CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-866

MEDICAL REVIEW

MEMORANDUM

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

DATE: August 28, 2006

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 21-866 (This overview should be filed with the 11-30-2005 original submission.)

SUBJECT: Recommendation of Approval Action for Aripiprazole IM Injection for the Treatment of Agitation associated with Schizophrenia or Bipolar Disorder, Mania or Mixed.

1. BACKGROUND

Aripiprazole (ABILIFY) is an atypical antipsychotic agent. The oral tablet formulation is approved in the treatment of schizophrenia and bipolar I disorder, mania or mixed, in the U.S. since November, 2002. Aripiprazole's efficacy in schizophrenia is thought to be mediated through a combination of partial agonism at centrally-active dopamine D2 and serotonin 5HT1a receptors, and antagonism of serotonin 5-HT_{2A}.

IND 60,158 for aripiprazole injection (7.5 mg/ml strength) was originally submitted on 04/14/2000 by Otsuka Pharmaceutical Co., Ltd. (OPC). The IND was developed collaboratively by OPC and Bristol-Myers Squibb Company (BMS). During the IND development program, the Division (previously DNDP) met with the sponsor on June 9, 2004. The discussions included:

- Secondary key efficacy measures: CGI-I or CGI-S would be acceptable.
- Adequacy of one positive study for each indication would be sufficient to support the claim.
- Requirement for an NDA.

The sponsor submitted the above referenced NDA on November 30, 2005. The results of three efficacy trials using the IM formulation of aripiprazole were included in this NDA submission. The proposed dose range of IM aripiprazole in the treatment of agitation in schizophrenia or bipolar disorder is 5-15 mg.

This NDA has been reviewed by Yeh-Fong Chen, Ph.D., from the Office of Biostatistics (review dated 07/14/2006), and Earl Hearst, M.D., Medical Officer, DPP (review dated 08/14/06). The Office of Clinical Pharmacology (OCP) review was completed by Andre Jackson, Ph.D. (review dated 8/23/06). The CMC reviewer for this NDA is Donghao Lu, Ph.D., and the pharmacology/toxicology reviewer is Sonia Tabacova, Ph.D. At the time of completing this memo, the Chemistry and the pharmacology/ toxicology are not finalized.

2.0 CHEMISTRY

I am not aware of any CMC concerns that would preclude an approvable action on this NDA.

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology issues that would preclude an approvable action for this NDA.

4.0 CLINICAL PHARMACOLOGY

The biopharm review included the results from 3 clinical pharmacology studies (CN138-016, CN138-017, CN138-132) and an assessment of the relationship between plasma levels of aripiprazole and QTc in the study CN138-050. I refer to the review by Dr. Jackson for detail.

Briefly, it was noted that the median time to the peak plasma concentration was at 3 hours. The absolute bioavailability was 0.87 for the tablet and 1.01 for the IM formulation. The geometric mean maximum concentration achieved after an intramuscular injection was on average 19% higher than the Cmax of the oral tablet. While the systemic exposure was generally similar between aripiprazole administered via IM injection and given as oral tablet formulation, the aripiprazole AUC in the first 2 hours after an IM injection was 90% greater than the AUC after the same dose as an oral tablet. Aripiprazole was dose proportional over the range of 1 to 45 mg on day 1 and 1 to 30 mg on day 4 following QD dosing.

According to the study CN138-132, the results of the co-administration of IM aripiprazole 15 mg and IM lorazepam 2 mg showed no effect on the pharmacokinetics of either compound. Based on the assessment of the relationship between aripiprazole plasma concentration and QTc changes from baseline in the study CN138-050, aripiprazole does not seem to have a QTc interval prolongation effect.

The OCP review provided some labeling changes to the labeling proposed by the sponsor. There was no issues identified that would preclude an approvable action for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 3 short-term, double-blind, placebo-controlled trials. Two studies (CN138-050 and CN138-012) were the randomized, double-blind, placebo and active controlled (haloperidol), fixed-dose studies designed to evaluate the efficacy and safety of aripiprazole IM in acutely agitated patients with schizophrenia or schizoaffective disorder. The study CN138-050 also allowed inclusion of subjects with schizophreniform disorder. The other single study (CN138-013) was a randomized, double-blind, placebo and active controlled (lorazepam), fixed-dose study designed to evaluate the efficacy and safety of aripiprazole IM in acutely agitated patients with bipolar I disorder, mania or mixed. The doses of IM aripiprazole used

were 5, 10, and 15 mg per single injection in study CN138-050; 10 mg per single injection in study CN138-012; and 10 and 15 mg per single injection in study CN138-013.

The sponsor indicated that results of the 3 pivotal clinical studies demonstrated that all doses of IM aripiprazole tested were superior to placebo on the primary efficacy variable. It seemed that IM aripiprazole did not differ from the active control used in these fixed dose studies in adults (haloperidol 6.5 mg in study CN138-012, haloperidol 7.5 mg in study CN138-050, lorazepam 2 mg in study CN138-013). The result from the active control group was also used for assay sensitivity analysis. In order to examine the effect of aripiprazole specifically on patients with schizophrenia (excluding patients with schizophreniform or schizoaffective disorder), data were analyzed separately and similar results were obtained.

I would briefly describe the results of each of these studies pertinent to efficacy claim in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

Study CN138-012

This was a multicenter, randomized, double-blind, placebo and active-controlled study comparing aripiprazole (10 mg per single injection) vs. placebo. This study consisted two phases: a 24 hour IM phase [with three intramuscular dose arms: aripiprazole (10mg per single injection), haloperidol (6.5mg), and placebo] and a 4-day oral phase. Patients were randomized in a 2:2:1 ratio. The study began with a 2-12 hour screening period. Baseline assessments were performed within 1 hour of the first IM dose. Immediately following administration of the first IM dose, a 24 hour inpatient evaluation period commenced. Patients could have received up to 3 injections based on the judgment of the investigator. A second IM dose were allowed, if needed, at least 2 hours after the first IM dose followed by a third IM dose, if needed, at least 2 hours after the second dose. The second and/or third IM dose was given no later than 20 hours after administration of the first IM dose. For the placebo patients, the first and second doses contained placebo and the third dose contained aripiprazole 10mg. Patients who did not receive a concomitant benzodiazepine during the 24 hour IM phase and completed that phase would receive oral medication under blinded conditions for the next 4 days. Patients initially randomized to aripiprazole or placebo would receive aripiprazole 15mg tablets (with the option of decreasing the dose to 10mg) and those randomized to haloperidol would receive haloperidol 10mg tablets (with the option of decreasing to 7mg).

The study was conducted at 68 centers (40 U.S. and 28 non-U.S. including Eastern and Western European Countries, Puerto Rico and South Africa) in adult (age 18 or older) for the treatment of acute agitation in hospitalized patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder. The total number of subjects enrolled in this study was 469; 448 subjects were randomized to the double-blind treatment in which 175 subjects in the aripiprazole IM treatment group. Of these 448 subjects, 325 subjects were diagnosed with schizophrenia and 123 subjects with schizoaffective disorder. The ITT samples (total N=445) for aripiprazole (10 mg), haloperidone (6.5mg) and placebo were 173, 184, and 88, respectively. The subjects enrolled were mostly white (66%), mean age was 41.5 yrs, and had approximately 60% male and 40% female subjects. There seemed to be no significant differences in demographic characteristics among the treatment groups. A total of 435 subjects (97%) completed the IM phase of the double-blind study and a total of 380 subjects entered the oral phase. 3% of study subjects discontinued from the IM

phase of the study. The most common reason for discontinuation from the study was withdrawal of consent in 5 patients (1%).

The efficacy assessment included the PEC [i.e., the PANSS Excited Component (PEC) consists of the following five items from the PANSS: hostility, uncooperativeness, excitement, poor impulse control, and tension], and the CGI-I. The primary end point was the change in the mean change from baseline to 2 hours post-first IM injection the PEC score for the LOCF dataset. The ANCOVA was the statistical model employed, with terms for treatment, and baseline score using LOCF methodology. Analyses were also done on the Observed-Cases dataset. Dr. Chen confirmed the primary efficacy results including the country factor into the ANCOVA model. She also applied Cochran-Mantel-Haenszel Row Mean Score test for each time point after the first IM injection using the LOCF and OC data sets for analysis of the treatment differences on the CGI-I. The results are as follows:

Efficacy Results on PEC Scores for schizophrenia subpopulation in Study CN138-012 (LOCF):

	Mean Baseline PEC±SD (number of subjects with schizophrenia or schizoaffective disorder)	Mean Baseline PEC (number of subjects with schizophrenia)	Change from Baseline Mean (SD) at 120 min post-first inj. (number of schizophrenia subjects)	P-values (vs. placebo)
Aripiprazole IM 10 mg	18.74 ±2.71(N=175)	18.79 (N=123)	-7.99 (N=123)	0.003
Haloperidol IM 6.5 mg	18.79 ±2.59 (N=185)	18.78 (N=134)	-8.25 (N=134)	<0.001
Placebo	18.82 ±2.67 (N=88)	18.89 (N=65)	-5.68 (N=65)	

Efficacy Results on CGI-I for schizophrenia subpopulation in Study CN138-012 (LOCF):

	Change from Baseline Mean at 120 min post-first inj. (number of schizophrenia subjects)	P-values (vs. placebo)
Aripiprazole IM 10 mg (N=123)	2.41	<0.001
Haloperidol IM 6.5 mg (N=134)	2.39	<0.001
Placebo (N=65)	3.03	

Comment:

Both Drs. Hearst and Chen considered this a positive study for aripiprazole IM, and I agree with them.

Study CN138-050

This was a multicenter, randomized, double-blind study comparing 4 doses of IM aripiprazole (1, 5, 10 and 15 mg per single injection), vs. placebo in the treatment of acute agitation in patients with a DSM-IV diagnosis of schizophrenia, schizoaffective or schizophreniform disorder. IM haloperiodol (7.5mg) was the active-control. Baseline assessments were performed within 1 hour of the first IM dose. Immediately following administration of the first IM dose, a 24 hour inpatient evaluation period commenced. Patients could have received up to 3 injections based on the

judgment of the investigator. A second IM dose were allowed, if needed, at least 2 hours after the first IM dose followed by a third IM dose, if needed, at least 2 hours after the second dose. The second and/or third IM dose was given no later than 20 hours after administration of the first IM dose.

The study was conducted at 50 centers (30 U.S. and 20 non-U.S. including Canada, France, Spain and Eastern European Countries) in adult (age 18 or older) for the treatment of acute agitation in hospitalized patients with a diagnosis of schizophrenia, schizoaffective or schizophreniform disorder. The total number of subjects enrolled in this study was 378; 357 subjects were randomized to the double-blind treatment in which 235 subjects in the aripiprazole IM treatment group. Of these 357 randomized subjects, 237 subjects (66%) were diagnosed with schizophrenia, 113 subjects with schizoaffective disorder and 7 with schizophreniform disorder. The ITT samples (total N=350) for aripiprazole (1, 5, 10, 15 mg), haloperidone (7.5mg) and placebo were 56, 62, 56, 58, 57, and 61, respectively. The subjects enrolled were mostly white (60-70%), mean age was approximately 40 yrs, and had approximately 65% male and 35% female subjects in aripiprazole and haloperidol groups while placebo group had approximately equal distribution. There seemed to be no significant differences in demographic characteristics among the treatment group. A total of 338 subjects (95%) completed the double-blind study; 19 subjects (5%) discontinued from the study. The most common reason for discontinuation from the study was withdrawal of consent (12 patients).

The efficacy assessment included the PEC [i.e., the PANSS Excited Component (PEC) consists of the following five items from the PANSS: hostility, uncooperativeness, excitement, poor impulse control, and tension], and the CGI-I. The primary end point was the change in the mean change from baseline to 2 hours post-first IM injection the PEC score for the LOCF dataset. The ANCOVA was the statistical model employed, with terms for treatment and baseline score using LOCF methodology. For multiple comparisons of IM aripiprazole doses (5, 10 and 15 mg) with placebo, the statistical testing was carried out using the pre-specified Hochberg procedure. Analyses were also done on the Observed-Cases dataset. Dr. Chen confirmed the primary efficacy results including the country factor into the ANCOVA model. She also applied Cochran-Mantel-Haenszel Row Mean Score test after the first IM injection with adjustments for country and treatment group in her analysis of the treatment differences on the CGI-I. The results are as follows:

Efficacy Results on PEC Scores for schizophrenia subpopulation in Study CN138-050 (LOCF):

	Mean Baseline PEC (number of subjects with schizophrenia, schizoaffective or schizophreniform disorder)	Change from Baseline Mean at 120 min post-first inj.	P-values (vs. placebo)
Aripiprazole IM 1 mg (N=30)	18.87	-4.87	0.935
Aripiprazole IM 5 mg (N=40)	19.08	-6.94	0.05
Aripiprazole IM 10 mg (N=36)	18.97	-7.82	0.008
Aripiprazole IM 15 mg (N=44)	19.2	-6.94	0.045
Haloperidol IM 7.5 mg (N=43)	18.67	-7.32	0.02
Placebo (N=38)	19.46	-4.78	

Efficacy Results on CGI-I for schizophrenia subpopulation in Study CN138-050 (LOCF):

	Change from Baseline Mean at 120 min post-first inj. (number of schizophrenia subjects)	P-values (vs. placebo)
Aripiprazole IM 1 mg	3.3	0.689
Aripiprazole IM 5 mg	2.65	<0.001
Aripiprazole IM 10 mg	2.67	0.004
Aripiprazole IM 15 mg	2.68	0.002
Haloperidol IM 7.5 mg	2.65	<0.001
Placebo	3.38	

Comment:

Both Drs. Hearst and Chen considered this a positive study for aripiprazole IM at three higher dose groups (5, 10 and 15 mg), and I agree with them.

Study CN138-013

This was a multicenter, randomized, double-blind study comparing 2doses of IM aripiprazole (10 and 15 mg per single injection), IM lorazepam (2 mg per single injection) vs. placebo in the treatment of acute agitation in patients with a diagnosis of bipolar I disorder, manic or mixed. Baseline assessments were performed within 1 hour of the first IM dose. Immediately following administration of the first IM dose, a 24 hour inpatient evaluation period commenced. Patients could have received up to 3 injections based on the judgment of the investigator. A second IM dose were allowed, if needed, at least 2 hours after the first IM dose followed by a third IM dose, if needed, at least 2 hours after the second dose. The second and/or third IM dose was given no later than 20 hours after administration of the first IM dose. The maximum lorazepam dose was 6 mg. For the placebo patients, the first and second doses contained placebo and the third dose contained aripiprazole 10mg.

The study was conducted at 37 centers (35 U.S. and 2 non-U.S. in Latvia and Poland) in adult (age 18 or older) for the treatment of acute agitation in patients with a diagnosis of bipolar I disorder, manic or mixed. The total number of subjects enrolled in this study was 329; 301 subjects were randomized to the double-blind treatment in which 156 subjects in the aripiprazole IM treatment group. The ITT samples (total N=291) for aripiprazole (10, 15 mg), lorazepam (2mg) and placebo were 78, 78, 70, and 73, respectively. The subjects enrolled were mostly white (70%), mean age was approximately 40.8 yrs, and had approximately equal distribution of male and female in aripiprazole group; slightly higher percentage of male subjects (57%) in the placebo group and similarly, a slightly higher number of female subjects (57%) in the lorazepam group. There seemed to be no significant differences in demographic characteristics among the treatment groups. A total of 282 subjects (94%) completed the double-blind study; 19 subjects (6%) discontinued from the study. The most common reason for discontinuation from the study was withdrawal of consent (8 patients).

The efficacy assessment included the PEC [i.e., the PANSS Excited Component (PEC) consists of the following five items from the PANSS: hostility, uncooperativeness, excitement, poor impulse

control, and tension], and the CGI-I. The primary end point was the change in the mean change from baseline to 2 hours post-first IM injection the PEC score for the LOCF dataset. The ANCOVA was the statistical model employed, with terms for treatment and baseline score using LOCF methodology. For multiple comparisons of IM aripiprazole doses (10 and 15 mg) with placebo, the statistical testing was carried out using the Hochberg procedure. Analyses were also done on the Observed-Cases dataset. Dr. Chen confirmed the primary efficacy results. She also applied Cochran-Mantel-Haenszel Row Mean Score test after the first IM injection with stratification by center in her analysis of the treatment differences on the CGI-I. The results are as follows:

Efficacy Results on PEC Scores for schizophrenia subpopulation in Study CN138-013 (LOCF):

Treatment Group	Mean Baseline PEC	Change from Baseline Mean at 120 min post-first inj.	P-values (vs. placebo)
Aripiprazole IM 10 mg (N=75)	18.84	-8.74	<0.001
Aripiprazole IM 15 mg (N=75)	18.25	-8.67	<0.001
Lorazepam IM 2 mg (N=68)	18.47	-9.57	<0.001
Placebo (N=73)	18.04	-5.76	

Efficacy Results on CGI-I for schizophrenia subpopulation in Study CN138-013 (LOCF):

Treatment Group	Change from Baseline Mean at 120 min post-first injection	P-values (vs. placebo)
Aripiprazole IM 10 mg	2.17	<0.001
Aripiprazole IM 15 mg	2.33	<0.001
Lorazepam 2 mg	2.1	<0.001
Placebo	3.05	

Comment:

I agreed with both Drs. Hearst and Chen that this study with acutely agitated bipolar I patients be considered a positive study for aripiprazole IM.

5.1.3 Comments on Other Important Clinical Issues

Additional Analysis for Efficacy and Exposure-Response Relationships

The doses included in the all positive studies were: 10 mg per single injection in study CN138-012; and 5, 10 and 15 mg in study CN138-050 for treatment of agitation in patients with schizophrenia. The dose used in study CN138-013 for treatment of agitation in patients with bipolar I disorder was 10 and 15 mg per single injection. No increase in efficacy was observed with the 15-mg dose. For those patients who did not respond adequately to a single dose, the second dose administered after the first dose demonstrated significant clinical improvement.

Efficacy of IM aripiprazole was also demonstrated in agitated patients associated with schizophrenia or bipolar I disorder who did not exhibit sedation during the first two hours of the respective efficacy studies. The sponsor reported that this was evidenced by a significant mean change relative to placebo from baseline to 2 hours post first IM injection in the PEC score in the

subpopulation of patients with low and moderate ACES scores and also in the subpopulation reported having no AEs related to sedation.

In addition, the sponsor performed non-inferiority analysis for the comparison between aripiprazole and haloperidol. During the IND development, the clinical reviewer Dr. Dubitsky had already mentioned in his review of the protocol CN138-012 that this would not be acceptable. The statistical reviewer Dr. Chen did not review this part of the NDA submission.

The sponsor has recommended a target dose of 10 mg as was supported by the efficacy on the PEC scale. Dr. Hearst agreed with the dosing recommendation and I agree as well. The proposed labeling should include information regarding the demonstrated efficacy.

Subgroup Analyses

Exploratory subgroup analyses were done by the sponsor and the Statistical Reviewer to detect subgroup interactions on the basis of gender, age and race. The sponsor did not perform any further subgroup analysis for the schizophrenia subpopulation but Dr. Chen did the analysis for both schizophrenia studies. As can be seen in Dr. Chen's review, although the number of subjects was considerably larger in the male group, the gender did not seem to have an effect on the significance level of the treatment on the primary efficacy endpoint.

For the Bipolar study, the sponsor performed the subgroup analysis for the underlying diagnosis of manic or mixed episode. The mean decreases from baseline in these subpopulations were numerically greater in the aripiprazole group than the placebo group.

Overall, there is no clear indication of subgroup differences in response based on these variables.

Secondary Efficacy Variables

In the proposed labeling, the sponsor intends to claim efficacy evaluation using the CGI-I. We would need two positive well-controlled studies for any pre-specified key secondary to be included in the labeling. I note the meeting minutes dated 6/9/2004 stated that CGI-I or CGI-S would be acceptable as the key secondary variable but I did not see any documentation that the sponsor followed up with a pre-specified analysis plan declaring either one of these two as a key secondary variable. Although the results both the CGI-I and the CGI-S were found to be positive, Dr. Chen noted that it's unclear which one of the two scores was chosen as a key secondary endpoint before the data was unblinded for study CN138-050. The studies CN138-050 and CN138-013 were the multiple dose studies of aripiprazole IM but they used different patient population. The study CN138-012 had only one dose of aripiprazole as one of the treatment groups. We should not accept the sponsor's proposal to include the CGI-I in the labeling unless the sponsor could provide documentation that the studies were prospectively planned to include such claim.

Duration of Treatment

The studies were conducted for intended use of aripiprazole IM is in the treatment of acute agitation associated with schizophrenia or bipolar I disorder. There is no data pertinent to the longer-term efficacy of aripiprazole IM in this submission.

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analyses of all 3 studies supported the efficacy claim of aripiprazole IM in the treatment of acute agitation associated with schizophrenia or bipolar I disorder, mania or mixed, in all dose groups tested.

5.2 Safety Data

5.2.1 Safety Database

Dr. Hearst's safety review of this NDA was based on an integrated database covering 7 clinical trials in the drug development program for IM aripiprazole. This included:

1) 3 clinical pharmacology studies
2) 4 phase 2/3 clinical studies
    - 3 completed phase 3 double-blind studies in subjects with acutely agitated subjects diagnosed with schizophrenia (2 studies); 1 study with bipolar I disorder
    - 1 dose tolerance study with acutely agitated dementia patients

Dr. Hearst's safety review included data from the submission with a cut-off date of 04/27/2005.

In the 3 clinical pharmacology studies, a total of 60 subjects received aripiprazole alone; 40 subjects received both aripiprazole and lorazepam.

In the 4 phase 2/3 clinical trials, a total of 749 subjects received IM aripiprazole out of 1214 subjects enrolled, with 660 patients received aripiprazole as initial treatment while 245 subjects received placebo.

The patient distribution for the sample in the phase 2/3 studies was as follows:

- 795 subjects with schizophrenia, schizoaffective or schizophreniform disorder
- 291 subjects with a diagnosis of bipolar I disorder
- 128 subjects with a diagnosis of dementia

Based on the IND protocol reviews, the Division has previously agreed that IM aripiprazole exposure of 400 patients with at least 50 patients exposed to IM aripiprazole 15 mg in the protocol CN138-050 should be sufficient for the assessment of safety. As stated above, the submitted data in this NDA comprised of 749 subjects exposed to IM aripiprazole including a total of 58 subjects who received IM aripiprazole 15 mg dose per single injection in the protocol CN138-050.

There were no deaths reported in the aripiprazole treatment group in the clinical pharmacology studies. There were two reports of deaths in phase 2/3 clinical studies. Briefly, a 41 yr old male with bipolar disorder was found deceased in bed at home at 3 days after participation in the study CN138-013. The subject was randomized to the 10 mg of IM aripiprazole group and received a total of 20 mg aripiprazole. No clinically significant laboratory results, abnormal ECG findings or vital sign measurements were observed during the study. Autopsy report listed the cause of death as undetermined. In the protocol CN138-131, a 89-yr old female with dementia received 2x5mg aripiprazole IM during the study. The patient was hospitalized for delirium 12 days after

completing the study. Delirium resolved but the patient died on day 25. For both cases, the investigator designated the event as not likely related to study medication.

Serious adverse events were available from these trials. Thirty-two of the 1214 patients in the 4 double-blind clinical studies experienced SAE. The total number of patients who discontinued from the 3 pooled pivotal trials (CN138-012, 013 and 050) was similar across the treatment groups (aripiprazole: 2%; placebo: 2%; haloperidol: 5%; lorazepam 3%). There were no post-marketing data since this IM formulation is not marketed any country in the world.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk).

In the double-blind placebo-controlled studies, the AE of somnolence was higher in the aripiprazole treatment group (6.79%) than in the placebo group (3.6%) while sedation was similar between the groups (2.3%). Akathesia was higher in the aripiprazole group (2%) than the placebo group (0%) while other EPS related AEs was similar (2.4% vs. 1.8%). Other AEs occurred more frequently in subjects who received aripiprazole included tachycardia, nausea, vomiting, dyspepsia, drymouth, headaches and dizziness.

5.2.2.2 Neuroleptic Malignant Syndrome

There were no reports of NMS in any of the studies. The proposed language is similar to the oral aripiprazole labeling. It seems acceptable to me.

5.2.2.3 Vital Sign and ECG

The incidence of treatment emergent tachycardia was higher in the aripiprazole group (1.6%) than the placebo group (0.5%). Orthostasis was reported as an AE in 0.6% of aripiprazole treated group vs none in placebo group. Changes in vital sign measurements were transient and not clinically meaningful after the first injection or subsequent injections with aripiprazole. There were no clinically significant differences in QTc across treatment groups at any timepoint.

5.2.2.4 Laboratory Tests

No clinically meaningful differences in change from baseline to 24 hours post injection for any serum chemistry or hematology parameters between the treatment groups. There was a higher incidence of increased fasting serum glucose in aripiprazole-treated patients than placebo-treated patients.

5.2.3 Conclusion Regarding Safety of IM Aripiprazole

Overall, this submission revealed safety findings of aripiprazole IM formulation consistent with the previously observed safety profile of oral tablets. Dr. Hearst pointed out in his review that there are

no new safety concerns that would prevent aripiprazole IM from being approved and I agree with his conclusion.

6.0 WORLD LITERATURE

The sponsor has indicated that they conducted an update to previously submitted literature searches for published articles published through 3/25/2005 pertaining to the safety and efficacy of aripiprazole. Dr. Hearst reviewed the reference list and agreed with the sponsor's conclusion that there were no reports found that would adversely affect the safety profile of IM aripiprazole.

7.0 FOREIGN REGULATORY ACTION

To my knowledge, this IM formulation is not approved for any indication in any country at this time. We may ask for an update on the regulatory status.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 3 study sites. DSI recommended that data from these inspected sites appear acceptable in support of this NDA. Inspectional findings did not seem to raise any major concern on integrity of study data.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed language has been modified. Our proposed labeling should be included in the action letter.

10.2 Foreign Labeling

At this time, I am not aware that aripirazole IM formulation is approved for the treatment of acute agitation associated with schizophrenia or bipolar I disorder anywhere else.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that aripiprazole IM formulation is effective and reasonably safe in the treatment of agitation associated with schizophrenia or bipolar I disorder. I recommend that we issue an approvable action letter with our labeling proposal. We may consider approval of this NDA provided that an agreement is reached between the sponsor and the Agency regarding the language in the labeling.

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

/s/

Ni Aye Khin
8/29/2006 12:06:00 PM
MEDICAL OFFICER

Appears This Way
On Original

CLINICAL REVIEW

Application Type	NDA 21-866
Submission Number	000
Submission Code	PN
Letter Date	11/29/2005
Stamp Date	11/30/2005
PDUFA Goal Date	9/30/2006
Reviewer Name	Earl D. Hearst, M.D.
Review Completion Date	8/14/06
Established Name	Aripiprazole Intramuscular
(Proposed) Trade Name	Abilify Intramuscular
Therapeutic Class	Antipsychotic
Applicant	BMS & Otsuka
Priority Designation	S
Formulation	Solution in Captisol
Dosing Regimen	—
Indication	acute agitation
Intended Population	Schizophrenia and Bi-Polar,Manic or Mixed

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend that ABILIFY Injection be approved for the treatment of acute agitation associated with schizophrenia or bipolar disorder, manic or mixed.

1.2 Recommendation on Postmarketing Actions

I have no recommendations at this time.

1.2.1 Risk Management Activity

I have no recommendations at this time.

1.2.2 Required Phase 4 Commitments

I have no recommendations at this time.

1.2.3 Other Phase 4 Requests

I have no recommendations at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical pharmacology program consisted of 3 completed studies: 1 absolute bioavailability study in healthy subjects (CN138016), 1 pharmacokinetic study in patients with schizophrenia (CN138017), and 1 pharmacokinetic interaction study (aripiprazole and lorazepam) in healthy subjects (CN138132). In addition, a limited number of plasma samples for the measurement of aripiprazole and dehydro-aripiprazole concentrations were obtained in the dose-ranging safety and efficacy study (CN138050). A limited number of samples were also obtained on patients with dementia in Study CN138131 to gather pharmacokinetic information on patients in this population, and pharmacokinetic results from this study are pending. An additional study [redacted] evaluating an investigational [redacted], is currently ongoing and is being conducted in patients [redacted] Data from this study are not included in this submission.

The efficacy portion of the clinical program for registration of this IM formulation consisted of 3 adequate and well-controlled studies demonstrating efficacy of IM aripiprazole in the treatment of patients with acute agitation associated with schizophrenia or schizoaffective disorder (2 studies), or bipolar I disorder, manic or mixed (1 study) (CN138012, CN138050) and

(CN138013) and 1 dose-tolerance study CN138131. The IM portions of these studies were 24 hours in duration.

1.3.2 Efficacy

The aripiprazole 10-mg IM dose showed efficacy on the primary and secondary outcome measures in both the schizophrenia studies and the bipolar I disorder study. The 5-mg and 15-mg aripiprazole doses also showed efficacy on the primary efficacy measure in both populations, and the haloperidol (CN138012, CN138050) and lorazepam (CN138013) doses were effective. In order to examine the effects of aripiprazole specifically on patients with schizophrenia (excluding patients with schizophreniform or schizoaffective disorder), data were similarly analyzed and similar results were obtained.

1.3.3 Safety

There are no new safety concerns that would prevent ABILIFY Injection from being approved.

1.3.4 Dosing Regimen and Administration

In Studies CN138012, CN138050, and CN138013, 3 injections were allowed per protocol and the number given was based on investigator judgment. The first injection was administered within 1 hour of the baseline evaluations. A second IM injection was given, if needed, at least 2 hours after the first injection followed by a third injection of study medication, if needed, at least 2 hours after the second injection. A second or third injection of study medication was permitted no later than 20 hours after the administration of the first injection of study medication In Study CN138131, 2 injections were required per the protocol.

1.3.5 Drug-Drug Interactions

One drug-interaction study was conducted using the IM formulation. Study CN138132 evaluated co-administration of IM aripiprazole (15 mg) and IM lorazepam (2 mg) in healthy subjects. Results showed that co-administration of IM aripiprazole and IM lorazepam had no effect on the pharmacokinetics of either compound. There was an interaction in the pharmacodynamics when aripiprazole and lorazepam were co-administered. The intensity of sedation was greater and the orthostatic hypotension observed was similar with the combination as compared to that observed with aripiprazole alone. In contrast, the intensity of sedation was similar and the orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone.

1.3.6 Special Populations

In the 2 schizophrenia studies (CN138012 and CN138050), the efficacy of aripiprazole was demonstrated across all subsets including the DSM-IV schizophrenia group, as evidenced by

statistically significant treatment comparisons versus placebo, except for patients with age > upper quartile, race of "other," and patients with an underlying diagnosis of schizophreniform; however, there were greater mean decreases from baseline in the aripiprazole group than the placebo group in these subpopulations.

In the bipolar I disorder study (CN138013), aripiprazole was found to be statistically significantly different than placebo on all subset analyses except for patients with race of black or "other," for patients with an underlying diagnosis of mixed, and for patients with a baseline PEC Score > median; however, the mean decreases from baseline in these subpopulations were greater in the aripiprazole group than the placebo group.

There were no statistically significant events for gender, according to the Breslow-Day tests.

When analyzed by race (whites versus blacks), results of the Breslow-Day tests showed a statistically significant result for blood pressure increased. The incidence of this AE for whites was 1.7% for aripiprazole-treated patients versus 0% for placebo-treated patients, while the trend was reversed for blacks: 0% for aripiprazole-treated patients versus 1.7% for placebo-treated patients

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

ABILIFY (aripiprazole), a dihydrocarbostyril (quinolinone) derivative, was discovered by Otsuka Pharmaceutical Co, Ltd (OPC) and was developed collaboratively by OPC and Bristol-Myers Squibb Company. Aripiprazole's efficacy in schizophrenia is thought to be mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors.

The intramuscular (IM) formulation was developed to treat acutely agitated patients who require an injection to relieve their symptoms. The injection (7.5 mg/mL) is a ready-to-use solution in Captisol which is immediately absorbed. The same drug substance (aripiprazole anhydrous) is used for the tablets and the injection.

2.2 Currently Available Treatment for Indications

There are a number of injectable anti-psychotic major tranquilizers used for acute agitation currently on the market.

2.3 Availability of Proposed Active Ingredient in the United States

ABILIFY® (aripiprazole) is a newer generation antipsychotic developed by Bristol-Myers Squibb Company (BMS) and Otsuka Pharmaceutical Company, Ltd (OPC). The oral-tablet formulation is approved and marketed in the United States (US), European Union (EU), other

European, Middle Eastern, Asian, and Latin American countries for the treatment of schizophrenia. ABILIFY tablets are also approved and marketed for the treatment of bipolar I disorder, manic or mixed, in the US and several other countries.

The aripiprazole IM formulation was developed to enable the appropriate treatment of acutely agitated patients who require an injection for rapid onset of action to relieve their symptoms. This is the first marketing application for this formulation.

2.4 Important Issues With Pharmacologically Related Products

N/A.

2.5 Presubmission Regulatory Activity

Reference is made to approved NDA 21-436 for ABILIFY Tablets and to Submission No. 223 (dated November 16, 1999) to IND 42, 776 in which the Division was informed of the collaborative agreement between Otsuka Pharmaceutical Co. Ltd. (OPC) and Bristol-Myers Squibb Company (BMS) such that BMS is delegated to act on behalf of OPC in correspondence with this Division.

Further reference is made to the following key interactions with the Division concerning the development program for this formulation:

-April 17, 2002 correspondence from the Division provided in lieu of an EOP2 meeting

-November 17, 2003 teleconference regarding the required nonclinical toxicology program for registration of this drug product

-June 9, 2004 pre-NDA meeting and

-July 27, 2004 discussion with Dr. Tom Oliver in which agreement was reached to cross-refer to NDA 21-436 for aripiprazole API in this NDA

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Chemical Name

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril
7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone

Generic Name (USAN, INN and JAN)

Aripiprazole

Trade Name

ABILIFY

ABILIFY (aripiprazole) Injection drug product for intramuscular (IM) use is a sterile ready-to-use (RTU) solution formulated to deliver 7.5 mg/mL of aripiprazole. The solution is described as clear and colorless. The commercial product is filled into —

Aripiprazole injection is a single-dose drug product intended for intramuscular (IM) administration using a sterile syringe and needle. Each vial of aripiprazole injection drug product contains a sufficient amount of overfill to ensure that the commercial presentation meets USP requirements for minimum fill and deliverable volume.

ABILIFY Injection is formulated as a 7.5 mg/mL solution in Captisol® (cyclodextrin), and they cross-refer to the Cydex DMF and amendments in support of the use of this noncompendial excipient. The sponsor seeks approv al of one presentation, a single-use vial containing an adequate amount of solution to deliver the recommended dose of — (actual amount 9.75 mg). In the clinical program, given the availability of the product strengths, and to preserve the blind, doses were rounded to the nearest tenth mL; hence the recommended dose of — ; was actually administered as 1.3 mL (or 9.75 mg). The sponsor believes this small difference is clinically insignificant and they are thus seeking approval of a recommended dose of —.

We have negotiated with the sponsor to clarify the package label and they have recently accepted our proposal of 6/6/2006. Their reply is below.

Reference is made to Submission No. 223 (dated November 16, 1999) and to Submission No. 233 (dated January 4, 2000) to IND 42, 776 in which the Division was informed of the collaborative agreement between Otsuka Pharmaceutical Co. Ltd. (OPC) and Bristol-Myers Squibb Company (BMS) such that BMS is delegated to act on behalf of OPC in correspondence with this Division. Further reference is made to NDA 21-866 for ABILIFY Injection, submitted November 29, 2005 and to the FDA Information Request Letter of June 6, 2006. In that letter, the Division requested changes to the proposed dosing instructions and product description for this formulation.

This amendment is submitted to address the FDA's Information Request Letter of June 6, 2006. To address the concerns about an accurate description and precision of the dosing instructions in labeling, we propose to change the recommended dose of ABILIFY Injection to 9.75 mg, administered as a 1.3 mL injection of the 7.5 mg/mL solution and that the effective dose range would be stated as 5.25 mg (0.7 mL)- 15 mg (2 mL). In addition, we propose to change the vial and carton label to describe the product as a 9.75 mg/1.3 mL vial and propose that the 7.5 mg/mL concentration be given less prominence. The proposed revisions to the USPI, cartons and labels are provided herewith for your review and input.

One recommendation in the June 6, 2006 letter was to remove reference to the '[redacted]statement on the proposed labels. We believe this is important information to include on the labels in order to differentiate this product from concentrates and other products, which according to USPI, could also be named as 'Injection' formulations, but require further dilution or reconstitution, unlike our product. We believe this description is useful and will help to avoid unnecessary questions from health care providers, especially given that other products used in this same clinical setting often require further dilution or reconstitution.

DMETS accepts their revision with the following exception.

Dosage and Administration Section, Administration of Abilify Injection Subsection: Remove the trailing zero presented in table 6. The use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol. The FDA in conjunction with the ISMP launched a campaign on June 14, 2006 to reduce medication mistakes caused by unclear medical abbreviations. Thus in order to comply with these recommendations, we request all trailing zeroes be removed from the insert.

In summary, DMETS recommends implementation of the container label revision outlined above in order to minimize potential user error.

3.2 Animal Pharmacology/Toxicology

The absorption of aripiprazole following IM dose of aripiprazole (administered as a solution in [redacted]) in rats, dogs, and monkeys was rapid. Peak aripiprazole plasma concentrations in dogs were observed at the first pharmacokinetic sampling point (approximately 10 min) post-dose.

Aripiprazole is highly bound to mouse, rat, rabbit, dog, monkey, and human sera (≥99.4% bound). Aripiprazole and/or its metabolites distribute extensively into rat tissues, including brain. The distribution of aripiprazole and its metabolites from the systemic circulation following IM administration is expected to be similar to that after an IV or oral dose.

Metabolism is the major mechanism of clearance for aripiprazole in humans and the animal species studied to date. Aripiprazole was found to be extensively metabolized by Phase I metabolic pathways that are mediated by CYP450 enzymes. In rats, monkeys, and humans, aripiprazole was metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. The metabolic profile including different metabolites and the underlying pathways was found to be qualitatively similar across the species tested, i.e. rats, monkeys, and humans. The metabolism of aripiprazole and the metabolism of some of its metabolites observed in the preclinical species studied after IM administration were the same as those identified after IV and oral administration.

In the 1 month toxicity studies in rats and monkeys in which the IM formulation was administered by the IV and IM routes, respectively, the systemic exposures to aripiprazole increased as a function of the aripiprazole dose in both species, and a minimal to modest accumulation was observed after 1 month of dosing. The multiples of human exposures to aripiprazole achieved at the higher doses investigated in rats, monkeys, pregnant rats, and pregnant rabbits during various toxicological assessments were either similar to or greater than those seen at the potentially highest dose in human subjects to be treated with IM aripiprazole (30 mg within 1 day). The long-term toxicity studies with oral aripiprazole previously conducted to support the ABILIFY oral tablet formulation also generally produced high animal:human exposure multiples.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical pharmacology program consisted of 3 completed studies: 1 absolute bioavailability study in healthy subjects (CN138016), 1 pharmacokinetic study in patients with schizophrenia (CN138017), and 1 pharmacokinetic interaction study (aripiprazole and lorazepam) in healthy subjects (CN138132). In addition, a limited number of plasma samples for the measurement of aripiprazole and dehydro-aripiprazole concentrations were obtained in the dose-ranging safety and efficacy study (CN138050). A limited number of samples were also obtained on patients with dementia in Study CN138131 to gather pharmacokinetic information on patients in this population, and pharmacokinetic results from this study are pending. An additional study evaluating an investigational is currently ongoing and is being conducted in patients Data from this study are not included in this submission.

The Phase 2/3 clinical studies that were conducted to support the registration of the aripiprazole IM formulation included 3 adequate and well-controlled, placebo-controlled studies and 1 dose-tolerance study. The IM portions of these studies were 24 hours in duration. In Studies CN138012, CN138050, and CN138013, 3 injections were allowed per protocol and the number given was based on investigator judgment. In Study CN138131, 2 injections were required per the protocol. Please see Tables of All Studies below.

Table 1.1.1A: Tabular Listing of Completed Clinical Pharmacology Studies With Aripiprazole IM Formulation

Study Number	Number of Study Centers/ Location/ Study Dates	Design	Study Objectives	Study Drugs	Randomized/ Completed	Gender/ Median Age (Range)	Inclusion/Exclusion Criteria	Endpoints[a]
CN138016	01 center/ US/ 12/00 - 02/01	Open-label, randomized, 3-period, 3-treatment crossover study balanced for carryover effects	To assess absolute bioavailability of aripiprazole after IM and oral dosing	Aripiprazole 5 mg oral tablet Aripiprazole 5 mg IM Aripiprazole 2 mg Intravenous (IV) Infusion	18/13	17 Males 1 Female 36 years (20-44)	Healthy subjects as determined by no clinically significant deviation from normal in medical history, physical exam, laboratory tests, and electrocardiograms (ECGs).	**Pharmacokinetic:** Cmax, Tmax, AUC(0-T), AUC(INF), T-HALF, F, CLT (IV only), VSS (IV only) **Safety:** Adverse events, laboratory tests, vital sign measurements, 12-lead ECGs.
CN138017	01 center/ US/ 05/00 - 12/00	Open-label, non-randomized, sequential group, escalating dose study	To assess safety, tolerability, pharmacokinetics, and pharmacodynamics of aripiprazole after either 4 days of once-daily IM administration or 3 multiple IM injections in the same day.	**Once-Daily IM for 4 Days:** Aripiprazole 1 mg Aripiprazole 3 mg Aripiprazole 7.5 mg Aripiprazole 15 mg Aripiprazole 30 mg **Three Injections on Day 1:** Aripiprazole3x7.5mg Aripiprazole 3x15mg Haloperidol 3x5 mg	32/31	26 Males 6 Females 39 years (24-50)	Subjects with a diagnosis of schizophrenia disorder who otherwise had no clinically significant deviation from normal in physical exam, laboratory tests, and ECGs.	**Pharmacokinetic:** Cmax, Tmax, AUC(TAU), Cmin **Pharmacodynamic:** Positive and Negative Syndrome Scales, Clinical Global Impression Scale. **Safety:** Adverse events (AEs), EPS assessments (Simpson-Angus Scale and Barnes Akathisia Rating Scale), laboratory tests, vital sign measurements, 12-lead ECGs

Table 1.1.1A: Tabular Listing of Completed Clinical Pharmacology Studies With Aripiprazole IM Formulation

Study Number	Number of Study Centers/ Location/ Study Dates	Design	Study Objectives	Study Drugs	Randomized/ Completed	Gender/ Median Age (Range)	Inclusion/Exclusion Criteria	Endpoints[a]
CN138132	2 centers/ 2 US 03/04 - 08/04	Double-blind, randomized, 2-group, 2-period crossover study with an initial randomized open-label training phase.	To estimate the effect of IM lorazepam on PK of IM aripiprazole as well as the effect of aripiprazole on PK of lorazepam, and to estimate the degree of sedation of co-administration of single IM doses of aripiprazole and lorazepam compared to each agent alone.	**Training Phase:** aripiprazole placebo + lorazepam 2 mg; aripiprazole 15 mg + lorazepam 2mg **Main Group :** aripiprazole 15 mg + lorazepam placebo; aripiprazole placebo + lorazepam 2 mg; aripiprazole 15 mg + lorazepam 2 mg	**Training Phase:** 6/6 **Main Group:** 40/30	**Training Phase:** 6 Males 24 years (22-44) **Main Group :** 35 Males 5 Females 24 years (19-45)	Healthy subjects as determined by no clinically significant deviation from normal in medical history, physical exam, laboratory tests, and ECGs.	**Pharmacokinetic:** Cmax, Tmax, AUC(0-T), AUC(INF), T-HALF **Pharmacodynamic:** Observer's Assessment of Alertness/Sedation scale **Safety:** Adverse events, laboratory tests, vital sign measurements, pulse oximetry measurements, physical exam, 12-lead ECGs.

[a] AUC(0-T): area under plasma concentration-time curve from time zero to the last quantifiable time-point, AUC(INF): area under plasma concentration-time curve extrapolated to infinity, AUC(TAU); area under plasma concentration-time curve over a dosing interval, CLT: total body clearance, Cmax: peak plasma concentration, F: absolute bioavailability, T-HALF: terminal elimination half-life, Tmax: time to reach Cmax, VSS: volume of distribution at steady-state

Table 1.1.1B: Tabular Listing of Ongoing Clinical Pharmacology Study With Aripiprazole IM Formulation

Study Number	Number of Study Centers/ Location/ Study Dates	Design	Study Objective	Study Drugs	Randomized/ Completed[a]	Gender/ Median Age (Range)	Inclusion/ Exclusion Criteria	Endpoints[b]

[a] As of July 28, 2005.

[b] AUC(0-T): area under plasma concentration-time curve from time zero to the last quantifiable time-point, AUC(INF): area under plasma concentration-time curve extrapolated to infinity, Cmax: peak plasma concentration, T-HALF: terminal elimination half-life, Tmax: time to reach Cmax

4.2 Tables of Clinical Studies

Table 1.1.2: Tabular Listing of Completed Phase 2/3 IM Studies

Study Number	Number of Study Centers/ Location/ Study Dates	Design	Study Objectives	Study Drugs	Randomized/ Treated	Gender/ Median Age (Range)	Diagnosis/ Inclusion Criteria	Safety Endpoints
CN138050	50 centers/ 30 US 20 non-US/ 4/02 - 1/03	Randomized, double-blind, dose-ranging IM study comparing 4 fixed doses of aripiprazole (1, 5, 10, 15 mg per single injection) and 1 dose of haloperidol with placebo over 24 hours. Patients could receive up to 3 injections, , based on investigator judgment.	Efficacy, safety, and limited sampling for PK analysis	Aripiprazole 1 mg Aripiprazole 5 mg Aripiprazole 10 mg Aripiprazole 15 mg Haloperidol 7.5 mg Placebo	57/56 63/62 57/56 58/58 60/57 62/61	214 Males 143 Females 42 years (18-66)	Acute agitation in patients with schizophrenia, schizoaffective, or schizophreniform disorder PEC: at least 2 components ≥4 and sum of 5 components ≥15 but ≤ 32	AEs, EPS-related AEs, sedation-related and injection site reaction related AEs, Simpson-Angus Scale, Barnes Akathisia Rating Scale, laboratory tests, vital sign measurements, 12-lead ECGs (standard and ambulatory)
CN138012	68 centers/ 40 US 28 non-US 12/03 - 6/04	Randomized, double-blind, IM study comparing 1 fixed dose of aripiprazole (10 mg per single injection) and 1 dose of haloperidol with placebo over 24 hours. Patients could receive up to 3 injections., , based on investigator judgment. This was followed by 4 days of oral-tablet aripiprazole or oral-capsule haloperidol.	Efficacy and safety	IM: Aripiprazole 10 mg Haloperidol 6.5 mg Placebo **Number Transitioned to 4-Day Oral Phase** Aripiprazole 15 mg Haloperidol 10 mg	 175/175 185/183 88/87 229[a] 151	275 Males 173 Females 42 (18-69)	Acute agitation in patients with schizophrenia or schizoaffective disorder PEC: at least 2 components ≥4 and sum of 5 components ≥15 but ≤ 32	AEs, EPS-related AEs, sedation-related and injection site reaction related AEs, Simpson-Angus Scale, Barnes Akathisia Rating Scale, laboratory tests, vital sign measurements, 12-lead ECGs (standard and ambulatory)

Table 1.1.2: Tabular Listing of Completed Phase 2/3 IM Studies

Study Number	Number of Study Centers/ Location/ Study Dates	Design	Study Objectives	Study Drugs	Randomized/ Treated	Gender/ Median Age (Range)	Diagnosis/ Inclusion Criteria	Safety Endpoints
CN138013	37 centers/ 35 US 2 non-US 11/03 - 6/04	Randomized, double-blind, IM study comparing 2 fixed doses of aripiprazole (10 and 15 mg per single dose) and 1 dose of lorazepam with placebo over 24 hours. Patients could receive up to 3 injections, based on investigator judgment.	Efficacy and safety	Aripiprazole 10 mg Aripiprazole 15 mg Lorazepam 2 mg Placebo	78/75 78/75 70/69 75/72	156 Males 145 Females 41 years (18-79)	Acute agitation in patients with bipolar I disorder, manic or mixed PEC: at least 2 components ≥4 and sum of 5 components ≥15 but ≤ 32	AEs, EPS-related AEs, sedation-related and injection site reaction related AEs, Simpson-Angus Scale, Barnes Akathisia Rating Scale, laboratory tests, vital sign measurements, 12-lead ECGs (standard and ambulatory)
CN138131	16 US centers/ 12/03 - ongoing	Double-blind, placebo-controlled pilot study of tolerability of IM aripiprazole versus placebo in 3 patient cohorts. Patients were required per the protocol to receive 2 injections.	Assess tolerability and determine maximum tolerated dose, and limited[b] sampling for PK analysis	Cohort 1: aripiprazole 5 mg (2 x 2.5 mg) Cohort 2: aripiprazole 10 mg (2 x 5 mg) Cohort 3: aripiprazole 15 mg (first injection 10 mg; second 5 mg) Total Placebo for 3 Cohorts	12/12 78/76 13/15[c] 26/25	46 Males 83 Females 80 years (56 - 95)	Acute agitation in patients with Alzheimer's, vascular or mixed dementia	AEs, EPS-related AEs, sedation-related and injection site reaction related AEs, Mini Mental State Examination, Simpson-Angus Scale, Barnes Akathisia Rating Scale, laboratory tests, vital sign measurements, 12-lead ECGs (standard and ambulatory)

[a] Includes patients previously treated with aripiprazole and placebo in the IM Phase

[b] Samples were obtained on the first 45 patients from Cohorts 1, 2, and 3. Results from this study are pending.

[c] Two patients who were randomized to receive 10 mg (2 x 5 mg) received 15 mg (2 x 7.5 mg) instead.

US = United States

4.3 Review Strategy

The majority of my review focuses on the three double-blind efficacy studies CN138012, CN138050, and CN138013 listed above.

4.4 Data Quality and Integrity

In each of the studies in the aripiprazole IM clinical program, some protocol deviations and violations occurred, but were considered not to have affected the overall results of the studies. In addition, in Study CN138050, some planned pharmacokinetic sample collection times were missed, and sampling labeling errors occurred, which had an impact on the planned population pharmacokinetic assessment. Of the 357 plasma samples received by the analytical laboratory for determination of aripiprazole and dehydro-aripiprazole concentrations, 114 plasma samples were labeled with identical labels to at least 1 other sample (ie, 1 or more other samples had the same subject identification, nominal time, and unique sample code). An additional 40 plasma samples did not have complete information on either the plasma tube label and/or the case report form. However, in many instances, the plasma tube labels had been hand-annotated with information that matched subject identification and blood collection time and date data on the case report forms which allowed the identity of the individual sample to be determined. Overall, plasma samples for 13 patients in the 1-mg aripiprazole group (51 plasma samples), 14 patients in the 5-mg aripiprazole group (57 plasma samples), 12 patients in the 10-mg aripiprazole group (50 plasma samples), 15 patients in the 15-mg aripiprazole group (58 plasma samples), and for 4 patients randomized to the placebo group who received aripiprazole as rescue therapy (23 samples) were suitable for analysis. These 239 samples from 58 patients were analyzed for aripiprazole and dehydro-aripiprazole concentrations. These labeling errors were limited to the pharmacokinetic samples.

Due to the limited size of the plasma concentration-time data set and the high between-subject variability, the protocol specified analyses between the plasma concentrations and change from baseline in Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) score, and a population pharmacokinetic analysis to identify potential covariates associated with the disposition of aripiprazole IM were not performed.

4.5 Compliance with Good Clinical Practices

The trials included in this submission were performed in accordance with the principles of Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH). The trials, including those conducted outside the EU, were performed to meet the ethical requirements of Directive 2001/20/EC.

We received inspections reports from DSI which are reproduced in part below.

The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. Dr. Tam K. Tran-Johnson's site was selected for inspection due to large enrollment, and without this site the 5 mg arm of study # CN138050 is not statistically significant. Dr. Bum Soo Lee's and Dr. Michael Lesem's sites were selected for inspection due to large enrollments in both study numbers CN138012 and CN 1388013. The following protocols were audited:

#CN138012 entitled "A Randomized, Double-Blind Comparison of the Efficacy and Safety of Aripiprazole Intramuscular Formula, Haloperidol, or Placebo in the Treatment of Acutely Agitated Patients with a Diagnosis of Schizophrenia or Schizoaffective Disorder."
#CN138013 entitled "A Randomized, Double-Blind Comparison of the Efficacy and Safety of Aripiprazole Intramuscular Formula, Lorazepam, or Placebo in the Treatment of Acutely Agitated Patients Diagnosed with Bipolar I Disorder, Manic or Mixed."
#CN138050 entitled "A Randomized, Double-Blind, Dose-Ranging Study of Intramuscular Aripiprazole in the Treatment of Acute Agitation in Patients with a Diagnosis of Schizophrenia, Schizoaffective, or Schizophreniform Disorder."

As noted above, inspection of Drs. Tran-Johnson, Lesem, and Lee revealed that these investigators appear to have conducted the studies noted in accordance with FDA regulations. Data from these three clinical investigators are acceptable in support of NDA 21-866.

Sherbet Samuels, R.N., M.P.H.

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

4.6 Financial Disclosures

In compliance with 21 CFR Part 54.2 Financial Disclosure for Clinical Investigators, Bristol-Myers Squibb Company requested statements of financial interests and arrangements from a total of 221 investigators and 1461 subinvestigators in studies BMS CN138-012, -013, -016, -017, -050, -131 and -132.

Letters and forms to disclose financial arrangements were mailed with prepaid return mailers to the following:

CN138-012: 82 investigators and 455 subinvestigators
CN138-013: 54 investigators and 424 subinvestigators
CN138-016: 1 investigator and 1 subinvestigator
CN138-017: 1 investigator and 12 subinvestigators
CN138-050: 61 investigators and 416 subinvestigators
CN138-131: 20 investigators and 147 subinvestigators

CN138-132: 2 investigators and 6 subinvestigators

As of September 16, 2005 They have received a total of 221 statements of the 221 investigators, and 2 had disclosable income. They have received a total of 1453 statements of the 1461 subinvestigators. 1 individual had disclosable information. There are a total of 8 responses that have not been received to date.

I have reviewed these disclosures and believe they are acceptable.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The geometric mean Cmax and AUC values for aripiprazole and dehydro-aripiprazole following 1 to 45 mg intramuscular dosing appeared to increase approximately proportional to the increment in dose.

Overall, the pharmacokinetics of aripiprazole following intramuscular administration were generally similar to those observed after oral dosing.

ABILIFY administered intramuscularly distributes completely and rapidly. In 2 pharmacokinetic studies of aripiprazole injection administered intramuscularly to healthy subjects, the median times to the peak plasma concentrations were 1 and 3 hours. A 5-mg intramuscular injection of aripiprazole had an absolute bioavailability of 100%. The geometric mean maximum concentration achieved after an intramuscular dose was on average 19% higher than the Cmax of the oral tablet. While the systemic exposure was generally similar between aripiprazole injection given intramuscularly and after oral tablet administration, the aripiprazole AUC in the first 2 hours after an intramuscular injection was 90% greater than the AUC after the same dose as a tablet. In stable patients with schizophrenia or schizoaffective disorder, the pharmacokinetics of aripiprazole after intramuscular administration were linear over a dose range of 1 to 45 mg. Over this dose range for each mg of aripiprazole injected, the geometric mean Cmax and AUC over 24 hours were 3.7 ng/mL and 62.3 ng•h/mL, respectively. Although the metabolism of aripiprazole injection was not systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

5.2 Pharmacodynamics

The studies demonstrated that a single 10mg dose of IM aripiprazole was effective for acute relief of agitation.

5.3 Exposure-Response Relationships

For those patients who did not respond adequately to a single dose, a second dose, administered at 2 to 20 hours after the first dose, demonstrated continued and significant clinical improvement with an acceptable safety profile.

Doses of 5-, 10-, and 15-mg IM aripiprazole were effective in treating agitation associated with schizophrenia or schizoaffective disorder. The 10- and 15-mg doses were effective in treating agitation associated with bipolar I disorder, manic or mixed. The proposed recommended dose of 10-mg IM aripiprazole was initially established as effective in 1 dose-ranging study in schizophrenia or schizoaffective disorder and was confirmed as effective in 2 subsequent studies: 1 in schizophrenia or schizoaffective disorder and the other in bipolar I disorder. No increase in efficacy over the 10-mg dose was seen with the 15-mg dose in the 2 clinical trials where it was studied. The recommendation of 10-mg IM aripiprazole was supported by the efficacy on the PEC scale and by consistent demonstration of efficacy on a CGI-I key secondary measure, as well as across the other secondary measures (CGI-S, ACES, and CABS) across and within studies. Please see efficacy tables.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor would like ABILIFY injection to be indicated for the treatment of acute agitation associated with schizophrenia or bipolar disorder, manic or mixed.

6.1.1 Methods

The selected study populations were representative of agitated patients with schizophrenia, schizoaffective, or schizophreniform disorder or bipolar I disorder (manic or mixed), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, and, thus, were appropriate for the purpose of evaluating the efficacy and safety of IM aripiprazole in these populations. Schizophrenia only populations were used to establish efficacy in that population.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint, the mean change from baseline to 2 hours post first IM injection in the PEC Score, was evaluated using analysis of covariance (ANCOVA), with baseline PEC as the covariate, treatment as 1 main effect, and country (CN138012, CN138050) or study center (CN138013) as the other main effect.

6.1.3 Study Design

The IM clinical efficacy program consisted of 3 adequate and well-controlled, placebo-controlled studies:

- 2 studies were conducted in agitated patients with schizophrenia, schizoaffective, or schizophreniform disorder. Study CN138050 evaluated 4 doses (1 mg, 5 mg, 10 mg, 15 mg) of IM aripiprazole, haloperidol (7.5 mg), and placebo in agitated patients with schizophrenia, schizoaffective, or schizophreniform disorder. Based on the results from Study CN138050, the second study (CN138012) evaluated a dose of 10-mg IM aripiprazole, haloperidol (6.5 mg), and placebo in patients with schizophrenia or schizoaffective disorder, followed by 4 days of the aripiprazole oral-tablet formulation or haloperidol oral capsules
- 1 study was conducted in agitated patients with bipolar I disorder, manic or mixed. This study (CN138013) evaluated 2 doses of IM aripiprazole (10 mg and 15 mg), lorazepam (2 mg), and placebo

The design of the 3 adequate and well-controlled studies was similar, with the exception that Study CN138012 had 2 phases: a 24-Hour IM Phase and a 4-Day Oral Phase (patients completing the IM phase continued on oral-tablet aripiprazole or haloperidol for 4 days).

For entry into the studies, patients were required at baseline to have the following scores on the Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) scale: at least 2 components with scores ≥ 4 and the sum of 5 components with scores of ≥ 15 but ≤ 32. The studies began with a 2-hour screening period (maximum 12 hours in CN138012 and CN138013; maximum 24 hours in CN138050) before the first dose. The first injection was administered within 1 hour of the baseline evaluations. A second IM injection was given, if needed, at least 2 hours after the first injection followed by a third injection of study medication, if needed, at least 2 hours after the second injection. A second or third injection of study medication was permitted no later than 20 hours after the administration of the first injection of study medication. Rescue medication (lorazepam or other benzodiazepine) was permitted in Studies CN138012 and CN138050 at least 60 minutes after the second injection of study medication, if needed, and whenever needed thereafter, during the remainder of the 24-hour period. Patients were evaluated as an inpatient for a period of 24 hours after the administration of the first IM dose of study medication.

The primary efficacy endpoint for the 3 studies was the mean change from baseline to 2 hours after the first IM injection in the PEC Total Score. Secondary measures were the mean Clinical Global Impressions (CGI) Improvement Score (CGI-I) at 2 hours post first IM injection, and the mean change from baseline to 2 hours after the first injection in the CGI Severity of Illness Score (CGI-S), the Agitation-Calmness Evaluation Scale (ACES), and the Corrigan Agitated Behavior Scale[1] (CABS). In addition, PEC and CGI response rates were analyzed (a responder was defined as a patient who had $\geq 40\%$ decrease from baseline in the PEC or CGI).

Please see table of all studies in section 4.1.and study synopsis in appendix for additional details.

6.1.4 Efficacy Findings

This section presents the efficacy results of the 3 adequate and well-controlled studies. The primary efficacy endpoint was the mean change from baseline to 2 hours post first IM injection in the PEC Score. Secondary and other efficacy analyses were conducted in order to support the findings of the PEC scale and included the mean CGI-I Score at 2 hours post first IM injection, and the mean change from baseline to 2 hours post first IM injection in the CGI-S, ACES, and CABS Scores. In addition, PEC and CGI response rates were analyzed at 2 hours post first IM injection (a responder was defined as a patient who had ≥ 40% decrease from baseline in the PEC or CGI).

The PEC scale is used to assess agitation/disturbed behaviors including hostility, extreme excitement, poor impulse control, tension, and uncooperativeness. The scale contains the common core features of other agitation scales and has applicability across different patient populations. All items are rated on a 1 to 7 scale, with 1 being absent (the best score) and 7 being extreme (the worst score). A negative change score indicates improvement.

The CGI scale is designed to assess global severity of illness and change in the clinical condition over time. The scale consists of 3 subscales, but only 2 subscales were used in the IM program: the Severity of Illness subscale (CGI-S) and the Global Improvement subscale (CGI-I). The CGI-S is rated on a 7-point scale, with 1 being normal, not ill and 7 being among the most extremely ill patients. The CGI-I is also a 7-point scale, with 1 being very much improved and 7 being very much worse.

The ACES is a scale used to assess a patient's level of agitation. It is a 9-point scale that differentiates between agitation, calm, and sleep states, with 1 being marked agitation, 4 being normal, and 9 being unarousable.

The CABS rates the degree to which specific behaviors (eg, short attention span, uncooperative, sudden mood changes) are observed in acute agitation and consists of 14 items. Each item is rated on a 1 to 4 scale (1 = absent, 4 = extreme).

Overall Summary of Efficacy Results

The aripiprazole 10-mg IM dose showed efficacy on the primary and secondary outcome measures in both the schizophrenia studies and the bipolar I disorder study (Table 3.2A-1). The 5-mg and 15-mg aripiprazole doses also showed efficacy on the primary efficacy measure in both populations, and the haloperidol (CN138012, CN138050) and lorazepam (CN138013) doses were effective. **In order to examine the effects of aripiprazole specifically on patients with schizophrenia (excluding patients with schizophreniform or schizoaffective disorder), data were similarly analyzed and similar results were obtained (Table 3.2A-2).**

In study CN138050, a hierarchical testing procedure was applied to the key secondary efficacy measures. The statistical significance flags (** denotes p-value ≤ 0.01, * denotes p-value ≤ 0.05) for the secondary efficacy measures in Table 3.2A-1 do not take this into account and thus are

unadjusted for the hierarchy defined in CN138050. If this is accounted for, only the 10-mg aripiprazole dose was statistically superior to placebo on all the secondary measures. While the treatment comparisons for the 5-mg and 15-mg doses did not meet the sequential testing criteria because of failure on the ACES Score, both doses showed robust efficacy compared with placebo on the CABS Score (5 mg, $p=0.007$; 15 mg, $p<0.001$), the CGI-I Score (5 mg and 15 mg, $p<0.001$), and the CGI-S Score (5 mg, $p=0.034$: 15mg, $p=0.003$).

Doses of 5-, 10-, and 15-mg IM aripiprazole were effective in treating agitation associated with schizophrenia or schizoaffective disorder. The 10- and 15-mg doses were effective in treating agitation associated with bipolar I disorder, manic or mixed. The proposed recommended dose of 10-mg IM aripiprazole was initially established as effective in 1 dose-ranging study in schizophrenia or schizoaffective disorder and was confirmed as effective in 2 subsequent studies: 1 in schizophrenia or schizoaffective disorder and the other in bipolar I disorder. No increase in efficacy over the 10-mg dose was seen with the 15-mg dose in the 2 clinical trials where it was studied. The recommendation of 10-mg IM aripiprazole was supported by the efficacy on the PEC scale and by consistent demonstration of efficacy on a CGI-I key secondary measure, as well as across the other secondary measures (CGI-S, ACES, and CABS) across and within studies.

Table 3.2A-1: Efficacy Results at 2 Hours Post First IM Injection: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample

Study/ Treatment		N	PEC Score Mean Change	CGI-I Score Mean	CGI-S Score Mean Change	ACES Score Mean Change	CABS Score Mean Change
Schizophrenia, Schizoaffective							
CN138012	Placebo	88	-4.78	3.10	-0.71	0.83	-4.51
	Aripiprazole 10mg	173	-7.27**	2.42**	-1.16**	1.41*	-8.03**
	Haloperidol 6.5mg	184	-7.75**	2.37**	-1.17**	1.64**	-8.28**
Schizophrenia, Schizoaffective, Schizophreniform							
CN138050	Placebo	61	-3.28	3.46	-0.42	0.66	-2.95
	Aripiprazole 1mg	56	-4.47	3.07*	-0.63	0.65	-5.16
	Aripiprazole 5mg	62	-5.65**	2.82**	-0.82*	1.01	-5.97**
	Aripiprazole 10mg	56	-6.69**	2.64**	-1.08**	1.50**	-7.08**
	Aripiprazole 15mg	58	-5.72**	2.66**	-0.99**	0.99	-7.04**
	Haloperidol 7.5mg	57	-6.38**	2.72**	-0.91*	1.50**	-8.13**
Bipolar 1 Disorder							
CN138013	Placebo	73	-5.76	3.05	-0.94	1.00	-6.37
	Aripiprazole 10mg	75	-8.74**	2.17**	-1.48**	1.87**	-9.60**
	Aripiprazole 15mg	75	-8.67**	2.33**	-1.34*	2.32**	-9.08**
	Lorazepam 2mg	68	-9.57**	2.10**	-1.61**	2.34**	-10.35**

** p <= 0.01, * p <= 0.05

ANCOVA model, controlling for treatment, country (CN138-012,CN138-050) or pooled study center (CN138-013), and baseline value, is used for mean change from baseline comparisons.

CMH row means score test controlling for treatment, country (CN138-012,CN138-050) or pooled study center (CN138-013), is used for CGI-I score means.

Table 3.2A-2: Efficacy Results at 2 Hours Post First IM Injection: IM Placebo-Controlled Studies, Schizophrenia Only (CN138012, CN138050), LOCF Data Set, Efficacy Sample

Study/ Treatment		N	PEC Score Mean Change	CGI-I Score Mean	CGI-S Score Mean Change	ACES Score Mean Change	CABS Score Mean Change
CN138012	Placebo	65	-5.68	3.03	-0.85	1.20	-5.52
	Aripiprazole 10mg	123	-7.99**	2.41**	-1.29*	1.76*	-8.83**
	Haloperidol 6.5mg	134	-8.25**	2.39**	-1.30*	1.99**	-9.01**
CN138050	Placebo	39	-4.78	3.38	-0.56	0.99	-4.35
	Aripiprazole 1mg	30	-4.87	3.30	-0.53	0.79	-5.74
	Aripiprazole 5mg	40	-6.94*	2.65**	-0.95	1.21	-7.13*
	Aripiprazole 10mg	36	-7.82**	2.67**	-1.10*	1.84**	-7.51*
	Aripiprazole 15mg	44	-6.94*	2.68**	-1.14*	1.30	-7.47*
	Haloperidol 7.5mg	43	-7.32*	2.65**	-0.98	1.74*	-8.58**

** p <= 0.01, * p <= 0.05

ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline comparisons.

CMH row means score test controlling for treatment is used for CGI-I score means.

PEC Total Score

In the 2 studies in schizophrenia (CN138012, CN138050) and the study in bipolar I disorder (CN138013), the treatment comparisons for the 10-mg aripiprazole dose versus placebo were statistically significant ($p < 0.001$). In addition, the treatment comparisons for the 5-mg ($p = 0.008$) and 15-mg ($p = 0.007$) aripiprazole doses and 7.5-mg haloperidol dose ($p = 0.001$) in Study CN138050, the 6.5-mg haloperidol dose ($p< 0.001$) in Study CN138012, and the 15-mg aripiprazole dose ($p < 0.001$) and 2-mg lorazepam dose ($p < 0.001$) in Study CN138013, were statistically significant. The 1-mg aripiprazole dose, included as the no-effect dose, did not separate from placebo in Study CN138050 ($p = 0.191$) (Table 3.2B-1).

When data only for patients with a diagnosis of schizophrenia were analyzed separately, similar results were obtained. The treatment comparison for the 10-mg aripiprazole dose was statistically significant versus placebo in Study CN138012 ($p = 0.003$) and in Study CN138050 ($p = 0.008$), and the 5-mg ($p = 0.050$) and 15-mg ($p = 0.045$) aripiprazole doses were also statistically significantly different versus placebo in Study CN138050 (Table 3.2B-2). The haloperidol doses in these studies were also significantly better than placebo (6.5 mg: $p = 0.001$; 7.5 mg: $p = 0.020$).

Table 3.2B-1: Mean Change from Baseline to 2 Hours Post First IM Injection in PEC Score: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample

Study/ Treatment		N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
Schizophrenia, Schizoaffective						
CN138012	Placebo	88	19.32	-4.78	--	--
	Aripiprazole 10mg	173	19.25	-7.27	-2.48 (-3.77,-1.19)	<0.001
	Haloperidol 6.5mg	184	19.32	-7.75	-2.96 (-4.24,-1.69)	<0.001
Schizophrenia, Schizoaffective, Schizophreniform						
CN138050	Placebo	61	19.21	-3.28	--	--
	Aripiprazole 1mg	56	19.16	-4.47	-1.19 (-2.96, 0.59)	0.191
	Aripiprazole 5mg	62	19.46	-5.65	-2.37 (-4.10,-0.63)	0.008
	Aripiprazole 10mg	56	19.44	-6.69	-3.40 (-5.18,-1.62)	<0.001
	Aripiprazole 15mg	58	19.34	-5.72	-2.44 (-4.21,-0.68)	0.007
	Haloperidol 7.5mg	57	18.89	-6.38	-3.09 (-4.87,-1.32)	0.001
Bipolar 1 Disorder						
CN138013	Placebo	73	18.04	-5.76	--	--
	Aripiprazole 10mg	75	18.84	-8.74	-2.99 (-4.53,-1.44)	<0.001
	Aripiprazole 15mg	75	18.25	-8.67	-2.91 (-4.44,-1.38)	<0.001
	Lorazepam 2mg	68	18.47	-9.57	-3.81 (-5.38,-2.24)	<0.001

ANCOVA model, controlling for treatment, country (CN138-012,CN138-050) or pooled study center (CN138-013), and baseline value, is used for mean change from baseline comparisons.

Number and Percentage of PEC Responders: IM Placebo-Controlled Study (CN138013), LOCF Data Set, Efficacy Sample

		Number(%) PEC Responders(a)				
	N	30 Minutes	45 Minutes	60 Minutes	90 Minutes	120 Minutes
CN138013						
Placebo	73	13(18)	19(26)	27(37)	30(41)	27(37)
Aripiprazole 10mg	75	9(12)	28(37)	32(43)	43(57)*	52(69)**
Aripiprazole 15mg	75	10(13)	26(35)	36(48)	39(52)	47(63)**
Lorazepam 2mg	68	13(19)	20(29)	29(43)	42(62)*	47(69)**

(a) PEC response defined as >=40% decrease from baseline in PEC Score.
** p <= 0.01, * p <= 0.05
CMH general association test controlling for treatment and pooled study center.

Onset of Efficacy, PEC Score: Mean Change from Baseline to 2 Hours Post First IM Injection: IM Placebo-Controlled Study (CN138013), LOCF Data Set, Efficacy Sample

			PEC Score				
			30 Minutes	45 Minutes	60 Minutes	90 Minutes	120 Minutes
Study/ Treatment		N	Mean Change	Mean Change	Mean Change	Mean Change	Mean Change
CN138013	Placebo	73	-3.02	-4.14	-5.29	-6.08	-5.76
	Aripiprazole 10mg	75	-2.82	-5.14	-6.36	-8.09**	-8.74**
	Aripiprazole 15mg	75	-2.70	-5.18	-6.87*	-7.87*	-8.67**
	Lorazepam 2mg	68	-3.57	-5.58*	-7.07*	-8.80**	-9.57**

** p <= 0.01, * p <= 0.05

ANCOVA model, controlling for treatment, pooled study center and baseline value, is used for mean change from baseline comp

Table 3.2B-2: Mean Change from Baseline to 2 Hours Post First IM Injection in PEC Score: IM Placebo-Controlled Studies, Schizophrenia Population Only (CN138012, CN138050), LOCF Data Set, Efficacy Sample

Study/ Treatment		N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
CN138012	Placebo	65	18.89	-5.68	--	--
	Aripiprazole 10mg	123	18.79	-7.99	-2.30 (-3.80,-0.81)	0.003
	Haloperidol 6.5mg	134	18.78	-8.25	-2.57 (-4.05,-1.09)	0.001
CN138050	Placebo	39	19.46	-4.78	--	--
	Aripiprazole 1mg	30	18.87	-4.87	-0.10 (-2.44, 2.24)	0.935
	Aripiprazole 5mg	40	19.08	-6.94	-2.17 (-4.33,-0.00)	0.050
	Aripiprazole 10mg	36	18.97	-7.82	-3.05 (-5.27,-0.82)	0.008
	Aripiprazole 15mg	44	19.20	-6.94	-2.16 (-4.28,-0.05)	0.045
	Haloperidol 7.5mg	43	18.67	-7.32	-2.54 (-4.67,-0.41)	0.020

ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline comparisons.

Please see additional efficacy data in appendix section 10.2.

6.1.5 Clinical Microbiology

N/A

6.1.6 Efficacy Conclusions

The study drug was effective in controlling acute agitation in all studies with Schizophrenia and Manic-Depressive patients for doses of 5mg, 10mg or15mg. Please see tables above.

Yeh-Fong Chen, Ph D. did the statistical analysis and her conclusion is in quotes below.

"STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

For all three studies, this reviewer confirmed the sponsor's analysis results on the primary endpoint and all secondary endpoints. However, for two studies that patients' agitation due to schizophrenia, schizoaffective or schizophreniform disorder, the sponsor did not provide analysis results on other secondary endpoints for patients with only schizophrenia. The model they used to analyze for the primary endpoint also excluded the country factor, although this reviewer found that the results were consistent whether or not the factor of country was included in the model.

CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted three efficacy studies to seek the approval for the efficacy and safety of the IM injection formulation as a treatment of agitation in patients with schizophrenia or bipolar I disorder. After evaluation, this reviewer agreed with the sponsor that 10-mg IM aripiprazole was confirmed as effective in all three studies, in terms of the primary endpoint, PEC total score and on the key secondary endpoint CGI- Improvement score if it was determined that the CGI-Improvement as the pre-specified key secondary endpoint for the multiple dosed schizophrenia study (Study CN138050)."

The sponsor's efficacy summary is reproduced below in italics.

***EFFICACY**: The efficacy portion of the clinical program for registration of this IM formulation consisted of 3 adequate and well-controlled studies demonstrating robust efficacy of IM aripiprazole in the treatment of patients with acute agitation associated with schizophrenia or schizoaffective disorder (2 studies), or bipolar I disorder, manic or mixed (1 study):*

- *Schizophrenia or schizoaffective disorder (CN138012, CN138050): Efficacy was demonstrated by statistically significant improvement over placebo on the primary outcome measure, the mean change from baseline to 2 hours post injection on the PEC Score, and improvement as measured by the CGI-I. The 10-mg aripiprazole IM dose was shown to be*

non-inferior to 6.5-mg haloperidol IM in patients with agitation associated with schizophrenia or schizoaffective disorder, as measured by the mean change from baseline to 2 hours post initial IM injection in PEC Score. In addition, the 10-mg dose was statistically significantly better than placebo on each of the 5 individual items of disturbed behavior that comprised the PEC Score. Response rates were similar in both studies that enrolled agitated patients with schizophrenia (CN138012, CN138050): the 10-mg aripiprazole dose and the haloperidol doses demonstrated similar response rates at 2 hours post first IM injection.

- *Subgroup analyses showed that aripiprazole (5-, 10-, and 15-mg doses) also demonstrated efficacy in the subgroup of agitated patients with schizophrenia as demonstrated by significant improvement over placebo in the mean change from baseline to 2 hours post first IM injection in the PEC Score. The 10-mg aripiprazole IM dose was shown to be non-inferior to 6.5-mg haloperidol IM in the subpopulation of patients with an underlying diagnosis of schizophrenia, as measured by the mean change from baseline to 2 hours post initial IM injection in PEC Score.*
- *Bipolar I Disorder (CN138013): Efficacy was demonstrated by statistically significant improvement over placebo on the primary outcome measure, the mean change from baseline to 2 hours post injection on the PEC Score, and improvement as measured by the CGI-I. In addition, the 10-mg dose was statistically significantly better than placebo on each of the 5 individual items of disturbed behavior that comprised the PEC Score. Response rates for all 3 active treatment arms (10- and 15-mg aripiprazole and lorazepam) were also comparable.*

EFFICACY WITHOUT SEDATION:

- *Schizophrenia or schizoaffective disorder (CN138012, CN138050): Robust efficacy of IM aripiprazole was demonstrated in the agitated patients with schizophrenia or schizoaffective disorder who did not exhibit sedation during the first 2 hours of the studies (comprising the large majority of the population). This was evidenced by a statistically significant mean change relative to placebo from baseline to 2 hours post first IM injection in the PEC Score in the subpopulation of patients with low and moderate ACES Scores, and also in the subpopulation reported having no AEs related to sedation.*
- *Bipolar I Disorder (CN138013): Robust efficacy of IM aripiprazole was demonstrated in the agitated patients with bipolar disorder who did not exhibit sedation during the first 2 hours of the study (comprising the large majority of the population). This was evidenced by a statistically significant mean change relative to placebo from baseline to 2 hours post first IM injection in the PEC Score in the subpopulation of patients with low and moderate ACES Scores, and also in the subpopulation reported having no AEs related to sedation.*

***DOSAGE**: The proposed recommended dose of —— IM aripiprazole was confirmed as effective in all 3 studies. The recommendation of .— g IM aripiprazole is supported by the*

robust efficacy on the PEC Score and by consistent demonstration of efficacy on the CGI-I key secondary measure, as well as across the other secondary measures of CGI-S, ACES, and CABS.

- *Schizophrenia or schizoaffective disorder (CN138012, CN138050): 5-mg, 10-mg, and 15-mg doses of IM aripiprazole were shown to be effective in treating agitation associated with schizophrenia or schizoaffective disorder. The 5-mg dose did not show efficacy on the ACES at the prespecified 2 hour endpoint, and it showed statistically significant onset of effect in treating agitation associated with schizophrenia or schizoaffective disorder at a later time than the 10-mg dose. There was no observed increase in efficacy with the 15-mg dose.*
- *Bipolar I Disorder (CN138013): The 10-mg and 15-mg doses were shown to be effective in treating agitation associated with bipolar I disorder, manic or mixed. There was no observed increase in efficacy with the 15-mg dose.*

MULTIPLE DOSING:

- *Schizophrenia or schizoaffective disorder (CN138012, CN138050): While the studies were not prospectively designed specifically to assess efficacy of multiple doses of aripiprazole, in nonresponders who required a second IM injection for their agitation, the mean change in the PEC Scores for aripiprazole (10- and 15-mg doses) were statistically significant versus placebo. Efficacy was not hindered and continued to improve in patients who received up to 3 injections over 24 hours.*
- *Bipolar I Disorder (CN138013): While the studies were not prospectively designed specifically to assess efficacy of multiple doses of aripiprazole, in nonresponders who required a second IM injection for their agitation, the mean change in the PEC Scores for aripiprazole (10- and 15-mg doses) were statistically significant versus placebo. Efficacy was not hindered and continued to improve in patients who received up to 3 injections over 24 hours.*

TRANSITION FROM IM ARIPIPRAZOLE TO ORAL-TABLET ARIPIPRAZOLE IN STUDY CN138012:

- *Patients with schizophrenia or schizoaffective disorder who were treated for agitation with IM aripiprazole demonstrated successful transition from 1 day of IM aripiprazole dosing (10 mg) to 4 days of oral-tablet aripiprazole dosing (15 mg). This was demonstrated by the stable PEC Scores during and after the transition, along with other secondary measures.*

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The final analyses of the Phase II/III clinical trial data was based on the database lock for the last study , CN138131, which was April 27, 2005.

7.1.1 Deaths

Clinical Pharmacology Studies

There were no deaths reported in the clinical pharmacology studies.

Phase 2/3 Studies

There were 2 reports of death in patients who received study medication in the IM Phase 2/3 clinical program.

- Patient CN138013-48-309, a **41-year-old** male with bipolar I disorder (manic) with acute agitation and significant medical history of psoriasis, chronic obstructive pulmonary disease (COPD), tobacco use (1 pack per day), polysubstance drug abuse with no current use, a history of delirium tremens from cocaine and alcohol withdrawal and without reported history of suicidality, was randomized to 10-mg IM aripiprazole on Day 1. The patient received 2 doses of study therapy (20 mg total), completed the treatment, and returned to standard of care of alprazolam, divalproex sodium, olanzapine, and topiramate on Day 2, and was discharged from the hospital. **The following morning (Day 3), the patient was found deceased in bed at home.** The event was designated by the investigator as not likely related to study medication. There were no other adverse events ongoing at the time of the event. Medications taken within 14 days prior to the event include lorazepam, alprazolam, olanzapine, and topiramate. No clinically significant ECG findings (including QT_c), vital sign, or laboratory abnormalities were reported during the study period. Based on a full autopsy, the coroner's office classified the cause of death as undetermined. A therapeutic level of alprazolam (16.3 ng/mL) was found on blood toxicology screen at autopsy. The remainder of the toxicology panel was negative.

- Patient CN138131-28-7061, an **89-year old** female with mixed dementia since 2002 was randomized to double-blind intramuscular therapy (10 mg total daily dose of aripiprazole) on Day 1 [redacted]. Significant medical history includes blindness, retinal detachment, corneal transplant, cataract surgery, hypertension, transient ischemia attack (Sep 2003), gastric ulcer, GERD, constipation, mild renal insufficiency, partial hysterectomy, urinary retention, urinary tract infections, hypothyroidism, hypercholesterolemia, bilateral hip/knee replacements, gout, degenerative joint disease, torn rotator cuff, insomnia, depression secondary to dementia, allergy to paper tape, and carpal tunnel repair. The patient received 2 doses of intramuscular medication (5 mg each of aripiprazole) and completed the 24-hour study phase. On Day 13 (12 days after completing study treatment), the patient was hospitalized for delirium. The investigator rated the delirium as severe in intensity and not likely related to study medication. The delirium resolved on Day 20. On Day 25 (24 days after completing study treatment), the patient died due to organic dementia (Per death certificate). An autopsy was not done. The investigator rated the organic dementia as very

severe in intensity and not likely related to study treatment. There were no other ongoing adverse events reported for either event. Medications taken within 14 days of the events included acetylsalicylic acid, amlodipine, atenolol, allopurinol, escitalopram, acetaminophen/ hydocodone, trazodone, polyethylene glycol, lansoprazole, docusa levothyroxine, clonidine, fluorometholone, and gemfibrozil. There were no potentially clinically significant vital signs reported during the study period. A potentially clinically significant laboratory value for BUN of 31 mg/dL was noted at the 24-hour visit (normal range: 6-21 mg/dL, screening: 33 mg/dL). Potentially clinically significant ECG abnormalities are noted in the table below. Sinus tachycardia and 1st degree A-V block are noted at all visits including screening.

ECG Abnormalities

Study Visit[+] **(Post Dose 1)**	**PR interval (ms)**
Screening (Standard 12-lead)	203*
2 hour pre-dose	226
0.5 hour post dose	219*
1 hour post dose	208*
1.5 hours post dose	220*
2 hours post dose	226*
2.5 hours post dose	221*
3 hours post dose	210*
4 hours post dose	203*
12 hours post dose	217*
24 hours (Standard 12-lead) post dose	226*

+ Data from 12-lead ambulatory unless otherwise specified.
*Potentially Clinically Significant

Table 2.1.2.2: Deaths: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013, CN138131), Safety Sample

Relation Treat To Group	Patient Number	Age	G e n d e r	R a c e	Date/Time of AE Start	Date/Time of First Dosing	Number of Injections at AE Onset	Cumulative IM Dose(mg) of Active Drug at AE Onset	Date of Death
Severity	Adverse Event	Drug							
IM Arip	CN138013-48-309	41	M	W	[redacted]	UNK	[redacted]	2 Ari 20 mg	[redacted]
VERY SEVERE	DEATH	NOT LIKELY							
	CN138131-28-7061	89	F	W	[redacted]	:UNK	[redacted]	. 0 mg	[redacted]
VERY SEVERE	DEMENTIA	NOT LIKELY							

7.1.2 Other Serious Adverse Events

Clinical Pharmacology Studies:

There were no SAEs reported in Studies CN138016 and CN138017. One SAE was reported in the Main Group of Study CN138132. Subject CN138132-1-222, a 40-year old black female, experienced Grade 3 **neutropenia** that began on Day 27 after aripiprazole 15-mg treatment and lasted for 91 days. The subject was withdrawn from the study on what would have been Day 1 of Period 2 (prior to dosing with aripiprazole 15 mg + lorazepam 2 mg). The subject was dosed only during Period 1. The SAE was judged by the investigator to be possibly related to the study medication. During the following 3 months the subject continued to be followed, with complete blood counts obtained. The subject remained in good health, with leukocytes, absolute neutrophil counts, and relative neutrophils fluctuating between normal and mildly to moderate decreased values, but not reaching the level of neutropenia again. The subject refused a bone marrow biopsy and was discharged from the study with normal leukocytes, absolute neutrophil counts, and relative neutrophil values.

Phase 2/3 Studies

Thirty-two of the 1214 patients in the IM Safety Sample (CN138012, CN138050, CN138013, CN138131) experienced SAEs (Table 2.1.3.2). One SAE for a patient in the placebo group (CN138050-9-145) occurred after the third injection, which was 15-mg aripiprazole. Most events were related to patients' underlying psychiatric diseases, and only 1 event was considered by the investigators to be related to study medication (dystonia, 6.5-mg haloperidol). The narratives for these events may be found in the individual Clinical Study Reports and I have reviewed these.

Nine patients had events that were not related to the underlying psychiatric disease, and all were considered by the investigators to be not likely related or not related to study medication. There were 2 reported seizures: 1 in a placebo-treated patient (CN138050-9-145) who received aripiprazole for his third injection and 1 in a patient (CN138050-95-362) randomized to aripiprazole 10 mg who received 2 doses of study medication. One patient (CN138013-34-19) experienced an event of nephrolithiasis 20 days after completing study treatment. Six of the patients were elderly patients (> 70 years of age) enrolled in Study CN138131. These patients experienced the following SAEs: 1 patient (CN138131-25-7059) experienced moderate vomiting before receiving any treatment; 1 patient (CN138131-2-7030) experienced moderate hyperthyroidism 4 days after receiving 2 injections of aripiprazole (total 10 mg); 1 patient (CN138131-2-7086) experienced moderate anemia 9 days after receiving 2 injections of aripiprazole (total 10 mg); 1 patient (CN138131-2-7128) experienced severe urosepsis 27 days after receiving 2 injections of aripiprazole (total 10 mg); 1 patient (CN138131-28-7081) had a **severe cerebrovascular** accident 16 days after receiving 2 injections of aripiprazole (total 10 mg); and 1 patient (CN138131-19-7045) experienced a very severe fall and femoral neck fracture 3.7 hours after receiving the first injection of aripiprazole (total 2 injections, 15 mg).

Table 2.1.3.2: Serious Adverse Events: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013, CN138131), Safety Sample

Treat Group	Patient Number	Age	Gender	Race	Date/Time of AE Start	Date/Time of First Dosing	Number of Injections at AE Onset	Cumulative IM Dose(mg) of Active Drug at AE Onset	Severity	Adverse Event	Relation To Drug
IM Arip	CN138012-21-5108	43	M	W	24FEB04:01:30	19FEB04:09:25	2	Ari 20 mg	SEVERE	PSYCHOTIC DISORDER	NOT LIKELY
	CN138012-21-5319	43	M	W	24MAY04:UNK	11MAY04:10:20	1	Ari 10 mg	SEVERE	PSYCHOTIC DISORDER	NOT LIKELY
	CN138012-30-5188	50	M	W	10APR04:12:00	16MAR04:09:45	1	Ari 10 mg	MODERATE	SCHIZOPHRENIA	NOT RELATED
	CN138012-47-5147	34	M	W	17MAR04:UNK	03MAR04:10:50	3	Ari 30 mg	SEVERE	PSYCHOTIC DISORDER	NOT RELATED
	CN138013-34-19	52	M	B	30DEC03:19:00	09DEC03:10:00	1	Ari 10 mg	SEVERE	NEPHROLITHIASIS	NOT RELATED
	CN138013-39-82	54	F	W	13FEB04:17:00	28JAN04:12:15	2	Ari 30 mg	MILD	PSYCHOSOCIAL SUPPORT	NOT RELATED
	CN138013-48-309	41	M	W	[redacted]		2	Ari 20 mg	VERY SEVERE	DEATH	NOT LIKELY
	CN138050-32-256	37	F	W	11DEC02:UNK	04DEC02:11:17	1	Ari 5 mg	SEVERE	INTENTIONAL SELF-INJURY	NOT RELATED
					11DEC02:UNK	04DEC02:11:17	1	Ari 5 mg	SEVERE	PSYCHOTIC DISORDER	NOT RELATED
	CN138050-40-116	47	M	B	22SEP02:18:30	16SEP02:11:10	2	Ari 2 mg	SEVERE	SCHIZOAFFECTIVE DISORDER	NOT RELATED
	CN138050-42-64	43	M	W	25JUL02:UNK	18JUL02:11:00	1	Ari 10 mg	SEVERE	PANIC ATTACK	NOT LIKELY
	CN138050-44-276	49	M	W	12DEC02:11:00	11DEC02:09:35	1	Ari 10 mg	MILD	DELUSION	NOT LIKELY
					12DEC02:11:00	11DEC02:09:35	1	Ari 10 mg	MILD	HALLUCINATION, AUDITORY	NOT LIKELY
	CN138050-82-283	44	F	W	20DEC02:UNK	12DEC02:14:40	2	Ari 10 mg	MODERATE	SCHIZOAFFECTIVE DISORDER	NOT RELATED
	CN138050-95-362	49	M	W	18JAN03:09:45	17JAN03:11:00	2	Ari 20 mg	SEVERE	CONVULSION	NOT LIKELY
	CN138131-2-7007	82	F	W	26FEB04:UNK	27JAN04:08:55	2	Ari 5 mg	MODERATE	DEMENTIA	NOT RELATED
	CN138131-2-7010	80	F	W	10FEB04:18:00	09FEB04:17:30	2	Ari 5 mg	MODERATE	DEMENTIA	NOT RELATED
	CN138131-2-7015	79	M	W	05MAR04:16:00	04MAR04:09:05	2	Ari 5 mg	MODERATE	DEMENTIA	NOT RELATED

Table 2.1.3.2: Serious Adverse Events: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013, CN138131), Safety Sample

Treat Group	Patient Number	Age	Gender	Race	Date/Time of AE Start	Date/Time of First Dosing	Number of Injections at AE Onset	Cumulative IM Dose(mg) of Active Drug at AE Onset	Severity	Adverse Event	Relation To Drug
	CN138131-2-7030	70	F	W	21MAY04:UNK	17MAY04:07:36	2	Ari 10 mg	MODERATE	HYPERTHYROIDISM	NOT RELATED
	CN138131-2-7086	82	F	W	13NOV04:UNK	04NOV04:07:40	2	Ari 10 mg	MODERATE	ANAEMIA	NOT RELATED
	CN138131-2-7124	76	M	W	18FEB05:UNK	27JAN05:08:35	2	Ari 10 mg	MODERATE	AGITATION	NOT RELATED
	CN138131-2-7128	73	F	W	06MAR05:UNK	07FEB05:07:00	2	Ari 10 mg	SEVERE	UROSEPSIS	NOT RELATED
	CN138131-19-7045	82	F	W	[redacted]	[redacted]	2	Ari 15 mg	VERY SEVERE	FALL	NOT RELATED
							2	Ari 15 mg	VERY SEVERE	FEMORAL NECK FRACTURE	NOT RELATED
	CN138131-28-7061	89	F	W	[redacted]		2	Ari 10 mg	SEVERE	DELIRIUM	NOT LIKELY
							.	0 mg	VERY SEVERE	DEMENTIA	NOT LIKELY
	CN138131-28-7081	77	F	W	30OCT04:UNK	14OCT04:20:20	2	Ari 10 mg	SEVERE	CEREBROVASCULAR ACCIDENT	NOT LIKELY
IM Halop	CN138012-21-5051	46	F	B	29JAN04:UNK	20JAN04:09:55	1	Halo 6.5 mg	SEVERE	SCHIZOPHRENIA	NOT LIKELY
	CN138012-45-5118	44	M	W	19MAR04:UNK	21FEB04:14:30	3	Halo 19.5 m	SEVERE	HALLUCINATION	NOT RELATED
	CN138012-59-5186	27	M	W	17MAR04:15:00	16MAR04:08:00	2	Halo 13 mg	VERY SEVERE	DYSTONIA	CERTAIN
	CN138012-64-5078	30	M	B	02FEB04:22:00	30JAN04:14:10	2	Halo 13 mg	SEVERE	PSYCHOTIC DISORDER	NOT LIKELY
IM Pbo	CN138050-9-145	32	M	B	11OCT02:18:15	09OCT02:15:15	3	Ari 15 mg	MILD	CONVULSION	NOT LIKELY
	CN138131-2-7085	75	M	W	02NOV04:UNK	28OCT04:07:00	2	0 mg	MODERATE	AGITATION	NOT RELATED
					19NOV04:17:30	28OCT04:07:00	2	0 mg	MODERATE	AGITATION	NOT RELATED
	CN138131-2-7095	88	F	W	29NOV04:UNK	18NOV04:08:52	2	0 mg	MODERATE	AGITATION	NOT RELATED
	CN138131-25-7059	80	F	W	08SEP04:11:00	16SEP04:11:20	0	0 mg	MODERATE	VOMITING	NOT RELATED

7.1.3 Dropouts and Other Significant Adverse Events

Clinical Pharmacology Studies

A total of 5 subjects discontinued from the clinical pharmacology studies due to AEs (Table 2.1.4.1): In Study CN138016, 1 subject following administration of a single 5-mg oral dose of aripiprazole; in Study CN138017, 1 subject after the first 5-mg injection (of the total dose of 15 mg, 3 injections) of haloperidol; and in Study CN138132, 1 subject after administration of 15-mg aripiprazole IM, 1 subject after administration of aripiprazole 15 mg IM + lorazepam 2 mg IM, and 1 subject after administration of lorazepam 2 mg IM.

In Study CN138132, in the Training Group there was 1 AE that counted (a postural AE) in 1 of the 2 subjects who were administered lorazepam 2 mg IM, and 28 AEs that counted (10 [5.7%] were postural AEs) in the 4 subjects who were administered aripiprazole 15 mg IM + lorazepam 2 mg IM.

Table 2.1.4.1: Adverse Events That Led to Discontinuation, Clinical Pharmacology Studies (CN138016, CN138017, and CN138132) Safety Sample

Treatment/ Patient Number	Age	Gender	Race	Date/Time of AE Start	Date/Time of Dosing	Onset Dose (mg)[a]	Severity	AE	Relationship to Study Medication[b]
Aripiprazole/ CN138016-1-17[c]	43	Male	Black	26Jan01/16:00	09Jan01/08:10	5 mg Orally	Moderate	Chills	Unlikely related
				26Jan01/16:00	09Jan01/08:10	5 mg Orally	Moderate	Pharyngitis/Sore Throat	Unlikely related
				27Jan01/08:00	09Jan01/08:10	5 mg Orally	Moderate	Coughing	Unlikely related
Haloperidol / CN138017-1-30	25	Male	Black	22Dec00/11:00	22Dec00/09:19	5 mg IM	Moderate	Dystonia	Probably
				24Dec00/01:00	22Dec00/09:19	5 mg IM	Mild	Insomnia	Unlikely related
Aripiprazole/ CN138132-1-222	40	Female	Black	27Apr04/07:00	01Apr04/09:10	15 mg IM	Severe	Neutropenia[d]	Possibly
Aripiprazole + Lorazepam/ CN138132-1-336	20	Male	White	27May04/10:19	27May04/09:10	15 mg IM 2 mg IM	Moderate	Syncope	Possibly
Lorazepam/ CN138132-2-332	20	Male	White	28May04/14:21 28May04/21:20	28May04/08:12	2 mg IM	Mild	Pruritis/Urticaria	Certainly

[a] Total dose received prior to the AE.

[b] Investigator attributed relationship.

[c] Subject had received a single 2-mg dose of aripiprazole intravenously in period 1 of the study on 05Dec00. Subject discontinued from the study prior to receiving the 5-mg IM aripiprazole dose.

[d] SAE

Phase 2/3 Studies

Eight of the 1214 patients in the Safety Sample discontinued from the IM phase (CN138012, CN138050, CN138013, CN138131) because of AE (Table 2.1.4.2): 1 placebo-treated patient, 2 haloperidol-treated patients, and 5 aripiprazole-treated patients. According to the investigators, only 1 of the 5 aripiprazole-treated patients (10-mg) who discontinued did so because of events that were possibly related to study medication (agitation and musculoskeletal stiffness). The narratives for patients who discontinued because of an AE may be found in the individual Clinical Study Reports. I have reviewed these reports.

None of the 89 placebo-treated patients who received a third IM injection, which was either 10-mg or 15-mg aripiprazole, discontinued from the studies because of an AE.

Table 2.1.4.2: Adverse Events That Led to Discontinuation: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013, CN138131), Safety Sample

Treat Group	Patient Number	Age	Gender	Race	Date/Time of AE Start	Date/Time of First Dosing	Number of Injections at AE Onset	Cumulative IM Dose(mg) of Active Drug at AE Onset	Severity	Adverse Event	Relation To Drug
IM Arip	CN138012-38-5269	65	F	W	27APR04:16:23	27APR04:10:00	3	Ari 30 mg	MODERATE	AGITATION	POSSIBLE
					27APR04:16:25	27APR04:10:00	3	Ari 30 mg	MODERATE	MUSCULOSKELETAL STIFFNESS	POSSIBLE
	CN138013-31-55	41	F	W	14JAN04:00:35	13JAN04:18:30	1	Ari 15 mg	MILD	STOMACH DISCOMFORT	NOT RELATED
	CN138050-9-269	45	M	B	10DEC02:17:15	10DEC02:13:00	1	Ari 15 mg	VERY SEVERE	AGITATION	NOT LIKELY
	CN138050-95-362	49	M	W	18JAN03:09:45	17JAN03:11:00	2	Ari 20 mg	SEVERE	CONVULSION	NOT LIKELY
	CN138131-19-7045	82	F	W	13JUL04:15:00	13JUL04:11:20	2	Ari 15 mg	VERY SEVERE	FEMORAL NECK FRACTURE	NOT RELATED
IM Halop	CN138012-18-5216	48	M	B	01APR04:11:00	01APR04:10:45	1	Halo 6.5 mg	MODERATE	BLOOD GLUCOSE INCREASED	NOT RELATED
	CN138012-122-5398	47	M	W	27MAY04:12:00	27MAY04:09:05	1	Halo 6.5 mg	VERY SEVERE	AKATHISIA	CERTAIN
IM Pbo	CN138013-4-124	51	M	W	24FEB04:14:17	24FEB04:13:15	1	0 mg	MODERATE	HYPOTENSION	POSSIBLE

Race abbreviations: W=White B=Black
MEDDRA VERSION: 7.1

7.1.3.1 Overall profile of dropouts

Patient Disposition

Very few patients discontinued from IM study treatment. The total number of patients who discontinued from the 3 pooled IM studies (CN138012, CN138050, CN138013) was similar across treatment groups (placebo: 2%; haloperidol: 5%; lorazepam: 3%; aripiprazole: 2%) (Table 1.3.2B-1). The most frequently reported reason for discontinuation was patient withdrawal of consent. There was little difference among the treatment groups in the percentage of patients who discontinued because of AE (placebo: <1%; haloperidol: <1%; lorazepam: 0%; aripiprazole: 1%).

The number of patients who discontinued and reasons for discontinuation in the 2 schizophrenia studies (CN138012, CN138050) was similar to that of the 3 pooled studies (Table 1.3.2B-1).

In Study CN138131, very few patients discontinued the study for any reason (Table 1.3.2B-2): 1 patient discontinued because of AE and 1 patient discontinued because of lack of efficacy. Both of these patients were in the 15-mg aripiprazole group.

Table 1.3.2B-1: Patient Disposition, Overall and by Indication: IM Placebo-Controlled Studies (CN138012,CN138050,CN138013), Safety Sample

	Placebo	Haloperidol	Lorazepam	Aripiprazole(a)
(CN138012, CN138050, CN138013)	N=220	N=240	N=69	N=501
Total Discontinuations	5(2)	11(5)	2(3)	12(2)
Adverse Event	1(<1)	2(1)		4(1)
Lack of Efficacy	2(1)	1(<1)	1(1)	
Loss to Follow-up				1(<1)
Subject Withdrew Consent	2(1)	8(3)	1(1)	5(1)
Other				2(<1)
(CN138012, CN138050)	N=148	N=240		N=351
Total Discontinuations	3(2)	11(5)		7(2)
Adverse Event		2(1)		3(1)
Lack of Efficacy	2(1)	1(<1)		
Loss to Follow-up				1(<1)
Subject Withdrew Consent	1(1)	8(3)		2(1)
Other				1(<1)
(CN138013)	N=72		N=69	N=150
Total Discontinuations	2(3)		2(3)	5(3)
Adverse Event	1(1)			1(1)
Lack of Efficacy			1(1)	
Loss to Follow-up				
Subject Withdrew Consent	1(1)		1(1)	3(2)
Other				1(1)

(a) Does not include the 1-mg aripiprazole dose group.
For specific details regarding this dose group, refer to the Clinical Study Report CN138050.

Table 1.3.2B-2: Patient Disposition, Overall and by Indication: IM Placebo-Controlled Study (CN138131), Safety Sample

		Aripiprazole			
	Placebo	5 mg	10 mg	15 mg	Total
Safety Sample	N=25	N=12	N=76	N=15	N=103
Total Discontinuations				1(7)	1(1)
Adverse Event				1(7)	1(1)
Lack of Efficacy					
Loss to Follow-up					
Subject Withdrew Consent					
Other					

7.1.3.2 Adverse events associated with dropouts

There was little difference among the treatment groups in the percentage of patients who discontinued because of AE (placebo: <1%; haloperidol: <1%; lorazepam: 0%; aripiprazole: 1%). See section 7.1.3 above.

7.1.3.3 Other significant adverse events

Analyses of events of special interest performed on the data from the aripiprazole IM clinical program included excessive sedation, extrapyramidal symptoms ([EPS]-related AEs, EPS scales, anticholinergic medication for the treatment of EPS-related AEs), AEs related to injection site reaction, AEs related to tachycardia, bradycardia, and hypotension, seizure-related AEs, and neuroleptic malignant syndrome. In addition, an assessment of cerebrovascular events in elderly patients with dementia (Study CN138131) was performed.

7.1.5 Common Adverse Events

See table section 7.1.5.4.

The following points can be made about the phase 2/3 Studies: CN138012, CN138050, CN138013

- No AEs identified by study showed a statistical trend by dose
- An increased incidence of insomnia after a second injection for the 5-mg, 10-mg, and 15-mg aripiprazole dose groups
- The incidence of fatigue was higher in patients ≤ 48 years of age than in patients > 48 years of age
- No differences by gender
- A higher incidence of blood pressure increased for whites compared with blacks

There were no reports of neuroleptic malignant syndrome during any of the studies.

2 Pooled Studies in Schizophrenia (CN138012, CN138050)

When treatment-emergent AEs were evaluated for the 2 schizophrenia studies alone, events of nausea, headache, dizziness, and somnolence met the criteria for common AE (≥ 5% and twice the rate of placebo).

Adverse drug reactions (ADRs) were those AEs considered by the investigators to be certainly, possibly, or probably related to study medication. ADRs that had a placebo-corrected incidence of > 1% or < 10% were defined as common. ADRs that met these criteria in the 2 pooled schizophrenia studies alone were somnolence, dizziness, headache, akathisia, tachycardia, nausea, dry mouth, vomiting, and fatigue.

There was an increased incidence of insomnia after a second injection in the 5-mg and 10-mg aripiprazole dose groups in the 2 pooled schizophrenia studies, but no apparent dose-response relationship between aripiprazole and treatment-emergent AEs.

The incidences of AEs in patients who received only 1 injection were similar to the incidences of AEs in patients with first onset or increased severity after a second injection, with the exception of insomnia. The incidence of insomnia increased in both the 5-mg (from 2.9% to 7.4%) and 10-mg (from 1.5% to 9.5%) aripiprazole groups after a second injection.

Agitated Elderly Patients with Dementia (Study CN138131)

In Study CN138131, somnolence was the most frequently reported AE and ADR in these patients. Unlike studies CN138012, CN138050, and CN138013 in which a second or third injection was optional, a second injection was required per protocol in Study CN138131. The majority of patients received 2 injections per the protocol, and the overall incidence of AEs in these patients was low.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AEs were classified by primary system organ class and preferred term according to MedDRA. AEs were coded and summarized using the version of MedDRA that was in use at the time of database lock of the last study, which was CN138131 (Version 7.1). Differences in MedDRA coding between the Clinical Study Reports (CSRs) for CN138012, CN138050, and CN138013 (coded using Version 7.0) and this Clinical Summary of Safety (coded using Version 7.1) are presented in Appendix 1.1.2B. The incidence of treatment-emergent AEs was tabulated by treatment, dose, age, gender, race, and drug-relatedness. An AE was considered to be treatment emergent if the onset time was on or after the time of the first IM injection and within 25 hours of the first IM injection. AEs were also analyzed for patients who received only 1 IM injection and for patients who received a second or third IM injection. For patients who received a second or third injection, only AEs with first onset or AEs of increased severity after repeat IM injections were summarized. An AE was considered to be drug related if the investigator

considered the AE to be certainly, probably, or possibly related to study medication. All SAEs and AEs leading to discontinuation were reported regardless of the timing relative to the first IM injection. Any AEs occurring after a third injection in the randomized placebo group (which was either 10- or 15-mg aripiprazole) were excluded from the pooled analyses of placebo-controlled studies.

The Cochran-Mantel-Haenzel (CMH) correlation test, stratified by study, was performed to identify any positive dose response among these AEs. For the 2 placebo-controlled studies that included multiple aripiprazole doses (schizophrenia CN138050; bipolar disease CN138013), dose relatedness was examined for AEs with an incidence of $\geq$ 1% in the pooled aripiprazole dose group (excluding the 1-mg dose). Since large differences between aripiprazole and placebo incidence rates for a given AE may have affected the results of the test, the analysis was performed first on the 5 dose groups (placebo as zero dose, aripiprazole doses of 1, 5, 10, and 15 mg) and then on the 3 aripiprazole dose groups (excluding placebo and the 1-mg aripiprazole "no effect" dose). If both of these tests yielded p-values $\leq$ 0.05, the AE was considered potentially dose-related and warranted additional review for clinical relevance. Due to the limited sample sizes, this analysis was not repeated for the 2 pooled schizophrenia studies since only Study CN138050 provided information on more than 1 IM aripiprazole dose.

7.1.5.3 Incidence of common adverse events

The incidence of sedation was similar between the placebo group (2.3%) and the aripiprazole dose groups (5 mg 4.8%; 10 mg 2.3%; 15 mg 3.0%) and haloperidol dose groups (6.5 mg 2.7%; 7.5 mg 3.5%), and higher in the lorazepam group (11.6%). The incidence of somnolence was higher in the 7.5-mg haloperidol group (12.3%) and the 5-mg (8.1%) and 15-mg (9.0%) aripiprazole groups than in the placebo group (3.6%) and other treatment groups. No aripiprazole-treated patients discontinued from the studies or experienced an SAE of sedation or somnolence at any time during the studies.
The incidence of EPS-related AEs (excluding akathisia events) was similar in the aripiprazole group (2.4%) and the placebo group (1.8%), and higher in the haloperidol group (12.1%). The incidence of akathisia events was higher in the aripiprazole group (2.0%) than the placebo group (0%), but there was no average worsening in the SAS and Barnes Akathisia Global Clinical Assessment scores for all treatment groups. There was no noticeable increase in EPS-related AEs after a second injection. No aripiprazoletreated patients discontinued from the studies or experienced an SAE of EPS-related AEs at any time during the studies. A greater proportion of patients in the haloperidol (10.4%) and aripiprazole (3.8%) groups required anticholinergic medications for potential treatment of EPS-related AEs than patients in the placebo group (0.9%). Benztropine was the most frequently used EPS medication across all treatment groups.

The incidence of any treatment-emergent AE related to injection site reaction was < 2% and similar across all treatment groups. Most events were mild or moderate in severity, although 1 aripiprazole-treated patient experienced severe injection site burning. The patient's symptoms resolved after 1 minute and the patient required no treatment and experienced no sequelae related to this event.

Adverse Events Occurring at an Incidence of 1% or More Among Aripiprazole-Treated Patients and Greater than Placebo in Short-Term, Placebo-Controlled Trials of Patients with Agitation Associated with Schizophrenia or Bipolar Mania

Table 3 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (24 hour), including only those events that occurred in 1% or more of patients treated with aripiprazole injection (doses ≥5 mg/day) and for which the incidence in patients treated with aripiprazole injection was greater than the incidence in patients treated with placebo in the combined dataset.

Table 3: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials in Patients Treated with ABILIFY Injection

	Percentage of Patients Reporting Event[a]	
System Organ Class **Primary Term**	**Aripiprazole** **(n=501)**	**Placebo** **(n=220)**
Cardiac Disorders		
Tachycardia	2	<1
Gastrointestinal Disorders		
Nausea	9	3
Vomiting	3	1
Dyspepsia	1	<1
Dry mouth	1	<1
General Disorders and Administration Site Conditions		
Fatigue	2	1
Investigations		
Blood Pressure Increased	1	<1
Musculoskeletaland Connective Tissue Disorders		
Musculoskeletal Stiffness	1	<1
Nervous System Disorders		
Headache	12	7
Dizziness	8	5
Somnolence	7	4
Sedation	3	2
Akathisia	2	0

[a] Events reported by at least 1% of patients treated with aripiprazole injection, except the following events, which had an incidence equal to or less than placebo: injection site pain, injection site burning, insomnia, agitation.

7.1.5.4 Common adverse event tables

Please see table below.Table 15: Incidence of Treatment-Emergent Adverse Events That Occurred in at Least 1% of Patients in the Aripiprazole Group: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), Safety Sample

System Organ Class/ Preferred Term[a]	Number (%) Patients			
	Placebo N = 220	Haloperidol N = 240	Lorazepam N = 69	Aripiprazole[b] N = 501
Cardiac Disorders				
Tachycardia	1 (0.45)	2 (0.83)	1 (1.45)	8 (1.60)
Gastrointestinal Disorders				
Nausea	7 (3.18)	3 (1.25)	0	46 (9.18)
Vomiting	2 (0.91)	2 (0.83)	0	17 (3.39)
Dyspepsia	1 (0.45)	0	0	7 (1.40)
Dry Mouth	1 (0.45)	5 (2.08)	1 (1.45)	6 (1.20)
General Disorders and Administration Site Conditions				
Fatigue	3 (1.36)	6 (2.50)	2 (2.90)	11 (2.20)
Injection Site Pain	4 (1.82)	2 (0.83)	0	9 (1.80)
Injection Site Burning	2 (0.91)	0	1 (1.45)	7 (1.40)
Investigations				
Blood Pressure Increased	1 (0.45)	3 (1.25)	1 (1.45)	6 (1.20)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Stiffness	1 (0.45)	4 (1.67)	0	6 (1.20)
Nervous System Disorder				
Headache	16 (7.27)	17 (7.08)	3 (4.35)	62 (12.38)
Dizziness	10 (4.55)	11 (4.58)	7 (10.14)	40 (7.98)
Somnolence	8 (3.64)	13 (5.42)	5 (7.25)	34 (6.79)
Sedation	5 (2.27)	7 (2.92)	8 (11.59)	14 (2.79)
Akathisia	0	12 (5.00)	0	10 (2.00)
Psychiatric Disorder				
Insomnia	14 (6.36)	23 (9.58)	1 (1.45)	28 (5.59)
Agitation	6 (2.73)	9 (3.75)	0	14 (2.79)

Source: Table 2.1A, Module 2.7.4 Clinical Summary of Safety

[a] MedDRA Version 7.1.

[b] Does not include the 1-mg aripiprazole dose group since this was considered an ineffective dose.

7.1.5.5 Identifying common and drug-related adverse events

The standard criteria used to determine the common AEs in the aripiprazole IM program were those AEs with an incidence of ≥ 5% that also occurred with an incidence at least twice that of the placebo group. In the pooled presentation of the 3 studies (CN138012, CN138050, CN138013), nausea was the only event that met these criteria. The incidence of treatment-emergent AEs that occurred in ≥ 1% of the patients in the aripiprazole group is presented in Table 15. Aside from those events that are associated with the method of administration (eg, injection site pain), the profile of AEs reported with IM aripiprazole were generally similar to those observed with oral-tablet aripiprazole.

7.1.5.6 Additional analyses and explorations

The purpose of this section is to present results of excessive sedation, EPS-related AEs, AEs related to injection site reaction, and AEs related to tachycardia, bradycardia, and hypotension for Studies CN138012, CN138050, and CN138013. Results showed:

- Incidence of sedation in aripiprazole dose groups similar to the placebo group
- Incidence of somnolence higher in 5-mg and 15-mg aripiprazole groups than the placebo group
- No increase in sedation or somnolence after a second injection
- Number of patients with ACES score of 9 (unarousable) was low in all treatment groups
- Incidence of any EPS-related AE was higher in the aripiprazole group than placebo group, but lower than the haloperidol group
- There was no noticeable increase in EPS-related AEs after a second or third injection
- There was no average worsening in SAS and Barnes Akathisia Global Clinical Assessment scores
- Higher use of anticholinergic medication in haloperidol and aripiprazole groups than the placebo group
- Incidence of injection site reaction low in aripiprazole group and similar to placebo group, and majority of events mild or moderate in severity
- Incidence of AEs related to tachycardia higher in aripiprazole group than placebo group; bradycardia and hypotension low across all treatment groups

The incidence of any treatment-emergent AE related to injection site reaction was < 2% and similar across all treatment groups in the 3 placebo controlled studies. Most events were mild or moderate in severity, although 1 aripiprazole-treated patient experienced severe injection site burning. The patient's symptoms resolved after 1 minute and the patient required no treatment and experienced no sequelae related to this event. No aripiprazole-treated patients discontinued from the studies or experienced an SAE related to injection site reaction at any time during the studies.

Incidence of Sedation

The incidence of sedation was similar between the placebo group (2.3%) and all aripiprazole dose groups (range 2.3% to 4.8%), and higher for patients in the lorazepam group (11.6%). The incidence of somnolence was higher in the 7.5-mg haloperidol group (12.3%) and the 5-mg (8.1%) and 15-mg (9.0%) aripiprazole groups than in the placebo group (3.6%) and other treatment groups.

For patients who received a second injection, there were no patients in the 1-mg, 10-mg, or 15-mg aripiprazole groups who experienced a new report or had increased severity of sedation, and the incidence across the other treatment groups was low. The incidence of new reports or increased severity of somnolence was higher in the 7.5-mg haloperidol (6.7%) and lorazepam (4.2%) groups than the placebo group (0.8%) or aripiprazole treatment groups (range across doses: 0% to 3.7%)

There were no new events of sedation or somnolence, or events of increased severity in patients who received a third injection.

No aripiprazole-treated patients discontinued from the studies or experienced an SAE of sedation or somnolence at any time during the studies.

Incidence of EPS-Related Adverse Events

The incidence of EPS-related AEs (excluding akathisia events) was similar in the aripiprazole group (2.4%) and the placebo group (1.8%), and higher in the haloperidol group (12.1%). The incidence of akathisia events was higher in the aripiprazole group (2.0%) than the placebo group (0%), but lower than that of the haloperidol group (5%).

For patients who received a second injection, there was no noticeable increase of EPS-related AEs after a second injection or after a third injection.

No aripiprazole-treated patients discontinued from the studies or experienced an SAE of EPS-related AEs at any time during the studies.

EPS Scales

The SAS is used to assess extrapyramidal side effects, and has a total score ranging from 10 to 50. A negative change score indicates a reduction in extrapyramidal symptoms.

The Barnes Akathisia Global Clinical Assessment is used to assess the presence and severity of akathisia, and has a range of scores from 0 (absent) to 5 (severe akathisia). Negative change scores indicate improvement in akathisia.

In the 3 studies (CN138012, CN138050, CN138013), there was no average worsening in the SAS and Barnes Akathisia Global Clinical Assessment scores for all treatment groups. None of the mean change from baseline to 2 hours or 24 hours post first IM injection treatment comparisons was statistically significantly different from placebo.

Adverse Events Related to Tachycardia, Bradycardia, and Hypotension

The incidence of treatment-emergent tachycardia was higher in the aripiprazole group (1.6%) than the placebo group (0.5%), and the incidence of bradycardia was low (<1%). The incidence of orthostatic hypotension that was reported as an AE was 0.6% in aripiprazole-treated patients and 0% in placebo-treated patients, while the incidence of syncope was 0.4% in aripiprazole-treated patients and 0% in placebo-treated patients.

No aripiprazole-treated patient discontinued from the study or experienced an SAE related to tachycardia, bradycardia, or hypotension.

Seizure-Related Events: Studies CN138012, CN138050, CN138013, CN138131

The incidence of seizure-related events was low in the 3 pooled studies (CN138012, CN138050, CN138013): 0.2% (1/501) aripiprazole-treated patients reported convulsions versus 0% (0/220) placebo-treated patients. The 1 aripiprazole-treated patient (CN138050-95-362) received 2 injections of 10 mg. One additional event occurred in a patient randomized to placebo (CN138050-9-145) who received aripiprazole for his third injection. Both of the events were designated by the investigators as not likely related to study medication. The narratives for these patients may be found in the individual Clinical Study Reports.

No patient in Study CN138131 experienced a seizure-related event.

Neuroleptic Malignant Syndrome: Studies CN138012, CN138050, CN138013, CN138131

There were no AEs of NMS reported in any of the 4 IM aripiprazole studies.

7.1.6 Less Common Adverse Events

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole Injection

Following is a list of MedDRA terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with aripiprazole injection at doses ≥1 mg/day during any phase of a trial within the database of 749 patients. All reported events are included except those already listed in Table 2 or 3, or other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or

PRECAUTIONS, those event terms which were so general as to be uninformative, events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole injection, they were not necessarily caused by it.

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

Cardiac Disorders: Infrequent - sinus tachycardia.

Ear and Labyrinth Disorders: Infrequent - hyperacusis.

Gastrointestinal Disorders: Infrequent - aptyalism, oral hypoaethesia.

General Disorders and Administration Site Conditions: Infrequent - hot feeling, injection site stinging, abnormal feeling, injection site pruritus, injection site swelling, venipuncture site bruise.

Infections and Infestations: Infrequent - bacteruria, urinary tract infection, urosepsis.

Injury, Poisoning and Procedural Complications: Infrequent - skin laceration.

Investigations: Infrequent - heart rate increased, blood pressure decreased, blood pressure abnormal, heart rate irregular, blood glucose increased, body temperature increased, electrocardiogram T-wave abnormal, heart rate decreased.

Musculoskeletal and Connective Tissue Disorders: Infrequent - buttock pain, chest wall pain, groin pain, muscle rigidity, muscle tightness, sensation of heaviness.

Nervous System Disorders: Infrequent - dementia, dysgeusia, lethargy, parkinsonism.

Psychiatric Disorders: Infrequent - auditory hallucination, intentional self-injury, nightmare, tension.

Reproductive System and Breast Disorders: Infrequent - erectile dysfunction.

Respiratory, Thoracic and Mediastinal Disorders: Infrequent - pharyngolaryngeal pain, nasal congestion, rhinorrhoea.

Vascular Disorders: Infrequent - flushing, blood pressure fluctuation.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory data were analyzed and are presented both in terms of frequency of potentially clinically relevant events as well as median changes from baseline to endpoint. For each laboratory test, the incidence rate of potentially clinically relevant events is tabulated by baseline measurement. The primary presentation of the incidence summaries is based on treatment-emergent results of potential clinical significance and includes only patients who had a normal baseline value. Complete incidence summaries by baseline level are provided in the appendices. The stratum for "all patients" includes patients with a missing baseline value.

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

The short term placebo controlled studies were used for comparison purposes.

7.1.7.3 Standard analyses and explorations of laboratory data

Instances of transaminase elevation (AST or ALT $\geq$ 3 x ULN) accompanied by an elevation in bilirubin values (> 2 mg/dL) were reviewed to identify patients who had a potential liver injury as a result of drug therapy The distribution of the change from baseline to endpoint was compared (each treatment group versus placebo) using the Wilcoxon rank-sum test. The median change from baseline to endpoint was also presented as an estimate of central tendency.

Vital signs data were analyzed and are presented both in terms of frequency of potentially clinically relevant events as well as median changes from baseline. Criteria for identification of potentially clinically relevant vital signs as well as the identification of orthostatic hypotension may be found in Appendix 1.1.2D. Median changes from baseline in vital signs data are shown for each scheduled timepoint relative to each IM injection as well as for the endpoint, highest, and lowest evaluations. The distribution of the changes from baseline to endpoint, highest, and lowest evaluations were compared (each treatment group versus placebo) using the Wilcoxon rank-sum test. The median change from baseline to endpoint was also provided as a summary statistic for central tendency. Vital signs data occurring after a third injection in the randomized placebo group (which was either 10- or 15-mg aripiprazole) were excluded from the pooled analyses, but are included in the Appendix.

QT interval data were analyzed and are presented both in terms of frequency of potentially clinically relevant events as well as mean changes from baseline. Criteria for identification of potentially clinically relevant QT interval changes (noted as abnormalities in the title of appendices) include > 450 msec, >480 msec, > 500 msec, an increase from baseline of $\geq$ 30 msec, or an increase from baseline of $\geq$ 60 msec. The evaluation of QT intervals was done separately for data obtained from 12-lead standard and 12-lead ambulatory ECGs. The aripiprazole doses were pooled (excluding the 1-mg dose) and the haloperidol doses were pooled

for the evaluation of potentially clinically relevant QT interval changes. In addition, potentially clinically relevant QT interval changes occurring after a third injection in the randomized placebo group (which was either 10- or 15-mg aripiprazole) were excluded from the pooled analyses. Mean changes from baseline in QT intervals are shown for each scheduled timepoint relative to each IM injection as well as for the highest evaluation. An ANCOVA model was used to evaluate the mean change from baseline to highest evaluation. The model included baseline QT interval as a covariate and fixed terms for treatment and study (ie, CN138012, CN138050, and CN138013). Evaluations occurring after a third injection in the randomized placebo group (which was either 10- or 15-mg aripiprazole) were excluded from the analyses. The primary presentation of QT interval data used a fractional exponent correction method recommended by the FDA's Division of Neuropharmacological Drug Products using baseline measurement from the pool of the 3 studies (CN138012, CN138050, CN138013). The correction that was derived, denoted as QT_{cE}, was the value of the exponent k that generated the slope closest to zero in the regression of RR on QT/RR^k. This value was 0.34 for data obtained from 12-lead standard ECGs ($QT/RR^{0.34}$) and 0.38 for data obtained from 12-lead ambulatory ECGs ($QT/RR^{0.38}$). This difference in estimated corrections is likely due to sampling variability. Analyses and summaries for the uncorrected QT, and for the corrections of QT_{cB} (the Bazett's correction [$QT/RR^{0.50}$]) and QT_{cF} (Fridericia's correction [$QT/RR^{0.33}$]), are presented in the appendices. Similar analyses are presented separately for the 2 pooled schizophrenia studies (CN138012, CN138050).

For Study CN138131, a separate fractional exponent correction was derived using baseline data from that study. This value was 0.40 for data obtained from standard 12-lead ECGs ($QT/RR^{0.40}$) and 0.42 for data obtained from ambulatory 12-lead ECGs ($QT/RR^{0.42}$).

ECG data other than QT_c were analyzed and are presented both in terms of frequency of potentially clinically relevant events as well as mean changes from baseline. Criteria for identification of potentially clinically relevant ECGs may be found in Appendix 1.1.2E. These data were analyzed without respect to the ECG data source. Potentially clinically relevant changes occurring after a third injection in the randomized placebo group (which was either 10- or 15-mg aripiprazole) were excluded from the pooled analyses, but are presented in Appendix 4.2.2.5B. Mean changes from baseline in PR, QRS, RR, and heart rate were analyzed using the observed cases (OC) dataset for each scheduled timepoint relative to each IM injection as well as for the highest evaluation and lowest evaluations. An ANCOVA model was used to evaluate the mean change from baseline to highest and lowest evaluations. The model included baseline evaluation as a covariate and fixed terms for treatment and study (ie, CN138012, CN138050, and CN138013). Evaluations occurring after a third injection in the randomized placebo group (which was either 10- or 15-mg aripiprazole) were excluded from the analyses. Similar analyses are presented separately for the 2 pooled schizophrenia studies (CN138012, CN138050). For Study CN138131, only summary statistics are provided with no statistical testing performed because of limited sample sizes.

For Study CN138050, a post-hoc analysis to assess the potential of aripiprazole IM to affect QTc was performed. Linear regressions of ΔQTc on matched aripiprazole plasma concentrations and

on matched dehydro-aripiprazole plasma concentrations were estimated. Ninety-five percent CIs were constructed for the slopes and intercepts. These analyses were performed separately for measurements recorded on a standard 12-lead ECGs and ambulatory 12-lead ECGs. All available data from subjects who received aripiprazole and from whom ECG measurements and plasma concentrations were available within 30 minutes of each other were included in the data set for these analyses. For the statistical analysis and graphical representations, aripiprazole and dehydro-aripiprazole plasma concentrations below the lower limit of quantitation (<LLQ) were replaced by 0.5·LLQ, where LLQ=1 ng/mL.

7.1.7.3.1 Analyses focused on measures of central tendency

One finding in this pooled population was the higher incidence of increased fasting serum glucose observed in aripiprazole-treated patients and haloperidol-treated patients compared with placebo-treated patients. When only patients who had a normal fasting glucose at baseline were evaluated, the rate of increased fasting glucose was higher in the 5-mg (22.2%), 10-mg (20.9%), and 15-mg (27.8%) aripiprazole treatment groups and haloperidol treatment groups (6.5 mg: 24.0%; 7.5 mg: 20.0%) than the placebo group (5.0%). The sample size of patients who had fasting glucose samples obtained at baseline and sometime during the study was relatively small compared with the total number of patients in the studies. Furthermore, there were no statistically significant median changes from baseline to 24 hours post first IM injection in fasting glucose for any treatment group.

Although there were statistically significant differences in the distributions of changes from baseline to 24 hours post first IM injection in basophils (10-mg aripiprazole), hematocrit (5-mg aripiprazole), and leukocytes (1-mg aripiprazole) compared with placebo, none of the differences were clinically meaningful (Table 3.2.1.2B).

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

No aripiprazole-treated patients discontinued from the studies because of potentially clinically relevant serum chemistry laboratory results.

No aripiprazole-treated patients discontinued from the studies because of potentially clinically relevant hematology laboratory results.

7.1.7.4 Additional analyses and explorations

The purpose of this section is to present laboratory results of potential clinical significance for Studies CN138012, CN138050, and CN138013. Results showed:

- A higher incidence of increased fasting serum glucose in aripiprazole-treated patients than placebo-treated patients
- No differences between the groups in hematology parameters
- No clinically meaningful differences between the groups in median changes from baseline to 24 hours post first IM injection for any serum chemistry or hematology parameter

7.1.7.5 Special assessments

7.1.8 Vital Signs

7.1.8.3 Standard analyses and explorations of vital signs data

The incidence of potentially clinically relevant vital sign measurements was similar in the aripiprazole-treatment groups and placebo-treatment group, with the exception of standing systolic blood pressure decrease, standing diastolic blood pressure increase, and standing heart rate increase. These changes were generally transient in nature and none were of clinical concern. No aripiprazole-treated patients experienced SAEs or discontinued from the studies because of vital sign abnormalities.

While there were statistically significant differences between the aripiprazole group and placebo group in median changes from baseline to endpoint (LOCF), highest, and lowest evaluations in certain parameters (highest standing heart rate, lowest standing diastolic blood pressure, and lowest standing and supine systolic blood pressure), the differences were not clinically meaningful.

7.1.8.3.1 Analyses focused on measures of central tendencies

For all placebo-controlled studies, including the 3 pooled studies (CN138012, CN138050, CN138013), the 2 pooled studies (CN138012, CN138050), and Study CN138131, results showed:

- Transient changes in vital sign parameters that were not clinically meaningful after 1 injection or subsequent injections with aripiprazole
- No clinically meaningful differences among the treatment groups in median change from baseline to 24 hours post first IM injection in vital sign parameters

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The number of patients with at least a 30-mmHg decrease (supine to standing) in systolic blood pressure was assessed across treatment groups, and there was no difference in the incidence of this measurement between the aripiprazole (3.7%) and placebo (3.7%) groups.

In study CN138017, a total of 25 vital sign abnormalities were reported in 14 subjects who received aripiprazole, while none were reported for the subjects who received haloperidol. There were 11 elevated standing heart rate abnormalities. There were a total of 8 low standing blood pressure measurements (4 were both low standing systolic and diastolic blood pressures, 3 were low standing diastolic blood pressure, and 1 was a low standing systolic blood pressure). There was 1 high standing diastolic blood pressure and 1 low supine diastolic blood pressure. Decreases in systolic blood pressure (SBP) from supine to standing position that are in the ranges of 20 and < 30 mmHg or ≥ 30 mmHg are also reflected in the analysis of orthostatic hypotension.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no vital signs results that resulted in subject discontinuation in the clinical pharmacology studies.

No aripiprazole-treated patients experienced SAEs or discontinued from the phase 2-3 studies because of potentially clinically relevant vital sign changes.

7.1.8.4 Additional analyses and explorations

The incidence of treatment-emergent tachycardia was higher in the aripiprazole group (1.6%) than the placebo group (0.5%), and the incidence of bradycardia was low (<1%). The incidence of orthostatic hypotension that was reported as an AE was 0.6% in aripiprazole-treated patients and 0% in placebo-treated patients, while the incidence of syncope was 0.4% in aripiprazole-treated patients and 0% in placebo-treated patients.

No aripiprazole-treated patient discontinued from the study or experienced an SAE related to tachycardia, bradycardia, or hypotension.

7.1.9 Electrocardiograms (ECGs)

7.1.9.3 Standard analyses and explorations of ECG data

Criteria for identification of potentially clinically relevant QT interval changes included > 450 msec, > 480 msec, > 500 msec, an increase from baseline of ≥ 30 msec, or an increase from baseline of ≥ 60 msec. These criteria are consistent with recent European Agency for Medicinal Products (EMEA) QT measurement guidelines. Both standard and ambulatory 12-lead ECG measurements were taken during the IM clinical program and all results are presented in the dossier. In addition, various correction factors were applied in the analyses and numerous timepoints were assessed and are presented. The FDA correction, QT_{cE}, is highlighted in this section. QT_{cE} takes into account the baseline QT measures for the specific patient population under evaluation.

7.1.9.3.1 Analyses focused on measures of central tendency

3 Pooled Studies in Schizophrenia and Bipolar I Disorder (CN138012, CN138050, CN138013)

The incidence of abnormal QT_{cE} results at any time during the studies using standard 12-lead ECGs was similar for aripiprazole-treated patients and placebo-treated patients for all parameters. Using ambulatory 12-lead ECGs, the incidence of aripiprazole-treated patients with QT_{cE} > 450 msec (7% aripiprazole vs 7% placebo), > 480 msec (1% aripiprazole vs 2% placebo), and > 500 msec (0% aripiprazole vs 1% placebo) was less than or equal to the incidence seen in placebo-treated patients, but greater than placebo-treated patients for measurements of ≥ 30 msec increase (27% aripiprazole vs 22% placebo) and ≥ 60 msec increase (2% aripiprazole vs 1% placebo). When the data were analyzed at different timepoints for both the standard and ambulatory 12-lead ECGs, there were no clinically meaningful differences seen across treatment groups at any timepoint.

Results of the standard 12-lead ECGs showed no clinically meaningful differences between any aripiprazole dose group and the placebo group in the mean change from baseline to any timepoint, and no statistically significant difference in the mean change from baseline to highest value in QT_{cE}. The ambulatory 12-lead ECGs similarly showed no clinically meaningful results in the mean change from baseline to any timepoint and highest value for aripiprazole groups. Slight mean differences between treatment arms showed no consistent pattern. While there was 1 aripiprazole-treated patient and 1 placebo-treated patient with a QT_{cE} > 500 msec, this rare occurrence offers particular evidence of QT interval safety with aripiprazole, as this QT threshold has been of specific clinical concern during clinical trials of other medications. Mean

differences seen with ambulatory 12-lead ECGs may likely be a variation due to patients not being required to be at rest while wearing the ambulatory monitor.

When QT intervals were evaluated uncorrected and using other correction methods (QT_{cB}, QT_{cN}, and QT_{cF}), there were no clinically meaningful differences across treatment groups.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

For all placebo-controlled studies, including the 3 pooled studies (CN138012, CN138050, CN138013), the 2 pooled schizophrenia studies alone (CN138012, CN138050), and Study CN138131, results showed:

- There were no clinically meaningful differences in QT_{cE} across treatment groups at any timepoint
- Based on mean changes from baseline in QT_{cE} after 1 injection or subsequent injections, there was no evidence of a QT interval safety issue related to aripiprazole
- There were no clinically meaningful differences across treatment groups when QT intervals were evaluated uncorrected and using other correction methods (QT_{cB}, QT_{cN}, and QT_{cF})
- There were no clinical concerns regarding ECG measurements of rate, rhythm, conduction, infarction, or increased ST/T morphology
- Additionally, results from Study CN138050 suggests that dosing with IM aripiprazole is not associated with a concentration-dependent effect on QT interval changes from baseline

Results of the standard 12-lead ECGs showed no clinically meaningful differences between any aripiprazole dose group and the placebo group in the mean change from baseline to any timepoint, and no statistically significant difference in the mean change from baseline to highest value in QT_{cE}.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

No aripiprazole-treated patients discontinued from the studies because of potentially clinically relevant ECG results.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There were no adequate and well-controlled studies conducted using IM aripiprazole to assess withdrawal and rebound.

IM aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence.

7.1.14 Human Reproduction and Pregnancy Data

There were no adequate and well-controlled studies conducted in pregnant women using IM aripiprazole. In intravenous studies of embryo-fetal development in rats and rabbits using IM aripiprazole, there was no evidence of teratogenicity in either species at systemic exposures up to 15 (rat) and 29 times (rabbit) human exposures at the maximum recommended human dose (MRHD) of 30 mg. Fetal changes, including reduced fetal ossificiation, abortion, and fetal visceral and skeletal alterations, occurred only at doses that were maternally toxic. In the intravenous pre- and postnatal development assessment in rats, aripiprazole produced drug-related changes in the offspring, including stillbirths, increased neonatal mortality, transient decrease in pup body weights, and postweaning observations of increased incidence of dilated renal pelvis, at maternally toxic doses. Maternal systemic exposures to aripiprazole on postpartum Day 4 at the no-effect dose in offspring were equivalent to human exposures at the MRHD of 30 mg.

Given the limited IM clinical experience, it is not known whether IM aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. IM aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

No aripiprazole-treated patients became pregnant during the IM studies.

7.1.15 Assessment of Effect on Growth

N/A

7.1.16 Overdose Experience

IM aripiprazole has not been systematically studied in humans for its potential for accidental or intentional overdose. In clinical studies of the oral-tablet formulation, accidental or intentional acute overdosage of aripiprazole was identified in patients with estimated doses up to 1080 mg with no fatalities. The reported signs and symptoms observed with aripiprazole overdose included nausea, vomiting, asthenia, diarrhea, and somnolence. In the patients who were

evaluated in hospital settings, there were no reported observations indicating clinically significant adverse change in vital signs, laboratory assessments, or ECG.

7.1.17 Postmarketing Experience

N/A

7.2 Adequacy of Patient Exposure and Safety Assessments

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

7.2.1.1 Study type and design/patient enumeration

The Phase 2/3 clinical studies that were conducted to support the registration of the aripiprazole IM formulation included 3 adequate and well-controlled, placebo-controlled studies and 1 dose-tolerance study.

The Safety Sample comprised 1214 patients: 795 patients with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder (CN138012, CN138050), 291 patients with a diagnosis of bipolar I disorder, manic or mixed (CN138013), and 128 patients with a diagnosis of dementia (CN138131). A total of 660 patients received aripiprazole as initial treatment, 240 patients received haloperidol, 69 patients received lorazepam, and 245 patients received placebo. In addition, 62 placebo-treated patients received 10-mg aripiprazole as a third injection and 27 placebo-treated patients received 15-mg aripiprazole as a third injection. Therefore, from the 4 IM placebo-controlled Phase 2/3 studies a total of 749 patients received IM aripiprazole.

In the pool of 3 studies (CN138012, CN138050, CN138013), patients in the placebo group required more injections than patients in other treatment groups. This was also true in the pool of the 2 schizophrenia studies alone (CN138012, CN138050), where placebo-treated patients required more injections than aripiprazole-treated patients.

In Study CN138131, most patients received 2 injections per the protocol (Table 1.2.1.2D). Only a small number of patients received 1 injection (5.5%).

There were 86 patients in the pool of 3 studies who received ≥ 30 mg of IM aripiprazole over 24 hours. See section 1.7.5.

7.2.1.2 Demographics

Phase 2/3 Studies

Demographic Characteristics

Review of demographic characteristics showed that the treatment groups were similar with respect to mean age (range 18 to 79 years), for the pool of 3 studies (CN138012, CN138050, CN138013). The majority of patients (79%) were between the ages of 18 and 50 years. There were more men than women in all treatment groups, except for the lorazepam group in which there were more women than men. The distribution of patients for races of white and black was similar across treatment groups.

The distribution of patients in the 2 schizophrenia studies (CN138012, CN138050) (Table 1.3.2A-2), by mean age, gender, and race, was similar to that observed in the 3 pooled studies.

In Study CN138131, the treatment groups were similar with respect to overall mean age (79 to 90 years), but the distribution of patients within each age stratum varied by treatment group. There were more women than men, and more whites than blacks.

Of the 749 treated with IM aripiprazole, 99 (13%) were ≥ 65 years of age and 78 (10%) patients were ≥ 75 years of age.

Table 1.3.2A-1: Key Demographic Characteristics: IM Placebo-controlled Studies (CN138012,CN138050, CN138013), Safety Samples

		Placebo	Haloperidol	Lorazepam	Aripiprazole(a)
		N=220	N=240	N=69	N=501
Age (years)	Mean	40.25	41.45	41.46	41.43
	Median	40.00	42.00	43.00	42.00
	Min-Max	19-68	18-69	18-65	18-79
	SD	9.90	9.72	10.50	10.68
Age Group N(%)	18-50	186(85)	198(83)	56(81)	398(79)
	51-64	33(15)	40(17)	12(17)	99(20)
	>=65	1(<1)	2(1)	1(1)	4(1)
Gender N(%)	Men	127(58)	147(61)	31(45)	295(59)
	Women	93(42)	93(39)	38(55)	206(41)
Race N(%)	White	149(68)	153(64)	51(74)	358(71)
	Black	58(26)	76(32)	16(23)	118(24)
	Hispanic(b)	7(3)	3(1)		10(2)
	Asian	2(1)	1(<1)		5(1)
	Other Race	4(2)	6(3)	2(3)	10(2)
	Not Available		1(<1)		
Ethnicity(c) N(%)	Not Hispanic	122(77)	116(63)	62(90)	255(78)
	Hispanic	9(6)	16(9)	5(7)	21(6)
	Not Available	28(18)	51(28)	2(3)	49(15)

(a) Does not include the 1-mg aripiprazole dose group.
For specific details regarding this dose group, refer to the Clinical Study Report CN138050.
(b) CN138050 only.
(c) CN138012 and CN138013 only.

7.2.1.3 Extent of exposure (dose/duration)

Study Exposure

The number of patients exposed to study medication is presented in Table 14.

The clinical pharmacology program consisted of 3 completed studies: 1 absolute bioavailability study in healthy subjects (CN138016), 1 pharmacokinetic study in patients with schizophrenia (CN138017), and 1 pharmacokinetic interaction study (aripiprazole and lorazepam) in healthy subjects (CN138132). In addition, a limited number of plasma samples for the measurement of aripiprazole and dehydro-aripiprazole concentrations were obtained in the dose-ranging safety and efficacy study (CN138050). A limited number of samples were also obtained on patients with dementia in Study CN138131 to gather pharmacokinetic information on patients in this population, and pharmacokinetic results from this study are pending. An additional study [redacted] evaluating an investigational [redacted] is currently ongoing and is being conducted in patients [redacted] Data from this study are not included in this submission.

The Phase 2/3 clinical studies that were conducted to support the registration of the aripiprazole IM formulation included 3 adequate and well-controlled, placebo-controlled studies and 1 dose-tolerance study. The IM portions of these studies were 24 hours in duration. In Studies CN138012, CN138050, and CN138013, 3 injections were allowed per protocol and the number given was based on investigator judgment. In Study CN138131, 2 injections were required per the protocol. Specifics of the studies were as follows:

- 2 studies were conducted in agitated patients with schizophrenia, schizoaffective, or schizophreniform disorder. Study CN138050 evaluated 4 doses (1 mg, 5 mg, 10 mg, 15 mg per single injection) of IM aripiprazole, haloperidol (7.5 mg), and placebo in agitated patients with schizophrenia, schizoaffective, or schizophreniform disorder. Based on the results of this study, the 10-mg (per single injection) IM aripiprazole dose was chosen for Study CN138012 and was compared with IM haloperidol (6.5 mg) and placebo in patients with schizophrenia or schizoaffective disorder, followed by 4 days of the aripiprazole oral-tablet formulation or haloperidol oral-capsule formulation
- 1 study was conducted in agitated patients with bipolar I disorder, manic or mixed. This study (CN138013) evaluated 2 doses of IM aripiprazole (10 mg and 15 mg per single injection), lorazepam (2 mg), and placebo
- 1 placebo-controlled study (CN138131) was conducted in agitated elderly patients with dementia (Alzheimer's, vascular, or mixed) to determine the safety and dose tolerance of 2 injections of IM aripiprazole (total dose of 2 injections: 5 mg, 10 mg, 15 mg) in this population