

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-713

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21713

Sequence number/date/type of submission: 000/ November 20, 2003 (NDA electronic submission)

Information to sponsor: Yes () No (x)

Sponsor and/or agent:

Otsuka America Pharmaceutical, Inc.

2440 Research Boulevard, Rockville, MD 20850

Phone (301) 990-0036

Manufacturer for drug substance:

Otsuka Pharmaceutical Co., Ltd

2-9 Kanda Tsukasa-cho, Chiyoda-ku Tokyo, 101-8535, Japan

Reviewer name: Sonia Tabacova, Ph.D.

Division name: Neuropharmacological Drug Products, HFD #: 120

Review completion date: September 18, 2004

Drug:

Trade name: ABILIFY™ Oral Solution

Generic name (list alphabetically): Aripiprazole

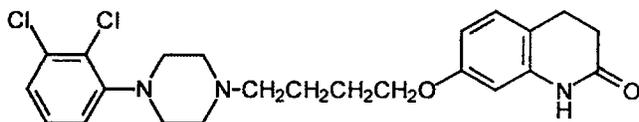
Code name: OPC-14597, BMS-337039

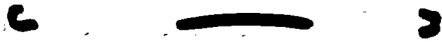
Chemical name: 7-[4-[4-(2, 3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone

CAS registry number: 129-22-12-9

Molecular formula/molecular weight: 448.39

Structure:



Relevant INDs/NDAs/DMFs: IND Nos. 42 776 & 62 216; NDA Nos. 21 436; 21713 (BC) June 8/2004 & 21713 (BZ) August 16/2004; DMF Nos. 

Drug class: Psychotropic (partial D₂ and 5HT_{1A} agonist, 5HT₂ antagonist)

Indication: Treatment of schizophrenia

Clinical formulation: Oral Solution (1 mg/ml)

Route of administration: Oral

Proposed use: N/A

Disclaimer: Tabular and graphical information from sponsor's submission is identified as such.

Executive Summary

- I. Recommendations
 - A. Recommendation on Approvability: Approvable
 - B. Recommendation for Nonclinical Studies: None
 - C. Recommendations on Labeling: None
- II. Summary of Nonclinical Findings

- A. Brief Overview of Nonclinical Findings:

PK/TK

The oral bioavailability of aripiprazole and the systemic exposure to the parent compound and its metabolites were approximately 3-fold higher from the oral solution formulation than from the clinical tablet in monkeys (a comparative study was not performed in the rat). The predominant metabolites in plasma of both monkeys and rats were the active metabolite dehydro-aripiprazole (BMS-337044) and BMS-337047 (OPC-3373, acid product of N-dealkylation). In the monkey, their mean AUC values (upon a single aripiprazole dose) were about 1.2 times and 1.4 times those of the parent, respectively; in the rat (upon aripiprazole daily administration for 12 weeks) they were 9.6, and 9.5% of the parent, respectively.

As pointed out by the sponsor, the difference in bioavailability of aripiprazole from the oral solution seen in the monkey "is not observed in humans because the extent of presystemic metabolism of aripiprazole differs between monkeys and humans".

General toxicology

In a thirteen-week oral toxicity study in rats, a 25-mg/kg/day dose of aripiprazole alone and a 22.5-mg/kg/day dose of aripiprazole combined with [redacted] 'day each of the degradants, [redacted]

The treatment resulted in similar effects in the groups with or without the degradants, including: comparable incidences of clinical signs (tremor, hypoactivity, ptosis), no differences between groups in body weights, food consumption, clinical pathology, organ weights, gross pathology, and similar incidences of drug-related microscopic changes (minimal or mild atrophy of the pituitary pars intermedia and a low incidence of minimal pulmonary alveolar histiocytosis in both sexes; minimal to mild mammary gland hyperplasia, with increased mammary gland secretion, and persistent diestrus with associated minimal to moderate vaginal mucification and minimal or mild uterine atrophy in females). These findings show that there were no toxicological differences between comparable doses of aripiprazole with and without the degradants, [redacted] administered orally for 13 weeks.

Genetic toxicology

Aripiprazole alone and in combination with [redacted] (each) was assessed for mutagenic potential in an Ames reverse-mutation study in *Salmonella* and *Escherichia coli*. In the definitive mutation assay, the mean histidine+ and tryptophan+ revertant values observed were not elevated significantly in any of the BMS-337039 or BMS-337039/degradants-treated cultures in comparison to the negative-control cultures. Cytotoxicity, as evidenced by a reduction in revertant frequency and/or a reduction in the bacterial background lawn density, was observed in each of the *Salmonella* and *E. coli* strains at the highest BMS-

2 Page(s) Withheld

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

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:	1
II. SAFETY PHARMACOLOGY:	1
III. PHARMACOKINETICS/TOXICOKINETICS:	1
IV. GENERAL TOXICOLOGY:	5
V. GENETIC TOXICOLOGY:	12
VI. CARCINOGENICITY:	23
VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:	23
VIII. SPECIAL TOXICOLOGY STUDIES:	24
IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:	24
X. APPENDIX/ATTACHMENTS:	25

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

No new studies submitted

II. SAFETY PHARMACOLOGY:

No new studies submitted

III. PHARMACOKINETICS/TOXICOKINETICS:

Studies submitted with this application:

- A PK study in monkeys; entitled “Pharmacokinetics of Various Formulations of BMS-337039 (aripiprazole) in Male Cynomolgus Monkeys” (Study MAP024; Protocol # 178/337039/004 and 178/337039/004A);
- A TK study in rats, entitled “Toxicokinetic analysis of BMS-337039 and its metabolites in a 13-week oral qualifying toxicity study in rats” (Study DM00031)

Pharmacokinetics of Various Formulations of BMS-337039 (aripiprazole) in Male Cynomolgus Monkeys (Study MAP024; Protocol # 178/337039/004 and 178/337039/004A):

This is a single-dose study in adult male Cynomolgus monkeys (n=3) to determine (a) the PK of aripiprazole and its metabolites upon administration of the oral solution formulation and (b) the bioavailability of aripiprazole from the oral solution vs. the tablet formulation. According to a five-period cross-over design, each monkey received a single 15 mg clinical tablet of aripiprazole, 15 mg oral solution (1 mg aripiprazole per ml), 8 mg ethanolic solution and 2 different 15-mg orally disintegrating tablet formulations, with a washout period of at least 3 days between consecutive doses. Plasma concentrations of aripiprazole and its metabolites were determined by LC/MS/MS in serial blood samples collected over 24 h. after dose administration (the lower limit of quantitation was for aripiprazole and its metabolites BMS-337044, BMS-337045, and DCPP, and for BMS-337040 and BMS-337047).

The mean PK parameters for aripiprazole and its metabolites are presented in the sponsor’s tables below and on the next page:

Mean (SD) pharmacokinetic values for aripiprazole after administration of various formulations to monkeys (N=3) in studies 178/337039/004 and 178/337039/004A

Formulation	Dose (mg)	C _{MAX} (ng/mL)	T _{MAX} ^a (h)	AUC(0-T) ^b (ng.h/mL)	F (%)
Tablet	15	12.8 (4.89)	4.00 (3.00, 10.0)	124 (29.4)	-
Oral Liquid (Solution)	15	54.2 (32.4)	2.00 (1.00, 3.00)	382 (252)	288 (136)

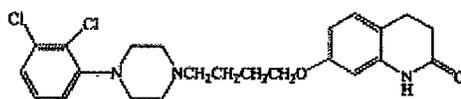
a reported as median (minimum, maximum)

b T = 10 to 24 h

Aripiprazole was more rapidly absorbed from the oral solution (Tmax=2 h) as compared to the tablet (Tmax=4 h.); the mean Cmax was about 4x greater, and the systemic exposure (AUC) was approximately 3x greater for the oral solution than for the tablet. The mean bioavailability of the oral liquid solution vs. the clinical tablet was 288%.

The predominant metabolites in the plasma (see figure below) were the active metabolite, dehydro-aripiprazole (BMS-337044), and BMS-337047 (OPC-3373, acid product of N-dealkylation); their mean AUC values were about 1.2 times and 1.4 times those of the parent, respectively. Metabolites BMS-337045 and DCPD had low plasma concentrations and their mean AUC values were <20% that of the parent (see table on the next page), and metabolite BMS-337040' plasma levels were below the lower limit of quantitation (PK values for this metabolite were not reported). The differences in the PK parameters of metabolites between the oral solution and tablet administration were similar to those of the parent compound.

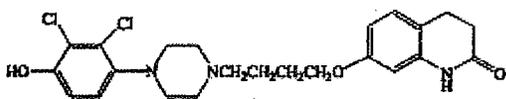
Chemical structures of aripiprazole and its metabolites BMS-337040, BMS-337044, BMS-337045, BMS-337047, and DCPD



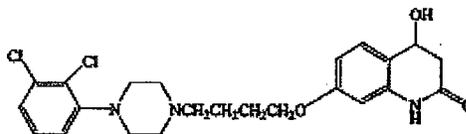
Aripiprazole (BMS-337039, OPC-1497, OPC-31)



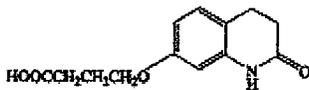
BMS-337044 (OPC-14857)



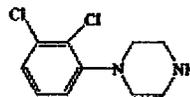
BMS-337040 (DM-1451)



BMS-337045 (DM-1452)



BMS-337047 (OPC-3373)



DCPD

Mean (SD) pharmacokinetic values for metabolites BMS-337044, BMS-337045, BMS-337047, and DCPD after administration of various formulations to monkeys (N=3) in studies 178/337039/004 and 178/337039/004A

Metabolite	Formulation	C _{MAX} (ng/mL)	T _{MAX} ^a (h)	AUC (0-T) ^b (ng.h/mL)	$\frac{AUC(\text{metabolite})}{AUC(\text{parent})}$
BMS-337044 (OPC-14857)	Tablet	13.5 (6.85)	4.00 (3.00, 10.0)	147 (36.1)	1.25 (0.44)
	Solution	36.7 (5.80)	3.00 (2.00, 4.00)	379 (133)	1.20 (0.48)
	FM1	15.2 (8.90)	8.00 (3.00, 8.00)	212 (138)	1.28 (0.43)
	FM2	27.3 (6.59)	3.00 (2.00, 3.00)	254 (87.5)	1.23 (0.35)
	Eth Soln	23.4 (6.61)	2.00 (1.00, 2.00)	190 (65.9)	1.09 (0.28)
BMS-337045 (DM-1452)	Tablet	2.86 (2.02)	4.00 (3.00, 24.0)	18.4 (5.66)	0.16 (0.07)
	Solution	7.99 (0.93)	2.00 (1.00, 3.00)	59.9 (9.76)	0.21 (0.13)
	FM1	2.77 (1.30)	8.00 (1.00, 10.0)	29.5 (18.2)	0.18 (0.06)
	FM2	5.21 (1.13)	3.00 (1.00, 3.00)	31.9 (6.53)	0.17 (0.09)
	Eth Soln	7.87 (2.08)	1.00 (1.00, 1.00)	32.1 (7.71)	0.19 (0.05)
BMS-337047 (OPC-3373)	Tablet	36.4 (24.7)	2.00 (0.75, 4.00)	156 (116)	1.45 (1.32)
	Solution	110 (16.0)	1.00 (0.75, 1.00)	376 (93.5)	1.45 (1.08)
	FM1	28.3 (17.4)	2.00 (1.00, 8.00)	189 (86.0)	1.31 (0.74)
	FM2	83.0 (19.3)	2.00 (2.00, 2.00)	276 (65.1)	1.56 (1.01)
	Eth Soln	103 (20.6)	3.00 (1.00, 3.00)	407 (102)	2.77 (1.69)
DCPD	Tablet	1.68 ^c	3.00 ^c (2.00, 4.00)	4.08 ^d	0.04 ^d
	Solution	3.63 (2.23)	2.00 (0.75, 2.00)	11.5 (6.31)	0.06 (0.06)
	FM1	1.10 ^c	4.50 ^c (1.00, 8.00)	3.10 ^d	0.04 ^d
	FM2	2.19 (2.09)	2.00 (2.00, 8.00)	6.28 ^c	0.06 ^c
	Eth Soln	2.44 (1.61)	1.00 (1.00, 2.00)	4.11 ^d	0.03 ^c

a reported as median (minimum, maximum)

b T = 24 h for BMS-337044; T = 10 to 24 h for BMS-337045 and BMS-337047; T = 2 to 4 h for DCPD

c N=2

d N=1

Toxicokinetic analysis of BMS-337039 and its metabolites in a 13-week oral qualifying toxicity study in rats (Study DM00031)

This study was conducted in the framework of a toxicology study that assessed the effect of aripiprazole containing the degradants [BMS-337040, BMS-337044, BMS-337045, BMS-337047, and DCPP] in comparison to aripiprazole alone administered orally to rats (10/sex/group) for 13 weeks.

For the TK study, the rats were exposed to aripiprazole (alone) oral formulation dose of 25-mg/kg/day for 13 weeks. Blood samples were collected from three or four rats/sex given aripiprazole alone at 1, 2, 4, 8, and 24 h after dosing on week 12 of the study. The samples were analyzed for aripiprazole (BMS-337039) and five metabolites [BMS-337040 (DM-1451), BMS-337044 (OPC-14857), BMS-337045 (DM-1452), BMS-337047 (OPC-3373), and 1-(2, 3-dichlorophenyl) piperazine (DCPP)] by a validated LC/MS/MS method with lower limits of quantitation of [BMS-337039, BMS-337044, BMS-337045, and DCPP], and [BMS-337040 and BMS-337047]. The plasma TK parameters for aripiprazole and two pharmacologically active metabolites, BMS-337040 and BMS-337044, at week 12 of the study are listed in the sponsor's table below.

TK parameters of aripiprazole (BMS-337039) and two pharmacologically active metabolites, BMS-337040 and BMS-337044, following a 25-mg/kg/day oral formulation dose of BMS-337039 for 12 weeks in rats

Dose [mg/kg/day]	Study Week	BMS-337039		BMS-337040		BMS-337044	
		Males	Females	Males	Females	Males	Females
25	12	C _{max} (ng/mL)					
		1730	1710	15.8	8.9	193	112
		AUC (ng.h/mL)*					
		24613	23832	191	108	2793	1850

* Calculated from time zero to 24 h.

The systemic exposure to aripiprazole was higher than the exposure to the five metabolites: the AUC values of BMS-337040, BMS-337044, BMS-337045, BMS-337047, and DCPP relative to the parent drug were 0.6, 9.6, 0.9, 9.5, and 3.9% respectively (males and females combined and corrected for molecular weights). BMS-337044 was the major metabolite. The overall systemic exposure of rats to the six compounds was in the following order: BMS-337039 (parent) > BMS-337044 > BMS-337047 > DCPP > BMS-337045 > BMS-337040.

PK/TK summary: The predominant metabolites in plasma of both monkeys and rats were the active metabolite dehydro-aripiprazole (BMS-337044), and BMS-337047 (OPC-3373, acid product of N-dealkylation). In the monkey, their mean AUC values (upon a single aripiprazole dose) were about 1.2 times and 1.4 times those of the parent, respectively; in the rat (upon aripiprazole daily administration for 12 weeks) they were 9.6, and 9.5% of the parent, respectively.

In monkeys, the oral bioavailability of aripiprazole was approximately 3-fold higher from the oral solution formulation than from the clinical tablet (such comparative study was not performed in the rat). The differences in the PK parameters of metabolites between the oral solution and tablet administration were similar to those of the parent compound.

As pointed out by the sponsor, "such a difference in bioavailability of aripiprazole from the oral solution is not observed in humans because the extent of presystemic metabolism of aripiprazole differs between monkeys and humans. The absolute bioavailability of aripiprazole from the tablet formulation (compared to intravenous administration) is about 87% in humans (Salazar, 2001, as referenced by the sponsor) versus about only 8% in monkeys (Kashiyama,

1996, as referenced by the sponsor). In humans, the geometric mean C_{max} for aripiprazole was about 22% higher following administration of a 30-mg dose of oral solution compared to that after a 30-mg dose of tablet” (Kornhauser, 2003, as referenced by the sponsor) .

References:

- Salazar DE. 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. Final Study Report for Protocol CN138-016. July 20, 2001. BMS Document Control No. 93000380.
- Kashiya E. Plasma concentrations of OPC-14597 after single intravenous administration in cynomolgus monkeys. Otsuka Report No. 009778. August 29, 1996. BMS Document Control No. 920001379.
- Kornhauser D. Relative bioavailability study to estimate the dose of aripiprazole administered as the proposed commercial oral solution formulation that will provide an aripiprazole exposure comparable to that obtained from 1x30 mg commercial tablet in healthy subjects. Final Study Report for Protocol CN 138-108. BMS Document Control No. 930005174.

PK/TK conclusions:

The oral bioavailability of aripiprazole, and the systemic exposure to the parent compound and its metabolites was approximately 3-fold higher from the oral solution formulation than from the clinical tablet in monkeys (a comparative study was not performed in the rat). The predominant metabolites in plasma of both monkeys and rats were the active metabolite dehydro-aripiprazole (BMS-337044), and BMS-337047 (OPC-3373, acid product of N-dealkylation). In the monkey, their mean AUC values (upon a single aripiprazole dose) were about 1.2 times and 1.4 times those of the parent, respectively; in the rat (upon aripiprazole daily administration for 12 weeks) they were 9.6, and 9.5% of the parent, respectively.

As pointed out by the sponsor, the difference in bioavailability of aripiprazole from the oral solution seen in the monkey “is not observed in humans because the extent of presystemic metabolism of aripiprazole differs between monkeys and humans”.

IV. GENERAL TOXICOLOGY:

Studies submitted with this application:

Study title: BMS-337039 Thirteen-week oral qualifying toxicity study in rats

Key study findings: A 25-mg/kg/day dose of aripiprazole alone and a 22.5-mg/kg/day dose of aripiprazole combined with [redacted] for 13-weeks to CD (SD) IGS BR rats (10/sex/group). The treatment resulted in similar effects in the groups with or without the degradants, including: comparable incidences of clinical signs (tremor, hypoactivity, ptosis), no differences between groups in body weights, food consumption, clinical pathology, organ weights, gross pathology, and similar incidences of drug-related microscopic changes (minimal or mild atrophy of the pituitary pars intermedia and a low incidence of minimal pulmonary alveolar histiocytosis in both sexes; minimal to mild mammary gland hyperplasia, with increased mammary gland secretion, and persistent diestrus with associated minimal to moderate vaginal mucification and minimal or mild uterine atrophy in females). These findings show that there were no toxicological differences between comparable doses of aripiprazole with and without the degradants [redacted] administered by oral gavage for 13 weeks.

Study no: DM00031

Volume # 2

Conducting laboratory and location: BRISTOL-MYERS SQUIBB

Pharmaceutical Research Institute
Departments of Toxicology and Pathology
Mt. Vernon, Indiana USA

Date of study initiation: November, 2000

GLP compliance: Yes

QA report: yes

Drug, lot #, radiolabel, and % purity:

Aripiprazole (BMS-337039), Lot No. C00B92M, purity

Formulation/vehicle:

Aripiprazole: Suspension in

Methods (unique aspects): Comparisons made between groups treated with aripiprazole alone (25 mg/kg/day) or with a combination of aripiprazole (22.5 mg/kg)

Dosing:

Species/strain: CD₁(SD)IGS BR rats

#/sex/group or time point (main study): 10

Satellite groups used for toxicokinetics or recovery: # 3-4 sex/group for TK

Age: 7 weeks

Weight: 208 to 235g (males) and 150 to 178g (females).

Doses in administered units: a total daily dose of 25 mg/kg containing 22.5 mg/kg aripiprazole (BMS-337039) and each (dose levels and groups shown in sponsor's table below):

GROUP NUMBER	TOTAL DAILY DOSE (mg/kg)	DAILY DOSE VOLUME (ml/kg)	CONCENTRATION (mg/ml)	NUMBER OF RATS
1	25 ^a	8.3	3	10 M, 10 F
2	25 ^b	8.3	2.7/0.15 ^b	10 M, 10 F

^a BMS-337039 without degradants

^b Represents a total daily dose for a mixture comprised of 22.5 mg/kg (2.7 mg/ml) BMS-337039

Aripiprazole dose selection was based on a 26-week oral toxicity study with BMS-337039 in rats at 10, 30, and 60 mg/kg/day (Bristol-Myers Squibb Study No. 99353), showing "minimal to moderate clinical toxicity" at 30 and 60 mg/kg/day, and morphologic changes in adrenal, pituitary, reproductive, and/or mammary tissues (exaggerated pharmacologic effects of treatment) at all doses. For the degradants, the dose selection was made as "an approximately multiple on a mg/kg basis of the anticipated highest level of each degradant at the maximum intended clinical dose (30 mg) of the oral liquid formulation", or approximately an of the maximum qualification threshold level of each degradant at the maximum intended daily clinical dose (30 mg) of the oral liquid formulation under refrigerated conditions.

Route, form, volume, and infusion rate: Oral (gavage), Suspension in gum arabic /Sterile water for irrigation, USP. Daily dose volume = 8.3 ml/kg

Observations and times:

Clinical signs: Twice daily

Body weights: baseline, prior to the first dose, and once weekly during the dosing period.

Food consumption: baseline, and once weekly during the dosing period.

Ophthalmoscopy: pretest and after the daily dose during weeks 6 and 12.

EKG: No

Hematology: Prior to necropsy. (Bone marrow smears were not evaluated "since hematology parameters were unremarkable and there were no histopathologic alterations in slides of fixed bone marrow").

Clinical chemistry: Prior to necropsy

Urinalysis: Prior to necropsy

Gross pathology: All animals, full list of organs

Organs weighed: Adrenals, Brain, Heart, Kidney, Liver, Ovary, Pituitary, Prostate, Spleen, Testis, Thymus, Thyroid, Uterus.

Histopathology: Samples of all protocol-specified organs (full list) and all gross lesions were processed, stained with hematoxylin and eosin and examined by light microscopy.

Toxicokinetics: Plasma concentrations of aripiprazole (BMS-337039) and five metabolites (BMS-337040, BMS-337044, BMS-337045, BMS-337047, DCP) were determined for Group 1 (BMS-337039 without degradants). After a daily dose during Week 12, blood samples were collected from 3 to 4 M and 3 to 4 F at approximately 1, 2, 4, 8, and 24 hours. A similar blood sample volume was drawn from the Group 2 animals and discarded.

Results:

Mortality: None

Clinical signs: Post-dose tremor, hypoactivity, and ptosis and hyperactivity prior to the next daily dose were present at similar incidences in both groups. Hyperactivity (increased sniffing, cage biting, and pawing), not associated with an increase in locomotor activity, appeared after third week of dosing and was comparable between the groups. There were no effects attributable to the degradants (see sponsor's tables below).

Summary Daily Clinical Observations for Males
(Group 1 = Aripiprazole only; Group 2 = Aripiprazole + Degradants)

	Group 1 25 ng/kg/day	Group 2 25 ng/kg/day
End-of-Dose sacrifice		
Number of Observations	10	10
Number of Animals	10	10
Days from - to	93 93	93 93
Tremor		
Number of Observations	3	2
Number of Animals	3	2
Days from - to	6 10	6 49
Hyperactivity		
Number of Observations	146	82
Number of Animals	10	9
Days from - to	14 90	14 93
Hypoactivity		
Number of Observations	787	803
Number of Animals	10	10
Days from - to	2 92	2 92
Ptosis		
Number of Observations	596	629
Number of Animals	10	10
Days from - to	2 92	2 92

Summary Daily Clinical Observations for Females
(Group 1 = Aripiprazole only; Group 2 = Aripiprazole + Degradants)

	Group 1 25 ng/kg/day	Group 2 25 ng/kg/day
End-of-Dose sacrifice		
Number of Observations	10	10
Number of Animals	10	10
Days from - to	93 93	93 93
Tremor		
Number of Observations	5	7
Number of Animals	3	4
Days from - to	35 81	7 39
Hyperactivity		
Number of Observations	370	246
Number of Animals	10	10
Days from - to	16 93	16 93
Hypoactivity		
Number of Observations	738	750
Number of Animals	10	10
Days from - to	2 92	2 92
Salivation		
Number of Observations	1	.
Number of Animals	1	.
Days from - to	36 36	.
Ptosis		
Number of Observations	572	575
Number of Animals	10	10
Days from - to	2 92	2 92

Body weights: No differences between groups (see sponsor's summary tables below)

Summary Group Mean Body Weights for Males

		Bodyweights (Gram)												
		Week numbers relative to Start Date												
Group	Sex	-1	1	2	3	4	5	6	7	8	9	10	11	12
1m	Mean	165.34	228.07	265.28	301.34	343.22	372.87	397.32	408.75	424.35	438.15	450.45	459.57	460.69
	S.D.	5.54	5.40	8.39	16.62	21.28	25.57	32.57	32.95	36.85	38.88	42.31	42.82	48.46
	N	10	10	10	10	10	10	10	10	10	10	10	10	10
2m	Mean	164.84	220.57	266.83	308.27	347.68	377.24	401.77	412.60	429.26	441.72	457.04	463.56	473.13
	S.D.	4.96	8.23	14.68	17.06	22.07	23.22	23.17	19.90	22.23	19.97	20.82	22.26	21.76
	N	10	10	10	10	10	10	10	10	10	10	10	10	10

Summary Group Mean Body Weights for Females

		Bodyweights (Gram)												
		Week numbers relative to Start Date												
Group	Sex	-1	1	2	3	4	5	6	7	8	9	10	11	12
	Mean	135.40	163.54	190.70	205.90	231.79	238.78	253.90	254.61	265.70	265.92	279.06	279.75	288.05
	S.D.	4.68	6.95	8.74	13.39	15.28	16.63	15.04	20.83	16.29	16.50	15.68	17.75	15.37
	N	10	10	10	10	10	10	10	10	10	10	10	10	10
	Mean	135.62	162.34	189.04	203.17	228.47	239.24	251.56	255.82	264.43	268.41	274.32	282.20	286.75
	S.D.	4.60	6.76	11.16	17.26	20.05	21.94	26.43	24.48	25.54	30.88	28.35	30.04	29.64
	N	10	10	10	10	10	10	10	10	10	10	10	10	10

Food consumption: No differences between groups

Ophthalmoscopy: No differences between groups

Hematology: Decrease in reticulocyte counts in group 2 [significant in M (by 27%), non-significant in F (by 17%)], see table below. Increase in the mean activated partial thromboplastin

time in group 2 [significant in F (by 18%), non-significant in M (by 25%)]. Otherwise, there were no notable differences in mean or individual hematology or coagulation parameters.

Reticulocyte counts, individual data (reproduced from sponsor's table)

(Group 1 = Aripiprazole only; Group 2 = Aripiprazole + Degradants)

Males		Females	
Group 1	Group 2	Group 1	Group 2
RET	RET	RET	RET
%	%	%	%
3.2	2.3	3.4	2.1
----	----	----	----
3.4	2.6	5.5	2.4
----	----	----	----
2.1	3.2	2.6	2.7
----	----	----	----
2.7	1.8	2.2	2.7
----	----	----	----
4.1	2.3	2.5	2.0
----	----	----	----
2.8	2.4	3.2	3.5
----	----	----	----
2.4	2.3	3.0	2.6
----	----	----	----
2.9	2.1	3.6	1.7
----	----	----	----
4.3	1.7	2.7	2.4
----	----	----	----
3.4	2.1	1.8	3.1
Mean	Mean	Mean	Mean
3.13	2.28 (p<0.01)	3.05	2.52

Clinical chemistry: There were no notable inter-group differences in the clinical chemistry parameters.

Urinalysis: There were no notable inter-group differences in the clinical chemistry parameters.

Organ weights: Lower mean absolute and relative liver weight (by 10%) and absolute kidney weight (by 14%) in Group 2 females were most likely attributable to biological variations. There were no other inter-group differences in organ weights.

Gross pathology: No notable findings

Histopathology: Drug-related microscopic changes of comparable incidence and severity were present in both dose groups and included: “minimal or mild atrophy of the pituitary pars intermedia and a low incidence of minimal pulmonary alveolar histiocytosis in both sexes; minimal to mild mammary gland hyperplasia, minimally increased mammary gland secretion (distention with secretion), and a high incidence of persistent diestrus with associated minimal to moderate vaginal mucification and minimal or mild uterine atrophy in females”. There were no notable differences in the microscopic findings between rats in Groups 1 and 2 (see sponsor's table below).

Incidence of BMS-337039- and BMS-337039 (plus degradants)-related Microscopic Findings in the Pituitary Gland, Lungs, Female Reproductive Tissues, and Mammary Gland

Dose (mg/kg/day):	25	22.5 + Degradants
No. of Rats: (M/F)	10/10	10/10
Sex:	M/F	M/F
<u>Pituitary Gland:</u>		
Atrophy, pars intermedia		
Minimal severity	0/1	2/1
Mild severity	9/8	8/8
<u>Lungs:</u>		
Histiocytosis, alveolar		
Minimal severity	1/0	3/1
<u>Stage of the Estrus Cycle^a</u>		
Diestrus (persistent)	10(8)	9(7)
<u>Vagina:</u>		
Mucification, mucosal epithelium		
Minimal severity	2	4
Mild severity	6	3
Moderate severity	1	0
<u>Uterus:</u>		
Atrophy		
Minimal severity	0	1
Mild severity	1	0
<u>Mammary Gland:</u>		
Hyperplasia		
Minimal severity	0/3	0/8
Mild severity	0/4	0/1
Increased secretion (distention with secretion)		
Minimal severity	0/3	0/4

^a Based on vaginal and uterine histomorphology

Toxicokinetics: TK data are reviewed in the PK/TK part of this review.

Toxicology summary: (See Key Study Findings)

Toxicology conclusions: There were no notable differences in the clinical signs, body weight, food consumption, clinical chemistry parameters, organ weight, or pathomorphological findings between rats given 25 mg/kg/day of aripiprazole alone, or 22.5 mg/kg/day aripiprazole plus degradants (— — — — —). Drug-related histopathological changes in the pituitary gland, lungs, female reproductive tissues, and mammary gland were comparable in both dose groups. These findings show that no additional toxicity is induced by

degradants _____ administered by oral gavage for 13 weeks.

Histopathology Inventory for NDA # 21713

Study	DM00031 BMS-337039 Thirteen-week oral qualifying toxicity study in rats			
Species	Rat			
Adrenals	x			
Aorta	x			
Bone Marrow smear	x (-)			
Bone (femur)	x			
Brain	x			
Cecum	x			
Cervix	x			
Colon	x			
Duodenum				
Epididymis	x			
Esophagus	x			
Eye	x			
Fallopian tube				
Gall bladder				
Gross lesions	x			
Harderian gland	x			
Heart	x			
Ileum	x			
Injection site				
Jejunum	x			
Kidneys	x			
Lachrymal gland				
Larynx				
Liver	x			
Lungs	x			
Lymph nodes, cervical	x			
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland	x			
Nasal cavity				

Optic nerves				
Ovaries	x			
Pancreas	x			
Parathyroid	x			
Peripheral nerve	x			
Pharynx				
Pituitary	x			
Prostate	x			
Rectum				
Salivary gland	x			
Sciatic nerve				
Seminal vesicles	x			
Skeletal muscle	x			
Skin	x			
Spinal cord	x			
Spleen	x			
Sternum				
Stomach	x			
Testes	x			
Thymus	x			
Thyroid	x			
Tongue	x			
Trachea	x			
Urinary bladder	x			
Uterus	x			
Vagina	x			
Zymbal gland				
Standard List				

X, histopathology performed
 *, organ weight obtained

V. GENETIC TOXICOLOGY:

Study title: BMS-337039 Ames Reverse-Mutation Qualifying Study in Salmonella and Escherichia coli

Key findings:

Aripiprazole alone and in a combination containing [redacted] was not mutagenic in a microbial mutagenicity study in *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* tester strain WP2 *uvrA*, tested in triplicate cultures at concentrations ranging from 0.5-50 µg/plate in strains TA98, TA100, TA1535, and TA1537, and from 1.6-160 µg/plate in *E. coli* WP2 *uvrA*, both with and without S-9 metabolic activation. (The concentrations were selected on the basis of a range-finding study at five concentrations ranging from 16-1600 and from 50-5000 µg/plate in the *Salmonella* and *Escherichia coli* strains, respectively; cytotoxicity was observed at concentrations ≥ 50 and ≥ 160 µg/plate in the *Salmonella* and *E. coli*, respectively. Based on this study, the top concentrations for the definitive study were 50 and 160 µg/plate for the *Salmonella* and *E. coli* strains, respectively). In the definitive study, cytotoxicity, as evidenced by a reduction in revertant frequency and/or a reduction in the bacterial background lawn density, was observed in each of the *Salmonella* and *E. coli* strains at the highest concentration(s) tested, both with and/or without S-9 activation. These findings support the conclusion that when tested up to cytotoxic concentrations, BMS-337039 and BMS-337039/degradants were not mutagenic in the microbial mutagenicity assay.

Study no: DS01055

Volume # 2

Conducting laboratory and location:

Bristol-Myers Squibb Pharmaceutical Research Institute
Department of Genetic Toxicology
Syracuse, New York

Date of study initiation: March, 2001

GLP compliance: Yes

QA reports: yes

Drug, lot #, radiolabel, and % purity:

BMS-337039, Lot No. C00B92M, purity [redacted]

Formulation/vehicle: BMS-337039 and BMS-337039 containing [redacted] of the degradants [redacted]

Methods:

Strains/species/cell line:

S. typhimurium histidine auxotrophs TA98, TA100, TA1535, and TA1537

E. coli WP2 *uvrA* tryptophan auxotroph

Dose selection criteria:

Basis of dose selection:

Range finding studies: A non-GLP range-finding assay was performed to assess the mutagenicity and cytotoxicity of BMS-337039 and BMS-337039/degradants in tester strains TA98, TA100, TA1535, TA1537, and WP2 *uvrA* in both the presence and absence of S-9 metabolic activation

and to determine concentrations for the definitive study. The degradants were evaluated at concentrations ranging from _____/plate in the Salmonella and *Escherichia coli* strains, respectively. Cytotoxicity as evidenced by reductions in the revertant frequency and/or reductions in the bacterial background lawn, was observed at concentrations ≥ 50 and ≥ 160 $\mu\text{g}/\text{plate}$ in the Salmonella and *E. coli* strains, respectively. Based on this study, the top concentrations for the full study were 50 and 160 $\mu\text{g}/\text{plate}$ for the Salmonella and *E. coli* strains, respectively.

Metabolic activation system: Crude rat-liver extract (S-9) obtained from male Sprague-Dawley rats, administered a single intraperitoneal injection of Aroclor 1254 (500 mg/kg) 5 days prior to sacrifice.

Controls: Vehicle: DMSO

Negative controls: DMSO, 100 $\mu\text{l}/\text{plate}$

Positive controls:

PC1: 2-aminoanthracene (2-AA), 2.5 $\mu\text{g}/\text{plate}$

PC2: 2-aminoanthracene (2-AA), 10.0 $\mu\text{g}/\text{plate}$

PC3: 2-nitrofluorene (2-NF), 2.0 $\mu\text{g}/\text{plate}$

PC4: sodium azide (Na azide), 2.0 $\mu\text{g}/\text{plate}$

PC5: 9-aminoacridine (9-AA), 100.0 $\mu\text{g}/\text{plate}$

PC6: methyl methane-sulfonate (MMS), 2.5 $\mu\text{l}/\text{plate}$

The positive-control articles prepared in DMSO, with the exception of sodium azide (dissolved in water)

Exposure conditions:

Incubation and sampling times: Cultures incubated in darkness at 37°C for 46-50 h.

Doses used in definitive study: 160, 50, 16, 5, 1.6, and 0.5 $\mu\text{g}/\text{plate}$.

Study design: All test article/ degradants concentrations were evaluated in triplicate cultures in both the presence and in the absence of S-9 metabolic activation. The concentrations ranged from 0.5-50 $\mu\text{g}/\text{plate}$ and from 1.6-160 $\mu\text{g}/\text{plate}$ in the Salmonella and *E. coli* strains, respectively. Five concentrations were evaluated per strain. The negative controls were evaluated in replicates of five cultures also in the presence and absence of S-9 metabolic activation, and the positive controls in duplicate cultures.

Analysis:

No. of replicates: As described above

Counting method: The number of revertant colonies was determined by either counting colonies manually or with an automated counter. The mean number of histidine+/tryptophan+ revertants in all test-article treatment groups were compared to the mean number of revertants in the negative-control treatments.

Criteria for positive results:

1. A two-fold increase in the mean number of revertants per plate above the negative control in strains TA98, TA100, and WP2 *uvrA*.
2. A three-fold increase in the mean number of revertants per plate above the negative control in strains TA1535 and TA1537.
3. Increases in revertant counts for all strains must be related to increases in test-article concentration in order to warrant the designation of positive.
4. A positive response in one tester strain either with or without exogenous metabolic activation is sufficient to designate the test article as a bacterial mutagen.

Results:

The results of the definitive mutation assay are summarized in the sponsor's tables below and on the next two pages. In the definitive mutation assay, the mean histidine+ and tryptophan+ revertant values observed were not elevated significantly in any of the aripiprazole (BMS-337039) or aripiprazole +degradants-treated cultures in comparison to the negative-control cultures. Cytotoxicity, as evidenced by a reduction in revertant frequency and/or a reduction in the bacterial background lawn density, was observed in each of the Salmonella and *E. coli* strains at the highest BMS-337039 and/or BMS-337039/degradants concentration(s) tested, either with and/or without S-9 activation. Significant increases in the histidine+/tryptophan+ revertant frequencies were observed in cultures treated with the positive controls.

Table: Aripiprazole alone

**BMS-337039 Summary
Mean Histidine⁺ and Tryptophan⁺ Revertant Counts
from the Full Assay**

**In the Presence of S-9 Metabolic Activation
Mean ± Standard Deviation¹**

Test Article	Concentration (µg/plate)	TA98	TA100	TA1535	TA1537	WP2 uvrA
		Mean ± SD ¹				
DMSO	100 µl/plate	27 ± 6	107 ± 8	10 ± 4	4 ± 3	20 ± 7
BMS-337039	0.5	25 ± 5	105 ± 14	10 ± 3	7 ± 3	-
	1.6	23 ± 2	100 ± 9	10 ± 0	5 ± 1	19 ± 5
	5	28 ± 1	101 ± 5	7 ± 3	3 ± 4	26 ± 7
	16	20 ± 6	94 ± 8	10 ± 4	6 ± 3	21 ± 6
	50	25 ± 9	99 ± 5	8 ± 2	4 ± 1	15 ± 5
	160	-	-	-	-	13 ± 6
2-Aminoanthracene	2.5	2510	2895	443	445	-
2-Aminoanthracene	10	-	-	-	-	608

**In the Absence of S-9 Metabolic Activation
Mean ± Standard Deviation¹**

Test Article	Concentration (µg/plate)	TA98	TA100	TA1535	TA1537	WP2 uvrA
		Mean ± SD ¹				
DMSO	100 µl/plate	21 ± 4	89 ± 10	7 ± 3	5 ± 2	28 ± 5
BMS-337039	0.5	18 ± 2	94 ± 11	9 ± 1	5 ± 0	-
	1.6	18 ± 3	94 ± 13	8 ± 3	5 ± 1	18 ± 4
	5	19 ± 5	85 ± 11	9 ± 1	5 ± 2	14 ± 3
	16	17 ± 3	91 ± 7	8 ± 1	7 ± 2	21 ± 4
	50	15 ± 3	82 ± 6	5 ± 2	4 ± 2	15 ± 2
	160	-	-	-	-	16 ± 4
2-Nitrofluorene	2	853	-	-	-	-
Sodium azide	2	-	1067	957	-	-
9-Aminoacridine	100	-	-	-	946	-
Methyl methane-sulfonate	2.5 µl/plate	-	-	-	-	733

- indicates not tested at this concentration

Table: Aripiprazole in combination with degradants

**BMS-337039/degradants Summary
Mean Histidine⁺ and Tryptophan⁺ Revertant Counts
from the Full Assay**

**In the Presence of S-9 Metabolic Activation
Mean ± Standard Deviation¹**

Test Article	Concentration (µg/plate)	TA98	TA100	TA1535	TA1537	WP2 uvrA
		Mean ± SD ¹				
DMSO	100 µl/plate	27 ± 6	107 ± 8	10 ± 4	4 ± 3	20 ± 7
BMS-337039/ degradants	0.5	21 ± 1	107 ± 14	9 ± 3	8 ± 3	-
2-Aminoanthracene	2.5	2510	2895	443	445	-
2-Aminoanthracene	10	-	-	-	-	608

**In the Absence of S-9 Metabolic Activation
Mean ± Standard Deviation¹**

Test Article	Concentration (µg/plate)	TA98	TA100	TA1535	TA1537	WP2 uvrA
		Mean ± SD ¹				
DMSO	100 µl/plate	21 ± 4	89 ± 10	7 ± 3	5 ± 2	28 ± 5
BMS-337039/ degradants	0.5	15 ± 5	95 ± 17	9 ± 2	5 ± 1	-
2-Nitrofluorene	2	853	-	-	-	-
Sodium azide	2	-	1067	957	-	-
9-Aminoacridine	100	-	-	-	946	-
Methyl methane-sulfonate	2.5 µl/plate	-	-	-	-	733

- indicates not tested at this concentration

Aripiprazole alone

Bacterial Background Lawn Evaluation from the Full Assay with BMS-337039

In the Presence of S-9 Metabolic Activation^a

BMS-337039	TA98	TA100	TA1535	TA1537	WP2 uvrA
0 ^b	0	0	0	0	-
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	1	0
0	1	2	3	3	0
-	-	-	-	-	1

In the Absence of S-9 Metabolic Activation^a

BMS-337039	TA98	TA100	TA1535	TA1537	WP2 uvrA
0 ^b	0	0	0	0	-
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	1	2	0
0	3	3	3	3	0
-	-	-	-	-	1

^aConcentrations in terms of µg of test article. █ /plate

^bTreated plates were compared to the negative controls and graded on a scale of 0-4
 - indicates not tested at this concentration

Grading system:

- 0 = No reduction of the bacterial background lawn
- 1 = Minimal reduction of the bacterial background lawn
- 2 = Moderate reduction of the bacterial background lawn
- 3 = Marked reduction of the bacterial background lawn
- 4 = Complete annihilation of the bacterial background lawn

Aripiprazole in combination with degradants

Bacterial Background Lawn Evaluation from the Full Assay with BMS-337039/degradants

In the Presence of S-9 Metabolic Activation^a

BMS-337039/degradants	TA98	TA100	TA1535	TA1537	WP2 uvrA

In the Absence of S-9 Metabolic Activation^a

BMS-337039/degradants	TA98	TA100	TA1535	TA1537	WP2 uvrA

Summary of individual study findings:

Aripiprazole alone and in combination containing [REDACTED] (each) was assessed for mutagenic potential in an Ames reverse-mutation study in *Salmonella* and *Escherichia coli*. In the definitive mutation assay, the mean histidine+ and tryptophan+ revertant values observed were not elevated significantly in any of the BMS-337039 or BMS-337039/degradants-treated cultures in comparison to the negative-control cultures. Cytotoxicity, as evidenced by a reduction in revertant frequency and/or a reduction in the bacterial background lawn density, was observed in each of the *Salmonella* and *E. coli* strains at the highest BMS-337039 and/or BMS-337039/degradants concentration(s) tested, either with and/or without S-9 activation. Significant increases in the histidine+/tryptophan+ revertant frequencies were observed in cultures treated with the positive-controls.

Study validity: This study is valid because satisfied the validity criteria for the definitive assay.

Study outcome: Aripiprazole alone and in combination containing [REDACTED] was not mutagenic in the Ames reverse-mutation assay when tested to the maximum concentrations required.

Study title: Oral Qualifying Micronucleus Study in Mice

Key findings: The *in vivo* genotoxic potential of aripiprazole (BMS-337039) containing the degradants [REDACTED] was evaluated in a GLP mouse bone-marrow erythrocyte micronucleus assay. Treatment of two groups of mice (10/sex/group) with aripiprazole (BMS-337039) with and without degradants [REDACTED] (administered as a single oral dose of 45 mg/kg of BMS-337039 with [REDACTED] of each degradant, or 50 mg/kg of BMS-337039 without degradants) did not result in decreases in polychromatic erythrocytes (PCE) indicative of bone-marrow toxicity, neither in increased frequencies of micronucleated PCE in femoral bone-marrow samples collected at 24 hr and 48 hr post dose, when compared to the negative-control group. Drug-related clinical signs, limited to decreased activity in males, were present in both aripiprazole-treated groups, with and without degradants. The tested degradants' dose was approximately an [REDACTED] multiple [REDACTED] of the maximum qualification threshold level of each degradant [REDACTED] at the maximum intended daily clinical dose (30 mg) of the oral liquid formulation under refrigerated conditions. These findings support the conclusion that treatment with BMS-337039, with and without degradants [REDACTED] was non-genotoxic in the oral mouse bone-marrow micronucleus test.

Study no: DS01006

Volume # 2

Conducting laboratory and location:

Bristol-Myers Squibb
Pharmaceutical Research Institute
Department of Genetic Toxicology
Syracuse, New York, USA

Date of study initiation: February, 2001

GLP compliance: Yes

QA reports: yes

Drug, lot #, radiolabel, and % purity:

Aripiprazole (BMS-337039) Lot No. C00B92M, purity

[redacted]

Formulation/vehicle:

[redacted]

Methods:

Strains/species/cell line: ICR(CD-1) mice

Dose selection criteria:

Basis of dose selection:

The dose selected for this study was 50 mg/kg (45 mg/kg of BMS-337039, 2.5 mg/kg of degradant [redacted] of degradant [redacted]. At this dose, aripiprazole without degradants induced decreases in spontaneous motor activity, hypothermia, and body weight decreases in previous studies in mice (Otsuka's Study Report Nos. 004910, 004911, 012763, 012858, and 013049, as cited by the sponsor). The tested degradants' dose was approximately an [redacted] multiple of the maximum qualification threshold level of each degradant [redacted] at the maximum intended daily clinical dose (30 mg) of the oral liquid formulation under refrigerated conditions.

Range finding studies: No

Test agent stability: Stable

Controls:

Vehicle (Negative). [redacted]

Positive controls: Cyclophosphamide, Lot No. 108H05681, intraperitoneal injection at a dose of 25 mg/kg as a single dose.

Exposure conditions:

Doses used in definitive study: 50 mg/kg of BMS-337039 alone or 45 mg/kg of BMS-337039, [redacted]

Study design:

Two groups (10 animals/sex/group) received either 45 mg/kg of BMS-337039 and [redacted] or 50 mg/kg of BMS-337039 without degradants, respectively. An additional group of the same size served as negative control and received [redacted] (see sponsor's table below). Bone marrow samples (femur) were collected at 24 and 48 h. post-dose from 5 animals/sex/group for micronucleus evaluation. Bone-marrow smears were fixed in 100% methanol and stained with acridine orange.

Experimental Design

Group Number	Test Article	Total Dose (mg/kg)	Dose Volume (ml/kg)	Concentration (mg/ml)	No. of Animals	Animal No.
1	0 ^a	0	16.7	0	5 M, 5 F ^e 5M, 5 F ^f	1101-1105, 1201-1205 1106-1110, 1206-1210
2	BMS-337039	50 ^b	16.7	2.7/0.15/0.15 ^c	5 M, 5 F ^e 5M, 5 F ^f	2101-2105, 2201-2205 2106-2110, 2206-2210
3	BMS-337039	50 ^d	16.7	3.0	5 M, 5 F ^e 5M, 5 F ^f	3101-3105, 3201-3205 3106-3110, 3206-3210
4	Cyclophosphamide	25	10	2.5	5 M, 5 F ^e	4101-4105, 4201-4205

^a The negative- (vehicle-) control was

^b BMS-337039 (45 mg/kg).

^c BMS-337039 (2.7 mg/ml).

^d BMS-337039 without degradants.

^e Euthanatized approximately 24 hr postdose.

^f Euthanatized approximately 48 hr postdose.

Analysis:

Bone-marrow smear slides from the test article, negative-, and positive-control (CP) group animals were collected and blind coded prior to performing the micronucleus evaluations. A minimum of 1000 PCE was scored by each of two individual scorers (for a minimum total of 2000 PCE).

For each animal, the following parameters were calculated:

- a. Total erythrocytes evaluated = Normochromatic erythrocytes (NCE) + polychromatic erythrocytes (PCE) + MN-PCE.
- b. Mean percent PCE in approximately 1000 erythrocytes = $PCE / (NCE + PCE + MN-PCE) \times 100$.
- c. Mean percent MN-PCE in total PCE evaluated = $MN-PCE / (PCE + MN-PCE) \times 100$.

Criteria for positive results: (directly reproduced from the report)

The mean MN-PCE value at any dose level is statistically significant, exceeds the highest value for this parameter observed for the negative-control group means tested previously in our laboratory (i.e., the micronucleus frequency in any test-article group must exceed the upper limit [mean + 2 standard deviations] of the current historical range of MN- PCE values) and is at least three-fold greater than the concurrent negative-control mean value.

(Note: The historical negative-control range for the percent PCE in the bone marrow of mice ranged from approximately 46 to 58%, with a mean percentage of approximately 53%. The historical value for negative-control group mean percent micronucleated-PCE (MN-PCE) in the bone marrow of mice was 0.18% (±0.04%); on an individual animal basis, the range was from 0 to 0.45%).

Results:

Clinical signs of drug-related toxicity, limited to moderately decreased activity, were seen in males given aripiprazole with or without degradants at 24 and 48 h. post-dose. No mortality was observed. As shown in sponsor's tables below and on the next page, no bone-marrow cytotoxicity (as measured by decreases in PCE relative to the negative-control group) was observed in aripiprazole-treated groups with or without degradants at both 24 and 48 hr postdose.

Likewise, the frequencies of MN-PCE in the bone marrow of both treated groups (with and without degradants) were not increased in comparison to the negative-control at both 24 and 48 hr postdose.

At 24 hr postdose, the mean frequencies of MN-PCE in the bone marrow in aripiprazole-treated groups were 0.07% without degradants (both sexes) and 0.07% (M) and 0.10% (F) in the group with degradants, vs. 0.05 and 0.10% in the negative control for males and females, respectively. The higher mean % MN-PCEs in males treated with aripiprazole with no degradants was due to one individual outlier and was not reproduced at 48 h. At 48 hr postdose, the MN-PCE frequencies in the group with degradants were 0.07% (M) and 0.10% (F); in the group without degradants, the mean values were 0.05% for males and females, respectively, vs. 0.05% negative-control frequency for both sexes. A positive micronucleus response was seen in the positive control (Cyclophosphamide) group (see sponsor's tables on the next page).

BMS-337039: Oral Qualifying Micronucleus Study in Mice

24 Hour

Summary of Bone-Marrow Analysis

Article	Total Dose (mg/kg)	Sex	No. Mice Evaluated	Mean % PCE (±SD)	Mean % MN-PCE (±SD)
Vehicle ^a	0	M	5	48 ± 2.4	0.05 ± 0.03
BMS-337039	BMS-337039 ^b	M	5	47 ± 4.6	0.07 ± 0.06
	BMS-337039 ^c	M	5	49 ± 6.0	0.22 ± 0.19
CP ^d	25	M	5	46 ± 2.1	1.27 ± 0.22**
Vehicle ^a	0	F	5	50 ± 6.9	0.10 ± 0.07
BMS-337039	BMS-337039 ^b	F	5	49 ± 4.0	0.07 ± 0.08
	BMS-337039 ^c	F	5	53 ± 5.3	0.09 ± 0.04
CP ^d	25	F	5	49 ± 4.8	1.48 ± 0.25**

^a The negative (vehicle) control article was

^b BMS-337039 (45 mg/kg).

^c BMS-337039 (50 mg/kg), without degradants.

^d Cyclophosphamide

** Statistically significant at P<0.01

BMS-337039: Oral Qualifying Micronucleus Study in Mice

48 Hour

Summary of Bone-Marrow Analysis

Article	Total Dose (mg/kg)	Sex	No. Mice Evaluated	Mean % PCE (±SD)	Mean % MN-PCE (±SD)
Vehicle ^a	0	M	5	52 ± 5.8	0.06 ± 0.08
BMS-337039	BMS-337039 ^b	M	5	46 ± 7.2	0.03 ± 0.04
	BMS-337039 ^c	M	5	48 ± 3.6	0.04 ± 0.04
Vehicle ^a	0	F	5	53 ± 4.8	0.06 ± 0.04
BMS-337039	BMS-337039 ^b	F	5	49 ± 2.3	0.08 ± 0.06
	BMS-337039 ^c	F	5	53 ± 6.3	0.12 ± 0.10

^a The negative (vehicle) control article was

^b BMS-337039 (45 mg/kg),

^c BMS-337039 (50 mg/kg), without degradants.

Summary of individual study findings: (see key study findings)

Study validity: The study met the validity criteria (reproduced below from the study report)

CRITERIA FOR AN ACCEPTABLE ASSAY

1. The mean percentage of MN-PCE in the negative-control group must not exceed 0.5%.
2. In bone-marrow smears, 2000 scorable PCE per animal must be available.
3. The mean MN-PCE value for the positive-control group must be statistically significant, exceed the upper limit (mean + 2 standard deviations of the current historical range of MN-PCE values); and be at least three-fold greater than the concurrent negative-control mean MN-PCE value.
4. A minimum of four males and four females at each time point (24 hr and 48 hr) must survive test-article treatment for bone-marrow sampling and subsequent microscopic analyses.

Study outcome: Treatment with aripiprazole, with and without degradants was non-genotoxic in the oral mouse bone-marrow micronucleus test at doses of either 50 mg/kg aripiprazole alone, or 45 mg/kg of aripiprazole in combination with of each degradant. The tested degradants' dose was approximately an multiple of the maximum qualification threshold level of each degradant at the maximum intended daily clinical dose (30 mg) of the oral liquid formulation under refrigerated conditions.

Genetic toxicology summary:

Aripiprazole alone and in combination containing [redacted] of degradants [redacted] (each) was assessed for mutagenic potential in an Ames reverse-mutation study in *Salmonella* and *Escherichia coli*. In the definitive full mutation assay, the mean histidine+ and tryptophan+ revertant values observed were not elevated significantly in any of the BMS-337039 or BMS-337039/degradants-treated cultures in comparison to the negative-control cultures. Cytotoxicity, as evidenced by a reduction in revertant frequency and/or a reduction in the bacterial background lawn density, was observed in each of the *Salmonella* and *E. coli* strains at the highest BMS-337039 and/or BMS-337039/degradants concentration(s) tested, either with and/or without S-9 activation. These findings support the conclusion that when tested up to maximum concentrations limited by cytotoxicity, BMS-337039 and BMS-337039/degradants were not mutagenic in the microbial mutagenicity assay.

The *in vivo* genotoxic potential of aripiprazole containing the degradants [redacted] was evaluated in a GLP mouse bone-marrow erythrocyte micronucleus assay. Treatment of two groups of mice (10/sex/group) with aripiprazole (BMS-337039) with and without degradants [redacted] (administered as a single oral dose of 45 mg/kg of BMS-337039 with [redacted] of each degradant, or 50 mg/kg of BMS-337039 without degradants) did not result in decreases in polychromatic erythrocytes (PCE) indicative of bone-marrow toxicity, neither in increased frequencies of micronucleated PCE in femoral bone-marrow samples collected at 24 hr and 48 hr post dose, when compared to the negative-control group. Drug-related clinical signs, limited to a decreased activity in males, were present in both aripiprazole-treated groups, with and without degradants. (%). The tested degradants' dose was approximately an [redacted] multiple [redacted] of the maximum qualification threshold level of each degradant [redacted] at the maximum intended daily clinical dose (30 mg) of the oral liquid formulation under refrigerated conditions. These findings support the conclusion that treatment with BMS-337039, with and without degradants [redacted], was non-genotoxic in the oral mouse bone-marrow micronucleus test.

Genetic toxicology conclusions: Aripiprazole, with and without degradants [redacted] was not mutagenic in the microbial mutagenicity assay when tested to the maximum concentrations limited by cytotoxicity and non-genotoxic in the *in vivo* oral mouse bone-marrow micronucleus test.

VI. CARCINOGENICITY:

No studies submitted with this application.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

No studies submitted with this application.

VIII. SPECIAL TOXICOLOGY STUDIES:

No studies submitted with this application.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

- The oral bioavailability of aripiprazole, and the systemic exposure to the parent compound and its metabolites was approximately 3-fold higher from the oral solution formulation than from the clinical tablet in monkeys (such comparative study was not performed in the rat). The predominant metabolites in plasma of both monkeys and rats were the active metabolite dehydro-aripiprazole (BMS-337044), and BMS-337047 (OPC-3373, acid product of N-dealkylation). In the monkey, their mean AUC values (upon a single aripiprazole dose) were about 1.2 times and 1.4 times those of the parent, respectively; in the rat (upon aripiprazole daily administration for 12 weeks) they were 9.6, and 9.5% of the parent, respectively.
- As pointed out by the sponsor, the difference in bioavailability of aripiprazole from the oral solution seen in the monkey "is not observed in humans because the extent of presystemic metabolism of aripiprazole differs between monkeys and humans".
- There were no notable differences in the general toxicity manifestations (clinical signs, body weight, food consumption, clinical chemistry parameters, organ weight, or pathomorphological findings) between rats given 25 mg/kg/day of aripiprazole alone, or 22.5 mg/kg/day aripiprazole plus degradants [redacted]. Drug-related histopathological changes in the pituitary gland, lungs, female reproductive tissues, and mammary gland were comparable in both dose groups. These findings show that no additional toxicity is induced by degradants [redacted] administered by oral gavage for 13 weeks.
- Aripiprazole, with and without degradants [redacted], was not mutagenic in the microbial mutagenicity assay when tested to the maximum concentrations required internationally and non-genotoxic in the oral mouse bone-marrow micronucleus test.

General Toxicology Issues:

Two degradation products [redacted] and an impurity [redacted] that is a metabolite [the active metabolite dehydro-aripiprazole (BMS-337044)] are formed in this drug formulation at levels above [redacted] under room temperature storage conditions. In the filing review, the Division pointed out that the specification for degradants [redacted] respectively) exceeded the qualification threshold of [redacted] for degradants in the drug product (according to ICH-Q3B, Impurities in New Drug Products). The sponsor assessed the [redacted] degradants in a 13-week oral toxicity study in rats and two genotoxicity studies (Ames test, *in vivo* micronucleus assay in mice). The Division requested that the sponsor needed to conduct additional genotoxicity studies on these degradants ["either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse

1 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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

/s/

Sonia Tabacova
9/21/04 03:43:35 PM
PHARMACOLOGIST

Lois Freed
9/21/04 04:10:45 PM
PHARMACOLOGIST