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APPLICATION NUMBER:

21-713

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21713

Drug: Aripiprazole Oral Solution 1mg/mL

Trade Name: Abilify™

Applicant: Bristol Myers Squibb

Indication: Treatment of Schizophrenia

OND Division: DNDP (HFD-120)

OCPB Division: DPE 1 (HFD-860)

Submission Type: New Formulation

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1. Executive Summary	2
1.1. Recommendation	2
1.2. Phase 4 Commitments	2
1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings	2
2. Question Based Review	5
2.1. General Attributes	5
2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?	5
2.1.3. What are the proposed mechanism of action and therapeutic indication?	5
2.2. General Clinical Pharmacology	6
2.2.2. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?	6
2.2.3. Exposure-Response	6
2.2.4. What are the Pharmacokinetic Characteristics of the Drug?	7
2.3. Intrinsic Factors	7
2.4. <i>Extrinsic Factors</i>	7
2.5. General Biopharmaceutics	8
2.5.1 What is the composition of the oral solution formulation?	8
2.5.3. Is aripiprazole oral solution bioequivalent to the tablet formulation?	9
2.5.4. Is the concentration of aripiprazole proportional to dose after administration of the oral solution?	11
2.5.5. What dosing recommendations are necessary?	13
2.5.7. What is the effect of food on the bioavailability of aripiprazole?	14
2.6. Analytical Section	14
2.6.1. What analytical methods were used to identify aripiprazole and its metabolite, dehydro-aripiprazole?	14
3. <i>Detailed Labeling Recommendations</i>	15
4. <i>Appendices</i>	16
4.1 Package insert (proposed)	16
4.2. Individual Study Review	50
4.3. Cover Sheet and OCPB filing/review form	91

1. Executive Summary

1.1. Recommendation

Based on the review of the data submitted to the Human Pharmacokinetics and Bioavailability Section of NDA 21-713 to fulfill section 320 and 201.5 of 21 CFR, the application is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). OCPB supports a recommendation for approval provided that satisfactory agreement is reached between the sponsor and the agency regarding the language in the labeling.

Labeling recommendations are provided in Section 3 of this review

1.2. Phase 4 Commitments

There are no phase 4 commitments recommended.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Background: Aripiprazole (OPC-14597, BMS-337039), a dihydrocarbostyryl (quinolinone) derivative, is an antipsychotic. Aripiprazole (Abilify™) is currently approved (NDA 21-346) for the treatment of schizophrenia at the recommended starting and target dose of 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. Abilify has been systematically evaluated and shown to be effective in the dose range of 10 to 30 mg/day. A solution formulation was developed to provide an alternate means to administer aripiprazole to patients who have difficulties swallowing the tablet and, therefore, to increase compliance.

Comparative Exposures and Bioequivalence: Aripiprazole oral solution was determined in a preliminary relative bioavailability study not to be bioequivalent to the oral tablet per standard regulatory criteria. Therefore, the clinical pharmacology program was designed to estimate doses of oral solution formulation that would produce comparable aripiprazole exposures to those obtained following administration of the tablets. Clinical studies to assess the safety and efficacy of the oral solution formulation in patients with schizophrenia or schizoaffective disorders have not been performed.

Two pivotal pharmacokinetic studies (CN138063 and CN138108) were performed to evaluate pharmacokinetics of oral solution relative to the tablet for single doses from 5 to 30 mg. The geometric mean aripiprazole C_{max} and AUC(∞) values were generally higher (approximately 14 to 30%) for the oral solution formulation than the values observed for the tablet formulation, with somewhat larger differences being evident for C_{max} than for AUC(∞). A *post-hoc* statistical analysis to determine bioequivalence was conducted on the C_{max} and AUC(∞) data at each dose. For aripiprazole C_{max}, the 90% CIs for all doses fell outside the standard 0.80-1.25 interval to conclude equivalence. But the 90% CI values for aripiprazole AUC(∞) ratios for oral solution to tablet formulations at all dose levels were contained entirely within the regulatory requirements of 0.80-1.25 to conclude equivalence. Summaries of the statistical analyses are provided in Tables 1 and 2. The point estimates (95% CI) for the doses of the solution formulation that were predicted to give equivalent aripiprazole C_{max} values to the 5, 10, and 15 mg tablets are provided in Table 3. A log-log relationship approach was used to estimate the solution dose that would provide an equivalent aripiprazole exposure to the 30 mg tablet. The Oral solution dose (OSD) that would produce comparable aripiprazole C_{max} to that of the 30 mg tablet was estimated to be 24.1 mg (95% CI: 20.8 to 27.1). The OSD that is estimated to produce comparable aripiprazole AUC to that after administration of the 30 mg tablet is 25.0 mg (95% CI: 22.7 to 27.6 mg).

The range of Tmax values for aripiprazole in all studies suggest a more rapid absorption of aripiprazole from the oral solution formulation compared to that from the tablet formulation. However, median Tmax values for the two formulations were the same or were within 1 h of each other. The median values and ranges for dehydro-aripiprazole Tmax were similar for both formulations in all studies. The mean terminal phase half-life values for aripiprazole and dehydro-aripiprazole were also similar for both formulations in all studies.

Table 1: Summary of Statistical Analysis Results for Aripiprazole Cmax and AUC(∞)

Dose (mg)	Cmax Ratio		AUC (∞) Ratio	
	Pt. Estimate (90% CI)		Pt. Estimate (90% CI)	
5	1.136 (0.994, 1.298)		1.028 (0.943, 1.121)	
10	1.265 (1.111, 1.440)		1.118 (1.027, 1.216)	
15	1.285 (1.131, 1.460)		1.058 (0.976, 1.148)	

Table 2: Summary of Statistical Analysis Results for Aripiprazole Cmax and AUC(∞)

Pharmacokinetic Parameter	Adjusted ^a Geo. Means		Ratio of C:A Adj. Geo. Means	
	A: 30 mg Tablet	C: 30 mg Oral Solution	Pt Estimate Ratio C:A	90% CI Interval for Ratio
Cmax (ng/mL)	114.1	139.3	1.221	(1.132, 1.318)
AUC (∞) (ng*h/mL)	8432	9645	1.144	(1.089, 1.202)

Adjusted^a for other factors in the ANOVA model

Table 3: Estimated Dose of Aripiprazole Oral Solution to Produce Equivalent Aripiprazole AUC(∞) and Cmax

Tablet Strength (mg)	Estimated Dose of Oral solution (95% CI) to Produce Equivalent	
	Cmax	AUC(∞)
5	4.35 (3.70, 5.12)	4.76 (4.29, 5.29)
10	8.01 (7.31, 8.78)	9.30 (8.75, 9.88)
15	11.5 (10.2, 12.9)	13.8 (12.6, 15.0)
30	24.1 (20.8, 27.1)	25.0 (22.7, 27.6)

Dosing recommendation: The recommended dose of the approved Abilify tablets is 10 to 15 mg/day. Doses up to 30 mg/day have been shown to be effective and safe. Aripiprazole tablets are not bioequivalent to the oral solution. But there is extensive safety information available for the tablet up to and including 30 mg/day and exposures obtained for solution doses between 5 to 15 mg doses are bracketed by exposures observed for tablet doses up to 30 mg. There is some information on usage of aripiprazole tablets up to about 90 mg doses. According to the reviewing medical officer, there are no major concerns from studies that have used doses up to about 90 mg/day for about two weeks. There is limited information on the safety of aripiprazole oral solution at or above the 30 mg dose. Exposures at the 30 mg dose are expected to be higher after administration of the oral solution than the tablet formulation. Therefore, the sponsor is recommending that doses up to 20 mg be given on mg per mg basis compared the tablet. The maximum dose of the oral solution that is being recommended is 25 mg/day and should be substituted for the 30 mg tablet dose. This approach should allow for plasma concentrations after administration of the solution that are bracketed by concentrations observed after administration of 5 to 30 mg tablets. And within the range of concentrations for which there is adequate safety experience. The reviewer agrees with the sponsor's recommendation and recommends that the

oral solution should be given on a mg/mg basis as the tablet up to 15 mg. If doses higher than 15 mg of the oral solution are needed, it can be given on a mg/mg basis as the tablet up to a maximum of 25 mg/day. For the highest approved dose of the tablet (30 mg), a 25 mg of the oral solution should be substituted.

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CC: NDA 21-713, HFD-120, HFD-860 (Mehta, RahmanA, Baweja, Yasuda, KumiK), CDR (Biopharm)

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2. Question Based Review

2.1. General Attributes

2.1.1. *What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?*

Abilify™ (aripiprazole) is currently approved (NDA 21-436) as oral tablets in strengths of 5, 10, 15, 20 and 30 mg strengths. At the End of Phase 2 (EOP2) meeting in October 2002, the sponsor indicated that the initial clinical pharmacokinetic studies conducted with the oral solution were unlikely to meet the requirements to declare bioequivalence to the approved Abilify tablets, given the more rapid absorption and greater maximum plasma concentrations observed with the solution. Therefore the registration program included three clinical pharmacology studies that were designed to estimate the doses of the oral solution that would be expected to deliver equivalent exposures to the approved Abilify tablet formulation. According to the EOP2 meeting minutes, it was determined that registration would not require demonstration of safety and efficacy in a clinical trial since the blood levels of aripiprazole after administration of the solution will be bracketed by the levels achieved with soon to be approved doses of the approved tablet product. And, the safety experience with aripiprazole tablets should be sufficient to support registration of the oral solution up to the solution dose that produces exposure not exceeding that of the 30 mg tablet. The proposed labeling recommends a “capped” dose of the oral solution at 25 mg of the oral solution.

2.1.2. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*

Abilify is a psychotropic drug indicated for the treatment of schizophrenia. The drug substance used for the manufacture of aripiprazole oral solution is identical to that used for the manufacture of Abilify (aripiprazole) Tablets. This submission is for Abilify (aripiprazole) Oral Solution, 1 mg/mL. The equilibrium solubility of aripiprazole in the proposed formulation at room temperature is about 6.75 mg/mL (pH before and after equilibrium solubility was 3.11 and 3.57, respectively). Thus, at 1 mg/mL the concentration of aripiprazole in the proposed commercial formulation is well below saturation levels.

Aripiprazole oral solution, 1 mg/mL, is a ready-to-use solution containing aripiprazole, glycerin, propylene glycol, DL-lactic acid, sodium hydroxide, methylparaben, propylparaben, sucrose, fructose, natural orange cream flavor WONF (with other natural flavors), and purified water. The composition of the formulation used in clinical bioequivalence studies (CN138-019, CN138-063 and CN138-108) is identical to the commercial formulation.

2.1.3. *What are the proposed mechanism of action and therapeutic indication?*

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D₂ and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Aripiprazole is indicated for the treatment of schizophrenia.

2.1.4. What are the proposed dosage(s) and route of administration?

Aripiprazole solution is intended for oral administration. The proposed dosing regimen is similar to that approved for the tablet formulation 10 or 15 mg/day.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology program was designed to estimate doses of oral solution formulation that would produce aripiprazole exposures comparable to those obtained following administration of tablets. Clinical studies to assess the safety and efficacy of the oral solution formulation in patients with schizophrenia or schizoaffective disorders have not been performed.

2.2.2. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

Yes the active moieties (aripiprazole and dehydro-aripiprazole) have been appropriately identified. (See Section 2.6, Analytical Section)

2.2.3. Exposure-Response

Exposure-response relationships were not evaluated for this application.

Exposure-response relationships based on the tablet application (NDA 21-436) were cross-referenced in this application and was the basis for the clinical pharmacology program. Dosing recommendation for Aripiprazole oral solution is based on comparable exposures that will be obtained after the oral tablet and solution administration.

2.2.3.1 What safety profiles were reported?

A total of 122 subjects were enrolled in the clinical pharmacology studies. The sponsor stated that there were no deaths or serious AEs reported in any of the studies. Two-hundred twenty-nine (229) AEs were reported in 86 (70.5%) of 122 subjects. The most common AEs (with frequencies > 10%), for subjects receiving any formulation of aripiprazole, were: nausea (24.6%), headache (21.3%), insomnia (18%), lightheadedness (13.9%), and vomiting (10.7%). Among the 229 AEs reported by subjects exposed to aripiprazole, 215 (93.9%) were considered by investigators to be mild in intensity and 14 (6.1%) were considered by Investigators to be moderate in intensity. The only AEs of moderate intensity occurring in more than 1 subject were vomiting (4 subjects) and headache (2 subjects). No AEs were classified as severe or very severe for any subject. Overall, the severity was comparable between the oral tablet and solution formulations. The sponsor reported that overall, the safety profile of aripiprazole in oral solution in healthy subjects was similar to that of the tablet. According to the approved labeling for the tablet, the only adverse event to have a possible dose-response relationship was somnolence.

2.2.3.2 Does this drug prolong the QT or QTc interval?

According to OCPB review of the original NDA 21-436, no change in QTc was detected as a function of dose or concentration within the recommended dosage range of 15 – 30 mg. However, at doses of 45 – 90 mg, the original review of NDA 21-436 indicated larger increases in QTc were observed.

2.2.4. What are the Pharmacokinetic Characteristics of the Drug?

The pharmacokinetics of aripiprazole were characterized in NDA 21-436 for the tablet formulation and cross-referenced in this application. Based on the conclusions of the reviewer of NDA 21-436 and information in the approved label, aripiprazole is well absorbed after oral administration with peak plasma concentrations occurring within 3-5 hours after dosing. The absolute oral bioavailability of the tablet formulation is 87%. Aripiprazole is widely distributed ($V_d = 4.94$ L/kg after I.V. administration) despite plasma protein binding in excess of 99%. Aripiprazole is mainly metabolized with less than 1% of an oral dose excreted in the urine unchanged. Approximately 18% is excreted in the feces unchanged. Aripiprazole is metabolized by Cytochrome P450 (CYP) 3A4 and CYP2D6. Aripiprazole is the major moiety in the system circulation; the active metabolite (dehydro-aripiprazole) represents about 40% of aripiprazole AUC in plasma at steady state. The mean elimination half-life of aripiprazole is about 75 hours. The pharmacokinetics of aripiprazole is reported to be linear between 5 to 30 mg after administration of the tablet dose. Also, the OCPB review of NDA 21-436 indicated that the pharmacokinetics of aripiprazole appears to be linear between 30 to 75 mg in schizophrenic patients. In OCPB review of NDA 21-436, intersubject variability was 16 – 57% for C_{max} and 16 – 57% for AUC in healthy subjects and patients. Intersubject variability in the present submission was 20 – 40% in healthy subjects.

2.3. Intrinsic Factors

Cross-reference to studies performed under NDA 21-436.

According to the OCPB review of NDA 21-436 and information in the approved label, dosage adjustments is not recommended for renal and hepatic impairment patients, due to gender, age differences or for ethnic differences. In the original review of NDA 21-436, it was reported that in renal impaired patients, C_{max} increased by 36%, clearance decreased by 20% in the elderly and C_{max} and AUC increased by 30 to 40% in women.

2.4. Extrinsic Factors.

Cross-reference to studies performed under NDA 21-436.

According to the OCPB review of NDA 21-436 and information in the approved label for the tablet, ethanol blood concentrations were not significantly affected by co-administration of ethanol and aripiprazole. Dosage adjustment is not recommended based on ethanol or smoking status. Several drugs have been evaluated, in NDA 21-436, for their effect on aripiprazole pharmacokinetics. Famotidine decreased aripiprazole C_{max} approximately 37% and valproate decreased aripiprazole C_{max} and AUC approximately 25%. No dosage adjustments were recommended when aripiprazole is administered concomitantly with famotidine or valproate. Ketoconazole, quinidine and carbamazepine have greater effects on exposure (>50% changes) and dosage adjustments are recommended for aripiprazole when co-administered with these drugs.

2.5. General Biopharmaceutics

2.5.1 What is the composition of the oral solution formulation?

The composition of the oral solution is provided in the following table (Table 4)

Table 4: Composition of Aripiprazole Oral Solution, 1 mg/mL

Component	Reference	Function	Quantity (mg/mL)
Aripiprazole	NC ^a	Active	1.0
Glycerin	USP		
DL-Lactic Acid	USP		
Sodium Hydroxide	NF		
Propylene Glycol	USP		
Methylparaben	NF		
Propylparaben	NF		
Sucrose	NF		
Fructose	USP		
Natural Orange Cream Flavor WONF ^d	NC ^{a,c}		
Purified Water	USP		

^a Noncompendial

^b The amount shown is based on an assay value [redacted] for DL-lactic acid. The exact amount may vary depending on the actual assay value of DL-lactic acid.

^c The amount of sodium hydroxide may be varied to adjust the pH of each batch of solution to between [redacted]

^d WONF means With Other Natural Flavors

^e [redacted], DMF No. [redacted]. A letter of authorization from [redacted] is provided in Section [3.2.P.4.1.2]

^f Processing agent not present in the final drug product

2.5.2. What is the bioavailability of the proposed to be marketed oral solution relative to the approved tablet formulation?

In a relative bioavailability study (CN138019) comparing 3 mg of oral solution to 15 mg of tablet formulation, the dose-normalized aripiprazole C_{max} values for the oral solution formulation were 1.43-fold higher than those observed for the tablet formulation. The dose-normalized aripiprazole AUC (∞) values for the oral solution formulation were 1.40-fold higher than those observed for the tablet formulation. Based on dose-normalized geometric mean C_{max} values for dehydro-aripiprazole, the ratio of the oral solution formulation to the tablet formulation was 1.26. Based on dose-normalized geometric mean AUC (0-T) values for dehydro-aripiprazole, the ratio of the oral solution formulation to that of the tablet formulation was 0.99; however, the variability of the solution formulation AUC(0-T) values was high (52%).

The sponsor assessed the oral bioavailability of aripiprazole when administered as a solution (3mg) relative to the tablet formulation (15 mg) in healthy subjects. The study was an open-label, randomized, two-period, two treatment, crossover study in healthy subjects. On Day 1, following a 10 hr fast, each subject received 15 mg aripiprazole as the reference formulation (1 x 15 mg tablet, commercial formulation) or 3 mg aripiprazole as the test formulation (3 mg oral solution formulation). Each treatment was separated by a washout period of at least 21 days. Serial blood samples for pharmacokinetic assessments were collected over a period of 384 hours (17 days). The following table contains the summary of the statistical analysis for AUC(0-t), AUC(0-∞) and Cmax.

Table 5: Summary of Statistical Analysis Results of Dose Normalized Aripiprazole Pharmacokinetic Parameters, n= 14

Dose Normalized Parameter	Adjusted ^a Geometric Means		Ratio of Adjusted Geo. Means (Test: Reference)	90% Confidence Interval for the Ratio
	15 mg tablet (reference)	3 mg oral solution (test)		
Cmax (ng/mL/mg)	3.1	4.4	1.431	(1.231, 1.663)
AUC(INF) (ng·h/mL/mg)	187	262	1.398	(1.259, 1.552)
AUC(0-T) (ng·h/mL/mg)	174	209	1.201	(1.079, 1.338)

In another study that compared 30 mg oral solution to 30 mg tablet, the Cmax and AUC of aripiprazole were about 22% and 14%, respectively, higher after oral solution compared to tablet administration (See Table 7 section 2.5.3 below).

2.5.3. Is aripiprazole oral solution bioequivalent to the tablet formulation?

The sponsor did not conduct formal bioequivalence studies to evaluate whether the aripiprazole oral solution is bioequivalent to the tablet formulation. However, in two studies to evaluate the dose that will produce similar exposures using 5, 10,15 mg (Study CN138063),and 30 mg (study CN138108) doses, post-hoc statistical analysis was performed for each dose studied to calculate 90% confidence intervals for the oral solution to tablet aripiprazole geometric mean ratios of AUC(∞) and Cmax for the two formulations. For Cmax, the 90% CIs for all doses fell outside the standard 0.80-1.25 interval to conclude bioequivalence. The point estimates and 90% CI values for the adjusted aripiprazole geometric mean AUC(∞) ratios of oral solution to tablet formulations all met the regulatory requirements for bioequivalence of 0.80-1.25.

In Study CN138063, the sponsor conducted a study to determine doses of the aripiprazole oral solution that produced equivalent aripiprazole exposure, AUC(∞) and Cmax, to the 5, 10, 15 mg tablets and to assess the dose proportionality of the pharmacokinetics (PK) of aripiprazole oral solution formulation

The study was an open-label, randomized, three-period, six-treatment incomplete crossover study in healthy subjects. Sixty subjects were enrolled and randomized in this study. Subjects received three of six possible treatments (5, 10, and 15 mg oral solution formulation and 5, 10, and 15 mg oral tablets) in one of thirty (30) randomly assigned sequences selected to minimize the common variance of pairwise comparisons among the six treatments. There was a washout period of at least 21 days between each dose. Blood samples were collected for PK analysis for 384 h (17 days) post-dose. The results of the post hoc statistical analysis are provided in the following table

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Table 6: Point Estimates and 90% C.I. for Oral Solution: Tablet of Adjusted Geometric Mean Cmax and AUC(∞)

Dose (mg)	Cmax Ratio		AUC (∞) Ratio	
	Pt. Estimate (90% CI)		Pt. Estimate (90% CI)	
5	1.136 (0.994, 1.298)		1.028 (0.943, 1.121)	
10	1.265 (1.111, 1.440)		1.118 (1.027, 1.216)	
15	1.285 (1.131, 1.460)		1.058 (0.976, 1.148)	

Within each formulation type (oral solution or tablet), the geometric mean Cmax and AUC(∞) both increased approximately proportionally with dose. The median Tmax for dehydro-aripiprazole was the same (48 h) for all of the treatments.

In another relative bioavailability study (CN 138108), the sponsor estimated the dose of oral solution that will provide a comparable exposure to that obtained from 30 mg commercial tablet. The study was an open-label, randomized, three-period, three-treatment, crossover study in healthy subjects. Each subject received single oral doses of 30 mg aripiprazole commercial tablet formulation, 20 mg aripiprazole as 20 mL of 1 mg/mL proposed commercial oral solution formulation and 30 mg aripiprazole as 30 mL of 1 mg/mL proposed commercial oral solution formulation. Each treatment was administered after a 10 h overnight fast. There was a washout period \geq 28 days between each treatment. Blood samples were collected for PK analysis up to 384 h (17 days) post-dose. Post-hoc statistical analysis was performed for each dose studied to calculate 90% confidence intervals for the oral solution to tablet aripiprazole geometric mean ratios of AUC(∞) and Cmax for the two formulations. Summary of statistical analysis are provided in the following table

Table 7: Summary of Statistical Analysis Results for Aripiprazole Cmax and AUC(∞)

Pharmacokinetic Parameter	Adjusted ^a Geo. Means		Ratio of C:A Adj. Geo. Means	
	A: 30 mg Tablet	C: 30 mg Oral Solution	Pt Estimate Ratio C:A	90% CI Interval for Ratio
Cmax (ng/mL)	114.1	139.3	1.221	(1.132, 1.318)
AUC (∞) (ng*h/mL)	8432	9645	1.144	(1.089, 1.202)

Adjusted^a for other factors in the ANOVA model

The exposure (AUC and Cmax) of aripiprazole after administration of the oral solution was higher than after the tablet formulation. The dose-adjusted geometric mean AUC (∞) values for aripiprazole following dosing with the 20 and 30 mg oral solution (332.5 and 326.4 ng.h/mL/mg) were higher than that observed following the 30 mg tablet (283.9 ng.h/mL/mg). The dose-normalized geometric mean Cmax values for the oral solution formulation (4.90 and 4.69 ng/mL/mg for the 20 and 30 mg doses, respectively) were also higher than that observed for the tablet formulation (3.82 ng/mL/mg). The higher dose-adjusted aripiprazole AUC(∞) values for the oral solution lead to an oral solution dose of 25.0 mg (95% confidence interval: 22.7 to 27.6 mg) being predicted to give a comparable systemic exposure to the 30 mg tablet. Analysis performed for aripiprazole Cmax indicated that the oral solution dose of 24.1 mg (95%

confidence interval: 20.8 mg to 27.8 mg) would produce comparable aripiprazole C_{max} to that of the 30 mg tablet. In another study, the doses of the oral solution to produce similar exposure as 5, 10 and 15 mg tablet formulation was evaluated. The estimated doses of oral solution to produce equivalent AUC(∞) and C_{max} were lower than the tablet doses particularly at the 10 and 15 mg doses. The estimated aripiprazole oral solution doses to produce equivalent C_{max} to the tablet doses appeared to be lower than those estimated to produce equivalent AUC(∞). For each dose, the geometric mean C_{max} and AUC(∞) for dehydro-aripiprazole were higher for the oral solution than the tablet. Summary statistics for Aripiprazole pharmacokinetics are provided in the following table.

Table 8: Summary Statistics for Aripiprazole Pharmacokinetic Parameters

Pharmacokinetic Parameter	Aripiprazole 30 mg Tablet (n=33)	Aripiprazole 20 mg Oral Solution (n=32)	Aripiprazole 30 mg Oral Solution (n= 31)
C _{max} (ng/mL) Geo. Mean (CV%)	114.6 (28)	98.0 (20)	140.8 (26)
Dose Norm. C _{max} Geo. Mean (CV%)	3.82 (28)	4.90 (20)	4.69 (26)
AUC(0-T) (ng*h/mL) Geo. Mean (CV%)	8117 (36)	6277 (31)	9301 (35)
Dose Norm AUC(0-T) Geo. Mean (CV%)	270.6 (36)	313.9 (31)	310.0 (35)
AUC(∞)(ng*h/mL) Geo. Mean (CV%)	8518 (38)	6650 (33)	9793 (38)
Dose Norm AUC(∞) Geo. Mean (CV%)	283.9 (38)	332.5 (33)	326.4 (38)
T _{max} (h) Median (min, max)	3.0 (1.5, 12.0)	3.0 (1.0, 6.0)	3.0 (1.0, 8.0)
T _{1/2} (h) Mean (SD)	97.2 (27.9)	101.5 (34.3)	99.1 (34.2)

The median T_{max} values (3 h) were the same for the tablet and the oral solution formulation at both doses. However, the minimum and maximum T_{max} values were 0.5 h and 4 to 6 h longer following the tablet formulation compared to the oral solution formulation. The mean T_{1/2} values were comparable between the oral solution and the tablet formulations.

2.5.4. Is the concentration of aripiprazole proportional to dose after administration of the oral solution?

The dose-adjusted C_{max} and AUC(∞) of aripiprazole were comparable for the solution doses, suggesting dose proportionality for the solution between doses of 5 to 30 mg. The geometric mean C_{max} and AUC(∞) of dehydro-aripiprazole increased approximately proportionally with dose.

The sponsor evaluated whether the concentration of aripiprazole was proportional to the dose of the oral solution administered as a secondary objective in two studies. The first study was an open-label, randomized, three-period, six-treatment incomplete crossover study in healthy subjects. Sixty subjects were enrolled and randomized in this study. Subjects received three of six

possible treatments (5, 10, and 15 mg oral solution formulation and 5, 10, and 15 mg oral tablets) in one of thirty (30) randomly assigned sequences selected to minimize the common variance of pairwise comparisons among the six treatments. In another study, each subject received single oral doses of 30 mg aripiprazole as 1 x 30 mg commercial tablet formulation (Treatment A), 20 mg aripiprazole as 20 mL of 1 mg/mL proposed commercial oral solution formulation (Treatment B) and 30 mg aripiprazole as 30 mL of 1 mg/mL proposed commercial oral solution formulation (Treatment C). The following table contains the geometric mean values for the C_{max} and AUC of aripiprazole after administration of 5 – 30 mg oral solution and tablets.

Table 9: Geometric Mean (%C.V.) Aripiprazole C_{max} and AUC(∞) Values Following Administration of Aripiprazole Oral Solution and Tablets to Healthy Subjects

Parameter	Oral Solution in mg						Tablets Doses in mg			
	3	5	10	15	20	30	5	10	15	30
C _{max} (ng/mL)	13.1 (33)	26.5 (38)	52.3 (22)	77.4 (23)	98.0 (20)	140.8 (26)	23.8 (30)	41.9 (28)	60.2 (30)	114.6 (28)
AUC (∞) (ng*h/mL)	772 (76)	1479 (31)	3256 (37)	4914 (43)	6650 (33)	9793 (38)	1577 (35)	2771 (40)	4219 (35)	8518 (38)

The following table contains the geometric mean values for the pharmacokinetic parameters of dehydro-aripiprazole.

Table 10: Summary Statistics of Dehydro-Aripiprazole Pharmacokinetic Parameters

Treatment (n)	C _{max} (ng/mL) Geo. Mean (%CV)	AUC (0-T) (ng*h/mL) Geo. Mean (%CV)	T _{max} (h) Median (min – max)
5 mg OS (24)	3.26 (25)	511.26 (35)	48.0 (24.0 – 96.0)
10 mg OS (24)	6.23 (26)	1166.53 (33)	48.0 (24.0 – 96.0)
15 mg OS (23)	8.81 (28)	1624.08 (31)	48.0 (24.0 – 96.0)

Figure 1: Aripiprazole Geometric Mean (SD) C_{max} Values Versus the Dose of Aripiprazole Administered in Oral Solution and Tablets in Various Studies

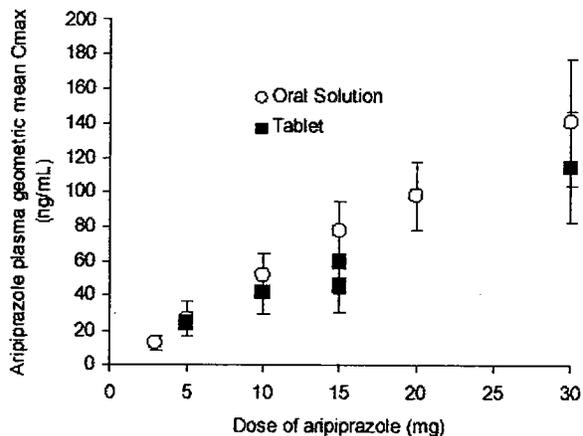
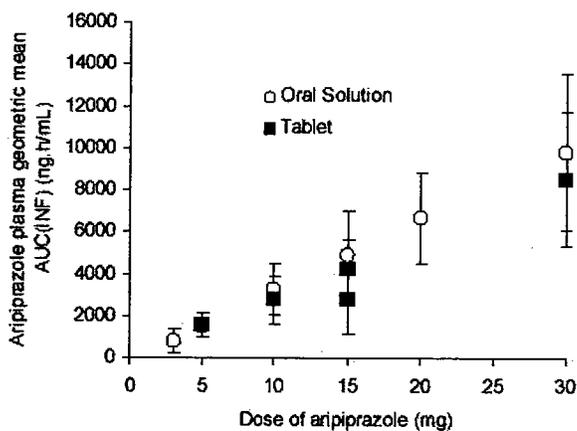


Figure 2: Aripiprazole Geometric (S.D.) AUC(∞) Values Versus the Dose of Aripiprazole Administered in Oral Solution and Tablets in Various Studies



2.5.5. What dosing recommendations are necessary?

Aripiprazole oral solution is not bioequivalent per regulatory criteria for declaring two formulations to be bioequivalent (90% confidence interval (CI) for AUC and Cmax must fall within 0.8 to 1.25). Aripiprazole doses of 10 to 15 mg/day are currently recommended for the tablet formulation. There is extensive safety information available for the tablet up to and

including 30 mg/day and exposures obtained for solution doses between 5 to 15 mg doses are lower than that observed for the 30 mg tablet dose. Therefore, oral solution doses up to 15 mg given on a mg per mg basis compared to the tablet should be safe and efficacious. However, there is limited information on the safety of aripiprazole oral solution at the 30 mg dose and exposures at the 30 mg dose are expected to be higher after administration of the oral solution than the tablet formulation. Therefore, doses higher than 15 mg may be given on a mg/mg basis up to a maximum dose of 25 mg/day for the oral solution. The maximum dose of 25 mg/day of the oral solution is estimated to provide comparable exposure to the 30 mg/day of the tablet.

In the two relative bioavailability studies to estimate the dose of oral solution that will provide a comparable exposure after administration of the oral solution and tablet formulation, the doses were estimated using a log relationship of the observed aripiprazole AUC versus dose. The predicted doses are provided in the following tables.

Table 11: Estimated Dose of Aripiprazole Oral Solution to Produce Equivalent Aripiprazole AUC(∞) and Cmax

Tablet Strength (mg)	Estimated Dose of Oral solution (95% CI) to Produce Equivalent	
	Cmax	AUC(∞)
5	4.35 (3.70, 5.12)	4.76 (4.29, 5.29)
10	8.01 (7.31, 8.78)	9.30 (8.75, 9.88)
15	11.5 (10.2, 12.9)	13.8 (12.6, 15.0)
30 ^a	24.1 (20.8, 27.1)	25.0 (22.7, 27.6)

^aData from another study (CN138108, Section 2.5.5)

2.5.7. What is the effect of food on the bioavailability of aripiprazole?

Food did not affect the exposure (AUC and Cmax) of the oral tablet formulation. Food is not expected to have an effect on the bioavailability of aripiprazole after administration of the oral solution.

2.6. Analytical Section

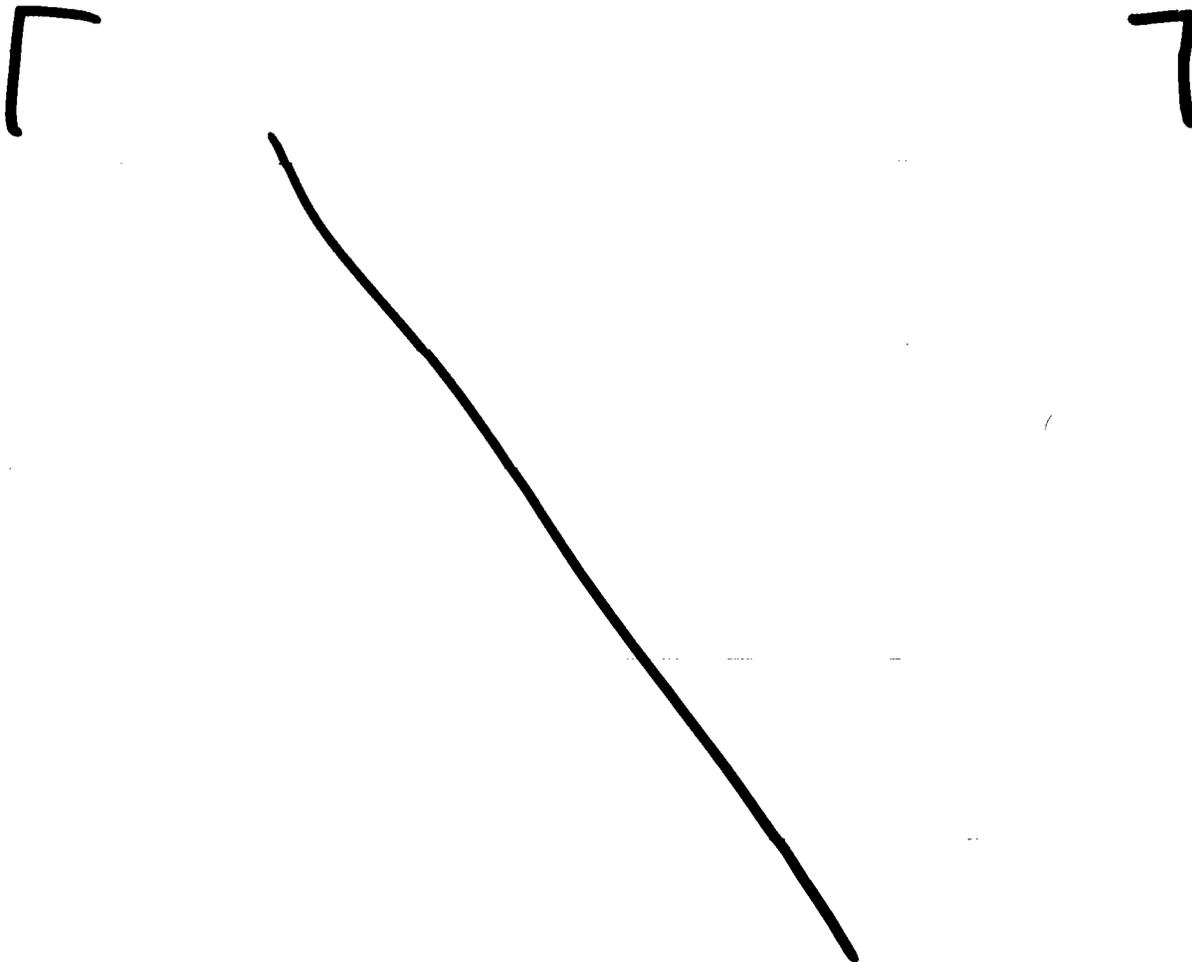
2.6.1. What analytical methods were used to identify aripiprazole and its metabolite, dehydro-aripiprazole?

Plasma samples from all clinical studies were analyzed for aripiprazole and dehydro-aripiprazole using a liquid chromatography tandem mass spectrometry (LC/MS/MS) method. The standard curves ranged from 1.0 to 250.0 ng/mL for both analytes. A report on the assay validation was provided in the original marketing application for aripiprazole tablets (NDA 21-436) and was found to be acceptable by the reviewer of NDA 21-436.

Aripiprazole and internal standard (OPC-14714, a structural analogue of aripiprazole) were extracted from human plasma by protein precipitation with ██████████. After evaporation to dryness, the residue was resuspended and an aliquot was analyzed by LC-API/MS/MS. The lower limit of quantitation (LLQ) was established by analyzing a single aliquot from six independent sources of control plasma. At the LLQ, the mean percent deviation from nominal concentrations was -0.6% for aripiprazole and 8.5% for

dehydro-aripiprazole. Between and within run precision (C.V.%) values were within $\pm 6.4\%$ for both analytes. The mean assay accuracy values were within $\pm 7.8\%$ of the nominal concentrations for both analytes. Aripiprazole and dehydro-aripiprazole were stable (within $\pm 15\%$ of nominal concentrations) in reconstituted extracts when stored at room temperature for at least 23 h and for at least 77 h at 4C. In process control for each study report is provided in the individual study reports.

3. Detailed Labeling Recommendations



34 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

than $\pm 1.5\%$. The standard curve and QC data indicated that the aripiprazole plasma assay method was precise and accurate. For dehydro-aripiprazole, the between-run precision and the within-run precision for analytical quality control samples were no greater than 3.4 and 8.5% coefficient of variation (CV), respectively, with deviations from the nominal concentrations of no more than $\pm 2.8\%$. The standard curve and QC data indicated that the dehydro-aripiprazole plasma assay method was precise and accurate.

Data Analysis: The plasma concentration-time data for aripiprazole and dehydro-aripiprazole were analyzed by a noncompartmental method. The distributions of aripiprazole and dehydro-aripiprazole PK variables were summarized by formulation. Geometric means and coefficient of variations were reported for C_{max}, AUC(0-T), and AUC(INF). Medians, minima, and maxima were reported for T_{max}. Means and SD were presented for T-HALF. To estimate the relative bioavailabilities of the oral solution formulation to the commercial tablet, analyses of variance were performed on log-transformed, dose-normalized C_{max}, AUC(INF), and AUC(0-T). The factors in the analysis were sequence, subject within sequence, period, and formulation. Since subjects were random effects nested within sequences, F-statistics for sequence effects were the ratios of the type I mean square for period and the mean square for error. Point estimates and 90% confidence intervals for treatment differences on the log scale were exponentiated to obtain estimates for geometric means and ratios of geometric means on the original scale.

Results: The demographic parameters for the subjects who participated in the study are provided in the following table

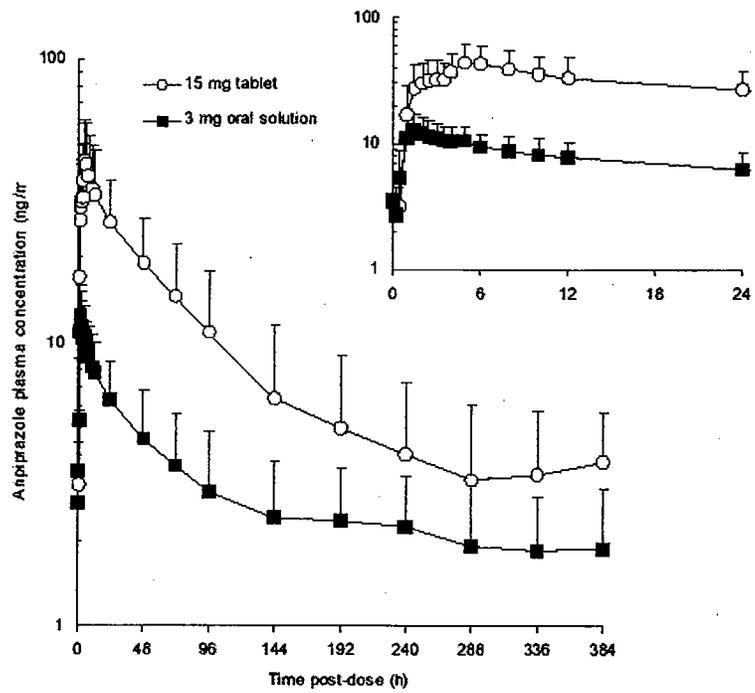
Characteristic		Study Population (N = 16)
Age, years	Mean (SD)	28 (7.3)
	Range	19 - 40
Gender, n (%)	Male	13 (81.2%)
	Female	3 (18.8%)
Race, n (%)	White	6 (37.5%)
	Black	7 (43.7%)
	Hispanic/Latino	2 (12.5%)
	Other	1 (6.3%)
Weight, kg	Mean (SD)	81.4 (11.93)
	Range	63.9 - 111.2
Height, cm	Mean (SD)	175.9 (8.24)
	Range	159 - 194
Body Mass Index, kg/m ²	Mean (SD)	26.5 (3.09)
	Range	21.4 - 29.9

Table 1: Demographic Characteristics

The mean plasma concentration-time profile for aripiprazole are provided in the following figure (Fig 1). Mean pharmacokinetic parameters and the statistical analyses of dose-normalized C_{max}, AUC(INF) and AUC(0-T) are presented in Tables 2 and 3. The aripiprazole dose-normalized C_{max} adjusted geometric mean for the oral solution formulation was 1.43-fold higher than that observed for the tablet formulation. The observed aripiprazole median T_{max} for the solution (1.5 h) was shorter than that for the tablet (5 h). Based on the comparison of dose-normalized AUC(INF) adjusted geometric mean values, the bioavailability of aripiprazole from the oral solution formulation relative to the tablet was 140%. Overall, the higher dose-normalized C_{max}

and AUC values and shorter Tmax values for the oral solution formulation indicated an increased rate and extent of aripiprazole absorption for solution compared to the tablet.

Fig 1: Mean (SD) Plasma Concentration vs Time Profiles of Aripiprazole in Humans after Administration of 1 x 15 mg Aripiprazole Commercial Tablet and 3 mg Oral Solution Formulation



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Table 2: Summary Statistics for Aripiprazole PK Parameters (N=14)

Pharmacokinetic Parameter	Treatment	
	Aripiprazole 15 mg tablet (Reference)	Aripiprazole 3 mg oral solution (Test)
C _{max} (ng/mL) Geometric Mean (C.V.%)	46.1 (33)	13.1 (33)
Dose Normalized C _{max} (ng/mL/mg) Geometric Mean (C.V.%)	3.1 (33)	4.4 (33)
AUC(INF) (ng·h/mL) Geometric Mean (C.V.%)	2791 (60)	772 (76)
Dose Normalized AUC(INF) (ng·h/mL/mg) Geometric Mean (C.V.%)	186 (60)	257 (76)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V.%)	2591 (57)	615 (72)
Dose Normalized AUC(0-T) (ng·h/mL/mg) Geometric Mean (C.V.%)	173 (57)	205 (72)
T _{max} (h) Median (Min, Max)	5.00 (1.50, 8.00)	1.50 (1.00, 10.00)
T-HALF (h) Mean (SD)	76 (37)	94 (58)

Table 3: Summary of Statistical Analysis Results of Dose Normalized Aripiprazole Pharmacokinetic Parameters, n= 14

Dose Normalized Parameter	Adjusted ^a Geometric Means		Ratio of Adjusted Geo. Means (Test: Reference)	90% Confidence Interval for the Ratio
	15 mg tablet (reference)	3 mg oral solution (test)		
C _{max} (ng/mL/mg)	3.1	4.4	1.431	(1.231, 1.663)
AUC(INF) (ng·h/mL/mg)	187	262	1.398	(1.259, 1.552)
AUC(0-T) (ng·h/mL/mg)	174	209	1.201	(1.079, 1.338)

Mean plasma concentrations-time profile for dehydro-aripiprazole is provided in the following figure (Fig. 2). Summary statistics for dehydro-aripiprazole are summarized by formulation in the table following. Based on dose-normalized geometric mean C_{max} values for dehydro-aripiprazole in 11 subjects, the ratio of the oral solution formulation to the tablet formulation was 1.26. Based on dose-normalized geometric mean AUC(0-T) values for dehydro-aripiprazole in 8 subjects, the ratio of the oral solution formulation to that of the tablet formulation was 0.99; however, the variability of the solution formulation AUC(0-T) values was high (52%). Due to a 5-fold lower dose of oral solution, there were fewer measurable concentrations of dehydro-aripiprazole for the oral solution formulation compared to the tablet.

Figure 2: Mean (SD) Plasma Concentration vs. Time Profiles of Dehydro-aripiprazole in Humans after Administration of 1 x 15 mg Aripiprazole Commercial Tablet and 3 mg Oral Solution Formulation

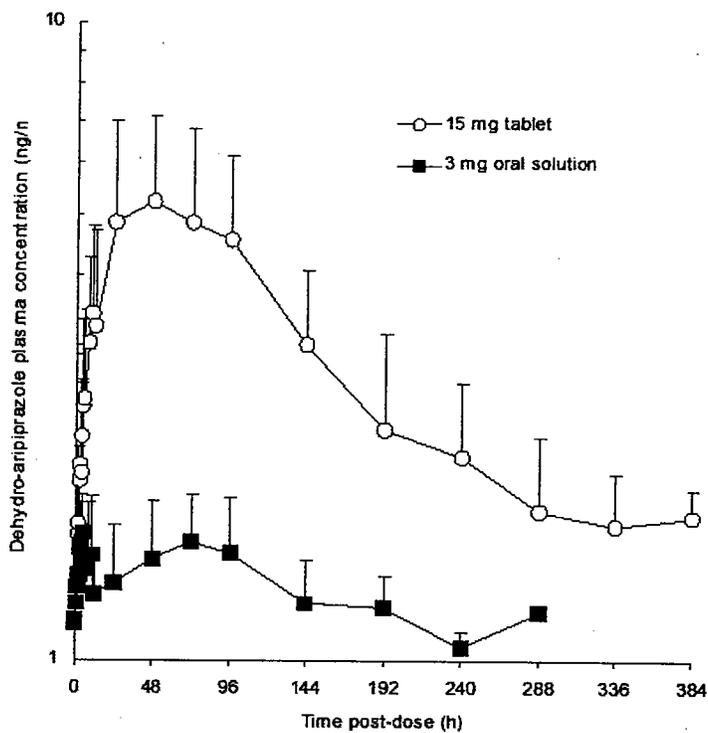


Table 4: Summary Statistics for Dehydro-aripiprazole PK Parameters (N=11)

Pharmacokinetic Parameter	Formulation	
	Aripiprazole 15 mg tablet (Reference)	Aripiprazole 3 mg oral solution (Test)
C _{max} (ng/mL) Geometric Mean (C.V.%)	5.7 (37)	1.4 (23)
Dose normalized C _{max} (ng/mL/mg) Geometric Mean (C.V.%)	0.38 (37)	0.48 (23)
AUC(0-T) (ng·h/mL) ^a Geometric Mean (C.V.%)	1005 (28)	199 (52)
Dose normalized AUC(0-T) (ng·h/mL/mg) Geometric Mean (C.V.%)	67 (28)	66 (52)
T _{max} (h) Median (Min, Max)	72.0 —	48.0 —

Summary of Pharmacokinetics: The dose-normalized aripiprazole C_{max} values for the oral solution formulation were 1.43-fold higher than those observed for the tablet formulation. The median T_{max} value for aripiprazole for the oral solution formulation (1.5 h) was shorter than that observed for the tablet (5 h). The dose-normalized aripiprazole AUC(INF) values for the oral solution formulation were 1.40-fold higher than those observed for the tablet formulation. The higher dose-normalized C_{max} and AUC(INF) values along with a shorter T_{max} for the oral solution formulation suggest an increased rate and extent of absorption of aripiprazole from the oral solution compared to the tablet. The mean T_{1/2} value for aripiprazole for the oral solution formulation (94 h) was 1.23-fold higher (18 hrs) longer than that for the tablet (76 h). The adjusted dose-normalized geometric mean values for AUC(0-T) were ≥ 80% of the corresponding AUC(INF) values for both formulations. The dose-normalized geometric mean AUC(0-T) values for dehydro-aripiprazole from the oral solution formulation and the tablet formulation were similar. Therefore, the relatively higher bioavailability of aripiprazole from the oral solution compared to tablet would be expected to also result in relatively higher AUC(0-T) values for dehydro-aripiprazole from oral solution compared to the tablet formulation. However, due to the 5-fold lower dose of oral solution, there were fewer quantifiable concentrations of dehydro-aripiprazole for the oral solution formulation compared to the tablet. Hence, the AUC(0-T) values of dehydro-aripiprazole for the oral solution formulation were likely to have been underestimated. However, the comparison of C_{max} values indicated that the ratio of dose-normalized geometric mean C_{max} value for dehydro-aripiprazole in eleven subjects for the oral solution formulation to that of tablet formulation was 1.26. The percentage of geometric mean AUC(0-T) values for dehydro-aripiprazole with respect to aripiprazole, corrected for molecular weight, averaged 32% for the oral solution formulation and 39% for the tablet.

Summary of Safety: The sponsor reported that fewer subjects reported AEs on the oral solution formulation compared to the tablet formulation (5/14, 36% vs 10/17, 63%). The most frequently reported treatment-emergent AE in this study was nausea reported by four subjects (25.0%) after receiving 15 mg aripiprazole tablet formulation and one subject (7.1%) after receiving 3 mg oral solution formulation. The onset ranged from 1 to 8 h after dose with the duration ranging from 5 min to 1.25 h. The second most reported treatment emergent AE was lightheadedness and third was headache. Overall, both formulations were generally well-tolerated, although the oral solution was apparently better tolerated than the tablet. This apparent difference is due to a 5-fold lower dose of oral solution compared to the commercial tablet formulation. The sponsor reports that overall, the types of AEs reported for both treatments are consistent with the AE profile of the aripiprazole tablet observed in previous studies in healthy subjects.

Reviewer Comments: *Dose normalized C_{max} and AUC of aripiprazole after administration of oral solution was about 40 to 43% higher than after administration of the tablet formulation. Equal doses of the two formulations are not bioequivalent.*

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Atipiprazole
BMS-337039

PROTOCOL: CN138019

Clinical Study Report
CN138019

Table S.11.2.1C: Summary Statistics for BMS-337039 Pharmacokinetic Parameters

PAGE: 1

TREATMENT	STATISTIC	C _{MAX} (NG/ML)	AUC (T _{INF}) (NG*H/ML)	AUC (0-T) (NG*H/ML)	T _{MAX} (H)	T- _{HALF} (H)	DOSE		F	
							NORMALIZED C _{MAX} (NG/ML/MG)	NORMALIZED AUC (T _{INF}) (NG*H/ML/MG)		
A	N	14	14	14	14	14	14	14	0	
	MEAN	48.68	3256.04	2998.36	4.61	76.19	3.25	217.07		199.89
	S.D.	15.99	1964.72	1710.97	1.84	37.07	1.07	130.98		114.06
	GEQ. MEAN	46.06	2790.90	2590.97	4.17	68.36	3.07	186.06		172.73
	C.V. %	32.84	60.34	57.06	39.97	48.66	32.84	60.34		57.06
	MEDIAN	44.68	2319.34	2175.96	5.00	67.53	2.98	154.62		145.06
MIN										
MAX										
B	N	14	14	14	14	14	14	14	0	
	MEAN	13.81	958.01	762.72	2.29	93.62	4.60	319.34		254.24
	S.D.	4.60	732.70	549.37	2.44	58.41	1.53	244.23		183.12
	GEQ. MEAN	13.14	771.57	614.59	1.74	81.03	4.38	257.19		204.86
	C.V. %	33.31	76.48	72.03	106.72	62.39	33.31	76.48		72.03
	MEDIAN	12.16	672.74	559.53	1.50	67.25	4.05	224.25		186.51
MIN										
MAX										

TREATMENT CODES
A = Atipiprazole 15 mg Tablet
B = Atipiprazole 3 mg Oral Liquid
PROGRAM SOURCE: //S PROJ/CN/138//Dev/strata/Adj. report. 2011

PROTOCOL: CN138019

Page: 1

Table S.11.2.1D: Statistical Analysis of BMS-337039 Dose Normalized Cmax (ng/mL/ng)
Analysis of Variance of Log-Transformed Data

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F	P
SEQUENCE	1	0.047	0.047	0.233	0.638
SUBJECT (SEQUENCE)	12	2.411	0.201	4.115	0.010
PERIOD	1	0.005	0.005	0.096	0.762
TREATMENT	1	0.881	0.881	18.036	0.001
ERROR	12	0.586	0.049		

ROOT MEAN SQUARE ERROR = 0.221

INDIVIDUAL TREATMENT SUMMARIES

TREATMENT	LOG-TRANSFORMED SCALE			ORIGINAL (UNTRANSFORMED) SCALE		
	ADJ'D MEAN	S.E.	90% C.I.: (LCL, UCL)	ADJ'D MEAN		90% C.I.: (LCL, UCL)
A	1.126	0.095	(0.956, 1.296)	3.084		(2.601, 3.655)
B	1.484	0.095	(1.314, 1.655)	4.413		(3.723, 5.231)

TREATMENT COMPARISONS

TREATMENT COMPARISON	DIFFERENCES ON THE LOG TRANSFORMED SCALE				RATIOS ON THE ORIGINAL SCALE			
	PT. EST.	S.E.	T	P	90% C.I.: (LCL, UCL)	PT. EST.	90% C.I.: (LCL, UCL)	
B vs. A	0.358	0.084	4.247	0.001	(0.208, 0.509)	1.4310	(1.2312, 1.6633)	

TREATMENT CODES
A = Aripiprazole 15 mg Tablet
B = Aripiprazole 3 mg Oral Liquid

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Table S.11.2.1E: Statistical Analysis of BMS-337039 Dose Normalized AUC(0-T) (ng.h/mL/mg) Analysis of Variance of Log-Transformed Data Page: 1

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F	P
SEQUENCE	1	0.177	0.177	0.226	0.643
PERIOD	12	9.424	0.785	31.239	0.000
TREATMENT	1	0.029	0.029	1.137	0.307
ERROR	12	0.231	0.0231	9.183	0.010
ROOT MEAN SQUARE ERROR =		0.1586			

INDIVIDUAL TREATMENT SUMMARIES

TREATMENT	LOG-TRANSFORMED SCALE			ORIGINAL (UNTRANSFORMED) SCALE		
	ADJ'D MEAN	S.E.	90% C.I.: (LCL, UCL)	ADJ'D MEAN	90% C.I.: (LCL, UCL)	
A	5.157	0.172	(4.850, 5.463)	173.605	(127.792, 235.841)	
B	5.340	0.172	(5.034, 5.647)	208.569	(153.530, 283.339)	

TREATMENT COMPARISONS

TREATMENT COMPARISON	DIFFERENCES ON THE LOG TRANSFORMED SCALE				RATIOS ON THE ORIGINAL SCALE			
	PT. EST.	S.E.	T	P	90% C.I.: (LCL, UCL)	PT. EST.	90% C.I.: (LCL, UCL)	
B vs. A	0.183	0.061	3.030	0.010	(0.076, 0.291)	1.2014	(1.0785, 1.3383)	

TREATMENT CODES
A = Arripiprazole 15 mg Tablet
B = Arripiprazole 3 mg Oral Liquid

Program Source: /S PROJ/ON/138/019/NER/STRAT/ANALYSIS/1

Aripiprazole
BMS-337039

PROTOCOL: CN138019

CN138019
Clinical Study Report

Table S.11.2.1F: Statistical Analysis of BMS-337039 Dose Normalized AUC(TMF) (ng·h/mL/mg)
Analysis of Variance of Log-Transformed Data

Page: 1

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F	P
SEQUENCE	1	0.195	0.195	0.253	0.624
SUBJECT (SEQUENCE)	12	9.280	0.773	32.860	0.000
PERIOD	1	0.006	0.006	0.263	0.617
TREATMENT	1	0.769	0.769	32.665	0.000
ERROR	12	0.282	0.024		
ROOT MEAN SQUARE ERROR =		0.1534			

INDIVIDUAL TREATMENT SUMMARIES

TREATMENT	ADJ'D MEAN	S.E.	90% C.I.: (LCL, UCL)	ORIGINAL (UNTRANSFORMED) SCALE	ADJ'D MEAN	90% C.I.: (LCL, UCL)
A	5.233	0.170	(4.929, 5.536)	187.277	(138.214, 253.757)	
B	5.567	0.170	(5.264, 5.871)	261.756	(193.181, 354.675)	

TREATMENT COMPARISONS

TREATMENT COMPARISON	PT. EST.	S.E.	T	P	90% C.I.: (LCL, UCL)	RATIOS ON THE ORIGINAL SCALE	PT. EST.	90% C.I.: (LCL, UCL)
B vs. A	0.335	0.059	5.715	0.000	(0.230, 0.439)	1.3977	(1.2591, 1.5515)	

TREATMENT CODES
A = Aripiprazole 15 mg Tablet
B = Aripiprazole 3 mg Oral Liquid

Program Summary: /s/ DDOT/INT/130/01A/Forms/Summary V. 1.1

Title of Study (Study CN138063): Pharmacokinetic Dose Finding and Proportionality Study of Aripiprazole Oral Liquid in Healthy Subjects

Objectives: 1) The primary objective was to determine doses of the aripiprazole oral solution that produced equivalent aripiprazole exposure, $AUC(\infty)$ and C_{max} , to the 5, 10, 15 mg tablets

2) The secondary objectives were a) to assess the dose proportionality of the pharmacokinetics (PK) of aripiprazole oral solution formulation b) to assess the tolerability of aripiprazole when administered as single doses of 5, 10 and 15 mg oral tablets to healthy subjects c) to assess the PK of aripiprazole's metabolite, dehydro-aripiprazole d) to collect palatability data from subjects who received the aripiprazole oral solution formulation

Study Design: This was an open-label, randomized, three-period, six-treatment incomplete crossover study in healthy male and female subjects. Sixty subjects were enrolled and randomized in this study. Subjects received three of six possible treatments (5, 10, and 15 mg oral solution formulation and 5, 10, and 15 mg oral tablets) in one of thirty (30) randomly assigned sequences selected to minimize the common variance of pairwise comparisons among the six treatments. The mean age and weight of the subjects were 35 ± 7 years and 71 ± 9.3 kg, respectively. The following were the treatment categories:

Treatment A: Aripiprazole 5 mg oral solution (1 mg/mL)

Treatment B: Aripiprazole 10 mg solution (1 mg/mL)

Treatment C: Aripiprazole 15 mg oral solution (1 mg/mL)

Treatment D: Aripiprazole 5 mg tablet

Treatment E: Aripiprazole 10 mg tablet

Treatment F: Aripiprazole 15 mg tablet

Each dose was administered following a 10-hour overnight fast. Treatments A, B, C were dispensed using an oral dosing syringe. Following administration of study drug, subjects were administered 240 mL of water in a separate cup. Treatments D, E, F were administered to subjects along with 240 mL of water. There was a washout period of at least 21 days between each dose. Subjects completed a taste questionnaire after administration of the oral solution formulation. There was a washout period of at least 21 days between each treatment administration. For each treatment period, subjects were admitted to the clinical facility the evening prior to dosing (Day -1) and were confined until 48 h post-dose. Subjects were required to remain in a supine position for approximately 8 h post-dose. Blood samples were collected for PK analysis for 384 h (17 days) post-dose. Subjects were monitored closely for adverse events (AEs) throughout the study. The following is the drug information of aripiprazole used in the study: Aripiprazole tablets (5 mg tablets, Batch No. 00D81A005A; 10 mg tablets, Batch No. 00D88A010A; and 15 mg tablets, Batch No. 00D95A015A). Aripiprazole oral solution formulation (1 mg/mL, administered as 5, 10, and 15 mg oral doses orally), Batch No. 8FMC190. All aripiprazole tablets were administered orally.

Analytical Method: Plasma samples were assayed for aripiprazole and dehydro-aripiprazole concentration by a validated LC/MS/MS method for the simultaneous measurement of aripiprazole and dehydro-aripiprazole. QC samples were analyzed along with the study samples to assess the accuracy and precision of the assay. The acceptance criteria established for the analyses of aripiprazole in plasma specified that the predicted concentrations of at least three-fourths of the standards and two-thirds of the QC samples be within $\pm 15\%$ of their individual nominal concentration values ($\pm 20\%$ for the lowest concentration standard). In addition, at least

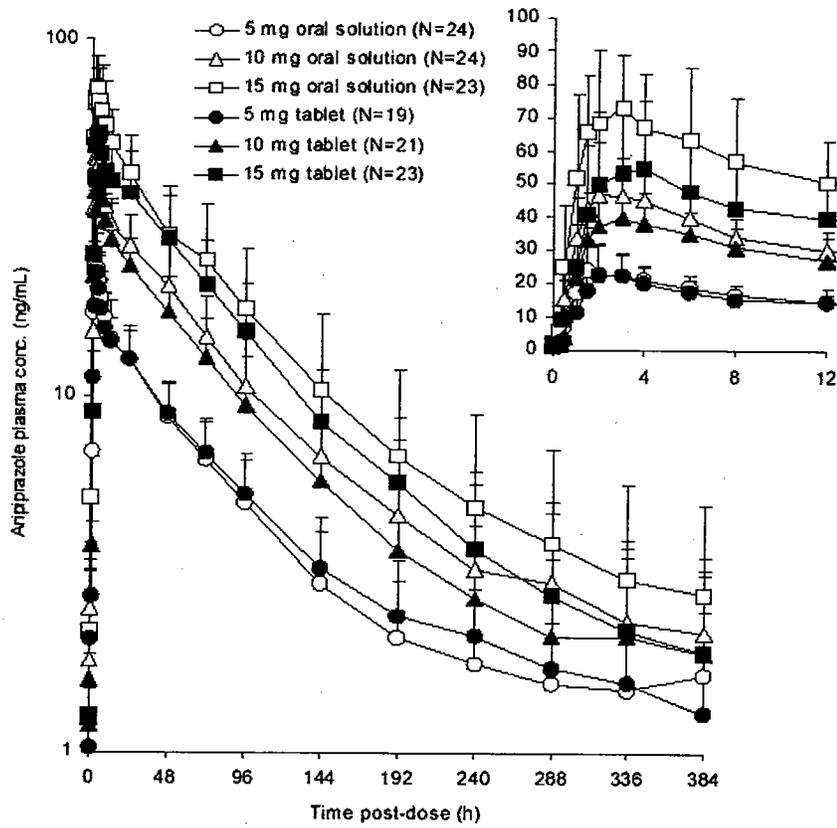
one QC sample at each concentration must be within $\pm 15\%$ of its individual nominal concentration values. The range of the standard curves in plasma, (1.00 to 250 ng/mL for each analyte) were used to define the quantifiable limits for study samples. If the predicted concentration of a study sample was less than that of the lowest standard, then the value of the predicted concentration was reported as $< LLQ$ (less than the lower limit of quantitation). If the predicted concentration of a study sample was greater than that of the highest standard, then the value of the predicted concentration was reported as $> ULQ$ (greater than the upper limit of quantitation), and the sample was reanalyzed following dilution. Values for the between-run precision and the within-run precision for analytical quality control samples were no greater than 9.3% coefficient of variation (C.V.), with deviations from the nominal concentrations of no more than $\pm 2.7\%$. The standard curve and QC data indicated that the aripiprazole plasma assay method was precise and accurate for analysis of samples in this study. For dehydro-aripiprazole, the between-run precision and the within-run precision for analytical quality control samples were no greater than 9.4% coefficient of variation (C.V.), respectively, with deviations from the nominal concentrations of no more than $\pm 4.3\%$. The standard curve and QC data indicated that the dehydro-aripiprazole plasma assay method was precise and accurate for analysis of samples in this study.

Data Analysis: The PK results were determined using a non-compartmental methods. Single-dose PK parameters of aripiprazole and its pharmacologically active metabolite, dehydro-aripiprazole, were derived from plasma concentration versus time data. The PK parameters which were assessed included: C_{max} , T_{max} , AUC (0-T), AUC (∞), and $T_{1/2}$. The sponsor reported that the 95% confidence interval for dose proportionally was incorrectly stated in the protocol as 0.8 to 1.25. The interval should be 0.84 to 1.16. Inverse regression was used to estimate the dose of aripiprazole oral solution for which the predicted exposures would be the same as those from the 5, 10, and 15 mg tablets.

All original electrocardiograms were processed for ECG interval measurements (PR, QRS, QT and RR) by specialists using a [REDACTED] measurement system. Measurements were made typically across 4 consecutive complexes on the [REDACTED] ECG if the rhythm strip was not available. QTc was calculated according to Bazett's formula, Fridericia's formula and an intermediate formula. Following each analyst's determination of the beginning and end of the intervals, the computer-programmed calculation of the mean interval duration measurements (IDMs) and the QTc (calculated using specified formula), the data were then transferred automatically through ECG Management System to produce printed worksheets. The ECGs and associated worksheets were submitted to a cardiologist for interpretation. A single cardiologist was assigned to this study. Abnormality descriptions were based on specifications provided by the Sponsor. Specifically, the ECG was marked as Abnormal when the bradycardia or tachycardia criteria fell out of the specified BMS range (bradycardia: heart rate less than 60 bpm = abnormal; tachycardia: heart rate greater than 100 bpm = abnormal).

Pharmacokinetic Results: Mean plasma concentration-time profiles for aripiprazole are shown in the following figure.

Figure 1: Mean \pm SD Plasma Concentration-Time Profile for Aripiprazole Following Dosing with 5, 10, and 15 mg Oral solution and Tablet Formulation of Aripiprazole in Study Formulations of Aripiprazole in Study CN138063. The Insert shows only Aripiprazole Concentration-Time Points up to 12 hour Post-Dose



The mean pharmacokinetic parameters for all treatment groups are provided in the following table (Table 1).

Table 1: Summary Statistics of Aripiprazole Pharmacokinetic Parameters

Treatment (n)	Cmax (ng/mL) Geometric Mean (%CV)	AUC _∞ Geometric Mean (ng*h/mL)	Tmax (h) Median (min – max)	T ½ (h) Mean (S.D.)
5 mg OS (24)	26.5 (38.0)	1479 (31.1)	2.0 (1.0 – 6.0)	85.6 (30.7)
5 mg Tab (19)	23.8 (29.7)	1577 (34.9)	3.0 (1.5 – 6.0)	97.8 (43.6)
10 mg OS (24)	52.3 (21.8)	3256 (37.3)	3.0 (1.0 – 6.0)	97.1 (39.8)
10 mg Tab (21)	41.9 (27.8)	2771 (39.7)	3.0 (1.5 – 12.0)	95.1 (52.3)
15 mg OS (23)	77.4 (23.0)	4914 (43.4)	3.0 (1.0 – 6.0)	101.7 (50.2)
15 mg Tab (23)	60.2 (30.3)	4219 (35.1)	3.0 (1.5 – 48.0)	97.8 (35.4)

The geometric means for aripiprazole Cmax and AUC(∞) were generally higher for the oral solution than the tablet, particularly at the 10 and 15 mg doses. Median Tmax was comparable among all treatments. The mean T ½ of aripiprazole was comparable between all treatments.

The following table (Table 2) summarizes the projected doses of aripiprazole oral solution that will produce aripiprazole AUC (∞) values comparable to those from the specified tablet size.

Table 2: Estimated Dose of Aripiprazole Oral Solution to Produce Equivalent Aripiprazole AUC(∞) and Cmax

Tablet Strength (mg)	Estimated Dose of Oral solution (95% CI) to Produce Equivalent	
	Cmax	AUC(∞)
5	4.35 (3.70, 5.12)	4.76 (4.29, 5.29)
10	8.01 (7.31, 8.78)	9.30 (8.75, 9.88)
15	11.5 (10.2, 12.9)	13.8 (12.6, 15.0)

The estimated doses of oral solution to produce equivalent AUC(∞) and Cmax were lower than the tablet doses particularly at the 10 and 15 mg doses. The estimated aripiprazole oral solution doses to produce equivalent Cmax to the tablet doses appeared to be lower than those estimated to produce equivalent AUC(∞).

Both Cmax and AUC (∞) for aripiprazole from the oral solution formulation satisfied the pre-specified criterion for dose proportionality. The estimated regressions are

$$\text{Predicted AUC } (\infty) = 380.11 * \text{Dose}^{0.97}$$

and

$$\text{Predicted Cmax} = 5.47 * \text{Dose}^{0.99}$$

The 90% confidence intervals for the exponents on dose in the above power models are (0.88, 1.05) for AUC(∞) and (0.90, 1.08) for Cmax. Both of these are contained within the pre-specified interval (0.84, 1.16) for concluding dose proportionality.

The following table summarizes the estimates and 90% C.I. for AUC(∞) and Cmax oral solution: tablet geometric mean ratios, following doses of 5, 10, and 15 mg aripiprazole.

Table 3: Point Estimates and 90% C.I. for Oral Solution: Tablet of Adjusted Geometric Mean Cmax and AUC(∞)

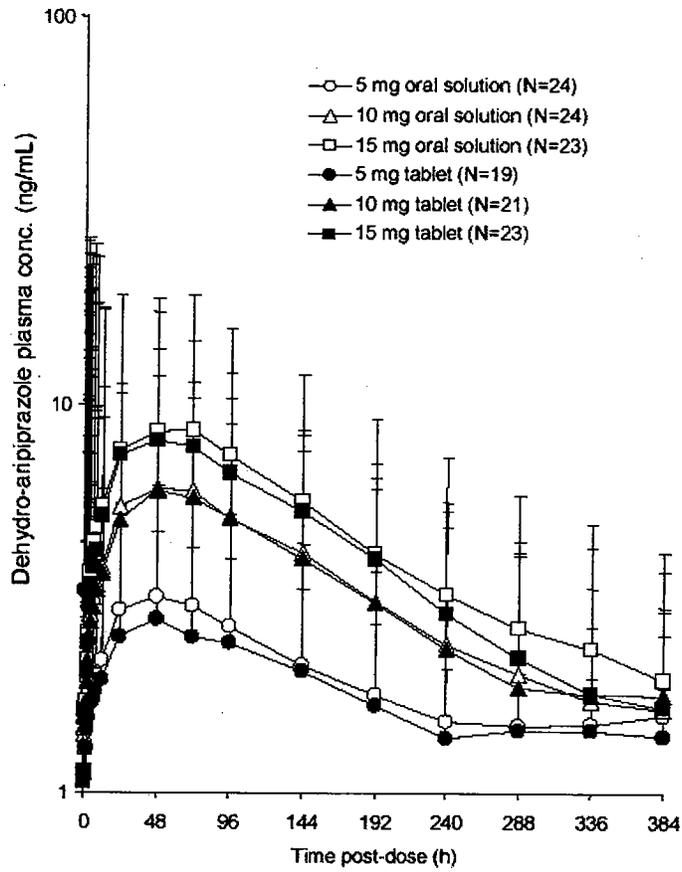
Dose (mg)	Cmax Ratio	AUC (∞) Ratio
	Pt. Estimate (90% CI)	Pt. Estimate (90% CI)
5	1.136 (0.994, 1.298)	1.028 (0.943, 1.121)
10	1.265 (1.111, 1.440)	1.118 (1.027, 1.216)
15	1.285 (1.131, 1.460)	1.058 (0.976, 1.148)

Pharmacokinetics of Dehydro-Aripiprazole

Mean plasma concentration-time profiles for dehydro-aripiprazole are shown in the following figure

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Figure 2: Mean \pm SD Plasma Concentration-Time Profiles for Dehydro-Aripiprazole Following Dosing with 5, 10 and 15 mg Oral Solution and Tablet Formulation of Aripiprazole



The summary of the pharmacokinetic parameters are provided in the following table

Table 4: Summary Statistics of Dehydro-Aripiprazole Pharmacokinetic Parameters

Treatment (n)	Cmax (ng/mL) Geo. Mean (%CV)	AUC (0-T) (ng*h/mL) Geo. Mean (%CV)	Tmax (h) Median (min – max)
5 mg OS (24)	3.26 (25)	511.26 (35)	48.0 (24.0 – 96.0)
5 mg Tablet (19)	2.58 (36)	377.60 (58)	48.0 (24.0 – 96.0)
10 mg OS (24)	6.23 (26)	1166.53 (33)	48.0 (24.0 – 96.0)
10 mg Tablet (21)	5.92 (32)	1059.22 (32)	48.0 (24.0 – 96.0)
15 mg OS (23)	8.81 (28)	1624.08 (31)	48.0 (24.0 – 96.0)
15 mg Tablet (23)	8.08 (31)	1506.92 (30)	48.0 (24.0 – 96.0)

For each dose, the geometric mean Cmax and AUC(∞) for dehydro-aripiprazole were higher for the oral solution than the tablet. Within each formulation type (oral solution or tablet), the geometric mean Cmax and AUC(∞) both increased approximately proportionally with dose. The median Tmax for dehydro-aripiprazole was the same (48 h) for all of the treatments.

Safety Summary: The most frequently reported AE was insomnia (26 subjects; 12 received the oral solution formulation and 14 received the tablet formulation). The second most common treatment-emergent AE was headache (18 subjects; 9 received the oral solution formulation, 9 received the tablet formulation, and 1 subject experienced this AE prior to dosing). The third most common AE was nausea (16 subjects; 8 received the oral solution formulation and 8 received the tablet formulation). Overall, the frequencies of common AEs between the tablet formulation and the oral solution formulation are comparable. Five (5) subjects experienced 8 episodes of vomiting (7 episodes attributed to the tablet formulation and 1 episode attributed to the oral solution formulation). Overall, both formulations of aripiprazole were reported to be safe and generally well-tolerated. The frequency of AEs (55% versus 43%) was slightly higher in subjects who received aripiprazole administered as the tablet formulation as compared to subjects who received the oral solution formulation.

As this study was not designed to assess changes in ECGs, measurements were only obtained at screening and discharge. Therefore, all ECG abnormalities occurred prior to administration of aripiprazole or at study discharge. Thirty-four (34) ECG abnormalities (31 findings of sinus bradycardia, 2 findings of left axis deviation, and 1 finding of ventricular premature beat) were reported in 27 of 60 subjects (45%) enrolled in this study. None of the ECG abnormalities resulted in discontinuation from the study.

Summary of Pharmacokinetics

The pharmacokinetic data indicate a more extensive absorption of aripiprazole from the oral solution formulation as compared to the tablet formulation. The generally higher aripiprazole AUC(∞) values for the oral solution lead to the lower oral solution doses of 4.76 mg, 9.3 mg and 13.8 mg, that were predicted by the linear interpolation analysis to give a comparable systemic exposure to the 5, 10, and 15 mg tablets, respectively.

While the objective of this study was to estimate a dose of oral solution that would produce a comparable aripiprazole Cmax and AUC(∞) to the 5, 10, and 15 mg tablets, the absolute increase in the systemic exposure to aripiprazole from the oral solution formulation compared to the tablet formulation was not large, particularly for AUC(∞). *Post-hoc* statistical analysis was performed for each dose to calculate 90% confidence intervals for the oral solution to tablet aripiprazole geometric mean ratios of AUC(∞) and Cmax for the two formulations. For Cmax, the 90% CIs

for all doses fell outside the standard 0.80-1.25 interval used to conclude bioequivalence. The point estimates and 90% CI values for the adjusted aripiprazole geometric mean AUC(∞) ratios of oral solution to tablet formulations all met the regulatory requirements for bioequivalence of 0.80-1.25. These results indicate that the oral solution and oral tablet are equivalent with respect to systemic exposure.

Reviewer Comments: Aripiprazole concentrations were higher after administration of the oral solution than after the tablet formulation. Based on post hoc analysis, the 90% confidence interval fell within 0.8 to 1.25 for AUC but Cmax did not fall within this range. Dose proportionality between 5 and 15 mg was predicted using the power model.

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S.11.2.1C: SUMMARY STATISTICS FOR ARIPIPRAZOLE PHARMACOKINETIC PARAMETERS

TREATMENT	STATISTIC	QMAX (mcg/mL)	TMAX (h)	AUC (0-T) (mcg*h/mL)	AUC (INF) (mcg*h/mL)	T-HALF (h)
A	N	24	24	24	24	24
	MEAN	27.93	2.56	1379.34	1542.02	85.59
	S.D.	10.61	1.26	407.46	479.60	30.67
	Geo. MEAN	26.53	2.30	1327.57	1479.28	80.76
	C.V. %	37.99	49.27	29.54	31.10	35.83
	MEDIAN	25.03	2.00	1249.10	1385.44	78.91
MIN						
MAX						
B	N	24	24	24	24	24
	MEAN	53.52	2.96	3192.20	3461.35	97.14
	S.D.	11.68	1.47	1042.74	1292.52	39.75
	Geo. MEAN	52.27	2.64	3036.30	3256.16	90.13
	C.V. %	21.83	49.82	32.67	37.34	40.91
	MEDIAN	51.00	3.00	2957.18	3138.04	97.19
MIN						
MAX						
C	N	23	23	23	23	23
	MEAN	79.40	2.74	4969.29	5347.54	101.69
	S.D.	18.26	1.41	1961.53	2322.12	50.23
	Geo. MEAN	77.42	2.41	4620.17	4914.52	92.84
	C.V. %	23.00	51.30	39.47	43.42	49.39
	MEDIAN	81.99	3.00	4449.05	4622.17	86.84
MIN						
MAX						

Treatments Codes:

Txt A = 5mg Oral Solution
 Txt B = 10mg Oral Solution
 Txt C = 15mg Oral Solution

Txt D = 5 mg Tablet
 Txt E = 10 mg Tablet
 Txt F = 15 mg Tablet

Program Source: /S PROJ/cn/138/063/dev/stats/chks sunstats.sas

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S.11.2.1C: SUMMARY STATISTICS FOR ARIPIPRAZOLE PHARMACOKINETIC PARAMETERS

TREATMENT	STATISTIC	QMAX (mcg/mL)	TM _{1/2} (h)	AUC(0-T) (mcg+h/mL)	AUC(∞) (mcg+h/mL)	T-HALF (H)
D	N	19	19	19	19	19
	MEAN	24.91	2.92	1471.31	1661.23	97.83
	S.D.	7.39	1.06	471.06	580.25	43.59
	GRD.MEAN	23.77	2.76	1403.60	1576.65	89.54
	C.V. %	29.65	36.20	32.02	34.93	44.56
	MEDIAN	24.23	3.00	1269.37	1482.90	93.03
E	N	21	21	21	21	21
	MEAN	43.29	3.19	2677.87	2926.99	95.06
	S.D.	12.01	2.30	855.75	1161.26	52.26
	GRD.MEAN	41.93	2.75	2569.19	2771.42	84.94
	C.V. %	27.75	72.24	31.96	39.67	54.97
	MEDIAN	42.89	3.00	2485.80	2624.84	83.88
F	N	23	23	23	23	23
	MEAN	62.78	6.43	4195.38	4441.23	97.82
	S.D.	19.04	10.24	1439.25	1556.93	35.42
	GRD.MEAN	60.19	3.90	3993.06	4219.15	92.21
	C.V. %	30.32	159.14	34.31	35.06	36.21
	MEDIAN	59.36	3.00	3859.41	4013.36	92.34

Treatments Codes:

- Txt A = 5mg Oral Solution
- Txt B = 10mg Oral Solution
- Txt C = 15mg Oral Solution
- Txt D = 5mg Tablet
- Txt E = 10mg Tablet
- Txt F = 15mg Tablet

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S.11.2.C: SUMMARY STATISTICS FOR OPC-14857 PHARMACOKINETIC PARAMETERS

TREATMENT	STATISTIC	QMAX (mcg/mL)	TMAX (h)	AUC(0-T) (mcg ² h/mL)
A	N	24	24	24
	MEAN	3.38	50.00	540.07
	S.D.	0.86	22.29	190.07
	GRD.MEAN	3.26	45.21	511.26
	C.V. %	25.31	44.57	35.19
	MEDIAN	3.42	48.00	526.05
B	N	24	24	24
	MEAN	6.48	54.00	1226.17
	S.D.	1.66	21.52	400.83
	GRD.MEAN	6.23	49.54	1165.53
	C.V. %	25.59	39.86	32.69
	MEDIAN	6.87	48.00	1205.11
C	N	23	23	23
	MEAN	9.17	56.35	1716.98
	S.D.	2.61	19.96	526.01
	GRD.MEAN	8.81	52.69	1624.08
	C.V. %	28.48	35.42	30.64
	MEDIAN	9.52	48.00	1764.50

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Treatments Codes:

Trt A = 5mg Oral Solution
Trt B = 10mg Oral Solution
Trt C = 15mg Oral Solution

Trt D = 5 mg Tablet
Trt E = 10 mg Tablet
Trt F = 15 mg Tablet

S.11.2.2C: SUMMARY STATISTICS FOR OPC-14857 PHARMACOKINETIC PARAMETERS

TREATMENT	STATISTIC	OMAX (mcg/mL)	TMAX (h)	AUC(0-T) (mcg*h/mL)
D	N	19	19	19
	MEAN	2.79	59.37	465.27
	S.D.	1.01	24.49	268.42
	GEOM. MEAN	2.58	54.22	377.60
	C.V. %	36.26	41.24	57.69
	MEDIAN	2.92	48.00	430.74
E	N	21	21	21
	MEAN	6.23	54.86	1121.19
	S.D.	1.99	18.81	355.41
	GEOM. MEAN	5.92	51.44	1059.22
	C.V. %	31.89	34.29	31.70
	MEDIAN	6.27	48.00	1112.12
F	N	23	23	23
	MEAN	8.58	56.35	1613.32
	S.D.	2.66	19.96	488.88
	GEOM. MEAN	8.08	52.30	1506.92
	C.V. %	31.06	35.42	30.30
	MEDIAN	9.11	48.00	1750.70

Treatments Codes:

Txt A = 5mg Oral Solution
 Txt B = 10mg Oral Solution
 Txt C = 15mg Oral Solution

Txt D = 5 mg Tablet
 Txt E = 10 mg Tablet
 Txt F = 15 mg Tablet

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Title (Protocol CN138108): A Relative Bioavailability Study To Estimate The Dose Of Aripiprazole Administered As The Proposed Commercial Oral Solution Formulation That Will Provide An Aripiprazole Exposure Comparable To That Obtained From 1x 30 mg Commercial Tablet In Healthy Subjects

Objectives: Primary: To estimate the dose of aripiprazole (BMS-337039, OPC-14597) that when administered in the proposed commercial oral solution formulation would produce an aripiprazole exposure (AUC) comparable to the exposure observed after a 30 mg dose of the aripiprazole commercial tablet formulation.

Secondary: 1) To assess the safety of single doses of aripiprazole administered as 20 mg and 30 mg doses of the proposed aripiprazole commercial oral solution formulation and as 1 x 30 mg commercial tablet in healthy subjects 2) To assess the pharmacokinetics (PK) of aripiprazole's active metabolite, dehydro-aripiprazole (BMS-337044, OPC-14857)

Study Design: This was an open-label, randomized, three-period, three-treatment, crossover study in healthy subjects. Each subject received single oral doses of 30 mg aripiprazole as 1 x 30 mg commercial tablet formulation (Treatment A), 20 mg aripiprazole as 20 mL of 1 mg/mL proposed commercial oral solution formulation (Treatment B) and 30 mg aripiprazole as 30 mL of 1 mg/mL proposed commercial oral solution formulation (Treatment C). Each treatment was administered after a 10 h overnight fast. Subjects were required to remain in a supine position for ≥ 8 h post-dose in each period. Subjects were served a standard meal 4 h post-dose. There was a washout period ≥ 28 days between each treatment. For each period, subjects were admitted to the clinical facility on Day -1 and were confined until 48 h post-dose. Blood samples were collected for PK analysis up to 384 h (17 days) post-dose. Subjects were monitored for adverse events (AEs) throughout the study. Forty-six (46) subjects were enrolled to ensure that at least 24 subjects complete the study. Thirty-seven (37) subjects (80%) received aripiprazole 30 mg commercial tablet formulation, 35 subjects (76%) received aripiprazole 20 mg oral solution formulation and 38 subjects (83%) received aripiprazole 30 mg oral solution formulation. Sixteen (16) subjects (35%) terminated the study early; 5 subjects (11%) discontinued due to AEs of emesis; 6 subjects (13%) discontinued due to non-compliance; and 5 subjects (13%) discontinued for other reasons. The batch numbers of the test and reference formulations were 8MEE185 and 2M49370, respectively.

Analytical Method: Plasma samples were assayed for aripiprazole and dehydro-aripiprazole concentration by a validated LC/MS/MS method. 2,3 Quality control (QC) samples were analyzed along with the study samples to assess the accuracy and precision of the assay. The acceptance criteria established for the analyses of aripiprazole and dehydro-aripiprazole in plasma specified that the predicted concentrations of at least three-fourths of the standards and two-thirds of the QC samples be within $\pm 15\%$ of their individual nominal concentration values ($\pm 20\%$ for the lowest concentration standard).

For aripiprazole, values for the between-run precision and the within-run precision for analytical quality control samples were no greater than 4.9 and 5.9% coefficient of variation (C.V.), respectively, with deviations from the nominal concentrations of no more than $\pm 5.4\%$. The standard curve and QC data indicated that the plasma assay method was precise and accurate. For dehydro-aripiprazole, values for the between-run precision and the within-run precision for analytical quality control samples were no greater than 3.6 and 4.9% coefficient of variation (C.V.), respectively, with deviations from the nominal concentrations of no

more than $\pm 5.7\%$. The standard curve and QC data indicated that the plasma assay method was precise and accurate.

Data Analysis: Plasma aripiprazole and dehydro-aripiprazole concentration *versus* time data were analyzed by non-compartmental methods. The oral solution dose (OSD) of the proposed commercial oral solution formulation that produced aripiprazole exposure ($AUC(\infty)$) comparable to that obtained for the 30 mg commercial tablet was estimated as follows: for each subject, a log-log linear relationship of the observed aripiprazole $AUC(\infty)$ values versus dose of the oral solution was estimated by determining each subject's intercept $b_{0,i}$ and slope $b_{1,i}$ of the regression line calculated from the observed $AUC(\infty)$'s for the two solution doses:

$$\text{observed } \log(AUC(\infty)_i) = b_{0,i} + b_{1,i} * X_i \text{ where } X_i = \log(\text{Dose}_i)$$

The logarithm of the subject's oral solution dose ($\log(\text{OSD})$) was then estimated by linear interpolation from the observed $\log(AUC(\infty))$ value, for the commercial 30 mg tablet:

$$X_i = \log(\text{OSD}_i) = [\log(AUC(\infty)_{\text{tab}})_i - b_{0,i}] / b_{1,i}$$

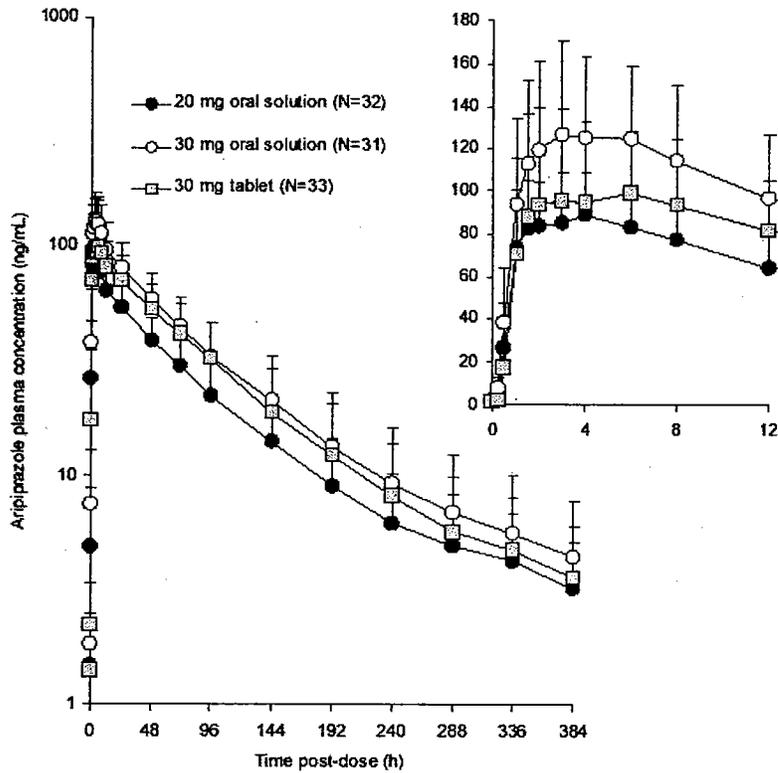
using the above fitted regression line. From these subject-specific estimates, a point estimate was calculated for the population geometric mean OSD, and 95% confidence limits were obtained by exponentiating the corresponding confidence limits on the log scale:

$$\hat{X}_{\text{OSD}} \pm t_{0.025, n-1} \cdot SE(\hat{X}_{\text{OSD}})$$

Although not originally planned, 90% confidence intervals were constructed for the 30 mg oral solution to the 30 mg tablet ratio of geometric mean C_{max} and $AUC(\infty)$ following these two treatments. These were based on the results from analyses of variance of $\log(C_{\text{max}})$ and $\log(AUC(\infty))$. The factors in the analysis were sequence group, subject within sequence, period, and treatment. Point estimates and 90% confidence intervals for treatment differences on the log-scale were exponentiated to obtain point estimates for ratios of geometric means on the original scale. Additionally an analysis, not originally planned in the protocol, was carried out to estimate the OSD that would produce comparable aripiprazole C_{max} to that of the 30 mg tablet using the same approach described earlier for aripiprazole $AUC(\infty)$.

Results: Mean plasma concentration-time profiles for aripiprazole are shown in the following figure (Fig 1).

Fig. 1: Mean (Plus SD) Plasma Concentration –Time Profiles for Aripiprazole Following Dosing with 20 and 30 mg Oral Solution and 30 mg Tablet Formulation of Aripiprazole. The Inset Shows Only Aripiprazole Concentration-Time Points Up to 12h Post-Dose



Summary statistics for aripiprazole pharmacokinetic parameters are presented in the following table

Table 1: Summary Statistics for Aripiprazole Pharmacokinetic Parameters

Pharmacokinetic Parameter	Aripiprazole 30 mg Tablet (n=33)	Aripiprazole 20 mg Oral Solution (n=32)	Aripiprazole 30 mg Oral Solution (n= 31)
Cmax (ng/mL) Geo. Mean (CV%)	114.6 (28)	98.0 (20)	140.8 (26)
Dose Norm. Cmax Geo. Mean (CV%)	3.82 (28)	4.90 (20)	4.69 (26)
AUC(0-T) (ng*h/mL) Geo. Mean (CV%)	8117 (36)	6277 (31)	9301 (35)
Dose Norm AUC(0-T) Geo. Mean (CV%)	270.6 (36)	313.9 (31)	310.0 (35)
AUC(∞)(ng*h/mL) Geo. Mean (CV%)	8518 (38)	6650 (33)	9793 (38)
Dose Norm AUC(∞) Geo. Mean (CV%)	283.9 (38)	332.5 (33)	326.4 (38)
Tmax (h) Median (min, max)	3.0 [redacted]	3.0 [redacted]	3.0 [redacted]
T ½ (h) Mean (SD)	97.2 (27.9)	101.5 (34.3)	99.1 (34.2)

The dose-adjusted C_{max} and AUC(∞) geometric means were comparable for the two solution doses. The dose-adjusted geometric mean C_{max} and AUC(∞) were lowest for the 30 mg tablet. The median T_{max} was comparable among all treatments, although the maximum T_{max} tended to be higher following the 30 mg tablet. The mean T_{1/2} was comparable among all treatments. The 90% confidence intervals for the C_{max} and AUC(∞) geometric mean ratios of the 30 mg Solution to the 30 mg Tablet were calculated based on the results of analyses of variance on log(C_{max}) and log(AUC(∞)). Summary statistical analysis results for aripiprazole are provided in the following table (Table 2)

Table 2: Summary of Statistical Analysis Results for Aripiprazole C_{max} and AUC(∞)

Pharmacokinetic Parameter	Adjusted ^a Geo. Means		Ratio of C:A Adj. Geo. Means	
	A: 30 mg Tablet	C: 30 mg Oral Solution	Pt Estimate Ratio C:A	90% CI Interval for Ratio
C _{max} (ng/mL)	114.1	139.3	1.221	(1.132, 1.318)
AUC (∞) (ng*h/mL)	8432	9645	1.144	(1.089, 1.202)

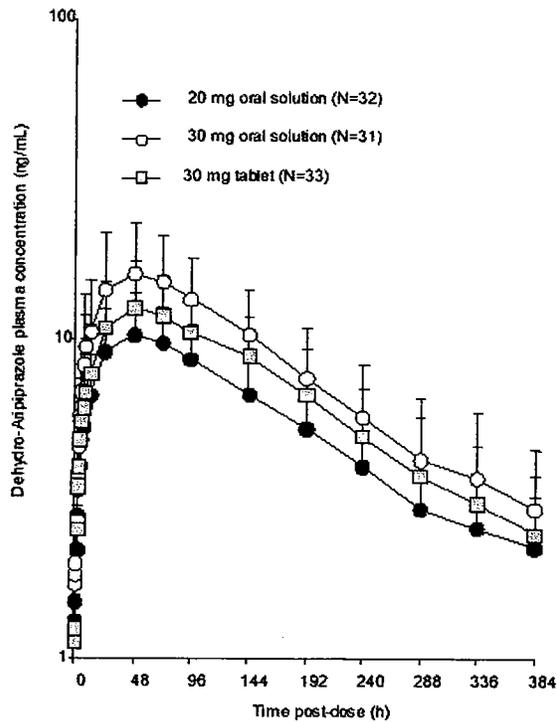
Adjusted^a for other factors in the ANOVA model

The 30 mg oral solution formulation satisfied the (0.80, 1.25) bioequivalence criterion to the 30 mg commercial tablet with respect to AUC(∞), but not with respect to C_{max}. An analysis not originally planned in the protocol, was carried out to estimate the OSD that would produce comparable C_{max} to that of the 30 mg tablet. The observed C_{max} for the 30 mg tablet and each subject's estimated OSD that would produce the same C_{max} and the corresponding point estimate and 95% confidence interval of the OSD are provided in the attachments. The OSD that would produce comparable aripiprazole C_{max} to that of the 30 mg tablet was estimated to be 24.05 mg (95% confidence interval: 20.8 to 27.8 mg).

Mean plasma concentration-time profiles for dehydro-aripiprazole are shown in the following figure (fig 2).

Appears This Way
On Original

Fig 2: Mean (Plus SD) Plasma Concentration-time Profiles for Dehydro-aripiprazole (BMS-337044) Following Dosing with 20 and 30 mg Oral Solution and 30 mg Tablet Formulations of Aripiprazole



The summary statistics for dehydro-aripiprazole pharmacokinetics are provided in the following table

Table 3: Summary Statistics for Dehydro-Aripiprazole Pharmacokinetic Parameters

Pharmacokinetic Parameter	Aripiprazole 30 mg Tablet (n=33)	Aripiprazole 20 mg Oral Solution (n=32)	Aripiprazole 30 mg Oral Solution (n= 31)
Cmax (ng/mL) Geo. Mean (CV%)	12.5 (35)	10.1 (34)	15.4 (43)
Dose Norm. Cmax Geo. Mean (CV%)	0.42 (35)	0.50 (34)	0.51 (33)
AUC(0-T) (ng*h/mL) Geo. Mean (CV%)	2539 (30)	2014 (27)	3033 (33)
Dose Norm AUC(0-T) Geo. Mean (CV%)	84.6 (30)	100.7 (27)	101.1 (33)
Tmax (h) Median (min, max)	72 ()	60 ()	48 ()

Safety Summary: The most frequently reported AE was nausea (15 subjects; 1 subject received the 30 mg tablet formulation, 6 subjects received the 20 mg oral solution formulation, and 8 subjects received the 30 mg oral solution formulation). The second most common AE was

sweating (9 subjects; 3 subjects received the 30 mg tablet formulation, 2 subjects received the 20 mg oral solution formulation, and 4 subjects received the 30 mg oral solution formulation). The third most common AE was headache (9 subjects; 3 subjects received the 30 mg tablet formulation, 3 subjects received the 20 mg oral solution formulation, and 3 subjects received the 30 mg oral solution formulation). The fourth most common AE was vomiting (7 subjects; 1 subject received the 30 mg tablet formulation, 2 subjects received the 20 mg oral solution formulation, and 4 subjects received the 30 mg oral solution formulation). There were more reported AEs of nausea (21.1% versus 2.7%) and vomiting (10.5% versus 2.7%) following administration of aripiprazole 30 mg administered as the oral solution formulation as compared to the tablet formulation.

Summary: The dose-adjusted geometric mean $AUC(\infty)$ values for aripiprazole following dosing with the 20 and 30 mg oral solution (332.5 and 326.4 ng.h/mL/mg) were higher than that observed following the 30 mg tablet (283.9 ng.h/mL/mg). The dose-normalized geometric mean C_{max} values for the oral solution formulation (4.90 and 4.69 ng/mL/mg for the 20 and 30 mg doses, respectively) were also higher than that observed for the tablet formulation (3.82 ng/mL/mg). The higher dose-adjusted aripiprazole $AUC(\infty)$ values for the oral solution lead to an oral solution dose of 25 mg being predicted by the linear interpolation analysis to give a comparable systemic exposure to the 30 mg tablet. Similar analysis performed for aripiprazole C_{max} , on a *post hoc* basis, indicated that the oral solution dose of 24 mg would produce comparable aripiprazole C_{max} to that of the 30 mg tablet.

Although not originally planned for in the protocol, *post-hoc* statistical analyses were performed to calculate 90% confidence intervals for the 30 mg oral solution to the 30 mg tablet geometric mean ratio for C_{max} and $AUC(\infty)$ following administration of these two formulations. The point estimates and 90% confidence intervals for these ratios were 1.22 (1.13, 1.32) and 1.14 (1.09, 1.20), respectively. The 90% CI for the 30 mg oral solution to tablet ratio of adjusted geometric means for aripiprazole C_{max} fell outside the standard boundaries for bioequivalence of 0.80-1.25.

The median T_{max} values (3 h) were the same for the tablet and the oral solution formulation at both doses. However, the minimum and maximum T_{max} values were 0.5 h and 4 to 6 h longer following the tablet formulation compared to the oral solution formulation. The mean $T_{1/2}$ values were comparable between the oral solution and the tablet formulations.

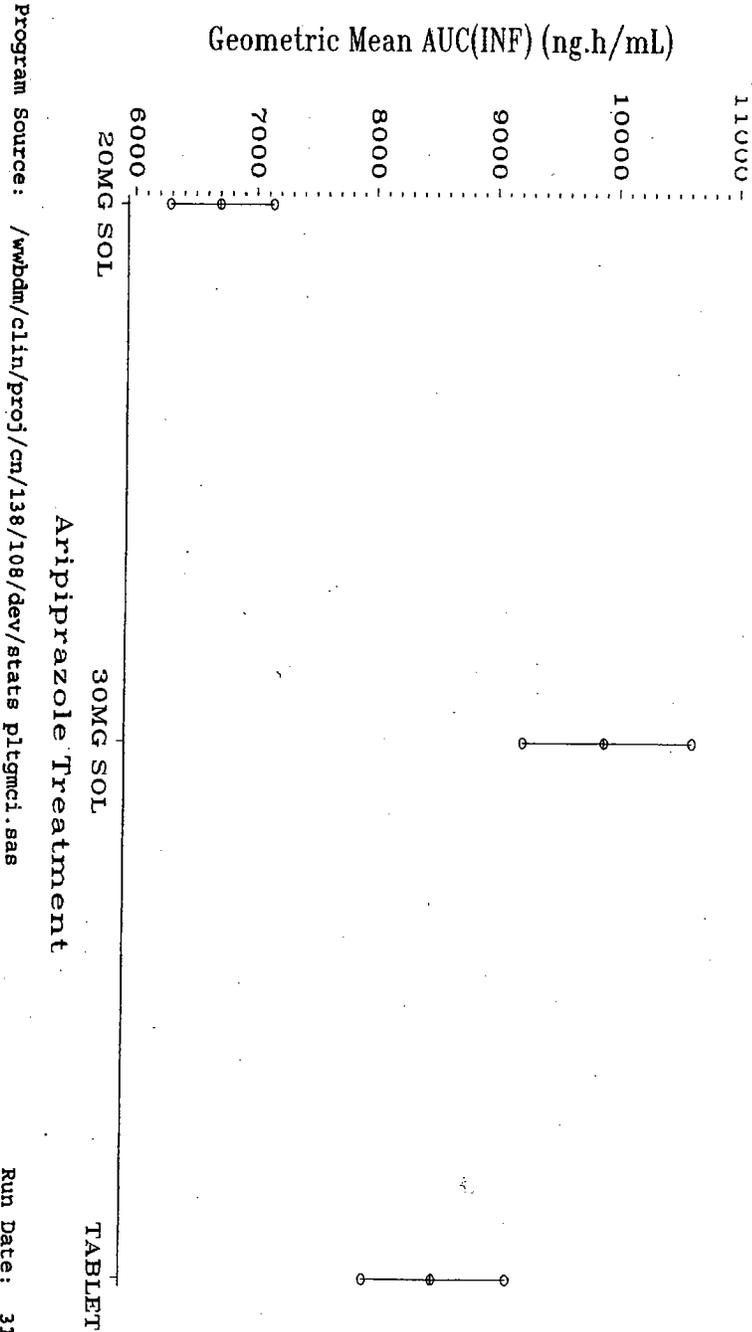
Reviewer's Comment: *The extent of exposure (AUC and C_{max}) to aripiprazole was higher after administration of the same dose of the oral solution compared to the tablet formulation.*

Aripiprazole
BMS-337039

CN138108
Clinical Study Report

Protocol: CN138108
Figure S.11.2.1: Plot of Geometric Mean (95% C.I.) AUC(INF) versus Aripiprazole Treatment

Page : 1



Run Date: 31JUL03

Protocol CN138-108 Table s.11.2.1D: Listing of Subjects' Estimated Arripirazole Oral Solution Dose (OSD) Page : 1

Subject ID	Tablet AUC(INF) (ng.h/ml)	Subject Slope	Subject Intercept	Estimated OSD (mg)
CN138108-1-1	8373	0.73	6.65	26.56
CN138108-1-2	13372	1.39	4.95	26.25
CN138108-1-4	11137	0.87	6.62	22.66
CN138108-1-6	8256	0.86	6.04	31.90
CN138108-1-7	10349	1.12	5.50	28.07
CN138108-1-8	12026	1.12	5.95	21.33
CN138108-1-9	8560	0.46	7.65	21.24
CN138108-1-10	4428	1.07	4.90	25.86
CN138108-1-11	6397	1.03	5.30	29.14
CN138108-1-12	8169	1.45	4.35	24.71
CN138108-1-13	3970	0.54	6.58	22.86
CN138108-1-14	9351	0.94	6.12	25.24
CN138108-1-15	10165	0.30	8.11	40.28
CN138108-1-16	5518	0.93	5.52	28.24
CN138108-1-17	4194	0.94	5.12	30.96
CN138108-1-18	8843	1.11	5.58	23.28

Estimated OSD produces comparable AUC (INF) to the subject's 30mg Arripirazole Tablet
Intercept and Slope parameters are from the fitted regression line of log(AUC (INF)) on log(dose) of solution formulation
Program Source: /wdbdn/clin/proj/cv/138/108/dev/stats/pks_sfnanal.sas Run Date: 21JUL03

Protocol CN138-108 Table S.11.2.ID: Listing of Subjects' Estimated Arpiprazole Oral Solution Dose (OSD)

Subject ID	Tablet AUC (INP) (ng.h/mL)	Subject Slope	Subject Intercept	Estimated OSD (mg)
CN138108-1-19	9629	0.82	6.48	26.28
CN138108-1-22	12999	0.78	6.92	26.05
CN138108-1-24	5170	0.27	7.88	12.18
CN138108-1-25	10647	1.07	5.54	32.81
CN138108-1-26	8770	0.53	7.39	24.18
CN138108-1-29	7083	0.68	6.55	29.92
CN138108-1-31	4571	0.67	6.81	11.20
CN138108-1-33	5500	1.48	3.84	25.24
CN138108-1-35	12900	1.05	6.13	24.10
CN138108-1-37	9979	1.20	5.38	24.31
CN138108-1-38	10441	1.27	5.06	27.13
CN138108-1-39	15923	1.45	4.86	27.96
CN138108-1-42	7361	0.62	6.89	25.36

Estimated OSD produces comparable AUC (INP) to the subject's 30mg Arpiprazole Tablet
Intercept and Slope parameters are from the fitted regression line of log(AUC (INP)) on log(dose) of solution formulation
Program Source: /w:\odm\clin\proj\cn\138\108\dev\stats\pks_stcna1.sas Run Date: 21JUL03

Protocol CN138-108

Table S.11.2.ID: Listing of Subjects' Estimated Aripiprazole Oral Solution Dose (OSD)

Page : 2

Subject ID	Tablet AUC (INP) (ng.h/ml)	Subject Slope	Subject Intercept	Estimated OSD (mg)
CN138108-1-19	9629	0.82	6.48	26.28
CN138108-1-22	12999	0.78	6.92	26.05
CN138108-1-24	5170	0.27	7.88	12.18
CN138108-1-25	10647	1.07	5.54	32.81
CN138108-1-26	8770	0.53	7.39	24.18
CN138108-1-29	7083	0.68	6.55	29.92
CN138108-1-31	4571	0.67	6.81	11.20
CN138108-1-33	5500	1.48	3.84	25.24
CN138108-1-35	12900	1.05	6.13	24.10
CN138108-1-37	9979	1.20	5.38	24.31
CN138108-1-38	10441	1.27	5.06	27.13
CN138108-1-39	15923	1.45	4.86	27.96
CN138108-1-42	7361	0.62	6.89	25.36

Estimated OSD produces comparable AUC (INP) to the subject's 30mg Aripiprazole Tablet Intercept and Slope parameters are from the Fitted regression line of log(AUC(INP)) on log(dose) of solution formulation
 Program Source: /w/odm/clin/proj/cn/138/108/dev/stats/pks_stranal.sas Run Date: 21JUL03

Protocol CN138108

S.11.2.1E: Summary Statistics and 95% C.I. for the Estimated Oral Solution Dose

Page :

1

STATISTIC	Oral Solution Dose (mg)	95% LCL	95% UCL
N	29		
MEAN	25.70		
S.D.	5.49		
95% MEAN	25.02	22.71	27.57
C.V.	21.35		
MEDIAN	25.86		
MIN			
MAX			

Estimated Oral Solution Dose (ESD) with Comparable AUC (INF) from the 30mg Aripiprazole Commercial Tablet
Based on 29 subjects with evaluable data for all three Aripiprazole formulations
Program Source: /wbdm/clin/proj/CN138108/pke_estdoest.sas

Run Date: 21JUL03

Protocol CN138-108
Table S.11.2.1H: Listing of Subjects' Aripiprazole Oral Solution Dose (OSD) Estimated Based on Cmax Page : 1

Subject ID	Tablet Cmax (ng.h/mL)	Subject Slope	Subject Intercept	Estimated OSD (mg)
CN138108-1-1	124	0.72	2.50	25.21
CN138108-1-2	135	0.85	2.13	26.00
CN138108-1-4	163	0.69	2.84	26.68
CN138108-1-6	173	0.63	2.92	34.90
CN138108-1-7	105	0.57	2.77	27.26
CN138108-1-8	145	1.21	1.17	23.43
CN138108-1-9	87	0.92	1.78	18.57
CN138108-1-10	97	1.05	1.07	28.18
CN138108-1-11	144	1.19	0.93	29.53
CN138108-1-12	153	1.91	-0.99	23.42
CN138108-1-13	80	-0.01	4.43	
CN138108-1-14	85	1.44	0.37	16.91
CN138108-1-15	139	-0.20	5.47	
CN138108-1-16	112	1.63	-0.46	24.02
CN138108-1-17	86	0.77	1.89	27.95

Estimated OSD produces comparable Cmax to that of the subject's 30mg Aripiprazole Tablet
 Intercept and Slope parameters are from the fitted regression line of log(Cmax) on log(dose) of oral solution formulation
 Subjects CN138108-1-13, CN138108-1-15 are not used in estimating the OSD, since Cmax decreased with increasing oral solution dose
 Program Source: /w/tdm/clin/proj/cn/138/108/dev/strats/pls_stramax.sas
 Run Date: 17SEP03

Protocol CN138-108 Page : 2
Table S.11.2.1H: Listing of Subjects' Aripiprazole Oral Solution Dose (OSD) Estimated Based on C_{max}

Subject ID	Tablet C _{max} (ng.h/ml)	Subject Slope	Subject Intercept	Estimated OSD (mg)
CN138108-1-18	141	1.62	-0.20	23.97
CN138108-1-19	139	0.87	2.17	23.76
CN138108-1-22	100	0.40	3.25	30.72
CN138108-1-24	60	0.65	2.36	14.60
CN138108-1-25	152	0.82	2.29	28.26
CN138108-1-26	136	0.40	3.73	19.50
CN138108-1-29	139	0.63	2.71	33.50
CN138108-1-31	44	0.82	2.28	6.31
CN138108-1-33	121	0.85	1.96	28.21
CN138108-1-35	92	0.68	2.53	19.14
CN138108-1-37	107	1.54	-0.31	25.32
CN138108-1-38	111	0.96	1.58	26.19
CN138108-1-39	180	1.44	0.30	30.19
CN138108-1-41	137	0.20	4.11	53.82
CN138108-1-42	79	0.56	2.77	16.99

Estimated OSD produces comparable C_{max} to that of the subject's 30mg Aripiprazole Tablet
Intercept and Slope parameters are from the fitted regression line of log(C_{max}) on log(dose) of oral solution formulation
Subjects CN138108-1-13, CN138108-1-15 are not used in estimating the OSD, since C_{max} decreased with increasing oral solution dose

Program Source: /wobot/clin/proj/cn/138/108/dev/stats/pks_stcmax.sas

Run Date: 17SEP03

Protocol CN138108
S.11.2.11: Summary Statistics and 95% C.I. for an Estimated Oral Solution Dose Based on Cmax Page : 1

STATISTIC	Oral Solution Dose (mg)	95% LCL	95% UCL
N	28		
MEAN	25.45		
S.D.	8.23		
GED.MEAN	24.05	20.81	27.81
C.V.	32.33		
MEDIAN	25.66		
MIN			
MAX			

Estimated Oral Solution Dose (OSD) with Comparable Cmax from the 30mg Aripiprazole Commercial Tablet

Subjects CN138108-1-13, CN138108-1-15 were not used to estimate the OSD since Cmax decreased with increasing oral solution dose.

Program Source: /wkdir/clin/proj/CN138108/pks_cmcdoct.sas

Protocol: CN138108

Page: 2

Table S.11.2.1F: Statistical Analysis of BMS-337039 Cmax (ng/ml)

TREATMENT	INDIVIDUAL TREATMENT SUMMARIES			ADJ'D MEAN	90% C.I.: (LCL, UCL)	ORIGINAL (UNTRANSFORMED) SCALE		
	LOG-TRANSFORMED SCALE	ADJ'D MEAN	90% C.I.: (LCL, UCL)			ADJ'D MEAN	90% C.I.: (LCL, UCL)	
A	4.737	0.047	(4.658, 4.816)	114.072	(105.423, 123.432)			
B	4.589	0.048	(4.509, 4.668)	98.372	(90.842, 106.525)			
C	4.937	0.048	(4.856, 5.017)	139.300	(128.527, 150.975)			

TREATMENT COMPARISON	DIFFERENCES ON THE LOG TRANSFORMED SCALE				RATIOS ON THE ORIGINAL SCALE			
	PT. EST.	S.E.	T	P	PT. EST.	90% C.I.: (LCL, UCL)	PT. EST.	90% C.I.: (LCL, UCL)
B vs. A	-0.148	0.045	-3.289	0.002	0.8624	(0.7999, 0.9298)	1.2212	(1.1316, 1.3178)
C vs. A	0.200	0.046	4.384	0.000	1.2212	(1.1316, 1.3178)	1.2212	(1.1316, 1.3178)

TREATMENT CODES
A = Atipiprazole 30mg Tab
B = Atipiprazole 20mg Sol
C = Atipiprazole 30mg Sol

SUBJECTS EXCLUDED INSUFFICIENT DATA: CN138108-1-20, CN138108-1-21, CN138108-1-28, CN138108-1-44, CN138108-1-47
Program Source: /s_PROD/CN/138/108/EKS_BAEB.SAS
Run Date: 31JUL03

Protocol: CN138108

Page: 2

Table S.11.2.1G: Statistical Analysis of BMS-337039 AUC (INF) (ng.h/mL)

TREATMENT	INDIVIDUAL TREATMENT SUMMARIES			LOG-TRANSFORMED SCALE		ORIGINAL (UNTRANSFORMED) SCALE	
	ADJ'D MEAN	S.E.	90% C.I.: (LCL, UCL)	ADJ'D MEAN	90% C.I.: (LCL, UCL)	ADJ'D MEAN	90% C.I.: (LCL, UCL)
A	9.040	0.068	(8.927, 9.153)	8431.997	(7530.686, 9441.182)	8431.997	(7530.686, 9441.182)
B	8.815	0.068	(8.701, 8.928)	6732.189	(6011.109, 7539.768)	6732.189	(6011.109, 7539.768)
C	9.174	0.068	(9.061, 9.288)	9644.903	(8609.488, 10804.84)	9644.903	(8609.488, 10804.84)

TREATMENT COMPARISON	DIFFERENCES ON THE LOG TRANSFORMED SCALE				RATIOS ON THE ORIGINAL SCALE	
	PT. EST.	S.E.	T	P	90% C.I.: (LCL, UCL)	90% C.I.: (LCL, UCL)
B vs. A	-0.225	0.029	-7.757	0.000	(-0.274, -0.177)	(0.7606, 0.8381)
C vs. A	0.134	0.029	4.571	0.000	(0.085, 0.194)	(1.0890, 1.2015)

TREATMENT CODES
A = Atipiprazole 30mg Tab
B = Atipiprazole 20mg Sol
C = Atipiprazole 30mg Sol

SUBJECTS EXCLUDED INSUFFICIENT DATA: CN138108-1-20, CN138108-1-21, CN138108-1-28, CN138108-1-44, CN138108-1-47

Program Source: /s_/PROJ/CN/138/108/PKS_PARE.SAS

Run Date: 31JUL03

Protocol CN138108

S.11.2.2C: Summary Statistics for BMS-337044 Pharmacokinetic Parameters

Page : 1

TREATMENT CODE	STATISTIC	Q _{MAX} (ng/mL)	Dose Norm Q _{MAX} (ng/mL)/mg	AUC(0-T) (ng·h/mL)	Dose Norm AUC(0-T) (ng·h/mL)/mg	T _{MAX} (h)
A	N	33	33	33	33	33
	MEAN	13.29	0.44	2658.72	88.62	71.42
	S.D.	4.68	0.16	793.14	26.44	23.00
	GEQ,MEAN	12.52	0.42	2539.29	84.64	68.14
	C.V.	35.22	35.22	29.83	29.83	32.21
	MEDIAN	13.22	0.44	2467.43	82.25	72.00
MIN						
MAX						
B	N	32	32	32	32	32
	MEAN	10.62	0.53	2085.42	104.27	63.05
	S.D.	3.57	0.18	559.41	27.97	25.69
	GEQ,MEAN	10.07	0.50	2014.10	100.71	58.83
	C.V.	33.63	33.63	26.82	26.82	40.75
	MEDIAN	9.34	0.47	2048.90	102.45	59.96
MIN						
MAX						
C	N	31	31	31	31	31
	MEAN	16.63	0.55	3185.86	106.20	60.43
	S.D.	7.17	0.24	1036.46	34.55	29.66
	GEQ,MEAN	15.35	0.51	3032.58	101.09	54.53
	C.V.	43.11	43.11	32.53	32.53	49.08
	MEDIAN	14.96	0.50	2885.26	96.18	48.00
MIN						
MAX						

Treatment Codes:
A = Aripiprazole 30mg Tablet
B = Aripiprazole 20mg Solution
C = Aripiprazole 30mg Solution
Program Source: /wddm/clin/proj/CN138-108/pks_sunst044.sas

4.3. Cover Sheet and OCPB filing/review form

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
• General Information About the Submission				
	Information			Information
NDA Number	21-713	Brand Name	Abilify	
OCPB Division (I, II, III)	I	Generic Name	Aripiprazole	
Medical Division	DNDP	Drug Class	• Antipsychotic	
OCPB Reviewer	• Kofi Kumi	Indication(s)	• Tx of Schizophrenia	
OCPB Team Leader	Raman Baweja	Dosage Form	Oral solution	
		Dosing Regimen	10 – 25 mg/day	
Date of Submission	11/20/03	Route of Administration	Oral	
Estimated Due Date of OCPB Review	7/20/04	Sponsor	Otsuka/BMS	
PDUFA Due Date	09/26/04	Priority Classification	• Standard	
Division Due Date	•			
• 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				
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) -				
Healthy Volunteers-				
single dose:	2	2	2	
multiple dose:	•			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:	•			
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
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:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
	•			
• <i>Filability and QBR comments</i>				
		"X" if yes	• <i>Comments</i>	
<i>Application filable ?</i>		• X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
<i>Comments sent to firm ?</i>		X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. =	
QBR questions (key issues to be considered)	<ol style="list-style-type: none"> 1. Is the exposure of aripiprazole after the administration of the same dose of the oral solution similar to that after the approved tablet formulation? 2. Is the concentration of aripiprazole proportional to dose after administration of the oral solution? 			

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CC: NDA 21-713, HFD-850 (Electronic Entry or Lee), HFD-120, HFD-860 (Mehta, RahmanA, Baweja, KumiK), CDR (B. Murphy)

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

/s/

Kofi Kumi
8/25/04 04:28:56 PM
BIOPHARMACEUTICS

Sally Yasuda
8/25/04 04:36:47 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-713	Brand Name	Abilify
OCPB Division (I, II, III)	1	Generic Name	Aripiprazole
Medical Division	DNDP	Drug Class	Antipsychotic
OCPB Reviewer	Kofi Kumi	Indication(s)	Tx of Schizophrenia
OCPB Team Leader	Raman Baweja	Dosage Form	Oral solution
		Dosing Regimen	10 – 25 mg/day
Date of Submission	11/20/03	Route of Administration	Oral
Estimated Due Date of OCPB Review	7/20/04	Sponsor	Otsuka/BMS
PDUFA Due Date	09/26/04	Priority Classification	Standard
Division Due Date			

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				
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) -				
<i>Healthy Volunteers-</i>				
single dose:	2	2		
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
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:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	<ol style="list-style-type: none"> 1. Is the exposure of aripiprazole after the administration of the same dose of the oral solution similar to that after the approved tablet formulation? 2. Is the concentration of aripiprazole proportional to dose after administration of the oral solution? 			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Clinical Pharmacology and Biopharmaceutics Memo to File

NDA: 21-713

Drug: Aripiprazole Oral Solution, 1 mg/mL

Trade Name: Abilify®

Sponsor: Otsuka/Bristol Myers Squibb

Indication: Treatment of Schizophrenia

Submission Type: 45-Day NDA filing Memo

Submission Date: 11/20/03

Reviewer: Kofi A. Kumi, Ph.D.

Team Leader: Raman Baweja, Ph.D.

Background: Abilify tablets were approved in November 2002 for the treatment of schizophrenia. The sponsor has developed Abilify oral solution to provide an alternate dosage formulation for those patients who cannot swallow the tablet formulation. This application is for the oral solution. The sponsor indicated that in a meeting in October of 2002, the reported preliminary pharmacokinetic studies indicated that the oral solution was unlikely to declare bioequivalence to the approved tablets, given the more rapid absorption and greater maximum plasma concentrations observed with the solution.

The submission included three clinical pharmacology studies, two of which were designed to estimate the doses of the oral solution that would be expected to deliver equivalent exposures to the approved Abilify tablet formulation. The third study assessed the bioavailability of aripiprazole administered as an oral solution relative to the commercial tablet formulation. The sponsor indicated the formulation used in the clinical pharmacology/biopharmaceutics (CPB) studies were the proposed commercial formulations. Clinical studies to assess the safety and efficacy of the oral solution formulation in patients with schizophrenia or schizoaffective disorders were not performed.

The submission is fully electronic and was provided electronically in lieu of paper.

Comments

From a CPB perspective, the application is fileable.

The clinical division decided to file the application on 1/20/04.

Kofi A. Kumi, Ph.D. _____

RD/FT Initialed by Raman Baweja, Ph.D _____

CC: NDA 21-713, HFD-120, HFD-860 (Mehta, Sahajwalla, Baweja, KumiK), CDR (Biopharm.)

**TABULAR LISTING OF CLINICAL PHARMACOLGY STUDIES
FOR ARIPIPRAZOLE (BMS-337039) - ORAL SOLUTION**

Table 1: List of Clinical Pharmacology Studies

Type of Study	Study ID	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects/ Discontinuations due to AEs	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Relative Bioavailability Study	019	The primary objective of this study was to assess the bioavailability of aripiprazole administered as an oral solution (3 mg) relative to the aripiprazole commercial tablet formulation (15 mg tablet).	Open-label, randomized, two-period, two-treatment, crossover study in healthy adult subjects.	3 mg oral solution 15 mg tablet	16 subjects 0 subjects discontinued due to an AE	Healthy Subjects	2 single doses separated by a 21 day washout period	Complete; Full

Table 1: List of Clinical Pharmacology Studies

Type of Study	Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects/ Discontinuations due to AEs	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK Dose Finding and Proportionality Study	063	The primary objective of this study was to determine the doses of aripiprazole oral solution that produced equivalent aripiprazole exposure, AUC(INF) and C _{max} , to the 5, 10, and 15 mg tablet.	Open-label, randomized, three-period, six-treatment incomplete crossover study in healthy adult subjects	5, 10 and 15 mg tablets 5, 10 and 15 mg oral solution	60 subjects 1 subject discontinued due to an AE	Healthy Subjects	3 single doses separated by a 21 day washout period	Complete; Full

Table 1: List of Clinical Pharmacology Studies

Type of Study	Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects/ Discontinuations due to AEs	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Relative Bioavailability Study	108	The primary objective of this study was to estimate the dose of aripiprazole that when administered in the proposed commercial oral solution formulation would produce an aripiprazole exposure (AUC) comparable to the exposure observed after a 30 mg dose of the aripiprazole commercial tablet formulation.	Open-label, randomized, three-period, three-treatment, crossover study in healthy adult subjects.	20 and 30 mg oral solution 30 mg tablet	46 subjects 5 subjects discontinued due to AEs	Healthy Subjects	3 single doses separated by a 28 day washout period	Complete; Full

Appendix 1: Table of Clinical Pharmacology Studies

2 page(s) excluding cover page

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Item 3 summary-clin-pharm.pdf

Appendix 1: Table of Clinical Pharmacology Studies

Study Protocol (Country)	Study Design	Dose	Start Date to Stop Date	No. Subjects/ Gender: Age (y): Mean (min, max)	Endpoints	Conclusions
CN138019 (USA)	Open-label, randomized, two-period, two-treatment, crossover study in healthy adult subjects.	3 mg oral solution 15 mg tablet	05/Oct/00 to 02/Dec/00	16 (13/3) 28 (19, 40)	Single-dose PK Safety and tolerability	The rate and extent of absorption of aripiprazole for the 3 mg oral solution formulation were greater than the rate and extent of absorption of aripiprazole from the 15 mg tablet, based on the dose-normalized parameter values. Based on the comparison of dose-normalized adjusted geometric mean AUC(INF) values, the bioavailability of aripiprazole from the oral solution formulation relative to the tablet was 140%. The safety results for both formulations were consistent with the safety profile of aripiprazole observed in previous studies in healthy subjects.
CN138063 (USA)	Open-label, randomized, three-period, six-treatment incomplete crossover study in healthy adult subjects	5, 10, and 15 mg as oral solution 5, 10, and 15 mg as tablet	15/Aug/01 to 12/Oct/01	60 (23/37) 35 (20, 44)	Single-dose PK Safety and tolerability	The dose of the proposed oral solution formulation that would produce comparable aripiprazole AUC(INF) to that from the 5, 10, and 15 mg tablets was estimated to be 4.37, 9.4, and 13.9 mg, respectively. Based on a <i>post hoc</i> analysis, the 90% confidence interval for the solution to tablet ratio for aripiprazole systemic exposure fell within the boundaries of 0.8 to 1.25 for all doses. The safety results for both formulations were consistent with the safety profile of aripiprazole observed in previous studies in healthy subjects.

cc

Appendix 1: Table of Clinical Pharmacology Studies

Study Protocol (Country)	Study Design	Dose	Start Date to Stop Date	No. Subjects/ Gender: (M/F)/ Age (Y): Mean (min, max)	Endpoints	Conclusions
CN138108 (USA)	Open-label, randomized, three-period, three-treatment, crossover study in healthy adult subjects.	30 mg oral solution 30 mg oral tablet	16/Jan/03 to 09/Apr/03	46 (44/2) 34 (18, 45)	Single-dose PK Safety and tolerability	<p>The dose of the proposed oral solution formulation that would produce comparable aripiprazole AUC(INF) to that from the 30mg commercial tablet is estimated to be about 25 mg.</p> <p>Based on a <i>post hoc</i> analysis, the 90% confidence interval for the 30 mg solution to 30 mg tablet ratio for aripiprazole systemic exposure fell within the boundaries of 0.8 to 1.25.</p> <p>The frequency of AEs (54.1% versus 40.5%) was slightly higher in subjects who received aripiprazole 30 mg administered as the oral solution formulation as compared to subjects who received the commercial tablet formulation. This apparent difference may be attributed to a 1.23-fold higher C_{max} for the aripiprazole 30 mg oral solution formulation as compared to the tablet formulation.</p> <p>Overall, both formulations of aripiprazole were safe and generally well tolerated. The types of adverse events (AEs) reported for both formulations are consistent with the AE profile of aripiprazole observed in previous studies in healthy subjects.</p>

Table 3.2.P.1.T01: Composition of Aripiprazole Oral Solution, 1 mg/mL

Component	Reference	Function	Quantity (mg/mL)
Aripiprazole	NC ^a	Active	1.0
Glycerin	USP		
DL-Lactic Acid	USP		
Sodium Hydroxide	NF		
Propylene Glycol	USP		
Methylparaben	NF		
Propylparaben	NF		
Sucrose	NF		
Fructose	USP		
Natural Orange Cream Flavor WONF ^d	NC ^{a,e}		
Purified Water	USP		

^a Noncompendial

^b The amount shown is based on an assay value of [redacted] for DL-lactic acid. The exact amount may vary depending on the actual value of DL-lactic acid and pH adjustment.

^c The amount of sodium hydroxide may be varied to adjust the pH of each batch of solution to between [redacted]

^d WONF means With Other Natural Flavors

^e [redacted], DMF No. [redacted]. A letter of authorization from [redacted] is provided in Section [3.2.P.4.1.2].

^f Processing agent not present in the final drug product

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

/s/

Kofi Kumi
1/21/04 03:54:53 PM
BIOPHARMACEUTICS

Raman Baweja
1/21/04 04:42:27 PM
BIOPHARMACEUTICS