

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-866

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

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Abilify® Aripiprazole

NDA: 21866

FORMULATION: IM Injection

APPLICANT: BMS/Otsuka

PRIMARY REVIEWER: Andre Jackson

TYPE: NDA

STRENGTH: 7.5 mg/ml

Submission Dates: November 29, 2005

INDICATIONS: Agitation Associated with Schizophrenia or Bipolar Mania
Generic Name: Abilify

EXECUTIVE SUMMARY

Abilify was submitted for use as an intramuscular injection for the treatment of patients with agitation associated with schizophrenia and bipolar mania.

The following studies were done by the firm to support their Clinical data.

Study Number	Type of Study Start of Clinical Study
CN138016	Three-way crossover study of the absolute bioavailability of aripiprazole 5 mg commercial tablet and aripiprazole 5 mg im injection with reference to 2 mg iv infusion in healthy subjects
CN138132	A double-blind, randomized study to evaluate pharmacodynamic and pharmacokinetic interactions between intramuscular aripiprazole and intramuscular lorazepam when co-administered in healthy subjects
CN138017	Pharmacokinetics and pharmacodynamics of multiple intramuscular doses of 1 to 30 mg aripiprazole in patients with schizophrenia.
CN138050	Assessment of the relationship between aripiprazole and dehydro-aripiprazole plasma concentrations and qtc changes from baseline in study cn138050

The Absolute Bioavailability of the dose normalized AUCinf data indicated the absolute BA was 0.87 for the tablet and 1.01 for the IM formulation

The results of the co-administration of IM aripiprazole (15 mg) and IM lorazepam (2 mg) had no effect on the pharmacokinetics of either compound.

Based on the results of a power model analysis, aripiprazole was dose proportional over the range of 1 to 45 mg on day1 and 1-30 mg on day 4 following QD dosing.

The 95% confidence intervals for the slopes of the regression analyses of changes from baseline in QTcN, QTcF, and QTcB for both paper and ambulatory 12-lead ECG recordings all included zero which indicates that aripiprazole does not result in QTc interval prolongation.

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QUESTION BASED REVIEW

WHAT IS THE ABSOLUTE BIOAVAILABILITY OF THE IM FORMULATION COMPARED TO THE IV FORMULATION?

Table 11.3.1B: Summary of Statistical Analysis Results for Dose-Normalized Aripiprazole Pharmacokinetic Parameters

Pharmacokinetic Parameter	Formulation	Adjusted Geom. Mean	Ratio	Point Estimate (90% C.I.)
AUC(INF) (ng·h/mL)	A	305	—	—
	B	263	B/A	0.8663 (0.7928, 0.9463)
	C	309	C/A	1.0105 (0.9277, 1.1007)
AUC(0-T) (ng·h/mL)	A	223	—	—
	B	227	B/A	1.0202 (0.9335, 1.1149)
	C	266	C/A	1.1953 (1.0972, 1.3021)
C _{max} (ng/mL)	B	3.9	—	—
	C	4.64	C/B	1.1897 (0.9746, 1.4522)
AUC(0-2HR) (ng·h/mL)	B	3.37	—	—
	C	6.42	C/B	1.9037 (1.5373, 2.3575)

CN138-016

Source: Supplemental Tables S.11.3.1B-G

Formulation codes: A = Aripiprazole 2 mg IV reference

B = Aripiprazole 3 mg tablet

C = Aripiprazole 5 mg IM

It was 1.01 for the IM vs the IV solution and 0.86 for the tablet vs the IV solution.

ARE THE PHARMACOKINETICS OF ARIPIPRAZOLE LINEAR?

A study conducted in 26 male and 6 female schizophrenic patients ages 24-50 years gave the following results:

Table 1: Dose Proportionality Results for Aripiprazole (BMS-337039)

Study Day	Parameter	Estimated β	Lower 95% CI	Upper 95% CI
1	C _{max}	1.05	0.90	1.20
1	AUC(TAU)	1.06	0.96	1.15
4	C _{max}	1.04	0.92	1.17
4	AUC(TAU)	1.06	0.98	1.15

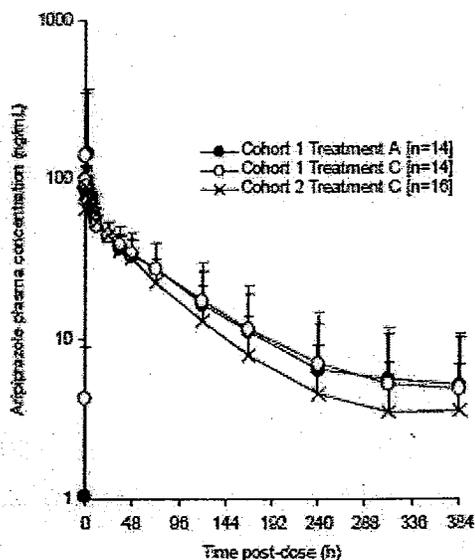
Source: Supplemental Table S1

In all cases, the estimated values of β were within 10% of 1.0, and confidence intervals for β always contained the value 1.0. Thus, there was no evidence that suggests there was a departure from dose-proportionality for over the dose range studied in CN138017 (1 to 45 mg on Day 1 or on Day 4 following 1 to 30 mg QD doses).

DOES ARIPIPRAZOLE INTERACT WITH LORAZEPAM?

A study done in 40 subjects under 60 years of age (35 males and 5 females) showed that aripiprazole does not effect lorezapam pharmacokinetics and that lorazepam does not have any effect on aripiprazole plasma concentrations.

Figure 11.2.1: Mean (+ S.D.) Plasma Concentration-time Profiles for Aripiprazole Following a Single 15 mg IM Dose of Aripiprazole With and Without the Co-administration of a Single 2 mg IM Dose of Lorazepam



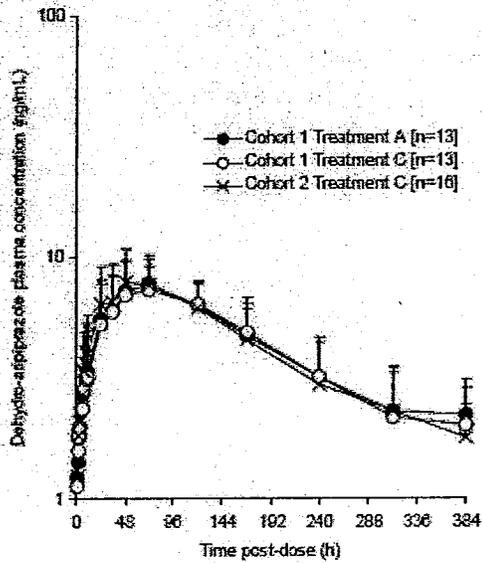
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Notes:

- Treatment A = Single 15 mg IM dose of aripiprazole + IM lorazepam placebo
- Treatment C = Single 15 mg IM dose of aripiprazole + single 2 mg IM dose of lorazepam
- Cohort 1 received treatments A and C, Cohort 2 received treatments B (single 2 mg IM dose of lorazepam + IM aripiprazole placebo) and C

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Figure 11.2.2: Mean (+ S.D.) Plasma Concentration-time Profiles for Dehydro-aripiprazole Following a Single 15 mg IM Dose of Aripiprazole With and Without the Co-administration of a Single 2 mg IM Dose of Lorazepam



CN138133

Source: Supplemental Table S.11.2.2A

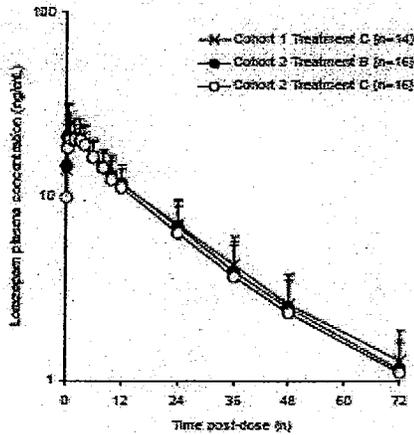
Notes:

- Treatment A = Single 15 mg IM dose of aripiprazole+ IM lorazepam placebo
- Treatment C = Single 15 mg IM dose of aripiprazole+ single 2 mg IM dose of lorazepam
- Cohort 1 received treatments A and C. Cohort 2 received treatments B (single 2 mg IM dose of lorazepam + IM aripiprazole placebo) and C

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Figure 11.2.3: Mean (+ S.D.) Plasma Concentration-time Profiles for Lorazepam Following a Single 2 mg IM Dose of Lorazepam With and Without the Co-administration of a Single 15 mg IM Dose of Aripiprazole



CN138133

Source: Supplemental Table S.11.2.3.A

Notes:

- Treatment B = Single 2 mg IM dose of lorazepam + IM aripiprazole placebo
- Treatment C = Single 15 mg IM dose of aripiprazole + single 2 mg IM dose of lorazepam
- Cohort 1 received treatments A (single 15 mg IM dose of aripiprazole + IM lorazepam placebo) and C.
- Cohort 2 received treatments B and C.
- Only data from subjects included in the pharmacokinetic parameters summary statistics are presented above (see Section 8.2)
- LLQ = 0.1 ng/mL
- <LLQ or missing data were treated as "missing" in the calculation of mean and SD values

The Co-administration of IM aripiprazole (15 mg) and IM lorazepam (2 mg) had no effect on the pharmacokinetics of either compound.

WERE THERE ANY EFFECT OF IM ARIPIPRAZOLE ON CARDIAC REPOLARIZATION (I.E., QT) ?

A double-blinded, randomized, dose-ranging, multicenter study comparing 4 doses of IM aripiprazole (1 mg, 5 mg, 10 mg and 15 mg) and haloperidol to placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia, was used for QT data analysis. Maximum doses of 3 to 45 mg intramuscular doses of aripiprazole (administered in 1 to 3 doses was administered within a 24 h period).

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Table 11.2: Results of Linear Regression Analyses of QTc Changes from Baseline (Ambulatory 12-Lead ECGs) on Aripiprazole Plasma Concentrations

Δ QTc (msec)	Aripiprazole C _p (ng/mL)				
	n ^a	Intercept		Slope	
		Point Estimate	95% C.I.	Point Estimate	95% C.I.
Δ QTcN	25	0.79	(-8.59, 10.16)	0.0659	(-0.2211, 0.3528)
Δ QTcF	25	-0.30	(-9.19, 8.59)	0.0656	(-0.2066, 0.3378)
Δ QTcB	25	3.94	(-8.45, 16.33)	0.0788	(-0.3003, 0.4579)

CN138050

Source: Appendix 11.2C

Note: Aripiprazole plasma concentrations < LLQ were replaced by 0.5-LLQ where LLQ=1 ng/mL

^a n is the number of data pairs in the analyses

The results show based upon the 95% CI for the slope there is approximately a 0.07 msec change in QTc with a 1 unit increase in concentration and the CI contain zero meaning that there is a minimal effect of aripiprazole on QTc.

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SIGNATURES

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DETAILED STUDY REPORTS

Protocol No.: CN138-016

OPEN-LABEL, RANDOMIZED, THREE-WAY CROSSOVER STUDY OF THE ABSOLUTE BIOAVAILABILITY OF ARIPIPRAZOLE 5 MG COMMERCIAL TABLET AND ARIPIPRAZOLE 5 MG IM INJECTION WITH REFERENCE TO 2 MG IV INFUSION IN HEALTHY SUBJECTS

OBJECTIVES

The primary objective of this study was to assess absolute bioavailability of the 5 mg aripiprazole tablet formulation and 5 mg aripiprazole IM formulation with reference to 2 mg aripiprazole IV infusion.

The secondary objectives of this study were: 1) to assess the safety and tolerability of aripiprazole following oral, IV and IM administration; 2) to assess the pharmacokinetics of aripiprazole's metabolite, OPC-14857 (BMS-337044).

METHODS

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This was an open-label, randomized, three-period, three-treatment, crossover study balanced for carryover effects in healthy subjects. Eighteen subjects were enrolled to ensure that 12 subjects complete the study. Subjects underwent screening evaluations to determine eligibility within 21 days prior to study enrollment. Subjects were admitted to the clinical facility the evening prior to dosing (Day -1) for each period. During Period 1, subjects were randomized to one of six sequences which included Treatment A, Treatment B, and Treatment C. Treatment A was a single 2 mg IV infusion of aripiprazole solution, Treatment B was a single 5 mg oral dose of aripiprazole (commercial tablet formulation), and Treatment C was a single 5 mg IM dose of aripiprazole solution. There was a washout period of at least 21 days between each dose. For each treatment period, subjects were confined in the clinical facility until 48 hours post-dose. Blood samples were collected for pharmacokinetic analysis up to 384 hours (17 days) post-dose. Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations were performed at selected times throughout the study. Subjects were closely monitored for adverse events throughout the study.

Treatment A: Aripiprazole 2 mg parenteral solution for IM injection, given intravenously.

Treatment B: Aripiprazole 5 mg commercial tablet for oral administration

Treatment C: Aripiprazole 5 mg parenteral solution for IM injection, given intramuscularly into the gluteus maximus muscle.

All subjects fasted for at least 10 h prior to dosing.

Treatment A was delivered as a 15 minute IV infusion through an intravenous catheter. For the infusion, micro-infusion pumps fitted with low dead-space tubing and a 3 mL dosing syringe were used. At the time of dosing, the total vial volume of 2 mL 2 mg/mL aripiprazole IM solution was withdrawn into the dosing syringe. The syringe was fitted to the infusion pump and a total volume of 1 mL (i.e., 2 mg) was delivered over 15 minutes at a speed of 4 mL/h.

For Treatment B, a single 5 mg oral tablet was administered with 240 mL of water.

Treatment C was administered as a single 0.67 mL injection (using 7.5 mg/mL stock concentration) into gluteus maximus muscle.

The time of dose administration was called "0" hour.

SUBJECT DEMOGRAPHICS

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Characteristic		Enrolled Population (N = 18)
Age, years	Mean	35
	SD	6.7
	Range	20-44
Gender, n (%)	Male	17 (94%)
	Female	1 (6%)
Race, n (%)	White	4 (22%)
	Black	14 (78%)
Weight, kg	Mean	80.0
	SD	11.49
	Range	59.0-98.0
Height, cm	Mean	176.7
	SD	9.24
	Range	152.0-193.0
Body Mass Index	Mean	25.5
	SD	2.94
	Range	20.0-31.0

PHARMACOKINETIC SAMPLING SCHEDULE

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Table 5.10: Pharmacokinetic Sampling Schedule

Study Day	TIME (RELATIVE TO DOSING)	PK BLOOD SAMPLE
	Hour	
1	0 (pre-dose)	X
	5 min	X ^a
	10 min	X
	30 min	X
	45 min	X ^b
	1 hour	X
	1.5	X
	2	X
	2.5	X
	3	X
	3.5	X
	4	X
	5	X
	6	X
	8	X
	10	X
	12	X
	2	24
3	48	X
4	72	X
5	96	X

Study Day	TIME (RELATIVE TO DOSING)	PK BLOOD SAMPLE
	Hour	
7	144	X
9	193	X
11	240	X
13	288	X
15	336	X
17	384	X

Analyses of Pharmacokinetic Data

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The distributions of aripiprazole and OPC-14857 pharmacokinetic 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}.

To estimate the absolute bioavailabilities of the 5 mg tablet and IM injection formulations to the reference 2 mg IV formulation, analyses of variance were performed on log-transformed dose normalized aripiprazole AUC(INF) and AUC(0-T). The factors in the analyses were sequence group, subject within sequence, period, and formulations. Since subject effects were 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-statistics for the period effects were the ratios of the type I mean squares for period and the mean squares for error. An additional analysis of variance evaluated the significance of first-order treatment carryover effects. 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. In addition, the same analyses were performed to compare dose-normalized aripiprazole C_{max} and AUC(0-2HR) between the tablet and IM formulations. No adjustments were made for multiplicity.

Since OPC-14857 was not well characterized in most of the study subjects for the 2 mg IV formulation, summary statistics for the OPC-14857 pharmacokinetic parameters were not computed for the IV formulation.

ASSAY

Total Storage Time-120 days

Study Number	Start of Clinical Study	End of Clinical Study	Start of Sample Analysis	End of Sample Analysis	Total Storage Time
CN138016	Dec 4, 2000	Feb 15, 2001	Jan 17, 2001	Mar 2, 2001	~120 days

Assay Validation - CN138016

Parameter	BMS-337039 (OPC-14597)	BMS 337044 (OPC-14857)
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection	LC\ Mass Spectrometric \ Mass Spectrometric Detection
Number of Freeze-thaw	3 Cycles (DCN 920010829)	3 Cycles (DCN 920010829)

Benchtop Stability at RT	22 hrs (DCN 920010507)	22 hrs (DCN 920010507)
Long term at -20° C	782 days (DCN 920010507)	782 days (DCN 920010507)
Extraction Recovery		
Low	81.0% (DCN 920010507)	82.4% (DCN 920010507)
High	82.9% (DCN 920010507)	88.2% (DCN 920010507)

Plasma Analysis Results

CN138016

Clinical study began: December 4, 2000

Clinical Study ended: February 15, 2001

Sample analysis began: January 17, 2001

Sample analysis completed: March 2, 2001

Parameter	BMS 337039	BMS 337044
Method	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	1 ng/mL	1 ng/mL
Linearity (Standard curve samples)	1, 2, 10, 50, 100, 150, 200, 225, & 250 ng/mL	1, 2, 10, 50, 100, 150, 200, 225, & 250 ng/mL
Quality Control (QC) Samples	3, 100, & 200 ng/mL	3, 100, & 200 ng/mL
Precision of Standards (%CV)	3.2 to 7.5%	3.3 to 7.1%
Precision of QC Samples (%CV)	Between run: 5.2 to 5.5% Within Run: 3.4 to 6.1% Total Variation: 6.3 to 8.0%	Between run: 3.3 to 7.1% Within Run: 3.0 to 5.9% Total Variation: 5.3 to 9.2%
Accuracy of Standards (%)	-1.0 to 2.6%	-1.1 to 2.7%
Accuracy of QC Samples (%)	-4.7 to -1.3%	-7.0 to -1.7%

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RESULTS

Table S.11.3.1A: Mean Subject Data Plasma Concentration of BMS-337039 (Ng/mL)

A				B				C			
Time	Mean	SD	CV(%)	Time	Mean	SD	CV(%)	Time	Mean	SD	CV(%)
0	<LLQ			0	<LLQ			0	<LLQ		
0.0833	9.093	8.0409	88.4286	0.1667	<LLQ			0.1667	1.24888	7.99018	63.994
0.1667	16.4421	4.8916	29.7706	0.5	1.0967	1.1588	105.663	0.5	210.797	12.6098	59.8196
0.5	10.8484	3.3814	31.1896	1	9.1894	4.1415	450.731	1	200.376	10.5929	52.3631
0.75	9.8739	3.3493	32.8472	1.5	16.4496	6.3403	37.9253	1.5	51.341	10.768	21.0434
1	9.4363	3.2578	34.5341	2	18.1964	5.1628	28.3726	2	202.694	9.8309	48.3999
1.5	9.3564	2.4341	26.0153	2.5	18.1054	4.3146	24.0351	2.5	204.860	8.8757	43.2867
2	8.3056	2.7141	32.1447	3	18.0079	4.0843	22.6817	3	203.328	8.4357	41.4894
2.5	8.19	2.2928	27.9931	3.5	17.9953	4.4042	24.474	3.5	189.379	6.3729	33.6731
3	7.6061	1.9161	24.0601	4	17.6363	4.8604	27.5747	4	184.961	5.5413	29.9567
3.5	7.4814	2.1459	28.9328	4	17.9067	4.9347	27.569	5	180.967	5.1723	28.5826
4	7.3276	2.1683	29.5936	6	16.723	4.733	28.339	6	178.523	4.5723	24.4817
5	6.9982	2.0708	29.5922	8	15.4273	4.4923	29.1192	8	173.414	3.6933	21.3103
6	6.398	1.6964	26.5143	10	13.6908	3.7949	27.8296	10	157.234	3.9216	24.9233
8	6.0479	1.3518	22.1908	12	12.4903	3.4319	27.3967	12	149.339	3.3253	22.2663
10	5.4013	1.7384	32.1846	24	9.8086	2.3394	23.8969	24	11.8389	2.4276	20.3103
12	5.0499	1.6333	32.3668	48	6.9936	2.0481	29.2853	48	8.3467	2.3366	27.9626
24	4.2163	1.3613	29.9194	72	5.3386	1.6234	30.2217	72	6.6889	2.2363	33.5884
48	3.1558	0.8963	28.4017	96	4.2164	1.3166	31.2979	96	4.963	2.0133	40.3597
72	2.5977	0.8644	33.4703	144	2.6456	1.2931	45.5411	144	3.263	1.593	48.5864
96	2.0671	0.8363	40.4763	192	1.7456	1.2337	70.7772	192	2.1942	1.5628	71.1346
144	1.3493	0.7804	57.8288	240	1.3120	0.9637	73.4471	240	1.4349	1.3361	103.581
192	0.8712	0.6007	119.394	288	0.6679	0.9872	147.807	288	0.7191	1.1833	164.839
240	0.3908	0.6039	154.329	336	0.3174	0.7766	190.097	336	0.5408	1.071	196.04
288	0.1429	0.5779	264.636	384	0.3076	0.647	213.889	384	0.3816	0.8951	234.563
336	LLQ										
384	LLQ										

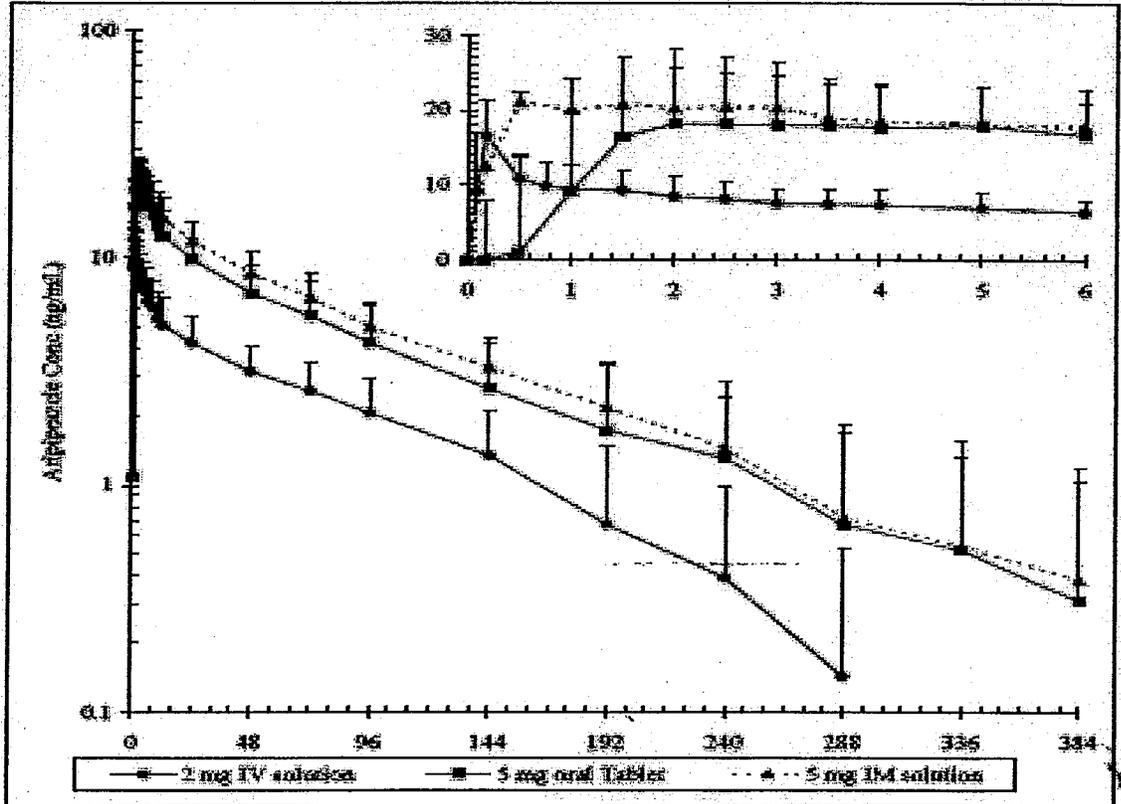
TREATMENT CODES
A = Arifloprazole 2 mg IV, N = 16
B = Arifloprazole 1 mg PO, N = 14
C = Arifloprazole 1 mg IR, N = 15

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Figure 11.3.1:

Mean (SD) Plasma Concentration vs Time Profiles of Aripiprazole in Humans Following Administration of 2 mg IV Infusion, 5 mg Aripiprazole Commercial Oral Tablet, and 5 mg IM Injection



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Table 11.3.1A: Summary Statistics for Aripiprazole Pharmacokinetic Parameters

Pharmacokinetic Parameter		Aripiprazole Formulation		
		2 mg IV (Reference) (N=16)	5 mg tablet (N=14)	5 mg IM (N=15)
C _{max} (ng/mL) Geometric Mean (C.V.%)	Not Dose Normalized	16.3 (32)	19.9 (23)	23.7 (41)
	Dose Normalized	8.2 (32)	4.0 (23)	4.7 (41)
AUC _(0-∞) (ng·h/mL) Geometric Mean (C.V.%)	Not Dose Normalized	620 (37)	1290 (38)	1324 (38)
	Dose Normalized	310 (37)	252 (38)	305 (38)
AUC ₍₀₋₂₄₎ (ng·h/mL) Geometric Mean (C.V.%)	Not Dose Normalized	453 (41)	1108 (37)	1316 (37)
	Dose Normalized	227 (41)	222 (37)	263 (37)
T _{max} (h) Median (Min, Max)		0.17 (0.08, 0.30)	2.75 (1.30, 6.00)	3.00 (0.30, 10.00)
T _{1/2} (h) Mean (SD)		98.8 (39.3)	103.4 (37.0)	91.8 (32.1)
CLT (mL/min) Mean (SD)		58.7 (27.3)	-	-
Weight normalized CLT (mL·min/kg) Mean (SD)		0.72 (0.29)	-	-
CLT/F (mL/min) Mean (SD)		-	69.2 (27.4)	58.6 (22.7)
Weight normalized CLT/F (mL/min/kg) Mean (SD)		-	0.87 (0.33)	0.73 (0.26)
VSS (L) Mean (SD)		404 (101)	-	-

Pharmacokinetic Parameter	Aripiprazole Formulation		
	2 mg IV (Reference) (N=16)	5 mg tablet (N=14)	5 mg IM (N=15)
Weight normalized VSS (L/kg) Mean (SD)	4.94 (0.95)	-	-
MRT* (h) Mean (SD)	130.5 (30.5)	124.4 (49.9)	112.4 (44.1)
F Geometric Mean (C.V.%)	-	0.85 (12)	0.98 (20)
Dose Normalized AUC ₍₀₋₂₄₎ (ng·h/mL) Geometric Mean (C.V.%)	-	3.3 (36)	6.6 (33)

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Table 11.3.1B: Summary of Statistical Analysis Results for Dose-Normalized Aripiprazole Pharmacokinetic Parameters

Pharmacokinetic Parameter	Formulation	Adjusted Geom. Mean	Ratio	Point Estimate (90% C.I.)
AUC(INF) (ng·h/mL)	A	303	-	-
	B	265	B/A	0.8663 (0.7928, 0.9463)
	C	309	C/A	1.0103 (0.9277, 1.1007)
AUC(0-T) (ng·h/mL)	A	223	-	-
	B	227	B/A	1.0202 (0.9333, 1.1149)
	C	266	C/A	1.1953 (1.0973, 1.3021)
C _{max} (ng/mL)	B	3.9	-	-
	C	4.64	C/B	1.1897 (0.9746, 1.4322)
AUC(0-2HR) (ng·h/mL)	B	3.37	-	-
	C	6.42	C/B	1.9037 (1.5373, 2.3373)

CN138-016

Source: Supplemental Table S.11.3.1D-G

Formulation codes: A = Aripiprazole 2 mg IV reference

B = Aripiprazole 5 mg tablet

C = Aripiprazole 5 mg IM

Based on the ratio of adjusted dose normalized AUC(INF) the absolute bioavailability (F) was 0.87 for the tablet formulation and 1.01 for the IM formulation. The estimated dose-normalized AUC(0-2HR) of the aripiprazole IM formulation was 90% higher than that of the tablet formulation, indicating faster absorption for the IM formulation during the first 2 h after dosing.

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Protocol Number: CN138132

**A DOUBLE-BLIND, RANDOMIZED STUDY TO EVALUATE
PHARMACODYNAMIC AND PHARMACOKINETIC INTERACTIONS
BETWEEN INTRAMUSCULAR ARIPIPRAZOLE AND INTRAMUSCULAR
LORAZEPAM WHEN CO-ADMINISTERED IN HEALTHY SUBJECTS**

STUDY OBJECTIVES

The primary objectives of this study were to estimate the effect of lorazepam on the pharmacokinetics of aripiprazole as well as the effect of aripiprazole on the pharmacokinetics of lorazepam, and to estimate the acute pharmacodynamic effect (the degree of sedation) of co-administration of single doses of IM aripiprazole and IM lorazepam as compared to when each agent was administered alone.

STUDY DESIGN

This was a double-blind, randomized, 2-group, 2-period crossover study in healthy subjects who were not to be on any concomitant medications. The study was conducted at two (2) sites. An open-label training subject group was added to ensure that the raters for the Observer's Assessment of Alertness/Sedation (OAA/S) scale were appropriately trained. The raters for the OAA/S scale were to be sufficiently experienced to administer the scale, but no formal certification with regard to the scale administration was required.

Training Group: This part of the study was open-label and was to be conducted prior to the beginning of the main study. Six (6) healthy subjects were to be enrolled and randomized in a 1:2 ratio to receive either a single-dose of placebo matching aripiprazole + 2 mg lorazepam IM (Treatment B) or a single-dose of 15 mg aripiprazole + 2 mg lorazepam IM (Treatment C). Subjects were to undergo screening procedures to determine eligibility within 21 days prior to study drug administration. The subjects were to enter the clinical facility on Day -1. A physical examination, pregnancy test, drug screen, and clinical laboratory evaluations were to be performed at screening, on Day -1 and at Study Discharge (Day 17). The subjects who received Treatment C were to fast for 10 hours overnight from Day -1 to Day 1 and the subjects who received Treatment B were to fast for 6 hours prior to dosing. All subjects were to continue to fast for 4 hours after study drug administration on Day 1.

These subjects were to be administered the study treatment on Day 1 and were to continue with all the procedures included in the main study on Days 1 to 3, with

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Plasma aripiprazole, dehydro-aripiprazole, and lorazepam concentration *versus* time data were analyzed by non-compartmental methods¹⁵ using the program Kinetica. The peak aripiprazole, dehydro-aripiprazole, and lorazepam concentrations in plasma, C_{max}, and the times to reach peak concentrations, T_{max}, were recorded directly from experimental observations. The area under the aripiprazole, dehydro-aripiprazole, and lorazepam concentration-time curves from time zero to the last quantifiable plasma concentration, AUC(0-T), was calculated by log- and linear-trapezoidal summations. Using no weighting factor, the slopes of the terminal phases of the aripiprazole, dehydro-aripiprazole, and lorazepam plasma concentration-time profiles, λ , was determined by log-linear regression of at least three data points which yielded a minimum mean square error. The absolute values of λ were used to estimate the apparent terminal half-lives, T-HALF, of aripiprazole, dehydro-aripiprazole, and lorazepam by: $T-HALF = \ln 2/\lambda$. The areas under the aripiprazole, dehydro-aripiprazole, and lorazepam concentration-time curves from zero extrapolated to infinite time, AUC(INF), were calculated by log- and linear-trapezoidal summations over the collection period, with the last quantifiable plasma concentration being divided by λ and the product added to the total area.

Main Group

To assess the effect of IM lorazepam on the pharmacokinetics of IM aripiprazole, analyses of variance were performed on C_{max}, AUC(INF) and AUC(0-T) of aripiprazole. The factors in the analysis of variance were sequence group, subject within sequence, period and treatment. Since subjects are random effects nested within sequences, F-statistics for sequence effects were the ratios of type I mean squares for sequence and subjects within sequence. The F-statistic for period was the ratio of the type III mean square for period and the mean square for error. A priori, the variables C_{max}, AUC(INF) and AUC(0-T) were log-transformed. Point estimates and 90% confidence intervals for treatment differences on the log scale were exponentiated to obtain point estimates and 90% confidence intervals for the ratios of geometric means (with and without lorazepam) of C_{max}, AUC(INF) and AUC(0-T) of aripiprazole on the original scale of measurement.

To assess the effect of IM aripiprazole on the pharmacokinetics of IM lorazepam, analyses of variance were performed on C_{max}, AUC(INF) and AUC(0-T) of lorazepam. The factors in the analysis of variance were sequence group, subject within sequence, period and treatment. Since subjects are random effects nested within sequences, F-statistics for sequence effects were the ratios of type I mean squares for sequence and subjects within sequence. The F-statistic for period was the ratio of the type III mean square for period and the mean square for error. A priori, the variables C_{max}, AUC(INF) and AUC(0-T) were log-transformed. Point estimates and 90% confidence intervals for treatment differences on the log scale were exponentiated to obtain point estimates and 90% confidence intervals for the ratios of geometric means (with and without aripiprazole) of C_{max}, AUC(INF) and AUC(0-T) of lorazepam on the original scale of measurement.

DEMOGRAPHICS

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Table S.8.3A:
Summary of Demographic Characteristics

Table 1: Training Group

	Total N=6
Age (years)	
N	6
Mean	28
Standard Deviation	8
Median	24
Min-Max	22-44
Q1-Q3	22-35
Age Category n(N)	
< 65 years	6 (100)
≥ 65 years	0
Not Reported	0
Gender n(N)	
Male	6 (100)
Female	0
Not Reported	0
Race n(N)	
White	6 (100)
Black/African American	0
Asian	0
Other	0
Not Reported	0

Table S.8.3B:
Summary of Demographic Characteristics

Table 2: Main Group

	Total N=49
Age (years)	
N	49
Mean	27
Standard Deviation	8
Median	24
Min-Max	19-45
Q1-Q3	21-33
Age Category n(N)	
< 65 years	49 (100)
≥ 65 years	0
Not Reported	0
Gender n(N)	
Male	35 (88)
Female	5 (13)
Not Reported	0
Race n(N)	
White	33 (83)
Black/African American	6 (15)
Asian	0
Other	1 (3)
Not Reported	0

Analytical
Assay Validation - CN138132

Parameter	BMS-337039 (OPC-14597)	BMS 337044 (OPC-14857)	Lorazepam
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection	LC\ Mass Spectrometric \ Mass Spectrometric Detection	LC\ Mass Spectrometric \ Mass Spectrometric Detection

Samples	a 10-fold dilution QC at 1000 ng/mL in 1 run	and a 10-fold dilution QC at 1000 ng/mL in 1 run	
Precision of Standards (%CV)	2.1 to 6.4%	2.4 to 5.7%	1.6 to 5.1%
Precision of QC Samples (%CV)	Between run: 1.9 to 4.0% Within Run: 3.0 to 7.2% Total Variation: 3.6 to 8.2%	Between run: 2.4 to 5.6% Within Run: 2.8 to 7.0% Total Variation: 3.7 to 8.9%	Between run: 1.5 to 2.9% Within Run: 1.4 to 3.5% Total Variation: 2.1 to 4.5%
Accuracy of Standards (%)	-3.0 to 1.6%	-2.4 to 1.5%	-1.8 to 2.8%
Accuracy of QC Samples (%)	0.0 to 4.8%	-6.1 to 0.5%	-4.7 to -2.3%

RESULTS

ARIPRAZOLE

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Supplemental Table S.II.2.1A

Summary Statistics for Aripiprazole Plasma Concentrations by Nominal Collection Time Point Following 15 mg IM Aripiprazole in Treatments A and C (Cohort 1) or in Treatment C (Cohort 2) in Study CN138132

Time post-dose (h)	Mean (SD) [n] Plasma Aripiprazole Concentrations (ng/mL)		
	Cohort 1		Cohort 2
	Treatment A (15 mg IM Aripiprazole+ IM placebo)	Treatment C (15 mg IM Aripiprazole + 2mg IM Lorazepam)	Treatment C (15 mg IM Aripiprazole + 2mg IM Lorazepam)
0	1.1 (0.0) [2]	4.3 (4.6) [2]	<LLQ (NC) [0]
0.25	90.0 (65.7) [14]	141.3 (206.1) [14]	63.7 (38.6) [16]
0.5	89.9 (32.6) [14]	99.7 (53.3) [14]	81.6 (38.2) [16]
1	99.1 (24.3) [14]	91.8 (26.8) [14]	89.4 (23.6) [16]
2	146.4 (223.9) [14]	86.5 (19.6) [14]	81.7 (20.5) [16]
3	78.7 (12.1) [14]	77.7 (16.1) [14]	81.3 (22.8) [16]
4	73.7 (14.1) [14]	74.7 (14.3) [14]	74.1 (18.8) [16]
6	68.2 (11.7) [14]	68.4 (12.7) [14]	68.0 (14.7) [16]
8	63.1 (10.8) [14]	63.9 (13.2) [14]	65.5 (19.7) [16]
10	57.0 (9.4) [14]	57.0 (9.4) [14]	60.7 (19.2) [16]
12	51.4 (7.9) [14]	52.0 (8.9) [14]	54.0 (10.4) [16]
24	44.8 (8.4) [14]	44.5 (10.3) [14]	44.2 (10.2) [16]
36	37.3 (8.3) [14]	39.0 (11.2) [14]	35.9 (8.9) [16]
48	33.0 (8.7) [14]	34.1 (11.8) [14]	32.0 (9.9) [16]
72	27.4 (12.2) [14]	27.7 (12.2) [14]	22.5 (9.1) [15]
120	16.3 (10.0) [14]	17.4 (13.0) [13]	13.1 (8.1) [16]
168	11.2 (7.7) [13]	11.6 (10.1) [14]	7.8 (6.1) [16]
240	6.4 (6.0) [13]	7.1 (7.6) [13]	4.5 (4.5) [15]
312	5.6 (5.2) [9]	5.3 (6.5) [10]	3.5 (3.5) [11]
384	5.1 (5.0) [7]	4.9 (6.0) [8]	3.6 (3.4) [6]

CN138132

Source: Appendix 11.2.1B (subjects who completed the study only)

NC=Not calculated

LLQ = 1.0 ng/mL

<LLQ or missing data were treated as "missing" in the calculation of mean and SD values

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Table S.11.2.1B:
Main Group - Summary Statistics for Aripiprazole Pharmacokinetic Parameters

COHORT	TREATMENT	STATISTIC	C _{MAX} (ng/mL)	T _{MAX} (h)	AUC(INF) (ng* ^h /mL)	AUC(O-T) (ng* ^h /mL)	T-HALF (h)
1	A	N	14	14	14	14	14
		MEAN	175.25	1.05	6547.92	5846.77	84.61
		S.D.	221.94	0.79	3887.56	2546.35	58.82
		GEO.MEAN	127.70	0.80	5784.89	5382.32	71.92
		C.V.	126.64	75.14	59.37	43.55	69.53
		MEDIAN	101.83	1.00	5337.78	5108.70	69.64
		MIN	75.13	0.25	2843.52	2727.03	26.44
		MAX	922.15	3.00	17987.40	11889.67	262.21
1	C	N	14	14	14	14	14
		MEAN	169.76	0.95	6703.54	6091.40	82.12
		S.D.	195.45	0.83	4509.77	3270.61	39.50
		GEO.MEAN	127.35	0.69	5813.34	5481.22	73.88
		C.V.	115.13	87.41	67.27	53.69	48.10
		MEDIAN	114.57	0.50	5491.16	5288.49	85.89
		MIN	62.66	0.25	2833.97	2781.66	28.36
		MAX	829.10	3.00	20688.99	15506.36	185.91
2	C	N	16	16	16	16	16
		MEAN	102.27	1.48	5348.57	5036.22	70.51
		S.D.	29.36	1.48	2500.66	2049.74	29.82
		GEO.MEAN	98.22	1.03	4915.74	4692.67	66.07
		C.V.	28.71	100.01	46.75	40.70	42.30
		MEDIAN	97.18	1.00	4713.74	4585.14	66.91
		MIN	56.90	0.25	2609.55	2465.92	31.28
		MAX	151.05	6.00	12355.42	9832.95	167.98

Table 90% CI for Aripiprazole
Parameter
C_{max}

CI

PT. EST.	90% C.I.:	(LCL, UCL)
0.997	(0.850, 1.170)

AUC_{inf}

PT. EST.	90% C.I.:	(LCL, UCL)
1.005	(0.951, 1.062)

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LOREZAPAM

Supplemental Table S.11.2.3A

Summary Statistics for Lorazepam Plasma Concentrations by Nominal Collection Time-Point Following 2 mg IM Lorazepam in Treatment C (Cohort 1) or Treatments B and (Cohort 2) in Study CNI38132

Time post-dose (h)	Mean (SD) [n] Plasma Lorazepam Concentrations (ng/mL)		
	Cohort 1	Cohort 2	
	Treatment C (15 mg IM Aripiprazole + 2mg IM Lorazepam)	Treatment B (2mg IM Lorazepam+ IM placebo)	Treatment C (15 mg IM Aripiprazole + 2mg IM Lorazepam)
0	<LLQ (NC) [0]	<LLQ (NC) [0]	<LLQ (NC) [0]
0.25	14.6 (9.7) [16]	9.9 (5.9) [16]	14.0 (12.1) [14]
0.5	21.1 (10.5) [15]	18.2 (9.1) [16]	19.7 (12.6) [14]
1	20.9 (4.5) [16]	20.3 (5.2) [16]	21.2 (7.4) [14]
2	21.0 (3.6) [16]	20.2 (3.9) [16]	20.5 (6.2) [14]
3	20.3 (4.2) [16]	20.0 (3.3) [16]	20.6 (5.4) [14]
4	19.3 (4.6) [16]	18.9 (3.1) [16]	19.4 (4.7) [14]
6	16.2 (4.0) [16]	16.3 (3.3) [16]	16.6 (3.8) [14]
8	14.4 (3.4) [16]	14.3 (3.1) [16]	14.5 (3.3) [14]
10	13.2 (3.7) [16]	12.3 (3.2) [16]	12.8 (3.4) [14]
12	11.7 (3.0) [16]	11.2 (2.9) [16]	11.7 (3.2) [14]
24	6.8 (2.6) [16]	6.3 (2.5) [16]	7.0 (2.6) [14]
36	3.9 (1.7) [16]	3.7 (1.7) [16]	4.2 (1.8) [14]
48	2.5 (1.3) [16]	2.3 (1.2) [16]	2.6 (1.2) [14]
72	1.1 (0.5) [11]	1.1 (0.5) [11]	1.3 (0.6) [11]

CNI38132

Source: Appendix 11.2.3B (subjects who completed the study only)

NC=Not calculated

LLQ = 0.5 ng/mL

<LLQ or missing data were treated as "missing" in the calculation of mean and SD values

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Table 2.11.2.35:
Main Group - Summary Statistics for Lorazepam Pharmacokinetic Parameters

COHORT	TREATMENT	STATISTIC	C _{MAX} (ng/mL)	T _{MAX} (h)	AUC(INF) (ng*h/mL)	AUC(0-T) (ng*h/mL)	T
1	C	N	14	14	14	14	
		MEAN	25.09	2.09	481.24	450.45	1
		S.D.	10.51	1.65	165.06	148.79	
		GEO.MEAN	23.32	1.48	455.17	427.45	1
		C.V.	41.89	79.04	34.30	33.03	1
		MEDIAN	23.67	1.50	468.31	439.00	1
		MIN	12.56	0.25	264.71	251.84	1
		MAX	49.54	6.00	760.75	691.98	2
2	B	N	16	16	16	16	
		MEAN	25.22	1.55	463.99	437.41	1
		S.D.	8.23	1.29	148.61	137.03	
		GEO.MEAN	24.08	1.10	440.10	415.76	1
		C.V.	32.64	83.50	32.03	31.33	2
		MEDIAN	22.22	1.00	449.29	435.41	1
		MIN	14.80	0.25	215.82	207.30	1
		MAX	42.70	4.00	721.23	673.32	2
2	C	N	16	16	16	16	
		MEAN	23.17	1.94	441.08	415.52	1
		S.D.	5.82	1.36	137.69	127.53	
		GEO.MEAN	22.50	1.46	420.44	396.55	1
		C.V.	25.11	70.44	31.22	30.69	1
		MEDIAN	22.80	1.50	434.41	419.70	1
		MIN	14.63	0.50	204.67	192.78	1
		MAX	34.22	4.00	772.01	724.34	2

ments: A-Aripiprazole 15mg IM, B-Lorazepam 2mg IM, C-Aripiprazole 15mg IM + Lorazepam 2mg IM.
M SOURCE: /w/bch/clin/proj/cn/138/132/dev/stats pks_sumstats.sas

Table 90% CI for Lorazepam
Parameter
C_{max}

CI

PT. EST.	90% C.I.:	(LCL, UCL)
0.928	(0.846, 1.017)

AUC_{inf}

PT. EST.	90% C.I.:	(LCL, UCL)
0.953	(0.907, 1.001)

CONCLUSION:

Co-administration of IM aripiprazole (15 mg) and IM lorazepam (2 mg) had no effect on the pharmacokinetics of either compound.

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Protocol No.: CN138017

**SAFETY, TOLERABILITY, PHARMACOKINETICS AND
PHARMACODYNAMICS OF MULTIPLE INTRAMUSCULAR DOSES OF 1 TO
30 MG ARIPIPRAZOLE IN PATIENTS WITH SCHIZOPHRENIA**

OBJECTIVES

The primary objective of this study was to assess the safety and tolerability profile of aripiprazole following either 4 days of once daily intramuscular (IM) administration or 3 multiple IM injections in a single day as compared with 3 multiple IM injections of haloperidol in a single day in subjects with schizophrenia.

The secondary objectives were to assess the pharmacokinetics and pharmacodynamics of aripiprazole following 4 days of once daily IM administration and the pharmacokinetics of aripiprazole following three multiple IM injections in a single day in subjects with schizophrenia.

SUBJECT DEMOGRAPHICS

Table 8.3: Demographic Characteristics

Characteristic	All Subjects (n=32)
Age, years	
Mean (S.D.)	39 (7)
Range	24 - 50
Gender, n (%)	
Male	26 (81)
Female	6 (19)
Race, n (%)	
White	15 (47)
Black	10 (31)
Hispanic/Latino	5 (16)
Asian/Pacific Islanders	1 (3)
Mix	1 (3)
Weight, kg	
Mean (S.D.)	91.2 (19.4)
Range	57.6 - 137.8
Height, cm	
Mean (S.D.)	174.6 (8.9)
Range	156.2 - 193.0
BMI, kg/m ²	
Mean (S.D.)	30.2 (5.8)
Range	19.0 - 47.8

CN138017

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METHODS

This was an open-label, non-randomized, sequential group, escalating dose study in subjects with schizophrenia. Four (4) subjects with a diagnosis of schizophrenia according to criteria given in DSM IV Section 295 (Appendix 5.1A) were to be assigned to each of the 5 sequential treatment groups (1, 3, 7.5, 15, and 30 mg). Four (4) subjects were to be assigned to each of the 3 additional treatment groups who were to receive aripiprazole IM (22.5 or 45 mg) or haloperidol IM (15 mg).

All subjects were to undergo screening evaluations to determine eligibility between 28 and 5 days prior to study enrollment and were to be admitted to the research facility on Day -4. Previous medications were to be discontinued 14 days prior to Day 1 of dosing. Baseline assessments were to be performed between Day -4 and Day -1. For treatment groups 1 to 5, starting on Day 1 and continuing for 4 days, subjects were to receive IM injections of aripiprazole (1, 3, 7.5, 15 or 30 mg QD, respectively). Subjects were to be confined to the research facility until Day 6, and return for follow-up visits on Days 9 and 11.

For treatment groups 6 to 8, on Day 1 subjects were to receive 3 equal doses of aripiprazole IM (7.5 or 15 mg) or haloperidol IM (5 mg), respectively at 0 h (first dose), 2 h and 4 h after the first dose. Subjects were to be confined to the research facility until Day 3 and return for follow-up visits on Days 6 and 8.

Table 5.5.1: Treatment Administration

Treatment Group	Treatment	Total Daily Dose (mg)	Stock Solution (mg/mL)	Volume per Injection (mL)	Number of Injections	Total Volume Injected (mL)
1	aripiprazole IM	1	2	0.5	1	0.5
2	aripiprazole IM	3	2	1.5	1	1.5
3	aripiprazole IM	7.5	7.5	1.0	1	1.0
4	aripiprazole IM	15	7.5	1.0	2	2.0
5	aripiprazole IM	30	7.5	2.0	2	4.0
6	aripiprazole IM	22.5	7.5	1.0	3	3.0
7	aripiprazole IM	45	7.5	2.0	3	6.0
8	haloperidol IM	15	5.0	1.0	3	3.0

5.10 Pharmacokinetics

A total of 2 mL venous blood was to be obtained in lavender-top _____ tubes in

(45 mg aripiprazole) were only dosed on Day 1 and therefore no comparison with groups 1 (1 mg/day aripiprazole) to 5 (30 mg/day aripiprazole) could be made.

Dose proportionality was assessed using the power model

$$y_{ijk} = \alpha(D_k)^\beta$$

from Gough et al. (1995).¹ A simplification was necessary as there was only one measurement per subject, hence subject and period effects were not estimable. Dose proportionality in this model corresponds to the case that $\beta=1.0$. Point estimates and 95% confidence intervals for β were calculated for C_{max} and AUC(TAU) for both aripiprazole (BMS-337039) and dehydro-aripiprazole (BMS-337044) on the study days and doses outlined above. All parameters were log-transformed for analysis.

ANALYTICAL

Study Number	Start of Clinical Study	End of Clinical Study	Start of Sample Analysis	End of Sample Analysis	Total Storage Time
CN138017	May 29, 2000	Dec 29, 2000	Jun 27, 2000	Jan 15, 2001	~240 days

Assay Validation - CN138017

Parameter	BMS-337039 (OPC-14597)	BMS 337044 (OPC-14857)
Method	DCN 920010810	DCN 920010810
Number of Freeze-thaw	3 Cycles (DCN 920010829)	3 Cycles (DCN 920010829)
Benchtop Stability at RT	22 hrs (DCN 920010507)	22 hrs (DCN 920010507)
Long term at -20° C	782 days (DCN 920010507)	782 days (DCN 920010507)
Extraction Recovery		
Low	81.0% (DCN 920010507)	82.4% (DCN 920010507)
High	82.9% (DCN 920010507)	88.2% (DCN 920010507)

CN138017

Plasma Analysis Results

Clinical study began: May 29, 2000

Clinical Study ended: December 29, 2000

Sample analysis began: June 27, 2000

Sample analysis completed: January 15, 2001

Parameter	BMS 337039	BMS 337044
Method	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	1 ng/mL	1 ng/mL
Linearity (Standard curve samples)	1, 2, 50, 100, 150, 200, 225, & 250 ng/mL	1, 2, 50, 100, 150, 200, 225, & 250 ng/mL
Quality Control (QC) Samples	3, 100, & 200 ng/mL & dil QC 2500 in 3 runs	3, 100, & 200 ng/mL & dil QC 2500 in 1 runs
Precision of Standards (%CV)	3.2 to 8.9%	4.1 to 5.8%
Precision of QC Samples (%CV)	Between run: 3.8 to 7.0% Within Run: 4.1 to 8.9% Total Variation: 8.0 to 11.3%	Between run: 1.4 to 6.3% Within Run: 3.6 to 6.1% Total Variation: 6.1 to 7.2%
Accuracy of Standards (%)	-2.0 to 1.4%	-2.0 to 3.0%
Accuracy of QC Samples (%)	0.4 to 1.6%	-3.3 to 11.1%

RESULTS

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Supplemental Table S.11.2.1A: Mean (SD) Plasma Concentrations of Aripiprazole Following Intramuscular Doses to Schizophrenic Subjects in Study CN138017

Time post-dose (days:hrs:mins)	Number of samples	Mean Aripiprazole Plasma Concentration (ug/mL)	SD
1 mg aripiprazole IM once daily for 4 days			
0:0:0	0		
0:0:10	4	3.51	2.01
0:0:30	3	3.66	1.41
0:2:0	4	2.59	1.14
0:6:0	4	2.45	0.45
0:12:0	4	2.28	0.25
1:0:0	4	1.92	0.10
2:0:0	4	4.15	1.12
3:0:0	4	5.06	0.47
3:0:10	4	6.17	1.01
3:0:30	4	7.97	1.59
3:2:0	4	7.86	0.96
3:6:0	4	7.65	1.36
3:12:0	4	6.61	0.40
4:0:0	4	5.92	0.43
5:0:0	4	4.28	0.50
8:0:0	4	2.50	0.41
10:0:0	4	1.87	0.38
3 mg aripiprazole IM once daily for 4 days			
0:0:0	1	10.98	0.00
0:0:10	4	9.21	7.62
0:0:30	4	9.12	4.70
0:2:0	4	8.13	4.11
0:6:0	4	8.47	2.27
0:12:0	4	6.98	1.00
1:0:0	4	8.25	3.29
2:0:0	4	12.35	3.86
3:0:0	4	18.56	6.16
3:0:10	4	31.00	8.82
3:0:30	4	37.02	8.20
3:2:0	4	28.70	6.96
3:6:0	4	20.86	4.67
3:12:0	4	20.78	5.92
4:0:0	4	17.72	6.58
5:0:0	4	12.19	9.14
8:0:0	4	5.99	7.29
10:0:0	3	5.37	7.10
7.5 mg aripiprazole IM once daily for 4 days			
0:0:0	0		
0:0:10	4	8.67	3.99

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Time post-dose (days:hrs:mins)	Number of samples	Mean Aripiprazole Plasma Concentration (ng/mL)	SD
0:0:30	4	11.84	6.86
0:2:0	4	13.36	4.15
0:6:0	4	20.40	4.81
0:12:0	4	18.78	3.27
1:0:0	4	17.03	1.40
2:0:0	4	20.29	4.01
3:0:0	4	41.30	4.38
3:0:10	4	48.73	4.35
3:0:30	4	54.96	6.69
3:2:0	4	58.85	6.71
3:6:0	4	62.13	9.18
3:12:0	4	56.14	5.76
4:0:0	4	48.06	8.87
5:0:0	4	39.26	7.68
8:0:0	4	27.03	7.01
10:0:0	4	31.06	7.77
15 mg aripiprazole IM once daily for 4 days			
0:0:0	0		
0:0:10	4	51.34	66.50
0:0:30	4	31.31	19.71
0:2:0	4	54.64	44.98
0:6:0	4	50.28	25.34
0:12:0	4	47.09	19.72
1:0:0	4	40.63	12.94
2:0:0	4	69.94	17.32
3:0:0	4	100.88	29.59
3:0:10	4	120.70	55.01
3:0:30	4	146.35	75.41
3:2:0	4	149.39	66.27
3:6:0	4	148.42	60.52
3:12:0	4	130.11	41.47
4:0:0	4	119.73	25.43
5:0:0	4	100.34	25.68
8:0:0	4	51.69	19.94
10:0:0	4	37.33	18.78
30 mg aripiprazole IM once daily for 4 days			
0:0:0	0		
0:0:10	3	85.83	81.62
0:0:30	4	151.47	177.17
0:2:0	4	134.69	87.32
0:6:0	4	106.23	50.34
0:12:0	4	99.59	33.66
1:0:0	4	86.92	28.34
2:0:0	4	146.28	41.12
3:0:0	4	190.01	46.17
3:0:10	4	323.91	184.05

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Time post-dose (days:hrs:min)	Number of samples	Mean Aripiprazole Plasma Concentration (ng/mL)	SD
3:0:30	4	368.37	205.63
3:2:0	4	307.13	117.47
3:6:0	4	253.72	66.00
3:12:0	4	243.13	87.33
4:0:0	4	207.98	34.50
5:0:0	4	187.09	40.44
8:0:0	4	90.35	27.98
10:0:0	4	56.47	19.10
3 doses of 7.5 mg aripiprazole IM every 2 h on a single da			
0:0:0	0		
0:0:15	4	21.33	16.07
0:0:45	4	20.49	12.13
0:2:0	4	24.47	15.81
0:2:15	4	40.04	24.28
0:2:45	4	47.33	33.58
0:4:15	4	47.70	31.00
0:4:45	4	79.47	20.69
0:6:0	4	83.76	23.26
0:10:0	4	75.92	24.15
0:16:0	4	64.72	15.76
1:0:0	4	45.61	9.89
2:0:0	4	52.03	12.20
3:0:0	4	33.18	7.32
5:0:0	4	17.42	6.07
7:0:0	4	11.59	6.46
3 doses of 15 mg aripiprazole IM every 2 h on a single day			
0:0:0	0		
0:0:15	4	53.57	33.74
0:0:45	4	68.13	36.97
0:2:0	4	59.07	33.11
0:2:15	4	122.56	45.91
0:2:45	4	141.88	59.44
0:4:15	4	121.06	44.22
0:4:45	4	194.39	75.98
0:6:0	4	198.49	77.60
0:10:0	4	177.06	58.32
0:16:0	4	146.10	51.18
1:0:0	4	126.82	36.77
2:0:0	4	118.99	39.54
3:0:0	4	103.08	34.52
5:0:0	4	59.99	25.44
7:0:0	4	42.52	19.58

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Summary Statistics for Aripiprazole Pharmacokinetic Parameters

Aripiprazole Dose (mg)	Study Day	STATISTIC	C _{MAX} (ng/mL)	T _{MAX} (h)	AUC(0-T) (ng ² h/mL)	AUC(TSD) (ng ² h/mL)
1: ARI 1.0mg	DAY 1	N	4	4	4	4
		MEAN	4.09	3.21	55.31	55.31
		S.D.	1.74	5.86	5.73	5.73
		Geo. MEAN	3.82	0.64	55.09	55.09
		C.V.	42.52	182.75	10.37	10.37
		MEDIAN	3.78	0.33	54.35	54.35
		MIN	2.55	0.17	49.68	49.68
		MAX	6.23	12.00	62.85	62.85
1: ARI 1.0mg	DAY 4	N	4	4		4
		MEAN	8.53	2.25		164.14
		S.D.	1.29	2.60		12.82
		Geo. MEAN	8.45	1.32		163.76
		C.V.	15.08	115.47		7.81
		MEDIAN	8.99	1.25		164.20
		MIN	6.68	0.50		148.75
		MAX	9.45	6.00		179.43
2: ARI 3.0mg	DAY 1	N	4	4	4	4
		MEAN	11.35	13.54	187.68	187.68
		S.D.	5.55	12.31	48.70	48.70
		Geo. MEAN	10.35	4.90	182.35	182.35
		C.V.	48.85	90.90	25.95	25.95
		MEDIAN	10.58	15.00	200.71	200.71
		MIN	5.74	0.17	122.65	122.65
		MAX	18.51	24.00	226.65	226.65

Table S.11.2.10: Summary Statistics for Aripiprazole Pharmacokinetic Parameters

Aripiprazole Dose (mg)	Study Day	STATISTIC	C _{MAX} (ng/mL)	T _{MAX} (h)	AUC(0-T) (ng ² h/mL)	AUC(TSD) (ng ² h/mL)
2: ARI 3.0mg	DAY 4	N	4	4		4
		MEAN	36.08	1.08		509.89
		S.D.	4.27	1.06		130.06
		Geo. MEAN	35.88	0.58		496.03
		C.V.	11.84	97.71		25.51
		MEDIAN	37.99	1.08		527.90
		MIN	29.73	0.17		334.79
		MAX	38.63	2.00		648.99
3: ARI 7.5mg	DAY 1	N	4	4	4	4
		MEAN	21.07	12.00	422.49	422.49
		S.D.	3.93	8.49	73.57	73.57
		Geo. MEAN	20.80	10.09	417.69	417.69
		C.V.	18.64	70.71	17.41	17.41
		MEDIAN	20.73	9.00	419.13	419.13
		MIN	17.11	6.00	338.67	338.67
		MAX	25.73	24.00	513.05	513.05
3: ARI 7.5mg	DAY 4	N	4	4		4
		MEAN	64.52	6.13		1332.01
		S.D.	6.29	4.70		111.81
		Geo. MEAN	64.29	3.83		1328.58
		C.V.	9.75	76.69		8.39
		MEDIAN	64.54	6.00		1306.77
		MIN	58.67	0.50		1231.58
		MAX	70.33	12.00		1482.92

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Table S.11.2.1C:
Summary Statistics for Aripiprazole Pharmacokinetic Parameters

Aripiprazole Dose (mg)	Study Day	STATISTIC	C _{MAX} (ng/mL)	T _{MAX} (h)	AUC (0-T) (ng ² h/mL)	AUC (TAD) (ng ² h/mL)
4: ARI 15.0mg	DAY 1	N	4	4	4	4
		MEAN	68.77	10.54	1109.65	1109.65
		S.D.	55.20	10.19	531.77	531.77
		GEO. MEAN	56.58	4.12	1025.56	1025.56
		C.V.	80.27	96.67	47.92	47.92
		MEDIAN	45.98	9.00	969.78	969.78
		MIN	32.11	0.17	629.08	629.08
MAX	150.93	24.00	1869.94	1869.94		
4: ARI 15.0mg	DAY 4	N	4	4	4	4
		MEAN	155.69	8.13	3214.62	3214.62
		S.D.	69.25	10.83	1086.63	1086.63
		GEO. MEAN	146.12	3.46	3092.71	3092.71
		C.V.	44.48	133.35	33.80	33.80
		MEDIAN	129.78	4.00	2865.76	2865.76
		MIN	105.79	0.50	2361.65	2361.65
MAX	257.42	24.00	4765.31	4765.31		
5: ARI 30.0mg	DAY 1	N	4	4	4	4
		MEAN	185.38	9.63	2472.34	2472.34
		S.D.	159.84	10.86	1119.93	1119.93
		GEO. MEAN	142.96	4.12	2296.51	2296.51
		C.V.	86.22	112.81	45.30	45.30
		MEDIAN	128.58	7.00	2196.84	2196.84
		MIN	69.48	0.50	1522.35	1522.35
MAX	414.89	24.00	3973.32	3973.32		

TABLE S.11.2.1D:
Summary Statistics for Aripiprazole Pharmacokinetic Parameters

Aripiprazole Dose (mg)	Study Day	STATISTIC	C _{MAX} (ng/mL)	T _{MAX} (h)	AUC (0-T) (ng ² h/mL)	AUC (TAD) (ng ² h/mL)
5: ARI 30.0mg	DAY 4	N	4	4	4	4
		MEAN	374.40	2.25	5981.74	5981.74
		S.D.	196.99	2.60	1838.80	1838.80
		GEO. MEAN	338.02	1.32	5783.43	5783.43
		C.V.	52.61	115.47	30.74	30.74
		MEDIAN	323.11	1.25	5511.02	5511.02
		MIN	218.40	0.50	4470.44	4470.44
MAX	632.99	6.00	8434.46	8434.46		
6: ARI 22.5mg	DAY 1	N	4	4	4	4
		MEAN	84.70	4.63	1289.74	1289.74
		S.D.	24.26	0.25	342.62	342.62
		GEO. MEAN	82.05	4.62	1253.10	1253.10
		C.V.	28.64	5.41	26.57	26.57
		MEDIAN	85.64	4.75	1326.01	1326.01
		MIN	61.11	4.25	866.77	866.77
MAX	106.43	4.75	1640.19	1640.19		
7: ARI 45.0mg	DAY 1	N	4	4	4	4
		MEAN	207.12	4.63	3190.45	3190.45
		S.D.	76.62	0.25	1029.62	1029.62
		GEO. MEAN	193.14	4.62	3032.89	3032.89
		C.V.	36.99	5.41	32.27	32.27
		MEDIAN	230.55	4.75	3528.18	3528.18
		MIN	97.55	4.25	1705.94	1705.94
MAX	269.82	4.75	3999.49	3999.49		

DOSE ANALYSIS

The results of the dose proportionality analysis for aripiprazole and dehydro-aripiprazole are shown in Supplemental Tables 1 and 2, respectively. The results of the dose proportionality analysis for aripiprazole and dehydro-aripiprazole are summarized in Tables 1 and 2, respectively.

Table 1: Dose Proportionality Results for Aripiprazole (BMS-337039)

Study Day	Parameter	Estimated β	Lower 95% CI	Upper 95% CI
-----------	-----------	-------------------	--------------	--------------

1	Cmax	1.05	0.90	1.20
1	AUC(TAU)	1.06	0.96	1.15
4	Cmax	1.04	0.92	1.17
4	AUC(TAU)	1.06	0.98	1.15

Source: Supplemental Table S1

Table 2: Dose Proportionality Results for Dehydro-Aripiprazole (BMS-337044)

Study Day	Parameter	Estimated β	Lower 95% CI	Upper 95% CI
1	Cmax	0.91	0.63	1.18
1	AUC(TAU)	0.93	0.60	1.26
4	Cmax	1.00	0.87	1.12
4	AUC(TAU)	1.08	0.88	1.29

Source: Supplemental Table S1

CONCLUSIONS

In all cases, the estimated values of β were within 10% of 1.0, and confidence intervals for β always contained the value 1.0. Thus, there was no evidence that suggests there was a departure from dose-proportionality for either aripiprazole or dehydro-aripiprazole following IM doses of aripiprazole over the dose range studied in CN138017 (1 to 45 mg on Day 1 or on Day 4 following 1 to 30 mg QD doses).

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Protocol No.: CN138050

**ASSESSMENT OF THE RELATIONSHIP BETWEEN
ARIPIPRAZOLE AND DEHYDRO-ARIPIPRAZOLE PLASMA
CONCENTRATIONS AND QTC CHANGES FROM BASELINE IN
STUDY CN138050**

OBJECTIVES

To assess the relationship between plasma concentrations of aripiprazole and of dehydro-aripiprazole, and changes in QTc interval from baseline in study CN138050.

STUDY DESIGN

This trial was a double-blinded, randomized, dose-ranging, multicenter study comparing 4 doses of IM aripiprazole (1 mg, 5 mg, 10 mg and 15 mg) and haloperidol to placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder. The study began with a screening evaluation, followed by baseline assessments that were performed within 1 hour prior to administration of the first dose of study drug, followed by an inpatient evaluation period of 24 hours. Three hundred six (306) evaluable patients were to be randomly assigned in a 1:1:1:1:1:1 ratio to receive an initial dose in one of the six dosage groups (1 mg, 5 mg, 10 mg, or 15 mg aripiprazole, 7.5 mg haloperidol or placebo). A second dose was to be given, if needed, at least 2 hours after the initial dose followed by a third dose of study medication, if needed, which was to be given at least 4 hours after the initial dose and at least 2 hours after the second dose. For patients randomized to placebo, the first and second doses contained placebo and the third dose contained 15 mg aripiprazole. The maximum aripiprazole IM doses for the 1 mg, 5 mg, 10 mg and 15 mg dose groups were 3 mg, 15 mg, 30 mg and 45 mg, respectively. The maximum haloperidol IM dose was 22.5 mg. If rescue medication was needed, a dose of lorazepam could have been administered at least 60 minutes after the second dose of study medication, and whenever needed thereafter to a maximum of 4 mg/day during the remainder of the 24 hour period, at the Investigator's discretion.

Patients were continuously monitored throughout the 24-hour treatment and observation period with a 12-lead digital ECG monitor (holter). Baseline ECG tracings were evaluated every 30 minutes for 2 hours prior to the first study medication injection. Intermittent post-dose tracings were evaluated at 30 minutes, and at 1, 1.5, 2, 3, 4, 6, 12, and 24 hours after the first dose of study medication. Additional ECGs were also performed at 30 minutes and 1 hour after each repeat dose of study medication (if administered). Patients who refused the 12-lead digital ECG monitor during the screening period were considered ineligible for enrollment into the study. If after randomization a

patient refused the 12-lead digital monitor, standard 12-lead ECG tracings (paper) were performed according to the ECG time schedule

Blood Collection and Processing

Plasma samples were to be collected at baseline, at 2 hours 15 minutes after each dose of study medication, and at approximately 12 hours and approximately 120 hours after the last dose of study medication.

METHODS

The study was not designed for double delta analysis. Instead, a simple linear regression analyses based on changes from baseline was conducted. Placebo patients were included in the analyses only if they received rescue medication as their third injection and had a time matched ECG reading. (SAS Code in the Appendix).

Linear regressions of delta QTc on aripiprazole plasma concentrations and linear regressions of delta QTc on dehydro-aripiprazole plasma concentrations were then performed separately for "matched PK/Paper" and "matched PK/Holter" data. The analyses were performed on QT corrected for heart rate based on 3 different methods: Bazett, Fridericia and FDA Division of Neuropharmacology Drugs correction - the corrected QT values for heart rate (QTcB, QTcF and QTcN) are included in the data sets as well as the uncorrected QT values and heart rate.

All concentrations shown in the listings as < LLQ (because PK samples were collected while subjects received placebo, or prior to study drug administration or because concentrations were just below the lower limit of detection) were replaced by half of the LLQ value (the LLQ value for both aripiprazole and dehydro-aripiprazole is 1 ng/mL, so those nominal concentrations of < LLQ were replaced by 0.5) for the linear regression analyses.

The baseline ECG values were the mean of the pre-dose ECG values for each patient, and if a patient had only 1 pre-dose ECG reading so then the mean value is the same as the individual reading. For other subjects with multiple pre-dose readings, the mean is that of the multiple readings.

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For each subject and each ECG parameter (QTcN, QTcF, QTcB) the baseline was defined as the mean of all ECG measurements available at screening and baseline visits for that subject and ECG parameter.

Individual QTc changes from baseline (Δ QTcN, Δ QTcF, Δ QTcB) and matched (within 30 minutes of the ECG measurement) aripiprazole and dehydro-aripiprazole plasma concentrations (Cp) were listed. Linear regressions of Δ QTc on matched aripiprazole plasma concentrations and on matched dehydro-aripiprazole plasma concentrations were estimated. Ninety-five percent (95%) confidence intervals were constructed for the slopes and intercepts. Scatter plots and fitted regression lines were also presented.

These analyses were performed separately for measurements recorded on a paper ECG and for measurements recorded on an ambulatory 12-lead ECG.

Time points prior to dosing are shown as '-' and '-0.25' would be 15 minutes prior. No pre-baseline values were used in the linear regression analyses

The ECG value closest to the plasma sample (within 30 minutes) was used for the analyses, whether it occurred before or after the sampling time.

The half-life for aripiprazole is approximately 100 hrs, therefore the analysis scheme of using samples within 30 min of the ECG is acceptable.

Plasma Analysis Results

Study Number	Start of Clinical Study	End of Clinical Study	Start of Sample Analysis	End of Sample Analysis	Total Storage Time
CN138050	Apr 2, 2003	Jan 26, 2003	Feb 10, 2004	Mar 29, 2004	~330 days

Assay Validation - CN138050

Parameter	BMS-337039 (OPC-14597)	BMS 337044 (OPC-14857)
Method	DCN 920010507	DCN 920010507
Number of Freeze-thaw	3 Cycles (DCN 920010829)	3 Cycles (DCN 920010829)
Benchtop Stability at RT	22 hrs (DCN 920010507)	22 hrs (DCN 920010507)
Long term	782 days (DCN 920010507)	782 days (DCN 920010507)

at -20° C		
Extraction Recovery		
Low	← (DCN 920010507)	← (DCN 920010507)
High	← (DCN 920010507)	← (DCN 920010507)

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Plasma Analysis Results

Clinical study began: April 2, 2003

Clinical Study ended: January 26, 2003

Sample analysis began: February 10, 2004

Sample analysis completed: March 29, 2004

Parameter	BMS 337039	BMS 337044
Method	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	1 ng/mL	1 ng/mL
Linearity (Standard curve samples)	1, 2, 10, 50, 100, 150, 200, 225, & 250 ng/mL	1, 2, 10, 50, 100, 150, 200, 225, & 250 ng/mL
Quality Control (QC) Samples	3, 100, & 200 ng/mL	3, 100, & 200 ng/mL
Precision of Standards (%CV)	3.3 to 9.5%	6.1 to 8.0%
Precision of QC Samples (%CV)	Between run: 0.0 to 4.2% Within Run: 2.5 to 6.5% Total Variation: 4.9 to 5.9%	Between run: 1.2 to 3.8% Within Run: 3.4 to 5.8% Total Variation: 4.1 to 6.9%
Accuracy of Standards (%)	-0.5 to 0.5%	-1.0 to 2.0%
Accuracy of QC Samples (%)	-4.0 to 0.9%	-6.3 to -4.3%

RESULTS

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Table 9: Numbers of patients and plasma samples by dose group and number of injections in patients administered aripiprazole

Dose Group	Number of Injections of Aripiprazole	Number of Patients	Number of Plasma Samples
Placebo	1	4	23
1 mg	1	7	25
	2	5	20
	3	1	6
5 mg	1	11	40
	2	1	5
	3	2	12
10 mg	0 ^a	1	1
	1	6	24
	2	3	14
	3	2	11
15 mg	1	9	31
	2	3	12
	3	3	15

^a One patient (CN138050-39-5) was randomized to the 10 mg dose group but was not dosed.
CN138050

PROTOCOL: CN138050

Appendix 11.2D:

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Scatter Plots and Fitted Linear Regressions for Q₀₅ Changes from Baseline (Holter ECG) vs. Plasma Concentrations

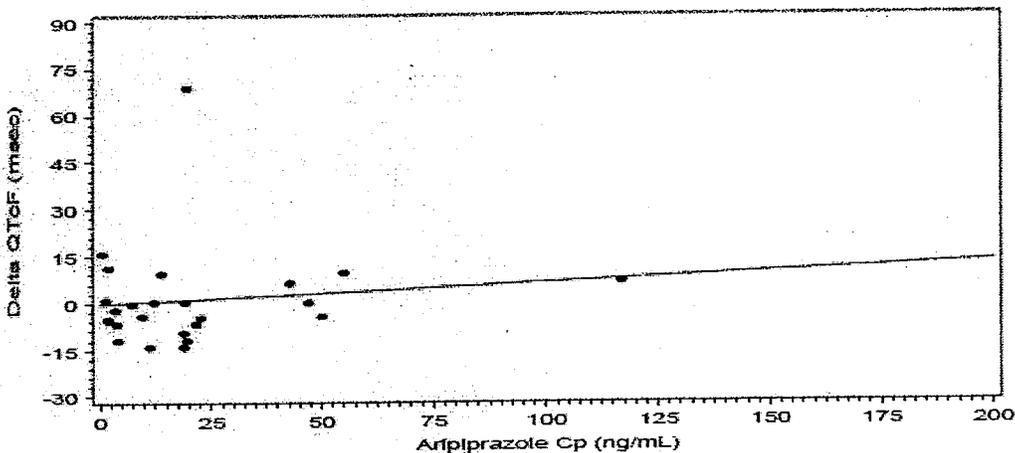


Table 11.2: Results of Linear Regression Analyses of QTc Changes from Baseline (Ambulatory 12-Lead ECGs) on Aripiprazole Plasma Concentrations

Δ QTc (msec)	Aripiprazole Cp (ng/mL)				
	n ^a	Intercept		Slope	
		Point Estimate	95% C.I.	Point Estimate	95% C.I.
Δ QTcN	25	0.79	(-8.59, 10.16)	0.0659	(-0.2211, 0.3528)
Δ QTcF	25	-0.30	(-9.19, 8.59)	0.0656	(-0.2066, 0.3378)
Δ QTcB	25	3.94	(-8.45, 16.33)	0.0788	(-0.3003, 0.4579)

CN138050

Source: Appendix 11.2C

Note: Aripiprazole plasma concentrations < LLQ were replaced by 0.5-LLQ where LLQ=1 ng/mL

^a n is the number of data pairs in the analyses

The 95% confidence intervals for the slopes of the regression analyses of changes from baseline in QTcN, QTcF, and QTcB for both paper and ambulatory 12-lead ECG recordings all included zero. Similarly, the 95% confidence intervals for the slopes of the regression analyses of changes from baseline in QTcN, QTcF, and QTcB for paper ECG recordings also all included zero. Thus, 1 to 45 mg intramuscular doses of aripiprazole (administered in 1 to 3 doses within a 24 h period, see Table 9 for a summary of numbers of injections per subject in each dose group) were not associated with aripiprazole or dehydro-aripiprazole concentration-dependent effects on changes in QTc interval from baseline in acutely agitated patients with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder.

THE FIRMS ANALYSIS WAS REPRODUCED BY THE REVIEWER.

APPENDIX

SAS CODE FOR ARPIPIRAZOLE QT ANALYSIS

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Andre Jackson
8/23/2006 11:16:49 AM
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Raman Baweja
8/23/2006 02:16:07 PM
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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-866	Brand Name	Abilify IM
OCBP Division (I, II, III)	I	Generic Name	Aripiprazole
Medical Division	DPP	Drug Class	Anti-psychotic
OCBP Reviewer	Kofi Kumi	Indication(s)	Schizophrenia
OCBP Team Leader	Raman Baweja	Dosage Form	Injection
		Dosing Regimen	5 - 15 mg/day
Date of Submission	12/29/05	Route of Administration	IM
Estimated Due Date of OCPB Review	8/12/06	Sponsor	BMS/OTSUKA
PDUFA Due Date	9/30/06	Priority Classification	Standard
Division Due Date	8/29/06		

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:	X	1		
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		
In-vivo effects of primary drug:	X	1		
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:				
Effect of Aripiprazole on QTc	X	1		
Pediatric development plan				
Literature References				
Total Number of Studies		4		
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)	1. Is Exposure after IM administration similar to the oral formulation(s)? 2. Is the proposed dosing supported by the pharmacokinetics of Aripiprazole after IM administration? 3. Are potential drug-drug interactions identified and addressed?			
Other comments or information not included above	This application is all electronic. Link to EDR \\CDSESUB1\N21866\N 000\2005-11-29			
Primary reviewer Signature and Date	Kofi A. Kumi 1/25/06			
Secondary reviewer Signature and Date				

CC: NDA 21-866, HFD-850 (Electronic Entry or Lee), HFD-130, HFD-860 (Mehta, Baweja, KumiK), CDR (B. Murphy)

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Kofi Kumi
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Raman Baweja
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