CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202971Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	202,971
Proposed Brand Name:	ABILIFY MAINTENA
Generic Name:	Aripiprazole
Dosage Form:	IM Depot (Extended-Release Suspension for IM Injection)
Dosage Strength:	300-mg Vial, 400-mg Vial
Indication:	Maintenance Treatment of Schizophrenia
Sponsor:	Otsuka
Submission Type:	505(b)(1)
Submission Date:	Sep. 26, 2011
OCP Review Team:	Huixia Zhang, Satjit Brar, Mike Pacanowski, Atul Bhattaram, Hao Zhu

OCP Required Inter-Division Briefing was held on May 14, 2012.

Table of Contents

1. EXECUTIVE SUMMARY

Otsuka is seeking approval of ABILIFY MAINTENA, aripiprazole extended-release suspension for intramuscular (IM) injection, for the maintenance treatment of schizophrenia in adult patients, via 505(b)(1) approach. Aripiprazole intramuscular (IM) depot product is a sterile, single-dose, lyophilized cake for reconstitution, extended-release injectable suspension to deliver 300 mg of aripiprazole in 300-mg/vial strength and 400 mg of aripiprazole in 400-mg/vial strength. The drug product is for gluteal injection. Currently there are four formulations available for aripiprazole: ABILIFY oral tablets, oral solution, orally disintegrating tablets, and intramuscular injection (immediate-release). For the treatment of schizophrenia in adults, the recommended initial dose is 10-15 mg/day, with recommended dose of 10-15 mg/day, and maximal dose of 30 mg/day.

The efficacy of aripiprazole extended release suspension for injection was established in a 52-week, double-blind, placebo-controlled maintenance trial in adult patients who met DSM-IV-TR criteria for schizophrenia (Trial 31-07-246). The single-dose (Trial CN138-020) and multiple-dose (Trial 31-05-244) pharmacokinetics of aripiprazole IM depot formulation were characterized in patients with schizophrenia or schizoaffective disorder.

We found that the proposed dosing and reinitiation regimens are acceptable. A maintenance dose of 300 mg of aripirprazole given once (b) (4) is expected to be efficacious. Further dose adjustments in CYP2D6 poor metabolizers and in patients receiving CYP2D6 and/or CYP3A4 inhibitors are recommended (Table 1). In addition, aripirprazole IM injection is not recommended to be used with long-term coadministration of CYP3A4 inducers.

1.1. Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in the NDA to support a recommendation of approval of Aripiprazole IM depot formulation. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comment
Overall	Yes	Pending labeling
Evidence of effectiveness	Yes	One positive registration trial in adults
Proposed dose for adult patients	No	Refer to Table 1.
Labeling	No	Pending satisfactory agreement with the sponsor

1.1.1. Labeling Recommendations

Major labeling changes are listed as follows. The final labeling language is subject to change pending satisfactory agreement with the sponsor.

1 INDICATIONS AND USAGE

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Limitation of Use: the effect of ABILIFY MAINTENA may decrease with concomitant use of CYP3A4 inducers (eg. carbamazepine). Concomitant use should be avoided.

2.3 Dosage Adjustments (b) (4) **for Missed Doses**

(b) (4)

Table 1: Dose Adjustments in Patients Taking Concomitant CYP2D6 inhibitors, 3A4 inhibitors, and/or CYP3A4 inducers for greater than 14 days (b) (4)

	Adjusted Dose
Patients Taking 400 mg of ABILIFY (b) (4)	
Strong CYP2D6 inhibitors **or** strong CYP3A4 inh bitors	300 mg
CYP2D6 **and** CYP3A4 inhibitors	200 mg
CYP3A4 inducers	Avoid Use
Patients Taking 300 mg of ABILIFY (b) (4)	
strong CYP2D6 OR strong CYP3A4 inhibitors	200 mg
CYP2D6 **and** CYP3A4 inhibitors	160 mg
CYP3A4 inducers	Avoid Use
Patients Who are Poor Metabolizers of CYP2D6	
Poor Metabolizers of CYP2D6	300 mg
Poor Metabolizers of CYP2D6 taking concomitant strong CYP3A4 inhibitors	160 mg

When the inhibitor or inducer is withdrawn, change the ABILIFY MAINTENA dose *[see Dosage and Administration (2.1)]*.

1.2. Phase IV Requirements/Commitments

No Phase IV study recommendation.

1.3. Summary of Clinical Pharmacology Findings

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 patients, and one efficacy and safety Phase III 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. The results indicated the following:

- Aripiprazole IM depot is efficacious in the maintenance treatment of schizophrenia in adults.
- Based on simulation results, the sponsor proposed and the agency recommended dosing regimens are listed in Table 1. FDA recommendations are italicized.

Table 1: Sponsor-Proposed and FDA-Recommended Dosing of Aripipraozle IM Depot

Sponsor Proposed Dosing	FDA's Assessment and Recommendations
Dosing Initiation an Maintenance	
The recommended starting and maintenance dose is 400 mg administered (b) (4) . (b) (4) (b) (4)	We concur based on 1) multiple dose pharmacokinetic study and 2) population pharmacokinetic simulations.
Dosing Interval and Re-initiation after Missed Doses	
(b) (4)	We concur based on pharmacokinetic simulations.
(b) (4)	We concur based on pharmacokinetic simulations.
Dosing Recommendations for Drug Interactions	
(b) (4)	We concur based on pharmacokinetic simulations.
(b) (4)	We concur based on pharmacokinetic simulations.

(b) (4)	
(b) (4)	We recommend the following dosing regimen based on pharmacokientic simulations. *For patients taking 300 mg dose:* *Patients taking aripiprazole concomitantly with long term (≥14 days) CYP 2D6 and/or CYP3A4 inhibitors require a dose adjustment.* • *200 mg IM every 4 weeks with concomitant strong CYP3A4 inhibitor* • *200 mg IM every 4 weeks with concomitant strong CYP2D6 inhibitor* • *160 mg IM every 4 weeks with both concomitant CYP2D6 and CYP3A4 inhibitor.*
(b) (4)	We recommend the following: *Long term coadministration of CYP3A4 inducer with Aripiprazole IM depot injection is not recommended.*
Dosing Recommendations for CYP 2D6 Poor Metabolizer Status Patients	
(b) (4)	We recommend the following dosing regimen based on pharmacokinetic simulations: *For patients who are known to be CYP2D6 poor metabolizers, the recommended dose is 300 mg.*

Furthermore, the pharmacokinetic features of aripprazole following the IM depot administration are summarized as follows:

- After aripiprazole IM depot administration (15 mg to 400 mg), absorption of aripiprazole from the site of injection into the systemic circulation is slow and prolonged. Median T_{max} was 7-24 days and 7-25 days for aripiprazole and dehydro-

aripiprazole, respectively. Mean $T_{1/2}$ was 11-34 days and 12-40 days for aripiprazole and dehydro-aripiprazole, respectively. More than dose-proportional increase in AUC was observed after single dose administration in the range of 15-400 mg.

- After multiple dose administration of 200 mg, 300 mg, and 400 mg of IM depot formulations, maximum aripiprazole concentrations were reached within 5 to 7 days with mean aripiprazole apparent terminal $T_{1/2}$ of 30 to 47 days; maximum dehydro-aripiprazole concentrations were reached within 6 to 13 days. Approximate dose proportional increase in AUC was observed after multiple doses of 300 mg and 400 mg.
- After monthly (b) (4) administration of aripiprazole IM depot, steady state was reached by the 4th IM depot injection, with no significant accumulation observed after the 4th administration.
- Aripiprazole is extensively metabolized, mainly by CYP3A4 and CYP2D6. Active metabolite (equipotent to aripiprazole) dehydro-aripiprazole circulates at a level about ~ 30% of the parent at steady state (oral tablet steady state: ~40%). Notably, the ratios of dehydro-aripiprazole to aripiprazole for mean Cmax and AUC0-τ (dose interval AUC) PK parameters after the fifth monthly injection of aripiprazole IM Depot in the range of 200 mg to 400 mg were 29.1% to 33.2%. As this ratio is comparable to the oral dosing, the dehydro-aripiprazole concentrations were not considered in the simulation to asses dosing recommendations for the IM Depot.
- After aripiprazole IM depot administration, aripiprazole dissolves slowly due to the low water solubility and the crystal structure of aripiprazole monohydrate, and is absorbed into the systemic circulation from the site of injection. The physiochemical properties of the aripiprazole IM depot formulation makes it unlikely that dose dumping into the systemic circulation would occur. No evidence of dose dumping was observed in the clinical trials.

2. QUESTION BASED REVIEW

2.1. Specific Questions

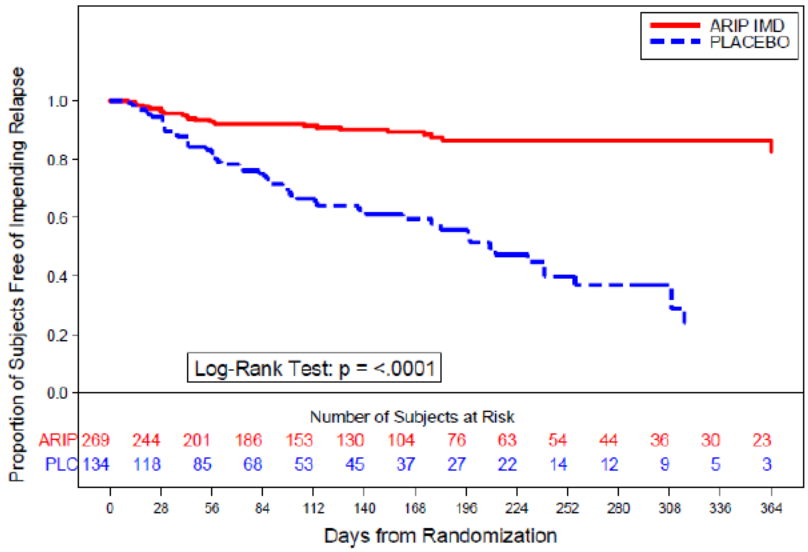
2.1.1. Is there evidence of effectiveness for aripiprazole IM depot in schizophrenic adult patients (prescribability)?

Yes. The efficacy of IM depot in schizophrenic patients was demonstrated in study 31-07-246.

Study 31-07-246 was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of aripiprazole IM depot compared with placebo, in subjects with schizophrenia who had maintained stability on aripiprazole IM depot for at least 12 weeks. The trial consisted of a screening phase and 4 treatment phases: Phase A (conversion to oral aripiprazole monotherapy), Phase B (oral aripiprazole stabilization phase), Phase C (single-blind aripiprazole IM depot stabilization phase), and Phase D (double-blind, placebo-controlled phase). The primary efficacy endpoint of the trial was the time from randomization to impending relapse in the double-blind, placebo-controlled phase (Phase D).

The study results showed that the time to impending relapse was significantly shorter for the subjects in the placebo group compared with subjects in the aripiprazole IM depot group (Figure 1). The subjects in the placebo group had a 5-fold greater risk of experiencing impending relapse than subjects in the aripiprazole IM depot group.

Figure 1: Kaplan-Meier Product Limit Plot of Time to Impending Relapse (Study 31-07-246)



2.1.2. Is the proposed dosing regimen appropriate?

Yes. The sponsor's proposed regimen is tabulated in Table 2. Based on individual patient tolerability, some patients may benefit from 300 mg dose.

Table 2: Proposed Dosing Regimen for Aripiprazole IM Depot

Dose	Oral Tablet (10mg-20 mg/Day)	IM Depot Injection
Initial Dose	Consecutive 14 days with the 1st Injection	400 mg on the 1st day
Maintenance	None	400 mg* (b) (4)

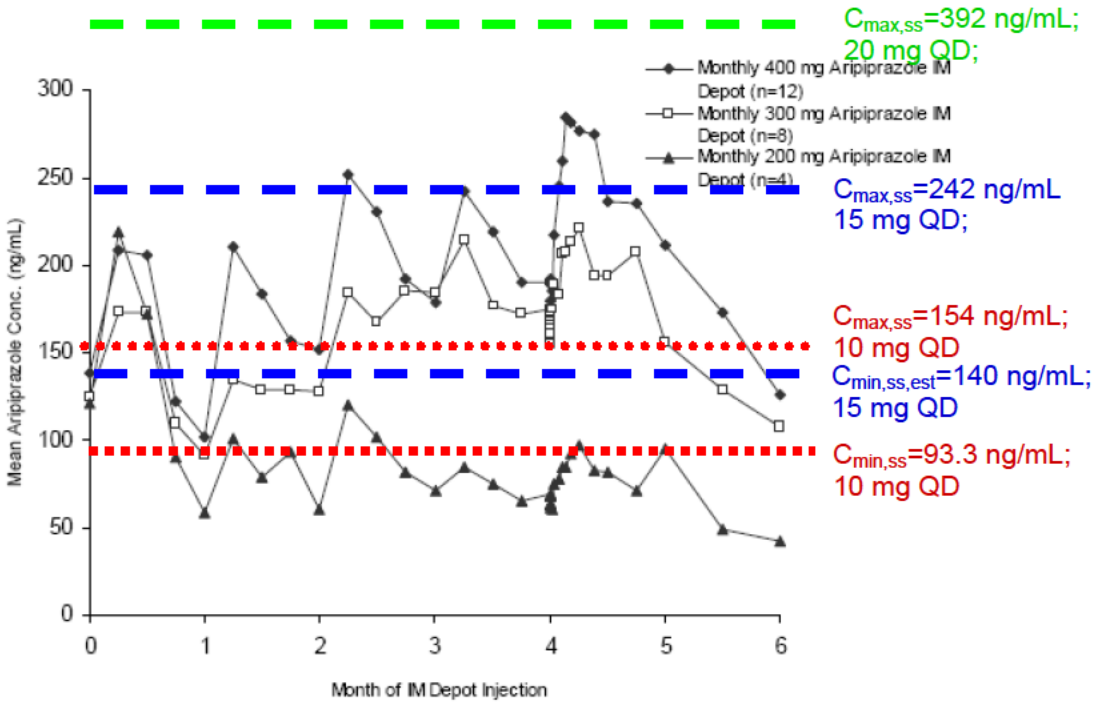
* Note: patients may have dose reduced to 300 mg depending on tolerability.

- ***Assessment of the proposed initiation dosing regimen***

From a PK perspective, the proposed initiation dosing regimen is appropriate. The multiple dose phase I PK study was conducted under similar design as the proposed regimen. Before patients received the 1st injection, all patients were stabilized on 10 mg oral aripiprazole tablet. The 1st IM injection was accompanied by 14 days of oral aripiprazole. For the last four doses of IM depot injection, the dose was given (b) (4). The aripiprazole concentration time profile was shown in Figure 2. 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 levels. Mean steady state concentrations of aripiprazole after 200 mg depot injection, were below the

Cmin levels of 10 mg QD, which was not recommended under standard conditions. Oral supplementation, for the first 2 weeks was also performed during the pivotal trial. There were no tolerability issues or lack of efficacy during this phase. Therefore, the proposed initiation dosing regimen is appropriate.

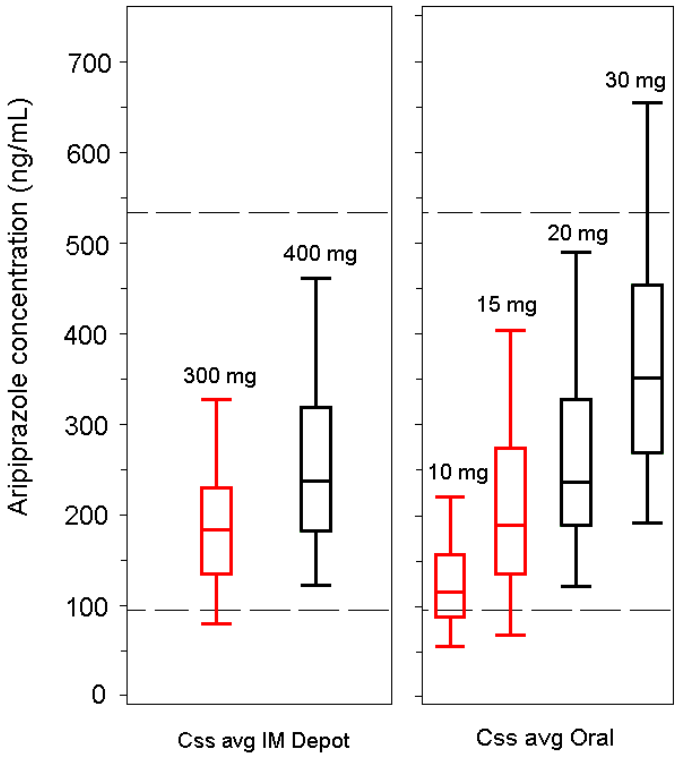
Figure 2: Mean Steady State Aripiprazole Concentrations After 200 mg, 300 mg, and 400 mg IM Depot Injection



- ***Assessment of the proposed maintenance dosing regimen***

In addition to 400 mg, a 300-mg maintenance dose is considered appropriate. The effectiveness of aripiprazole, as demonstrated in Trial 31-07-246, is likely driven by patients receiving 400 mg aripiprazole IM depot injection (300 mg dose was given to only 16 (~6%) patients). Population pharmacokinetic simulations were conducted to assess whether 300 mg is an acceptable maintenance dose. For oral aripiprazole, the maintenance trial was conducted in patients receiving 15 mg daily dosing. Steady state average aripiprazole exposure following 300 mg dose once [redacted] (b) (4) is similar to that following 15 mg oral daily dosing (Figure 3). In addition, the minimum aripriprazole concentration (Cmin) in patients receiving 300 mg dose once [redacted] (b) (4) is above the steady state Cmin in patients administered with 15 mg oral daily dosing (Figure 2).

Figure 3: Simulated Average Steady State Aripiprazole Concentrations for IM Depot 300mg and 400 mg (left plot) and Oral 10, 15, 20, and 30 mg (right plot). The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole.



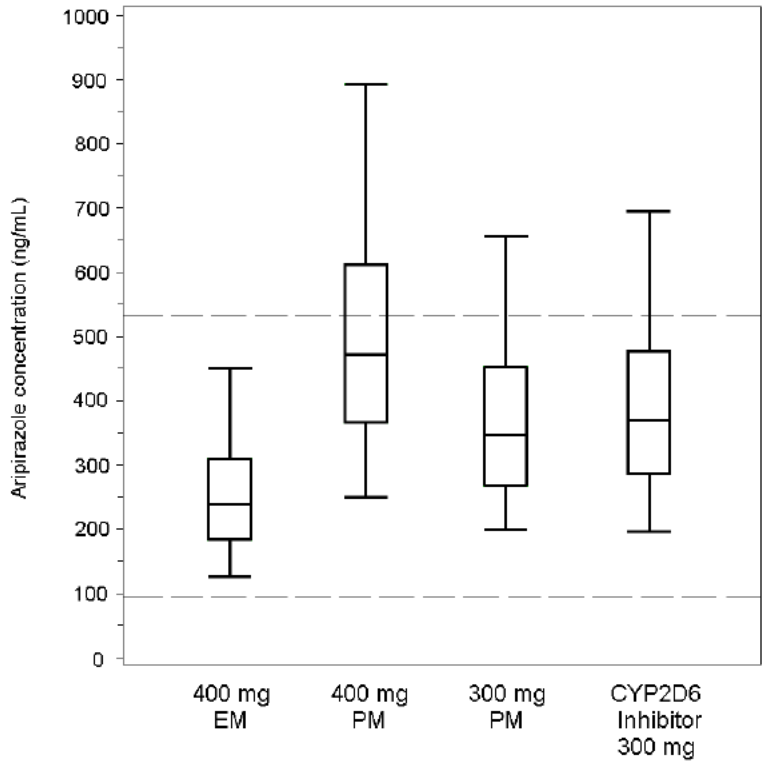
2.1.3. What is the recommended dose for patients who are CYP2D6 poor metabolizers?

A 300 mg IM Depot dose is recommended for patients who are CYP2D6 poor metabolizers (PM). As presented in Table 3 and Figure 4, steady state aripiprazole exposures are higher in PMs compared to extensive metabolizers (EM), in which approximately a two-fold difference in exposures is observed. According to steady state aripiprazole exposures and mean $AUC^{ss}_{(0\text{-}28\ days)}$, a 300 mg IM Depot dose is recommended for patients who are CYP2D6 PMs and the exposures are consistent for the dosing recommendation for patients taking concomitant CYP2D6 inhibitors for more than 14 days (the upper 75% percentiles are similar between the two scenarios). Based on clinical need, the dosing may be increased to 400 mg.

Table 3: Simulated Exposure ($AUC^{ss}_{(0\text{-}28\ days)}$) of 300mg and 400 mg IM Depot for Patients who are CYP2D6 PM and EM Status.

Dosing	Mean	SD	Median	25th percentile	75th percentile
CYP2D6 Metabolizing status $AUC^{ss}_{(0\text{-}28\ days)}$					
400 mg EM status	172.6	69.2	160.2	124.0	207.8
400 mg PM status	340.5	136.6	316.0	244.6	410.0
300 mg PM status	255.4	102.5	237.0	183.4	307.5
Concomitant administration of a Long-term CYP2D6 Inhibitor - $AUC^{ss}_{(0\text{-}28\ days)}$					
300 mg IM Depot with 2D6 Inhibitor	264.7	106.2	245.6	190.1	318.7

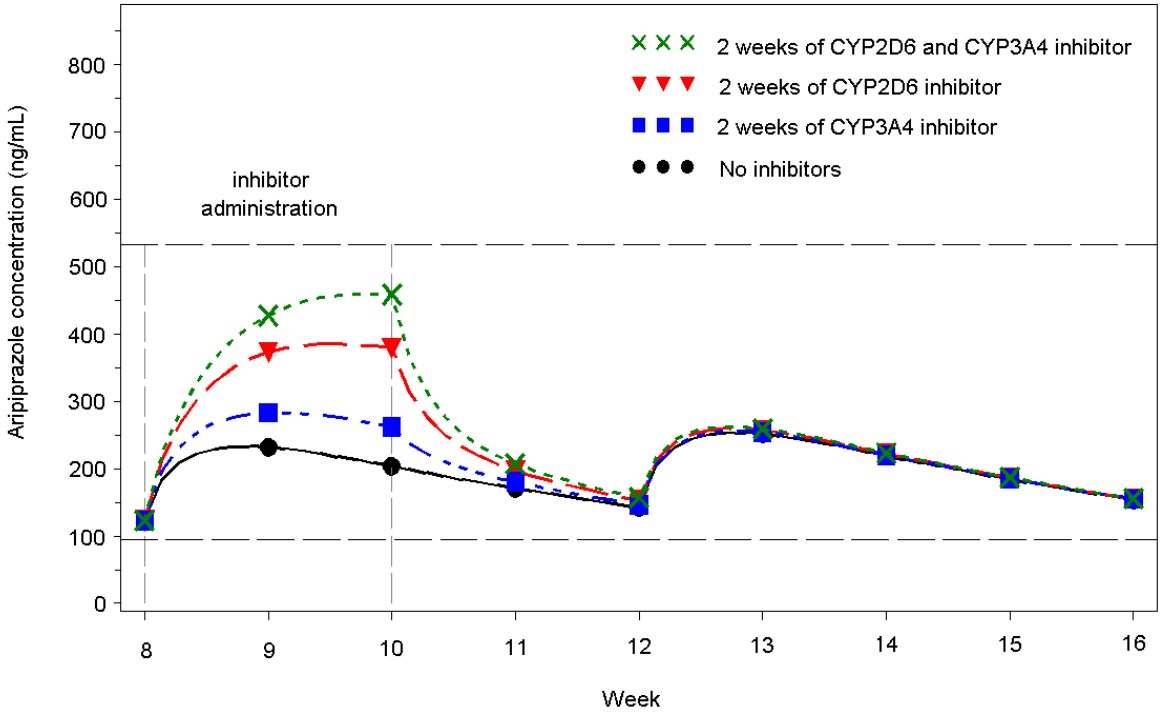
Figure 4: Simulated Average Steady State Aripiprazole Concentrations for IM Depot 400mg in Extensive Metabolizers (EM), 400 mg and 300 mg in Poor Metabolizers (PM), and 300 mg in EM with long term concomitant CYP2D6 Inhibitor.



2.1.4. What is the recommended dose for patients taking aripiprazole IM depot formulation concomitantly with short-term CYP3A4 and/or CYP2D6 inhibitors?

The sponsor's suggestion of no dose reduction of IM Depot, in this case of short term inhibitor use, is appropriate. Upon evaluation of simulated steady state aripiprazole concentrations after 400 mg IM depot administration in conjunction with a CYP3A4 inhibitor, a CYP2D6 inhibitor, or both CYP3A4 and CYP2D6 inhibitor for 14 days, aripiprazole concentrations are maintained within the therapeutic window (Figure 5). In each case, effects of the inhibitor dosing are washed out by 14 days post-inhibitor dosing.

Figure 5. Median Aripiprazole Concentrations vs. Time for presence of short-term (<14 days) administration of CYP2D6 and/or 3A4 Inhibitor after the 3rd IM dose. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Vertical lines denotes the time of inhibitor administration.



2.1.5. What is the recommended dose for patients taking aripiprazole IM depot formulation concomitantly with long-term CYP3A4 and/or CYP2D6 inhibitors?

Under the regular maintenance dose of 400 mg, the dose should be reduced to 300 mg IM if given concomitantly with either a strong CYP3A4 *or* CYP2D6 inhibitor. Moreover, a 200 mg IM Depot dose should be given with concomitant CYP3A4 *and* CYP2D6 inhibitor. The sponsor's recommendation is appropriate. Similarly, for patients receiving 300 mg maintenance dose, we recommend the dose should be reduced to 200 mg IM if given concomitantly with either a strong CYP3A4 or CYP2D6 inhibitor. In addition, the dose should

be further reduced to 160 mg if given concomitantly with both CYP3A4 and CYP2D6 inhibitors.

Assessment of simulated steady state aripiprazole concentrations after IM Depot administration in conjunction with chronic use (>14 days) CYP3A4 inhibitor, a CYP2D6 inhibitor and both CYP3A4 and/or CYP2D6 inhibitor, show that aripiprazole concentrations are increased (Figure 6). Steady-state exposures ($AUC^{ss}_{(0\text{-}28\ days)}$) for the recommended dosing regimen adjustment are provided in Table 4 below. The 75th percentile exposures for all dosing recommendations are below the upper margin of the therapeutic window while the 25th percentile is above the lower margin of the therapeutic window. Therefore, for patients stabilized on 400 mg, the current recommendation of decreasing the dose to 300 mg IM if given concomitantly with either a CYP3A4 *or* CYP2D6 inhibitor (Figure 7) is appropriate. Moreover, a 200 mg IM Depot dose should be given with concomitant CYP3A4 *and* CYP2D6 inhibitor. The sponsor's recommendation is appropriate. Following the same rationale, for patients stabilized on 300 mg IM depot, further dose adjustment is recommended to ensure the exposure falls within the established therapeutic window.

Figure 6 Median Aripiprazole Concentrations vs. Time for presence of long-term (>14 days) administration of a CYP 3A4 Inhibitor, a CYP2D6 Inhibitor and both a CYP3A4 and CYP2D6 Inhibitor after the 10th and 11th IM dose of 400 mg. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Dosing of IM Depot is at steady state.

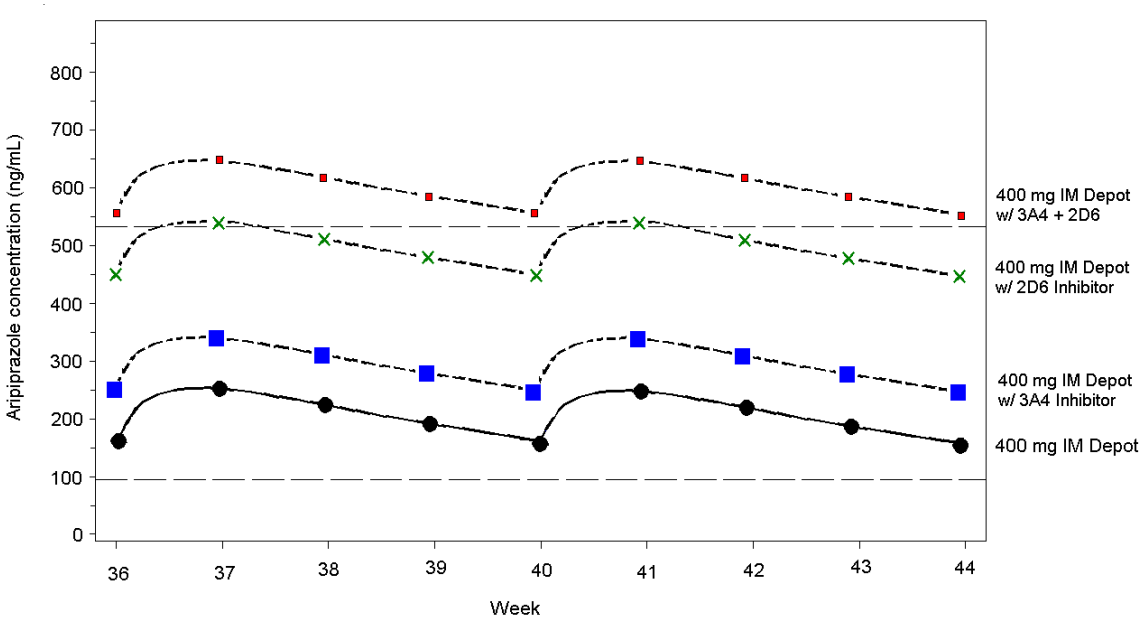
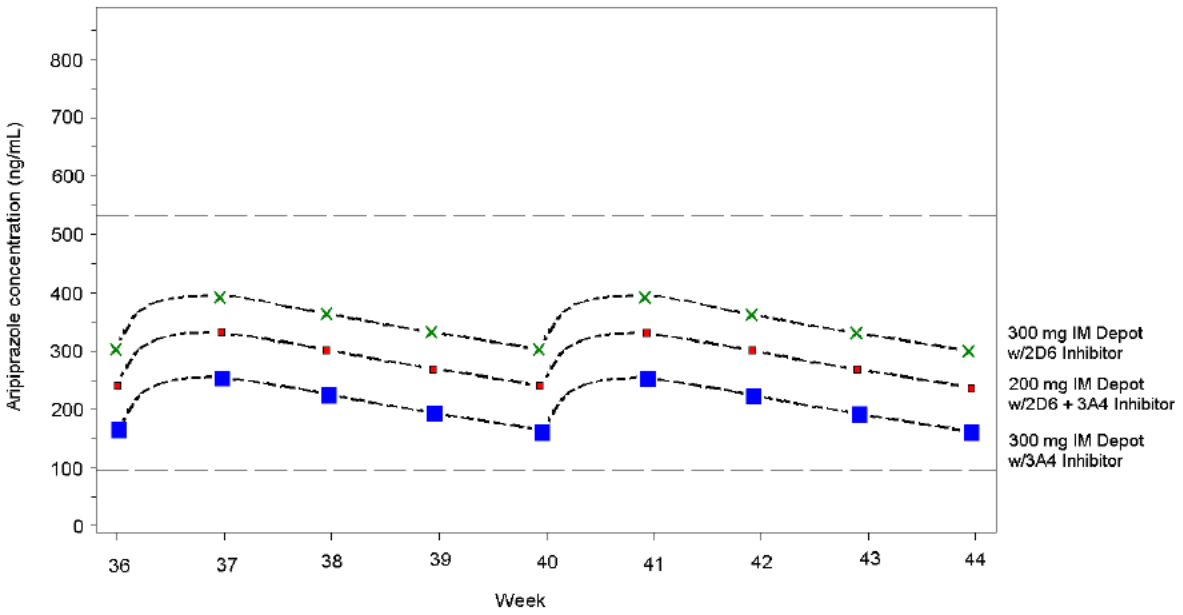


Table 4. Simulated Exposure ($AUC^{ss}_{(0\text{-}28\ days)}$) of the Recommended Adjusted Dosing Regimens for Concomitant Long Term Administration of CYP2D6 and/or CYP3A4 Inhibitors.

Dosing	Mean	SD	Median	25th percentile	75th percentile
Without Inhibitor - $AUC^{ss}_{(0\text{-}28\ days)}$					
400 mg IM	172.6	69.2	160.2	124.0	207.8
Concomitant administration of a Long-term Inhibitor - $AUC^{ss}_{(0\text{-}28\ days)}$					
300 mg IM Depot with 2D6 Inhibitor	264.7	106.2	245.6	190.1	318.7
300 mg IM Depot with 3A4 Inhibitor	169.6	68.1	157.4	121.8	204.2
200 mg IM Depot with 2D6 and 3A4 Inhibitor	231.2	92.8	214.6	166.1	278.4

Figure 7 Median Aripiprazole Concentrations vs. Time for presence of long-term (>14 days) administration of a CYP 3A4 Inhibitor, a CYP2D6 Inhibitor and both a CYP3A4 and CYP2D6 Inhibitor for the recommended dosing. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Dosing of IM Depot is at steady state. Of note, the 400 mg IM Depot PK profile mimics the 300 mg IM Depot profile given with a 3A4 inhibitor.



2.1.6. What is the recommended dose for CYP2D6 PMs taking aripiprazole IM depot formulation concomitantly with long-term CYP3A4 inhibitors?

For CYP2D6 PMs, we recommend that the dose be further reduced to 160 mg if given concomitantly with CYP3A4 inhibitors.

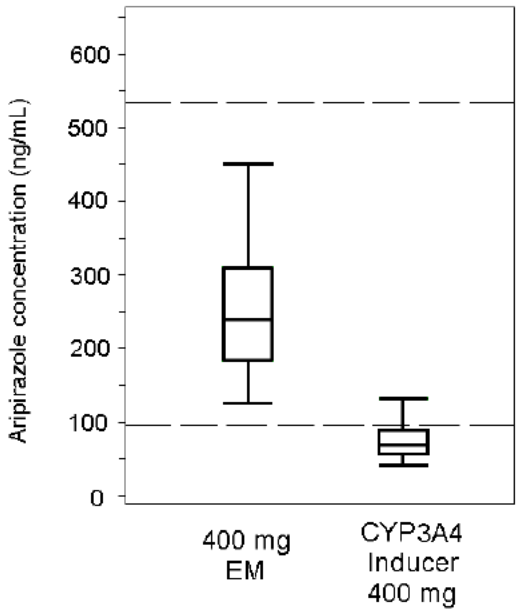
Similar aripiprazole exposure increase is expected in CYP2D6 PMs concomitantly receiving long-term CYP3A4 inhibitors as compared to CYP2D6 EMs receiving long-term CYP3A4 and CYP2D6 inhibitors. Therefore, a dose reduction to 160 mg IM depot is necessary to ensure the exposure falls within the established therapeutic window.

2.1.7. What is the recommended dose for patients taking aripiprazole IM depot formulation concomitantly with long-term CYP3A4 inducers?

As 400 mg is the largest dosage form for the IM Depot formulation, dosing adjustment for this interaction may not be feasible and it is suggested that patients be warned not to use a combination of CYP3A4 inducers with this formulation.

Based on the original label for oral aripirazole (Abilify®), concomitant administration of a CYP3A4 inducer greatly decreases the exposure of plasma aripiprazole. For example, the coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg/day) resulted in an approximate 70% decrease in Cmax and AUC values of both aripiprazole. In this case, doubling the dose is recommended. Based on simulations, an approximate four-fold decrease in steady state aripiprazole plasma concentrations is evident upon long-term concomitant administration of a CYP3A4 inducer with 400 mg IM Depot (Figure 8). Individuals in the pivotal clinical trial were not permitted to take concomitant CYP3A4 inducers, so it is unsure of what the clinical implications are of this interaction. The current proposal for the label does not suggest any dosing recommendations for this interaction.

Figure 8. Simulated Average Steady State Aripiprazole Concentrations for IM Depot 400mg and With Concomitant Long-Term Administration of a CYP3A4 Inducer. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole.



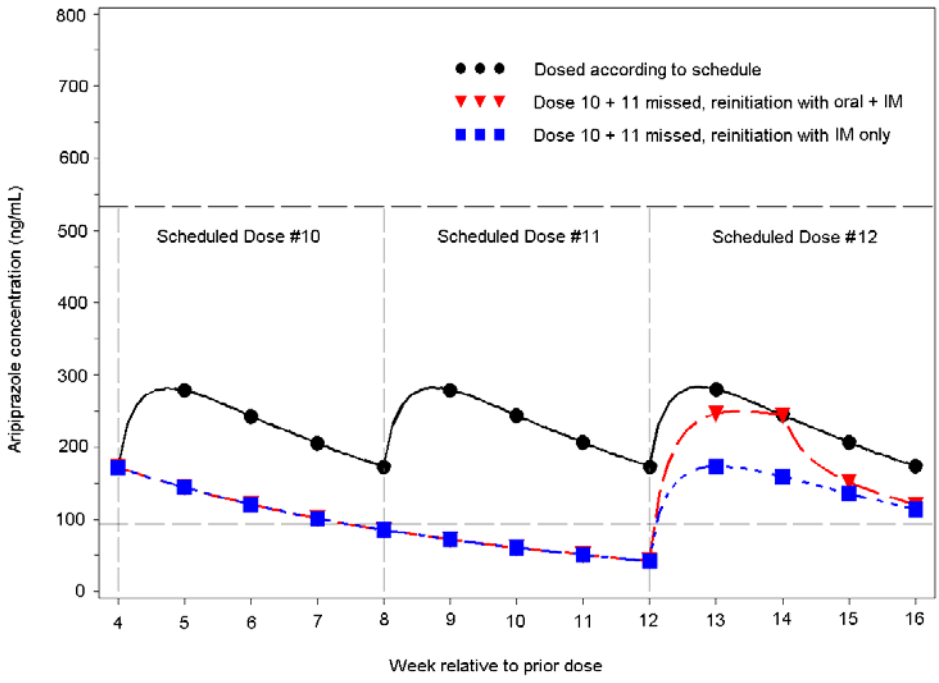
2.1.8. What is the flexible dosing window for aripiprazole IM depot injection? What is the reinitiation dosing strategy?

The proposed dosing for the IM Depot formulation is once (b) (4) but no sooner than (b) (4) from the last injection. After initiation, the recommended dosing interval is once (b) (4). The current recommendation for dosing re-initiation is 14 days of oral aripiprazole 10 mg along with the IM Depot dose of 400 mg, and is acceptable. To avoid re-initiation of oral aripiprazole administration, the following dosing guideline should be adhered to:

- The 2nd and 3rd administration of aripiprazole IM Depot should occur within 5 weeks (up to one week delay of scheduled dose). If beyond 5 weeks, the re-initiation regimen is: concomitant oral aripiprazole for 2 weeks + 400 mg IM Depot.
- After the 4th aripiprazole IM depot administration (patient at steady state), the subsequent administrations of aripiprazole IM depot should occur within 6 weeks (up to 2 weeks delay of scheduled dose). If beyond 6 weeks, the re-initiation regimen is: concomitant oral aripiprazole for 2 weeks + 400 mg IM Depot.

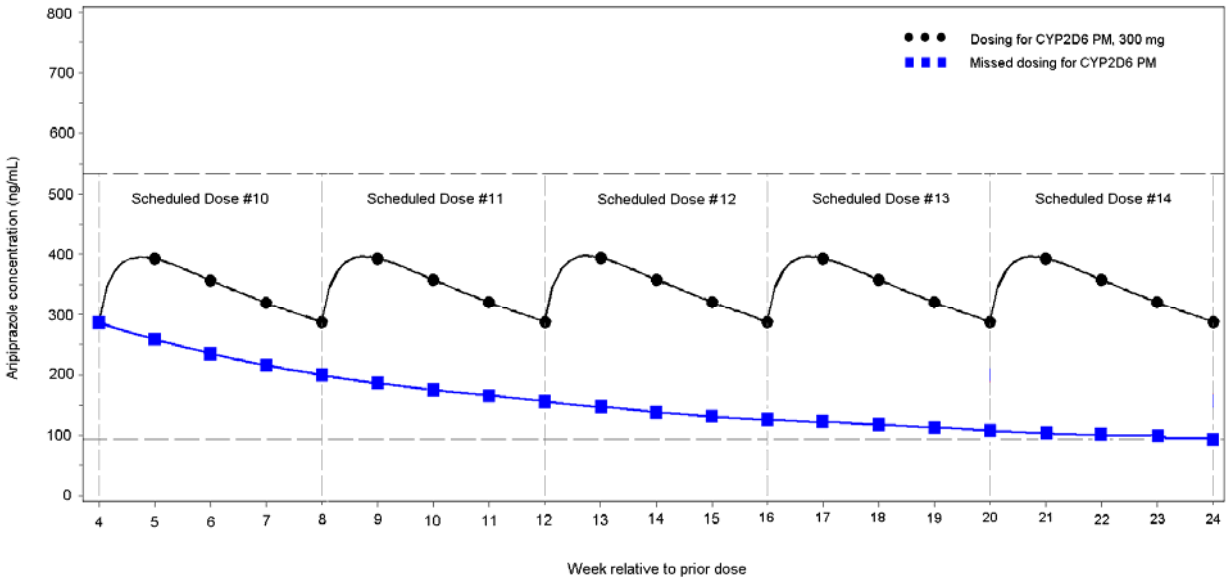
Figure 9 shows that when that when aripiprazole IM Depot dosing is re-initiated with 14 days of orally aripiprazole doses of 10 mg, median aripiprazole concentrations are similar to a scenario in which subjects did not miss any doses within 2 weeks post-dose and remain within the therapeutic window for the remainder of the dosing interval.

Figure 9 Median Aripiprazole Concentrations vs. Time for when 10th and 11th doses missed, and reinitiation with 400 mg IM only and 400 mg IM + 10 mg Oral for 14 days. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Dosing of IM Depot is at steady state.



For patients who are CYP2D6 PM status, or on long-term CYP2D6 inhibitors, the adjusted dose is 300 mg. Presumably, aripiprazole concentrations would remain within the therapeutic window for a longer period of time for these individuals compared to CYP 2D6 EM patients. Figure 10 shows that when that when aripiprazole IM Depot dosing is stopped at the 10th scheduled dose (at steady state), concentrations remain therapeutic for approximately 5 months after the dosing has stopped. In this case, reinitiating oral dosing can occur at any time after 6 weeks after the last IM depot dose out to 6 months after the last IM depot dose. For patients who are CYP2D6 PM status, or on long-term CYP2D6 inhibitors, the same re-initiation strategy employed for CYP 2D6 EM patients is appropriate. For these patients, re-initiation of oral dosing is with 14 days of the recommended oral aripiprazole dose, along with 300 mg IM Depot dose.

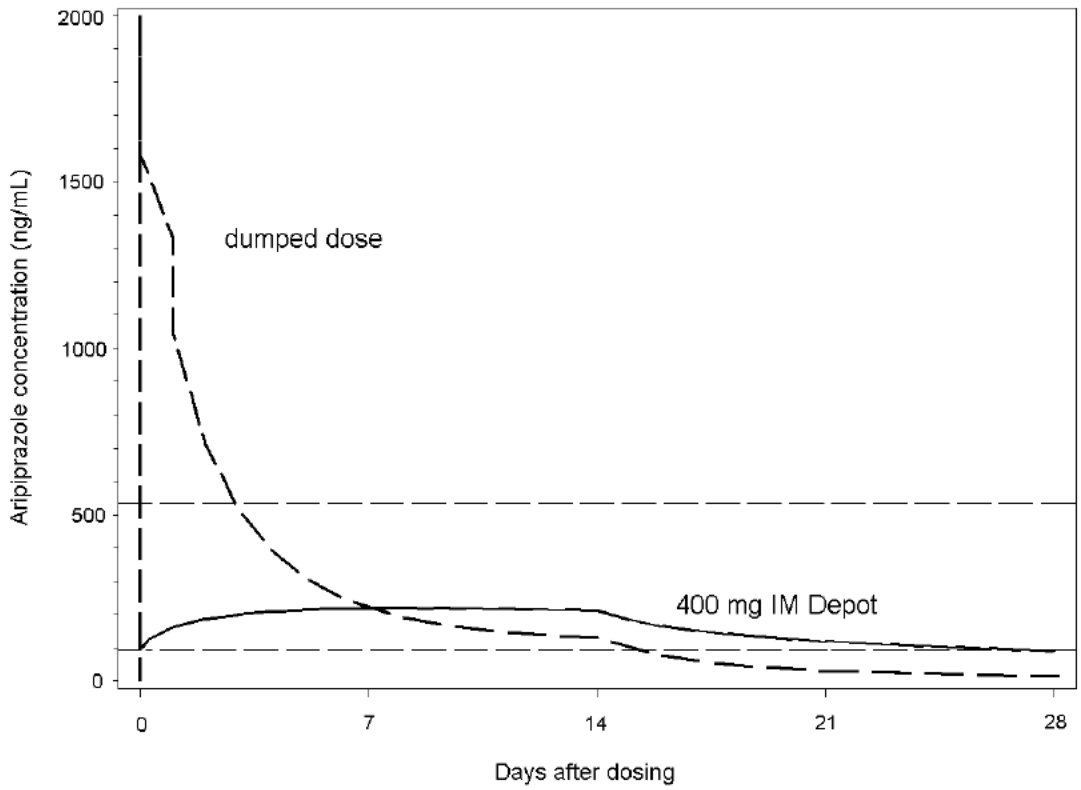
Figure 10 Median Aripiprazole Concentrations vs. Time for patients who are CYP2D6 PM status or on long-term (>14 days) CYP2D6 inhibitors (300mg IM Depot maintenance). The blue line denotes the time course of aripiprazole after dosing is stopped at the 10th scheduled dose. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Dosing of IM Depot is at steady state.



2.1.9. What is the scenario if there is a dosing dumping after injection of aripiprazole IM depot formulation?

Based on the safety data and the results of safety data in the pivotal trial (Study 31-07-246), no evidence of dose dumping was observed in this trial. Simulated aripiprazole concentrations following dose dumping, show a decline to concentrations normally observed following the administration of 400 mg IM depot within 3 days after the entire aripiprazole IM depot dose is absorbed in the systemic circulation (see Figure 11). It is important to note, that the peak would reach ~4,500 ng/mL (about 9 times above the therapeutic window) but the concentrations would descend rapidly.

Figure 11. Simulated Median Aripiprazole Concentrations vs. Time for Dose Dumping of 400 mg IM Depot (same as IV bolus). The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Of note, concentrations peaked at ~ 4,500 ng/mL and scale only to 2,000 ng/mL.



2.2. Standard Questions

2.2.1. What are the single dose PK characteristics of Aripiprazole IM depot formulation in adult patients?

Aripiprazole absorption into the systemic circulation is slow and prolonged following intramuscular injection, due to low solubility of aripiprazole particles. Following a single intramuscular dose, flip-flop kinetics was demonstrated for aripiprazole. The plasma concentrations of aripiprazole gradually rise to reach maximum plasma concentrations at a median Tmax of 7 to 24 days (Table 5). The mean aripiprazole terminal elimination half-life was determined by the absorption rate of aripiprazole into the systemic circulation, and was about 11 to 35 days after single dose gluteal injection of IM depot formulation. In the dose range of 15 mg to 400 mg, aripiprazole demonstrated nonlinear kinetics after single dose administration of IM depot formulation. Based on its plasma concentration-time profiles, aripiprazole release from the IM depot injection occurred within 4 hours after single 400 mg dose injection.

Table 5: PK parameters (mean (SD)) of aripiprazole after single gluteal administration of IM depot formulation

PK Parameters	15 mg (n=2)	50 mg (n=2)	100 mg (n=4)	200 mg (n=3)	300 mg (n=3)	400 mg (n=3)
T_{max} [a] (day)	7.5 (4-10)	9.5 (4-15)	24.0 (4-25)	7.0 (4-7)	7.0 (4-11)	22 (4-22)
C_{max} (ng/ml)	4.8 (3.1)	10.6 (2.2)	44.5 (29.4)	67.3 (24.2)	86.0 (20.6)	92.1 (82.0)

$AUC_{0\text{-}inf}$ (hr*µg/mL)	4.5 (0.07)	12.7 (2.4)	41.7 (15.8)	71.0 (19.9)	115 (23)	80.4 (82.8)
$T_{1/2}$ (day)	27.4 (19.1)	34.3 (10.3)	19.5 (8.5)	18.9 (3.6)	24.9 (10.8)	10.5 (3.9)
[a] reported as median (range) *Source: Table 9.2A of CN138020 Study Report*						

Following a single intramuscular aripiprazole IM depot formulation, the active metabolite dehydro-aripiprazole gradually reached its peak level in the plasma within 7 to 25 days. The terminal plasma half life was about 12 to 40 days (Table 6). Based on its plasma concentration-time profiles, dehydro-aripiprazole reached the systemic circulation within 36 hours after single 400 mg dose injection.

Table 6: PK parameters (mean (SD)) of dehyrdro-aripiprazole after single gluteal administration of aripiprazole IM depot formulation

PK Parameters	15 mg (n=1)	50 mg (n=2)	100 mg (n=4)	200 mg (n=3)	300 mg (n=3)	400 mg (n=3)
T_{max} [a] (day)	11 (-)	13 (11-15)	24.5 (11-34)	7.0 (7-11)	15.0 (11-54)	22 (8-34)
C_{max} (ng/ml)	2.37 (-)	2.57 (1.3)	11.2 (5.8)	19.9 (8.0)	21.7 (8.6)	33.2 (13.6)
$AUC_{0\text{-}inf}$ (hr*µg/mL)	1.5 (-)	3.9 (0.08)	12.3 (2.8)	27.8 (8.5)	35.6 (10.1)	31.3 (17.3)
$T_{1/2}$ (day)	12.5 (-)	40.2 (11.7)	30.5 (22.6)	17.4 (3.3)	32.9 (24.5)	12.1 (3.8)
[a] reported as median (range) *Source: Table 9.3 of CN138020 Study Report*						

2.2.2. What are the multiple dose PK characteristics of Aripiprazole IM depot formulation in adult patients?

After multiple dose administration of aripiprazole IM depot formulation, the plasma concentrations of aripiprazole gradually rise to reach maximum plasma concentrations at a median T_{max} of 5-7 days. The mean aripriprazole terminal elimination half life was 30 days and 47 days after Q4W injections of IM depot 300 mg and 400 mg, respectively (Table 7). After monthly (every 28 days) administration of aripiprazole IM depot, steady state was reached by the 4th IM depot injection, with no significant accumulation observed after the 4th administration. Aripiprazole $C_{ss,max}$, AUC_{τ}, and $C_{ss,min}$ increased almost dose-proportionally; when the 300 and 400 mg injections were compared.

Table 7: PK parameters (mean(SD)) of aripiprazole after multiple gluteal administration of IM depot formulation

PK Parameters	200 mg (n=4)	300 mg (n=8)	400 mg (n=10)
$C_{max,ss}$ (ng/ml)	100 (68.4)	269 (128)	316 (160)
$C_{min,ss}$ [a] (ng/ml)	95.0 (86.2)	156 (67.7)	212 (113)

$C_{ave,ss}$ (ng/ml)	81.1 (58.7)	208 (87)	242 (132)
AUC_{τ} (hr*µg/mL)	54.5 (39.4)	140 (58.4)	163 (88.8)
T_{max} [b] (day)	5.0 (4.0-27.9)	6.5 (0.5-21.2)	7.1 (3.0-11.2)
$T_{1/2}$ (day)	ND[c]	29.9 (8.0) [d]	46.5 (10.8) [e]
[a] Css,min=aripiprazole conc. at 672 hrs [b] median (min-max) [c] not determined [d] n=4 [e] n=6 *Source:* Table 9.2.3.2.1-1 of Clinical Study Report 31-05-244			

After multiple dose administration of aripiprazole IM depot formulation, the plasma concentrations of dehydro-aripiprazole gradually rise to reach maximum plasma concentrations at a median T_{max} of 5.5-12.5 days (Table 8). The ratios of dehydro-aripiprazole to aripiprazole for mean $C_{ss,max}$ and AUC_{τ} after the fifth Q4W injection of aripiprazole IM depot were about 29% .

Table 8: PK parameters (mean(SD)) of dehydro-aripiprazole after multiple gluteal administration of aripiprazole IM depot formulation

PK Parameters	200 mg (n=4)	300 mg (n=8)	400 mg (n=10)
$C_{max,ss}$ (ng/ml)	30.3 (19.8)	74.7 (20.8)	89.4 (37.9)
$C_{min,ss}$ [a] (ng/ml)	26.2 (24.7)	54.1 (21.1)	64.1 (27.0)
AUC_{τ} (hr*ng/mL)	14.7 (9.47)	38.9 (13.2)	47.8 (19.1)
T_{max} [b] (day)	5.5 (0-27.9)	12.5 (0.5-22.2)	6.6 (3.0-14.0)
[a] Css,min=dehydro-aripiprazole conc. at 672 hrs [b] median (min-max) *Source:* Table 9.2.3.2.2-1 of Clinical Study Report 31-05-244			

SIGNATURES

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3. APPENDICES

3.1. Individual Study Reports

3.1.1. Single-Dose Pharmacokinetics of Aripiprazole in Schizophrenia or Schizoaffective Disorder

Report # CN138-020	**Study Period**: 9/19/2003-12/02/2005 Analytical Period: [redacted] (b) (4)	EDR Link
Title	Assessment of the In Vivo Release Characteristics and Safety of an Intramuscular Depot Formulation of Aripiprazole in Subjects with Schizophrenia or Schizoaffective Disorder	

Study Design: This was an open-label, two-phase, non-randomized, ascending dose, sequential-panel study in subjects with schizophrenia or schizoaffective disorder.

Enrolled subjects received a single dose of 5 mg aripiprazole standard intramuscular (IM) formulation (Phase 1) followed by safety and pharmacokinetic (PK) monitoring. After 28 day washout interval, subjects returned to the clinical facility to receive a single dose of either 15, 50, 100, 200, 300 or 400 mg of aripiprazole IM depot formulation (Phase 2), followed by safety and PK monitoring.

Number of Subjects: 10 completed	**Drug Administered:** Aripiprazole IM depot formulation & Aripiprazole standard IM formulation

Dose (mg): IM depot: 15, 50, 100, 200, 300, 400
IM standard: 5

PK Sampling Times: Blood samples (2 mL per sample) were collected at pre-dose (0 hr), 0.25 (15 min), 0.5 (30 min), 1, 2, 3, 4, 6, 8, 10, 12, 24, and 36 hr after dosing on Days 1 and 2 and on Days 3, 4, 5, 6, 8, 12, 16, 20, and 23 for Phases 1 and 2, and on Weeks 4, 5, 6, 8, 12, 16, 20, 24, and 28 for Phase 2 relative to dosing.

Analytical Method:

Type: LC/MS/MS	**Range:** 1.0 -250 ng/mL
The performance of the analytical method is acceptable.	☑ Yes ☐ No

Study Population :

Randomized/Completed/ Discontinued Due to AE	21/10/0
Age [Mean (range)]	39 (19-57)
Male/Female	18/3
Race (Caucasian/Black/Asian/other)	8/10/0/3

Results

- Aripiprazole

Table 1: Pharmacokinetics Parameters (Geometric mean (%CV)) of Aripiprazole in Patients with Schizophrenia or Schizoaffective Disorder

PK Parameters	Aripiprazole Standard IM 5 mg (n=20)	Aripiprazole IM Depot					
		15 mg (n=2)	50 mg (n=2)	100 mg (n=4)	200 mg (n=3)	300 mg (n=3)	400 mg (n=3)
$AUC_{0\text{-}inf}$ (hr*ng/mL)	1439 (42.0)	4515 (1.7)	12707 (19.0)	41709 (37.7)	71008 (28.3)	114540 (20.4)	80415 (103)
$AUC_{(0\text{-}T)}$ (hr*ng/mL)	1243 (44.8)	2763 (42.9)	11452 (17.2)	40020 (38.6)	68035 (31.8)	101275 (30.5)	78400 (101)
C_{max} (ng/ml)	28.0 (35.8)	4.82 (64)	10.6 (20.6)	44.5 (66.4)	67.3 (36.2)	86.0 (23.7)	92.1 (88.9)
$T_{1/2}$[a] (hr)	97.5 (30.8)	657 (459)	824 (247)	467 (204)	453 (86.5)	597 (260)	252 (93.8)
T_{max}[b] (hr)	0.50 (0.25-10.0)	180 (96.0-240)	228 (96.0-360)	577 (96.0-600)	167 (96.0-168)	168 (96.0-265)	528 (96.0-528)
Frel based on $AUC_{(0\text{-}T)}$	-	0.90 (39.1)	1.44 (24.1)	1.17 (23.1)	1.22 (19.8)	1.24 (31.0)	1.10 (32.9)
Frel based on Cmax	-	0.04 (72.6)	0.05 (10.8)	0.07 (76.3)	0.04 (50.1)	0.07 (88.2)	0.05 (92.7)

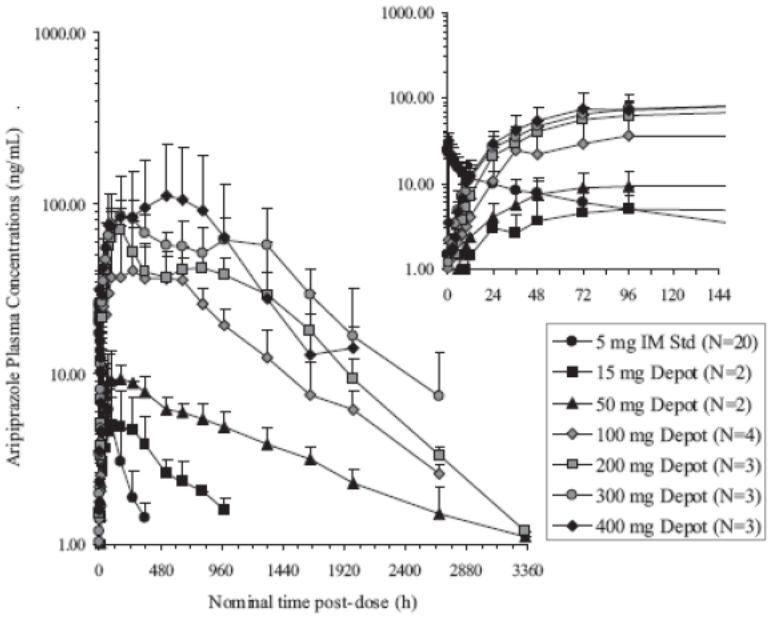
[a] reported as mean (SD); [b] reported as median (range)
Source: Table 9.2A of CN138020 Study Report

In general, for aripiprazole single doses with IM depot formulation ranging between 15 to 400 mg, Cmax of aripiprazole increased approximately in a dose-proportional manner to aripiprazole dose up to 200 mg, and less than proportionally between 200 and 400 mg (Table 2). $AUC_{(0\text{-}T)}$ of aripiprazole increased more than proportional with aripiprazole dose between 15 to 400 mg dose range with IM depot formulation (Table 2).

Table 2: Aripiprazole Cmax and AUC Ratios across the Dose Range

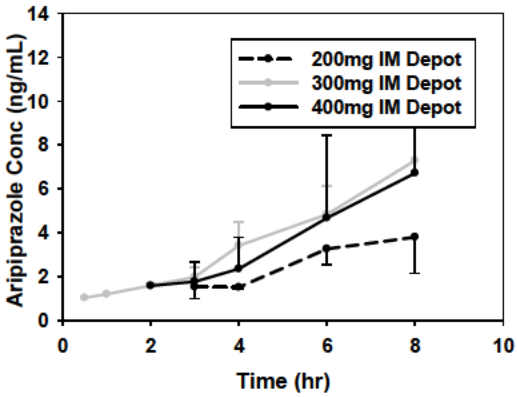
Dose (mg)	15	50	100	200	300	400
Dose ratio	1	3.3	6.7	13.3	20	26.7
Cmax ratio	1	2.2	9.2	14	17.8	19.1
$AUC_{(0\text{-}T)}$ ratio	1	4.1	14.5	24.6	36.7	28.4

Figure 1: Mean Plasma Concentrations Versus Time Profiles for Aripiprazole Following IM administration of Aripiprazole Depot Formulation



Source: Figure 9.2A of CN138020 Study Report

Figure 2: Mean Plasma Concentrations Versus Time Profiles for Aripiprazole Following IM administration of Aripiprazole Depot Formulation (First 8 hrs post dose)



After single dose administration of aripiprazole IM depot formulation, there was a lag time before aripiprazole reached systemic circulation. For the 400mg treatment group, by 2 hr postdose, only one subject have quantifiable concentration of aripiprazole; by 3hr post dose, two out of three subjects have quantifiable concentration of aripiprazole with a mean of 1.77 ng/mL. By 4 hr postdose, all three subjects have measured concentration of aripiprazole with a mean of 2.35 ng/mL.

- Dehydro-Aripiprazole

Table 3: Pharmacokinetics Parameters (Geometric mean (%CV)) of Dehydro-Aripiprazole in Patients with Schizophrenia or Schizoaffective Disorder

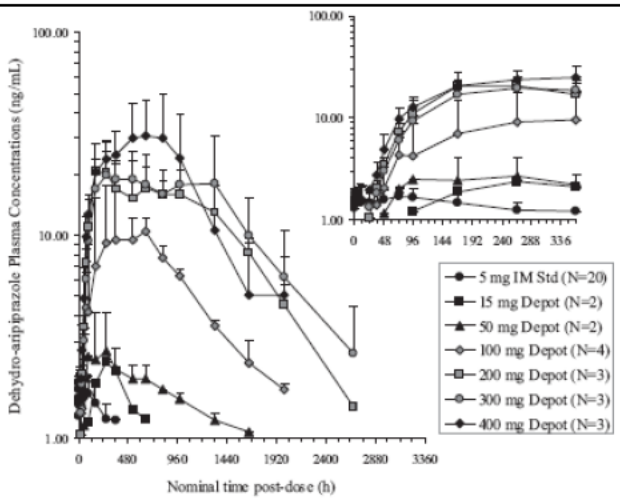
	5 mg (n=20)	(n=1)	(n=2)	(n=4)	(n=3)	(n=3)	(n=3)
$AUC_{0\text{-}inf}$ (hr*ng/mL)	849 (71.2)	1454 (-)	3922 (2.21)	12255 (22.9)	27796 (30.7)	35551 (28.3)	31256 (55.3)
$AUC_{(0\text{-}T)}$ (hr*ng/mL)	262 (53.0)	915 (-)	2368 (11.5)	10420 (26.1)	26293 (34.5)	28795 (41.0)	29864 (50.8)
C_{max} (ng/ml)	1.73 (21.1)	2.37 (-)	2.57 (49.9)	11.2 (52.0)	19.9 (40.2)	21.7 (39.6)	33.2 (41.1)
$T_{1/2}$[a] (hr)	388 (405)	301 (-)	964 (281)	731 (542)	418 (80.1)	789 (588)	290 (91.6)
T_{max}[b] (hr)	72 (48-96)	264 (264-264)	312 (264-360)	588 (264-816)	168 (167-264)	361 (264-1296)	528 (192-816)
Frel based on $AUC_{(0\text{-}T)}$	-	- (-)	- (-)	2.16 (0.45)	1.61 (0.47)	2.35 (2.36)	3.72 (-)
Frel based on Cmax	-	- (-)	- (-)	0.45 (46.5)	0.27 (31.9)	0.24 (19.7)	0.24 (-)
Source: Table 9.3 of CN138020 Study Report [a] reported as mean (SD); [b] reported as median (range)							

In general, for aripiprazole single doses ranging between 15 to 400 mg with IM depot formulation, Cmax of dehydro-aripiprazole increased less than dose proportionally with aripiprazole dose, and AUC(0-T) of dehydro-aripiprazole increased more than proportionally with aripiprazole dose (Table 4).

Table 4: Dehydro-Aripiprazole Cmax and AUC Ratios across the Dose Range

Aripiprazole Dose (mg)	15	50	100	200	300	400
Dose ratio	1	3.3	6.7	13.3	20	26.7
Cmax ratio	1	1.1	4.7	8.4	9.2	14
$AUC_{(0\text{-}T)}$ ratio	1	2.6	11.4	28.7	31.5	32.5

Figure 2: Mean Plasma Concentrations Versus Time Profiles for Dehydro-Aripiprazole Following IM administration of Aripiprazole Depot Formulation



Source: Figure 9.3 of CN138020 Study Report

- Was the pharmacokinetics dose proportional? ☐Yes ☑ No
  In general, for aripiprazole single doses with IM depot formulation ranging between 15 to 400 mg, Cmax of aripiprazole increased dose proportionally with aripiprazole dose up to 200 mg and less than proportionally between 200 and 400 mg. $AUC_{(0\text{-}T)}$ of aripiprazole increased more than proportional with aripiprazole dose between 15 to 400 mg dose range with IM depot formulation.
- The pharmacokinetics is best described by:
  ☐Mono-exponential decay, ☑ Bi-exponential decay, ☐ Tri-Exponential Decay
- Was there a lag time in absorption? ☑ Yes ☐ No

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- What is the maximum tolerated dose? 400 mg.
- What are the safety profiles of the highest dose?

Treatment with aripiprazole (5-400 mg IM formulation) was generally safe and well-tolerated by the subjects in this study. The most common AEs were mild to moderate headache (19% of subjects) and mild anxiety (14.3% of subjects). There were no deaths or discontinuation due to AEs.

Comments

Aripiprazole is mainly metabolized by two enzymes CYP3A4 and CYP2D6, and poor metabolizers of CYP2D6 are expected to have higher level of exposure of aripiprazole. No genotype information of the enrolled subjects were collected for this study, therefore, the effect of CYP2D6 genotype on the exposure of aripiprozole after IM depot injection could not be evaluated.

In terms of data quality, the PK samples appear to be collected in a reasonable manner. However, a large variability was observed for 400 mg dose group (CV ~ 100% for AUC) vs other dose groups (CV ~ 20-30%). The reason is unclear.

3.1.2. Multiple-Dose Pharmacokinetics of Aripiprazole in Patients with Schizophrenia

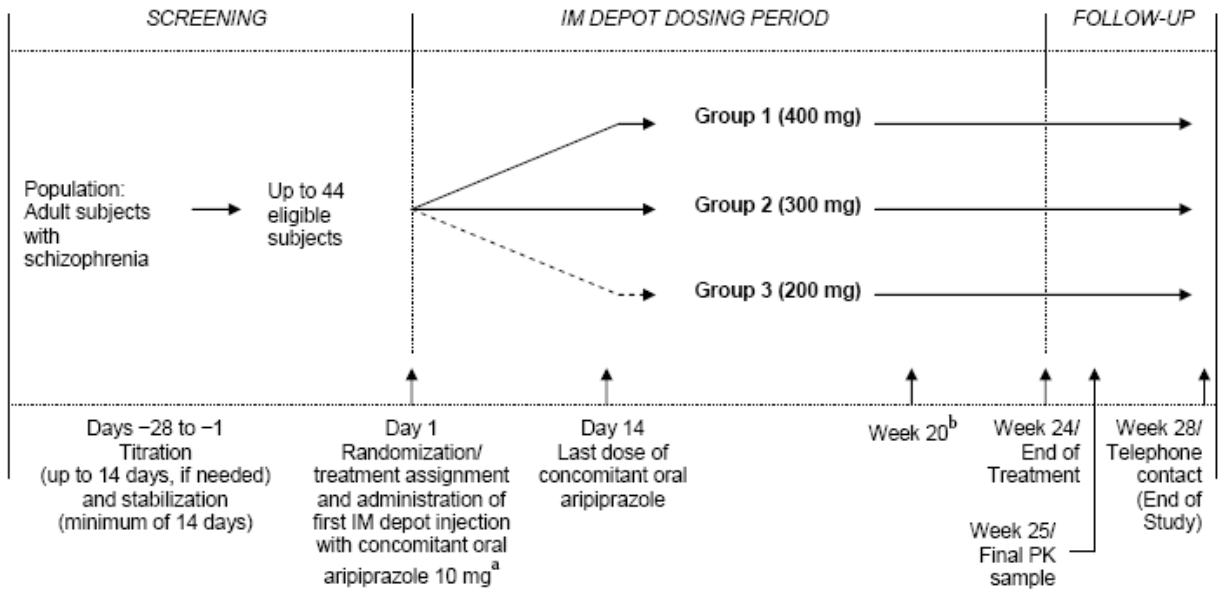
Report # 31-05-244	**Study Period**: 11/07/2007-10/20/2008 Analytical Period: (b) (4)	EDR Link
Title	An Open–label Parallel Arm Multiple Dose Tolerability, Pharmacokinetics and Safety	

	Study in Adult Patients with Schizophrenia Following Administration of Aripiprazole IM Depot Formulation Once Every Four Weeks

Study Design: This study was an open-label, parallel-arm, multiple-dose, multi-center study that included three groups of subjects with a diagnosis of schizophrenia. After titration/stabilization on oral aripiprazole, the following doses of aripiprazole IM depot were to be administered every 4 weeks for 5 months (total of IM injections per subject in each group):
Dose Level 1: 400 mg dose group (Group 1)
Dose Level 2: 300 mg dose group (Group 2)
Dose Level 3: 200 mg dose group (Group 3)

Initially, up to 32 subjects were to be randomized to either Group 1 (400 mg) or Group 2 (300 mg). Once randomization had completed for Groups 1 and 2, 10 to 12 subjects were to be enrolled in Group 3 (200 mg). At least 5 subjects within each dose group were to receive a minimum of 3 injections of aripiprazole IM depot and have PK samples collected through at least 672 hours following the last dose.

Figure 1: Study Design Scheme



Source: Figure 5.1-1 of Clinical Study Report 31-05-244

Number of Subjects:	**Drug Administered:**
41 enrolled/22 completed	Aripiprazole IM depot formulation & oral Aripiprazole

Dose (mg): Oral aripiprazole: 10
IM depot: 200, 300, 400

PK Sampling Times: Blood samples were collected predose (ie, before an IM depot injection and before oral aripiprazole dosing when the latter was to occur) at each injection visit (ie, Day 1 and Weeks 5, 9, 13, and 17). Single PK samples were also obtained at Weeks 2, 3, 4, 6, 7, 8, 10, 11, 12, 14, 15, and 16. After the fifth IM depot injection at Week 17, blood samples for PK analysis were collected at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168 (Week 18), 264 (Week 18.5), 336 (Week 19), 504 (Week 20), 672 (Week 21), 1008 (Week 23), and 1344 (Week 25) hours.

Analytical Method:

Type: LC/MS/MS	**Range:** 0.5 -250 ng/mL
The performance of the analytical method is acceptable.	☑ Yes ☐ No

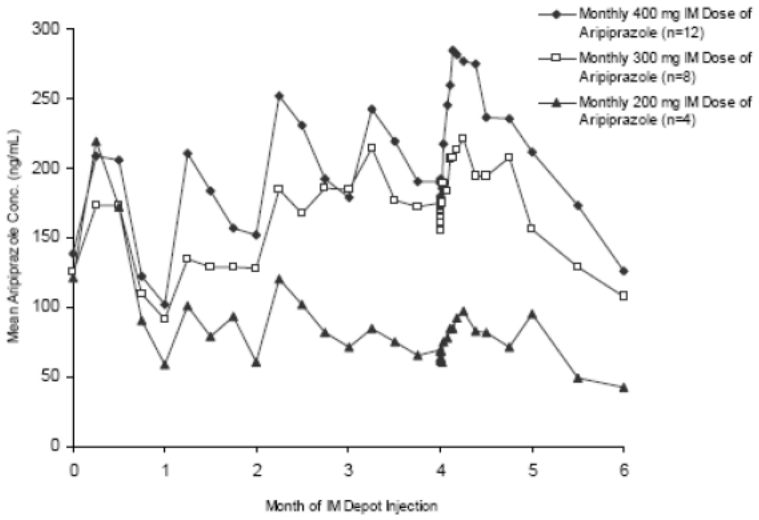
Study Population (All Randomized Subjects):

Randomized/Completed/ Discontinued Due to AE	41/22/5
Age [Mean (range)]	45 (19-62)
Male/Female	29/12
Race (Caucasian/Black/Asian/other)	15/22/1/3

Results

- Aripiprazole

Figure 1: Mean Aripiprazole Plasma Concentrations Following Administration of 400 mg, 300 mg, and 200 mg Monthly IM Depot Injections



Source: Figure 9.2.3.1-1 Clinical Study Report 31-05-244

Table 1: Mean (SD) Aripiprazole Pharmacokinetic Parameters in Subjects with Schizophrenia After Aripiprazole IM Depot Administration

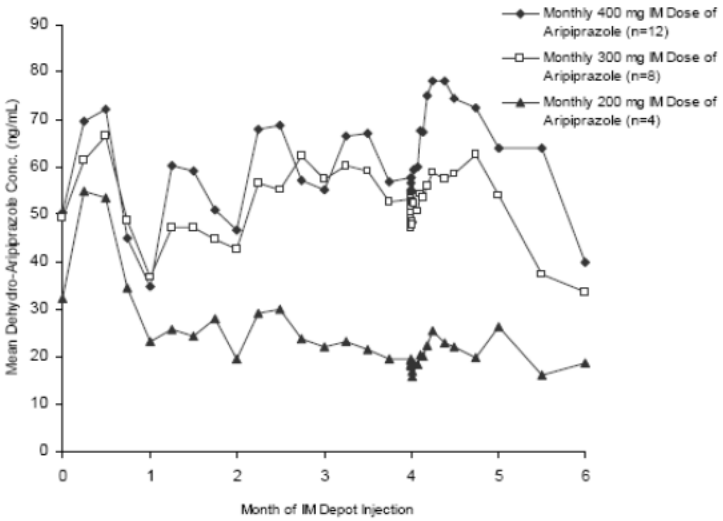
PK Parameters	200 mg (n=4)	300 mg (n=8)	400 mg (n=10)
$C_{max,ss}$ (ng/ml)	100 (68.4)	269 (128)	316 (160)
$C_{min,ss}$ [a] (ng/ml)	95.0 (86.2)	156 (67.7)	212 (113)
$C_{ave,ss}$ (ng/ml)	81.1 (58.7)	208 (87)	242 (132)
AUC_{τ} (hr*ng/mL)	54.5 (39.4)	140 (58.4)	163 (88.8)
T_{max} [b] (day)	5.0 (4.0-27.9)	6.5 (0.5-21.2)	7.1 (3.0-11.2)
$T_{1/2}$ (day)	ND	29.9 (8.0) [c]	46.5 (10.8) [d]

[a] Css,min=aripiprazole conc. at 672 hrs [b] median (min-max) [c] n=4 [d] n=6
Source: Table 9.2.3.2.1-1 of Clinical Study Report 31-05-244

- Dehydro-Aripiprazole

Figure 2: Mean Dehydro-aripiprazole Plasma Concentrations Following

Administration of 400 mg, 300 mg, and 200 mg Monthly IM Depot Injections



Source: Figure 9.2.3.1-2 Clinical Study Report 31-05-244

Table 2: Mean (SD) Dehydro-Aripiprazole Pharmacokinetic Parameters in Subjects with Schizophrenia After Aripiprazole IM Depot Administration

PK Parameters	200 mg (n=4)	300 mg (n=8)	400 mg (n=10)
$C_{max,ss}$ (ng/ml)	30.3 (19.8)	74.7 (20.8)	89.4 (37.9)
$C_{min,ss}$ [a] (ng/ml)	26.2 (24.7)	54.1 (21.1)	64.1 (27.0)
AUC_{τ} (hr*ng/mL)	14.7 (9.47)	38.9 (13.2)	47.8 (19.1)
T_{max} [b] (day)	5.5 (0-27.9)	12.5 (0.5-22.2)	6.6 (3.0-14.0)

[a] Css,min=dehydro aripiprazole conc. at 672 hrs [b] median (min-max)
Source: Table 9.2.3.2.2-1 of Clinical Study Report 31-05-244

The ratios of dehydro-aripiprazole to aripiprazole for mean $C_{ss,max}$ and AUC_{τ} PK parameters after the fifth monthly injection of aripiprazole IM depot 200 mg, 300 mg, and 400 were about 29% (Table 3).

Table 3: Steady State PK Parameter Ratio (%) of Dehydro-Aripriprazole to Aripiprazole at Different Dose Levels

PK Parameters	200 mg	300 mg	400 mg
$C_{max,ss}$	30.3	27.8	28.3
$C_{min,ss}$	27.6	34.7	30.2

- Was the pharmacokinetics dose proportional? ☐Yes ☑ No

After the fifth Q4W injection of aripiprazole IM depot 300 mg and 400 mg, aripiprazole $C_{ss,max}$, AUC_{τ}, $C_{ss,min}$ and $C_{ss,avg}$ PK parameters increased almost proportionally to the dose administered; however, the PK parameters after the fifth monthly injection of aripiprazole IM depot 200 mg were not proportional to the dose administered when compared with the 300 and 400 mg injections (Table 4).

Table 4: Aripiprazole Steady State Concentration and AUC Ratios

Aripiprazole Dose (mg)	200	300	400
Dose ratio	0.5	1	1.33
AUC $_{(0-\tau)}$ ratio	0.39	1	1.16
Cmax,ss ratio	0.37	1	1.17
Cmin,ss ratio	0.61	1	1.36
Cave,ss ratio	0.39	1	1.16

After the fifth Q4W injection of aripiprazole IM depot 300 mg and 400 mg, dehydeo-aripiprazole $C_{ss,max}$, AUC_{τ}, and $C_{ss,min}$ PK parameters increased almost dose-proportionally; however, the PK parameters after the fifth monthly injection of aripiprazole IM depot 200 mg were not dose-proportional when compared with the 300 and 400 mg injections (Table 5).

Table 5: Aripiprazole Steady State Plasma Concentration and AUC Ratios

Aripiprazole Dose (mg)	200	300	400
Dose ratio	0.5	1	1.33
Cmax,ss ratio	0.41	1	1.20
Cmin,ss ratio	0.48	1	1.18
AUC $_{(0-\tau)}$ ratio	0.38	1	1.23

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- What is the maximum tolerated dose? 400 mg.
- What are the safety profiles of the highest dose?

Aripiprazole IM depot was generally well tolerated by subjects with schizophrenia who received monthly doses of 400 mg, 300 mg, or 200 mg for up to 5 months. The majority of TEAEs were reported as mild or moderate. The most common TEAEs (overall incidence) were vomiting (4 subjects), injection site pain (4 subjects), URTI (4 subjects), and tremor (4 subjects). Three (7.7%) subjects (all from the aripiprazole IM depot 300 mg group) reported a total of 4 SAEs and 4 (10.3%) subjects discontinued treatment due to TEAEs (3 in the aripiprazole IM depot 300 mg group and 1 in the aripiprazole IM depot 200 mg group.)

Comments

The ratios of dehydro-aripiprazole to aripiprazole for mean $C_{ss,max}$ and $AUC_{0-\tau}$ after the fifth monthly injection of aripiprazole IM depot 200 mg, 300 mg, and 400 mg were 0.27 to 0.29, which were slightly lower than those of daily administration of the 30 mg aripiprazole oral tablet (0.33 to 0.39).

The PK parameters after the fifth monthly injection of aripiprazole IM depot 200 mg were not proportional to the dose administered when compared with the 300 and 400 mg injections. This might be due to the limited number of subjects who completed this treatment (n=4).

CYP2D6 genotype information of the enrolled subjects were collected on an optional basis in this study, therefore, no evaluation was performed to assess the effect of CYP2D6 poor metabolizers on the exposure of aripiprazole and dehydro-aripiprazole after multiple aripiprazole IM depot administration.

3.1.3. Pharmacometrics Review

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

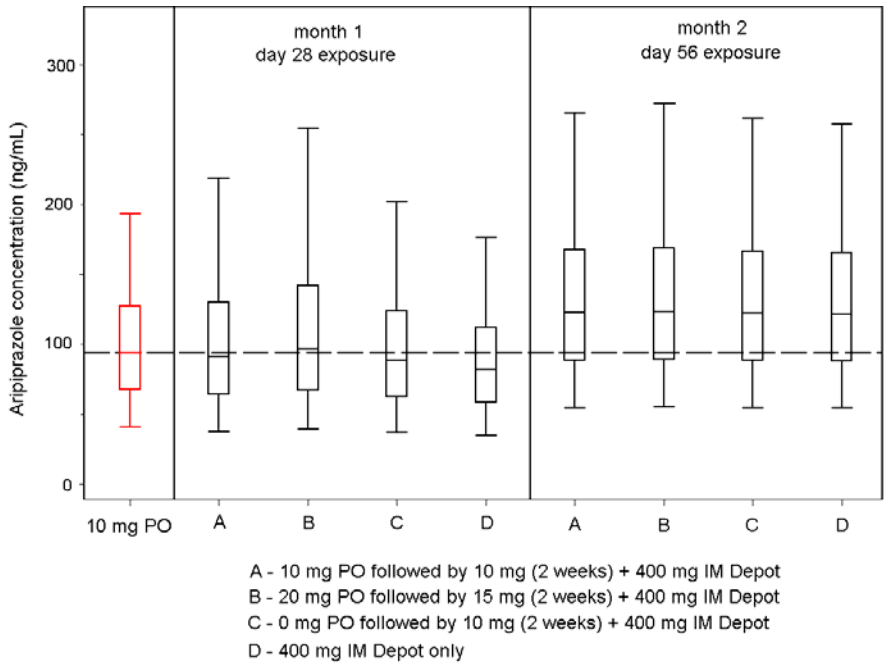
The purpose of this review is to address the following key questions.

1.1.1 Is the proposed dosing regimen acceptable?

1.1.1.1 Assessment of initiation dosing regimen

Yes. The recommended starting dose of aripiprazole IM depot is 400 mg accompanied by 14 consecutive days of concurrent daily administration of 10 mg to 20 mg of oral aripiprazole. The scenarios below (**Error! Reference source not found.**) suggest that median aripiprazole Cmin remains above the therapeutic window with oral supplementation plus 400 mg IM Depot within the first month. The median of the simulated 10-mg oral steady-state Cmin values (94.0 ng/mL) was used to establish the minimum of the therapeutic window. The 75th percentile of the simulated 30-mg oral steady-state Cmax values (534 ng/mL) was selected as the upper bound for the therapeutic window.

Figure 1 Simulated Trough (Cmin) Steady State Aripiprazole Concentrations vs. after the first (right panel) and second (left panel) dose of IM Depot. The dashed line represents the lower boundary for the therapeutic window.



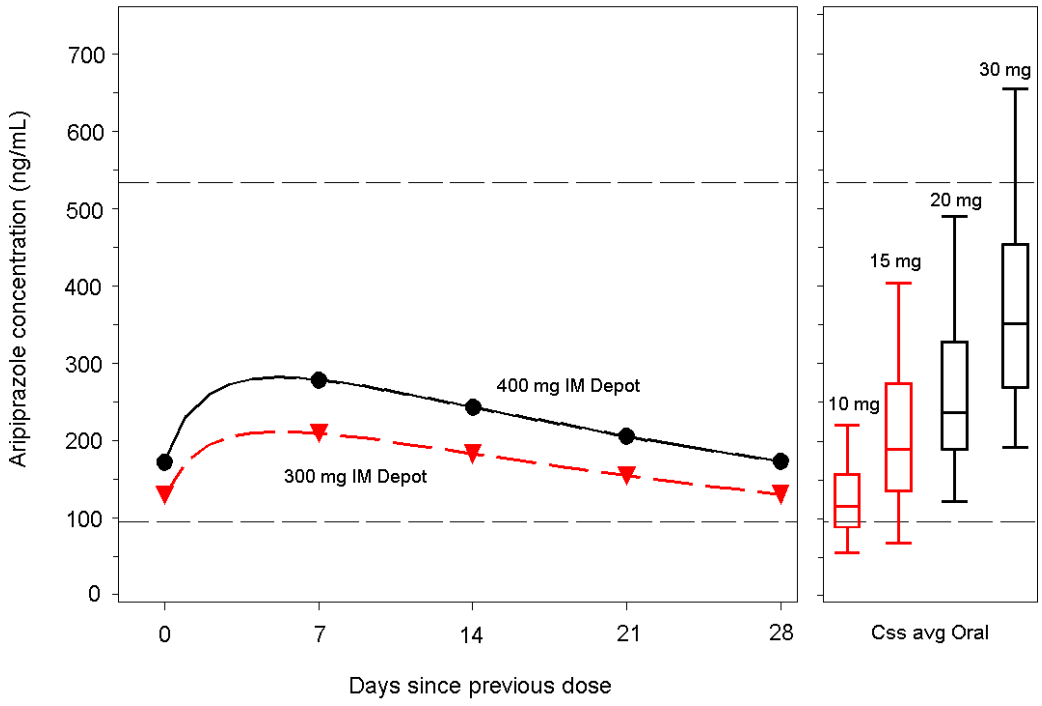
Evaluation of exposures of the 400 mg IM Depot with no oral supplementation shows that >50% of the population would be sub-therapeutic at the end of the first month. Ultimately, regardless of oral supplementation, aripiprazole median Cmin concentrations are eventually in the therapeutic window. For each dosing scenario, the upper 75% of Cmax were all under the upper boundary of the therapeutic window. Oral supplementation for the first 2 weeks was also performed during the pivotal trial. There were no tolerability issues or lack of efficacy during this phase.

Moreover, the multiple dose phase I PK study was conducted under similar design as the proposed regimen. Before patients received the 1st injection, all patients were stabilized on 10 mg oral aripiprazole tablet. The 1st IM injection was accompanied by 14 days of oral aripiprazole. For the latter four doses of IM depot injection, the dose was given every 4 weeks. The aripiprazole concentration time profile was shown in Figure 2 of the QBR. Steady state concentrations of aripiprazole after 300 mg and 400 mg depot injections, fell within the steady state concentration obtained from 10 mg and 15 mg oral tablet administration, which were the approved therapeutic dose levels. Mean steady state concentrations of aripiprazole after 200 mg depot injection, were below the Cmin levels of 10 mg QD, which was not recommended under standard conditions. Oral supplementation, for the first 2 weeks was also performed during the pivotal trial. There were no tolerability issues or lack of efficacy during this phase. Therefore, the proposed initiation dosing regimen is appropriate.

1.1.1.2 Assessment of maintenance dosing regimen

In addition to 400 mg, a 300-mg maintenance dose is considered appropriate. The effectiveness of aripiprazole, as demonstrated in Trial 31-07-246, is likely driven by patients receiving 400 mg aripiprazole IM depot injection (300 mg dose was given to only 16 (~6%) patients). Population pharmacokinetic simulations were conducted to assess whether 300 mg is an acceptable maintenance dose. For oral aripiprazole, the maintenance trial was conducted in patients receiving 15 mg daily dosing. Steady state average aripiprazole exposure following 300 mg dose once every 4 weeks is similar to that following 15 mg oral daily dosing (Figure 3). In addition, the minimum aripriprazole concentration (Cmin) in patients receiving 300 mg dose once every 4 weeks is above the steady state Cmin in patients administered with 15 mg oral daily dosing (Figure 2).

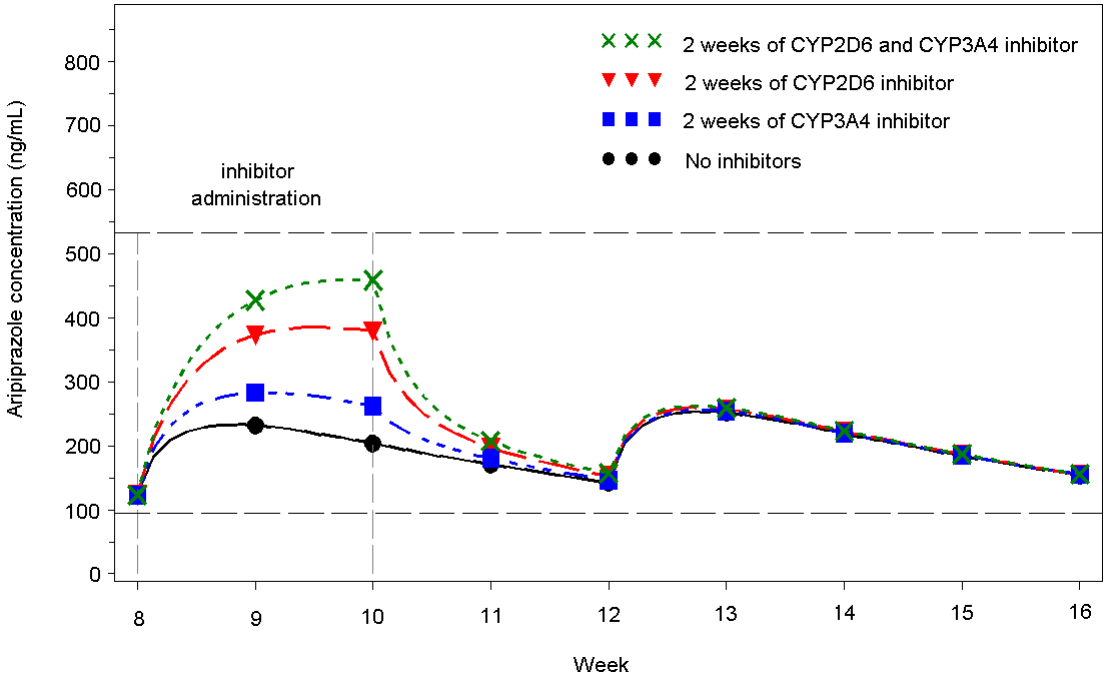
Figure 2 Simulated Average Steady State Aripiprazole Concentrations vs. Time for IM Depot 300mg and 400 mg (left plot) and Oral 10, 15, 20, and 30 mg (right plot). The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole.



1.1.2 What is the recommended dose for patients taking aripiprazole IM depot formulation concomitantly with short-term (< 14 days) CYP3A4 and/or CYP2D6 inhibitors?

The sponsor's suggestion of no dose reduction of IM Depot, in this case of short term inhibitor use, is appropriate. Upon evaluation of simulated steady state aripiprazole concentrations after 400 mg IM Depot administration in conjunction with a CYP3A4 inhibitor, a CYP2D6 inhibitor, or both CYP3A4 and CYP2D6 Inhibitor for 14 days, aripiprazole concentrations are maintained within the therapeutic window (Figure 3). In each case, effects of the inhibitor dosing are washed out by 14 days post-inhibitor dosing.

Figure 3 Median Aripiprazole Concentrations vs. Time for presence of short-term (<14 days) administration of CYP2D6 and/or 3A4 Inhibitor after the 3rd IM dose. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Vertical lines denotes the time of inhibitor administration.



1.1.3 What is the recommended dose for patients taking aripiprazole IM depot formulation concomitantly with long-term CYP3A4 and/or CYP2D6 inhibitors?

Under the regular maintenance dose of 400 mg, the dose should be reduced to 300 mg IM if given concomitantly with either a CYP3A4 *or* CYP2D6 inhibitor. Moreover, a 200 mg IM Depot dose should be given with concomitant CYP3A4 *and* CYP2D6 inhibitor. The sponsor's recommendation is appropriate. Similarly, for patients receiving 300 mg maintenance dose, we recommend the dose should be reduced to 200 mg IM if given concomitantly with either a CYP3A4 or CYP2D6 inhibitor. And the dose should be further reduced to 160 mg if given concomitantly with both CYP3A4 and CYP2D6 inhibitors.

Assessment of simulated steady state aripiprazole concentrations after IM Depot administration in conjunction with chronic use (>14 days) CYP3A4 inhibitor, a CYP2D6 inhibitor and both CYP3A4 and/or CYP2D6 inhibitor, show that aripiprazole concentrations are increased (Figure 4). Steady-state exposures ($AUC^{ss}_{(0\text{-}28\ days)}$) for the recommended dosing regimen adjustment are provided in Table 1 below. The 75th percentile exposures for all dosing recommendations are below the upper margin of the therapeutic window while the 25th percentile is above the lower margin of the therapeutic window. Therefore, the current recommendation of decreasing the dose to 300 mg IM if given concomitantly with either a CYP3A4 *or* CYP2D6 inhibitor (Figure 5) is appropriate. Moreover, a 200 mg IM Depot dose should be given with concomitant CYP3A4 *and* CYP2D6 inhibitor. The sponsor's recommendation is appropriate.

Figure 4 Median Aripiprazole Concentrations vs. Time for presence of long-term (>14 days) administration of a CYP 3A4 Inhibitor, a CYP2D6 Inhibitor and both a CYP3A4 and CYP2D6 Inhibitor after the 10th and 11th IM dose of 400 mg. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Dosing of IM Depot is at steady state.

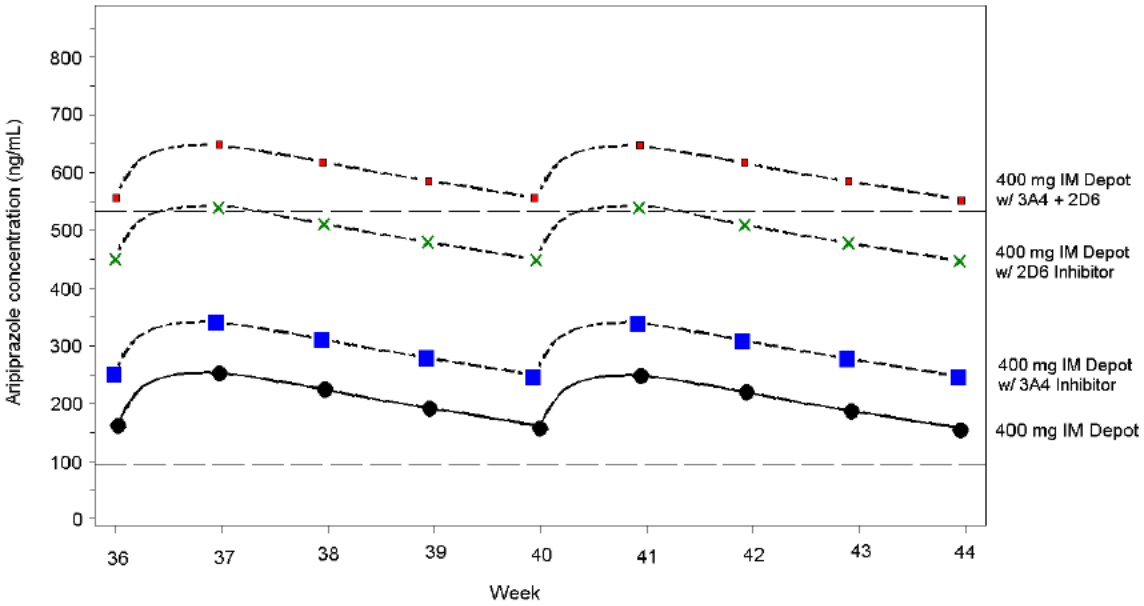
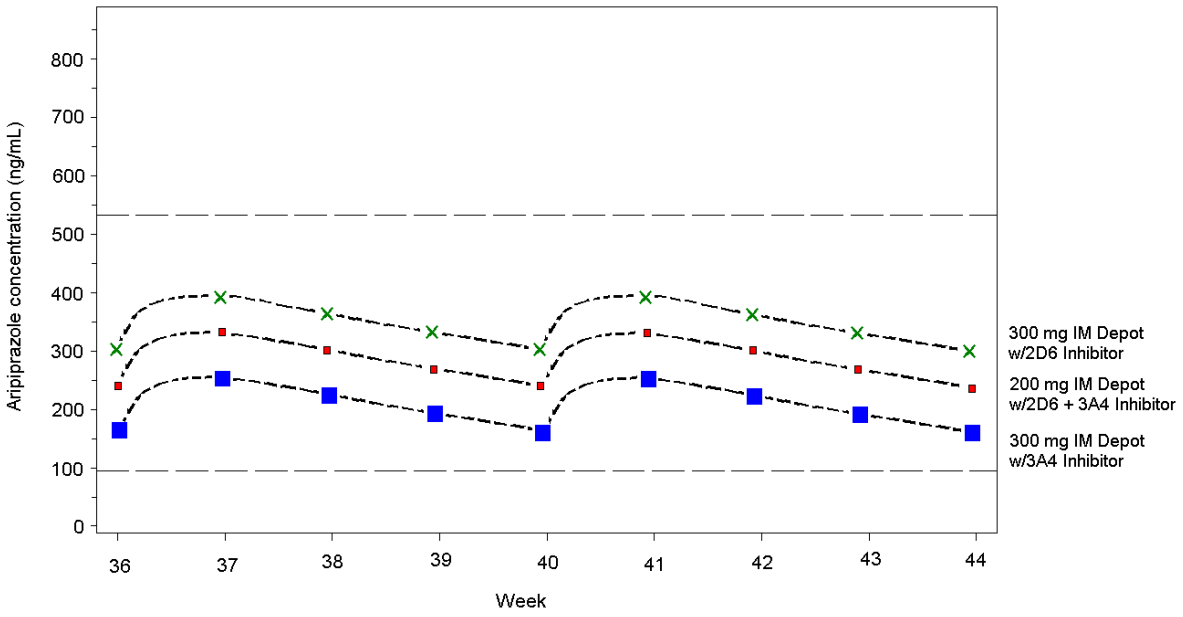


Table 1. Simulated Exposure ($AUC^{ss}_{(0\text{-}28\ days)}$) of the Recommended Adjusted Dosing Regimens for Concomitant Long Term Administration of CYP2D6 and/or CYP3A4 Inhibitors.

Dosing	Mean	SD	Median	25th percentile	75th percentile
Without Inhibitor - $AUC^{ss}_{(0\text{-}28\ days)}$					
400 mg IM	172.6	69.2	160.2	124.0	207.8
Concomitant administration of a Long-term Inhibitor - $AUC^{ss}_{(0\text{-}28\ days)}$					
300 mg IM Depot with 2D6 Inhibitor	264.7	106.2	245.6	190.1	318.7
300 mg IM Depot with 3A4 Inhibitor	169.6	68.1	157.4	121.8	204.2
200 mg IM Depot with 2D6 and 3A4 Inhibitor	231.2	92.8	214.6	166.1	278.4

Figure 5 Median Aripiprazole Concentrations vs. Time for presence of long-term (>14 days) administration of a CYP 3A4 Inhibitor, a CYP2D6 Inhibitor and both a CYP3A4 and CYP2D6 Inhibitor for the recommended dosing. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Dosing of IM Depot is at steady state. Of note, the 400 mg IM Depot PK profile mimics the 300 mg IM Depot profile given with a 3A4 inhibitor.



1.1.5 What is the flexible dosing window for aripiprazole IM depot injection? What is the reinitiation dosing strategy?

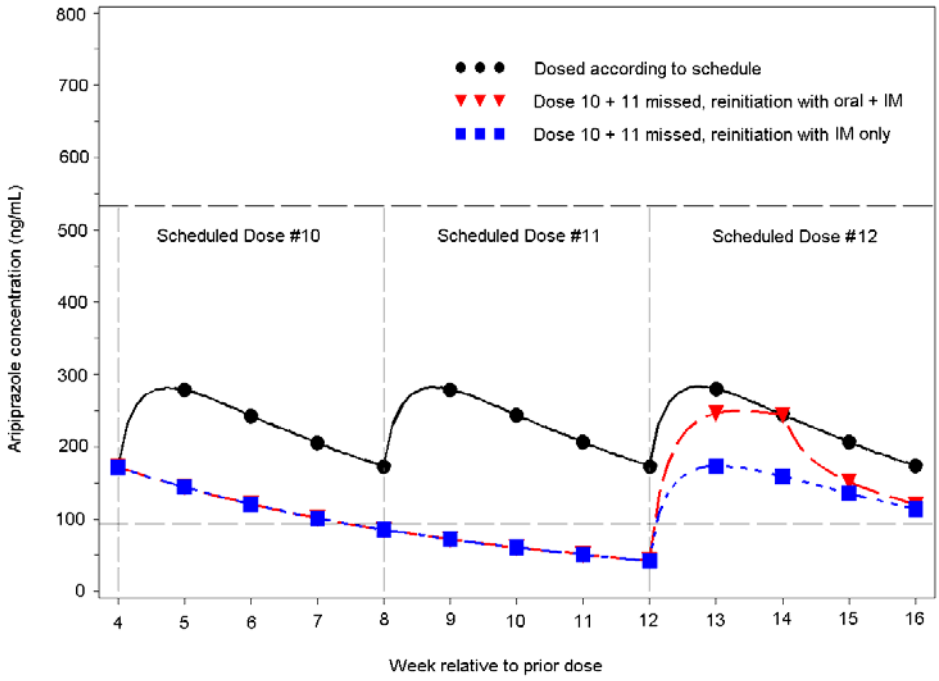
The proposed dosing for the IM Depot formulation is once (b) (4) but no sooner than (b) (4) from the last injection. After initiation, the recommended dosing interval is once every 4 weeks. The current recommendation for dosing re-initiation is 14 days of oral aripiprazole 10 mg along with the IM Depot dose of 400 mg, and is acceptable. To avoid re-initiation of oral aripiprazole administration, the following dosing guideline should be adhered to:

- The 2nd and 3rd administration of aripiprazole IM Depot should occur within 5 weeks (up to one week delay of scheduled dose). If beyond 5 weeks, the reinitiation regimen is: concomitant oral aripiprazole for 2 weeks + 400 mg IM Depot.
- After the 4th aripiprazole IM depot administration (patient at steady state), the subsequent administrations of aripiprazole IM depot should occur within 6 weeks (up to 2 weeks delay of scheduled dose). If beyond 6 weeks, the reinitiation regimen is: concomitant oral aripiprazole for 2 weeks + 400 mg IM Depot.

Figure 6 shows that when that when aripiprazole IM Depot dosing is re-initiated with 14 days of orally aripiprazole doses of 10 mg, median aripiprazole concentrations are similar to a

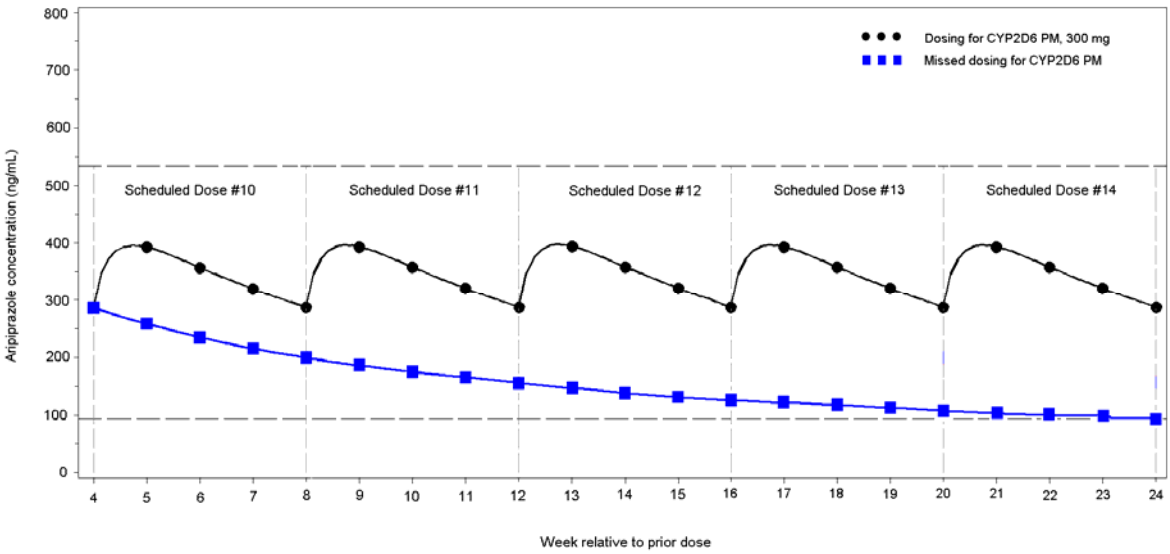
scenario in which subjects did not miss any doses within 2 weeks post-dose and remain within the therapeutic window for the remainder of the dosing interval.

Figure 6 Median Aripiprazole Concentrations vs. Time for when 10th and 11th doses missed, and reinitiation with 400 mg IM only and 400 mg IM + 10 mg Oral for 14 days. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Dosing of IM Depot is at steady state.



For patients who are CYP2D6 PM status, or on long-term CYP2D6 inhibitors, the adjusted dose is 300 mg. Presumably, aripiprazole concentrations would remain within the therapeutic window for a longer period of time for these individuals compared to CYP 2D6 EM patients. Figure 10 shows that when that when aripiprazole IM Depot dosing is stopped at the 10th scheduled dose (at steady state), concentrations remain therapeutic for approximately 5 months after the dosing has stopped. In this case, reinitiating oral dosing can occur at any time after 6 weeks after the last IM depot dose out to 6 months after the last IM depot dose (Figure 7). For patients who are CYP2D6 PM status, or on long-term CYP2D6 inhibitors, the same reinitiation strategy employed for CYP 2D6 EM patients is appropriate. For these patients, reinitiation of oral dosing is with 14 days of the recommended oral aripiprazole dose, along with 300 mg IM Depot dose.

Figure 7 Median Aripiprazole Concentrations vs. Time for patients who are CYP2D6 PM status or on long-term (>14 days) CYP2D6 inhibitors (300mg IM Depot maintenance). The blue line denotes the time course of aripiprazole after dosing is stopped at the 10th scheduled dose. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole. Dosing of IM Depot is at steady state.



1.1.6 What is the impact of dose dumping on aripiprazole exposure?

Based on the safety data and the results of safety data in the pivotal trial (Study 31-07-246), no evidence of dose dumping was observed in this trial. Simulated aripiprazole concentrations following dose dumping, show a decline to concentrations normally observed following the administration of 400 mg IM depot within 3 days after the entire aripiprazole IM depot dose is absorbed in the systemic circulation (see Figure 11 11 of QBR). It is important to note, that the peak would reach ~4,500 ng/mL (about 9 times above the therapeutic window) but the concentrations would descend rapidly.

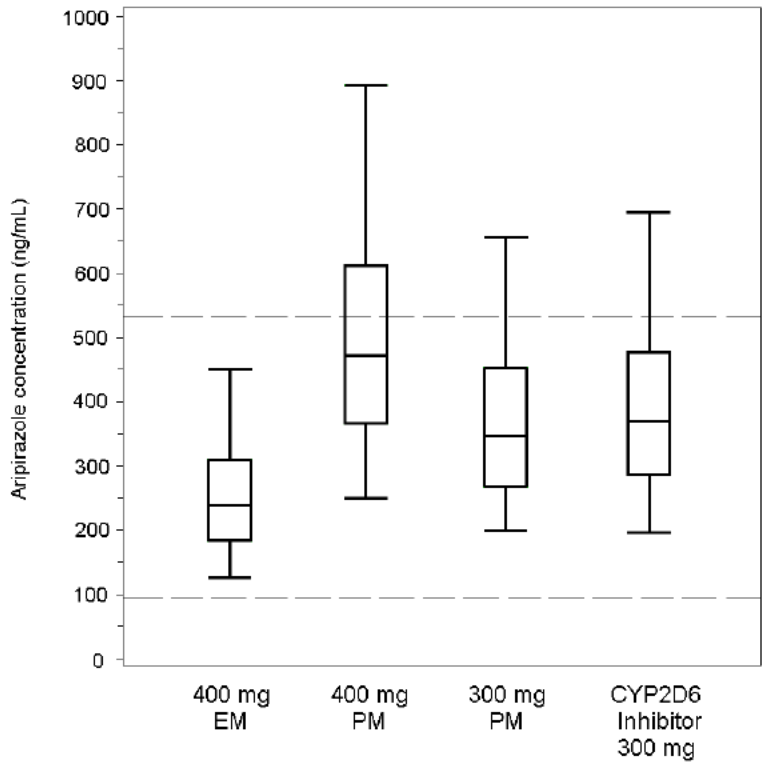
1.1.7 What is the recommended dose for patients who are CYP2D6 poor metabolizers?

A 300 mg IM Depot dose is recommended for patients who are CYP2D6 poor metabolizer (PM) status. As presented in Table 2 and Figure 4 8, steady state aripiprazole exposures are higher in PM status in comparison to extensive metabolizer (EM) status subjects, in which approximately a two-fold difference in exposures is observed. According to steady state aripiprazole exposures and mean $AUC^{SS}_{(0\text{-}28\ days)}$, a 300 mg IM Depot dose is recommended for patients who are CYP2D6 PM status and the exposures are consistent for the dosing recommendation for patients taking concomitant CYP2D6 inhibitors for more than 14 days (the upper 75% percentiles are similar between the two scenarios). Based on clinical need, the dosing may be increased to 400 mg.

Table 2 Simulated Exposure ($AUC^{ss}_{(0\text{-}28\ days)}$) of 300mg and 400 mg IM Depot for Patients who are CYP2D6 PM and EM Status.

Dosing	Mean	SD	Median	25th percentile	75th percentile
CYP2D6 Metabolizing status $AUC^{ss}_{(0\text{-}28\ days)}$					
400 mg EM status	172.6	69.2	160.2	124.0	207.8
400 mg PM status	340.5	136.6	316.0	244.6	410.0
300 mg PM status	255.4	102.5	237.0	183.4	307.5
Concomitant administration of a Long-term CYP2D6 Inhibitor - $AUC^{ss}_{(0\text{-}28\ days)}$					
300 mg IM Depot with 2D6 Inhibitor	264.7	106.2	245.6	190.1	318.7

Figure 8 Simulated Average Steady State Aripiprazole Concentrations for IM Depot 400mg in Extensive Metabolizers (EM), 400 mg and 300 mg in Poor Metabolizers (PM), and 300 mg in EM with long term concomitant CYP2D6 Inhibitor.

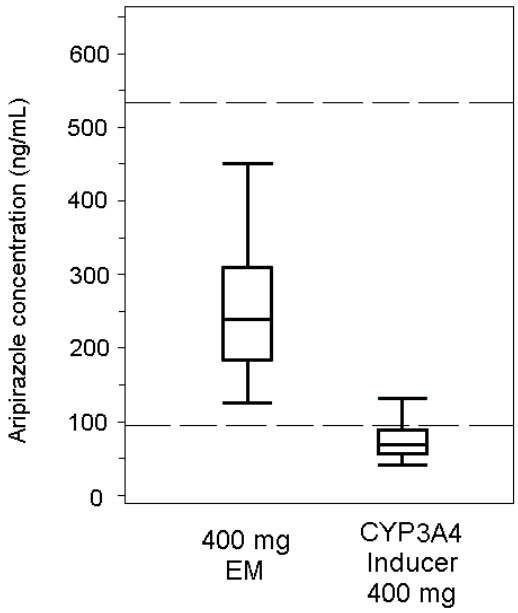


1.1.8 What is the recommended dose for patients taking aripiprazole IM depot formulation concomitantly with long-term CYP3A4 inducers?

As 400 mg is the largest dosage form for the IM Depot formulation, dosing adjustment for this interaction may not be feasible and it is suggested that patients be warned not to use a combination of CYP3A4 inducers with this formulation.

Based on the original label for oral aripirazole (Abilify®), concomitant administration of a CYP3A4 inducer greatly decreases the exposure of plasma aripiprazole. For example, the coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg/day) resulted in an approximate 70% decrease in Cmax and AUC values of both aripiprazole. In this case, doubling the dose is recommended. Based on simulations, an approximate four-fold decrease in steady state aripiprazole plasma concentrations is evident upon long-term concomitant administration of a CYP3A4 inducer with 400 mg IM Depot (Figure 9). Individuals in the pivotal clinical trial were not permitted to take concomitant CYP3A4 inducers, so it is unsure of what the clinical implications are of this interaction. The current proposal for the label does not suggest any dosing recommendations for this interaction.

Figure 9 Simulated Average Steady State Aripiprazole Concentrations for IM Depot 400mg and With Concomitant Long-Term Administration of a CYP3A4 Inducer. The dashed lines represent the upper and lower boundary of the therapeutic window for aripiprazole.



1.2 Recommendations

The Pharmacometrics reviewer finds this application for a new aripiprazole formulation acceptable, pending labeling revisions.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

2 PERTINENT REGULATORY BACKGROUND

Aripiprazole (Abilify®) is an atypical antipsychotic approved in the US (November 2002, NDA 21-436) as an oral form for multiple indications. The indications include treatment of schizophrenia in adults and children (ages 13 to 17), acute treatment of manic or mixed episodes associated with bipolar I disorder in adults and children (ages 10 to 17) as both monotherapy and as an adjunct to lithium or valproate. Moreover, aripiprazole is indicated for maintenance treatment in adults with bipolar I disorder as both monotherapy and as an adjunct to lithium or valproate, and irritability associated with autistic disorder in children (ages 6 to 17). Oral aripiprazole is also approved for the treatment of schizophrenia and the treatment of manic or mixed episodes associated with bipolar I disorder in a number of countries in Europe, Asia, and Latin America. Thus, the efficacy, safety, and tolerability of oral aripiprazole have been well-established in several patient populations. An immediate-release IM formulation of aripiprazole is approved in the US and the European Union (EU) for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults (NDA 21-866) at a doses of 9.75 mg to 30 mg/day.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Summary of the Clinical Study Report: (31-07-246)

The pivotal efficacy trial, Trial 31-07-246 was a 52-week, multicenter, randomized, double-blind, placebo-controlled design to evaluate the efficacy, safety, and tolerability of aripiprazole IM depot as maintenance treatment in subjects with schizophrenia. Specifically, the intent of the trial was to evaluate the efficacy of aripiprazole IM depot compared with placebo, as measured by time to impending relapse, in subjects with schizophrenia who had maintained stability on aripiprazole IM depot for at least 12 weeks at doses of 400 mg or 300 mg IM. Subjects enrolled in the trial included male and female subjects, ages 18 to 60 years with a diagnosis of schizophrenia as defined by DSM-IV-TR criteria and a history of the illness for at least 3 years prior to screening. The trial consisted of a screening phase and 4 treatment phases (Conversion, Oral Stabilization, IM Depot Stabilization, and Double-blind, Placebo-controlled). Specifically, the following phases are summarized below.

Conversion phase: Subjects had their dose cross-titrated from other antipsychotic(s) to oral aripiprazole monotherapy (trial medication) over a minimum of 4 weeks and a maximum of 6 weeks. The goal of the oral conversion phase was for all subjects to achieve a monotherapy target dose of 10 or 15 mg/day oral aripiprazole at Week 4 and no later than Week 6 of the Conversion Phase, although higher target doses were acceptable based on clinical need.

Oral Stabilization Phase: Subjects successfully converted to oral aripiprazole monotherapy, were stabilized on an oral dose of aripiprazole ranging from 10 mg to 30 mg daily. During this phase, which was a minimum of 4 weeks and a maximum of 12 weeks in duration, subjects were assessed biweekly.

IM Depot Stabilization Phase: Subjects fulfilling the oral stabilization requirement in the Oral Stabilization Phase were assigned to receive aripiprazole IM depot 400 mg and began the IM depot Stabilization Phase for a minimum of 12 weeks and a maximum of 36 weeks. All

subjects received aripiprazole IM depot 400 mg as the initial dose in the IM Depot Stabilization Phase, irrespective of the final oral dose in the Oral Stabilization Phase. A single decrease to aripiprazole 300 mg was permitted for tolerability, as was a single return to the original 400 mg dose, if required. Oral dosing with aripiprazole (10 to 20 mg/day) continued for the first 2 weeks concomitant to the first IM depot injection in the IM Depot Stabilization Phase to achieve therapeutic plasma concentrations of aripiprazole. Subjects were dosed with aripiprazole IM depot monthly (every 28 days) during the IM Depot Stabilization Phase. The minimum allowable interval between IM depot injections was 26 days.

Double-blind, Placebo-controlled Phase: Subjects eligible for the Double-blind, Placebo-controlled Phase were randomly assigned in a 2:1 ratio to double-blind treatment with aripiprazole IM depot or placebo, respectively. It was projected that the target number of impending relapse events (125) could be observed with 225 subjects randomized into this phase. The initial IM depot dose (aripiprazole or placebo) for the Double-blind, Placebo controlled Phase was the stabilization dose of aripiprazole IM depot from the IM Depot Stabilization Phase (last dose in the IM Depot Stabilization Phase). All IM depot injections (aripiprazole 400 mg, aripiprazole 300 mg, and placebo) were administered monthly. During this phase, subjects were evaluated biweekly in the clinic and at any unscheduled visits for signs of exacerbation of psychotic symptoms/impending relapse.

A schematic of the study design is included in Figure 10 below.

Figure 10 Schematic Presentation of Study 31-07-246

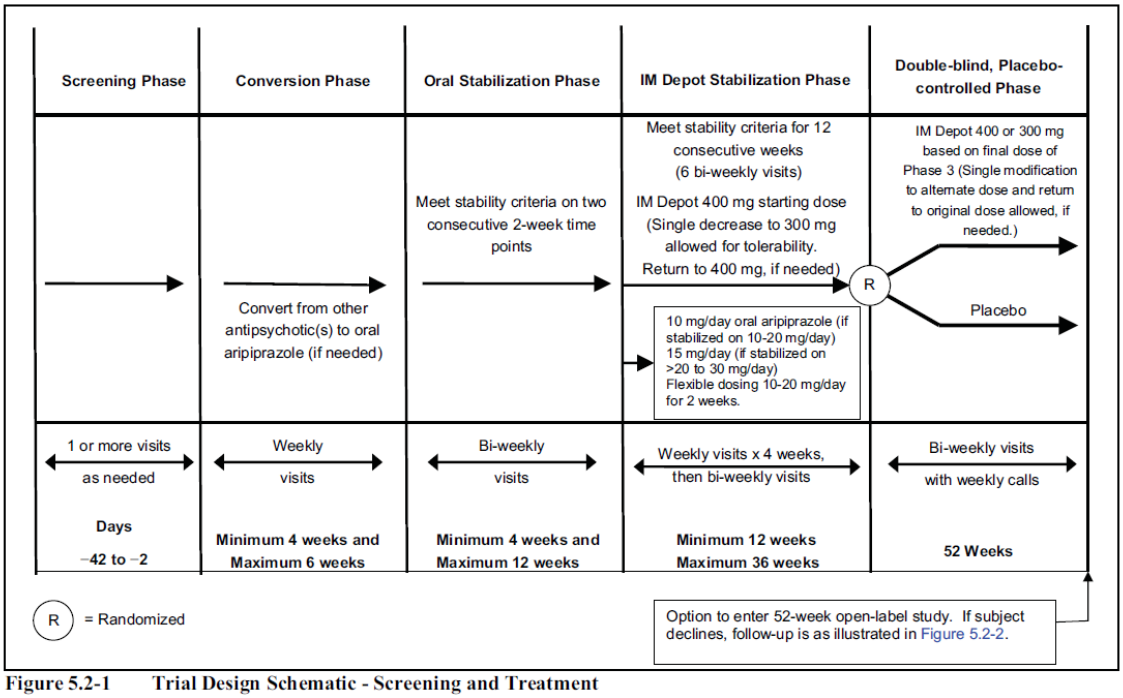


Figure 5.2-1 Trial Design Schematic - Screening and Treatment

Source: CSR 31-04-246 pg 91

Assuming that each subject was followed for 12 months after randomization and allowing

for a 25% loss to follow-up, the projected total number of subjects to be randomly assigned to treatment in the trial was 225. Due to the lower than expected impending relapse rate, enrollment and randomization continued beyond the planned estimates (225 planned; 403 actual) to achieve the target number of impending relapse events of 125.

Blood samples for PK was collected from 542 subjects during the IM Depot Stabilization Phase and 358 subjects during the Double-blind, Placebo-controlled Phase of the trial were analyzed for aripiprazole and dehydro-aripiprazole. Samples collected from subjects for CYP2D6 isozyme metabolism status were analyzed and results were reported. For the IM Depot Stabilization Phase PK samples were collected pre-dose, 7, 14, and 28 days after the first injection, and at 28 days after injections 2, 3, and 4. For the Randomized Phase, PK samples were taken 14 days and 28 days after the first and second injection.
Efficacy and safety were evaluated regularly throughout the study. PK samples were evaluated by using non-linear mixed effects modeling.

The primary efficacy endpoint of this trial was time to event of impending relapse. The time origin for measuring this event time was date of randomization into the Double-blind, Placebo-controlled Phase. The primary analysis compared the 2 treatment groups (aripiprazole IM depot 400/300 mg vs. placebo) with respect to the primary efficacy endpoint of time to impending relapse (comparison of survival curves via log-rank test).
Safety was monitored by the evaluation of adverse events, extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], Simpson and Angus Rating Scale [SAS]) scores, clinical laboratory test results, vital signs measurements, electrocardiograms (ECGs), and physical examination findings. In addition, the tolerability of injections was assessed; the investigators evaluated injection sites and the subjects assessed injection pain.

The final efficacy analysis included 403 randomized subjects and 80 impending relapse events. The results from the final analysis 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 ($p < 0.0001$; 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. According to the sponsors analysis, 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).

Table 3 below described the overall summary of treatment-emergent adverse events for each phase of the trial. According the Sponsor, compared to placebo, aripiprazole was generally well tolerated.

Table 3. Summary of Adverse Events for Study 31-07-246

Parameter	Oral Stabilization Phase (N = 709) n (%)[a]	IM Depot Stabilization Phase (N = 576) n (%)[a]	Double-blind, Placebo-controlled Phase	
			Aripiprazole IM Depot (N = 269) n (%)[a]	Placebo (N = 134) n (%)[a]
Subjects treated with aripiprazole oral tablets	709 (100)	575 (99.8)	-	-
Subject days of aripiprazole oral tablet exposure	26816	8004	-	-
Subjects treated with aripiprazole IM depot	-	576 (100)	269 (100)	134 (100)
Subject total aripiprazole IM depot injections	-	1814	1466	568
Subjects with AEs[b]	296 (41.7)	345 (59.9)	170 (63.2)	83 (61.9)
Number of AEs	622	970	552	259
Subjects with TEAEs	289 (40.8)	345 (59.9)	170 (63.2)	83 (61.9)
Number of TEAEs	548	861	478	230
Subjects with serious TEAEs	10 (1.4)	25 (4.3)	11 (4.1)	9 (6.7)
Subjects with severe TEAEs	12 (1.7)	23 (4.0)	12 (4.5)	6 (4.5)
Subjects discontinued trial medication due to TEAEs	21 (3.0)	28 (4.9)	19 (7.1)	18 (13.4)
Subjects who died due to TEAEs	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)

Source: CSR 31-04-246 pg 276

3.2 Summary of the Population PK Study Report: (31-11-287)

A pooled population PK analysis was performed from four (4) phase 1 trials and trial 31-04-246. The final analysis dataset had 6,153 aripiprazole concentrations records from 663 subjects. Table 4 summarizes the trials used along with the pertinent PK information for each trial. The PK model was shown in **Error! Reference source not found.** 11. The Sponsor's analysis showed that a linear 3-compartment model with sigmoid absorption for orally administered and first-order absorption for the IM Depot formulation was found to best characterize both the oral and IM Depot concentrations over the sample collection times. The sigmoid absorption model allowed the oral dose to enter the depot compartment as an infusion and transfer to the central compartment as a first-order process. Covariate analysis was performed to assess the effect of CYP2D6 polymorphism, and demographic and other subject factors on inter-subject variability of PK parameters. Moreover, the analysis attempted to quantify the effect of strong inhibitors of CYP2D6 and CYP3A4 on inter-subject variability on PK parameters.

The sponsor took various steps in order to evaluate the model including a visual predictive check. The model prediction appeared to be in good agreement with the PK observations from the acquired data (**Error! Reference source not found.** 12). The model prediction was quantitatively compared with the observations for both the oral and IM formulations (Table 5). For the observed oral data, the frequencies indicate that 4% of the oral data are above the simulated 95th percentile and 1% of the observed oral data are below the simulated 5th percentile. For the IM Depot administration, 3.3% of the observed data are below the simulated 5th percentile and 5.2% of the observed data are above the simulated 95th percentile.

The goodness of fit plots for the execution of the final model on the combined data indicated that current model adequately described PK observations from the new study (Figure 13). All PK parameters for the final model are included in Table 6.

Reviewer's comments:
The sponsor's population PK model adequately describes the aripiprazole PK observations for both the oral and IM formulations.

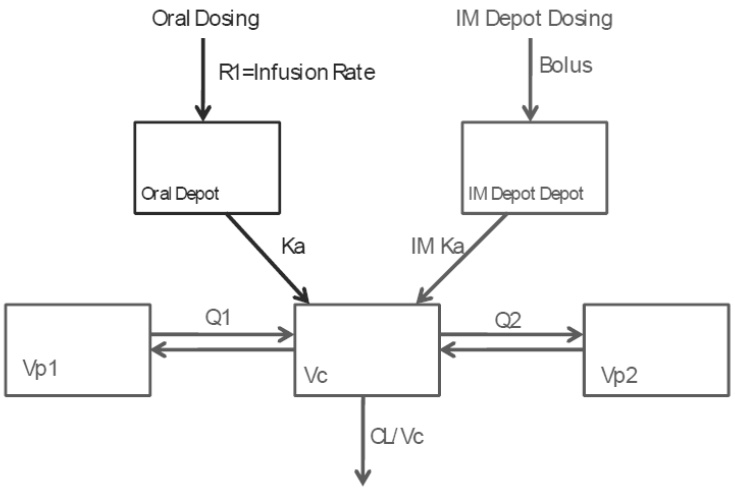
Table 4. Summary of Data Used for Population Pharmacokinetic Analysis

Trial	Population	Treatment arms	Dosing period	Sampling times (relative to previous dose (h))
31-98-206 (phase 1)	Healthy (N=29)	Oral aripiprazole 15 mg Days 1 and 16. Oral ketocon 200 mg once daily on Days 15 – 28.	Day 1 & Day 16 (single doses with washout)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 168, 216, 312
31-98-207 (phase 1)	Healthy (N=29) (24 CYP2D6 PM, 5 EM)	Group 1 (PM): One dose oral aripiprazole 10 mg. Group 2 (PM): One dose oral aripiprazole 10 mg on Day 1 and oral quinidine QD on Days 1 – 13. Group 3 (EM): One dose oral aripiprazole 10 mg	Day 1	Pre-dose, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312
CN138020 (phase 1)	Schizophrenia/ schizoaffective disorder (N=21)	Phase 1: One 5 mg dose IM standard formulation Phase 2: One 15-, 50-,100-, 200-, 300- or 400-mg dose IM Depot formulation	Day 1 or IM Depot	Pre-dose, 0.083, 0.167, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 144, 193, 240, 288, 336, 384
31-05-244 (phase 1)	Schizophrenia (N=44)	Group 1: 400 mg Group 2: 300 mg Group 3: 200 mg aripiprazole IM Depot injection Q4 wk for 5 mo	Injections 1- 4 (Day 1, 28, 56, 112) Injection 5 (Day 140)	Pre-dose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 168, 264, 360, 456, 528 For doses > 200 mg: Day 28, 35, 42, 56, 70, 84, 112, 140, 168 or until 2 consecutive LLOQ
31-07-246 (phase 3)	Schizophrenia (N=1000)	Phase 4: 400 mg or 300 mg aripiprazole IM Depot Q4 wk for 52 wk	Phase 3 Injection 1, 2, 3 and 4 Phase 4 Injection 1 and 2	Pre-dose, 7 days, 14 days, and 28 days

There were an additional 732 samples and 23 subjects excluded. Final analysis dataset had 6,153 aripiprazole concentrations records from 663 subjects.

Source: CSR 31-11-287 pg 72

Figure 11 Schematic Presentation of the Population Pharmacokinetic Model



Note: CL=clearance; Q = inter-compartmental clearance; IM=intramuscular; Ka=first order absorption rate constant; Vc=volume of distribution for central compartment; Vp=volume of distribution for peripheral compartment; *(Source: CSR 31-11-287 pg 111)*

Table 5. Summary of Visual Predictive Check *(Source: CSR 31-11-287 pg 95)*

Administration Route	Observed Concentrations Below Simulated 5th Percentile		Observed Concentrations Above Simulated 95th Percentile	
	Number	Percentage	Number	Percentage
Oral	14	1.1	55	4.2
IM Depot	20	3.3	32	5.2

Source: /d1pk/nm/valid/ph13-final-01.ctl.

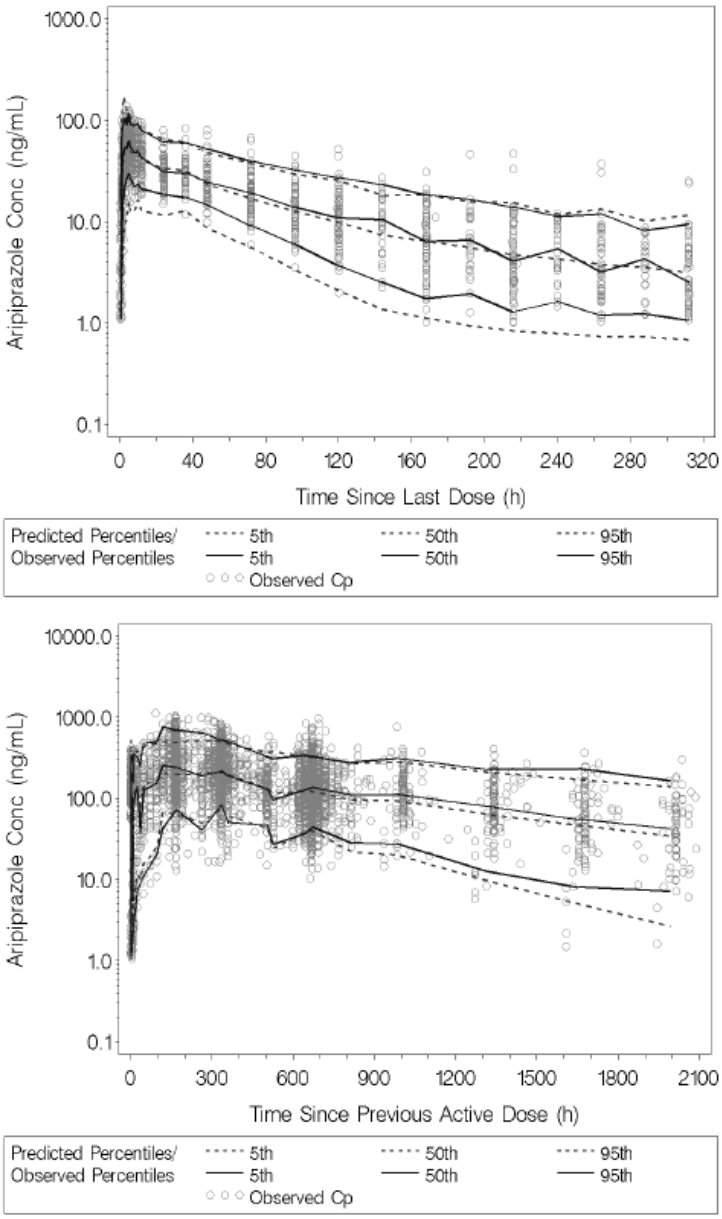
Table 6. Final Model Parameters with IM and Oral Aripiprazole Data *(Source: CSR 31-11-287 pg 95)*

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
Ka: oral first-order absorption rate (1/h)	0.540	Fixed	65.88	Fixed
CL: clearance for EM (L/h)	3.71	4.0	38.34	6.9
CL: clearance for PM (L/h)	1.88	6.9		
CL: proportional change in CL for 2D6 inhibitor	-0.511	Fixed		
CL: proportional change in CL for 3A4 inhibitor	-0.237	Fixed		
Vc: central volume (L)	93.4	8.8	124.50	15.2
Q1: inter-cmt CL (L/h)	0.591	Fixed	NE	NA
Vp1: peripheral volume (L)	118	Fixed	NE	NA
Q2: second inter-cmt CL (L/h)	28.8	Fixed	NE	NA
Vp2: second peripheral volume (L)	134	Fixed	NE	NA
R1: rate of dose into depot (mg/h)	9.33	Fixed	NE	NA
IM Ka: IM Depot first-order absorption rate (1/h)	0.000904	5.3	55.59	8.2
F2: relative bioavailability for IM Depot	1.48	4.9	NE	NA
IM Ka: power for (BMI/28)	-0.975	11.5	NE	NA
IM Ka: proportional shift for Males	0.346	28.9	NE	NA
Phase 1 RV (%CV)	24.23	8.4	NA	NA
Phase 3 RV (%CV)	28.11	4.7	NA	NA
Minimum value of the objective function = 48892.907				

cmt = compartmental; EM = extensive metabolizer; NA = not applicable; NE = not estimated; %CV = percent coefficient of variation; %SEM = percent standard error of the mean; PM = poor metabolizer; RV = residual variability.

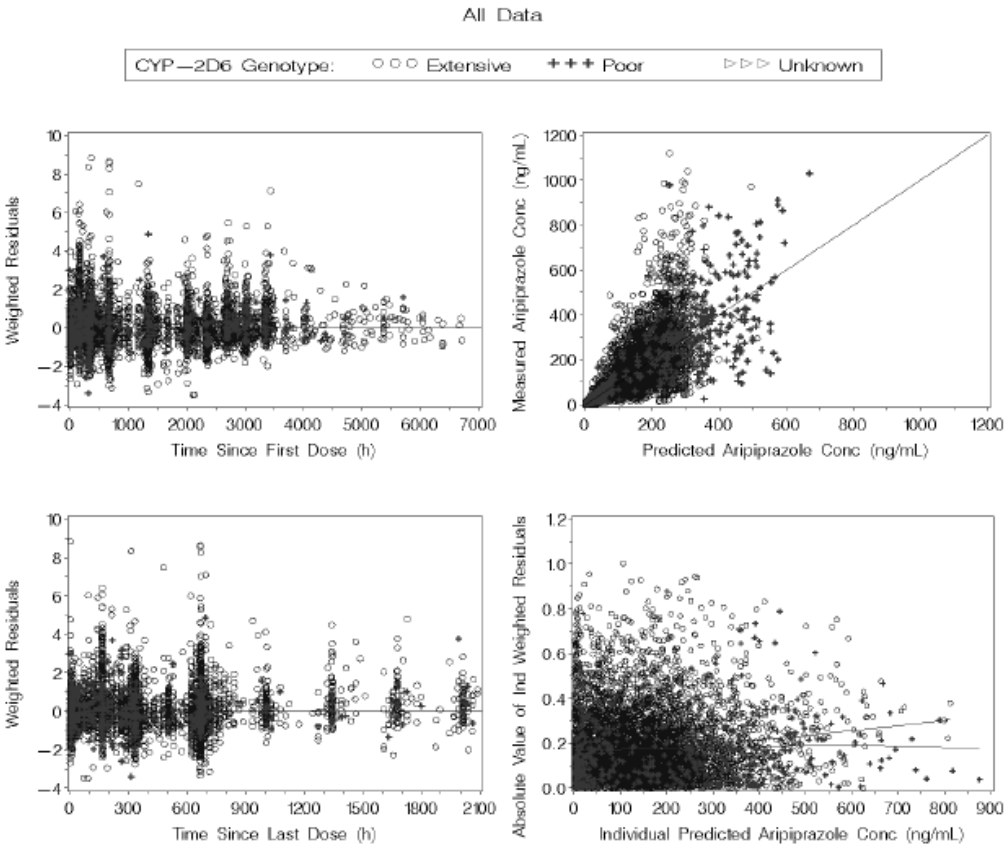
Note: The estimate of the clearance for extensive metabolizers was correlated with the estimate of the relative bioavailability for IM Depot (r = 0.901).

Figure 12 Comparison of Population PK Simulation and Actual Plasma Concentration Data for Oral (top) and IM Depot (bottom)



Source: CSR 31-11-287 pg 122

Figure 13 Goodness of Fit Plots for Pooled Data (IM Depot and Oral Data)



Source: CSR 31-11-287 pg 121

3.3 Summary of the Population PK Simulation Results

Along with population PK modeling, the sponsor submitted PK simulation results to assess the following aspects of the dosing strategy for IM aripiprazole:

- Dose initiation schemes.
- The influence of extensive and poor metabolism of CYP2D6 substrates.
- Subjects who take concomitant medications that are inhibitors of CYP-3A4 and/or CYP2D6.
- Subjects who delay a regularly scheduled IM Depot dose during initiation and maintenance of dosing (2nd, 3rd, 4th, and 10th doses).
- Subjects who miss 2 consecutive doses during initiation and maintenance of dosing.
- Implications of dose dumping (i.e., subjects who rapidly absorb an entire IM Depot dose immediately after the intramuscular injection).

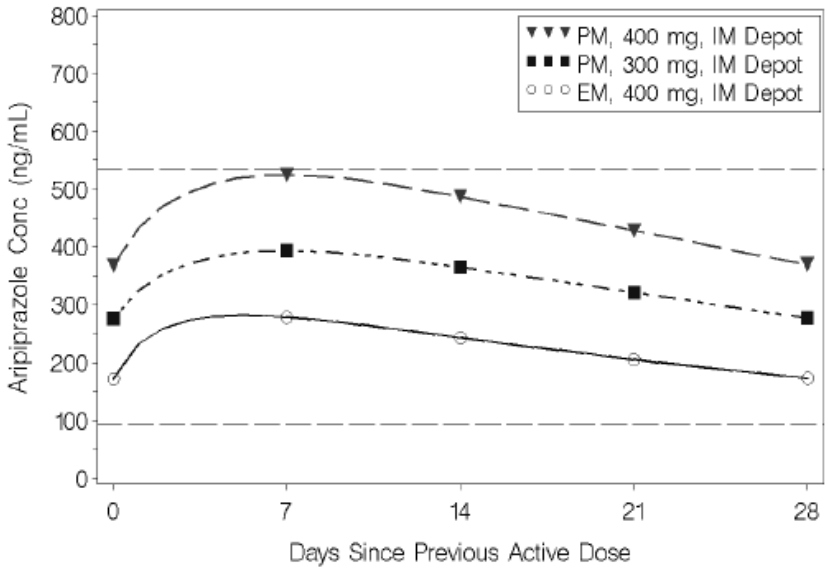
Simulations of 10 mg and 30 mg oral aripiprazole administered once daily using the final population PK model to allow direct comparison of the exposures achieved with IM Depot dosing scenarios versus those achieved with established oral dosing regimens.

A therapeutic window was used for referencing the PK simulations, in which simulations of 10mg/day and 30 mg/day oral dosing (recommended oral dosing) at steady state were performed and used for comparison with the different simulation scenarios. The median of the simulated 10-mg oral steady-state Cmin values (94.0 ng/mL) was used to establish the minimum of the therapeutic window. The 75th percentile of the simulated 30-mg oral steady-state Cmax values (534 ng/mL) was selected as the upper bound for the therapeutic window. The range for the therapeutic window was based on examination of the safety, tolerability, and PK data from the aripiprazole IM Depot phase 3 pivotal trial, Trial 31-07-246.

3.3.1 Comparison of Dosing With Extensive and Poor Metabolism of CYP2D6 Substrates

Based on previous information and analyses, CYP2D6 metabolism status is a significant predictor of aripiprazole clearance. The sponsor simulated doses of 300 mg and 400 mg to subjects with CYP2D6 poor metabolizing (PM) status and compared that to those subjects with extensive metabolizing (EM) status (Figure 14). The sponsors conclude that the median aripiprazole plasma concentration-time profiles of a CYP2D6 PM subject following monthly administration of aripiprazole IM Depot doses of 300 mg and 400 mg remain within the therapeutic window. Steady-state exposure parameters for the monthly IM Depot of 400 mg in CYP2D6 PM status are ~2 fold higher for the EM status subjects administered the same dose. Despite this difference in exposures, the sponsor *does not* suggest dose adjustment for the CYP2D6 PM status patients as the adverse event profile following the 400 mg monthly aripiprazole dose in the CYP2D6 PM subjects was similar to that of CYP2D6 EM subject.

Figure 14 Median Aripiprazole Steady-State Concentrations vs. Day Since Previous Dose for CYP2D6 PM, Stratified by Dose.



All groups: 10 mg oral SS, 10 mg (14 days) + 400 mg IM Depot
EM= Extensive Metabolizer, PM= Poor Metabolizer
Dashed lines represent the therapeutic range.

Source: CSR 31-11-2876 pg 129

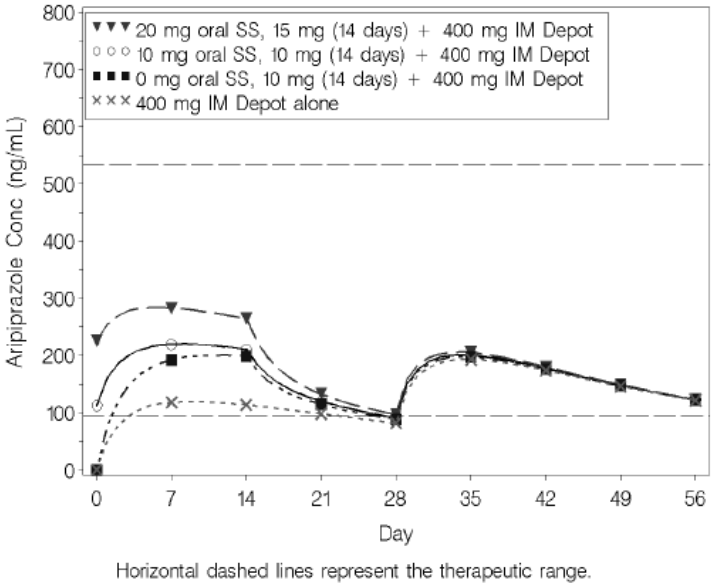
3.3.2 Dose Initiation Schemes

PK simulations of the aripiprazole concentration-time profiles using various aripiprazole oral dosing initiation schemes were performed to evaluate differences in time to achieve therapeutic concentrations. The simulations included:

(1) subjects stabilized on 10 mg PO aripiprazole followed by 14 days of 10 mg PO doses beginning with the administration of the first IM Depot 400 mg dose,
(2) subjects stabilized on 20 mg PO aripiprazole followed by 14 days of 15 mg PO doses beginning with the administration of the first IM Depot 400-mg dose,
(3) subjects who were not administered oral aripiprazole prior to IM Depot dosing and then received orally administered 10-mg doses for 14 days beginning with the administration of the first IM Depot 400-mg dose, and
(4) subjects were not administered oral aripiprazole prior to IM Depot dosing and then began IM Depot 400-mg dosing without concomitant oral therapy.

The simulations for the first 2 IM Depot dose administrations are shown in **Error! Reference source not found.** 15 below. The sponsor claims the median aripiprazole concentration profile is within the therapeutic window for all dosing initiation schemes by 3 days post IM Depot dosing. After 14 days, oral aripiprazole administration is completed, therefore concentrations decline to a profile of the IM Depot dose.

Figure 15 Median Aripiprazole Concentrations vs. Day for the First 2 Doses, Stratified by Dosing Initiation Scheme.



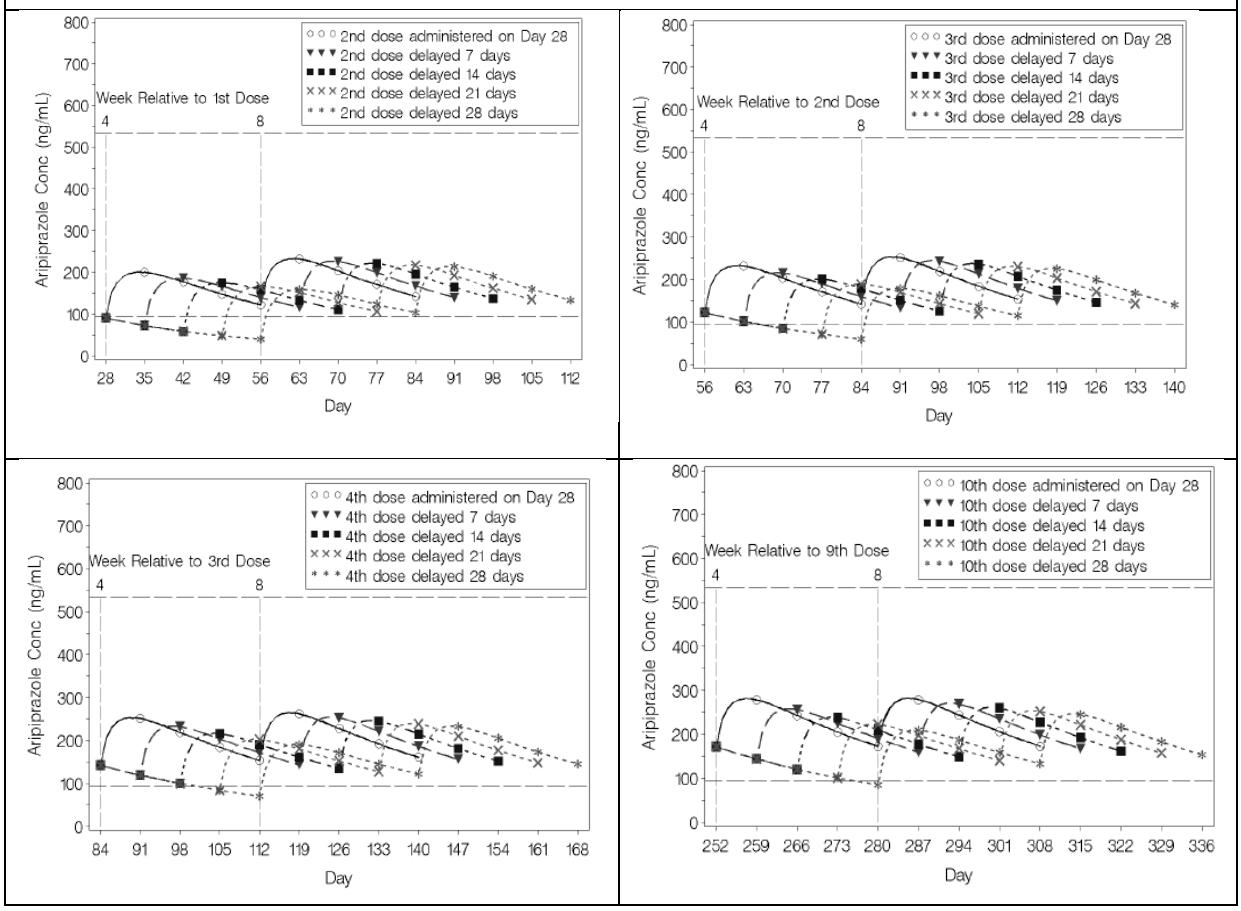
Source: CSR 31-11-2876 pg 131

3.3.3 Delayed Doses During Initiation and Maintenance of Therapy

The proposed dosing for the IM Depot formulation is once (b) (4) but no sooner than (b) (4) from the last injection. Simulations were performed to assess the impact of delaying the IM Depot administration beyond the recommended 28 day schedule. For the simulations, the Sponsor assumed an aripiprazole IM Depot dose of 400 mg was used and subjects were assumed to have been stabilized on orally administered aripiprazole doses of 10 mg daily and initiated aripiprazole IM Depot therapy with an oral aripiprazole dose of 10 mg for 14 days.

The simulations were performed to evaluate the effect of delaying the 2nd, 3rd, 4th, and 10th aripiprazole IM Depot doses for 7, 14, 21, and 28 days. **Error! Reference source not found.** shows the median aripiprazole plasma concentration time profiles for 2 consecutive dosing intervals when doses are delayed by 7, 14, 21, or 28 days as compared to the median aripiprazole plasma concentration-time profile when the doses are taken as scheduled. Delaying the second dose by 28 days show aripiprazole median concentration is below the therapeutic window during the full dose-delay period. The simulations delaying the third dose by 28 days show the median aripiprazole concentration does not drop below the therapeutic window until the dose has been delayed by 2 weeks. The simulations delaying the 4th and 10th doses by 28 days show the median aripiprazole concentration does not drop below the therapeutic window until the dose has been delayed by approximately 3 weeks. After the delayed aripiprazole IM Depot dose is administered, the aripiprazole median concentrations remain within the therapeutic window for the duration of the dosing interval.

Figure 16 Median Aripiprazole Concentrations vs. Day for a) 2nd dose delay b) 3rd dose delay c) 4th dose delay and d) 10th dose delay. The scheduled dose is day 28 after the last dose.



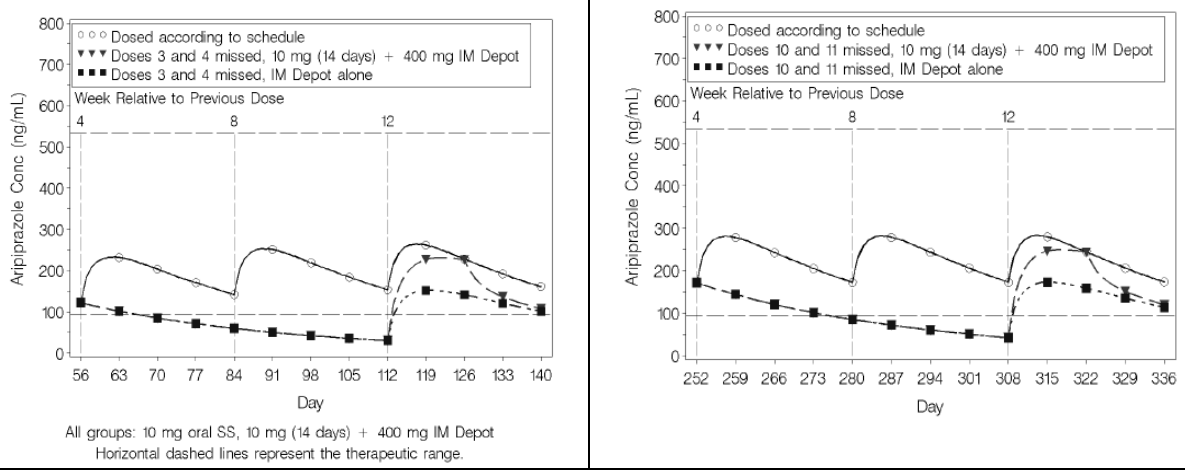
Source: CSR 31-11-2876 pg 132-135

3.3.4 Missed Doses During Maintenance of Therapy

The proposed dosing for the IM Depot formulation is once [redacted] (b) (4). Simulations were performed to assess the impact of missing 2 consecutive IM Depot doses: (1) during dose initiation (missed third and fourth doses), and (2) during maintenance of therapy (missed 10th and 11th doses). As missing 2 consecutive doses is a delay of 56 days, the simulations also evaluated the impact of re-initiating doses with and without concomitant oral therapy. As reference for the simulations, monthly administration of aripiprazole IM Depot 400 mg was used and subjects were assumed to have been stabilized on aripiprazole oral daily doses of 10 mg and initiated IM Depot therapy with an oral dose of 10 mg for 14 days (**Error! Reference source not found.** 17). The figures show that when aripiprazole IM Depot dosing is re-initiated with 14 days of orally administered aripiprazole doses of 10 mg, the median aripiprazole concentrations are equivalent to a scenario in which subjects did not miss any

doses within 2 weeks postdose and remain within the therapeutic window for the remainder of the dosing interval.

Figure 17 Median Aripiprazole Concentrations vs. Day for a) when 3rd and 4th doses missed (left panel) and b) when 10th and 11th doses missed (right panel)



Source: CSR 31-11-2876 pg 142-143

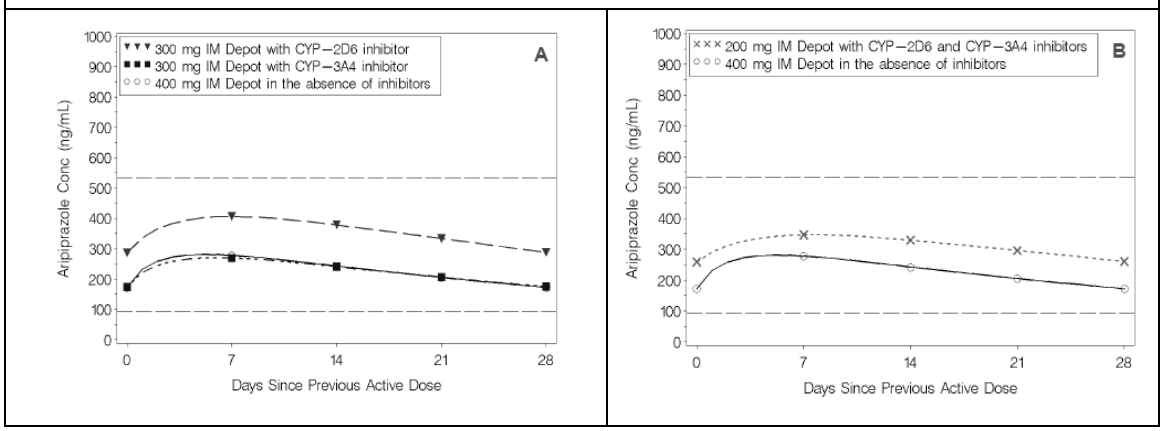
3.3.5 Simulations Concomitant Administration of CYP Inhibitors and Inducers

The sponsor reports that the co-administration of drugs that strongly inhibit the CYP2D6 or 3A4 isozymes has a significant effect on aripiprazole clearance, therefore simulations exploring the impact of these medications were conducted. Detailed PK data on metabolism and potential for drug-drug interactions after administration of aripiprazole as an oral formulation is provided in the Abilify® NDA package for schizophrenia (NDA 21-436).

3.3.5.1 Long-term Concomitant Administration of CYP Inhibitors

As shown in Figure 18, left panel, in the presence of long-term (>14 days) concomitant administration of either a CYP2D6 *or* a CYP3A4 inhibitor, median steady-state aripiprazole concentrations for IM Depot monthly dosing of 300 mg remain within the therapeutic window for the entire dosing interval. On the right panel of **Error! Reference source not found.**, median steady-state aripiprazole concentrations remain within the therapeutic window over the full dosing interval following monthly administration of aripiprazole IM Depot doses of 200 mg with long-term concomitant administration of *both* a CYP2D6 and a CYP3A4 inhibitor.

Figure 18 Median Aripiprazole Concentrations vs. Day for a) presence of chronic administration of CYP2D6 <u>or</u> 3A4 Inhibitor (left panel) and b) presence of chronic administration of CYP2D6 <u>and</u> 3A4 Inhibitor (right panel)



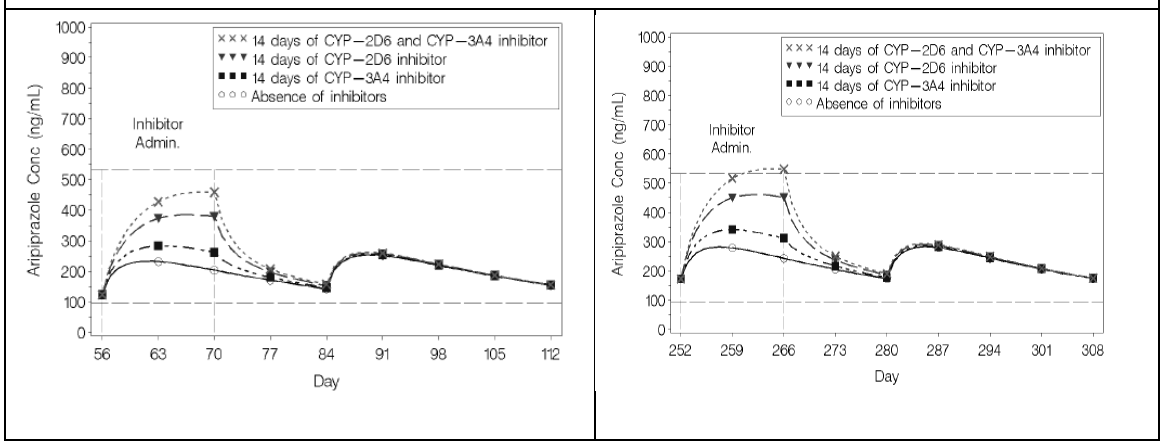
Source: CSR 31-11-2876 pg 144

Based on the simulations and prior information regarding the drug-drug interaction potential of aripiprazole, the sponsor suggest that dose reduction of the maintenance dose of 400 mg to 300 mg should be considered with long-term and concomitant administration of *either* CYP3A4 or CYP2D6 inhibitors with aripiprazole IM depot. If administration of *both* CYP3A4 and CYP2D6 inhibitors with aripiprazole IM depot, the dose should be reduced from a maintenance dose of 400 mg to 200 mg. Once the CYP3A4 and/or CYP2D6 inhibitors are discontinued, the next dose of aripiprazole IM depot can be resumed at its recommended.

3.3.5.2 Short-term Concomitant Administration of CYP Inhibitors

As shown in Figure 19, in the presence of short-term (14 days) concomitant administration of either a CYP2D6 and/or a CYP3A4 inhibitor during the 3rd (left panel) and 10th (right panel) IM Depot dose, median steady-state aripiprazole concentrations for IM Depot monthly dosing of 400 mg remain within the therapeutic window for the entire dosing interval. On the right panel of **Error! Reference source not found.**, aripiprazole concentrations approach the upper-threshold for the last 7 days of inhibitor dosing, with 14 days with long-term concomitant administration of <u>*both*</u> a CYP2D6 and a CYP3A4 inhibitor. For each case, essentially all effects of the inhibitor dosing are washed out by 14 days post-inhibitor dosing.

Figure 19 Median Aripiprazole Concentrations vs. Day for presence of short-term (<14 days) administration of CYP2D6 <u>and/or</u> 3A4 Inhibitor after a) the 3rd IM dose (left panel) and b) the 10th IM dose.



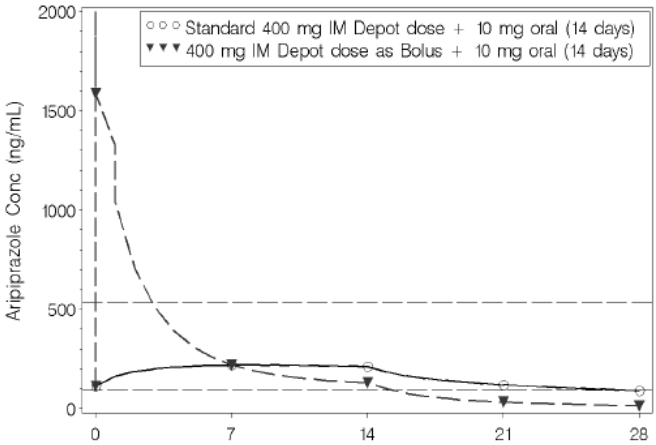
Source: CSR 31-11-2876 pg 148-149

Based on the results of modeling and simulations, the sponsor suggests that no dose adjustment in the recommended monthly maintenance dose of aripiprazole IM depot with short-term (less than 14 days) concomitant administration of CYP3A4 and CYP2D6 inhibitors, when administered individually or together with aripiprazole IM depot.

3.3.5.3 Impact of Dose Dumping

The sponsor's simulation was designed to assess the worst case scenario of dose dumping, administration of the first IM Depot dose as a bolus dose directly into the vasculature in conjunction with concomitant oral administration of daily doses of 10 mg for 14 days (Figure 20). The median aripiprazole concentration is predicted to reach a peak of approximately 4,500 ng/mL, then descends rapidly to therapeutic values by 3 days postdose and falls below the therapeutic window after 2 weeks. Based on the safety data and the results of the pivotal trial (study 31-07-246), no evidence of dose dumping was observed.

Figure 20 Median Aripiprazole Concentration When IM Depot is Administered as an IV Bolus.



Source: CSR 31-11-2876 pg 150

Based on the modeling and simulations performed by the sponsor, along with acquired clinical data from the pivotal trial, the following conclusions were made with regard to dosing of IM aripiprazole:

- Aripiprazole IM Depot Initiation: The recommended starting dose of aripiprazole IM depot is 400 mg. The first aripiprazole IM depot administration should be accompanied by 14 consecutive days of concurrent daily administration of 10 mg to 20 mg of oral aripiprazole.

- Aripiprazole IM Depot Maintenance: should be administered monthly (b) (4) at the recommended maintenance dose of 400 mg. However, the dose may be decreased to 300 mg at any time after the first dose if the 400 mg dose is not tolerated.

- Patients who are CYP2D6 Poor Metabolizers: CYP2D6 PM subjects exhibited about a two-fold higher aripiprazole concentrations as compared to the CYP2D6 EM subjects. However, the adverse event profile following the 400 mg monthly aripiprazole dose in the CYP2D6 PM subjects was similar to that of CYP2D6 EM subjects. Thus, no adjustment in the aripiprazole IM depot dose is necessary in CYP2D6 PM subjects receiving the 400mg dose. May decrease to 300 mg, based on clinical judgement.

- Short-term (<14 days) concomitant administration of a CYP3A4 and/or CYP2D6 inhibitor: No dose reduction of IM aripiprazole is needed.

- Long-term (>14 days) concomitant administration of a CYP3A4 and/or CYP2D6 inhibitor: dose reduction of the recommended monthly maintenance dose of 400 mg to 300 mg should be considered with long-term and concomitant administration of either CYP3A4 or CYP2D6 inhibitors with aripiprazole IM depot. Long-term concomitant

administration of both CYP3A4 and CYP2D6 inhibitors with aripiprazole IM depot requires a dose reduction from the recommended monthly maintenance dose of 400 mg to 200 mg.

- Missed doses: To avoid re-initiation of oral aripiprazole administration, the 2nd and 3rd administration of aripiprazole IM depot should occur within 5 weeks (up to 1 week delay from the scheduled (b) (4) administration). After reaching steady state by the 4th aripiprazole IM depot administration, the 4th and subsequent administrations of aripiprazole IM depot should occur within 6 weeks (up to 2 weeks delay from the scheduled (b) (4) administration) to avoid re-initiation of oral aripiprazole administration. If beyond 5 weeks for the 2nd and 3rd administrations and beyond 6 weeks for the 4th and subsequent injections, dosing requires concurrent administration of oral aripiprazole for 2 weeks with the aripiprazole IM depot injection the monthly maintenance dose of 400 mg.

- Dose dumping: Based on the safety data and the results of safety data in Trial 31-07-246, no evidence of dose dumping was observed in this trial. If dose dumping were to occur, aripiprazole concentrations may reach up to 9 times the concentrations achieved by a therapeutic dose of aripiprazole IM depot. Simulated aripiprazole concentrations following dose dumping, show a decline to concentrations normally observed following the administration of 400 mg IM depot within 3 days after the entire aripiprazole IM depot dose is absorbed in the systemic circulation.

Reviewer's comments:

The Sponsor has performed modeling and simulation of aripiprazole concentrations after the administration of the oral and IM Depot formulation. Upon assessment of the available trial data (e.g., demographics, dosing regimens, and PK sample scheme), the data used for modeling seems representative of the data for use in the intended population. Moreover, the results obtained from the modeling and the defined "therapeutic window" are adequate for performing simulations and to make dosing recommendations. However the Pharmacometrics reviewer has the following concerns:

1) *The initial and maintenance dosing recommendation for all patients taking oral aripiprazole is 400 mg of IM Depot formulation (b) (4). While this regimen was the studied regimen in the pivotal trial, patients taking lower oral doses (i.e., 10 or 15mg QD) may not necessarily need this high of a dose to maintain effectiveness and to prevent non-compliance. Nonetheless, for those patients who do not tolerate a dose of 400 mg IM Depot, a 300 mg maintenance dose is appropriate.*

2) *There is inconsistency in the dosing recommendation for those patients taking concomitant strong CYP2D6 inhibitors on a long term basis compared to individuals who are CYP2D6 poor metabolizing status. If given a CYP2D6 inhibitor long term (>14 days) the dosing*

recommendation is to decrease the dose to 300 mg (and further reduced to 200 mg if taken along with a CYP3A4 inhibitor).

The PK simulations show steady-state exposure parameters for the monthly IM Depot administration of 400 mg in CYP2D6 poor metabolizer subjects are approximately double the values for the CYP2D6 extensive metabolizer subjects administered the same dose. The mean (and SD) $AUC^{ss}_{0\text{-}28days}$ *for CYP2D6 poor metabolizer and extensive metabolizer are 340.6 (136.6) mg*h/L and 172.6 (69.2) mg*h/L, respectively. The sponsor states that, within the pivotal trial, the adverse event profile following the 400 mg monthly aripiprazole dose in the CYP2D6 PM subjects was similar to that of CYP2D6 EM subjects. The clinical trial included a nominal number of n=13 poor metabolizers in the Double-blind IM Depot Maintenance Phase (n=239 extensive metabolizers). Understanding the influence of CYP2D6 polymorphism on aripiprazole exposure, in conjunction with the small number of CYP2D6 PM subjects within the pivotal trial, warrants a dosing adjustment in this population that is consistent with the dosing recommendation for concomitant administration of a CYP2D6 inhibitor long term (>14 days) to an initial and maintenance dose of 300 mg. Dose adjustment to a higher 400 mg dose would be based on clinical judgment and need.*

3) *The influence concomitant administration of a CYP3A4 inducer on aripiprazole exposures has not been assessed nor has an adequate recommendation been given on the dosing adjustment required for the concomitant administration.*

4 REVIEWER'S ANALYSIS

4.1 Introduction

An independent simulation analysis was conducted to resolve the aforementioned outstanding issues.

4.2 Objectives

Analysis objectives are:

1. To evaluate the dosing recommendations for initiation, maintenance, missed and delayed doses and assess the influence of dose dumping.
2. To determine if additional dosing recommendations are warranted for patients that are initially stabilized on different doses of oral aripiprazole.
3. To ascertain the degree of exposure differences between CYP2D6 poor metabolizer and extensive metabolizer status patients requires the need for a dose adjustment that is similar to the recommendation of the concomitant administration of long term CYP2D6 inhibitors.
4. To evaluate of the potential exposures of aripiprazole after concomitant administration of a CYP3A4 inducer.

4.3 Methods

Simulations, using the sponsor's population PK model, were performed to assess different dosing regimens, and compared with the therapeutic window, for the following scenarios:

1) Transitioning from a prior steady state oral dose of 10, 15, 20 and 30 mg to a IM Depot maintenance dose of either 300 mg or 400 mg. This analysis evaluates the exposures of prior steady state oral administration to that of either 300 or 400 mg IM exposures.
2) Dosing of 300 mg or 400 mg IM to CYP 2D6 poor metabolizing status subjects.
3) Dosing of the proposed regimen of 400 mg IM concomitantly with a CYP3A4 inducer.

Along with the therapeutic window, average steady state concentrations and $AUC^{ss}_{(0\text{-}tau)}$ were calculated and compared to a scenario specific reference to determine the appropriateness of the dosing recommendation. The final PK model was used to simulate an inter-subject variability (eta) for the pertinent PK parameters for each of the simulated subjects using the distribution of each eta defined in the final PK model (used to define each of the 10,000 simulated subjects). Depending on the simulation scenario, the simulation programs assigned appropriate values of genotype status, CYP2D6 inhibitor absence or presence, CYP3A4 inducer absence or presence, and dose for each subject. These data were then used to compute the exposure measures for each simulation scenario.

4.3.1 Data Sets

Data sets used are summarized in Table 7.

Table 7. Analysis Data Sets

Study Number	Name	Link to EDR
Pooled PK	be1-cl-wtkg-lin-cov-01.ctl	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\AripiprazoleIM_NDA202971_SSB\PPK Analyses

4.3.2 Software

NONMEM 6.1.0 (Globomax, Inc) was used for population PK analysis and simulations and graphical analysis was performed via Tibco Spotfire S+ 8.1.

4.3.3 Models

The reviewer utilized the Sponsor's population PK model and final PK parameters to perform simulations (Table 6).

4.4 Results

See Section 1 (Summary of Findings) of this report.

4.5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Simulations	PK SIMS	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\AripiprazoleIM_NDA202971_SSB\PPK Analyses\PK SIMS

3.1.4. Genomics Group Review

NDA Number	202,971
Submission Date	26 September 2011
Drug Name	Aripiprazole extended-release suspension for injection
Applicant	Otsuka Pharmaceutical Company
Primary Reviewer	Michael Pacanowski, Pharm.D., M.P.H.

Executive Summary

Aripiprazole is a CYP2D6 substrate. The labeling for oral aripiprazole specifies that the dose should be reduced by 50% in CYP2D6 poor metabolizers (PMs) and 75% in PMs who are also taking a CYP3A4 inhibitor. The sponsor submitted CYP2D6 genotype data with the current NDA submission for aripiprazole intramuscular depot (IMD). Aripiprazole concentrations following IMD administration were approximately two times higher in CYP2D6 PMs compared to non-PMs. (b) (4) dose reduction for CYP2D6 PMs because differential adverse event rates by CYP2D6 phenotype were not observed in the Phase 3 trial. Overall, limited efficacy and safety data are available in the subgroup of patients who are genetic CYP2D6 PMs. The labeling should therefore specify dose reduction for patients who are known to be genetic CYP2D6 PMs to be consistent with IMD dose reductions recommended for patients receiving CYP2D6 inhibitors, considering 1) the high concentrations observed in this subgroup, 2) the potential risk for concentration-related adverse events, 3) the presence of genotype-specific dosing recommendations for the oral formulation, and 4) the persistence of the drug in the circulation following IMD administration.

1 Background

The current submission is for aripiprazole intramuscular depot (IMD) injection for the maintenance treatment of schizophrenia in adults. Aripiprazole is a CYP2D6 substrate. The labeling for oral aripiprazole specifies that the dose should be reduced by 50% in CYP2D6 poor metabolizers (PMs) and 75% in PMs who are also taking a CYP3A4 inhibitor. The sponsor submitted CYP2D6 genotype data in the current submission to support population PK modeling and simulations (see Pharmacometrics review, Satjit Brar), which demonstrated significant differences in the PK of aripiprazole by CYP2D6 genotype. The sponsor has proposed dose reduction for patients receiving CYP2D6 inhibitors, but has not proposed dose adjustment for CYP2D6 PMs, on the basis that differential safety by genotype was not observed. The purpose of this review is to evaluate the appropriateness of dosing recommendations of this new aripiprazole formulation for CYP2D6 PMs.

2 Submission Contents Related to Genomics

2.1 Contents

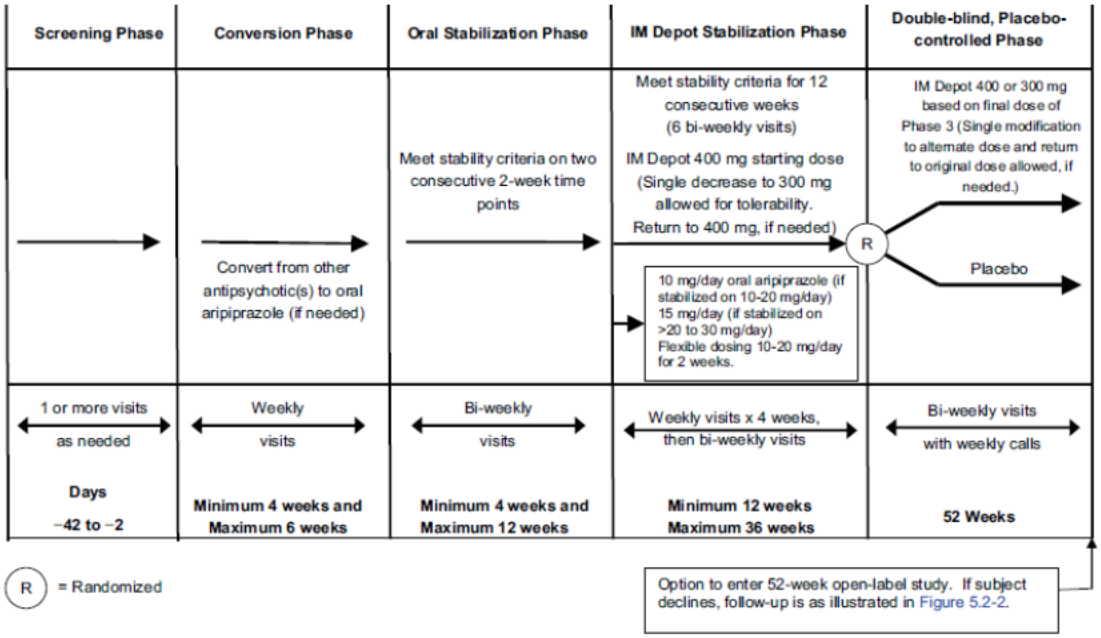
Pharmacogenetic dosing recommendations in the *Dosage and Administration* section of the labeling are shown below. No other information related to aripiprazole pharmacokinetics by CYP2D6 genotype is provided in the label.

> *Dosing recommendation in patients who are classified as CYP2D6 poor metabolizers (PM): Based on clinical trial data on patients who are PM,* (b) (4) *Dosing of [TRADENAME] should be adjusted according to patient response.*

The sponsor submitted CYP2D6 genotype data for clinical pharmacology studies and the pivotal efficacy trial, trial 31-07-246. The following documents reporting results of CYP2D6 phenotype analyses were reviewed: CSR 31-07-246, Summary of Clinical Safety, Summary of Clinical Pharmacology, Report 31-11-287 – Population Pharmacokinetics, (b) (4) genotyping protocols 11608002 and P11608003V1 (31-07-246 Appendices 2 and 3), (b) (4) CYP2D6 phenotyping guidelines (31-07-246 Appendix 4), and (b) (4) genotyping QC procedures (31-07-246 Appendices 5 and 6).

2.2 Methods

This review focused on clinical and PK data submitted for the pivotal efficacy trial, 31-07-246. The design of this trial is summarized below. DNA samples for CYP2D6 genotyping were collected at the end of the conversion phase/beginning of the oral stabilization phase.



Source: Figure 5.2-1 from CSR 31-07-246

Comment: Use of CYP2D6 inhibitors was not permitted in this trial.

Genotyping for *2, *3, *4, *5, *6, *7, *9, *10, *17, *21, *21, *41, and gene duplications was performed by (b) (4) using TaqMan, gel-based assays, and sequencing, under GLP. Phenotypes were assigned to each genotype as shown in the following table.

Genotype-phenotype translation

Gene Result Combination	Predicted Phenotype*
Ultrarapid Activity / Normal Activity	UltraRapid Metabolizer (UM)
Ultrarapid Activity / Reduced Activity	Extensive Metabolizer (EM)
Ultrarapid Activity / No Activity	Extensive Metabolizer (EM)
Ultrarapid / Normal Activity	Extensive Metabolizer (EM)
Normal Activity / Reduced Activity	Extensive Metabolizer (EM)
Normal Activity / No Activity	Intermediate Metabolizer (IM)
Reduced Activity / Reduced Activity	Intermediate Metabolizer (IM)
Reduced Activity / No Activity	Intermediate Metabolizer (IM)
No Activity / No Activity	Poor Metabolizer (PM)
* No activity alleles = *3, *4, *5, *6, *7, *21, *9; reduced activity alleles = *17, *29, *41, *10, ultrarapid activity alleles = duplication; normal activity alleles = *2	

Source: (b) (4) CYP2D6 phenotyping guidelines (Appendix 4)

*Comment: The genotyping methods and QC procedures are acceptable. It was noted that some phenotype inferences provided by the sponsor were inconsistent (e.g., unlike other subjects with the same genotype 31-05-244-0030 was called an EM but had the *2/*4 genotype, 31-05-244-3002 was called an IM but had the *2/*41 genotype, 31-05-244-3001 was called an EM but had the *2/*6 genotype). Consequently, phenotypes were redefined using alternate criteria (see section 2.3). Additionally, subjects 31-07-246-0851 and 31-07-246-0943 had discordant genotypes and were excluded.*

2.3 Reviewer analyses

To explore CYP2D6 phenotype effects on the efficacy and safety of aripiprazole IMD, subgroup analyses for the primary efficacy endpoint (efficacy population) and treatment emergent adverse events (TEAEs; safety population) were conducted for trial 31-07-246. Phenotypes were redefined in accordance with Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) guidelines, as shown below.

Alternate genotype-phenotype translation

Phenotype	CPIC*	DPWG**
PM	AS = 0	2 inactive alleles
IM	AS = 0.5	2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele
UM	AS >2.0	gene duplication in absence of inactive or decreased activity alleles
* AS, or activity score, determined by sum of values for each allele as follows: 0 = *3, *4, *4xN, *5, *6, *7, *16, *36, *40, *42, *56B; 0.5= *9, *10, *17, *29, *41, *45, *46; 1 = *1, *2, *35, *43, *45xN; 2 = *1xN, *2xN, *35xN ** Active alleles = *1, *2, *33, *35; decreased activity alleles = *9, *10, *17, *29, *36, *41; inactive alleles = *3-*8, *11-*16, *19-*21, *38, *40, *42		

Source: (b) (4)

3 Key Questions and Summary of Findings

3.1 Does aripiprazole IMD require dose adjustment based on CYP2D6 genotype?

Yes. Limited efficacy and safety data are available in the subgroup of patients who are genetic CYP2D6 PMs. The labeling should specify dose reduction for patients who are known to be genetic CYP2D6 PMs to be consistent with dose adjustments for CYP2D6 inhibitor use considering 1) the high concentrations observed in this subgroup, 2) the potential risk for concentration-related adverse events, 3) presence of genotype-specific dosing recommendations for the oral formulation administration, and 4) the persistence of the drug in the circulation following IMD.

3.1.1 CYP2D6 phenotype distribution

For the efficacy analysis, data were available for 78% (313/403) of subjects. The distribution of phenotypes for the efficacy population is summarized in the following table.

CYP2D6 phenotype distribution in the efficacy population of trial 31-07-246

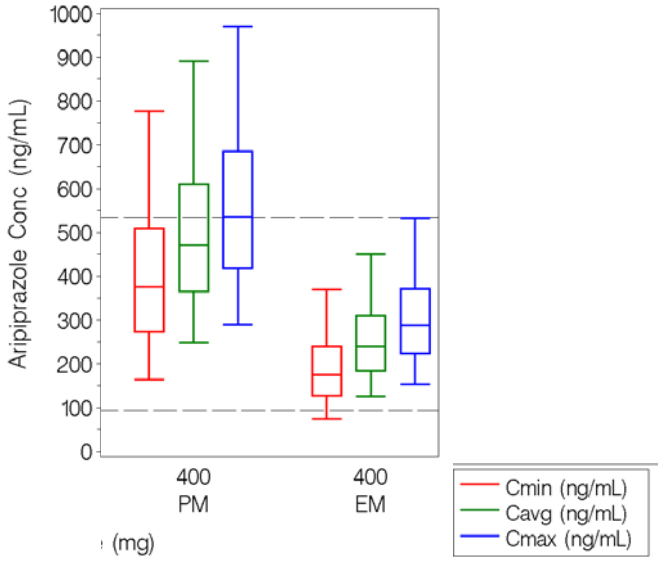
Race (Ethnicity)	N	CYP2D6 Phenotype* (%)			
		UM	EM	IM	PM
All PGx – efficacy	313	1.3	84	8.3	6.7
White (non-Hispanic)	162	0.6	82	10	7.4
White (Hispanic)	19	10	79	5.3	5.3
Black	69	0	84	8.7	7.2
Asian	42	2.3	90	2.4	4.8
Other	21	0	86	9.5	4.8
* Based on CPIC parameterization					

Source: Reviewer

3.1.2 CYP2D6 phenotype effects on aripiprazole IMD PK

3.1.2.1 Sponsor's analysis

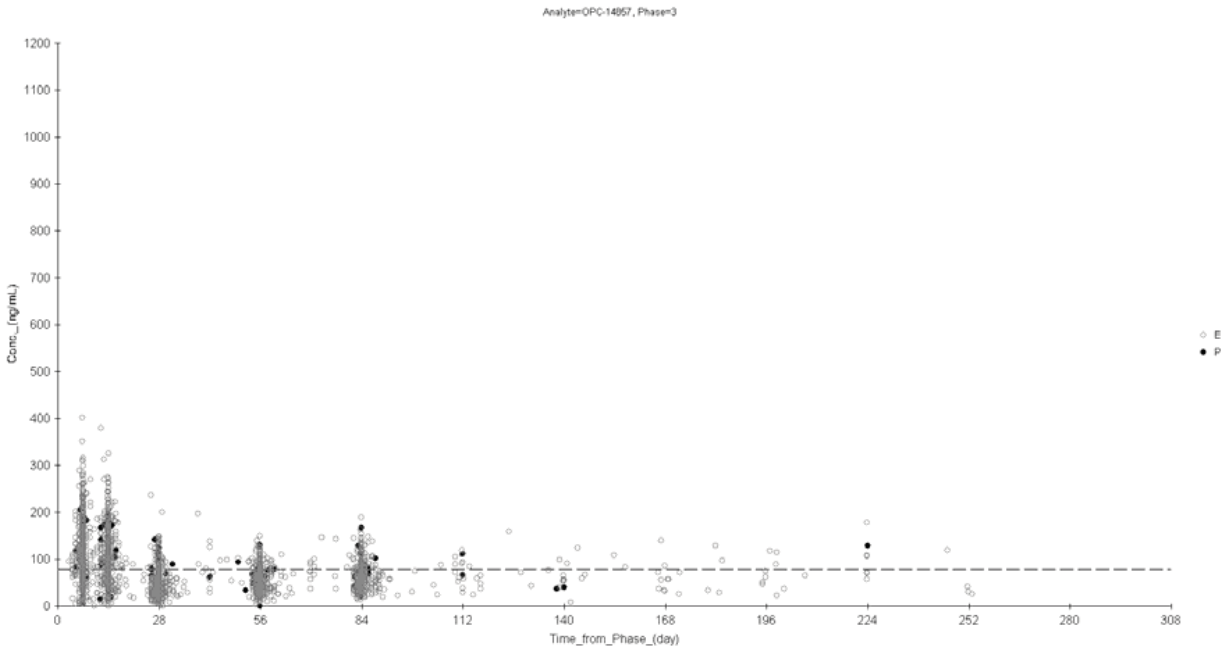
The sponsor's population PK analysis results for steady-state aripiprazole concentrations are summarized in the following figure. PMs had 50% lower clearance and approximately two times higher exposures than EMs treated with 400 mg aripiprazole IMD.



Source: Modified from figure S9-35, CSR 31-11-287

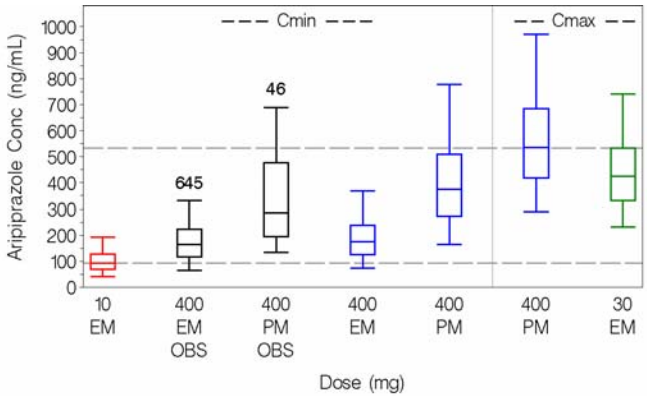
Comment: In the analysis datasets, it appeared that individuals who are heterozygous for reduced or null function alleles (i.e., IMs) were grouped with EMs or UMs, which may introduce a null bias. The sponsor's simulations generally did not assess the active metabolite or the total amount of active circulating drug.

Concentrations of the active metabolite, dehydro-aripiprazole, are expected to be lower in PMs, thus diminishing the clinical impact of higher parent drug exposures. As shown in the figure below, observed dehydro-aripiprazole concentrations in trial 31-07-246 (data for the IMD stabilization phase shown) were not uniformly lower than the rest of the population.



Source: CSR 31-07-246 Attachment 17.2.3.5 (page 4955)
Black circles represent PMs, open circles represent EMs.

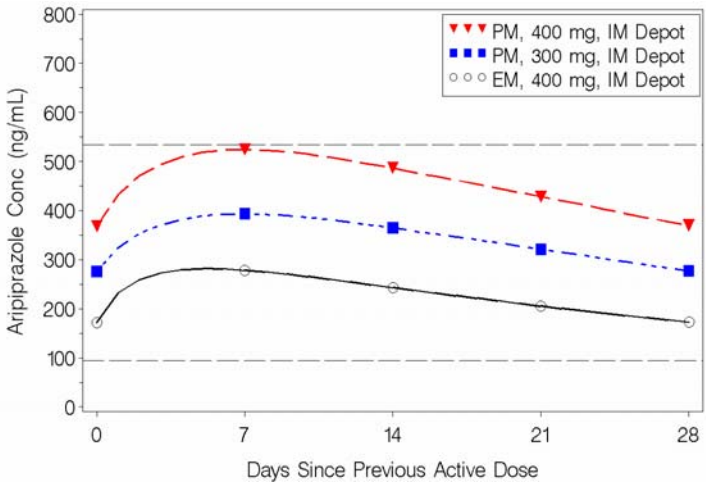
As shown in the figure below, Cmin values in EMs receiving 400 mg were similar those observed with 10 mg of oral aripiprazole, while Cmax values in PMs receiving 400 mg were similar to those observed with 30 mg of oral aripiprazole.



Observed values from 31-05-246
Source: Modified from 2.7.2.3-1 of Summary of Clinical Pharmacology

Comment: These results suggest that aripiprazole exposures across the range of CYP2D6 phenotypes from the IMD formulation were within the bounds observed across the dose range for oral aripiprazole.

Simulated exposures at 300 mg in PMs appeared to reduce exposure, albeit higher than the exposures observed in EMs receiving 400 mg.



Source: Figure 2.7.2.4.1.3.3-2 of Summary of Clinical Pharmacology

3.1.2.2 Reviewer's analysis

Please refer to the Pharmacometrics review for results of population PK analyses related to CYP2D6.

3.1.3 CYP2D6 phenotype effects on efficacy and safety

3.1.3.1 Sponsor's analysis

Safety analyses were performed for 31 poor metabolizers and 499 extensive metabolizers in the aripiprazole depot stabilization phase of trial 31-07-246, and 13 poor metabolizers and 239 extensive metabolizers in the double-blind, placebo-controlled phase. The sponsor's results are summarized in the table below. No apparent differences in TEAE rates were observed across CYP2D6 phenotype groups.

TEAEs by treatment phase and CYP2D6 phenotype

Phase	TEAE type	CYP2D6 Phenotype	n/N (%)	
			Aripiprazole	Placebo
Stabilization	All TEAE	EM	296/499 (59)	-
		PM	18/31 (58)	-
		Unknown	31/46 (67)	-
	Serious TEAE	EM	23/499 (4.6)	-
		PM	0/31 (0)	-
		Unknown	2/46 (4.3)	-
	Discontinuation	EM	24/499 (5.0)	-
		PM	0/31 (0)	-
		Unknown	3/46 (6.5)	-
Randomized	All TEAE	EM	148/239 (62)	69/112 (62)
		PM	10/13 (77)	8/11 (73)
		Unknown	12/17 (71)	6/11 (55)
	Serious TEAE	EM	9/239 (3.8)	6/112 (5.4)
		PM	0/13 (0)	1/11 (9.1)
		Unknown	2/17 (12)	2/11 (18)
	Discontinuation	EM	16/239 (6.7)	14/112 (12.5)
		PM	1/13 (7.7)	1/11 (9.1)
		Unknown	2/17 (12)	3/11 (27)

Source: Summary of Clinical Safety (page 162)

Comment: (b) (4) *The results of this analysis are difficult to interpret given the staged enrichment design of this trial. The sponsor did not perform subgroup analyses related to efficacy endpoints by CYP2D6 phenotype.*

3.1.3.2 Reviewer's analysis

The primary endpoint, time to relapse (as defined by clinical global impression of improvement, hospitalization, suicidality, or violent behavior) during the randomized treatment period, is summarized below by CYP2D6 phenotype. Aripiprazole had lower relapse rates than placebo in all phenotype subgroups, except PMs, which had a small number of subjects.

Relapse rates by CYP2D6 phenotype

CYP2D6 Phenotype	n/N (%)		P (chi-sq)	P (log-rank)
	Aripiprazole	Placebo		
All	27/269 (10)	53/134 (40)	<0.0001	<0.0001
PGx	19/206 (9.2)	40/107 (37)	<0.0001	<0.0001
UM	0/2 (0)	1/2 (50)	-	-

EM	14/177 (7.9)	30/85 (35)	<0.0001	<0.0001
IM	2/17 (12)	5/9 (56)	0.03	0.03
PM	3/10 (30)	4/11 (37)	1	0.96
EFF0.xpt+PGX.xpt				

Source: Reviewer

Moderate/severe TEAEs were assessed for each phase of the trial by CYP2D6 phenotype. Higher rates of TEAEs were not observed in the PM subgroup. Serious TEAEs tended to occur in the EM group. Discontinuation rates were similar among the phenotype groups.

Potentially-related moderate/severe TEAEs by treatment phase and CYP2D6 phenotype

Phase	CYP2D6 Phenotype	N	Frequency (%)		
			All	Serious	Discontinued
1 (aripiprazole 5-15 mg)	PGx	530	0.11	0.002	0.02
	EM	455	0.10	0.002	0.02
	IM	41	0.22	0	0.05
	PM	25	0.12	0	0.04
	UM	9	0.11	0	0
2 (aripiprazole 10-30 mg)	PGx	644	0.12	0.003	0.02
	EM	555	0.12	0.004	0.03
	IM	44	0.05	0	0
	PM	35	0.11	0	0.03
	UM	10	0.10	0	0
3 (aripiprazole 400/300 mg)	PGx	528	0.17	0.008	0.04
	EM	454	0.17	0.009	0.05
	IM	36	0.19	0	0.03
	PM	31	0.13	0	0
	UM	7	0.29	0	0.14
4 (aripiprazole 400/300 mg)	PGx	249	0.17	0.016	0.05
	EM	214	0.17	0.019	0.06
	IM	19	0.16	0	0.00
	PM	13	0.15	0	0.08
	UM	3	0.33	0	0
4 (placebo)	PGx	123	0.19	0.008	0.11
	EM	100	0.18	0	0.12
	IM	10	0.20	0	0.10
	PM	11	0.27	0.091	0.09
	UM	2	0.00	0	0
AE0.xpt+PGX.xpt					

Source: Reviewer

Comment: The efficacy and safety results in the CYP2D6 phenotype subgroups should be interpreted with caution because of the small sample size.

4 Summary and Conclusions

Aripiprazole concentrations following administration of the IMD formulation are approximately twice as high in PMs compared to EMs. (b) (4) based on CYP2D6 phenotype because a safety signal was not observed in the Phase 3 trial. However, the design of the Phase 3 trial enriched the population based on

response and tolerability of oral and IMD aripiprazole, and is consequently difficult to interpret from a safety standpoint. Nonetheless, even in the earlier stabilization phases of this trial, no differential TEAE rates were observed across the CYP2D6 phenotype groups.

Stabilizing patients on oral aripiprazole helps to accommodate exposure variability. However, individuals are administered the same dose of aripiprazole IMD regardless of the stable oral dose. Given that aripiprazole IMD persists in the systemic circulation for a long period of time, and that the IMD formulation will result in a sustained increase in aripiprazole concentrations in subjects maintained on lower oral aripiprazole doses, subjects who are known to be CYP2D6 PMs should be started on a lower IMD dose (i.e., 300 mg). Dose reductions to 300 mg aripiprazole IMD are recommended for chronic use of CYP2D6 inhibitors (it should also be noted that use of CYP2D6 inhibitors was prohibited in the Phase 3 trial), which should also apply to genetic CYP2D6 PMs.

5 Recommendations

Limited efficacy and safety data are available in the subgroup of patients who are genetic CYP2D6 PMs. The labeling should specify dose reduction for patients who are known to be genetic CYP2D6 PMs to be consistent with dose adjustments for CYP2D6 inhibitor use considering 1) the high concentrations observed in this subgroup, 2) the potential risk for concentration-related adverse events, 3) presence of genotype-specific dosing recommendations for the oral formulation administration, and 4) the persistence of the drug in the circulation following IMD.

5.1 Post marketing studies

None.

5.2 Labeling

2.5 Dosage Adjustment

(b) (4)

[redacted]

(b) (4)

3.2 NDA filing form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202971**	**Brand Name**	**ABILIFY MAINTENA**
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Aripiprazole**
Medical Division	**Psychiatry Drug Products**	**Drug Class**	**Antipsychotics**
OCP Reviewer	**Huixia Zhang**	**Indication(s)**	**Maintenance Treatment of Schizophrenia**
OCP Team Leader	**Hao Zhu**	**Dosage Form**	**Extended-Release Suspension for IM Injection**
Pharmacometrics Reviewer	**Satjit Brar**	**Dosing Regimen**	(b) (4)
Genomics Team Leader	**Mike Pacanowski**	**Route of Administration**	**IM Injection**
Date of Submission	**09/26/2011**	**Sponsor**	**Otsuka**
Estimated Due Date of OCP Review	**5/2/2012**	**Priority Classification**	**Standard 10 Months**
Medical Division Due Date	**6/21/2012**		
PDUFA Due Date	**7/26/2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x	5		
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	x	3		
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	x	2		
multiple dose:	x	1		
Dose proportionality -	x	2		
fasting / non-fasting single dose:	x			
fasting / non-fasting multiple dose:	x			
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:	x	1		
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x			
Data sparse:	x			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	x			
Chronopharmacokinetics				
Pediatric development plan	x			**Request for Waiver submitted**
Literature References	x			
Total Number of Studies		5		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		x		
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review	x			

	can begin?				
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			Additional data request (below).
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		x		Additional data request (below).
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		x		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		Exposure-response analysis for IM formulation was not performed
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			PK simulations were performed and assessed w.r.t. a therapeutic range.
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. In clinical practice, patients might not be able to receive the aripiprazole ER suspension injection exactly following the scheduled time. Therefore the sponsor is asked to conduct simulations exploring flexible dosing windows for the initial dose and maintenance dose (e.g., if the dose were to be given 2 days prior to and 2 days after the scheduled dosing time).

2. Please submit the datasets and codes/scripts for reviewers to recreate all the *simulations* described in Table S8-20 entitled "Description of Population and Dosing and Location of Corresponding Graphs and Statistics for Each Simulation Scenario Evaluated" from page 101 of Report 31-11-287 (Pop PK M&S Report).

   All model codes or control streams, output listings and scripts used to generate plots should be provided for all simulations performed. Files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)

3. With regard to the CYP2D6 pharmacogenetic analyses, please submit a dataset (in SAS .xpt format) containing individual CYP2D6 genotypes and subject identifiers that link the population PK and core trial datasets. Also, please submit a summary of the genotyping methods, tested alleles, quality control procedures, and phenotype parameterization.

4. Please submit individual aripiprazole and dehydro-aripiprazole plasma concentration data for both studies CN138020 and 31-05-244 in SAS .xpt format.

Huixia Zhang	11/14/2011
Reviewing Clinical Pharmacologist	Date
Hao Zhu	11/14/2011
Team Leader/Supervisor	Date

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

/s/

HUIXIA ZHANG
06/03/2012

SATJIT S BRAR
06/03/2012

MICHAEL A PACANOWSKI
06/04/2012

VENKATESH A BHATTARAM
06/04/2012

HAO ZHU
06/04/2012

ONDQA BIOPHARMACEUTICS FILING REVIEW

NDA#:	202-971
Submission Dates:	09/26/2011; 03/22/2012; 5/10/2012; 5/25/12
Brand Name:	N/A
Generic Name:	Aripiprazole Monohydrate
Formulation:	Extended-Release Injectable Suspension
Strength:	400 mg/vial and 300 mg/vial
Applicant:	Otsuka Pharmaceutical Co., Ltd.
Type of submission:	Original NDA, 505(b)(1), Standard Review
Reviewer:	Zedong Dong, Ph.D.

SUBMISSION

NDA 202-971 was submitted under FDC 505(b)(1) category for Aripiprazole extended release suspension for injection for the maintenance treatment of schizophrenia. Several drug products of aripiprazole have been approved, including a tablet formulation (NDA 21-436), an oral suspension (NDA 21-713), an orally disintegrating tablet (NDA 21-729), and an immediate release injection for intramuscular (IM) (NDA 21-866). This NDA is submitted for Aripiprazole IM Depot product which is a sterile, single-dose, lyophilized cake for reconstitution, extended-release injectable suspension to deliver 300 mg of aripiprazole in 300-mg/vial strength and 400 mg of aripiprazole in 400-mg/vial strength. Aripiprazole monohydrate is used to manufacture the drug product, with reduced API [redacted] (b) (4).

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of the method development and specification setting: [redacted] (b) (4) evaluation on proposed dissolution acceptance criteria.

The initially developed dissolution method [redacted] (b) (4)

(b) (4)

The Applicant (b) (4) extended dissolution time to eight hours, and proposed the dissolution acceptance criteria shown below. It appears that the eight-hour dissolution method (b) (4) is deemed acceptable.

8-hour test method for release testing of the commercial products

- Test medium: 900 mL of 0.25% SLS solution
- Paddle speed: 50 rpm
- Sample amount: Amount corresponding to 50 mg of aripiprazole
- Dissolution time: 8 hours
- Specification: Value at 15 minutes: (b) (4) Value at 2 hours: (b) (4) (b) (4) Value at 8 hours: (b) (4)

The dissolution results of the Phase 3 clinical lots and primary stability lots are summarized in Appendices A to G of this review. Based on the data, and through communication with the Applicant, on May 25, 2012, they accepted to implement

(b) (4)% at 15 minutes, (b) (4)% at 2 hours, and NLT (b) (4)% at 8 hours as the final dissolution acceptance criteria for their product.

For the LTSS-1 batches, within six months under accelerated conditions, no significant trend of change was observed in the dissolution profiles for both strengths of the drug product. Within 18 months under long term conditions, generally no significant trend of change was observed either; however, data variation was observed, particularly for the 2-hour time points. For the LTSS-2 batches, no significant trend of change was observed with six-month storage under the long term conditions. However, fluctuation in the dissolution results was observed in the samples under accelerated conditions. All dissolution results meet the proposed dissolution acceptance criteria within the reporting period.

(b) (4) The validation of the dissolution method was reviewed by Dr. David Claffey, CMC Reviewer and it was found acceptable.

RECOMMENDATION

The dissolution method as well as the acceptance criteria proposed for the drug product in NDA 202-971 are acceptable.

Dissolution Method and Acceptance Criteria for Aripiprazole Monohydrate ER Injectable Suspension					
USP Apparatus	**Spindle Rotation**	**Medium Volume**	**Temperature**	**Medium**	**Acceptance criteria % of Drug Dissolved**
No. 2 (paddle)	50 rpm	900 mL	37°C	0.25% SLS solution	15 min: (b) (4)% 2 hrs: (b) (4) 8 hrs: NLT (b) (4)%

NDA 202-971 is recommended for approval from the Biopharmaceutics perspective.

Zedong Dong, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Date

Angelica Dorantes, Ph.D.
Team Leader
ONDQA Biopharmaceutics

Date

CC: NDA 202-971
Sonny Saini, Teshara Bouie

BIOPHARMACEUTICS EVALUATION

REVIEWER NOTES

INTRODUCTION

NDA 202-971 is submitted under FDC 505(b)(1) category for Aripiprazole extended release suspension for injection for the maintenance treatment of schizophrenia. Several drug products of aripiprazole have been approved, including a tablet formulation (NDA 21-436), an oral suspension (NDA 21-713), an orally disintegrating tablet (NDA 21-729), and an immediate release injection for intramuscular (IM) (NDA 21-866). This NDA is submitted for Aripiprazole IM Depot product which is a sterile, single-dose, lyophilized cake for reconstitution, extended-release injectable suspension to deliver 300 mg of aripiprazole in 300-mg/vial strength and 400 mg of aripiprazole in 400-mg/vial strength. Aripiprazole monohydrate is used to manufacture the drug product, with reduced API (b) (4).

The composition of the formulation for the proposed product is presented in the table below.

Table 1. Composition of Aripiprazole IM Depot (300 mg/vial and 400 mg/vial)

Component	Reference Standard	Function	Quantity (mg/mL)[f]	Quantity per Vial (mg)	
				300-mg/vial	400-mg/vial
Sterile Aripiprazole Monohydrate	In-house	Active	200.0[a]	375.0[a]	475.0[a]
Carboxymethylcellulose Sodium	USP	(b) (4)			
Mannitol	USP				
Sodium Phosphate, Monobasic, Monohydrate	USP				
Sodium Hydroxide	NF				
(b) (4)	NF				
Water for Injection, USP	USP				
(b) (4)					

PROPOSED DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERIA

The proposed regulatory dissolution method (USP Apparatus 2) and acceptance criteria (compliant to USP<711>) for the Aripiprazole IM Depot are shown below.

8-hour test method for release testing of the commercial products

- Test medium: 900 mL of 0.25% SLS solution
- Paddle speed: 50 rpm
- Sample amount: Amount corresponding to 50 mg of aripiprazole
- Dissolution time: 8 hours
- Specification: Value at 15 minutes: (b) (4) (b) (4) Value at 2 hours: (b) (4) (b) (4) Value at 8 hours: (b) (4)

The review and evaluation are focused on method development and specification setting: (b) (4) (4) evaluation on proposed dissolution acceptance criteria.

(b) (4)

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(b) (4)

[redacted]

Evaluation of the proposed dissolution acceptance criteria

The dissolution results of the Phase 3 clinical lots and primary stability lots are summarized in the following table. Based on the data (Table 2, as well as Appendices A and E), the proposed specifications of (b) (4) % at 15 minutes, (b) (4) % at 2 hours, and

NLT (b) (4)% at 8 hours are recommended to be revised to (b) (4)% at 15 minutes, (b) (4)% at 2 hours, and NLT (b) (4)% at 8 hours.

> ***Comment#1:*** *Please revise the dissolution acceptance criteria to (b) (4)% at 15 minutes, (b) (4)% at 2 hours, and NLT (b) (4)% at 8 hours.*
>
> ***Response:*** *The Applicant agreed to revise the dissolution acceptance criteria at 15 minutes and 8 hours according to the FDA recommendation. However, the Applicant did not agree to revise the 2 hours time point based on the stability study results.*
>
> ***Evaluation:*** *Upon discussion with Dr. Angelica Dorantes, the response was deemed acceptable.*

Table 2. Summary of Dissolution Results of the Clinical and Primary Stability Lots (Compiled by Reviewer)

	Dissolution Results	Mean	St. Dev.
15 min			(b) (4)
2 hr			
8 hr			

Phase 3 Clinical Lots

Primary Stability Lots

Evaluation of Stability Data

Two sets of long term stability study (LTSS) batches of drug product for each strength were manufactured (Table 3). LTSS-2 was manufactured with (b) (4),

Table 3. Primary Stability Batches of LTSS Studies

Lot number	Manufacturing date	Strength	Purpose	Manufacturing site for drug substance	Manufacturing site for drug product	lyophilizer	Batch size
09F79A400	(b) (4)	400 mg	LTSS-1				(b) (4)
09F82A400		400 mg	LTSS-1				
09F96A300		300 mg	LTSS-1				
09F99A300		300 mg	LTSS-1				
09G77A400		400 mg	LTSS-1				
09G89A300		300 mg	LTSS-1				
11C86A400		400 mg	LTSS-2				
11C90A400		400 mg	LTSS-2				
11C94A400		400 mg	LTSS-2				
11C99A300		300 mg	LTSS-2				
11D72A300		300 mg	LTSS-2				
11D76A300		300 mg	LTSS-2				

(b) (4). In the submission, the Applicant provided 18 months of long term (5ºC, 30ºC/75% RH, 25ºC/60% RH) and 6 months accelerated (40ºC/75% RH) stability result for the LTSS-1 batches. The Applicant submitted an amendment on 3/22/2012 with the six months stability data for the LTSS-2 batches under both long term (5ºC, 30ºC/75% RH, 25ºC/60% RH) and accelerated (40ºC/75% RH) conditions.

For the LTSS-1 batches, within six months under accelerated conditions, no significant trend of change was observed in the dissolution profiles for both strengths of the drug product (see Appendix F). Within 18 months under long term conditions, generally no significant trend of change was observed either, however, data variation was observed, particularly for the 2-hour time points (see Appendix G). For the LTSS-2 batches, no significant trend of change was observed with six-month storage under the long term conditions. However, fluctuation in the dissolution results was observed in the samples under accelerated conditions. All dissolution results meet the proposed dissolution acceptance criteria within the reporting period.

No significant trend of change in dissolution results under stressed conditions (b) (4) was observed. The twenty four-hour in-use stability data for dissolution support the proposed in-use storage duration of four hours.

FINAL DISSOLUTION METHOD AND VALIDATION

(b) (4)

(b) (4)

The validation of the dissolution method was reviewed by Dr. David Claffey and it was found acceptable.

RECOMMENDATION

The dissolution method as well as the acceptance criteria proposed for the drug product in NDA 202-971 are acceptable. NDA 202-971 for Aripiprazole Monohydrate ER Injectable Suspension is recommended for approval from the Biopharmaceutics perspective.

COMMENTS TO BE COMMUNICATED TO THE APPLICANT

N/A

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/s/

ZEDONG DONG
05/30/2012

ANGELICA DORANTES
05/30/2012

ONDQA BIOPHARMACEUTICS FILING REVIEW

NDA#:	202-971
Submission Date:	09/26/2011
Brand Name:	N/A
Generic Name:	Aripiprazole Monohydrate
Formulation:	Extended-Release Injectable Suspension
Strength:	400 mg/vial and 300 mg/vial
Applicant:	Otsuka Pharmaceutical Co., Ltd.
Type of submission:	Original NDA, 505(b)(1), Standard Review
Reviewer:	Zedong Dong, Ph.D.

SUBMISSION

NDA 202-971 is submitted under FDC 505(b)(1) category for Aripiprazole extended release suspension for injection for the maintenance treatment of schizophrenia. Several drug products of aripiprazole have been approved, including a tablet formulation (NDA 21-436), an oral suspension (NDA 21-713), an orally disintegrating tablet (NDA 21-729), and an immediate release injection for intramuscular (IM) (NDA 21-866). This NDA is submitted for Aripiprazole IM Depot product which is a sterile, single-dose, lyophilized cake for reconstitution, extended-release injectable suspension to deliver 300 mg of aripiprazole in 300-mg/vial strength and 400 mg of aripiprazole in 400-mg/vial strength. Aripiprazole monohydrate is used to manufacture the drug product, with reduced API [redacted] (b) (4).

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review will be focused on the evaluation of the information/data supporting the proposed dissolution method and acceptance criteria.

The dissolution method development report is provided in the submission. The proposed dissolution method uses USP Apparatus 2 at 50 rpm, in 900 mL 0.25% SLS solution, with a proposed [redacted] (b) (4) dissolution specification: [redacted] (b) (4) % after 15 minutes; [redacted] (b) (4) % after 2 hours; [redacted] (b) (4) % after 8 hours. The suspension sample size for dissolution test is equivalent to 50 mg aripiprazole. Justification for the selection of apparatus type, dissolution medium and paddle speed was provided. Also, preliminary dissolution data were submitted to demonstrate the discriminating capability of the proposed dissolution method against API particle size change as well as process induced phase change. The dissolution method development report will be reviewed, and the acceptability of the proposed dissolution method and acceptance criteria will be determined. The analytical procedures of the dissolution method and method validation report were also included in the submission.

RECOMMENDATION

NDA 202-971 for aripiprazole extended release suspension for injection is fileable from the Biopharmaceutics perspective.

_____ _____

Zedong Dong, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes, Ph.D. Date
Supervisory Lead
ONDQA Biopharmaceutics

CC: NDA 202-971
Sonny Saini, Teshara Bouie

APPENDIX A

Formulation Compositions for Aripiprazole Extended Release Suspension for Injection

Component	Reference Standard	Function	Quantity (mg/mL)[f]	Quantity per Vial (mg)	
				300-mg/vial	400-mg/vial
Sterile Aripiprazole Monohydrate	In-house	Active	200.0[a]	375.0[a]	475.0[a]
Carboxymethylcellulose Sodium	USP	(b) (4)			
Mannitol	USP				
Sodium Phosphate, Monobasic, Monohydrate	USP				
Sodium Hydroxide	NF				
(b) (4)					
Water for Injection, USP	USP				

(b) (4)

APPENDIX B

Proposed Dissolution Acceptance Criteria and Method Conditions

Dissolution	After 15 minutes: (b) (4)% After 2 hours: (b) (4)% After 8 hours: (b) (4)%	Dissolution <711> Apparatus 2, 50 rpm, 900 mL of 0.25 w/v% Sodium lauryl sulfate solution; Suspension sample size - Equivalent to aripiprazole 50 mg

APPENDIX C

Summary of Dissolution Method Validation Results

Characteristics	Test results
Specificity	No interference of the excipients was observed.
Linearity	Over the range of 10 - 125% (5.0 - 62.5 mg/900 mL) of the aripiprazole concentration established, the linearity with a correlation coefficient of 0.999995 (Y = 0.01640X - 0.0035, mostly passing through the origin) was exhibited (cell-1). X: mg/900 mL, Y: Difference between the absorbances at 252 and 325 nm It was judged that each calibration curve shows the regression.
Accuracy	Over the range of 20 - 125% (10.0 - 62.5 mg/900 mL) to aripiprazole specified in the test method, the recovery rates were as follows: mean 96.6% (max.: 97.3%, min.: 95.8%) at 15 minutes, mean 97.1% (max.: 97.7%, min.: 96.2%) at 2 hours, and mean 97.8% (max.: 98.6%, min.: 96.9%) at 8 hours. The 95% confidence interval for the mean of recovery rates was as follows: 96.4 - 96.9% at 15 minutes, 96.7 - 97.4% at 2 hours, and 97.5 - 98.1% at 8 hours.
Range	The range with allowable linearity, accuracy and repeatability was 20 - 125% (10.0 - 62.5 mg/900 mL) of the concentration specified in the test method.
Repeatability	The SD and RSD for the recovery rates, along with 95% confidence interval for the SD, in 20 - 125% spiked amounts of aripiprazole (in the test on Accuracy), were 0.5%, 0.5%, and 0.4 - 0.8% at 15 minutes, 0.6%, 0.6% and 0.4 - 0.9% at 2 hours, and 0.6%, 0.6% and 0.4 - 0.9% at 8 hours, respectively. Further, the deviation of each measured value from the mean of measured values was -0.8 - 0.7% at 15 minutes, -0.9 - 0.6% at 2 hours, and -0.9 - 0.8% at 8 hours.
Intermediate precision	The SD, RSD and 95% confidence interval for SD were 1.2%, 2.8% and 0.8 - 2.1% at 15 minutes, 2.8%, 4.4% and 2.0 - 4.9% at 2 hours, and 2.0%, 2.1% and 1.3 - 4.1% at 8 hours, respectively. The maximum value in the difference among the mean values (on each testing date) was 5%.
Robustness	An investigation was carried out on the concentration (0.245% - 0.255%) of sodium lauryl sulfate in the dissolution medium and the influence of degassing. A difference between the mean dissolution rates obtained under the varied and standard operating conditions was ± 4% at maximum.
Comparison with manual sampling	In the test results (t-test) obtained by the present automated method and the manual sampling method, no significant differences at 5% level of significance were observed. Further, the difference (%) between the mean values was -1% at maximum.

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/s/

ZEDONG DONG
11/09/2011

ANGELICA DORANTES
11/10/2011