CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202971Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 5, 2012

FROM: Jing Zhang, MD. PhD.
Medical Team Leader, Division of Psychiatry Products
HFD-130

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 202971

Proprietary/ Established name: Aripiprazole for Extended Release Injectable Suspension

Dosage forms/ Strength: Powder for Suspension, 300 and 400 mg

Indication: Schizophrenia Maintenance Treatment in Adults

Recommendation: Approval

1. Introduction and Background

Aripiprazole is a dopamine presynaptic D_2 auto-receptor partial agonist and belongs to atypical antipsychotic family. Same as other atypical antipsychotics, aripiprazole also acts as an antagonist at serotonin 5-HT_{1A} receptor.

ABILIFY® (aripiprazole) is initially approved by FDA for the treatment of schizophrenia in adults in 2002. Subsequently it has been approved for indications of acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate; maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate; adjunctive treatment of major depressive disorder; and treatment of irritability associated with autistic disorder. The current approved indication for the immediate-release injectable formulation of aripiprazole is treatment of acute agitation associated with schizophrenia or bipolar I disorder. Currently there are four formulations available for aripiprazole: ABILIFY oral tablets, oral solution, orally disintegrating tablets, and intramuscular injection (immediate-release).

The IM depot formulation of aripiprazole is developed under IND 67,380 for the indication of maintenance treatment of schizophrenia. A pre-IND meeting was held between the Division and representatives from Otsuka and Bristol Myers Squibb on March 4, 2003 to discuss their development program. A pre-NDA meeting was held on June 7, 2011 to discuss the non-clinical and clinical study results and receive FDA feedback on the proposed NDA for aripiprazole IM depot for the maintenance treatment of schizophrenia.

This NDA application was submitted on September 26, 2011. A filing meeting was held on November 14, 2011 and the submission was considered to be adequate to file.

2. CMC

The drug product will be marketed in two strengths (300 and 400 mg/vial) as a kit which includes a vial containing lyophilized drug substance and excipients, a vial of diluent, two needles (1.5" and 2.0"), two syringes (one for reconstitution and one for administration) and a vial adapter. It requires reconstitution in a specified volume of the provided diluent (SWFI). David J. Claffey PhD. is the ONDQA Biopharmaceutics reviewer for this NDA. He did not identify any unresolved CMC issues for this drug product except the manufacturing site inspection results are still pending. A categorical exclusion was granted as the proposed product is intended as an alterative to daily administration for patients already stabilized on aripiprazole. Please refer to his review dated May 22, 2012 in DARRTS for details.

The Center for Devices and Radiological Health (CDRH) has been consulted regarding this kit as a combination product. Jacqueline Ryan is the reviewer and she has no unresolved issues for this combination kit.

Human Factors Study Review

Division of Medication Error Prevention and Analysis (DMEPA) was consulted to review the usabiltiy study conducted by the sponsor. Yelena Maslov, Pharm.D., is the primary reviewer for this submission. In her review, he conclude that the usability study demonstrated that the 300 mg dose and 400 mg dose of the product can be prepared correctly if the Instructions for Use (IFU) or Quick Reference Guide (QRG) is followed. However, the study did not test whether participants are able extract and prepare a 200 mg dose correctly.

She also concluded that the usability study also demonstrated that the product design is prone to dosing errors due to overfill of the active ingredient, diluent, and the use of the adapter if the IFU or QRG is not used. This is particularly concerning for 200 mg dose, especially since it was not evaluated and there is risk of significant overdose.

Dr. Maslov had specific comments on the vial labels, carton, prescribing information, product IFU, QRG, and Needle-Pro syringe and needle IFU. Please refer to her review dated May 18, 2012 in DARRTS for details.

3. Nonclinical Pharmacology/Toxicology

There are no unresolved nonclinical pharmacology/toxicology issues for this application.

4. Clinical Pharmacology/Biopharmaceutics

In the current submission, the sponsor has included the results from one single-dose pharmacokinetic study in schizophrenia or schizoaffective disorder (Trial CN138-020), one multiple-dose pharmacokinetic study (Trial 31-05-244) in schizophrenia, and one Phase III efficacy and safety trial in schizophrenic patients (Trial 31-07-246). A population PK analysis of aripiprazole IM depot as well as simulations that evaluated the impact of drug-drug interactions, missed doses and dose dumping on the aripiprazole plasma concentration-time profile, were submitted to support their application.

Huixia Zhang, PhD. and Satjit Brar PhD. are clinical pharmacology reviewers for this NDA. They all agree that the sponsor had provided sufficient clinical pharmacology information to support the proposed claim and recommended an approval action. They agree with the sponsor proposed starting and maintenance dose, 400 mg administered (b) (4), and the dosing recommendations for missing doses and re-initiation treatment.

Aripiprazole is extensively metabolized by CYP3A4 and CYP2D6. However, a dose adjustment is necessary in patients who are taking aripiprazole IM depot concomitantly with CYP2D6 and/or CYP3A4 inhibitors, CYP3A4 induces and who are CYP2D6 poor metabolizers. The OCP review team has made several specific recommendations which are summarized in section 5.1.3 Dose identification/selection and limitations in this review.

5. Clinical/Statistical

5.1 Efficacy

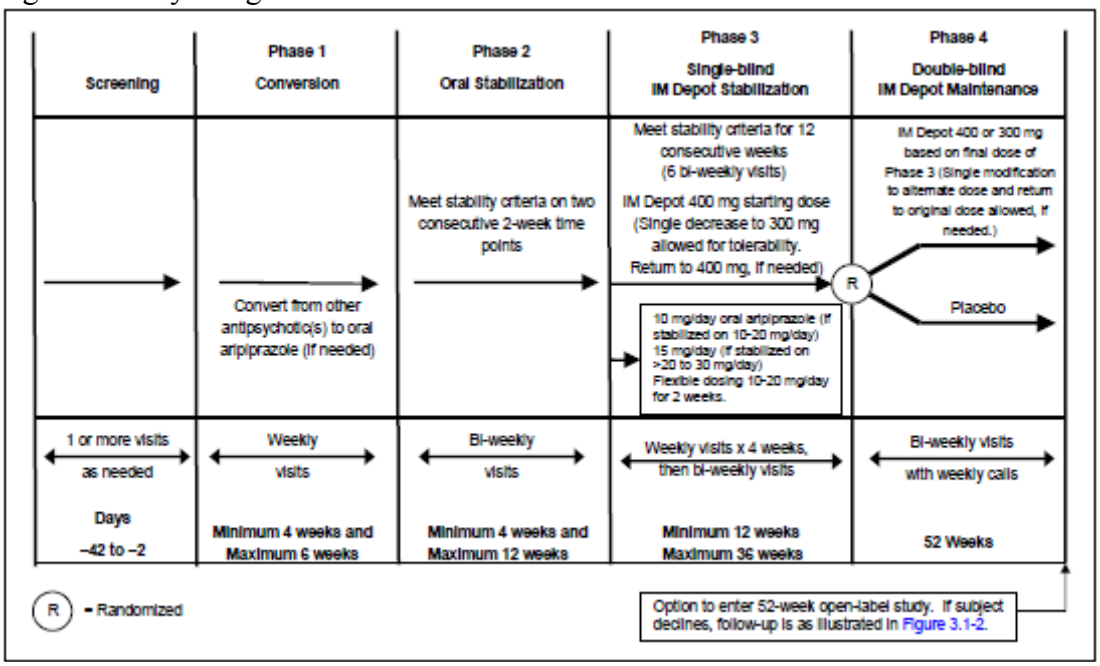
5.1.1 Clinical studies essential to regulatory decision (design, analytic features, and results)

The maintenance of efficacy of aripiprazole IM depot in adults has been established in one maintenance study, 31-07-246. This was a multi-center, double-blind, placebo-controlled, randomized withdrawal safety and efficacy study in adults (18-60 years) with a DSM-IV-TR diagnosis of schizophrenia for at least 3 years currently treated with one or more antipsychotics other than clozapine. Patients must have had a history of symptom exacerbation with interruption or discontinuation of antipsychotic treatment.

The study was conducted from 2008 to 2011 over 30 months at 108 clinical sites in 12 countries: Argentina, Bulgaria, India, Malaysia, Mexico, Philippines, Romania, Russia,

Serbia, Slovakia, Taiwan, and United States. The primary objective of the study was to demonstrate maintenance of efficacy of aripiprazole IM depot in adult in patients with schizophrenia who had maintained stability on aripiprazole IM depot for at least 12 weeks. This study was a randomized, double-blind, placebo-controlled trial consisting of a screening phase and 4 treatment phases: Conversion, Oral Stabilization, IM Depot Stabilization, and Double-blind Placebo-controlled maintenance phase (figure 1).

Figure1. Study design



After screening, subject receiving an antipsychotic other than aripiprazole were cross-titrated to oral aripiprazole 10 to 15 mg/day at the end of Phase 1. Subjects already receiving aripiprazole mono-therapy at screening entered the study at Phase 2 directly.

During Phase 2, patients were stabilized on an oral dose of aripiprazole in the range from 10 to 30 mg/day. Stability was defined as fulfilling all following criteria:

1) out-patient status
2) PANSS total score ≤80
3) PANSS score ≤4 on each of the following items:
   -conceptual disorganization.
   -suspiciousness.
   -hallucinatory behavior.
   -unusual thought content
4) CGI severity score ≤4 (moderately ill)
5) CGI-SS ≤2 (mildly suicidal) on Part 1 and ≤5 (minimally worse) on Part 2.

Patients meeting above criteria for 4 consecutive weeks (2 consecutive biweekly visits) entered Phase 3, and received single-blind aripiprazole IM depot 400mg every 4 weeks, regardless of the Phase 2 oral dose. During the IM Depot Stabilization Phase, a single decrease to aripiprazole IM depot 300 mg was permitted for tolerability, as was a single

return to the original aripiprazole IM depot 400 mg dose, if required. Oral dosing with aripiprazole (10 mg to 20 mg/day) continued for the first 2 weeks concomitant to the first IM depot injection to achieve therapeutic plasma concentrations of aripiprazole.

To proceed to the Double-blind, Placebo-controlled Phase, subjects had to meet stability criteria on single-blind aripiprazole IM depot 400 or 300 mg for 12 consecutive weeks (6 consecutive biweekly visits) in Phase 3. One excursion was allowed if the excursion did not occur on the final visit. Eligible subjects for the Double-blind, Placebo-controlled Phase were randomly assigned in a 2:1 ratio to either aripiprazole IM depot or placebo to observe for relapse. The primary efficacy endpoint was time from randomization to exacerbation of psychotic symptoms/impending relapse. The key secondary efficacy endpoint was the percentage of patients meeting criteria for exacerbation of psychotic symptoms/impending relapse. Exacerbation/impending relapse was defined as meeting any or all of the following 4 criteria:

1) CGI improvement score ≥5 (minimally worse) AND one of the following two criteria: a) an increase in any of the following PANSS item scores to a score >4 with an absolute increase ≥2 on that item since randomization: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, or b) an increase on any of these items to a score >4 and an absolute increase ≥4 on the combined score of these items since randomization, OR

2) Hospitalization due to worsening of psychotic symptoms (including partial hospitalization) but excluding hospitalization for psychosocial reasons, OR

3) CGI-SS score of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2, OR

4) Violent behavior resulting in clinically significant self-injury, injury to another person, or property damage.

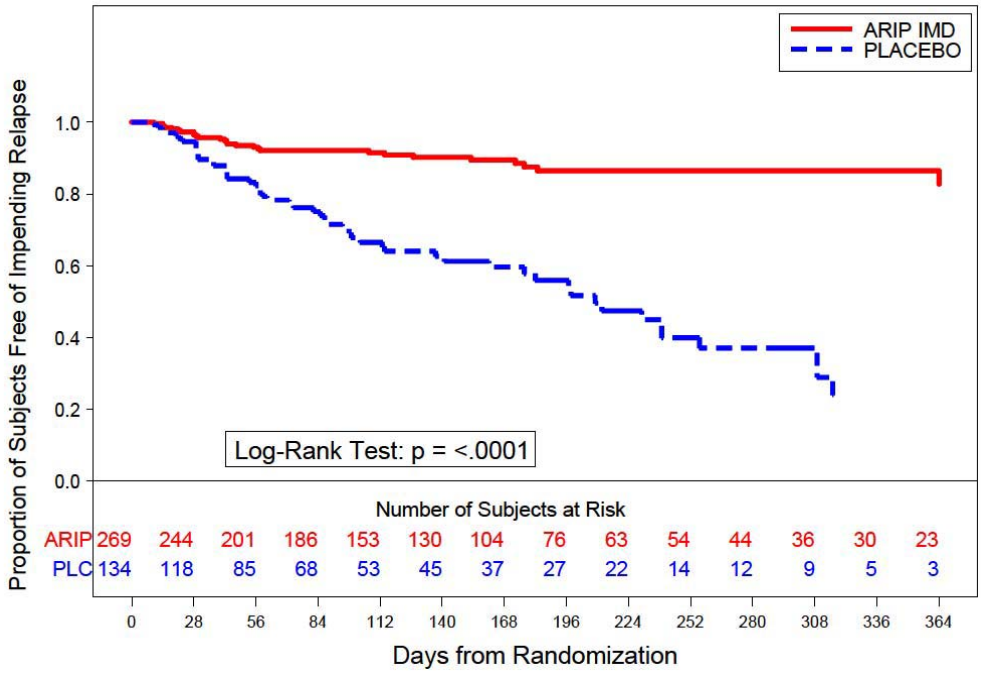
A total of 843 patients were enrolled, and 403 advanced to the Double-Blind Maintenance Phase. In the Double-Blind Maintenance Phase (randomized withdrawal phase), the demographic and baseline characteristics including baseline severity of illness were similar among the treatment group and placebo group. The mean age was 41 years (range 18-60) with a greater proportion of less than age 45 (60%). Over half were Caucasian (61%), but sizeable proportions were comprised of Black (20%) and Asian (14%) patients. The patients who entered the Double-Blind IM Depot Maintenance Phase had a mean PANSS total score of 54.5 (range 31-80) and a mean CGI-Severity score of 2.9 (range 1-4).

The first pre-specified interim analysis (after 50% of events had occurred) was conducted by the DMC using a data cut-off date of 08 June 2010. The efficacy data included 344 (230 in the aripiprazole IM depot group and 114 in the placebo group) randomized subjects and 64 events of impending relapse. Results of the interim analysis showed that time to impending relapse was significantly shorter for subjects randomized to placebo compared to subjects randomized to aripiprazole IM depot in the Double-blind, Placebo-controlled

Phase ($p < 0.0001$; log-rank test). The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole IM depot comparison was 4.72 (95% CI = 2.81, 7.94), thus subjects in the placebo group had a 4.72-fold greater risk of experiencing impending relapse than subjects in the aripiprazole IM depot group. The hazard ratio from the Cox proportional hazard model for the aripiprazole IM depot to placebo comparison was 0.212 (95% CI = 0.126, 0.357).

Because the pre-specified stopping rules have been met, the study was terminated earlier per protocol. The final efficacy analysis included 403 randomized subjects and 80 impending relapse events. The results from the final analysis were consistent with the interim analysis results in showing that the time to impending relapse was significantly shorter for subjects in the placebo group compared with subjects in the aripiprazole IM depot group (hazard ratio = 5.03, $p < 0.0001$; log-rank test). The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole IM depot comparison was 5.029 (95% CI = 3.154, 8.018), thus subjects in the placebo group had a 5.03-fold greater risk of experiencing impending relapse than subjects in the aripiprazole IM depot group. The hazard ratio from the Cox proportional hazard model for the aripiprazole IM depot to placebo comparison was 0.199 (95% CI = 0.125, 0.317). Kaplan-Meier estimates of the reliability (survival) functions for the final analyses are shown in the Figure 2.

Figure 2. Kaplan-Meier Plot of Time to Impending Relapse (Final Analysis, 80 Events)



Source: Computed by the sponsor

The key secondary efficacy endpoint, percentage of subjects meeting the impending relapse criteria, was significantly lower in the aripiprazole IM depot group (interim analysis, 9.6%; final analysis, 10.0%; $p < 0.0001$) than in the placebo group (interim analysis: 36.8%; final analysis: 39.6%).

Our statistic reviewer, Andrejus Parfionovas PhD., confirmed the sponsor's analysis results for the primary and key secondary efficacy endpoints.

During the quality assurance audit performed by the Quality Management department of Otsuka America Pharmaceutical, Inc., after completion of Trial 31-07-246, the site 046 was detected to have significant compliance issues—possible falsification of data by the study coordinator. A total of 13 subjects had been enrolled at Site 046 and 7 was advanced to Double-blind, Placebo-controlled Phases.

The inspection report from the Office of Scientific Inspection (OSI) obtained from site 002 (Dr. Khan) suggested that that data from this site may not be reliable because five subjects may not have had accurate schizophrenia diagnosis (diagnosis based on reported history without rigorous confirmation). Available medical records indicated that these five subjects had been enrolled in other clinical studies previously with primary diagnosis of ADHD (1), bipolar disorder (1), and MDD (3). A total of 27 subjects were enrolled in this site and 13 advanced to Double-blind, Placebo-Controlled Phase.

Dr. Parfionovas, repeated the primary efficacy analysis excluding site 002 as well as excluding both sites 002 and 046. The results of both reanalyses remained strongly positive ($p<0.0001$).

Dr. Parfionovas also conducted an exploratory analysis using Cox-proportional hazard model on the time to lapse in Phase 4 for the interim population subgroups. The data were grouped by gender, race, ethnicity, region (US vs. non-US), and drug dose. The subgroup analysis stratified by age was omitted because the entire population was under the age of 65. The results suggest consistent trends in favor of Aripiprazole in various subgroups except the Black/African American. The variability was quite large in this relatively small subgroup (Caucasion n=204, HR 0.184; Black n=78, HR1.462, Asian n=43 HR 0.356). Due to the lack of representation of Black/African American subgroup, no any efficacy conclusion can be drawn from this subgroup analysis.

5.1.2 Discussion of primary reviewers' comments and conclusions

Gregory Dubitsky MD., performed the clinical review and Andrejus Parfionovas, Ph.D., performed statistical review. Both of them concluded that study 31-07-246 has provided adequate evidence to support the claim that aripiprazole IM depot at doses of 400 mg or 300 mg every 4 weeks is superior to placebo in the maintenance treatment of schizophrenia in adult population. I agree with their conclusion.

5.1.3 Dose identification/selection and limitations

The sponsor proposed dose for schizophrenia maintenance treatment is 400 mg IM (b) (4) . Dose can be reduced to 300 mg IM (b) (4) if patients experience adverse events. After the first injection, oral antipsychotic should be continued for 14 consecutive days to maintain therapeutic antipsychotic concentration during initial therapy. Based on data from PK studies, the steady state concentrations of aripiprazole after 300 mg and 400

mg depot injections fell within the range of usual steady state concentration obtained from 10 mg and 15 mg oral tablet administration, which were the approved therapeutic dose for oral aripiprazole for schizophrenia indication. These doses and dosing regimen (co-administration with oral aripiprazole for 14 days) have been tested in study 31-07-246. The data showed these doses are effective and well tolerated by the patients. Even though only oral aripiprazole supplementation with IM depot was studied in study 31-07-246, there is no reason to believe that continuing other antipsychotics for 14 days after the 1st aripiprazole IM injection will cause any efficacy or safety concerns. In fact, in oral aripiprazole maintenance trial patients who were stabilized with other antipsychotics for 3 months or longer were directly randomized to oral aripiprazole and placebo in the randomized withdrawal phase to observe for relapse. The trial demonstrated the maintenance of efficacy of oral aripiprazole and led to the approval of this indication. Therefore, both clinical and clinical pharmacology review teams feel the sponsor proposed doses and dosing regimen are acceptable. They also have no objection to the proposed dosing recommendations for missing doses and re-initiation treatment. I agree with their conclusion.

Aripiprazole is extensively metabolized by CYP3A4 and CYP2D6. A dose adjustment in patients taking aripiprazole IM depot concomitantly with CYP2D6 and/or CYP3A4 inhibitors, CYP3A4 inducers or patients who are a CYP2D6 poor metabolizer should be considered. Our clinical pharmacological reviewers had several specific comments regarding these issues.

A dose adjustment in patients taking aripiprazole IM depot concomitantly with short-term (<14 days) use of CYP2D6 and/or CYP3A4 inhibitors is not required because aripiprazole IM depot dissolves slowly and the blood levels are low in the first two weeks. For patients who take aripiprazole IM depot concomitantly with long term (≥14 days) CYP2D6 and/or CYP3A4 inhibitors, a dose adjustment is required. For patients who are taking 400 mg (b) (4), the sponsor proposed to reduce dose to 300 mg IM (b) (4) with concomitant strong CYP3A4 or CYP2D6 inhibitor, and 200 mg IM (b) (4) with concomitant CYP2D6 and CYP3A4 inhibitor. However, the sponsor did not provide specific instruction for patients who take 300 mg dose. Both OCP reviewers have no objection to the proposed 400 mg dose adjustment. Additionally, they provided further dose recommendations for patients who take 300 mg every 4 weeks based on PK simulation: 200 mg IM every 4 weeks with concomitant strong CYP3A4 or CYP2D6 inhibitor, and 160 mg IM every 4 weeks with concomitant CYP2D6 and CYP3A4 inhibitor.

For patients who take a CYP3A4 inducer, the sponsor proposed no dose adjustment for short-term co-administration with a CYP3A4 inducer and use clinical judgment for long-term co-administration. Both OCP reviewers agreed that a dose adjustment is not necessary for short-term co-administration with a CYP3A4 inducer and suggest "avoid use" instead of (b) (4) for long term co-administration because (b) (4) is too vague to provide any useful advice to the health providers.

For patients who are CYP2D6 poor metabolizers (PM), [redacted] (b) (4) the safety profile collected in study 31-07-246. OCP reviewers disagree with the sponsor and suggest 300 mg IM every [redacted] (b) (4) for CYP2D6 PM because the exposures of CYP2D6 PM are consistent with that observed in long-term concomitant CYP2D6 inhibitors and 300 mg is the recommended dose for concomitant use of CYP2D6 inhibitors. Additionally, study 31-07-246 is relapse prevention study with a randomized withdrawal design. Only patients who had been tolerated the drug and were stable with the drug were selected to continue the study. Therefore, the safety profile of CYP2D6 PM in this study can not be used as the basis for dose selection.

5.1.4 Pediatric use/PREA waivers/deferrals

The sponsor requested a full waiver of requirements for pediatric studies. Their main arguments include:

1. Schizophrenia is less common overall in children and adolescents and a pediatric study may not be feasible. The onset of schizophrenia prior to age 13 is rare, with a prevalence estimated at 1 in 10,000. The estimated prevalence in adolescents (ages 13 through 17 years) is about 0.5%. Recruiting pediatric patients for a long-term placebo controlled study with aripiprazole IM depot can be very difficult and may also raise ethical concerns.

2. There is not substantial use in this population. Clinical practice guidelines for the treatment of schizophrenia in children and adolescents recommend the use of oral antipsychotics, with only limited use of depot preparations. The relapse and psychiatric hospitalization rate are low (< 10%) in pediatric population with schizophrenia. Depot formulation will not offer too much advantage when compared to oral formulation.

3. Compliance is a less concern in pediatric population. Compliance problems that make a depot formulation attractive are less common in pediatric population because medication is generally administered by a parent, guardian, or caregiver.

We consider the sponsor's arguments persuasive. The waiver request was discussed in the Pediatric Review Committee (PeRC) and a full waiver of Pediatric Rule requirements was granted by PeRC on May 9, 2012.

5.2 Safety

5.2.1 General safety considerations

As of January 16, 2012, a cumulative total of 1,324 patients had been exposed to aripiprazole IM depot in clinical trials, of which 1,233 patients participated in Phase 3 trials. There were 1,287 patients who received one or more IM doses of 300mg or 400mg, yielding a total of 1,281 patient-exposure years.

Across all trials as of the above cut-off date, 832 patients received aripiprazole IM depot 300mg or 400mg for at least 6 continuous months (7 consecutive injections) and 630 received injections of 300mg or 400mg for at least 12 continuous months (13 consecutive injections).

Dr. Dubitsky's safety review revealed no significant concerns that have not been reported with other formulations of aripiprazole with the exception of injection site reactions, which were mostly mild in severity. The safety profile of aripiprazole IM depot is very similar to that for oral Abilify products. He concluded there are no concerns or deficiencies that would preclude approval of this product or require substantial additional labeling.

5.2.2 Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

Study 31-07-246, a randomized withdrawal study, is the only pivotal study submitted to this NDA. In this study, only patients who have been exposed to 10 to 30 mg/d oral aripiprazole for at least 4 weeks and were stabilized with aripiprazole IM depot at doses of 400 mg or 300 mg for consecutively 12 weeks are eligible to enter the Double–Blind Maintenance Phase. That means subjects who entered in the Double-Blind Maintenance Phase of the study had been pre-selected and had been tolerated oral aripiprazole. Therefore, the value of the safety assessment using data from study 31-07-246 is limited. This safety review focus only on deaths, serious adverse events (SAEs), and discontinuations due to adverse events.

As of the cut off date of January 16, 2012, there were 12 deaths in patients receiving aripiprazole IM depot injections in clinical trials. Two deaths occurred during Study 31-07-246. No event leading to death was considered by the investigator to be related to treatment with aripiprazole IM depot.

A total of 14 patients experienced non-fatal SAEs during the Double-Blind Maintenance Phase of study 31-07-246—Psychotic Disorder (4 in each treatment arms), Schizophrenia (2 in each treatment arms), and Suicidal ideation (2 in Arip depot arm). These SAEs are most likely caused by patients underline psychiatric illness.

During the Double-Blind IM Depot Maintenance Phase of study 31-07-246, 7.1% (19/269) of patients treated with aripiprazole IM depot and 13.4% (18/134) of patients treated with placebo IM dropped out due to treatment-emergent adverse events (TEAEs). The adverse events most commonly resulting in dropout were related to psychosis. More placebo treated patients dropped out due to a psychosis-related adverse event (10.4% or 14/134) than did aripiprazole treated patients (3.3% or 9/269).

In study 31-07-246, all subjects began treatment at a dose of 400 mg during the IM Depot Stabilization Phase with an option to decrease once to 300 mg if they did not fully tolerate the 400 mg dose. Most subjects (518/576, 89.9%) had no dose reduction

during the IM Depot Stabilization Phase. During the Double-blind, Placebo-controlled Phase, 235/244 (96.3%) subjects starting aripiprazole IM depot 400 mg and 16/25 (64.0%) subjects starting aripiprazole IM depot 300 mg remained on their starting doses throughout the phase.

Injection site reactions

The IM administration of the aripiprazole depot formulation was well tolerated by subjects. During the IM Depot Stabilization Phase, 36/576 (6.3%) subjects experienced TEAEs related to the injection site. During the Double-blind, Placebo-controlled Phase, 13/269 (4.8%) aripiprazole IM depot and 5/134 (3.7%) placebo subjects experienced TEAEs related to the injection site.

The Injection site reaction assessments included investigator ratings of pain, redness, swelling, and induration at the injection site using a four-point scale and patient ratings of pain using a visual analog scale (VAS). Ratings were done both within 30 minutes before injection and one hour after injection. Overall, injection site reactions tended to be non-existent or mild in severity. In the double-blind phase, reaction severity was comparable between the aripiprazole IM and placebo IM treatment arms. The mean intensity of injection pain reported by subjects improved during treatment when comparing VAS scores after the first and the last injection. During Stabilization Phase, VAS was 6.1 after the first injection and 4.9 after the last injection. During the Double-blind, Placebo-controlled Phase, VAS was 5.1 (first injection) and 4.0 (last injection) in aripiprazole IM depot patients, and 5.1 (first injection) and 4.9 (last injection) in placebo patients.

6 Labeling Recommendations

There are extensive physician labeling revisions recommended by the Division, the Study Endpoints and Labeling Development (SEALD), the Pediatric Maternal Health Staff (PMHS), the Division of Professional Promotion/Office of Prescription Drug Promotion (OPDP), and the Patient Labeling Team (PLT)/the Office of Medical Policy Initiatives. We are in the process negotiating the labeling with the sponsor. The final agreed upon labeling will be attached to the action letter when this NDA is approved.

7 OSI Audits

The Office of Scientific Investigations (OSI) inspected three clinical study sites with the largest initial subject enrollment: Dr. Arifulla Khan, Site 002, 27 subjects; Dr. Mark Lerman, Site 007, 17 subjects; and Dr. Ahmad H. Sulaiman, Site 218, 15 subjects. Site 002 and 007 are located in the US and site 218 is located in Malaysia.

John Lee, MD., is the medical reviewer for this NDA in OSI. He concluded in his review that no significant deficiencies were observed at two of the three sites. A Form FDA 483 was not issued at Dr. Lerman's Site (007, US). This site conducted the study in accordance with the study protocol and applicable GCP regulations. At Dr. Sulaiman's Site (218, Malaysia), a Form FDA 483 was issued for two minor isolated deficiencies that are not

expected to impact the study outcome. The study data reviewed at these two sites appear reliable with respect to the study protocol as written and submitted to the NDA.

Several GCP violations were observed at Dr.Kahn's Site (002, US) including two violations that potential may compromise data reliability or subject safety: (1) establish schizophrenia diagnosis based on history without rigorous confirmation. Based on available medical records, five subjects were found participated in other non-schizophrenia studies previously with the primary diagnoses of ADHD (1), bipolar disorder (1), and MDD (3); (2) inadequate informed consent process, particularly with respect to assessing the subjects' contraception status. However, because this study is a multiple center study—study subjects were enrolled from 108 clinical sites in 12 countries, the violations at Site 002 had limited impact on the overall outcome of study 31-07-246. Our statistic reviewer had conducted sensitivity analyses with and without data from Site 002 and found that the overall efficacy outcome remains no change.

8 Conclusions and Recommendations

8.1 Recommended regulatory action

Due to the report of manufacturing sites inspection is still pending, a final recommendation regarding approval status on this NDA can not be made at this time. However, if the results of manufacturing site inspection are satisfactory, I will recommend an approval action on this NDA because Study 31-07-246 has demonstrated that aripiprazole IM depot was superior to placebo IM depot in delaying the time to impending relapse in patients with schizophrenia who had been stabilized on aripiprazole IM depot for at least 12 weeks. Additionally, study 31-07-246 has demonstrated that aripiprazole IM depot has a safety profile that is generally consistent with that observed in other oral aripiprazole studies.

8.2 Safety concerns to be followed postmarketing

There are no new safety concerns with aripiprazole IM depot that have become apparent from this adult maintenance trial that would require specific actions.

8.3 Risk Minimization Action Plan

Currently, I do not recommend any specific risk minimization actions.

8.4 Postmarketing studies required

I do not recommend any post-marketing study.

8.5 Comments to be conveyed to the applicant in the regulatory action letter

I do not have any comments to be conveyed to the applicant in the regulatory action letter.

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

/s/

JING ZHANG
07/05/2012