CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-729

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Comment

NDA:	21-729
Drug:	Aripiprazole Orally Disintegrating Tablet
Trade Name:	Abilify ODT Discmelt
Strengths:	[redacted] 10 mg, 15 mg, 20mg, 30 mg Oral Disintegrating Tablets
Applicant:	Bristol Myers Squibb
Indication:	Treatment of Schizophrenia
Submission Type:	Response to Approvable Letter
Submission Date:	12/12/05
OND Division:	DPP (HFD-130)
OCPB Division:	DCPB1 (HFD-860)
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

Background

The sponsor submitted NDA 21-729 for Abilify Discmelt Orally Disintegrating Tablets on December 22, 2003. An Approvable letter was issued on October 22, 2004. In this correspondence, the sponsor has submitted complete response to questions/comments that were included in the Approvable letter. This comment is related to Question No. 10, which was provided by OCPB to be included in the Approvable letter.

Question: We request that you adopt the following dissolution method and specification

Apparatus:	USP Apparatus II (Paddle)
Speed:	75 rpm
Media:	pH 4 Acetate Buffer
Volume:	1000 mL

Specification: Q NLT [redacted] in 30 minutes

The sponsor has agreed to adopt the method but would like to adopt an interim dissolution specification of Q NLT [redacted] in 30 minutes instead of a specification Q NLT [redacted] in 30 minutes.

The sponsor's rationale for an interim specification is that the proposed specification has no clinical relevance because the dissolution specification for the tablet was Q NLT [redacted]. However, the proposed method for the ODT and that for the tablet are different. The dissolution method for the tablet is

Apparatus:	USP Apparatus II (Paddle)
Speed:	60 rpm
Media:	pH 1.2 USP Buffer
Volume:	1000 mL

The Abilify tablet method was not chosen as the dissolution method for Abilify Discmelt ODT due to rapid dissolution, high variability, and loss of discriminatory ability for detecting changes in the ODT. Also, the sponsor indicates that a Q NLT [redacted] would increase [redacted] requirement as compared to the frequency of [redacted] that would occur under the dissolution specification of Q NLT [redacted] in 30 minutes. The sponsor argues that a dissolution specification tighter than NLT [redacted], in 30 minutes would not provide additional indication of product performance. Hence, the

sponsor is proposing an interim dissolution specification of Q NLT [redacted] in 30 minutes. A final dissolution specification would to be set for aripiprazole ODT once the sponsor gains experience in full-scale manufacturing of at least [redacted] batches.

Comment to Sponsor:

1. The sponsor's proposal for an interim specification of Q NLT [redacted] in 30 minutes is acceptable. However, the sponsor should provide full dissolution profiles for at least [redacted] batches or batches produced for 12 months, whichever comes first, and should also provide data indicating how many [redacted] would be performed if the specification is set at Q NLT [redacted] A final specification would be set after the data is provided and reviewed.
2. The sponsor should provide the data requested in #1 above within 16 months of the date of the action letter
3. Please forward comments 1 and 2 to sponsor.

Kofi A. Kumi, Ph.D._____

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

CC:NDA 21-729, HFD-130, HFD-860 (Mehta, Baweja, KumiK), EDR (Biopharm)

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/s/

Kofi Kumi
2/22/2006 12:25:30 PM
BIOPHARMACEUTICS

Raman Baweja
2/22/2006 06:29:56 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-729
Drug: Aripiprazole
Trade: Abilify™ ODT
Strengths: [redacted] 10 mg, 15 mg, 20mg, 30 mg Oral Disintegrating Tablets
Applicant: Bristol Myers Squibb
Indication: Treatment of Schizophrenia
Submission Type: New Formulation
Related IND and NDA: IND 62, 181 and NDA 21-436
Submission Dates: 12/22/03, 3/31/04, 7/8/04, 8/4/04
OND Division: DNDP (HFD-120)
OCPB Division: DPE1 (HFD-860)
Reviewer: Kofi A. Kumi, Ph.D.
Team Leader (Acting): Sally Yasuda, Pharm.D.

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1. Executive Summary

1.1 Recommendation

Based on the review of the data submitted to the Human Pharmacoknietics and Bioavailability Section of NDA 21-729 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.

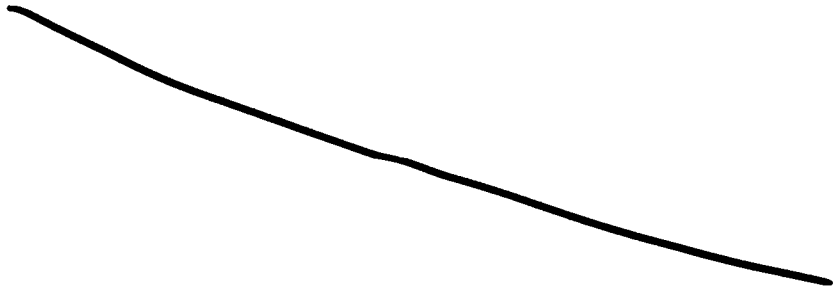
1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Background: Aripiprazole (OPC-14597, BMS-337039), a dihydrocarbostyril (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. An orally disintegrating tablet (ODT) formulation was developed to provide an alternate means to administer aripiprazole to patients who have difficulties swallowing the tablet and, therefore, to increase compliance. The clinical program for the ODT formulation consisted of [redacted] pivotal bioequivalence studies for the highest (30 mg) [redacted] ODT formulations. These strengths correspond to the 30 mg [redacted] aripiprazole commercial tablets. A waiver for the *in vivo* bioequivalence studies for lower strength (i.e. 20, 15, and 10 mg) ODTs is being requested, because the lower strength ODTs have the same drug-to-excipient ratio as the 30 mg ODT formulation (see Section 2.5.3) and the *in vitro* dissolution profiles at pH values of 1.2, 4.0, and 6.8 were found to be similar. Clinical studies to assess the safety and efficacy of the ODT formulations in patients with schizophrenia or schizoaffective disorders have not been performed.

Bioequivalence: Aripiprazole ODT was determined to be bioequivalent to the conventional tablet (CT) formulations. The 30 mg ODT and 30 mg conventional tablet (CT) were bioequivalent. [redacted] The point estimates and 90% CI values for the aripiprazole geometric mean Cmax and AUC ratios of ODT to CT formulations all met the regulatory requirements for bioequivalence of 0.80-1.25. On the basis of their bioequivalence, it is unlikely there will be any significant difference in the clinical efficacy and tolerability of the ODT and CT formulations. These two formulations can be used interchangeably.

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

Parameter	Geometric Means (Intra-subject CV%)		Ratio of 30 mg ODT: 30 mg Tablet (Adjusted Geometric Means)	
	A: 30 mg Tablet	B: 30 mg ODT	Pt. Estimate of Ratio B:A	90% CI for Ratio
Cmax (ng/mL)	101.6 (27.6)	104.9 (12.3)	1.03	(0.951, 1.121)
AUC(0-T) (ng*h/mL)	5702 (17.1)	5749 (14.7)	1.01	(0.938, 1.084)
AUC(∞) (ng*h/mL)	5922 (17.4)	5962 (14.5)	1.01	(0.938, 1.081)



Biowaiver: The sponsor is requesting a waiver of *in vivo* bioequivalence studies for lower strength (i.e., 20, 15, and 10 mg) ODTs. Bioequivalence between the highest (30 mg) strength of the ODT formulation proposed for marketing and the commercial tablet (30 mg) was established. The dissolution profiles for the 10 mg, 15 mg and 20 mg are similar to the 30 mg ODT. The qualitative and quantitative composition of the 10, 15 and 20 mg are similar to the 30 mg ODT. Therefore, the reviewer recommends that in vivo bioequivalence should be waived for aripiprazole 10 mg, 15 mg and 20 mg ODT formulations. The 10, 15 and 20 mg ODT can also be switched for their respective CT if needed.

Dissolution: After reviewing the dissolution data for the batches used in the pivotal bioequivalence and stability studies, there was not a significant difference in the dissolution

be adopted. Therefore, the reviewer recommends the following method and specification.

Apparatus: USP Apparatus II (Paddle)
Speed: 75 rpm
Media: pH 4 Acetate Buffer
Volume: 1000 mL

Specification: Q NLT in 30 mins

Dosing Recommendation: The dosing recommendation for Abilify™ ODT is the same as Abilify conventional tablets (CT). The following language is the current dosing recommendation for Abilify CT:

The recommended starting and target dose for ABILIFY is 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 a dose range of 10 to 30 mg/day, however, doses higher than 10 or 15 mg/day, the lowest doses in these trials, were not more effective than 10 or 15 mg/day. Dosage increases should not be made before 2 weeks, the time needed to achieve steady state.

Dosage in Special Populations
Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status (see **CLINICAL PHARMACOLOGY: Special Populations**).

Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP3A4 inhibitors: When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.
Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP2D6 inhibitors: When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.
Dosage adjustment for patients taking potential CYP3A4 inducers: When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be doubled (to 20 or 30 mg). Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 to 15 mg.

Kofi A. Kumi, Ph.D._____

RD/FT Initialed by Sally Yasuda, Pharm. D._____

CC: NDA 21-729, HFD-120 (Mehta, RahmanA, Baweja, Yasuda, KumiK), CDR (Biopharm)

CPB Briefing Date and Attendees: 9/23/04, HFD-120 (Greg Dubitsky),
ONDC (Gupreet Gill-Sangha), HFD-860 (Mehul Mehta, Atiqur Rahman, Sally Yasuda, Kofi Kumi), HFD-870 (Ting-eng Ong, Khoi Lam)

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?

The sponsor submitted preliminary dissolution information to IND 62, 181 requesting agency (OCPB) concurrence on the selection of their dissolution method. In a teleconference on 10/23/03, OCPB requested that the sponsor evaluate two dissolution methods and include the two proposed dissolution methods for aripiprazole ODT in the NDA for further consideration as the regulatory method. One of the methods uses acetate buffer pH 4.0 (1000 mL), with USP Apparatus II (paddles) at 75 rpm [redacted] The second method uses acetate buffer pH 4.0 (1000 mL), with paddles at 50 rpm [redacted]

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 same drug substance that has been approved for the ABILIFY tablets has been used for development of the ODT dosage form and is proposed to be used in the commercial batches of aripiprazole ODT. The [redacted] particle size, [redacted] and other solid state properties of aripiprazole remain unaltered with regard to its formulation in the ODT. This submission is for Abilify (aripiprazole) oral disintegrating tablets (ODT) [redacted] 10 mg, 15 mg, 20 mg and 30 mg. Calcium silicate [redacted] Calcium silicate [redacted]

[redacted]

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 D_2 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 ODT is intended for oral administration. The proposed regimen is similar to that approved for the tablet formulation. The recommended starting and target dose is 10 or 15

mg/day. ABILIFY has been systematically evaluated and shown to be effective in the dose range of 10 to 30 mg/day given orally.

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 program for the aripiprazole ODT formulation was designed to demonstrate bioequivalence for the highest (i.e., 30 mg) ODT formulations proposed for marketing to the corresponding 30 mg aripiprazole commercial tablets. clinical studies were conducted.

pivotal bioequivalence studies were performed. One study was conducted to demonstrate bioequivalence of the highest strength, 30 mg, ODT relative to the commercial tablet. . A waiver for the *in vivo* bioequivalence studies for lower strength (i.e., 20, 15, and 10 mg) ODTs is being requested because these lower strength ODTs have the same drug-to-excipient ratio as the 30 mg ODT formulation and the *in vitro* dissolution profiles at pH values of 1.2, 4.0, and 6.8 are similar.

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). The Division of Scientific Investigations (HFD-48) inspected one of the pivotal studies (CN 138067). The inspector concluded the plasma aripiprazole concentrations of three subjects in the study should not be accepted by the agency for review because the accuracy of aripiprazole concentration could not be assured.

2.2.3. Exposure-Response

Exposure-response relationships were not evaluated for this application.
Dosing recommendation for Aripiprazole is based on demonstrating comparable exposures that will be obtained after the administration of the approved tablet and the orally disintegrating tablets (ODT).

2.2.3.1. What safety profiles were reported?

For the ODT program, two-hundred twenty-one (221) AEs were reported in 71 (52.2%) of 136 subjects. The most common AEs (with frequencies of subjects >10%) were: headache (16.9%), nausea (16.2%), vomiting (15.4%), and lightheadedness (15.4%). Among the 221 AEs reported by subjects exposed to aripiprazole, 204 (92.3%) were considered by Investigators to be mild in intensity, 15 (6.8%) were considered by Investigators to be moderate in intensity, and 2 (1%) were considered by Investigators to be severe/very severe in intensity. The frequency of treatment-emergent AEs appeared to

be comparable between the ODT (34.7%) and the commercial tablet (36.4%) formulations. Overall, the safety profile of aripiprazole ODT formulations in healthy subjects was reported to be similar to that of the commercial tablets.

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. 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 (Vd = 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 Cmax and 16 – 57% for AUC in healthy subjects and patients. The intra-subject variability in the pivotal ODT bioequivalence studies ranged from 7.7 % to 27.6%.

2.3. Intrinsic Factors

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.

2.4. Extrinsic Factors

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. In NDA 21-436, several drugs were evaluated for their effect on aripiprazole pharmacokinetics. Famotidine decreased aripiprazole Cmax approximately 37% and valproate decreased aripiprazole Cmax 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 aripiprazole oral disintegrating tablet?

The composition of the various strengths of aripiprazole ODT is provided in the following table

Table 3: Quantitative Composition of Aripiprazole Orally Disintegrating Tablets

Component	Reference	Function	Quantity (mg) per unit dose			
			10 mg	15 mg	20 mg	30 mg
Aripiprazole	NC	API	10.00	15.00	20.00	30.00
Calcium Silicate	NF					
Croscarmellose Sodium	NF					
Crospovidone	NF					
Silicon Dioxide	NF					
Xylitol	NF					
Microcrystalline Cellulose [a]	NF					
Aspartame	NF					
Acesulfame Potassium	EP					
Crème de Vanilla (Natural & Artificial Flavors)	DMF[c]					
Tartaric Acid	NF					
Magnesium Stearate	NF					
Red Ferric Oxide	NF					
Yellow Ferric Oxide	NF					
FD&C Blue # 2 Aluminum Lake	FD&C					
Tablet Weight	--	--	200.00	100.00	150.00	200.00	300.00

NC = non compendial

2.5.2. Are aripiprazole ODTs bioequivalent to the approved conventional tablets?

Aripiprazole 30 mg ODT and 30 mg conventional tablet (CT) were bioequivalent. [redacted] The point estimates and 90% CI values for the aripiprazole geometric mean Cmax and AUC ratios of ODT to CT formulations all met the regulatory requirements for bioequivalence of 0.80-1.25. On the basis of their bioequivalence of aripiprazole, there is unlikely to be any substantial difference in the clinical efficacy and tolerability of the ODT and CT formulations. These two formulations can be used interchangeably.

In Study CN138067, the sponsor conducted a study to determine whether aripiprazole 30 mg ODT was bioequivalent to 30 mg CT. This was a single-site, single-dose, open-label, randomized, three-period, two-treatment, crossover study in healthy subjects. Forty-eight (48) subjects were enrolled to ensure that 32 subjects completed the study. Each subject was to be fasted for at least 10 hours and then was to receive 30 mg aripiprazole administered as a 1 X 30 mg CT (Treatment A) and as a 1 X 30 mg ODT (Treatment B) in a sequence determined by a computer generated randomization schedule. In Period 3, each subject was to receive the same treatment as in Period 2 (i.e., the treatment was repeated). At the time of dosing, 240 mL of water was to be administered to the subject along with the commercial tablet (Treatment A). Treatment B was to be administered without any fluid. The subject was to be instructed to place the ODT directly on the tongue and keep it there until it "melted" (disintegrated) completely before swallowing. Subjects were permitted to consume water *ad libitum* following 15 minutes post dose for Treatment B. Subjects were to remain supine for up to 8 h after dosing in each period. There was to be a washout period of ≥ 28 days between each treatment administration. Blood samples were collected for PK analysis for up to 384 hours (17 days) post dose. Summary of the statistical analysis are provided in the following table

Table 4: Summary of Statistical Analysis Results for Aripiprazole Cmax and AUC

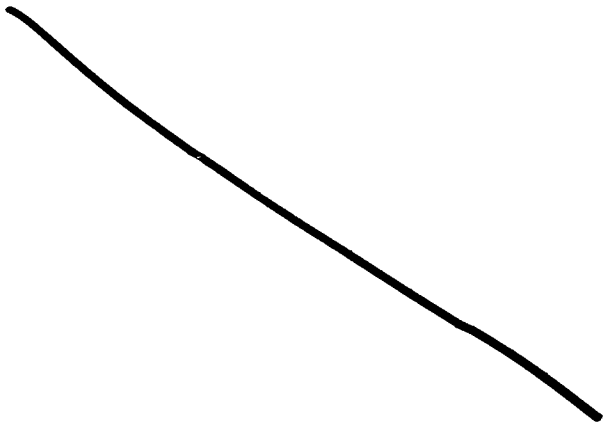
Parameter	Geometric Means (Intra-subject CV%)		Ratio of 30 mg ODT: 30 mg Tablet (Geometric Means)	
	A: 30 mg Tablet	B: 30 mg ODT	Pt. Estimate of Ratio B:A	90% CI for Ratio
Cmax (ng/mL)	101.6 (27.6)	104.9 (12.3)	1.03	(0.951, 1.121)
AUC(0-T) (ng*h/mL)	5702 (17.1)	5749 (14.7)	1.01	(0.938, 1.084)
AUC(∞) (ng*h/mL)	5922 (17.4)	5962 (14.5)	1.01	(0.938, 1.081)

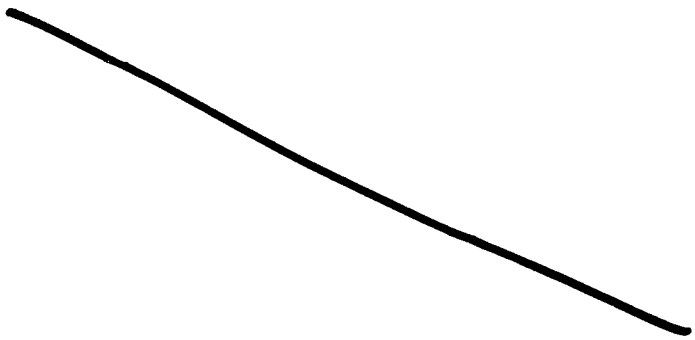
The Division of Scientific Investigation (HFD-48) inspected the site for the pivotal bioequivalent study CN138067. They concluded that plasma aripiprazole concentration data from three subjects

(14, 19 and 29) should not be accepted because the accuracy of aripiprazole concentration was not assured (Details of report is provided in appendix). The reviewer reanalyzed the pharmacokinetic data excluding these three patients. The 90% CI were within the regulatory criteria for declaring two products bioequivalent. Deleting the data for subjects 14, 19 and 29 did not alter the conclusion. Hence, aripiprazole 30 mg ODT is bioequivalent to 30 CT. Summary of statistical analysis after the data was reanalyzed is contained in the data following

Table 5: Point Estimate and 90% CI for Study CN138067 Without Subjects 14, 19 and 29

Pharmacokinetic Parameter	Ratio of 30 mg ODT: 30 mg Tablet	
	Pt. Estimate of Ratio B:A	90% CI for Ratio
Cmax	0.999	(0.92, 1.08)
AUCt	1.000	(0.92, 1.08)
AUC∞	0.966	(0.88, 1.06)





2.5.3. What data support or do not support a waiver of in vivo bioequivalence for the 10 mg, 15 mg and 20 mg ODT formulations?

The sponsor is requesting a waiver of *in vivo* bioequivalence studies for lower strength (i.e., 20, 15, and 10 mg) ODTs. Bioequivalence between the highest (30 mg) strength of the ODT formulation proposed for marketing and the commercial tablet (30 mg) was established. The rationale for exemption of bioequivalence studies for the lower strength [redacted] ODTs are presented below. The reviewer recommends that in vivo bioequivalence should be waived for aripiprazole 10 mg, 15 mg and 30 mg ODT formulations. The 10, 15 and 20 mg ODT can also be switched for their respective CT if needed.

The qualitative composition of the different strengths of ODT formulation is the same. Except for differences in coloring agents [redacted] used in the formulation, the excipient composition and proportion of aripiprazole to each of the other therapeutically inert ingredients in the 10, 15, and 20 mg aripiprazole ODT formulations are identical to the highest dose strength (30 mg) ODT formulation. The sponsor used [redacted] The chemistry reviewer indicated that [redacted] proportional to the dose of ODT for the 10, 15, 20 and 30 mg ODT. The chemistry reviewer stated that the sponsor indicated that [redacted] ODT and maintain a total tablet weight that is proportional to dose for the 10, 15, 20, 30 mg ODT.

[redacted]

The composition of the various aripiprazole ODT strengths is provided in Table 3 Section 2.5.1.

The clinical pharmacokinetics of aripiprazole administered in conventional tablets up to the highest therapeutic dose of 30 mg have been demonstrated to be linear and dose-proportional.

The 10, 15, and 20 mg aripiprazole ODT formulations have similar dissolution characteristics to the 30 mg aripiprazole ODT formulation. The 30 mg ODT has been demonstrated to be bioequivalent to the 30 mg aripiprazole tablet formulation. Therefore, it is expected that the 10, 15, and 20 mg aripiprazole ODT formulations will also have *in vivo* bioequivalence relative to their respective strength tablets. [redacted]

[redacted]

[redacted] Overall, the dissolution profiles of the 10, 15, and 20 mg strength ODTs were similar to the reference 30 mg strength formulation in all 3 dissolution media (i.e., at pH 1.2, 4.0, and 6.8).

8 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 5

2.5.5. What dosing recommendations are necessary?

The dosing recommendation for aripiprazole ODT are the same as that approved for the conventional tablets in NDA 21-436.

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

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

2.5.7. Based o the Biopharmecutics Classificatin System (BCS) principles, in what class is Aripiprazole?

The sponsor reported that aripiprazole falls under BCS class 2. However, based on the solubility, and permeability information submitted and reviewed under NDA 21-436, the reviewer of NDA 21-436 concluded that aripiprazole can be classified as a BCS class 4 drug. Aripiprazole, according to current BCS principles, does not qualify as BCS class 2.

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 [redacted] were extracted from human plasma [redacted] The lower limit of quantitation (LLQ) was established by analyzing a single aliquot from six independent sources of control plasma. Quality control samples (QC) prepared in human plasma were analyzed to determine accuracy and within run precision of the different methods. The deviations of the predicted concentrations from the nominal concentrations (% Deviation) values were within ± 15% for both analytes. Aripiprazole and dehydro-aripiprazole were stable (within ±15% of nominal concentrations) [redacted] In process control for each study report is provided in the individual study reports.

3. Detailed Labeling Recommendations

The reviewer agrees with the sponsor's changes in the clinical pharmacology (CP) and dosage and administration sections of the proposed label except the statement [redacted] The recommended changes by the sponsor in the CP are

underlined and OCPB changes are double underlined in the proposed label in the appendix and provided below

1. Pharmacokinetics

Pharmacokinetic studies showed that Abilify™ orally disintegrating tablets are bioequivalent to Abilify tablets

1. Dosage and Administration

Directions for Use of Abilify™ Orally Disintegrating Tablet

Do not open the blister until ready to administer. For single tablet removal, open the package and peel back the foil on the blister to expose the tablet. Do not push the tablet through the foil because this could damage the tablet. Immediately upon opening the blister, using dry hands, remove the tablet and place the entire Abilify™ orally disintegrating tablet on the tongue. Tablet disintegration occurs rapidly in saliva. [redacted] It is recommended Abilify ODT be taken without liquid. However, if needed, it can be taken with liquid. Do not attempt to split the tablet.

33 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 6

3 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 7

4.3. Individual Study Review

Title (Protocol No. CN138067): Bioequivalence Study Of Aripiprazole When Administered As A 30 Mg Orally Disintegrating Tablet Relative To A 30 Mg Commercial Tablet In Healthy Subjects

Objectives: The primary objective was to establish bioequivalence of aripiprazole when administered as a 30 mg orally disintegrating tablet (ODT) formulation relative to a 30 mg commercial tablet (CT) formulation. The secondary objectives were to assess the safety of single doses of 30 mg aripiprazole administered as an ODT and as a CT and to assess the intrasubject variability in the pharmacokinetics of aripiprazole and its pharmacologically active metabolite, dehydro-aripiprazole in healthy subjects.

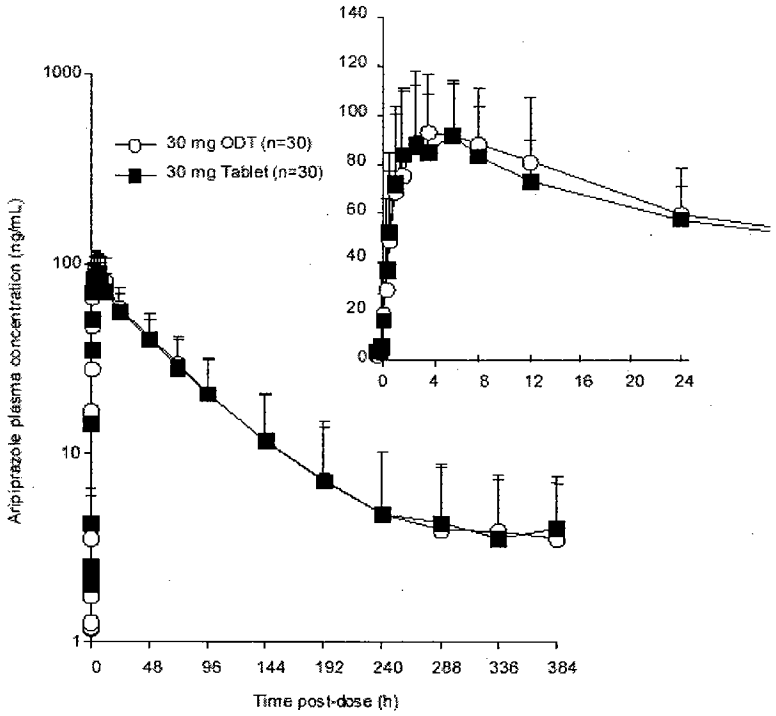
Study Design: This was a single-site, single-dose, open-label, randomized, three-period, two-treatment, crossover study in healthy subjects. Forty-eight (48) subjects were enrolled to ensure that 32 subjects completed the study. The mean ± SD age and weight 31 ± 8 years and 79.4 ± 11.7 kg, respectively. Subjects were admitted to the clinical facility the evening prior to dosing (Day -1) and remained confined until 48 hours post-dose (Day 3) for each period. Blood samples (2 mL per sample) for assessment of pharmacokinetic (PK) were collected at pre-dose (0 h) and at 0.083, 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 144, 192, 240, 288, 336, and 384 h post-dose in each period. Subjects were monitored closely for adverse events (AEs) throughout the study. Each subject was to be fasted for at least 10 hours and then was to receive 30 mg aripiprazole administered as a 1 X 30 mg CT (Treatment A) and as a 1 X 30 mg ODT (Treatment B) in a sequence determined by a computer generated randomization schedule. In Period 3, each subject was to receive the same treatment as in Period 2 (i.e., the treatment was repeated). Subjects were to remain supine for up to 8 h after dosing in each period. There was to be a washout period of ≥ 28 days between each treatment administration. Female subjects were to be not nursing, non-pregnant and not of childbearing potential. At the time of dosing, 240 mL of water was administered to the subject along with the Treatment A, while Treatment B was not given with any fluid. The subject was instructed to place ODT formulation (Treatment B) directly on their tongue until it "melted" (disintegrated) completely before swallowing. Subjects were permitted to consume water *ad libitum* following 15 minutes post dose for Treatment B. All treatments were administered orally. Frequent early blood collection time point sampling was incorporated into this study to examine for the potential for buccal absorption of aripiprazole from the ODT formulation, which breaks up into small particles once placed in the mouth. The test formulation was aripiprazole as 30 mg ODT formulation, Batch # 2M51562. The reference formulation was commercial aripiprazole as 30 mg oral tablets, Batch # 2B57253.

Analytical Method: Plasma samples for aripiprazole and dehydro-aripiprazole were assayed by a validated LC/MS/MS method for the simultaneous measurement of aripiprazole and dehydro-aripiprazole. 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 in plasma specified that the predicted concentrations of at least three-fourths of the standards and two-thirds of the QC samples be within ±15% of their individual nominal concentration values (± 20% for the lowest concentration standard). In addition, at least one QC sample at each concentration must be within ±15% of its individual nominal concentration values.

Data Analysis: Single-dose pharmacokinetics (PK) of aripiprazole and its pharmacologically active metabolite dehydro-aripiprazole were derived from plasma concentration versus time data. The single-dose PK parameters which were assessed included: maximum observed plasma concentration (Cmax), time of maximum observed plasma concentration (Tmax), area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC(0-T)), area under the plasma concentration-time curve from time zero extrapolated to infinite time (AUC(INF)), and terminal elimination half-life (T ½). To demonstrate bioequivalence of the 30 mg ODT to the 30 mg CT, analyses of variance were performed on log (Cmax), log(AUC(0-T)) and log(AUC(INF)) of aripiprazole. The factors in the analysis were sequence group, subject within sequence, period, and treatment group. Since subjects are random effects nested within sequences, F-statistics for sequence effects were the ratios of the type I mean squares for sequence and subjects within sequence. The F-statistic for period was the ratio of the type I mean square for period and the mean square for error. An additional analysis of variance evaluated the significance of first-order treatment carryover effects. Point estimates and 90% confidence intervals for formulation means and differences between the means on the log scale were exponentiated to obtain estimates for geometric means and ratios of geometric means on the original scale. No adjustments were made for multiplicity. Bioequivalence was to be concluded if the 90% confidence intervals for the ratios of the population geometric means of the 30 mg ODT formulation relative to the 30 mg CT were contained within 80% to 125% for Cmax and AUC(INF) of aripiprazole.

Results: A total of 48 subjects were enrolled and randomized to treatment in this study. Of these, 28 subjects (58%) completed the study and 20 subjects (33%) discontinued from the study. One (1) subject (2%) discontinued due to a non-serious AE (pharyngitis); 3 subjects (6%) discontinued due to non-compliance; 2 subjects (4%) withdrew consent; 1 subject (2%) was lost to follow-up and 13 subjects (29%) discontinued for other reasons. Of the 13 subjects who discontinued due to other reasons, 12 subjects (25%) were discontinued due to emesis. These episodes of emesis occurred within 6 hours of dosing in the first period and therefore evaluable PK could not be obtained from these subjects, and they were discontinued from the study. Mean plasma concentration-time profiles for aripiprazole are shown in the following figure.

Mean (plus S.D.) Plasma Concentration-Time Profiles for Aripiprazole Following Dosing with 30 mg Aripiprazole ODT and CT Formulations. (The insert shows only apripiprazole concentration-time points up to 24 h post-dose)



The following table provides a summary statistics are presented in the following table

Aripiprazole Treatment	Pharmacokinetic Parameter				
	Cmax (ng/mL) Geo. Mean (CV%)	AUC (0-T) (ng*h/mL) Geo. Mean (CV%)	AUC∞ (ng*h/mL) Geo. Mean (CV%)	Tmax (h) Median (min, max)	T ½ (h) Mean (S.D.)
A: 30 mg CT (n=43)	102.8 (23)	5776 (44)	6010 (52)	3.0 (1.5, 12.0)	75 (31)
B: 30 mg ODT (n=45)	103.5 (23)	5627 (41)	5824 (43)	4.0 (1.5, 12.0)	71 (28)

The statistical analyses with adjusted geometric mean, ratios of geometric means, and their 90% confidence intervals for Cmax, AUC(0-T) and AUC(INF), are summarized in the following table.

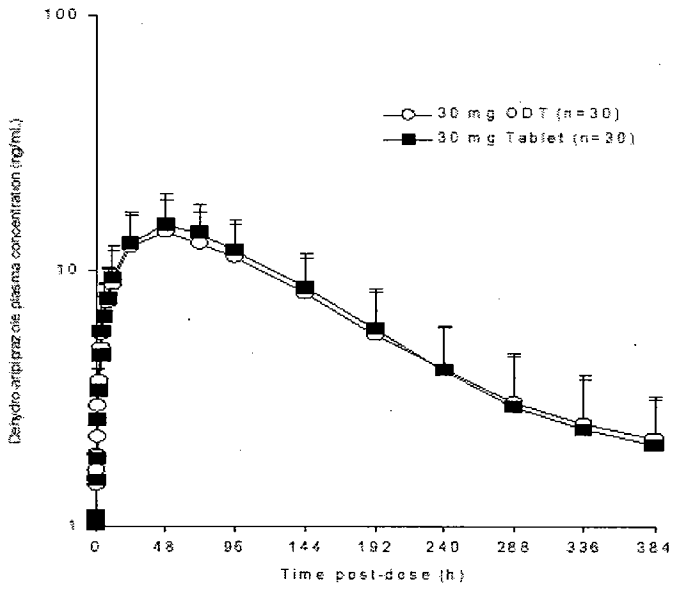
Summary of Statistical Analysis Results for Aripiprazole Cmax and AUC (n=30)

Parameter	Adjusted Geometric Means (Intra-subject CV%)		Ratio of 30 mg ODT: 30 mg Tablet (Adjusted Geometric Means)	
	A: 30 mg Tablet	B: 30 mg ODT	Pt. Estimate of Ratio B:A	90% CI for Ratio
Cmax (ng/mL)	101.6 (27.6)	104.9 (12.3)	1.03	(0.951, 1.121)
AUC(0-T) (ng*h/mL)	5702 (17.1)	5749 (14.7)	1.01	(0.938, 1.084)
AUC(∞) (ng*h/mL)	5922 (17.4)	5962 (14.5)	1.01	(0.938, 1.081)

Cmax, AUC(∞), and AUC(0-T), all satisfied the criteria for bioequivalence of the two aripiprazole formulations. For Cmax, the geometric mean of aripiprazole following an ODT formulation was 3% higher than that of aripiprazole when given as 30 mg CT. For AUC(∞) and AUC(0-T), the geometric means of the ODT aripiprazole formulation were 1% higher than that for aripiprazole given as 30 mg CT. The intra-subject C.V.s for AUC(INF), and AUC(0-T) following the ODT formulation were somewhat lower than those following the CT. The Cmax values following the ODT formulation were half as variable compared to the Cmax values following the 30 mg CT. The median Tmax of aripiprazole occurred one hour later following the 30 mg ODT (4 h) as compared to the 30 mg CT (3 h). Mean T ½ was comparable and only 4 h shorter following the ODT formulation (71 h) as compared to the 30 mg CT (75 h). There were no statistically significant sequence or period effects for any parameter or carryover effect for the AUC(∞) (or AUC(0-T)).

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

Mean (plus S.D.) Plasma Concentration-Time Profiles for Dehydro-Aripiprazole Following Dosing with 30 mg Aripiprazole ODT and CT Formulations



Summary Statistics for Dehydro-Aripiprazole Pharmacokinetic Parameters

Aripiprazole Treatment	Pharmacokinetic Parameter		
	Cmax (ng/mL) Geo. Mean (CV%)	AUC (0-t) (ng*h/mL) Geo. Mean (CV%)	Tmax (h) Median (min, max)
A: 30 mg CT (n=43)	14.4 (23)	2465 (24)	48 (24, 96)
B: 30 mg ODT (n=45)	15.0 (27)	2500 (28)	48 (24,192)

The geometric means of Cmax and AUC(0-T) of dehydro-aripiprazole after the 30 mg ODT formulation treatment were very similar in value to those following the 30 mg CT. The median Tmax of dehydro-aripiprazole was 48 hours for both aripiprazole tablet formulations.

Safety Summary: One hundred-eleven (111) unique AEs were reported in 34 of 48 subjects (71%) enrolled in this study. Fifty-three (53) AEs were reported in 17 of 40 subjects (42.5%) who received the 30 mg CT, 58 AEs were reported in 17 of 40 subjects (42.5%) who received the 30 mg ODT. All AEs were considered by the Investigator to be mild or moderate in intensity. The Investigator considered 16 AEs (16/111, 14.4%) to be unrelated to study drug. Eighty-four (84) AEs (75.7%) were considered to be possibly related to study drug, 11 AEs (9.9%) were considered to be not likely related to study drug, and no AEs (0%) were considered probably related to study drug. All AEs (111/111, 100%) resolved prior to subjects' discharge from the

study. A listing of the reported adverse events are provided in the attachments. There were no deaths or SAEs reported in this study. The sponsor reported that the frequencies of AEs described by a specific primary term were comparable between the two treatments except that lightheadedness was reported by 7 (17.5%) subjects receiving the ODT and only 3 (7.5%) subjects who received the CT.

The sponsor reported that the most frequently reported Treatment-Emergent AEs in this study were emesis (vomiting), lightheadedness, sweating, nausea, insomnia, vasodilation, and asthenia reported as events in a total of 60 subjects (28 subjects in the 30 mg CT group, 32 subjects in the 30 mg ODT group). All events of emesis, lightheadedness, sweating, asthenia, nausea, insomnia, and vasodilation were of mild or moderate intensity. Emesis, lightheadedness, sweating, asthenia, nausea, insomnia, and vasodilation were reported to be possibly or unrelated to study drug. The frequency of these AEs was similar for both formulations except lightheadedness was reported by 7 subjects who received the ODT formulation and only 3 subjects who received the CT. None of these AEs led to discontinuation from study therapy. None of these AEs led to discontinuation from study therapy. The sponsor reported that one (1) subject experienced a non-serious adverse event (mild pharyngitis) that led to discontinuation from the study. Twelve (12) subjects vomited after receiving study medication in Period 1. As no pharmacokinetic data would be available from these subjects, they were discontinued from the study. The sponsor reported 7 vital sign abnormalities in 3 subjects in this study that were considered clinically significant by the Investigator. One (1) subject experienced an elevated body temperature thought to be secondary to pharyngitis and was discontinued from the study. The other abnormalities did not cause discontinuation from the study.

Summary of Pharmacokinetics: The 30 mg ODT and 30 mg CT were bioequivalent. On the basis of their bioequivalence of aripiprazole, there is unlikely to be any substantial difference in the clinical efficacy and tolerability of the 30 mg ODT formulation and 30 mg CT. These two formulations can be used interchangeably. The median Tmax value for the 30 mg ODT formulation (4 h) was one hour later than the median Tmax observed for the 30 mg commercial tablet (3 h). However, the ranges of the Tmax values were the same for both formulations (1.5 to 12.0 h), and there appeared to be little difference in the Tmax between the two formulations. The mean T ½ values were similar for both formulations (75 and 71 h for the 30 mg CT and ODT formulation, respectively). The intra-subject variability in aripiprazole Cmax was lower for the ODT formulation than the CT (12.3% and 27.6% C.V., respectively), while intra-subject variability in aripiprazole AUC(∞) was similar between the formulations (14.5% and 17.4% C.V., respectively).

Frequent early blood collection time point sampling was incorporated into this study to examine for the potential for buccal absorption of aripiprazole from the ODT formulation which breaks up into small particles once placed in the mouth. An examination of the aripiprazole plasma concentrations at these early blood collection time-points (< 2 h post-dose) revealed that there was effectively no difference in the plasma concentration-time profile between the two formulations. Aripiprazole plasma concentrations were first observed between 0.1667 to 2 h post-dose (nominal collection times) for both the 30 mg CT and 30 mg ODT formulation. This suggested that buccal absorption of aripiprazole from the ODT formulation, if any, was not substantial. No formal comparative analysis was carried out on the pharmacokinetic parameters for the active metabolite dehydro-aripiprazole. The pharmacokinetic parameters of dehydro-aripiprazole were comparable between the 30 mg ODT formulation and 30 mg CT, consistent with the bioequivalence of parent aripiprazole. The values for dehydro-aripiprazole pharmacokinetic parameters were similar to those observed in previous clinical studies of the 30 mg CT.

Sponsor's conclusions: The 30 mg ODT formulation and 30 mg CT were bioequivalent with respect to aripiprazole Cmax and AUC(∞), with point estimate (90% C.I.) values for the ratio of ODT to CT adjusted geometric means of 1.03 (0.95, 1.12) and 1.01 (0.94, 1.08), respectively. The aripiprazole 30 mg ODT and 30 mg CT formulations can be used interchangeably. The adverse events reported in this study are similar to those reported in prior studies of aripiprazole in healthy subjects.

Reviewer's conclusions: The reviewer agrees with the sponsor's conclusions.

PROTOCOL: CN138-067

TABLE S.11.2.1G: SUMMARY STATISTICS FOR BMS-337039 Cmax by Sequence and Period

Treatment Sequence	STATISTIC	Cmax Period 1	Cmax Period 2	Cmax Period 3
ABB	N	15	15	15
	MEAN	102.32	104.22	98.50
	S.D.	20.04	19.24	22.63
	GEO.MEAN	100.52	102.50	96.21
	C.V.	19.58	18.46	22.97
	MEDIAN	98.50	105.49	98.96
	MIN	76.84	67.73	66.17
	MAX	139.76	133.42	149.99
BAA	N	15	15	13
	MEAN	116.60	99.10	116.72
	S.D.	28.62	25.06	24.42
	GEO.MEAN	112.43	95.87	114.30
	C.V.	24.55	25.28	20.92
	MEDIAN	109.28	97.36	110.38
	MIN	44.92	52.93	74.92
	MAX	157.02	135.02	155.16

Treatment Codes: A: Ari 30mg Commercial Tablet, B: Ari 30mg ODT

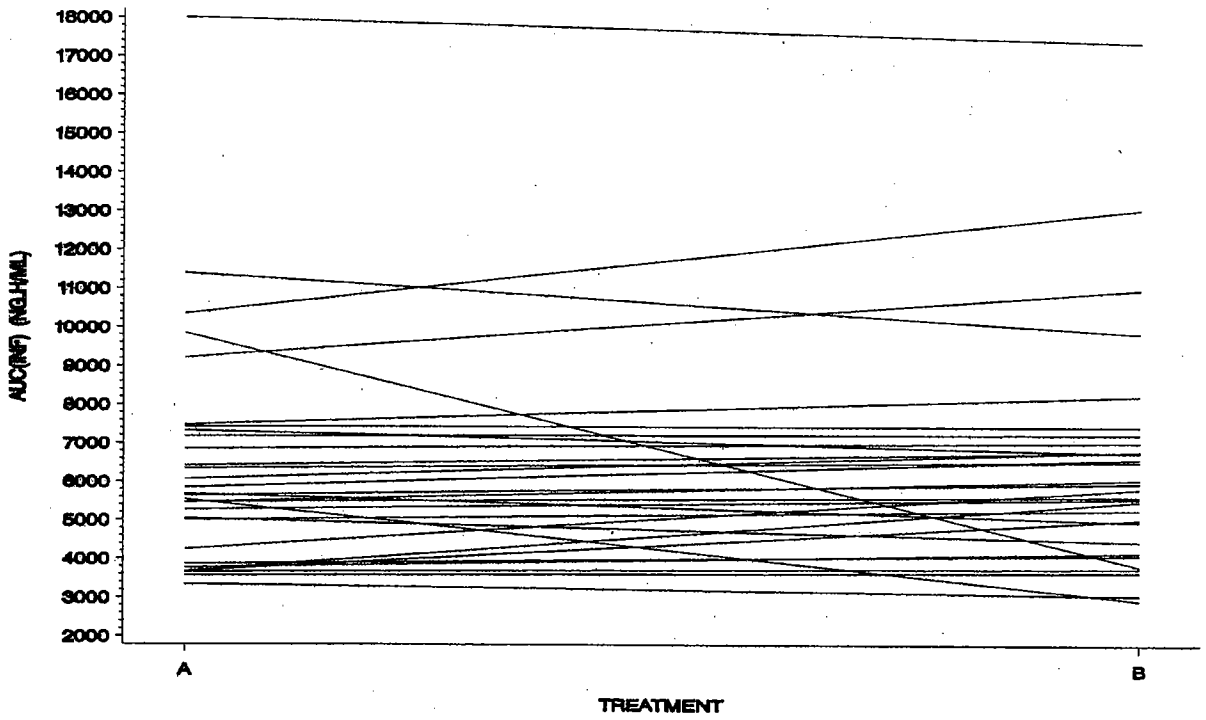
PROTOCOL: CN138067

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

TREATMENT	STATISTIC	CMAX (NG/ML)	AUC(0-T) (NG.H/ML)	TMAX (H)
A	N	43	43	43
	MEAN	14.9	2527	55.8
	S.D.	3.5	613	19.4
	GEO.MEAN	14.4	2465	52.6
	CV%	23	24	35
	MEDIAN	15.1	2463	48.0
	MIN	7.5	1688	24.0
	MAX	22.5	4655	96.3
B	N	45	45	45
	MEAN	15.7	2607	59.8
	S.D.	4.3	722	28.3
	GEO.MEAN	15.0	2500	55.5
	CV%	27	28	47
	MEDIAN	16.0	2614	48.0
	MIN	3.1	777	24.0
	MAX	25.0	5130	192.0

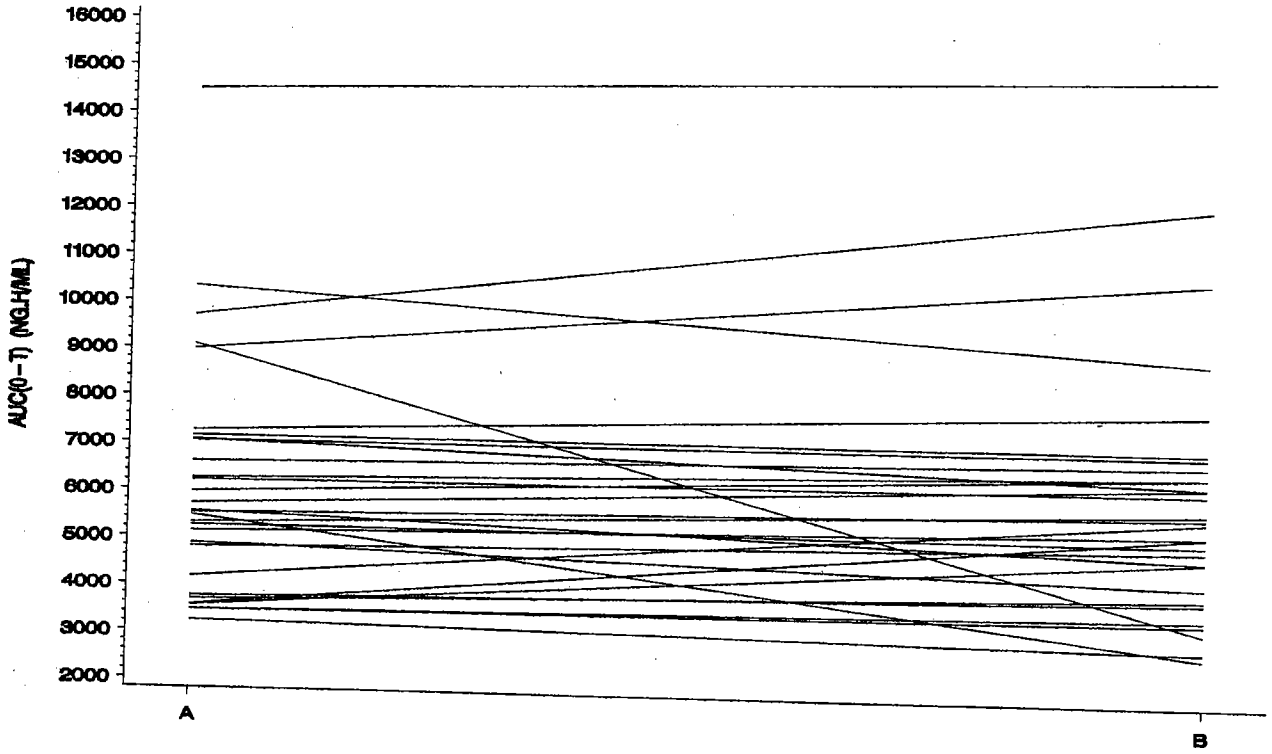
TREATMENT CODES
A = Ari 30mg Tablet
B = Ari 30mg ODT

Figure S.11.2.1I: Plot of Subject AUC(INF) (ng.h/mL) versus Treatment for BMS-337039



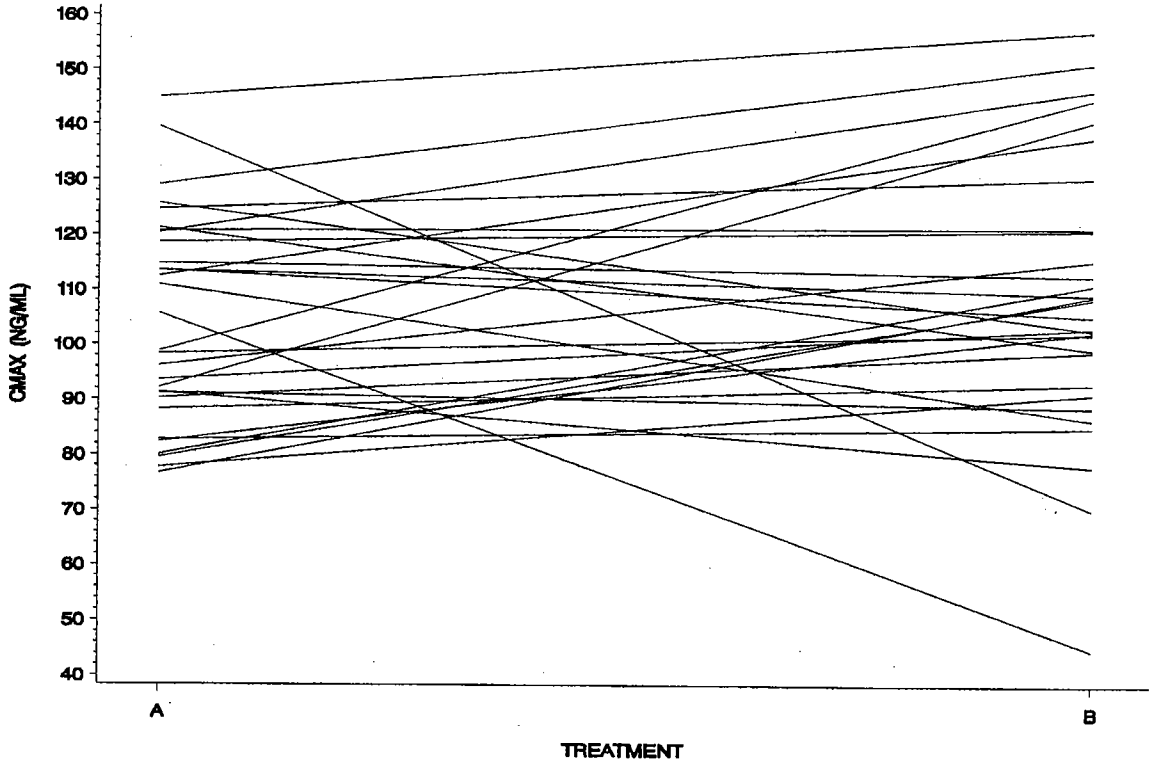
TEST – (B) Ari 30mg ODT
REFERENCE – (A) Ari 30mg Tablet

Figure S.11.2.1E: Plot of Subject AUC(0-T) (ng.h/mL) versus Treatment for BMS-337039



TEST – (B) Arl 30mg ODT
REFERENCE – (A) Arl 30mg Tablet

Figure S.11.2.1A: Plot of Subject Cmax (ng/mL) versus Treatment for BMS-337039



TEST – (B) Arl 30mg ODT
REFERENCE – (A) Arl 30mg Tablet

Each subject's observations from the replicate treatment have been averaged prior to plotting

Table S.11.2.1D: Statistical Analysis of BMS-337039 CMAX (NG/ML)

INDIVIDUAL TREATMENT SUMMARIES

	LOG-TRANSFORMED SCALE			ORIGINAL (UNTRANSFORMED) SCALE	
TREATMENT	ADJ'D MEAN	S.E.	90% C.I.: (LCL, UCL)	ADJ'D MEAN	90% C.I.: (LCL, UCL)
A	4.621	0.039	(4.555, 4.686)	101.585	(95.151, 108.453)
B	4.653	0.039	(4.588, 4.717)	104.889	(98.343, 111.872)

TREATMENT COMPARISONS

	DIFFERENCES ON THE LOG TRANSFORMED SCALE					RATIOS ON THE ORIGINAL SCALE	
TREATMENT COMPARISON	PT. EST.	S.E.	T	P	90% C.I.: (LCL, UCL)	PT. EST.	90% C.I.: (LCL, UCL)
B vs. A	0.032	0.049	0.649	0.519	(-0.051, 0.115)	1.0325	(0.9507, 1.1214)

TREATMENT CODES
A = Ari 30mg Tablet
B = Ari 30mg ODT

Table S.11.2.1D: Statistical Analysis of BMS-337039 CMAX (NG/ML)

INDIVIDUAL TREATMENT SUMMARIES

	LOG-TRANSFORMED SCALE			ORIGINAL (UNTRANSFORMED) SCALE	
TREATMENT	ADJ'D MEAN	S.E.	90% C.I.: (LCL, UCL)	ADJ'D MEAN	90% C.I.: (LCL, UCL)
A	4.621	0.039	(4.555, 4.686)	101.585	(95.151, 108.453)
B	4.653	0.039	(4.588, 4.717)	104.889	(98.343, 111.872)

TREATMENT COMPARISONS

	DIFFERENCES ON THE LOG TRANSFORMED SCALE					RATIOS ON THE ORIGINAL SCALE	
TREATMENT COMPARISON	PT. EST.	S.E.	T	P	90% C.I.: (LCL, UCL)	PT. EST.	90% C.I.: (LCL, UCL)
B vs. A	0.032	0.049	0.649	0.519	(-0.051, 0.115)	1.0325	(0.9507, 1.1214)

TREATMENT CODES
A = Ari 30mg Tablet
B = Ari 30mg ODT

Table S.11.2.1E: Statistical Analysis of BMS-337039 AUC(0-T) (NG.H/ML)

ANALYSIS OF VARIANCE OF LOG-TRANSFORMED DATA WITH CARRYOVER EFFECTS

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F	P
SEQUENCE	1	0.316	0.316	0.836	0.368
SUBJECT(SEQUENCE)	28	10.582	0.378	10.135	0.000
PERIOD	2	0.021	0.010	0.279	0.758
TREATMENT	1	0.001	0.001	0.023	0.880
CARRYOVR	1	0.019	0.019	0.506	0.480
ERROR	54	2.014	0.037		

ANALYSIS OF VARIANCE OF LOG-TRANSFORMED DATA WITHOUT CARRYOVER EFFECTS

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F	P
SEQUENCE	1	0.316	0.316	0.836	0.368
SUBJECT(SEQUENCE)	28	10.582	0.378	10.227	0.000
PERIOD	2	0.021	0.010	0.282	0.756
TREATMENT	1	0.001	0.001	0.031	0.862
ERROR	55	2.033	0.037		

ROOT MEAN SQUARE ERROR = 0.1922

TREATMENT CODES
A = Ari 30mg Tablet
B = Ari 30mg ODT

Table S.11.2.1E: Statistical Analysis of BMS-337039 AUC(0-T) (NG.H/ML)

INDIVIDUAL TREATMENT SUMMARIES

	LOG-TRANSFORMED SCALE			ORIGINAL (UNTRANSFORMED) SCALE	
TREATMENT	ADJ'D MEAN	S.E.	90% C.I.: (LCL, UCL)	ADJ'D MEAN	90% C.I.: (LCL, UCL)
A	8.649	0.069	(8.533, 8.764)	5701.778	(5081.753, 6397.454)
B	8.657	0.068	(8.542, 8.771)	5749.410	(5126.876, 6447.536)

TREATMENT COMPARISONS

	DIFFERENCES ON THE LOG TRANSFORMED SCALE					RATIOS ON THE ORIGINAL SCALE	
TREATMENT COMPARISON	PT. EST.	S.E.	T	P	90% C.I.: (LCL, UCL)	PT. EST.	90% C.I.: (LCL, UCL)
B vs. A	0.008	0.043	0.192	0.848	(-0.064, 0.081)	1.0084	(0.9378, 1.0842)

TREATMENT CODES
A = Ari 30mg Tablet
B = Ari 30mg ODT

Table S.11.2.1F: Statistical Analysis of BMS-337039 AUC(INF) (NG.H/ML)

ANALYSIS OF VARIANCE OF LOG-TRANSFORMED DATA WITH CARRYOVER EFFECTS

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F	P
SEQUENCE	1	0.380	0.380	0.900	0.351
SUBJECT(SEQUENCE)	28	11.833	0.423	11.897	0.000
PERIOD	2	0.026	0.013	0.371	0.692
TREATMENT	1	0.001	0.001	0.014	0.906
CARRYOVR	1	0.020	0.020	0.560	0.457
ERROR	54	1.918	0.036		

ANALYSIS OF VARIANCE OF LOG-TRANSFORMED DATA WITHOUT CARRYOVER EFFECTS

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F	P
SEQUENCE	1	0.380	0.380	0.900	0.351
SUBJECT(SEQUENCE)	28	11.833	0.423	11.993	0.000
PERIOD	2	0.026	0.013	0.374	0.689
TREATMENT	1	0.001	0.001	0.021	0.886
ERROR	55	1.938	0.035		

ROOT MEAN SQUARE ERROR = 0.1877

TREATMENT CODES
A = Ari 30mg Tablet
B = Ari 30mg ODT

Table S.11.2.1F: Statistical Analysis of BMS-337039 AUC(INF) (NG.H/ML)

INDIVIDUAL TREATMENT SUMMARIES

	LOG-TRANSFORMED SCALE			ORIGINAL (UNTRANSFORMED) SCALE	
TREATMENT	ADJ'D MEAN	S.E.	90% C.I.: (LCL, UCL)	ADJ'D MEAN	90% C.I.: (LCL, UCL)
A	8.686	0.072	(8.566, 8.807)	5922.270	(5248.771, 6682.191)
B	8.693	0.072	(8.573, 8.813)	5961.765	(5286.295, 6723.546)

TREATMENT COMPARISONS

	DIFFERENCES ON THE LOG TRANSFORMED SCALE					RATIOS ON THE ORIGINAL SCALE	
TREATMENT COMPARISON	PT. EST.	S.E.	T	P	90% C.I.: (LCL, UCL)	PT. EST.	90% C.I.: (LCL, UCL)
B vs. A	0.007	0.042	0.157	0.876	(-0.064, 0.077)	1.0067	(0.9379, 1.0805)

TREATMENT CODES
A = Ari 30mg Tablet
B = Ari 30mg ODT

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

TREATMENT	STATISTIC	CMAX (NG/ML)	AUC(0-T) (NG.H/ML)	TMAX (H)
A	N	43	43	43
	MEAN	14.9	2527	55.8
	S.D.	3.5	613	19.4
	GEO.MEAN	14.4	2465	52.6
	CV%	23	24	35
	MEDIAN	15.1	2463	48.0
	MIN	7.5	1688	24.0
	MAX	22.5	4655	96.3
B	N	45	45	45
	MEAN	15.7	2607	59.8
	S.D.	4.3	722	28.3
	GEO.MEAN	15.0	2500	55.5
	CV%	27	28	47
	MEDIAN	16.0	2614	48.0
	MIN	3.1	777	24.0
	MAX	25.0	5130	192.0

TREATMENT CODES
A = Ari 30mg Tablet
B = Ari 30mg ODT

Table 12.1.1: Number (Percentage) of Subjects with Treatment-Emergent Adverse or Investigator-Identified Laboratory Events, by Body System, Primary Term, and Treatment

Body System Primary Term	Treatment Number (Percentage) of Subjects	
	Aripiprazole 30 mg CT (n = 40)	Aripiprazole 30 mg ODT n = (40)
	n (%)	n (%)
Body as a whole		
Asthenia	4 (10.0)	1 (2.5)
Chills	1 (2.5)	1 (2.5)
Edema Peripheral	1 (2.5)	0
Fever	1 (2.5)	0
Headache	2 (5.0)	2 (5.0)
Pain	1 (2.5)	0
Pain Abdomen	1 (2.5)	0
Pain Arm Left	1 (2.5)	0
Pain Back	1 (2.5)	1 (2.5)
Pain Chest	1 (2.5)	0
Pain Extremity	1 (2.5)	1 (2.5)
Total Events:	**15**	**6**
Total Subjects:	**9 (22.5)**	**5 (12.5)**

Table 12.1.1: **Number (Percentage) of Subjects with Treatment-Emergent Adverse or Investigator-Identified Laboratory Events, by Body System, Primary Term, and Treatment**

Body System Primary Term	Treatment Number (Percentage) of Subjects	
	Aripiprazole 30 mg CT (n = 40)	**Aripiprazole 30 mg ODT n = (40)**
Cardiovascular System		
Hypotension	1 (2.5)	0
Pallor	3 (7.5)	0
Palpitation	1 (2.5)	1 (2.5)
Syncope	1 (2.5)	2 (5.0)
Total Events:	**6**	**3**
Total Subjects:	**4 (10.0)**	**3 (7.5)**
Digestive System		
Diarrhea	0	1 (2.5)
Disorder Dental	1 (2.5)	0
Disorder Mouth	0	1 (2.5)
Dry mouth	0	1 (2.5)
Dyspepsia	1 (2.5)	2 (5.0)
Gingivitis	0	1 (2.5)
Nausea	5 (12.5)	4 (10.0)
Vomiting	6 (15.0)	7 (17.5)
Total Events:	**13**	**17**
Total Subjects:	**9 (22.5)**	**11 (27.5)**
Musculoskeletal System		
Myalgia	2 (5.0)	3 (7.5)
Total Events:	**2**	**3**
Total Subjects:	**2 (5.0)**	**3 (3.75)**
Nervous System		
Anxiety	1 (2.5)	1 (2.5)
Emotional Liability	0	1 (2.5)
Impotence	0	1 (2.5)
Insomnia	3 (7.5)	4 (10.0)
Lightheadedness	3 (7.5)	7 (17.5)
Somnolence	0	1 (2.5)
Vasodilation	2 (5.0)	4 (10.0)
Total Events:	**9**	**19**
Total Subjects:	**6 (15.0)**	**12 (30.0)**

Table 12.1.1: **Number (Percentage) of Subjects with Treatment-Emergent Adverse or Investigator-Identified Laboratory Events, by Body System, Primary Term, and Treatment**

Body System Primary Term	Treatment Number (Percentage) of Subjects	
	Aripiprazole 30 mg CT (n = 40)	**Aripiprazole 30 mg ODT n = (40)**
Respiratory System		
Coughing	1 (2.5)	1 (2.5)
Pharyngitis	2(5.0)	2(5.0)
Rhinitis	0	1 (2.5)
Total Events:	**3**	**4**
Total Subjects:	**3 (7.5)**	**2 (5.0)**
Skin/Appendages		
Sweating	5 (12.5)	5 (12.5)
Total Events:	**5**	**5**
Total Subjects:	**5 (12.5)**	**5 (12.5)**
Special Senses:		
Blurred vision	0	1 (2.5)
Total Events:	**0**	**1**
Total Subjects	**0**	**1 (2.5)**
OVERALL TOTAL EVENTS[a]	**53**	**58**
OVERALL TOTAL SUBJECTS	**17 (42.5)**	**17 (42.5)**

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26 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 8

Request for Waiver of In Vivo Bioequivalence Studies for Lower Strengths of Orally Disintegrating Tablets

The sponsor is requesting a waiver of *in vivo* bioequivalence studies for lower strength (i.e., 20, 15, and 10 mg) ODTs is being requested. Bioequivalence between the highest (30 mg) strength of the ODT formulation proposed for marketing and the commercial tablet (30 mg) was established. The sponsor's rationale for exemption of bioequivalence studies for the lower strength [redacted] ODTs, and the appropriate data supporting the claim, are presented below.

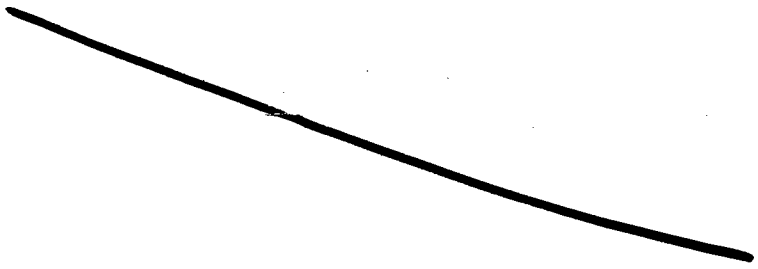
1) The qualitative composition of the different strengths of ODT formulation is the same. Except for differences in coloring agents, the excipient composition and proportion of aripiprazole to each of the therapeutically inert ingredients in the 10, 15, and 20 mg aripiprazole ODT formulations are identical to the highest dose strength (30 mg) ODT formulation.

[redacted]

The composition of the various aripiprazole ODT strengths is provided in the attachments.

2) The clinical pharmacokinetics of aripiprazole administered in conventional tablets up to the highest therapeutic dose of 30 mg have previously been demonstrated to be linear and dose-proportional

3) If the 10, 15, and 20 mg aripiprazole ODT formulations have similar dissolution characteristics to the 30 mg aripiprazole ODT formulation, which has been demonstrated to be bioequivalent to the 30 mg aripiprazole tablet formulation, then it follows that the 10, 15, and 20 mg aripiprazole ODT formulations will also have *in vivo* bioequivalence to their respective strength tablets.



. Overall, the dissolution profiles of the 10, 15, and 20 mg strength ODTs were similar to the reference 30 mg strength formulation in all 3 dissolution media (i.e., at pH 1.2, 4.0, and 6.8) [redacted]

Reviewer comments: The reviewer agrees with the sponsor's rationale for requesting waiver of bioequivalence studies [redacted]. The reviewer recommends that waiver of bioequivalence studies for the 10, 15, 20 mg ODT be granted.

Table 2.1: Compositions of Aripiprazole [redacted] 10, 15, 20 and 30 mg Orally Disintegrating Tablet (ODT) Formulations

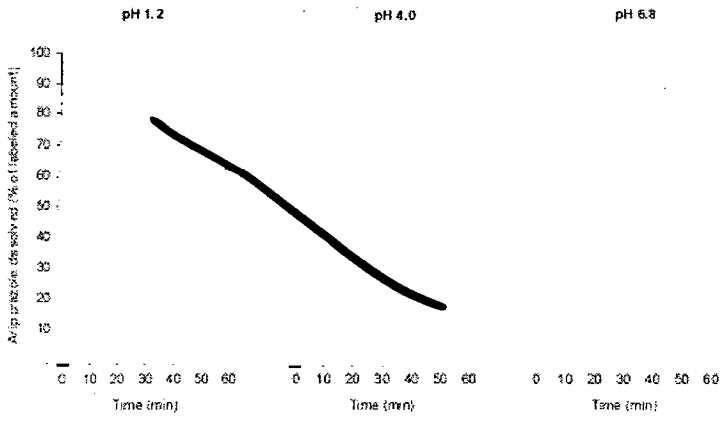
Ingredient	[redacted]	10-mg ODT		15-mg ODT		20-mg ODT		30-mg ODT	
		mg	%w/w	mg	%w/w	mg	%w/w	mg	%w/w
Aripiprazole		10.00	10.00	15.00	10.00	20.00	10.00	30.00	10.00
Calcium Silicate (NF)									
Croscarmellose Sodium (NF)									
Crospovidone (NF)									
Silicon Dioxide (NF)									
Xylitol (NF)									
Microcrystalline Cellulose[a] (NF)									
Microcrystalline Cellulose[b] (NF)									
Aspartame (NF)									
Acesulfame Potassium (EP)									
Creme de Vanilla (Natural & Artificial Flavors)									
Tartaric Acid (NF)									
Magnesium Stearate (NF)									
FD&C Blue No. 2 Aluminum Lake									
Red Ferric Oxide (NF)									
Yellow Ferric Oxide (NF)									
Total Tablet Weight (mg)		100		150		200		300	

Source: Module 3, Item 4 Chemistry, Manufacturing and Controls, Section 3.2.P.1 Description and Composition of the Drug Product.

[redacted]

EP = European Pharmacopeia, NF = National formulary

Mean aripiprazole dissolution vs. time profiles for 10, 15, 20 and 30 mg ODT formulations at pH 1.2, 4.0 and 6.8 [redacted] (50 rpm)



[redacted]

Best Possible Co[redacted]

2 Page(s) Withheld

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_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 9

4.4. 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	**21-729**	**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 disintegrating tablet**
		Dosing Regimen	**10 – 30 mg/day**
Date of Submission	**12/22/03**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**8/22/04**	**Sponsor**	**Otsuka/BMS**
PDUFA Due Date	**10/22/04**	**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:	3	3	2	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
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 -	[redacted]			
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	3			
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X		X	
(IVIVC):				
Bio-wavier request	X		X	
1 BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]		4	

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	Reasons if the application is not 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. As a Phase IV commitment, the sponsor agreed to conduct a food study with the 30 mg conventional immediate release tablet. The sponsor is requested to provide this study report latest by March 2004 with the dissolution information that is scheduled to be submitted at that time
QBR questions (key issues to be considered)	**1. Is the oral disintegrating tablet (ODT) [redacted] 30 mg bioequivalent to the oral tablets?** **2. Is there sufficient justification for the waiver of in vivo bioequivalent studies for 10, 15, 20 mg ODT?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-729, HFD-850 (Electronic Entry or Lee), HFD-120, HFD-860 (Mehta, Sahajwalla, Baweja, KumiK), CDR (B. Murphy)

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/s/

Kofi Kumi
9/23/04 03:20:57 PM
BIOPHARMACEUTICS

Sally Yasuda
9/23/04 03:29:45 PM
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