (maximum) switch study to assess the efficacy and safety of aripiprazole (15 or 30 mg per day) versus perphenazine (8 - 64 mg per day) in 300 adults ≥ 18 years of age with treatment-resistant schizophrenia aripiprazole (DSM-IV). Treatment phases were as follows: a 2- to 14-day Screening Phase, with a 48-hour washout, a 6-week, open-label (olanzapine or risperidone) neuroleptic treatment phase to verify that patients were resistant to neuroleptic treatment, followed by a 2- to 10-day, single-blind placebo phase, followed by randomization to the 6-week, double-blind (aripiprazole vs. perphenazine) treatment phase, followed by an optional, 109-week, open-label aripiprazole phase.
138047 extension	Randomized, open-label, flexible-dose, 52-week, extended-dosing study of aripiprazole (15 - 30 mg) or olanzapine (10 - 20 mg) in adults ≥ 18 years of age with schizophrenia who have completed the 26-week Acute Phase of Study CN138-047 or who relapsed after a minimum of 2 weeks of dosing on Study CN138-047.
95201	Multi-center, inpatient and outpatient, long-term study to determine the tolerability and safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) in schizophrenic adults (DSM-III-R or DSM-IV) aged 18

APPENDIX IV-1: TABLE OF STUDIES	
	to 65 years who participated in protocol 31-93-202 or 31-94-202. As part of the NDA submission, 143 patients have been enrolled.
97203	Multi-center, inpatient and outpatient, long-term study to determine the safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) as maintenance therapy in adults aged 18 to 65 years with schizophrenia or schizoaffective disorder (DSM-IV) who participated in protocol 31-97-201 or 31-97-202. As part of the NDA submission, 541 patients have been enrolled.
97303	Multi-center, outpatient, long-term study to determine the safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) as maintenance therapy in adults aged 18 years and over with schizophrenia (DSM-IV) who participated in protocol 31-97-301 or 31-98-304-01. As part of the NDA submission, 631 patients have been enrolled.
98204	Multi-center, 28-day, inpatient and outpatient study to determine the tolerability of aripiprazole (20 mg and 15 mg) in patients aged 15 to 35 years with first episode schizophrenia or schizoaffective disorder (DSM-IV) occurring not more than one year prior to study entry. As part of the NDA submission, 8 patients have been enrolled in the study.
98218	Multi-center, outpatient, long-term study to determine the safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) as maintenance therapy in adults aged 18 years and over with chronic schizophrenia (DSM-IV) who participated in protocol 31-98-217. As part of the NDA submission, 93 patients have been enrolled.
98220	Multi-center, outpatient, long-term study to determine the safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) as maintenance therapy in adults aged 18 to 65 years with chronic schizophrenia or schizoaffective disorder (DSM-IV) who participated in protocol 31-98-

APPENDIX IV-1: TABLE OF STUDIES	
	213. As part of the NDA submission, 104 patients have been enrolled.
98222	Multi-center, outpatient, long-term study to determine the safety of aripiprazole (flexible doses, 5 mg to 30 mg per day) as maintenance therapy in patients aged 15 years and over with psychotic disorders or psychotic behaviors of dementia (DSM-IV) who participated in protocol 31-98-215 or 31-98-204. As part of the NDA submission, 207 patients have been enrolled.
Bipolar Mania Studies	
138008	Randomized, double-blind, 12-week study to assess the efficacy and safety of aripiprazole (15 or 30 mg) vs. haloperidol (10 or 15 mg) in the maintained response to treatment in 347 adults 18-65 years of age with bipolar I disorder (DSM-IV), manic or mixed, in acute relapse. An optional Extension Phase allows for an additional 14 weeks of continued double-blind dosing of aripiprazole (15 or 30 mg) vs. haloperidol (10 or 15 mg).
138010	Randomized, double-blind, placebo-controlled study to assess the efficacy and safety of aripiprazole (15 or 30 mg) in the maintenance treatment of patients with bipolar I disorder (DSM-IV). Treatment phases are as follows: a 6- to 18-week Stabilization Phase, followed by a 26-week Maintenance Phase, followed by a 74 week (maximum) Extension Phase.
138037	Open-label, long-term study to assess the safety and efficacy of aripiprazole (15 or 30 mg) in the treatment of patients with bipolar I disorder (DSM-IV) who have completed a previous acute aripiprazole mania study. Treatment phases are as follows: acute 6- to 18-week, open-label (aripiprazole) Stabilization Phase, followed by an open-label, 26-week Maintenance Phase, followed by an Extension Phase of up to 50 additional weeks of dosing. Dosing will continue until

APPENDIX IV-1: TABLE OF STUDIES	
	aripiprazole is available as a marketed product, or until December 2002, whichever is sooner.
Psychosis in Alzheimer's Disease Studies	
138004	Randomized, double-blind, placebo-controlled, 10-week acute phase study of three fixed doses to assess the efficacy and safety of aripiprazole (2, 5, or 10 mg) in institutionalized patients 55 - 95 years of age with psychosis (delusions or hallucinations) associated with dementia of the Alzheimer's type (DSM-IV) present at least intermittently for one month or longer. An optional Extension Phase is a 130-week flexible-dose, open-label study of aripiprazole (2, 5, 10, or 15 mg) for patients who have completed the Acute Phase and for whom continued treatment is indicated.
138005	Randomized, double-blind, placebo-controlled, flexible-dose 10-week acute phase study to assess the efficacy and safety of aripiprazole (2, 5, 10, or 15 mg) in institutionalized patients 55 - 95 years of age with psychosis (delusions or hallucinations) associated with dementia of the Alzheimer's type (DSM-IV) present at least intermittently for one month or longer. An optional Extension Phase is a 130-week flexible-dose, open-label study of aripiprazole (2, 5, 10, or 15 mg) for patients who have completed the Acute phase and for whom continued treatment is indicated.
138006 extension	An optional extension Phase to a flexible-dose, 10-week randomized, double-blind, placebo-controlled study in institutionalized patients 55 - 95 years of age with psychosis (delusions or hallucinations) associated with dementia of the Alzheimer's type (DSM-IV). This extension phase is a 130-week flexible-dose, open-label study of aripiprazole (2, 5, 10, or 15 mg) for patients who have completed the Acute Phase and for whom continued treatment is indicated.

APPENDIX IV-1: TABLE OF STUDIES	
JAPANESE-STUDIES	
Phase 1	
91001a	Phase I clinical study to evaluate the safety and pharmacokinetics of OPC-14597 by single oral administration at 0.25, 0.5, 1, 2, 4, and 6 mg in comparison with haloperidol at 3 mg in 14 healthy adult male volunteers.
91001	Phase I clinical study to evaluate the safety and pharmacokinetics of OPC-14597 by 3-day repeated oral administration at 4 mg/day in 6 healthy adult male volunteers in comparison with haloperidol at 2 mg/day in 2 healthy adult male volunteers.
93003	Bioavailability study of non-deteriorated and deteriorated OPC-14597 tablets in healthy adult male volunteers. Twelve subjects were allocated to 2 groups of 6 subjects each. The study was conducted in a 2-treatment, 2-period, crossover manner with a washout period of at least 4 weeks between the 2 periods. In each period, the subjects received a single oral dose of either 1 non-deteriorated or 1 deteriorated OPC-14597 4-mg tablet. Because 1 subject dropped out after receiving treatment only in period 1, 1 additional subject was enrolled.
94002	Single-blind, placebo-controlled, parallel-group study of OPC-14597 at 1, 2, and 4 mg and haloperidol at 2 mg by single oral administration in 40 healthy adult male volunteers (8 on placebo) to investigate the characteristics and potency of OPC-14597 by quantitative pharmaco-EEG analysis.
94003	Bioavailability study (2) of non-deteriorated and deteriorated OPC-14597 tablets in healthy adult male volunteers with low gastric acidity. Six subjects were allocated to 2 groups of 3 subjects each.

APPENDIX IV-1: TABLE OF STUDIES	
	The study was conducted in a 2-treatment, 2-period, crossover manner with a washout period of at least 4 weeks between the 2 periods. In each period, the subjects received a single oral dose of either 1 non-deteriorated or 1 deteriorated OPC-14597 4-mg tablet in a fasted state in the morning.
99001	Open-label crossover bioequivalence study of OPC-14597 3-mg and 6-mg tablets in healthy adult male volunteers under a fasting condition. The objective of the study was to examine the bioequivalence between single oral administration of 2 OPC-14597 3-mg tablets and 1 OPC-14597 6-mg tablet in 26 healthy adult male volunteers under a fasting condition by measuring the plasma concentration of OPC-14597. The study was conducted in a 2-treatment, 2-period, crossover manner with a washout period of 28 days between the 2 periods. In each period (period I or II), the subjects received a single oral dose of either 2 3-mg tablets or 1 6-mg tablet under a fasting condition.
99002	Open-label pharmacokinetic study of OPC-14597 to investigate pharmacokinetics in the plasma, urinary excretion of OPC-14597 and its metabolites, and safety by 14-day repeated oral administration at 3 mg to 15 healthy adult male volunteers.
00001	Open-label crossover bioequivalence study of OPC-14597 to examine the bioequivalence between single oral administration of OPC-14597 1% powder (300 mg) and one OPC-14597 3-mg tablet in 14 healthy adult male volunteers under a fasting condition by measuring the plasma concentration of OPC-14597.
00002	Open-label crossover bioequivalence study of OPC-14597 to examine the bioequivalence between single oral administration of 3 OPC-14597 1-mg tablets and 1 OPC-14597 3-mg tablet in 14 healthy adult male volunteers under a fasting condition by measuring the plasma

APPENDIX IV-1: TABLE OF STUDIES	
	concentration of OPC-14597.
Phase 2/3	
91003	Multicenter, open-label study to investigate the efficacy and safety of OPC-14597 at 1-16 mg administered orally once daily for 4 weeks (up to 8 weeks if possible) in 26 patients aged 20-66 years hospitalized for the treatment of schizophrenia.
91004	Multicenter, open-label study to investigate the efficacy and safety of OPC-14597 at 1-10 mg administered orally once or twice daily for 4 weeks (up to 8 weeks if possible) in 30 patients aged 17-59 years hospitalized for the treatment of schizophrenia.
93001	Multicenter, open-label study to investigate the efficacy, safety, and optimum dose of OPC-14597 by oral administration at 4-30 mg (dose titration) in 138 schizophrenic patients aged 18-67 years.
93002	Late phase II, multicenter, open-label, follow-on study of the long-term (up to 12 months) effect of OPC-14597at 4-30 mg/day administered orally in 57 schizophrenic patients aged 18-63 years.
94001	Late phase II, multicenter, open-label, follow-on study of the long-term (up to 24 months) effect of OPC-14597at 4-30 mg/day administered orally in 8 schizophrenic patients aged 18-60 years.
95002	Multicenter, double-blind study of OPC-14597 at 6-24 mg/day and haloperidol at 3-12 mg/day administered orally for 8 weeks in 243 schizophrenic patients aged 17-65 years to determine the therapeutic efficacy and safety of OPC-14597 in schizophrenia in comparison with haloperidol.
95003	Multicenter, double-blind study of OPC-14597 at 6-24 mg/day and mosapramine hydrochloride (mosapramine) at 45-180 mg/day administered orally for 8 weeks in 245 schizophrenic patients aged 19-70 years to determine the therapeutic efficacy and safety of OPC-14597 in

APPENDIX IV-1: TABLE OF STUDIES	
	schizophrenia in comparison with mosapramine.
95004	Multicenter, open-label, long-term study of OPC-14597 at 6-24 mg/day administered orally for 24 and 52 weeks in 97 schizophrenic patients aged 18-72 years in the ~~~~ area to evaluate the long-term safety, as well as efficacy and usefulness, of OPC-14597.
95005	Multicenter, open-label, long-term study of OPC-14597 at 6-24 mg/day administered orally for 24 and 52 weeks in 116 schizophrenic patients aged 19-68 years in the area to evaluate the long-term safety, as well as efficacy and usefulness, of OPC-14597.
95006	Multicenter, open-label, long-term study of OPC-14597 at 6-24 mg/day administered orally for 24 and 52 weeks in 116 schizophrenic patients aged 22-70 years in the ~~~~ areas to evaluate the long-term safety, as well as efficacy and usefulness, of OPC-14597.

APPEARS THIS WAY
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APPENDIX IV-2: ENUMERATION OF SUBJECTS IN ALL NON-JAPANESE TRIALS BY TREATMENT AND STUDY TYPE[42]				
Study Type	Aripiprazole	Placebo	Haloperidol	Atypical[43]
Phase 1	924[44]	40[45]	0	0
Phase 2/3				
Short-Term, Placebo-Controlled				
Schizophrenia				
Fixed Dose	892	378	166	99
Flexible Dose	34	35	34	0
Bipolar Mania	393	260	0	0
Dementia	105	102	0	0
Long-Term Controlled				
Schizophrenia				
Flexible Dose	1141	0	431	282
Fixed Dose	153	153	0	0
Other Special Studies[46]	739	0	42	0
Ongoing (uncontrolled or OL)	2936	0	0	111
Total Phase 2/3	4710[47]	928	673	492
TOTAL PHASE 1/2/3	5634	968	673	492

[42] This table excludes an enumeration of patients in studies that were blinded as of 11-30-01.
[43] Includes olanzapine and risperidone.
[44] Includes 68 subjects who received an oral liquid formulation and 36 subjects who received a flashmelt formulation.
[45] Includes placebo and other protocol-specified drugs.
[46] Includes patients from four uncontrolled special studies, the open-label rescue phase of three trials (CN138-001, CN138-007, and CN138-009), and one discontinued trial (31-97-301).
[47] Patients who participated in more than one type of study (N=1683) are counted only once in this total.

APPENDIX IV-3: DEMOGRAPHIC CHARACTERISTICS OF PATIENTS TREATED WITH ARIPIPRAZOLE NON-JAPANESE PHASE 2/3 STUDIES				
	Schizophrenia N=3561	**Bipolar Mania N=645**	**Dementia N=504**	**TOTAL N=4710**
AGE				
Mean (years)	38.7	40.1	81.7	43.5
Range (years)	17.0-80.0	18.0-74.0	56.0-99.0	17.0-99.0
N by age range(yrs)				
<18	4	0	0	4
18-50	3045	526	0	3571
51-64	474	103	14	591
≥65	38	16	490	544
GENDER (N(%))				
Male	2398(67%)	285(44%)	127(25%)	2810(60%)
Female	1163(33%)	360(56%)	377(75%)	1900(40%)
RACE (N(%))				
White	2463(69%)	475(74%)	448(89%)	3386(72%)
Black	729(20%)	72(11%)	31(6%)	832(18%)
Hispanic	222(6%)	81(13%)	16(3%)	319(7%)
Asian	66(2%)	11(2%)	7(1%)	84(2%)
Other	81(2%)	6(1%)	2(0%)	89(2%)

APPENDIX IV-4: DEMOGRAPHIC CHARACTERISTICS OF CONTROL GROUP PATIENTS NON-JAPANESE PHASE 2/3 STUDIES				
	Placebo N=928	**Risperidone N=99**	**Olanzapine N=393**	**Haloperidol N=673**
AGE				
Mean (years)	44.6	38.6	39.5	37.4
Range (years)	18-99	18-64	18-77	18-65
N by age range(yrs)				
18-50	689	91	326	593
51-64	123	8	59	79
≥65	116	0	8	1
GENDER (N(%))				
Male	540(58%)	71(72%)	254(65%)	420(62%)
Female	388(42%)	28(28%)	139(35%)	253(38%)
RACE (N(%))				
White	640(69%)	54(55%)	269(68%)	537(80%)
Black	195(21%)	38(38%)	86(22%)	101(15%)
Hispanic	66(7%)	4(4%)	33(8%)	17(3%)
Asian	14(2%)	2(2%)	3(1%)	3(0%)
Other	13(1%)	1(1%)	2(1%)	15(2%)

APPENDIX IV-5: DEMOGRAPHIC CHARACTERISTICS OF PATIENTS BY TREATMENT GROUP NON-JAPANESE, SHORT-TERM, PLACEBO-CONTROLLED, PHASE 2/3 STUDIES IN SCHIZOPHRENIA				
	Aripiprazole N=926	**Placebo N=413**	**Haloperidol N=200**	**Risperidone N=99**
AGE				
Mean (years)	39.1	39.1	38.8	38.6
Range (years)	18.0-73.0	18.0-76.0	18.0-65.0	18.0-64.0
N by age range(yrs)				
18-50	791	367	179	91
51-64	127	40	20	8
≥65	8	6	1	0
GENDER (N(%))				
Male	699(75%)	309(75%)	149(75%)	71(72%)
Female	227(25%)	104(25%)	51(26%)	28(28%)
RACE (N(%))				
White	506(55%)	209(51%)	122(61%)	54(55%)
Black	283(31%)	144(35%)	58(29%)	38(38%)
Hispanic	93(10%)	42(10%)	14(7%)	4(4%)
Asian	21(2%)	10(2%)	1(1%)	2(2%)
Other	23(2%)	8(2%)	5(3%)	1(1%)

APPENDIX IV-6: ENUMERATION OF ARIPIPRAZOLE-TREATED PATIENTS BY DOSE AND DURATION OF TREATMENT NON-JAPANESE PHASE 2/3 STUDIES							
TX Duration (days)	Overall Mean Dose (mg/day)						
	Unknown/ Blinded	≤12.5	>12.5 ≤17.5	>17.5 ≤25	>25 ≤32.5	>32.5	Total
1-20	13	106	205	139	546	41	1050
21-41	11	84	116	182	352	0	745
42-89	12	95	82	162	439	1	791
90-119	2	42	23	43	130	0	240
120-149	0	41	16	31	112	0	200
150-179	1	45	39	14	72	0	171
180-269	2	115	62	37	140	1	357
270-359	2	81	25	38	108	0	254
360-719	4	41	25	78	333	0	481
≥720	0	8	17	84	312	0	421
Total	47	658	610	808	2544	43	4710

APPENDIX IV-7: ENUMERATION OF ARIPIPRAZOLE-TREATED PATIENTS BY DOSE AND DURATION OF TREATMENT NON-JAPANESE, SHORT-TERM, PLACEBO-CONTROLLED, PHASE 2/3 STUDIES IN SCHIZOPHRENIA								
TX Duration (Days)	Fixed Dose Studies[48]					Flexible Dose		Total
	Dose (mg/day)					N	Mean Dose (mg/day)[49]	
	2	10	15	20	30			
1-7	59	165	207	199	262	34	8.8	926
8-14	55	136	182	170	233	30	20.3	806
15-21	45	124	165	146	205	24	28.0	709
22-28	39	101	125	116	176	21	28.3	578
29-35	0	48	48	60	24	1	30.0	181
36-42	0	46	35	40	0	0	0	121
>42	0	13	6	12	0	0	0	31
Total	59	165	207	199	262	34	20.0	926

[48] For the fixed dose studies, the number in each cell represents the number of patients who received treatment during that study day interval by the dose received.
[49] The dose range for the flexible dose study was 5-30 mg/day. The mean dose represents the mean for all patients treated during each study day interval.

ITEMS UTILIZED IN THE REVIEW

APPENDIX V-1 ITEMS UTILIZED IN THE REVIEW[50]	
Submission Date	**Items Reviewed**
31-OCT-2001	Sponsor's Proposed Labeling NDA Application Summary Debarment Certification Financial Disclosure Certification Integrated Summary of Efficacy Integrated Summary of Safety Case Report Tabulations Case Report Forms Study Reports: 00230, 93202, 94201, 94202, 97201, 97202, 98202, 98203, 98213, 98215, 99224, and 138001.
17-JAN-2002*	Supplemental Vital Sign Data
12-FEB-2002	Table of Studies
27-FEB-2002	120-Day Safety Update Integrated Summary of Safety Case Report Tabulations Case Report Forms Study Reports: 138002 and 138006.
15-MAR-2002*	Literature Search
17-MAR-2002*	Reanalysis of Efficacy Data for Study 93202
22-MAR-2002	Case Report Forms for Non-Adverse Dropouts (for auditing)
29-MAR-2002*	CT Scan Report (Patient 91003-107-02)
10-APR-2002	Information on 4 Deaths

[50] * designates items submitted in hardcopy only. Other items were reviewed from electronic files in the CDER Electronic Document Room.

APPENDIX V-1 ITEMS UTILIZED IN THE REVIEW[50]	
Submission Date	**Items Reviewed**
15-APR-2002	Amended Table of Studies
16-APR-2002	Narrative Summaries for 3 Deaths
24-APR-2002	Alternate Tradename Proposal
29-APR-2002	Lab Data (3 patients), SAE Data (3 patients)
30-APR-2002	Narrative Summaries (3 patients)
8-MAY-2002	Lab Data (2 patients)
10-MAY-2002	Lab Data (2 patients)
15-MAY-2002	Efficacy Data in Schizoaffective Patients Supplemental Lab Data Demographic/Adverse Event Analysis Information on Adverse Event Classification
3-JUN-2002	Concomitant Antipsychotic Usage (97202 and 138001)

EFFICACY

APPENDIX VI-1: STUDY 93202 PRINCIPAL INVESTIGATORS			
Center	Investigator	Center	Investigator
02	John Csernansky, M.D.	08	Craig Karson, M.D.
04	James Garbutt, M.D.	09	Joseph P. McEvoy, M.D.
05	Donald C. Goff, M.D.	10	Mauricio Tohen, M.D.,
06	Alan I. Green, M.D.	11	Robert Litman, M.D.
07	Dilip V. Jeste, M.D.	12	Thomas N. Posever, M.D.

APPENDIX VI-2
STUDY 93202
BASELINE DEMOGRAPHICS (ALL RANDOMIZED PATIENTS)

TX Group	Gender	N	Age (years)		Race (N)		
			Mean	Range	White	Black	Other
OPC-14597	Male	32	32.4	18-57	18	13	1
	Female	2	42.5	37-48	1	1	0
Haloperidol	Male	30	38.6	21-65	15	13	2
	Female	4	38.8	26-46	2	2	0
Placebo	Male	29	36.9	21-52	15	12	2
	Female	6	42.5	31-59	3	3	0

APPENDIX VI-3
STUDY 93202
BASELINE SEVERITY OF ILLNESS (EFFICACY ITT)

TX Group	N	Mean BPRS Total Score	Mean CGI-Severity Score
OPC-14597	33	53.0	4.8
Haloperidol	33	50.3	4.7
Placebo	35	50.0	4.5

APPENDIX VI-4 STUDY 93202 ENUMERATION OF PATIENTS BY DISPOSITION			
	Treatment Group		
	OPC-14597	Haloperidol	Placebo
Randomized	34	34	35
Completed	21	20	12
Dropouts by Reason			
-screening criteria not met	0	0	1
-withdrawn consent	4	6	6
-non-compliance	1	0	0
-marked deterioration	2	1	7
-lack of response	6	4	8
-adverse event	0	2	0
-other	0	1[51]	1[52]

APPENDIX VI-5 STUDY 93202 PATIENT ENUMERATION BY NUMBER OF STUDY DAYS COMPLETED (N(% OF TOTAL RANDOMIZED))			
Days Completed	OPC-14597	Haloperidol	Placebo
1-7	34 (100%)	34 (100%)	35 (100%)
8-14	30 (88%)	30 (88%)	31 (89%)
15-21	24 (71%)	25 (74%)	26 (74%)
22 or more	21 (62%)	20 (59%)	15 (43%)

[51] Escaped from the hospital.
[52] Death in the family.

APPENDIX VI-6 STUDY 93202 MEAN CHANGE FROM BASELINE IN THE BPRS TOTAL SCORE (LOCF)				
	Baseline		Week 4	
	N	Mean BPRS	N	Δ
OPC-14597	33	53.0	33	-7.2
Placebo	35	50.0	35	-2.1
Haloperidol	33	50.3	33	-8.1
p-values (Wilcoxon Rank-Sum Test)				
OPC v. Plac	0.1732		0.173	
Hal v. Plac	0.8939		0.010	

APPENDIX VI-7 STUDY 93202 NUMBER AND PERCENTAGE OF PATIENTS WITH ≥1 POINT IMPROVEMENT ON THE CGI-SEVERITY SCALE (LOCF)				
	Baseline		Week 4	
	N	Mean CGI-S	n	%
OPC-14597	33	4.8	14	42.4%
Placebo	35	4.5	7	20.0%
Haloperidol	33	4.7	18	54.5%
p-values (Chi-Square)				
OPC v. Plac	-		0.045	
Hal v. Plac	-		0.003	
p-values (2-tailed Fisher's Exact Test)				
OPC v. Plac	-		0.066	
Hal v. Plac	-		0.005	

APPENDIX VI-8: STUDY 94202 PRINCIPAL INVESTIGATORS			
Center	**Investigator**	**Center**	**Investigator**
001	Joseph P. McEvoy, M.D.	012	Norman C. Moore, M.D. Samuel Shillcut, Pharm.D., Ph.D.
002	Bernard Beitman, M.D.	013	Peter Powchik, M.D.
003	Richard Borison, M.D., Ph.D.	014	Frederick W. Reimherr, M.D.
004	David Brown, M.D.	016	Neil M. Richtand, M.D., Ph.D.
005	Jose M. Canive, M.D. John Lauriello, M.D.	017	Murray H. Rosenthal, D.O.
006	James C.-Y. Chou, M.D.	018	Joyce G. Small, M.D.
007	David G. Daniel, M.D.	019	Manuel E. Tancer, M.D.
008	Arnold J. Friedhoff, M.D.	020	William C. Wirshing, M.D.
009	Donald C. Goff, M.D.	022	James C. Garbutt, M.D.
010	Mark Hamner, M.D.	023	Alan Green, M.D.
011	Gunnar Lawrence Larson, M.D.	025	Robert Litman, M.D.

APPENDIX VI-9
STUDY 94202
BASELINE DEMOGRAPHICS (ALL RANDOMIZED PATIENTS)

TX Group	Gender	N	Age (years)		Race (N)		
			Mean	Range	White	Black	Other
OPC 2mg	Male	47	40.1	22-65	22	19	6
	Female	12	38.8	19-51	11	1	0
OPC 10mg	Male	49	37.2	18-64	20	19	10
	Female	11	40.6	23-56	6	5	0
OPC 30mg	Male	46	38.8	18-61	19	23	4
	Female	15	38.9	24-57	11	3	1
Haloperidol	Male	52	38.0	19-60	28	19	5
	Female	11	43.2	25-63	9	2	0
Placebo	Male	53	37.5	19-57	28	20	5
	Female	11	40.5	28-55	5	4	2

APPENDIX VI-10
STUDY 94202
BASELINE SEVERITY OF ILLNESS (EFFICACY ITT)

TX Group	N	Mean BPRS Core Score	Mean CGI-Severity Score
OPC 2mg	58	16.2	4.7
OPC 10mg	57	16.8	4.8
OPC 30mg	60	16.2	4.7
Haloperidol	61	16.6	4.8
Placebo	64	16.0	4.7

APPENDIX VI-11
STUDY 94202
ENUMERATION OF PATIENTS BY DISPOSITION

	Treatment Group				
	OPC 2mg	OPC 10mg	OPC 30mg	Hal	Plac
Randomized	59	60	61	63	64
Completed	37	35	41	34	29
Dropouts by Reason					
-screening criteria not met					
-withdrawn consent	7	12	9	13	10
-non-compliance	0	0	1	0	0
-marked deterioration	3	4	0	4	8
-lack of response	8	3	6	8	12
-adverse event	4	2	4	4	1
-other	0	4	0	0	4

APPENDIX VI-12
STUDY 94202
PATIENT ENUMERATION BY NUMBER OF STUDY DAYS COMPLETED
(N(% OF TOTAL RANDOMIZED))

Days Completed	OPC 2mg	OPC 10mg	OPC 30mg	Hal	Plac
1-7	59(100%)	60(100%)	61(100%)	63(100%)	64(100%)
8-14	55(93%)	49(82%)	57(93%)	55(87%)	57(89%)
15-21	46(78%)	43(72%)	50(82%)	43(68%)	41(64%)
22 or more	39(66%)	39(65%)	42(69%)	35(56%)	32(50%)

APPENDIX VI-13
STUDY 94202 (EXCLUDING CENTER 003)
MEAN CHANGE FROM BASELINE IN THE BPRS CORE SCORE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
OPC 2mg	51	16.1	45	-1.7	36	-3.5	32	-4.8	51	-2.5
OPC 10mg	51	17.0	43	-2.7	39	-3.3	32	-3.6	51	-2.4
OPC 30mg	54	16.2	51	-2.6	41	-3.6	37	-4.4	54	-3.3
Haloperidol	54	16.6	45	-3.6	37	-4.4	31	-4.7	54	-3.8
Placebo	57	16.1	46	-2.2	34	-3.3	27	-5.1	57	-2.0
2-sided p-values										
2mg vs. Plac	0.7332		0.5806		0.7781		0.8521		0.7034	
10mg vs. Plac	0.1320		0.8103		0.6557		0.0881		0.8939	
30mg vs. Plac	0.9946		0.6317		0.7824		0.4901		0.1165	
Hal vs. Plac	0.4750		0.0897		0.2765		0.7817		0.0495	

APPENDIX VI-14
STUDY 94202 (EXCLUDING CENTER 003)
CGI-IMPROVEMENT SCORE

	Observed Cases						LOCF	
	Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Mean	N	Mean	N	Mean
OPC 2mg	46	3.7	36	3.1	32	2.9	51	3.7
OPC 10mg	43	3.4	39	3.2	32	3.1	51	3.5
OPC 30mg	51	3.3	41	2.9	37	2.7	54	3.1
Haloperidol	45	3.3	37	3.2	31	2.9	54	3.4
Placebo	45	3.6	34	3.2	27	2.9	57	3.9
2-sided p-values								
2mg vs. Plac	0.7029		0.6750		0.9639		0.5860	
10mg vs. Plac	0.2813		0.7792		0.4416		0.2260	
30mg vs. Plac	0.1275		0.2144		0.4731		0.0055	
Hal vs. Plac	0.1552		0.8036		0.9537		0.0811	

APPENDIX VI-15: STUDY 97201 PRINCIPAL INVESTIGATORS			
Center	**Investigator**	**Center**	**Investigator**
001	Faruk Abuzzahab, M.D., Ph.D.	023	Michael Lesem, M.D.
002	Bijan Bastani, M.D.	024	Robert Levine, M.D.
003	Robert Bielski, M.D.	025	Robert Litman, M.D.
004	Arthur Freeman, III, M.D. J. Gary Booker, M.D.	026	Michael McLarnon, M.D.
006	John Carmen, M.D.	027	Charles Merideth, M.D.
007	Stanley Cheren, M.D.	028	Alexander Miller, M.D. Larry Ereshefsky, Pharm.D.
008	Cal Cohn, M.D.	029	Richard Pearlman, M.D.
009	David Daniel, M.D.	030	Steven Potkin, M.D.
011	Ronald Centric, D.O.	031	Neil Richtand, M.D., Ph.D.
013	Jay Feierman, M.D.	032	Samuel Risch, M.D.
014	James Ferguson, M.D.	034	J. J. Rodos, D.O.
015	Arnold Friedhoff, M.D.	035	Anthony Rothschild, M.D.
016	Hal Goldberg, M.D.	036	David Sack, M.D.
018	Mahlon Hale, M.D.	037	Joyce Small, M.D.
019	James Hartford, M.D.	038	Kenneth Sokolski, M.D.
020	Mary Ann Knesevich, M.D.	039	Tram Tran-Johnson, Pharm. D.
021	Irving Kolin, M.D.	041	Scott West, M.D.
022	William Lawson, M.D.	043	Dan Zimbroff, M.D.

APPENDIX VI-16: DEMOGRAPHIC CHARACTERISTICS STUDY 97201 (ALL RANDOMIZED PATIENTS)							
	Age (years)		Gender (%)		Race (%)		
	Mean	Range	Male	Female	White	Black	Other
Ari 15mg	37.8	19-61	75%	25%	60%	25%	15%
Ari 30mg	39.3	19-65	69%	31%	59%	26%	15%
Placebo	38.5	19-68	70%	30%	51%	32%	17%
Hal 10mg	38.9	18-59	65%	35%	67%	23%	10%

APPENDIX VI-17 STUDY 97201 BASELINE SEVERITY OF ILLNESS (ALL RANDOMIZED PATIENTS)			
TX Group	N	Mean PANSS Total Score	Mean CGI-Severity Score
Ari 15mg	102	98.5	4.9
Ari 30mg	102	99.0	4.8
Placebo	106	100.2	4.9
Haloperidol	104	99.3	4.8

APPENDIX VI-18 STUDY 97201 ENUMERATION OF ALL PATIENTS BY DISPOSITION				
	Treatment Group			
	Ari 15mg	Ari 30mg	Plac	Hal
Randomized	102	102	106	104
Completed	68	60	58	62
Dropouts by Reason				
-adverse event	9	8	17	11
-lost to follow-up	0	1	1	0
-withdrew consent	15	10	12	20
-administrative reasons	1	1	1	0
-noncompliance	0	1	1	1
-poor clinical response	9	21	16	10

APPENDIX VI-19 STUDY 97201 ENUMERATION OF ITT PATIENTS IN-STUDY BY WEEK[53] (N(% OF ITT))				
Week	Ari 15mg	Ari 30mg	Placebo	Haloperidol
Baseline (ITT)	99	100	102	99
1	97(98%)	100(100%)	102(100%)	97(98%)
2	84(85%)	87(87%)	89(87%)	82(83%)
3	77(78%)	73(73%)	69(68%)	70(71%)
4	68(69%)	61(61%)	60(59%)	61(62%)

[53] Based on patients with PANSS total score data.

APPENDIX VI-20
STUDY 97201
MEAN CHANGE FROM BASELINE IN THE PANSS TOTAL SCORE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 15mg	99	97.9	84	-13.3	77	-14.8	68	-24.3	99	-15.5
Ari 30mg	100	98.5	87	-10.3	73	-14.0	61	-19.1	100	-11.4
Haloperidol	99	99.6	82	-12.0	70	-14.9	61	-16.6	99	-13.8
Placebo	102	100.2	89	-2.6	69	-9.4	60	-11.4	102	-2.9
2-sided p-values										
15mg vs. Plac	0.355		<0.001		0.120		<0.001		<0.001	
30mg vs. Plac	0.508		0.010		0.193		0.040		0.009	
Hal vs. Plac	0.804		0.002		0.124		0.163		0.001	

APPENDIX VI-21
STUDY 97201
MEAN CHANGE FROM BASELINE IN THE PANSS POSITIVE SUBSCALE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 15mg	99	24.6	84	-4.1	77	-4.5	68	-6.4	99	-4.2
Ari 30mg	100	24.4	87	-3.1	73	-4.5	61	-6.2	100	-3.8
Haloperidol	99	25.1	82	-3.7	70	-4.7	61	-5.0	99	-4.4
Placebo	103	24.9	89	-0.7	69	-2.8	60	-2.6	103	-0.6
2-sided p-values										
15mg vs. Plac	0.716		<0.001		0.088		<0.001		<0.001	
30mg vs. Plac	0.511		0.008		0.091		0.001		0.001	
Hal vs. Plac	0.707		0.001		0.072		0.023		<0.001	

APPENDIX VI-22
STUDY 97201
MEAN CHANGE FROM BASELINE IN THE CGI-SEVERITY OF ILLNESS SCORE

	Baseline		Observed Cases						LOCF	
			Week 2		Week 3		Week 4		Week 4	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
Ari 15mg	99	4.9	84	-0.5	77	-0.7	68	-0.9	99	-0.6
Ari 30mg	100	4.8	87	-0.3	73	-0.5	60	-0.7	100	-0.4
Haloperidol	99	4.9	82	-0.4	70	-0.6	61	-0.6	99	-0.5
Placebo	103	4.9	89	-0.1	69	-0.3	60	-0.4	103	-0.1
2-sided p-values										
15mg vs. Plac	0.766		<0.001		0.007		0.001		<0.001	
30mg vs. Plac	0.230		0.017		0.132		0.053		0.019	
Hal vs. Plac	0.397		0.004		0.091		0.147		0.002	

APPENDIX VI-23: STUDY 97202 PRINCIPAL INVESTIGATORS			
Center	**Investigator**	**Center**	**Investigator**
050	David Brown, M.D.	073	Denis Mee-Lee, M.D.
051	Jose Canive, M.D.	074	Herbert Y. Meltzer, M.D.
052	Aly Ahmed, M.D.	076	B. Rhett Myers, M.D.
053	James Chou, M.D.	078	Stephen Peterson, M.D.
054	Emmett Cooper, M.D.	079	Debra Brescan, M.D. Luis Ramirez, M.D.
055	John W. Crayton, M.D.	080	Christine Grissom, M.D. Timothy Reid, M.D.
056	David Daniel, M.D.	081	Robert Riesenberg, M.D.
057	Lawrence Adler, M.D.	082	Fred Schaerf, M.D., Ph.D.
058	Mohsain Essa, M.D.	083	Herbert Y. Meltzer, M.D.
059	Louis Fabre, M.D., Ph.D.	084	Philip Seibel, M.D.
060	Ira Glick, M.D.	086	Samuel Shillcutt, Pharm.D., Ph.D.
062	Alan Green, M.D.	087	Jeff Simon, M.D.
063	Barry Guze, M.D.	088	Thomas Smith, M.D.
064	Mark Hamner, M.D.	089	Vicky Spratlin, M.D.
066	Richard Josiassen, Ph.D.	090	Stephen Strakowski, M.D.
067	Steven Potkin, M.D.	091	Steven Targum, M.D.
068	Gunnar Larson, M.D.	092	Marshall Thomas, M.D.
069	Mark Lerman, M.D.	093	Cherian Verghese, M.D.
071	Robert Litman, M.D.	094	Kenneth Weiss, M.D.
072	Joseph McEvoy, M.D.	095	William Wirshing, M.D. Stephen Marder, M.D.