Table 4.
Parameter of blood concentration of radioactivity in rats after an oral and intravenous administration of ^{14}C-OPC-14597

dose	route		Tmax (hr)	Cmax (ng eq./ml)	T1/2(1) (hr)	T1/2(2) (hr)	AUC (0-24hr) (ng eq.·hr/ml)	AUC (0-∞hr) (ng eq.·hr/ml)
2mg/kg	po	fasting	1 ± 0	35.6±2.2	5.7±1.0 (Tmax-)	-	296±15	317±26 (0-48hr)
3mg/kg	po	fasting *	1 ± 0	55.5±2.8	7.6±0.5 (Tmax-24hr)	31± 5 (24hr-)	446±40	625±42 (0-96hr)
	po	non-fasting *	6 ± 1	29.8±2.5	14 ± 2 (Tmax-48hr)	54±12 (48hr-)	491±42	809±121 (0-96hr)
10mg/kg	po	fasting	1.3±0.3	278.5±84.0	6.7±0.3 (Tmax-24hr)	69±24 (24hr-)	1949±419	2514±376 (0-96hr)
30mg/kg	po	fasting	1.3±0.3	1117.0±224.5	6.7±1.0 (Tmax-24hr)	62±17 (24hr-168hr)	10011±2493	14429±3261 (0-168hr)
3mg/kg	iv	fasting			1.1±0.2 (5min-3hr)	7.6±1.8 (3hr-)	1051±53	-

Each value represents the mean ± S.D. of three rats (*:four rats)

Table 6
Pharmacokinetic parameters of radioactivity in blood after a single intravenous administration of ^{14}C-OPC-14597 at 3 mg/kg to fasting male rats

Animal No.	C_0 [1] (ng eq./mL)	C_{5min} (ng eq./mL)	AUC_{0-t} [1,2] (ng eq.·hr/mL)	0-t Calculated Range [2] (hr)	$AUC_{0-inf\ (predicted)}$ [1] (ng eq.·hr/mL)	$t_{1/2}$ (hr)	$t_{1/2}$ Calculated Range (hr)	Cl (predicted) (mL/hr/kg)	Vz (predicted) (mL/kg)
89110901	525	437	1063	0 – 24	1173	8.0	3 – 24	2558	29397
89110902	612	541	823	0 – 12	1131	10.4	3 – 12	2652	39817
89110903	789	566	992	0 – 12	1108	4.3	3 – 12	2709	16608
Mean	642	515	959	-[3]	1137	7.6	-[3]	2640	28607
SD	135	68	123	-[3]	33	3.1	-[3]	76	11625
SE	78	39	71	-[3]	19	1.8	-[3]	44	6711

1) C_0 was extrapolated and calculated by $C_{0,min}$ and $C_{0,25min}$, 2) t : terminal detected time (hr), 3) - : not calculated
Each data was calculated by the WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).

Table 3-1 Pharmacokinetic parameters of radioactivity in blood after a single oral administrationof ^{14}C-OPC-14597 at 3 mg/kg to fasting female rats

Animal No.	Dose (mg/kg)	Tmax (hr)	Cmax (ng/mL)	AUC_{0-last} (ng*hr/mL)	AUC_{0-last} Calculated Range (hr)	$AUC_{0-inf\ (predicted)}$ (ng*hr/mL)	$t_{1/2}$ (hr)	$t_{1/2}$ Calculated Range (hr)
90042001		1.0	48.9	480	0 – 96	544	41.5	24 – 96
90042002	3	1.0	52.5	454	0 – 72	503	34.5	24 – 72
90042003		1.0	60.8	482	0 – 72	551	38.3	24 – 72
90042004		1.0	59.6	466	0 – 96	517	39.8	24 – 96
Mean		1.0	55.5	471	-[1]	529	38.5	-[1]
SD		0.0	5.7	13	-[1]	23	3.0	-[1]
SE		0.0	2.8	7	-[1]	11	1.5	-[1]

1) - : not calculated
Each data was calculated by the WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).

Table 3-2 Pharmacokinetic parameters of radioactivity in blood after a single intravenous administrationof ^{14}C-OPC-14597 at 3 mg/kg to fasting female rats

Animal No.	C_0 [1] (ng/mL)	C_{last} (ng/mL)	AUC_{0-last} [1] (ng·hr/mL)	AUC_{0-last} Calculated Range [2] (hr)	$AUC_{0-inf(predicted)}$ [1] (ng·hr/mL)	$t_{1/2}$ (hr)	$t_{1/2}$ Calculated Range (hr)	Cl (predicted) (mL/hr/kg)	Vz (predicted) (mL/hr)
89110901	662.6	490	1115	0 - 12	1270	4.4	3 - 12	2362	15057
89110902	662.6	499	1032	0 - 24	1075	5.7	3 - 24	2792	22862
89110903	702.9	531	1328	0 - 24	1380	5.6	3 - 24	2174	17682
Mean	676.0	507	1158	- [2]	1242	5.2	- [2]	2443	18534
SD	23.3	22	153	- [2]	154	0.7	- [2]	317	3972
SE	13.4	12	88	- [2]	89	0.4	- [2]	183	2293

1) C_0 was extrapolated and calculated by $C_{0.083hr}$ and $C_{0.25hr}$, 2) - : not calculated
Each data was calculated by the WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).

Urinary, fecal, and biliary data are summarized in the table below [radioactivity data expressed as mean ± SE; units: % of dose]. Urine [up to 168 hr postdosing] and feces [up to 168 hr postdosing] were collected in the same animals; bile samples [up to 72 hr postdosing] were collected in a separate grp of bile-cannulated rats.

M/F	URINE	FECES	TOTAL	BILE
M	7.3 ± 1.2	88.6 ± 1.6	95.8 ± 0.5	0.3 ± 0.1
F	6.9 ± 0.5	91.5 ± 0.4	98.5 ± 0.8	77.6 ± 6.3

Biliary radioactivity following a 3-mg/kg intraduodenal dose [3 mg/kg] in males accounted for 0.7 ± 0.2% of dose radioactivity.

Plasma and brain levels, as well as urinary and fecal levels, of OPC 14597 were assessed in Sprague-Dawley rats [15/sex or 3/sex/time point] following an acute oral [30 mg/kg] dose of ^{14}C-OPC 14597 [Study No. 010694]. Blood samples were collected at 1, 2, 4, 8, and 24 hrs postdosing. Urine and fecal samples were collected for 24 hrs following dosing in the same animals used for blood sampling. Brains were collected at necropsy. OPC-14597 and metabolites were quantitated in the biological samples using . Total radioactivity, OPC 14597, and metabolites were quantitated in two separate regions of brain [forebrain, occipital] using similar methods used on plasma. The data were summarized in the following sponsor's tables:

Table 1. Pharmacokinetic parametars of radioactive unchanged drug and metabolites in plasma after an oral administration of ^{14}C-OPC-14597 at a dose of 30mg/kg to rats

Compound	Tmax(hr) male	Tmax(hr) female	Cmax(μg eq./ml) male	Cmax(μg eq./ml) female	AUC0-8hr(μg eq. · hr/ml) male	AUC0-8hr(μg eq. · hr/ml) female
Total radioactivity	4.0	2.0	0.67	1.14	4.23	4.93
OPC-14597	4.0	2.0	0.52	0.80	2.59	3.58
OPC-3373	1.0	2.0	0.13	0.11	0.39	0.33
OPC-14857	2.0	2.0	0.05	0.11	0.37	0.40
DM-1454	1.0	1.0	0.09	0.07	0.39	0.32
DM-1451	2.0	1.0	0.05	0.03	0.18	0.08

These data calculated by mean concentrations of three rats.
AUC0-8hr were calculated by trapezoidal rule.

Table 2. Pharmacokinetic parametars of total radioactivity in brain after an oral administration of ^{14}C-OPC-14597 at dose of 30mg/kg to rats

brain	Tmax(hr)		Cmax(μg eq./ml)		AUC0-8hr(μg eq. · hr/ml)	
	male	female	male	female	male	female
medura oblongata and pons	4.0	2.0	1.98	3.57	9.46	13.65
cerebellum	4.0	2.0	1.66	3.12	8.49	11.13
fore brain	4.0	2.0	1.56	3.44	8.26	11.90
occipital brain	4.0	2.0	1.63	3.38	8.35	12.30

These data calculated by mean concentrations of three rats.
AUC0-8hr were calculated by trapezoidal rule.

Table 3. Pharmacokinetic parametars of radioactive unchanged drug in brain after an oral administration of ^{14}C-OPC-14597 at a dose of 30mg/kg to rats

brain	Tmax(hr)		Cmax(μg eq./ml)		AUC0-8hr(μg eq. · hr/ml)	
	male	female	male	female	male	female
medura oblongata and pons	4.0	2.0	1.98	3.57	8.63 (91.3)	11.75 (86.0)
cerebellum	4.0	2.0	1.66	3.12	7.77 (91.5)	9.40 (84.5)
fore brain	4.0	2.0	1.33	3.44	7.21 (87.3)	10.36 (87.1)
occipital brain	4.0	2.0	1.61	3.38	7.42 (88.8)	11.90 (96.7)

These data calculated by mean concentrations of three rats.
AUC0-8hr were calculated by trapezoidal rule.
The value in parenthesis represents the percentage of unchanged drug to total radioactivity in the each part of brain.

Table 4. The radioactive proportion of OPC-14597 and its metabolites in urine and feces after an oral administration of ^{14}C-OPC-14597 at a dose of 30mg/kg to rats

Compound	Urine(%)		Feces(%)	
	male	female	male	female
OPC-3373	61.5	52.6	1.0	0.9
DM-1454	0.2	13.4	0.6	0.4
DM-1451	N.D.	7.3	48.9	44.6
OPC-14857	N.D.	N.D.	2.0	2.2
OPC-14597	N.D.	0.0	35.2	41.5

Value represents percentage of radioactivity in urine or feces.
Urine and feces were collected by 24hr after dosing.
Urinary excretion ratio of radioactivity were 4.4% (male) and 4.0% (female) of dose.
Feces excretion ratio of radioactivity were 71.1% (male) and 50.3% (female) of dose.
These data calculated by mean concentrations of three rats.
N.D.;not detected (<10dpm).

Tissue distribution of radioactivity was assessed in males [Report No. 005520] following an acute 3-mg/kg oral dose of ^{14}C-OPC-14597. Tissues were collected from 0.5 to 168 hrs postdosing. The data were summarized in the following sponsor's table:

Table 2. Tissue distributions of radioactivity after an oral administration of ^{14}C-OPC-14597 at 3mg/kg in male rats

Tissue / Time(hr)	Concentration of radioactivity (ng eq. / g tissue) 0.5	2	4	8	24	48	72	168
Plasma	130 ± 21	77 ± 7	74 ± 13	36 ± 3	4 ± 0	1 ± 0	N.D.	N.D.
Blood	84 ± 15	52 ± 4	49 ± 9	25 ± 0	3 ± 0	1 ± 0	N.D.	N.D.
Cerebrum	92 ± 21	142 ± 94	68 ± 30	18 ± 2	6 ± 2	N.D.	N.D.	N.D.
Cerebellum	90 ± 15	125 ± 61	72 ± 32	23 ± 1	5 ± 2	1 ± 0	N.D.	N.D.
M. Oblongata	130 ± 42	138 ± 62	107 ± 49	26 ± 1	11 ± 2	3 ± 0	2 ± 0	N.D.
Hypophysis	458 ± 180	1318 ± 810	405 ± 90	105 ± 29	30 ± 17	N.D.	N.D.	N.D.
Eye ball	101 ± 7	125 ± 20	140 ± 37	25 ± 7	9 ± 4	N.D.	N.D.	N.D.
H. Gland	228 ± 60	660 ± 113	899 ± 154	524 ± 15	277 ± 20	144 ± 15	70 ± 3	18 ± 2
Sub. Gland	319 ± 41	706 ± 77	667 ± 150	428 ± 84	270 ± 25	224 ± 60	55 ± 4	75 ± 45
Thymus	643 ± 411	221 ± 52	282 ± 54	96 ± 20	31 ± 8	9 ± 1	4 ± 0	N.D.
Thyroid	673 ± 186	1738 ± 756	340 ± 103	152 ± 37	N.D.	N.D.	N.D.	N.D.
Trachea	996 ± 445	3076 ±1979	617 ± 393	125 ± 19	28 ± 16	6 ± 3	N.D.	N.D.
Heart	324 ± 48	287 ± 54	228 ± 87	60 ± 1	13 ± 8	2 ± 1	N.D.	N.D.
Lung	1107 ± 310	975 ± 153	589 ± 203	167 ± 23	20 ± 3	6 ± 0	2 ± 1	N.D.
Liver	13352 ±3725	4690 ±1080	3528 ± 688	1728 ± 186	218 ± 17	105 ± 18	76 ± 14	24 ± 4
Pancreas	862 ± 273	688 ± 208	506 ± 276	123 ± 3	23 ± 5	6 ± 1	3 ± 0	3 ± 1
Spleen	765 ± 28	1263 ± 81	1226 ± 398	573 ± 93	203 ± 27	37 ± 3	15 ± 1	4 ± 1
Kidney	1087 ± 195	797 ± 126	655 ± 83	303 ± 20	58 ± 1	16 ± 1	10 ± 0	3 ± 2
Adrenal	1248 ± 359	2061 ± 117	1885 ± 127	1404 ± 172	1048 ± 85	605 ± 58	382 ± 19	94 ± 13
Testis	161 ± 27	251 ± 77	260 ± 88	124 ± 15	39 ± 3	13 ± 0	7 ± 1	5 ± 1
Ves. Semi.	243 ± 82	559 ± 258	234 ± 46	126 ± 40	19 ± 9	3 ± 1	N.D.	N.D.
Stomach	14369 ±6001	5357 ±3203	2125 ± 856	111 ± 28	24 ± 8	4 ± 0	1 ± 1	N.D.
Small Int.	14397 ±2272	9721 ±1402	6302 ±1066	953 ± 278	90 ± 28	8 ± 2	3 ± 0	N.D.
Large Int.	1280 ± 672	563 ± 93	450 ± 139	2091 ± 919	95 ± 17	11 ± 2	3 ± 1	N.D.
Skin	133 ± 10	252 ± 104	167 ± 45	49 ± 4	18 ± 2	5 ± 1	3 ± 1	N.D.
Muscle	219 ± 93	687 ± 232	119 ± 35	125 ± 37	13 ± 9	N.D.	N.D.	N.D.
Fat	428 ± 149	315 ± 73	206 ± 58	38 ± 6	N.D.	N.D.	N.D.	N.D.
Brown Fat	716 ± 208	555 ± 189	266 ± 98	160 ± 77	36 ± 19	N.D.	N.D.	N.D.
Lympho.	1296 ± 344	352 ± 38	381 ± 124	144 ± 53	29 ± 11	10 ± 4	3 ± 2	3 ± 2
B. Marrow	223 ± 44	311 ± 29	265 ± 77	59 ± 6	8 ± 5	N.D.	N.D.	N.D.
Bone	90 ± 22	188 ± 61	158 ± 82	26 ± 4	N.D.	N.D.	N.D.	N.D.

Each value represents the mean ± S.E. of three rats. N.D., <30 dpm

PK parameters were also assessed for the parent compound in a separate study [Protocol No. 178/337039/001A] in male Sprague-Dawley rats. Aripiprazole was administered as an acute dose of 3.75 mg/kg i.v. [10-min infusion]. Data are summarized in the following table:

C_{max} [ng/mL]	T_{max} [hr]	$AUC_{(0-\infty)}$ [ng•hr/mL]	$t_{1/2}$ [hr]	Cl [mL/min/kg]	V_{ss} [L/kg]
784	0.17	739	1.29	88.1	6.94

[The metabolism data from this study are summarized in the "Metabolism" subsection below.]

PK/ADME following repeat dosing [13-day] of OPC-14597 was assessed in male Sprague-Dawley rats [Study No's 006171, 006172, 006080]. 14C-OPC-14597 was administered daily for 13 days at a dose of 3 mg/kg p.o. Blood samples were collected [via tail vein] at 1-24 hrs postdosing [3rd, 5th doses], 1 and 24 hrs postdosing [9th, 11th doses], and 0 and 1-168 hrs postdosing [13th dose] for assessment of plasma/blood radioactivity. For assessment of tissue distribution, blood samples were collected at 1-24 hrs postdosing [1st, 7th doses] and 1-168 hrs postdosing [13th dose]; after blood collection, animals [3/time point] were sacrificed and tissue were collected for quantitation of radioactivity. Urine and fecal samples were collected "every 24 hrs" [n = 3] from the same animals used for quantitation of blood/plasma levels. [Tissue distribution was assessed in separate grps of animals.] Sample/tissue radioactivity was quantitated using

Peak blood levels [40-45 ng•eq/mL] occurred 1-4 hrs following dosing. Peak blood levels of radioactivity were 0.6 and ≈0.8 times that of plasma following acute and repeat dosing, respectively. This would suggest some accumulation of radioactivity in rbcs with repeat dosing. Urinary and fecal radioactivity accounted for 5.6 ± 0.3 and 79.6 ± 1.3% of dose radioactivity, respectively, after the 1st

daily dose, and ≈5 and 90% of dose radioactivity, respectively, after subsequent doses. The tissue distribution data were summarized in the following sponsor's tables [only 1st and last dose data shown here]:

Table 3.
Tissue distributions of radioactivity at 1day after repeated oral administration of ^{14}C-CPC-14597 at 3mg/kg/day for 13 days in male rats

	Concentration of radioactivity (ng eq. /g tissue)			
Tissue/Time(hr)	1 hr	4 hr	8 hr	24 hr
Plasma	53 ± 2	41 ± 4	27 ± 3	8 ± 2
Blood	33 ± 1	28 ± 3	19 ± 3	6 ± 4
Cerebrum	29 ± 7	32 ± 6	19 ± 3	N.D.
Cerebellum	38 ± 8	28 ± 2	19 ± 1	3 ± 1
M. Oblongata	22 ± 8	44 ± 2	27 ± 4	10 ± 1
Hypophsis	N.D.	265 ± 45	N.D.	N.D.
Eye Ball	40 ± 19	29 ± 2	11 ± 6	N.D.
H. Gland	314 ± 160	516 ± 67	420 ± 68	293 ± 41
Sub. Gland	395 ± 225	436 ± 31	334 ± 56	190 ± 45
Thymus	69 ± 6	123 ± 15	70 ± 7	24 ± 2
Thyroid	91 ± 46	187 ± 21	55 ± 29	N.D.
Trachea	69 ± 21	86 ± 26	59 ± 17	N.D.
Heart	111 ± 21	81 ± 9	32 ± 3	6 ± 3
Lung	503 ± 66	373 ± 72	134 ± 22	41 ± 21
Liver	3409 ± 361	2564 ± 244	1294 ± 83	337 ± 20
Pancreas	605 ± 78	767 ± 121	487 ± 77	134 ± 14
Spleen	281 ± 33	197 ± 18	78 ± 12	18 ± 1
Kidney	515 ± 88	373 ± 30	259 ± 14	66 ± 9
Adrenal	1372 ± 572	1390 ± 318	1365 ± 91	794 ± 67
Testis	82 ± 21	118 ± 27	85 ± 11	34 ± 9
Ves. Semi.	86 ± 19	110 ± 21	51 ± 8	8 ± 4
Stomach	3597 ± 516	803 ± 367	97 ± 20	17 ± 1
Small Int.	6834 ± 511	2698 ± 947	879 ± 237	74 ± 3
Large Int.	326 ± 73	696 ± 126	1832 ± 285	180 ± 6
Skin	54 ± 3	80 ± 4	52 ± 2	N.D.
Muscle	66 ± 9	33 ± 18	31 ± 17	N.D.
Fat	94 ± 9	107 ± 10	41 ± 8	N.D.
Brown Fat	135 ± 59	138 ± 15	82 ± 14	N.D.
Lympho.	600 ± 211	360 ± 73	149 ± 54	29 ± 17
B. Marrow	154 ± 50	105 ± 22	46 ± 8	N.D.
Bone	N.D.	N.D.	N.D.	N.D.

Each value represents the mean ± S.E. of three rats. N.D., <30 dpm

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Table 5.
Tissue distributions of radioactivity at 13day after repeated oral administration of ^{14}C-OPC-14597 at 3mg/kg/day for 13 days in male rats

Tissue / Time(hr)	Concentration of radioactivity (ng eq. / g tissue)							
	1	4	8	24	48	72	120	168
Plasma	56 ± 6	66 ± 2	44 ± 7	9 ± 2	4 ± 2	N.D.	N.D.	N.D.
Blood	49 ± 4	54 ± 4	43 ± 3	15 ± 0	10 ± 2	11 ± 0	9 ± 1	9 ± 1
Cerebrum	25 ± 5	24 ± 1	22 ± 2	N.D.	N.D.	N.D.	N.D.	N.D.
Cerebellum	23 ± 3	23 ± 1	32 ± 12	6 ± 1	N.D.	N.D.	N.D.	N.D.
M. Oblongata	32 ± 7	35 ± 3	28 ± 5	8 ± 4	N.D.	3 ± 2	N.D.	N.D.
Hypophysis	309 ± 86	319 ± 25	275 ± 66	N.D.	N.D.	N.D.	N.D.	N.D.
Eye ball	32 ± 3	27 ± 3	24 ± 2	N.D.	N.D.	N.D.	7 ± 3	N.D.
H. Gland	579 ± 46	733 ± 52	787 ± 53	441 ± 37	240 ± 36	155 ± 12	70 ± 5	53 ± 6
Sub. Gland	1614 ± 50	1595 ± 402	1334 ± 136	970 ± 174	1238 ± 622	1702 ± 674	1109 ± 659	782 ± 440
Thymus	91 ± 6	116 ± 2	95 ± 7	31 ± 2	23 ± 4	13 ± 0	7 ± 4	N.D.
Thyroid	104 ± 61	142 ± 26	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Trachea	47 ± 10	65 ± 2	67 ± 16	N.D.	N.D.	N.D.	N.D.	N.D.
Heart	82 ± 5	78 ± 8	51 ± 7	13 ± 2	15 ± 3	10 ± 1	N.D.	N.D.
Lung	396 ± 65	334 ± 28	240 ± 30	36 ± 2	21 ± 1	18 ± 2	13 ± 2	11 ± 1
Liver	3955 ± 134	2829 ± 685	2178 ± 404	751 ± 96	462 ± 25	431 ± 8	349 ± 62	166 ± 37
Pancreas	552 ± 45	738 ± 45	673 ± 37	220 ± 5	100 ± 6	60 ± 3	33 ± 4	27 ± 2
Spleen	200 ± 5	190 ± 13	138 ± 8	36 ± 8	42 ± 8	31 ± 2	27 ± 3	22 ± 5
Kidney	394 ± 126	518 ± 36	423 ± 16	138 ± 2	92 ± 10	88 ± 5	54 ± 1	51 ± 15
Adrenal	1944 ± 488	1758 ± 165	1589 ± 57	1008 ± 80	907 ± 114	532 ± 43	249 ± 20	189 ± 22
Testis	90 ± 14	114 ± 7	142 ± 8	67 ± 4	50 ± 6	50 ± 3	32 ± 1	22 ± 6
Ves. Semi.	50 ± 7	79 ± 4	77 ± 9	17 ± 1	8 ± 4	N.D.	N.D.	N.D.
Stomach	1935 ± 201	606 ± 99	527 ± 115	21 ± 1	8 ± 4	N.D.	N.D.	N.D.
Small Int.	8042 ±2053	3551 ± 533	2130 ± 84	121 ± 6	26 ± 2	16 ± 2	9 ± 5	9 ± 5
Large Int.	298 ± 37	318 ± 30	1134 ± 96	147 ± 24	22 ± 1	N.D.	N.D.	N.D.
Skin	52 ± 9	61 ± 2	62 ± 10	12 ± 6	N.D.	N.D.	N.D.	N.D.
Muscle	30 ± 16	54 ± 11	21 ± 13	N.D.	N.D.	N.D.	N.D.	N.D.
Fat	43 ± 24	80 ± 5	58 ± 3	N.D.	N.D.	N.D.	N.D.	N.D.
Brown Fat	141 ± 22	127 ± 8	136 ± 5	N.D.	N.D.	N.D.	N.D.	N.D.
Lympho.	184 ± 12	412 ± 93	200 ± 44	65 ± 4	59 ± 12	36 ± 9	50 ± 12	N.D.
B. Marrow	106 ± 4	124 ± 7	72 ± 12	18 ± 9	17 ± 9	N.D.	N.D.	N.D.
Bone	21 ± 11	20 ± 11	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

Each value represents the mean ± S.E. of three rats. N.D., <30 dpm

Tissue distribution of radioactivity following an acute oral dose of ^{14}C-BMS-337039 [10 mg/kg] was assessed in Sprague-Dawley rat [24/sex, 3/sex/time point; Study No. 178/337039/006.[redacted]]. One CM and 1 CF were included in the analysis. Treated animals were sacrificed at 0.5, 2, 4, 8, 24, 48, 72, and 168 hrs postdosing. A limited number of tissues was sampled in males in order to provide for a comparison to data collected in a tissue distribution study conducted by Otsuka Pharmaceuticals. Tissue radioactivity was quantitated. [redacted] The data were summarized in the sponsor's tables below. In males, the highest % of radioactivity was detected in liver; at T_{max} [for liver], radioactivity in liver accounted for 5.4% of dose. In females, other than GI, the highest % of radioactivity was detected in liver; at T_{max} [for liver], radioactivity in liver accounted for 4% of dose radioactivity.

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Table 4: **Pharmacokinetic Parameters for Radioactivity in Blood, Plasma, and Tissues from Male Rats Following a Single Oral Administration of [^{14}C]BMS-337039**

Tissue	C_{max} (ng eq/g)	t_{max} (hours)	Terminal $t_{1/2}$ (hours)	Terminal β (-hours)	AUC_{0-t} (ng eq·hours/g)	$AUC_{0-\infty}$ (ng-eq·hours/g)
Adrenal glands	3,490	4	39.6	0.0175	127,000	133,000
Aorta	385	4	4.54	0.153	2,980	3,070
Bladder (urinary)	599	2	4.21	0.165	4,390	4,490
Blood[a]	239	0.5	5.41	0.128	1,740	1,840
Cerebellum	137	2	1.67	0.416	705	737
Cerebrospinal fluid	ND	NA	NA	NA	NA	NA
Cerebrum	144	2	5.70	0.122	1,170	1,250
Epididymis	527	4	7.77	0.0892	5,030	5,090
Eyes (both)	132	2	2.84	0.244	685	818
Kidneys	2,330	2	63.6	0.0109	26,100	27,200
Liver	17,200	0.5	54.1	0.0128	140,000	144,000
Lungs	2,400	2	7.79	0.0889	17,200	17,400
Medulla oblongata	182	4	18.2	0.0381	1,980	2,050
Plasma[a]	389	0.5	7.18	0.0966	2,830	2,850
Prostate	933	4	14.7	0.0473	8,970	9,180
Sublingual glands	951	4	27.6	0.0252	13,400	16,200
Testes	447	4	101	0.0069	8,260	10,400

eq Equivalents.
NA Not applicable.
ND Not detectable.
a Concentrations of blood and plasma reported as ng equivalents [^{14}C]BMS-337039/mL, therefore AUC values are reported as ng eq·hours/mL.

Table 8: **Pharmacokinetic Parameters for Radioactivity in Blood, Plasma, and Tissues from Female Rats Following a Single Oral Administration of [^{14}C]BMS-337039**

Tissue	C_{max} (ng eq/g)	t_{max} (hours)	Terminal $t_{1/2}$ (hours)	Terminal β (-hours)	AUC_{0-t} (ng eq·hours/g)	$AUC_{0-\infty}$ (ng-eq·hours/g)
Adrenal glands	7,070	4	46.4	0.0149	119,000	125,000
Aorta	658	4	2.89	0.240	5,510	5,530
Bladder (urinary)	1,340	4	3.39	0.204	8,800	8,880
Blood[a]	263	0.5	3.83	0.181	1,420	1,800
Bone (femur, without marrow)	516	2	3.08	0.225	2,950	3,590
Bone marrow (from femur)	1,800	4	2.99	0.232	9,290	11,100
Cerebellum	268	4	2.00	0.347	1,380	1,470
Cerebrospinal fluid	ND	NA	NA	NA	NA	NA
Cerebrum	332	4	2.35	0.295	1,700	1,880
Eyes (both)	222	4	4.37	0.159	1,230	1,710
Fat (brown)	632	2	9.30	0.0745	4,280	4,340
Fat (reproductive)	1,680	4	2.30	0.302	11,100	11,100
Harderian gland	9,880	4	37.1	0.0187	133,000	134,000
Heart	992	4	2.56	0.270	5,580	6,320
Kidneys	2,590	2	94.3	0.0073	26,000	28,100
Large intestine (including cecum)	21,700	8	4.14	0.168	242,000	242,000
Liver	15,400	0.5	110	0.0063	125,000	138,000
Lungs	5,590	2	65.1	0.0106	37,800	38,300
Lymph nodes (mesenteric)	2,480	4	122	0.0057	21,900	23,600
Medulla oblongata	538	4	7.67	0.0904	3,680	3,710
Muscle (thigh)	736	4	3.09	0.225	3,500	4,160
Ovaries	3,310	4	64.5	0.0108	44,100	47,700
Pancreas	6,050	4	12.1	0.0574	63,700	64,100
Pituitary	2,210	4	25.0	0.0277	25,900	27,600
Plasma[a]	442	0.5	3.56	0.195	3,110	3,140
Skin	747	4	7.74	0.0896	5,910	5,960
Small intestine	61,100	4	4.04	0.172	399,000	399,000
Spleen	2,030	4	3.71	0.187	15,000	15,200
Stomach	149,000	0.5	3.09	0.224	210,000	210,000
Sublingual glands	2,000	4	43.3	0.0160	59,600	69,900
Submaxillary glands	5,690	4	69.0	0.0100	286,000	376,000
Thymus	1,830	4	17.9	0.0387	12,800	12,900
Thyroid/parathyroid	1,650	4	8.70	0.0796	13,100	13,300
Trachea	2,180	8	5.59	0.124	26,700	26,800
Uterus	1,690	4	6.06	0.114	12,200	12,300

A limited tissue distribution study was conducted in male Long-Evans rats in order to assess distribution into pigmented tissue [Study No. 178/337039/003]. Duel-labeled ^{14}C-BMS-337039 was administered as an acute oral dose [3 mg/kg] to male Long-Evan rats [1 C, 27 DT]. Animals were sacrificed [3/time point] at 0.5, 2, 4, 8, 24, 48, 72, 96, and 168 hrs postdosing. Tissue radioactivity was quantitated by ——The data were summarized in the following sponsor's table:

Table 5. Pharmacokinetic Parameters for Radioactivity in Blood, Plasma and Tissues from Male Rats After a Single Oral Administration of [^{14}C]BMS-337039

Tissue	C_{max} (ng equivalents/g)	T_{max} (hours)	Terminal $t_{1/2}$ (hours)	β (-hours)	AUC_{0-t} (ng equivalents hours/g)	$AUC_{0-\infty}$ (ng equivalents hours/g)
Adrenal glands	1490	4	29.6	0.023	53,800	54,800
Bladder (urinary)	935	2	8.28	0.084	4,350	4,390
Blood	140	0.5	5.97	0.116	589	620
Bone (femur, without marrow)	82.4	2	2.84	0.244	413	492
Bone marrow (from femur)	150	2	3.31	0.209	792	998
Brain	34.7	2	5.54	0.125	263	275
Eyes (both)	301	8	283	0.002	35,900	103,000
Heart	111	0.5	2.69	0.257	397	459
Kidneys	702	0.5	76.4	0.009	9,200	10,200
Large intestine (including cecum)	4560	8	4.76	0.146	60,500	60,600
Liver	10100	0.5	65.4	0.011	55,500	58,400
Lungs	589	0.5	4.88	0.142	2,530	2,590
Muscle (thigh)	61.5	0.5	3.01	0.23	294	356
Plasma	256	0.5	8.64	0.08	1,160	1,170
Skin (nonpigmented)	85.9	2	4.14	0.167	475	663
Skin (pigmented)	87.1	2	53.3	0.013	2,420	3,020
Small intestine	20800	0.5	6.42	0.108	82,500	82,500
Spleen	204	0.5	4.70	0.148	1,150	1,180
Stomach	22900	0.5	5.97	0.116	42,200	42,900
Testes	63.0	4	100	0.007	1,770	2,300
Thyroid	329	0.5	6.19	0.112	1,440	2,460

As in Sprague-Dawley rat, other than GI, the highest levels of radioactivity were detected in liver [11% of dose radioactivity at T_{max} for liver]. Peak levels of radioactivity in skin were similar in pigmented and nonpigmented areas; however, total exposure [AUC] was ≈5 times higher in pigmented as compared to nonpigmented skin. By 168 hrs postdosing, radioactivity was undetectable in all tissue except for adrenal gland, liver, kidney, eye, and testes.

Uptake of OPC-14597 and radioactivity into brain was assessed in male Sprague Dawley rat [Study No's 015198 and 015881, respectively]. In Study No. 015198, the BUI determined by intracarotid injection of ^{14}C-OPC-14597 in rat plasma was 25.21 ± 3.67%. In Study No. 015881, regional brain distribution of radioactivity was qualitatively assessed following a single i.v. bolus injection of ^{14}C-OPC-14597 [0.3 mg/kg]. Radioactivity rapidly entered the brain, with peak levels being detected by 1-2 min postdosing. As noted by the sponsor, highest levels of radioactivity were detected in "...the cerebral (lateral, third and fourth) ventricles, cerebral (frontal and parietal) cortex and thalamus. Distribution of radioactivity into "..the olfactory tubercle, inferior colliculus and thalamus were higher than that of striatum" and "...the levels of radioactivity in the hippocampus, cerebellum, medulla oblongata and hypothalamus were lower than that in the striatum". By 15 min postdosing, levels of radioactivity were diminished and "...in every cerebral region was nearly equivalent". Light microscopic examination of the autoradiographs indicated that radioactivity in the ventricles was localized "around/over" the choroid plexus at 1-5 min postdosing. Silver grains were also evident in csf and circumventricular tissue "with elapse of time". Therefore, the sponsor concluded that OPC-14597 rapidly enters the brain via both the BBB and the BCSFB [blood-csf barrier].

Cynomolgus Monkey

Plasma and urinary concentrations of aripiprazole were quantitated in male cynomolgus monkeys following single doses of 5, 12.5, and 25 mg/kg p.o. or a single 5-mg/kg i.v. dose [n = 3 for the i.v. dose] Following acute oral dosing, blood samples were collected from 30 min to 96 hrs postdosing. Urine samples were collected over 24-hr intervals from 0 to 96 hrs postdosing. Plasma data are summarized in the following sponsor's table:

Table 7. Pharmacokinetics parameters of OPC-14597 in cynomolgus monkeys (mean±S.D.)

Dose (mg/kg)	Tmax (hr)	Cmax (ng/ml)	$T_{1/2}$ (hr)	AUC (ng.hr/ml)
5 mg/kg	2.3±0.6	85± 15	3.4±1.6	328± 58 (0-T*hr)
12.5 mg/kg	2.3±0.6	167± 78	2.9±0.6	856±450 (0-T hr)
25 mg/kg	3.3±0.6	399±112	3.5±0.8	2888±204 (0-T hr)

T* : Terminal detected time

Urinary excretion of aripiprazole was negligible at all doses [0.0044, 0.0024, and 0.0045% of dose at 5, 12.5, and 25 mg/kg, respectively]. Following an acute i.v. dose, blood samples were collected from 5 min to 48 hrs postdosing. Plasma levels of OPC-14597 were quantitated using ——. PK parameters were determined to be as follows [mean ± SD]:

C_0 = 1622 ± 326 ng/mL, $AUC_{(0\text{-}T)}$ = 5010 ± 1211 ng•hr/mL, $AUC_{(0\text{-}\infty)}$ = 6247 ± 1774 ng•hr/mL, $t_{1/2}$ = 3.8 ± 0.7 hr, Cl = 846 ± 247 mL/hr/kg, V_z = 4575 ± 1513 mL/hr

The sponsor estimated the oral bioavailability in monkey to be 8.2% based on previous oral data at 5 mg/kg. Based on the data provided in this study, the absolute oral bioavailability was ≈5%.

PK/ADME was assessed in cynomolgus monkeys [n = 3] following an acute oral dose of ^{14}C-OPC 14507 [5 mg/kg]. Blood, urine, and fecal samples were collected in a previously conducted study [Study No. 010055]. Blood samples had been collected from 30 min to 24 hrs postdosing. Urine and fecal samples were collected from just after dose up to the time that ≥95% of dose radioactivity had been excreted. Total radioactivity, OPC 14597, and metabolites were quantitated by ——. following ——
The data were summarized in the following sponsor's tables:

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Table 1 Concentration of radioactivity, OPC-14597 and its metabolites in plasma after single oral administration of ^{14}C-OPC-14597 at 5mg/kg in monkeys

	Concn. (ng eq./ml)				
	30 min	2 hr	4 hr	8 hr	24 hr
Radioactivity *	130 ± 59	882 ± 628	500 ± 247	343 ± 236	116 ± 140
OPC-14597	6.41 ± 6.63 (8.44 ± 11.6)	83.4 ± 90.5 (12.5 ± 9.18)	72.5 ± 32.2 (17.8 ± 12.8)	104 ± 129 (22.8 ± 16.2)	26.7 ± 41.6 (14.2 ± 11.3)
OPC-14857	N.D. (< 1)	50.7 ± 64.0 (5.65 ± 4.03)	75.7 ± 83.6 (13.1 ± 9.36)	69.6 ± 40.5 (21.9 ± 12.5)	31.8 ± 42.8 (22.3 ± 11.4)
OPC-3373	112 ± 65.5 (80.7 ± 18.6)	547 ± 427 (60.9 ± 16.1)	173 ± 86.1 (36.0 ± 11.6)	62.7 ± 49.5 (19.5 ± 11.5)	18.9 ± 17.9 (22.2 ± 13.8)
DM-1451	N.D. (< 1)	N.D. (< 1)	11.4 ± 8.59 (1.99 ± 0.84)	8.73 ± 2.79 (2.99 ± 0.98)	2.11 ± 2.40 (2.02 ± 0.68)
DM-1454	3.98 ± 1.69 (3.44 ± 1.50)	85.2 ± 64.6 (8.83 ± 1.93)	59.4 ± 40.5 (11.3 ± 5.91)	33.2 ± 12.9 (12.1 ± 7.86)	19.1 ± 16.5 (22.6 ± 8.15)
DM-1451 -Sulfate	N.D. (< 1)	36.6 ± 40.7 (3.59 ± 2.39)	28.0 ± 15.3 (5.56 ± 0.52)	16.5 ± 15.8 (4.29 ± 1.26)	4.40 ± 5.91 (3.34 ± 1.39)

Each value represents the mean ± S.D. for three monkeys.
Number in lower parenthesis represents percentage of radioactivity in plasma.
N.D. : Less than 1 % of radioactivity in plasma
* : Report No. 010055 (Study No. 011466)

Table 2 Urinary and fecal excretions of radioactivity, OPC-14597 and its metabolites after single oral administration of ^{14}C-OPC-14597 at 5mg/kg in monkeys

	Excretion (% of dose)	
	Urine	Feces
Radioactivity *	34.0 ± 1.50	59.7 ± 0.32
OPC-14597	N.D. (< 1)	N.D. (< 1)
OPC-14857	N.D. (< 1)	N.D. (< 1)
OPC-3373	20.4 ± 2.64 (59.9 ± 5.26)	2.95 ± 1.11 (4.94 ± 1.87)
DM-1451	N.D. (< 1)	30.5 ± 2.78 (51.0 ± 4.48)
DM-1454	6.08 ± 0.41 (17.9 ± 0.45)	3.85 ± 1.86 (6.45 ± 3.14)
DM-1451 -Sulfate	N.D. (< 1)	N.D. (< 1)

Urine and feces were collected until 24, 48, 72, 120 and 144 hr, respectivery, after dosing.
Each value represents the mean ± S.D. for three monkeys.
Number in lower parenthesis represents percentage of radioactivity in urine and feces.
N.D. : Less than 1 % of radioactivity in urine and feces
* : Report No. 010055 (Study No. 011466)

In another acute dose study in cynomolgus monkey [Study No. 011466; n = 3], ^{14}C-OPC-31 was administered at a dose of 5 mg/kg p.o. Blood samples were collected at 30 min, 1, 2, 4, 6, 12, and 24 hrs, and at 24-hr intervals up to 168 hrs postdosing. Urine and fecal samples were collected over 24-hr intervals up to 168 hrs postdosing. Sample radioactivity was determined using ——. Data from 1 of the 3 original animals were considered to be not representative due to marked differences between this male and the other 2 males. In the 2 "representative" males, C_{max} for radioactivity in blood and plasma were 804.5 and 1243.0 ng/mL, respectively, the T_{max} was 2 hrs in both animals, the $t_{1/2}$ was 19-25 hrs, and the

$AUC_{(0-\infty)}$ in blood and plasma were stated to be 5.31 and 7.47 ng-eq•hr/mL, respectively. [It is presumed that the units should be µg•hr/mL.] Feces was the major route of elimination, with fecal radioactivity accounting for 61-63% of dose radioactivity; urinary radioactivity accounted for 34-36% of dose radioactivity.

Dog

PK parameters for aripiprazole were assessed in Beagle dog in two studies [Study No. 006750 (male only), Protocol No. DM00026 (female only)]. [Data from Protocol No. DM00026 were reviewed under the Metabolism subsection.]

In male Beagle dogs [3/grp], aripiprazole was administered as single i.v. [1 mg/kg] or oral [10 mg/kg] dose. Domperidone [2 mg/dog s.c.] was administered 30-min prior to i.v. or p.o. dosing to control vomiting. Blood samples were collected from 0.5 to 24 hrs after oral dosing and from 5 min to 24 hrs after i.v. dosing. Plasma levels of OPC-14597 were quantitated using [redacted]. The data [mean ± SD] are summarized in the following table [the sponsor provided data for mouse and rat (from previously conducted studies) for comparison]:

DOSE/ROUTE [mg/kg]	C_{max}* [ng/mL]	T_{max} [hr]	AUC** [ng•hr/mL]	$t_{1/2}$ [hr]	Cl [mL/min/kg]
DOG					
1 mg/kg i.v.	480.7 ± 198.6		681.7 ± 234.2	5.60 ± 5.15	1.6 ± 0.7
10 mg/kg p.o.	89 ± 20	1.7 ± 0.3	363	2.3	
MOUSE					
10 mg/kg p.o.	608 ± 38	2	3826	3.9	
RAT					
10 mg/kg p.o.	86 ± 6	2	249	2.2	

*$C_{5\ min}$ for i.v., **$AUC_{(0-8\ hr)}$ for dog, $AUC_{(0-12\ hr)}$ for mouse, $AUC_{(0-6\ hr)}$ for rat

In female Beagle dogs [n = 3], aripiprazole was administered as single i.v. [15 mg], i.m., s.c., and p.o. [15 mg] doses. [Only the i.v. and p.o. data were reviewed.] A 3-day (minimum) washout period separated doses. [Animals weighed 11.0-12.1 kg.] Blood samples were collected at 0, 10, 20, and 30 min, 1, 2, 4, 8, and 24 hrs following the oral dose; collection times following i.v. dosing were not specified. Plasma samples were assayed in order to quantitate circulating levels of aripiprazole and metabolites, BMS-337040, BMS-337044, BMS-337045, BMS-337047, and DCPP using [redacted].

The effect of gastric acidity on the absorption of OPC-14597 was assessed in male Beagle dogs following an acute oral dose of 10 mg/kg. To increase gastric acidity, 50 mL of 0.1 N HCl was administered to one grp of dogs [n = 3]; water was administered to a separate grp of dogs [n = 3]. Domperidone [2 mg/dog] was administered s.c. to all dogs in order to prevent vomiting. The gastric pH of the high-gastric acid and the C grps were 1.9 and 8.0, respectively. There was no notable difference in absorption between the two grps.

In vitro study

An *in vitro* study was conducted in Caco-2 cells [derived from human colon carcinoma] in order to investigate the extent of oral absorption of aripiprazole in humans. Penetration was assessed at pH 5.5, 6.5, and 7.4 and at aripiprazole concentrations of 4-83 µM. Metoprolol and mannitol were also studied in this model as examples of a well-absorbed and a poorly-absorbed compound, respectively.

Aripiprazole could not be assayed at pH 7.4 due to poor solubility at this pH. At pH 5.5 and 6.5, the permeability coefficient was 26 ± 15 and 47 ± 12 nm/sec, respectively. This was slightly greater than the permeability coefficient of mannitol [18-20 nm/sec] and less than that of metoprolol [71-154 nm/sec]. The sponsor noted that, based on data from numerous other compounds, a permeability coefficient in the range of that of aripiprazole corresponds to an *in vivo* absorption of ≈40-95% [pH 6.5 data]. *In vivo* data in humans indicate an absolute oral bioavailability of ≈85%.

Metabolism

Mouse

The metabolism of aripiprazole was assessed in ICR mice in four studies [Study No's 015126, 015310, 015695, and MAP Document No. MAP063/337039]. In Study No. 015126, OPC-14597 and metabolites were quantitated by ——— in mouse plasma following an acute oral dose [200 mg/kg; 6/sex]. OPC-14597 and metabolites, DM-1454, OPC-14857, and DM-1452 were detected in plasma. The peak area was greatest for parent compound. At 8 hrs postdosing, the ratio of peak areas of metabolite to parent compound was 23-17, 13-15, and 12-14% for DM-1454, OPC-14857, and DM-1452, respectively.

In Study No. 015310, the presence of unidentified metabolites [unknown-1 and 2] was investigated using ——— in plasma samples collected from mice [Report No. 012703] and rabbit [Study No. 015154] in previously conducted studies. In male mouse plasma, the peak area ratios of unknown-1 to parent compound were 0.124 and 0.237% at 3 and 8 hrs postdosing, respectively; unknown-2 could not be quantitated. In female mouse plasma, the peak area ratios of unknown-1 to parent compound were 0.534 and 0.544 at 3 and 8 hrs postdosing, respectively, and of unknown-2 to parent compound were 4.61 and 7.09% at 3 and 8 hrs postdosing, respectively. In rabbit, peak area ratios of unknown-1 to parent compound were 11.2, 14.7, and 9.87% at 1, 4, and 24 hrs postdosing, respectively, and of unknown-2 to parent were 161, 313, and 206% at 1, 4, and 24 hrs postdosing, respectively.

In Study No. 015695, the presence of metabolites, DM-1457, DM-1458, OPC-3952, and DM-1454 was investigated in plasma samples collected from mice [3/sex/time point] in a previously conducted study [Study No. 012703]. These metabolites were quantitated using ——— . DM-1457 was not detected in plasma samples. At 3 hrs postdosing, the ratio of peak areas of OPC-3952 to parent compound was 0.509 and 1.16% in males and females, respectively, and of DM-1458 to parent compound was 0.473 and 1.14% in males and females, respectively. The ratio of peak areas of OPC-3952 to metabolite DM-1454 [at 3 hrs postdosing] was 4.76 and 5.09% in males and females, respectively, and of DM-1458 to parent was 4.38 and 5.07%, respectively. The sponsor noted that the data indicate that OPC-3952, DM-1457, and DM-1458 are minor metabolites in the mouse.

In MAP Document No. MAP063/337039, the presence of conjugated metabolites was assayed in plasma and bile collected from bile-cannulated CD-1 mice following 1 wk of daily dosing with aripiprazole [60 mg/kg p.o.] Blood and bile samples were collected at 6 and 12 hrs after the last dose [2/sex/time point]. [Initially 11 animals were dosed (11 M, 6 F). In 2 animals, the cannula was not patent and 6 M died (Days 2-7).] Aripiprazole and metabolites, BMS-337041 [glucuronide conjugate of OH-aripiprazole], BMS-337042 [sulfate conjugate of OH-aripiprazole], and BMS-511426 [sulfate conjugate of OH-aripiprazole] were quantitated in blood; only the metabolites were quantitated in bile samples. The data [range; expressed in ng/mL] are summarized in the following table:

AMPLE	TIME	MALES				FEMALES			
		ARIPIP	BMS-337041 [DM-1454]	BMS-337042 [DM1458]	BMS-511426 [DM-1460]	ARIPIP	BMS-337041 [DM-1454]	BMS-337042 [DM1458]	BMS-511426 [DM-1460]
plasma	6	3260-790	3670-2930	5-7	<LLOQ	2430-1290	6460-1180	12-7	<LLOQ
	12	460-230	670-220	<LLOQ	<LLOQ	240-150	230-40	<LLOQ	<LLOQ
bile	6		102-66	<LLOQ	<LLOQ		29-53	<LLOQ	<LLOQ
	12		69-230	<LLOQ-0.75	<LLOQ-0.62		103-89	<LLOQ	<LLOQ

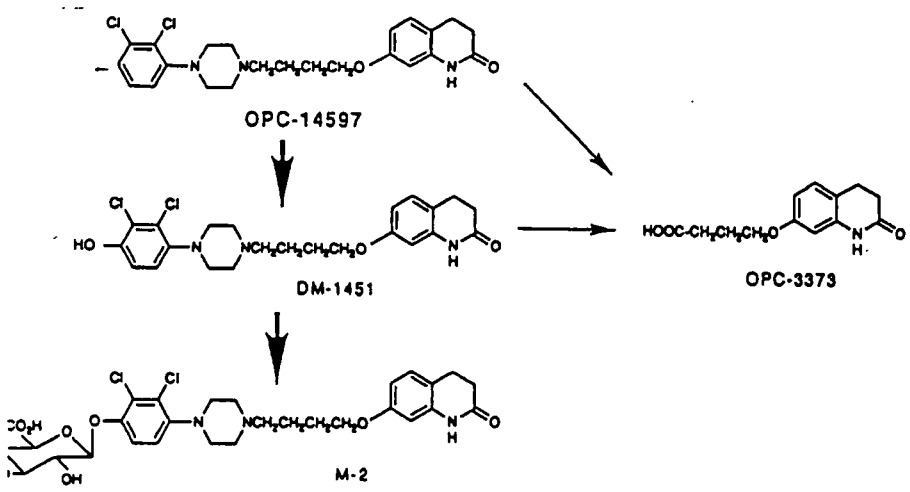
Rat

The metabolism of aripiprazole was assessed in male Sprague-Dawley rats in 5 studies [Protocol No. 178/337039/001A, Report No. 011337, Study No. 009368, Study No. 006749, MAP Document No. MAP065/337039]. [Circulating metabolites were also assessed following i.m. dosing; however, these data were not reviewed for this NDA.] Aripiprazole was administered as a single 3.75-mg/kg i.v. [10-min infusion via carotid artery] or a single 3-mg/kg oral dose. Following i.v. dosing, blood samples were collected from 10-min [end of infusion] to 24 hrs after the start of infusion. Aripiprazole and metabolites, BMS-337040 [DM-1451], BMS-337044 [OPC-14857], BMS-337045 [DM-1452], BMS-337047 [OPC-3373], and 1-(2,3-dichlorophenyl)piperazine [DCPP] were quantitated in plasma using ———. Following oral dosing, blood samples were collected at 0.5-24 hrs postdosing. Aripiprazole, OPC-14857, DM-1451, DM-1452, and DM-1454 were quantitated in plasma using ———

Following the 3.75-mg/kg i.v. dose, BMS-337047 [OPC-3373] and DCPP were <LLOQ in all animals [n. = 3]. Following the 3-mg/kg oral dose, only DCPP was <LLOQ. Plasma levels for aripiprazole and the other metabolites assayed are summarized in the following table [numbers in brackets reflect % of PC]:

DOSE/ROUTE [mg/kg]	COMPOUND	C_{max} [ng/mL]	T_{max} [hr]	$AUC_{(0-T)}$ [ng•hr/mL]	$t_{1/2}$ [hr]
3.75 mg/kg i.v.	aripiprazole	784	0.17	730	
	BMS-337040	33.4	0.33	89.7	
	BMS-337044	10.5	1.00	130	
	BMS-337045	4.92	0.50	7.24	
	BMS-337047	<LLOQ			
	DCPP	<LLOQ			
3.00 mg/kg p.o.	aripiprazole	15.1	2.0	64.3	1.71
	BMS-337040	10.4 [68.9]	2.0	50.2 [78.1]	2.64
	BMS-337044	2.0 [13.2]	2.0	6.0 [9.3]	4.82
	BMS-337045	0.8 [5.3]	2.0	2.3 [3.6]	4.82
	BMS-337047	6.1 [40.4]	1.0	31.7 [49.3]	2.83
	DM-1454	26.7 [176.8]	12.0	405.4 [630.5]	5.2
	DCPP	<LLOQ			

The identity of metabolites in plasma, bile, and urine was assessed in male Sprague-Dawley rat following an acute oral doses [≈100 mg/kg] [Study No. 006749]. Blood samples were collected at 4 hrs postdosing [n = 80]. Bile samples were collected via bile duct cannula [n = 10] for 24 hrs postdosing. Urine samples were collected from 12 rats for 24 hrs postdosing. Aripiprazole and metabolites were quantitated using —— separation followed by ——— Two metabolites, M1 and M2, were detected in bile, metabolite M3 was detected in urine, and aripiprazole and all three metabolites were detected in plasma. M1 was identified as a hydroxylated derivative [DM-1451], with hydroxylation at the p-position of the dichlorophenyl side chain of aripiprazole. M2 was identified as the glucuronidated conjugate of DM-1451. M3 and M4 were identified as 7-(3-carboxypropoxy)-3,4-dihydro-2(1H)-1uinolinone [OPC-3373]. Based on these data, the following metabolic pathways were presumed in rat:



The presence of aripiprazole and conjugated metabolites [BMS-337041, BMS-337042, BMS-511426] in plasma and bile of Sprague-Dawley rats [total n = 9/sex] was assessed following administration of aripiprazole [60 mg/kg p.o.] for 14 or 28 days. Blood samples were collected at 6 and 12 hrs following the last dose from "at least" 2/sex/grp per time point. Bile samples were collected from the same animals at 0-6 or 6-12 hrs after the last dose. Aripiprazole and metabolites were quantitated in plasma and bile using ——. The data [ranges; expressed as ng/mL for plasma, µg/mL for bile] are summarized in the following table:

MPLE	TIME	MALES				FEMALES			
		ARIPIP	BMS-337041 [DM-1454]	BMS-337042 [DM1458]	BMS-511426 [DM-1460]	ARIPIP	BMS-337041 [DM-1454]	BMS-337042 [DM1458]	BMS-511426 [DM-1460]
14-DAYS									
plasma	6	11804-4216	105-72	<LLQ	<LLQ	4160-1435	3836-44	<LLQ	<LLQ
	12	9497-3247	52-23	<LLQ	<LLQ	1240-1397	1646-15	<LLQ	<LLQ
bile	0-6		123-272	2-3.5	<LOQ-0.6		252-302	2.8-1.6	<LLQ
	6-12		102-203	1.7-2.4	<LLQ-0.6		126-274	<LLQ-1.3	<LLQ
28-DAYS									
plasma	6	2046-799	49-299	<LLQ	<LLQ	74-113	168-310	<LLQ	<LLQ
	12	399-2633	51-282	<LLQ	<LLQ	12-528	<LLQ	<LLQ	<LLQ
bile	0-6		286-370	5.9-4.7	1.54-0.77		173-437	2-0.6	<LLQ
	6-12		166-236	5.2-1.4	0.86-<LLQ		104-113	<LLQ-0.8	<LLQ

The sponsor noted that the biliary concentrations of the conjugated metabolites were "...much lower than their limits of solubility in bile", suggesting a lack of precipitation of these conjugates in bile.

Study No. 009368 was conducted in order to determine the extent of metabolism of aripiprazole to DCPP-derived metabolites in male Sprague-Dawley rat and in human. In rats, blood samples [2/time point] were collected at 2-24 hrs following an acute 100-mg/kg oral dose of OPC-14597; urine samples were collected from 2 rats over a 24-hr period postdosing. Urine samples were collected from 2 human subjects at 0-4, 4-8, and 8-12 hrs following the 3rd daily dose [4 mg/day]. Metabolites were identified using ——. DCPP-derived metabolites were not detected in rat plasma or human urine. 2,3-DCPP was detected in rat urine.

The effect of aripiprazole [3, 10, 20 mg/kg p.o. for 7 days in males; 20 mg/kg p.o. for 7 days in females] on hepatic metabolizing enzymes was tested using liver microsomes from Sprague-Dawley rats. No effects were observed in liver microsomes from male rats. In females, repeat doses of aripiprazole resulted in a significant increase [15%] in protein content and a significant decrease [21%] in EROD

activity. CYP 450 content, CYP b5 content, and NADPH-cytochrome c reductase, aniline hydroxylase, and aminopyrine N-demethylase activity were not affected.

Cynomolgus Monkey

Data on circulating metabolites in male cynomolgus monkey were collected in two studies [Protocol 178/337039/002, Study No. 013611]. [In Protocol 178/337039/002, circulating metabolites were assessed following i.m. dosing; however, these data were not reviewed for this application.] Aripiprazole was administered as either a single i.v. dose [3.75 mg/kg; 10-min infusion; n = 3] or a single oral dose [7.5 mg/kg; n = 3]. Following i.v. dosing, blood samples were collected from 10 min [i.e., end of infusion] to 24 hrs after the start of infusion. Plasma samples were used to quantitate aripiprazole and metabolites, BMS-337040 [DM1451], BMS-337044 [OPC 14857], BMS-337045 [DM 1452], BMS-337047 [OPC-3373], and DCPP [(1-(2,3-dichlorophenyl)piperazine] using ———. Following the 7.5-mg/kg oral dose, blood samples were collected from 0.5 to 48 hrs postdosing. Aripiprazole [OPC-14597] and metabolites, OPC-3373, OPC-14857, DM-1451, DM-1452, DM-1454, and DCPP, were quantitated in plasma using ———. The data from these studies are summarized in the following table:

DOSE/ROUTE [mg/kg]	COMPOUND	C_{max} [ng/mL]	T_{max} [hr]	$AUC_{(0-T)}$ [ng•hr/mL]	$t_{1/2}$ [hr]	Cl [mL/min/kg]	V_{ss} [L/kg]
3.75 mg/kg i.v.	aripiprazole	4097 ± 2173	0.17	4616 ± 1240	3.8 ± 0.69	14.0 ± 3.20	3.06 ± 0.56
	BMS-337040	8.11 ± 5.18	2.0	37.5			
	BMS-337044	64.3 ± 22.6	4.0	756 ± 513			
	BMS-337045	22.5 ± 5.73	2.0	129 ± 37.3			
	BMS-337047	118 ± 70.2	1.0	404 ± 197			
	DCPP	6.94 ± 6.03	2.0	47.2			
7.5 mg/kg p.o.	aripiprazole	54.2 ± 10.5	3.3 ± 1.2	506.4 ± 182.0	5.7 ± 1.9		
	BMS-337040	1.4 ± 0.4	2.0 ± 1.7	2.4 ± 1.4	-		
	BMS-337044	85.3 ± 21.7	3.3 ± 1.2	890.7 ± 212.4	6.4 ± 0.4		
	BMS-337045	20.9 ± 2.5	3.3 ± 1.2	152.6 ± 28.2	4.4 ± 0.7		
	BMS-337047	698.9 ± 204.3	2.0 ± 1.7	2520 ± 1005	5.6 ± 0.3		
	DM-1454	15.7 ± 9.0	8.0 ± 0.0	283.4 ± 111.4	16.1 ± 6.0		
	DCPP	16.3 ± 3.4	3.3 ± 1.2	161.4 ± 56.2	5.4 ± 1.2		

The sponsor noted that Cl following an i.v. dose was ≈60% of hepatic plasma flow in cynomolgus monkey. Based on these data, the absolute oral bioavailability of aripiprazole in cynomolgus monkey was ≈5-6%.

The sponsor conducted studies to investigate the ppt observed in bile in oral toxicity studies in cynomolgus monkey [Study No's 009378, 008285, MAP Document No. MAP036/337039].

In Study No. 008285, aripiprazole was administered to 3 cynomolgus monkeys at doses of 500-2000 mg/kg. In 2 monkeys, aripiprazole was administered at a dose of 2000 mg/kg on Day 0 and at a dose of 1000 mg/kg on Day 1. One animal [#00001] was sacrificed on Day 2 with no further dosing. The second animal [#00002] received two additional daily doses of 500 mg/kg [Days 2 and 3], and was sacrificed on Day 10. The 3rd animal [#00003] received a dose of 1000 mg/kg on Day 0 and a dose of 500 mg/kg on Day 1; this animal died on Day 3. Bile samples from animals #00002 and 00003 were analyzed; the "sludgy substance" detected in bile from the 1st animal could not be analyzed since it was insoluble in solvent [nos]. The substance obtained from the other animals was dissolved in DMSO and analyzed for the presence of metabolites. The "sludgy substance" was identified as the sulfate conjugate of metabolite DM1451 [an hydroxy derivative of aripiprazole]. This finding was confirmed in Study No. 009378, which involved further analysis of the bile samples collected in Study No. 008285.

The results of analyses conducted on bile, gallstone, and gallsand samples collected at the end of the 39-wk oral toxicity study in cynomolgus monkey [Study No. 99354: ——— Study No. 6108-335] were presented in MAP Document No. MAP036/337039. In the 39-wk study, aripiprazole was administered at doses of 25, 50, and 75 mg/kg; gallstones and gallsand were detected at all doses. Samples were analyzed for presence of drug-related material using ——————————. Six metabolites, M1-M4 and M6-M7, were detected in samples of gallstones and gallsand. M3 was identified as a glucuronide conjugate of hydroxy aripiprazole [i.e., BMS 337041]; all the other metabolites [M1-2, M4, M6-7] were identified as sulfate conjugates. M1 was identified as a trihydroxy sulfate conjugate, and was thought to be formed from M6 "...through epoxidation of the double bond followed by hydrolysis of the corresponding **epoxide** to the dihydro diol". M2 was identified as a dihydroxy sulfate conjugate, formed from either BMS-337040 or BMS337045 followed by sulfation. M4 was identified as the sulfate conjugate of dihydroxy aripiprazole. M6 was identified as the sulfate conjugate of dehydro hydroxy aripiprazole, and was thought to be formed from BMS-337044 [dehydro aripiprazole] as a result of hydroxylation followed by sulfation. M7 was identified as the sulfate conjugate of hydroxy aripiprazole. The relative abundance of these metabolites in gallstone and gallsand samples were summarized in the following sponsor's table:

Table 2: Percent Distribution by Weight of Various Aripiprazole-Related Metabolites in Gallsand and Gallstone Samples From a 39-Week Oral Gavage Toxicity Study in Cynomolgus Monkeys Administered Daily Doses of Aripiprazole

Animal Number	Dose (mg/kg)	Sex	Sample Type	Percent Relative Abundance[a]				
				M1[b]	M2[c]	M3 + M4[d]	M6	M7
6719	75	M	stone	0.55	1.77	2.5	8.60	39.5
6720	50	M	sand	0.5	1.68	2.5	5.50	27.0
6725	25	M	stone	0.6	1.74	3.9	17.10	37.9
6726	75	M	sand	-[e]	0.5	1.5	1.78	10.6
6733	75	M	stone	0.74	3.03	3.4	12.96	73.7
6736	50	F	sand	0.4	1.51	1.9	4.80	25.5
6739	25	F	sand	0.1	1.5	1.6	3.25	32.7
6743	75	F	sand	-	3.18	4.3	4.90	61.1
6744	25	F	sand	-	0.73	1.3	1.55	15.9
6745	50	F	sand	0.1	0.96	1.1	2.30	18.7
6746	75	F	stone	0.4	3.24	2.8	5.80	74.0
6748	50	F	sand	0.6	2.14	2.2	6.86	32.6
6749	75	F	stone	0.28	1.73	2.2	7.00	50.1
6752	50	F	sand	-	0.4	2.0	3.98	20.6
6753	25	F	sand	0.4	1.41	1.9	6.71	21.8
			mean ± SD	0.42 ± 0.20	1.7 ± 0.89	2.3 ± 0.91	6.20 ± 4.19	36.1 ± 20.2

[a] The samples were analyzed by ——— The ~ system used for semiquantitative analysis is described in Section 3.3.1. The retention time of metabolites M1, M2, combined M3 plus M4, M6 and M7 were 9.5, 10.5, 11.6, 13.1 and 13.7 min, respectively. The relative percent distribution by weight of the stone was calculated from a standard curve for BMS-337041, BMS-337042 and BMS-511426 at concentrations of 2.5, 25.0 and 250.0 µg/mL. The structures of the metabolite standards are shown in Table 1.

[b] This metabolite was identified by ——— (see Table 3) and —— (Figures 3 and 4) analysis. No standard for this metabolite was available. The percent distribution for M1, trihydroxy sulfate conjugate of aripiprazole, was calculated from the standard curve generated for BMS-337042 assuming no change in the molar absorptivity at 252 nm. The PDA spectrum is similar to that of BMS-337042 (see Table 3).

[c] This metabolite was identified by ——— (see Table 3) and ~ (Figures 3 and 5) analysis. No standard for this metabolite was available. The percent distribution for M2, dihydroxy sulfate conjugate of aripiprazole, was calculated from the standard curve generated for BMS-337042 assuming no change in the molar absorptivity at 252 nm. The PDA spectrum is similar to that of BMS-337042 (see Table 3).

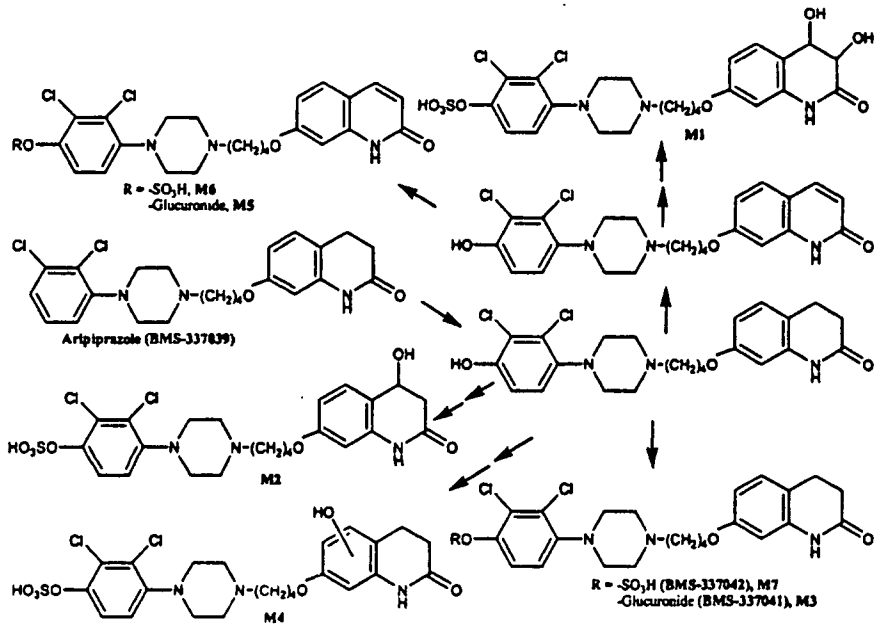
[d] This was a mixture of two metabolites, M3 (BMS-337041) and M4, a dihydroxy sulfate conjugate of aripiprazole, identified by ——— (see Table 3) and —— (Figures 3 and 6) analysis. The percent distribution of the two conjugates were calculated from the standard curve generated for BMS-337041 assuming no change in the molar absorptivity at 252 nm. The PDA spectrum is similar to that of BMS-337041 (see Table 3).

[e] Not detected (< 0.1%).

A quantitative assessment of metabolites in bile samples was not performed since the samples were, apparently, not systematically collected. Samples from each dose grp were pooled for analysis. Metabolites M3, M5-7 were detected in all pooled samples, with M3 and M5 being "prominent". M6 and M7 were detected in "significant amounts" in bile [and gallstones]. M1, M2, and M4 [and other metabolites] were detected in bile, but were considered minor metabolites.

The proposed metabolic pathways proposed as involved in formation of gallstones and gallsand were illustrated in the following sponsor's figure:

Figure 10 **Proposed Pathway for Biotransformation of Aripiprazole in Monkey Gallsand, Gallstone and Bile Samples**



In a follow-up study [MAP Document No. MAP054/447039], 2 bile-duct cannulated cynomolgus monkeys [3 M, 2 F] were administered aripiprazole [50 mg/kg/] for 9 days. Of the original 5 animals, 3 [2 M, 1 F] were sacrificed moribund [Days 7-9]; blood and bile samples were collected from these animals at time of sacrifice. In 1 M and 1 F, blood samples were collected at 0, 2, 6, and 12 hrs and bile samples were collected 0-6 and 6-12 hrs after the last dose. Metabolites BMS-337041, BMS-337042, and BMS-511426 were quantitated in both blood and bile; aripiprazole was quantitated only in blood. Quantitation of parent and metabolites was performed using ———— In plasma, aripiprazole was the major drug-related material [C_{max} = 1239 (male) and 807 (female) ng/mL, $AUC_{(0-T)}$ = 9917 (male) and 5536 (female) ng•hr/mL]. Whereas the plasma exposure for parent compound was somewhat higher in male, plasma exposure for all three metabolites were markedly higher in the female than in the male:

M/F	BMS-337041		BMS-337042		BMS-511426	
	C_{max} [ng/mL]	$AUC_{(0-T)}$ [ng•hr/mL]	C_{max} [ng/mL]	$AUC_{(0-T)}$ [ng•hr/mL]	C_{max} [ng/mL]	$AUC_{(0-T)}$ [ng•hr/mL]
M	22.5	--	10.2	91.1	2.48	--
F	346	3401	131	1052	8.92	77.7

All three metabolites were detected in bile samples from both animals; the data [units: µg/mL] are summarized below:

TIME [hr]	BMS-337041		BMS-337042		BMS-511426	
	M	F	M	F	M	F
0-6	72	462	116	477	28	65
6-12	35	318	53	404	18	55

The sponsor noted that, due to the large interanimal variability, no conclusions could be drawn regarding the metabolism of aripiprazole in monkeys.

Dog

The metabolism of aripiprazole was assessed in female Beagle dogs [n = 3] following single i.v. [15 mg], i.m., s.c., and p.o. [15 mg] doses [Protocol DM00026]. [Only the i.v. and p.o. data were reviewed.] A 3-day (minimum) washout period separated doses. [Animals weighed 11.0-12.1 kg.] Blood samples were collected at 0, 10, 20, and 30 min, 1, 2, 4, 8, and 24 hrs following the oral dose; collection times following i.v. dosing were not specified. Plasma samples were assayed in order to quantitate circulating levels of aripiprazole and metabolites, BMS-337040, BMS-337044, BMS-337045, BMS-337047, and DCPP using ———. The data [means ± SD] are summarized in the following table:

DOSE/ROUTE [mg/kg]	COMPOUND	C_{max} [ng/mL]	T_{max} [hr]	$AUC_{(0-T)}$ [ng•hr/mL]	$t_{1/2}$ [hr]	Cl [mL/min/kg]	V_{ss} [L/kg]	F [%]
15 mg i.v.	aripiprazole	1445 ± 813	0.08	1028 ± 159	4.84 ± 0.90	21.2 ± 3.01	5.14 ± 1.08	
	BMS-337040	2.14 ± 0.62	0.33	2.98 ± 1.44				
	BMS-337044	30.8 ± 11.7	2.0	269 ± 191				
	BMS-337045	17.7 ± 4.59	1.0	86.9 ± 30.6				
	BMS-337047	9.52 ± 1.88	1.0	31.2 ± 17.8				
	DCPP	1.97 ± 0.28	1.0	10.5 ± 4.12				
15 mg p.o.	aripiprazole	28.8 ± 32.1	2.0	118 ± 121	2.21			12.2
	BMS-337040	1.98	0.75	<LLOQ				
	BMS-337044	28.8 ± 29.5	2.0	221 ± 266				
	BMS-337045	19.0 ± 18.7	2.0	83.4 ± 72.7				
	BMS-337047	16.2 ± 9.05	1.0	29.5 ± 13.6				
	DCPP	2.56 ± 1.27	2.0	11.6				

The sponsor noted that the Cl rate in female dogs was 74-88% of hepatic blood flow, and characterized aripiprazole as a high hepatic extraction compound in dog.

Human

The sponsor provided a summary comparing the abundance of selected metabolites in rat, monkey, and human plasma [following table]:

Text Table 4: Plasma Metabolite to Aripiprazole AUC Ratios in Rats, Monkeys, and Human After Administration of Multiple Oral Doses of Aripiprazole

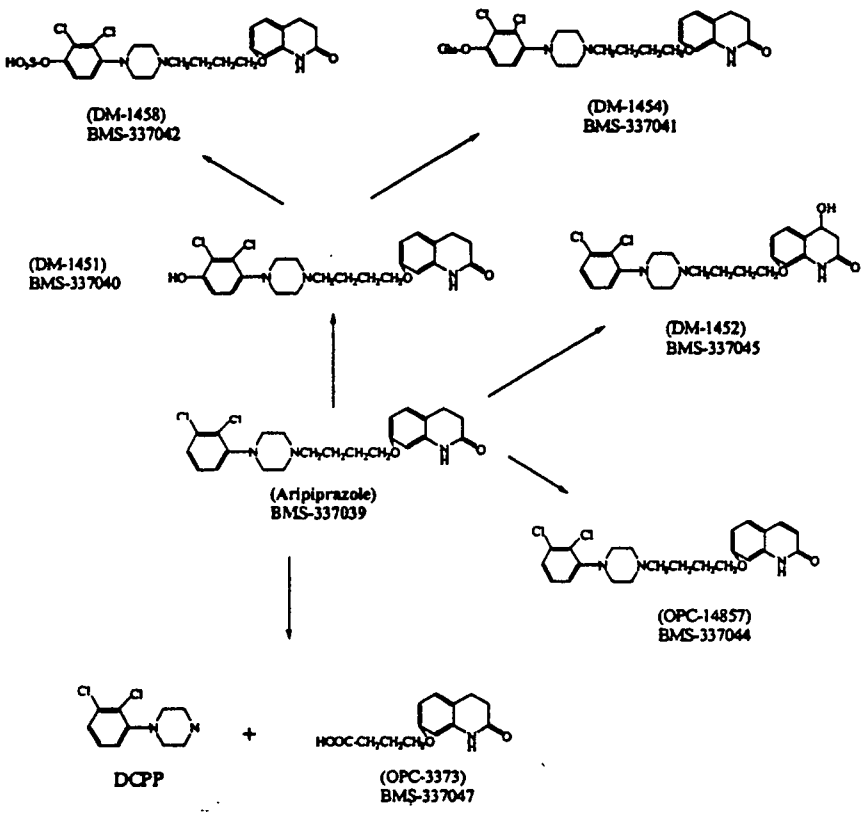
Species	Duration (Dose)	% AUC ratio of metabolite to aripiprazole						
		OPC-14857	DM-1451	DCPP	OPC-3373	DM-1454	DM-1458	DM-1460
Rat	4-26 week (60 mg/kg)	7.0-11.8%	0.22-0.27%	2.7-3.1%	5.4-14.8%	NA	<LLQ	<LLQ
Monkey	33 week (25-75 mg/kg)	44.3-96.3%	1.1-4.1%	18.3-42.3%	6.3-23.2%	NA	9.0-16.0%	0.8-2.3%
Human	1-2 week (15-30 mg)	40.0%	0.48%	ND	1.9%	<LLQ	0.9%	<LLQ

ND = not detected
NA = not analyzed
LLQ = 1-10 ng/mL

A comparison of *in vitro* metabolism by mouse, rat, monkey, and human hepatocytes [MAP Document No. MAP038/337039] indicated that the primary metabolic pathways in all species tested were as follows: (a) N-dealkylation to DCPP and BMS-337047, (b) hydroxylation to BMS-337040 and BMS-337045, and (c) dehydrogenation to BMS-337044. In mouse and rat, N-dealkylation and hydroxylation were the primary pathways, with small amounts of BMS-337044 formed; BMS-337040 was subsequently glucuronidated [BMS-337041]. In human and monkey, N-dealkylation and hydroxylation were evident, as well as "extensive" dehydrogenation to BMS-337044. In both human and monkey, BMS-337040 was conjugated. In monkey, primarily the sulfate conjugate was formed, whereas, in human, formation of the sulfate and glucuronide conjugates was fairly equal. Sulfation of BMS-337040 [= BMS-337042] occurred only in human and monkey hepatocytes.

The proposed metabolic pathways for aripiprazole in humans [based on *in vitro* data] was summarized in the following sponsor's figure:

Biotransformation Pathways of [^{14}C]BMS-337039 in Human Hepatocytes



An *in vitro* study using human recombinant cytochrome P450 enzymes indicated that CYP3A4 and CYP 2D6 were responsible for the *in vitro* metabolism of aripiprazole. Metabolites DM-1451, DM-1452, and OPC-14857 were formed by CYP2D6; these and DCPP were formed by CYP3A4. No metabolism was detected when aripiprazole was incubated with human recombinant CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, or 2E1. *In vitro* inhibition studies using human recombinant cytochrome P450 enzymes and human liver microsomes confirmed these findings.

Serum protein binding

Protein binding of BMS-337039 was assessed *in vitro* in mouse, rat, dog, rabbit, monkey, and human serum at concentrations of 500-5000 ng/mL using equilibrium dialysis [Study No. . In addition, serum

protein binding of BMS-337044 was assessed in human serum. BMS-337039 was extensively bound [99.2-99.9%] in serum of all species tested. BMS-337044 was extensively bound to human serum proteins [99.7-99.9%]. Over the concentration range tested, the % binding was not concentration-dependent.

Protein binding of metabolites, OPC-3373, DCPP, OPC-14857, and DM 1452, was tested *in vitro* in human serum using [OPC-3373, DCPP] or [PDMS-GB] [OPC-14857, DM-1452] [Study No. 014935]. The concentration range tested was 100-1000 ng/mL for DM-1452, OPC-14857, and DM-1452 and 100-5000 ng/mL for OPC-14857. Serum protein binding was as follows: 87-97%, 90%, 99%, 94-98%, and 88-91% for OPC-14597, OPC-3373, DCPP, OPC-14857, and DM-1452, respectively.

Whole blood/plasma distribution

Whole blood/plasma distribution of ^{14}C-OPC-14597 [20-2000 ng/mL] was tested *in vitro* in rat, mouse, rabbit, monkey, and human [Study No's 015826, 015827]. The blood/plasma partition ratio was 0.88-0.93 in fasting and fed rats, 0.79-0.82 in fasting mouse, 0.78-0.85 in fasting rabbit, 0.81-0.85 in fasting monkey, and 0.59-0.63 in fasting human.

TK

1. **Toxicokinetic study of OPC-14597: four-week repeated oral administration in rats** [Study No. 011774, TK data, apparently for the 13-wk, 5-wk, and 52-wk oral studies in rat]

Methods: OPC-14597 was administered orally to Sprague-Dawley rats [21/sex/grp] at doses of 1, 3, 10, 20, and 60 mg/kg for 4 wks. Blood samples were collected from 3/sex/grp/time point on Days 1 [1, 4 hr postdosing] and Day 28/29 [prior to, and at 1, 2, 4, and 8 hrs postdosing]. Plasma levels of OPC-14597 were quantitated using GC.

Results: the data for Day 28/29 were summarized in the following sponsor's tables:

Table 2-1
Toxicokinetic study of OPC-14597 in rats : Four-week repeated oral administration
ITEM : Parameter
Sex : Male Day : 28

DOSE Item	A3	A10	A20	A60
Cmax (ng/ml)	2.6	66.4	217.9	2601.3
Tmax (hr)	4.00	2.80	2.00	4.00
AUC (ng·hr/ml)	22.78 (0-24hr)	257.18 (0-24hr)	1838.68 (0-24hr)	38823.98 (0-24hr)

A3 : 3 mg/kg A10 : 10 mg/kg A20 : 20 mg/kg A60 : 60 mg/kg
: Predose values were considered as 24hr ones for calculation of AUCs(0-24)

Table 2-2
Toxicokinetics study of OPC-14597 in rats : Four-week repeated oral administration
ITEM : Parameter
Sex : Female Day : 28

DOSE Item	A1	A10	A20	A60
Cmax (ng/ml)	4.3	70.3	586.4	1932.7
Tmax (hr)	8.00	4.00	4.00	4.00
AUC (ng · hr/ml)	49.08 (0-24hr)	368.48 (0-24hr)	3747.98 (0-24hr)	26955.48 (0-24hr)

Accumulation was noted with repeated dosing. Although a direct comparison of Day 1 and Day 28/29 values was difficult due to differences in sampling times and T_{max}, Day 28/29 values were higher than Day 1 values [1.6-7 fold], except at the LD; at the LD, plasma values were higher on Day 1 in both males and females.

2. **TK analysis of BMS-337039 and metabolites in a 26-wk chronic oral toxicity study in rats**
[Protocol No. 99353; TK data for toxicity Study No. 99353]

Methods: BMS-337039 was administered to rats at doses of 0, 10, 30, and 60 mg/kg p.o. [by gavage] for 26 wks. Blood samples were collected [via tail vein] from 15/sex/grp [3/sex/grp/time point] at 1, 2, 4, 8, and 24 hrs following dosing on Days 1 and 177. Aripiprazole and metabolites, BMS-337040, BMS-337044, BMS-337045, BMD-337047, and DCPP, were quantitated in plasma using

Results: the data for Days 1 and 177 are summarized in the following table:

Day 1

DOSE [mg/kg]	COMPD	MALES			FEMALES		
		C_{max} [ng/mL]	T_{max} [hr]	$AUC_{(0-\tau)}$ [ng•hr/mL]	C_{max} [ng/mL]	T_{max} [hr]	$AUC_{(0-\tau)}$ [ng•hr/mL]
10 mg/kg	aripiprazole	23.8	2.0	100	49.0	2.0	233
	BMS-337040	12.3	1.0	60.9	8.82	1.0	46.4
	BMS-337044	5.29	2.0	25.5	9.96	2.0	57.8
	BMS-337045	3.88	2.0	10.3	5.15	2.0	23.5
	BMS-337047	18.8	1.0	194	24.1	1.0	93.9
	DCPP	1.31	2.0	<LLOQ	1.68	2.0	4.71
30 mg/kg	aripiprazole	200	4.0	2278	646	4.0	5965
	BMS-337040	27.4	2.0	143	17.1	1.0	86.6
	BMS-337044	32.1	8.0	183	49.0	4.0	299
	BMS-337045	13.6	4.0	83.4	20.4	4.0	126
	BMS-337047	59.3	1.0	168	91.0	1.0	300
	DCPP	9.10	4.0	50.5	10.2	4.0	61.7
60 mg/kg	aripiprazole	1093	2.0	13555	2526	8.0	34874
	BMS-337040	53.5	1.0	366	26.4	1.0	220
	BMS-337044	88.3	4.0	1266	158	8.0	2501
	BMS-337045	41.4	2.0	264	67.3	8.0	935
	BMS-337047	229	2.0	837	180	1.0	1414
	DCPP	39.5	2.0	520	31.4	4.0	523

Day 177

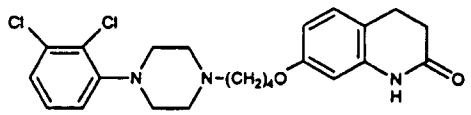
DOSE [mg/kg]	COMPD	MALES			FEMALES		
		C_{max} [ng/mL]	T_{max} [hr]	$AUC_{(0-\tau)}$ [ng•hr/mL]	C_{max} [ng/mL]	T_{max} [hr]	$AUC_{(0-\tau)}$ [ng•hr/mL]
10 mg/kg	aripiprazole	128	4.0	1213	340	2.0	3570
	BMS-337040	12.7	4.0	73.5	12.6	2.0	67.3
	BMS-337044	16.3	4.0	97.1	41.1	8.0	596
	BMS-337045	2.22	4.0	6.87	71.6	2.0	191
	BMS-337047	18.8	1.0	194	24.1	1.0	93.9
	DCPP	2.63	2.0	<LLOQ	4.91	2.0	26.8
30 mg/kg	aripiprazole	3420	8.0	50660	3405	8.0	52964
	BMS-337040	15.9	2.0	207	10.5	2.0	184
	BMS-337044	208	8.0	2874	208	8.0	4120
	BMS-337045	18.5	8.0	283	35.8	2.0	451
	BMS-337047	128	2.0	1348	110	2.0	1349
	DCPP	59.5	8.0	787	37.4	8.0	601
60 mg/kg	aripiprazole	6447	2.0	106693	4072	2.0	72377
	BMS-337040	18.0	4.0	243	11.2	2.0	206
	BMS-337044	403	2.0	7415	423	8.0	8512
	BMS-337045	26.2	8.0	443	57.3	2.0	832
	BMS-337047	343	2.0	3190	400	8.0	5935
	DCPP	108	4.0	1474	109	2.0	1148

3. **Toxicokinetic analysis of selected conjugated metabolites in plasma and concentrations of conjugated metabolites in bile in a 39-week oral gavage toxicity study of BMS-337039 (aripiprazole) in cynomolgus monkeys** [Protocol No. 99354; TK data for toxicity Study No. 99354; these analyses were not conducted under GLP]

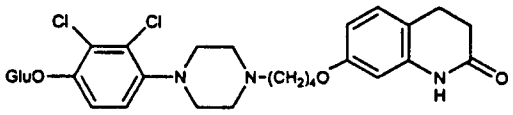
Methods: BMS-337039 was administered to monkeys at doses of 0, 25, 50, and 75 mg/kg p.o. for 39 wks. Blood samples were collected [4/sex/grp except for 3 males at 50 mg/kg] at 1-24 hrs postdosing during Wk 33. [Plasma samples were stored at -20° C for ≈1 yr and subjected to repeated freeze-thaw cycles prior to analysis. The sponsor noted that the stability of the compounds under these conditions of storage was not documented; however, stability was stated to have been documented under the following conditions: storage at -20° C for 2 wks, 3 freeze/thaw cycles, for 24 hrs at rm temperature.] Bile samples were collected at necropsy [≈24 hrs after the last dose]. [Bile samples were stored at -70° C until analyzed; stability was not tested.] BMS-337042 [DM-1458; sulfate conjugate] and BMS-511426 [DM-1460; sulfate conjugate] were quantitated in plasma samples using ——— [BMS-337041 (DM-1454; glucuronide conjugate] was not quantitated in plasma due to the lack of sufficient plasma sample volume.]

Results: structures of the conjugated metabolites were illustrated in the following sponsor's figure:

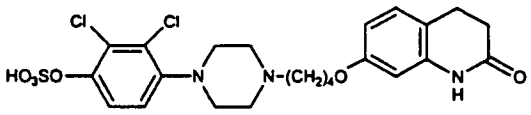
Figure 1: Chemical structures of aripiprazole, BMS-337041, BMS-337042, and BMS-511426



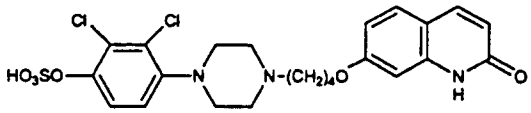
Aripiprazole (BMS-337039, OPC-14597)



BMS-337041 (DM-1454)



BMS-337042 (DM-1458)



BMS-511426 (DM-1460)

The plasma and bile data were summarized in the following sponsor's tables:

Table 8: Mean (SD) plasma toxicokinetic values for BMS-337042 and BMS-511426 in monkeys (N=4) during week 33 of Study 99354

BMS-337042

Dose	CMAX (ng/mL)		TMAX (h)		AUC* (ng.h/mL)		Metabolite/Parent	
(mg/kg/day)	Mean	SD	Median	(Min, Max)	Mean	SD	Mean	SD
Males								
25	178.22	73.68	3.00	(2.00,4.00)	943.42	256.55	0.108	0.022
50[a]	261.36	194.75	4.00	(2.00,4.00)	1557.48	834.88	0.135	0.021
75	375.24	193.11	4.00	(4.00,4.00)	2737.62	1773.16	0.105	0.044
Females								
25	202.20	108.26	2.00	(1.00,4.00)	958.99	415.90	0.093	0.016
50	586.42	376.59	4.00	(2.00,4.00)	2886.59	1546.54	0.156	0.052
75	787.83	344.88	4.00	(2.00,4.00)	4119.64	996.52	0.153	0.068

* Represents trapezoidal AUC(0-T) where, T ranges from 8 to 24 h

a N=3

BMS-511426

Dose	CMAX (ng/mL)		TMAX (h)		AUC* (ng.h/mL)		Metabolite/Parent	
(mg/kg/day)	Mean	SD	Median	(Min, Max)	Mean	SD	Mean	SD
Males								
25	18.32	7.42	4.00	(2.00,4.00)	119.05	76.62	0.012	0.008
50[a]	32.92	25.43	4.00	(4.00,4.00)	249.53	212.11	0.020	0.014
75	32.50	16.56	4.00	(4.00,4.00)	406.93[a]	204.61[a]	0.014[a]	0.007[a]
Females								
25	18.29	9.94	3.00	(1.00,4.00)	82.89	54.68	0.008	0.003
50	61.99	29.45	4.00	(4.00,4.00)	372.70	143.95	0.023	0.007
75	51.01	24.11	4.00	(2.00,4.00)	204.87	65.45	0.007	0.003

* Represents trapezoidal AUC(0-T) where, T ranges from 4 to 24 h

a N=3

Table 9: **Mean and SD biliary concentrations of BMS-337041, BMS-337042, and BMS-511426 in monkeys during week 39 Study 99354**

Dose (mg/kg/day)	Sex	BMS-337041 Bile Concentration (µg/mL)					
		N	Mean	SD	%CV	Minimum	Maximum
25	M	4	2201.34	1523.09	69.19		
	F	4	1439.95	1427.72	99.15		
50	M	3	2610.87	1665.42	63.79		
	F	4	1868.04	1178.75	63.10		
75	M	3	1564.04	1219.04	77.94		
	F	4	1716.44	771.42	44.94		

Dose (mg/kg/day)	Sex	BMS-337042 Bile Concentration (µg/mL)					
		N	Mean	SD	%CV	Minimum	Maximum
25	M	4	1416.04	451.75	31.90		
	F	4	6291.34	8348.41	132.70		
50	M	3	11007.14	15488.75	140 72		
	F	4	4373.17	3929.26	89.85		
75	M	3	8739.43	11808.71	135.12		
	F	4	2954.88	1426.61	48.28		

Dose (mg/kg)	Sex	BMS-511426 Bile Concentration (µg/mL)					
		N	Mean	SD	%CV	Minimum	Maximum
25	M	4	570.18	647.97	113.64		
	F	4	1652.74	2687.79	162.63		
50	M	3	2190.69	3046.51	139.07		
	F	4	1059.75	929.26	87.69		
75	M	3	534.60	389.00	72.76		
	F	4	828.83	849.31	102.47		

For comparison, the sponsor provided data from an in vitro solubility study [previously conducted; Document Control No. 930000197]; these data are provided below [sponsor's table]:

Table 10: ***In vitro* solubility of BMS-337041, BMS-337042, and BMS-511426 in monkey bile**

Lot	BMS-337041 (DM-1454) [µg/mL]	BMS-337042 (DM-1458) [µg/mL]	BMS-511426 (DM-1460) [µg/mL]
1	3900	290	920
2	6600	230	300
3	5500	600	400
4	7000	100	100
5	4500	500	400
6	2800	89	210
7	5200	1200	680
8	4100	260	460
Arithmetic Mean	4900	430	430
SD	1400	390	280
Geometric Mean	4800	300	350

4. **Twenty-six week oral toxicokinetics study in cynomolgus monkeys** [Study No. DM00001 ———— ———, Study completion date: 1/8/01].

The purpose of this study was to provide TK data relevant to the 52-wk oral toxicity study in cynomolgus monkey. Aripiprazole [Lot no. C99G74M] was administered to monkeys [3/sex/grp] at doses of 0.5 and 5 mg/kg p.o. [gavage] for 26 wks. Blood samples were collected on Days 1 and 182 at 1, 2, 4, 8, and 24 hrs postdosing. Aripiprazole and metabolites, BMS-337040, BMS-337044, BMS-337045, BMS-337047, and DCPP, were quantitated in plasma using a "validated method".

The data were summarized in the following table:

DAY	DOSE [mg/kg]	MALES			FEMALES		
		C_{max} [ng/mL]	T_{max} [hr]	$AUC_{(0-T)}$ [ng•hr/mL]	C_{max} [ng/mL]	T_{max} [hr]	$AUC_{(0-T)}$ [ng•hr/mL]
ARIPIPRAZOLE							
1	0.5	7.66 ± 2.83	2.0	37.1 ± 13.7	11.7 ± 0.81	2.0	42.0 ± 13.7
	5	141 ± 42.9	1.0	775 ± 392	144 ± 83.0	2.0	884 ± 542
182	0.5	12.6 ± 7.99	2.0	127 ± 67.7	13.0 ± 1.61	2	77.4 ± 41.8
	5	267 ± 189	2.0	2335 ± 1523	190 ± 104	4.0	1765 ± 1108
BMS-337040							
1	0.5	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	5	15.9 ± 4.57	1.0	38.8	9.86 ± 5.39	1.0	38.0 ± 22.3
182	0.5	1.12	2.0	--	<LLOQ	<LLOQ	<LLOQ
	5	2.09 ± 0.98	1.0	6.04	3.02 ± 0.60	2.0	--
BMS-337044							
1	0.5	6.93 ± 2.22	4.0	48.4 ± 26.6	8.24 ± 2.66	2.0	32.8 ±3.07
	5	94.7 ± 8.85	2.0	821 ± 318	80.3 ± 44.8	2.0	726 ± 508
182	0.5	10.2 ± 4.53	2.0	107 ± 68.8	8.69 ± 1.38	2.0	39.9 ± 1.70
	5	123 ± 69.0	2.0	1812 ± 1012	121 ± 66.8	4.0	1564 ± 1188
BMS-337045							
1	0.5	2.11 ± 0.88	4.0	11.0	1.97 ± 0.67	1.0	5.10
	5	27.6 ± 2.58	1.0	156 ± 87.3	23.0 ± 13.3	2.0	150 ± 120
182	0.5	2.09 ± 0.83	2.0	11.7 ± 4.75	2.17 ± 0.49	2.0	7.50 ± 2.55
	5	34.6 ± 19.3	2.0	367 ± 198	40.9 ± 25.2	2.0	411 ± 267
BMS-337047							
1	0.5	3.46 ± 2.13	2	36.1 ± 8.34	14.6 ± 11.3	1.0	93.3
	5	68.9 ± 64.2	1.0	129 ± 74.4	32.3 ± 16.2	1.0	80.3
182	0.5	3.18 ± 1.61	1. 0	28.7 ± 29.6	6.48 ± 4.3	2.0	20.1
	5	57.7 ± 19.3	1.0	128 ± 12.5	69.4 ± 63.3	2.0	231 ± 200
DCPP							
1	0.5	1.49 ± 1.31	2.0	40.8	3.11 ± 1.19	1.0	35.4
	5	15.6 ± 7.25	1.0	73.6	15.1 ± 11.4	1.0	79.5 ± 76.3
182	0.5	2.96 ± 3.18	2.0	19.9	4.10 ± 1.13	4.0	32.6 ± 9.03
	5	35.2 ± 21.7	1.0	278 ± 170	34.3 ± 17.9	4.0	302 ± 109

The sponsor summarized the data on biliary concentrations of conjugated metabolites in animal species and human in the following table:

Text Table 5: Bile Concentrations of Conjugated Metabolites of Aripiprazole in Mice, Rats, Monkeys and Humans after Daily Oral Administration of Aripiprazole

Species	N	Dose	Sample day	Sample Interval[a]	DM-1454 (μg/mL)[b]	DM-1458 (μg/mL)[b]	DM-1460 (μg/mL)[b]
Mice	4	60 mg/kg	7	0-6 h	29-102	<LLQ[c]	<LLQ[c]
	4			0-12 h	69-230	<LLQ-0.7	<LLQ-0.6
Rat	4	60 mg/kg	14	0-6 h	123-302	1.6-3.5	<LLQ-0.6
				6-12 h	102-273	<LLQ-2.4	<LLQ-0.6
	5		28	0-6 h	173-437	0-6-5.9	<LLQ-1.5
				6-12 h	104-235	<LLQ-5.2	<LLQ-0.8
Monkey	8	25 mg/kg	39-week	Terminal	496-4291	1148-18770	128-5682
	7	50 mg/kg			428-3886	927-28870	168-5695
	8	75 mg/kg			582-2928	1403-22372	209-2072
Human	8	15 mg	7	4-6	3.3-24.1	1.1-15.0	0.3-4.1
	8	30 mg					

[a] Bile samples were collected on the last day of the study after dosing.
[b] Data compiled here are from BMS reports with DCNs of 930000449, 930000450, 930000432, and 930000381.
[c]

PK/ADME/TK Summary and Conclusions

Mouse: following oral dosing in ICR mice, aripiprazole was fairly rapidly absorbed. Peak levels of parent compound were reached within 1-2 hrs of dosing. Absolute oral bioavailability was ≈46% in both males and females. Plasma exposure to aripiprazole increased fairly linearly with dose [0.3-30 mg/kg p.o.], although the increase was somewhat less than dose-proportional from 10 to 30 mg/kg in both males and females. The $t_{1/2}$ was 3 and 3-7 hrs following i.v. and p.o. dosing, respectively. The V_d following an acute i.v. dose [5.6 L/kg] was consistent with extensive distribution into tissues, and the Cl rate [1.2-1.3 L/hr/kg] was less than hepatic blood flow in this species. Peak brain levels of aripiprazole following both oral and i.v. dosing were 3-8 times higher than those in plasma, indicating significant brain penetration.

Metabolism studies indicated the presence of three primary metabolic pathways: (a) N-dealkylation, (b) hydroxylation, and (c) dehydrogenation. The parent compound was the major circulating drug-related material after both acute and repeat oral dosing. The major circulating metabolite was DM-1454 [BMS-33704] following acute dosing and OPC-14857 [BMS-337044] following repeat dosing. Dealkylated products were minor circulating metabolites in mouse. *In vitro* metabolism studies conducted in mouse hepatocytes identified the presence of the three primary pathways. However, the *in vitro* data identified the N-dealkylation and hydroxylation pathways as primary, with only small amounts of the dehydrogenated metabolite detected [i.e., BMS-337044]. Aripiprazole and BMS-337041 [DM-1454], the glucuronide conjugate of BMS-337040 [DM-1451], were detected in mouse plasma and bile following an oral dose of aripiprazole. BMS-337040 was not detected in plasma following oral dosing, suggesting rapid conjugation of the metabolite. Sulfate conjugates of DM-1451 [BMS-337040] and DM-1459 [BMS-511429], i.e., BMS-337042 [DM-1458] and BMS-511426 [DM-1460], respectively, were not detected in mouse plasma or most bile samples. Aripiprazole was extensively bound to serum proteins [>99%] as determined *in vitro*.

Rat: aripiprazole exhibited nonlinear kinetics in male and female rats. Plasma levels were higher in females than in males, with the difference being greater at higher doses. Absolute oral bioavailability was 16% and 54% at 10 and 30 mg/kg p.o., respectively. Studies using radiolabeled aripiprazole indicated an increase in oral absorption with dose. Oral absorption of radioactivity was delayed but greater [≈20% based on AUC] in fed as compared to fasted rats. The $t_{1/2}$ was calculated to be ≈1-2 and 1 hr following p.o. and i.v. dosing, respectively. The V_d following an acute i.v. dose in male and females was consistent with extensive tissue distribution, and the Cl rate [5-7 L/hr/kg] was greater than hepatic

plasma flow rate suggesting extrahepatic metabolism. Peak brain levels following acute and repeat oral dosing were 3-5 times higher than plasma levels in male rats, and 5-13 times higher than plasma levels following an acute oral dose in females. Feces was the major route of elimination. Particular at lower doses, fecal radioactivity probably represented both eliminated drug-related material and unabsorbed parent compound. In females, bile radioactivity accounted for the majority of fecally eliminated material; biliary radioactivity was very low in males. Metabolism studies indicated the presence of three primary metabolic pathways: (a) N-dealkylation, (b) hydroxylation, and (c) dehydrogenation. The parent compound was the major circulating drug-related material after acute and repeat oral doses. The major circulation metabolites following repeat oral dosing were BMS-337047 [OPC-3373] and BMS-337044 [OPC-14857]. As in mouse, *in vitro* metabolism studies identified the N-dealkylation and hydroxylation pathways as primary, with only small amounts of the dehydrogenated metabolite [BMS-337044] detected. An analysis of conjugated metabolites in plasma and bile indicated the presence of BMS-337041 [the glucuronide conjugate of DM-1451] in both samples. BMS-337042 and BMS-511426 were not detected in plasma, and were near or below the LLOQ in bile. Tissue distribution studies confirmed extensive distribution of radioactivity into tissues following p.o. and i.v. dosing. Highest levels of radioactivity were detected in GI, liver, submaxillary gland, and adrenal gland; however, substantial amounts of radioactivity were detected in numerous other tissues. In brain, distribution of radioactivity was fairly similar among the areas examined [forebrain, cerebellum, medulla oblongata/pons, occipital lobe]. In pigmented rat, distribution of radioactivity was fairly similar to that in nonpigmented in the selected tissue examined, except for pigmented tissues. Peak levels of radioactivity in pigmented skin were fairly similar to that in nonpigmented skin; however, total skin exposure was 5 times higher in pigmented tissue. At 168 hrs postdosing, radioactivity was still >LOD in a number of tissues, including adrenal gland, liver, kidney, testis, and in pigmented eye. In pigmented animals, the highest level of radioactivity [of the selected tissues examined] based on AUC was detected in eye. Aripiprazole was extensively bound to serum proteins [>99%] as determined *in vitro*.

Monkey: aripiprazole exhibited slightly nonlinear kinetics following acute oral dosing in cynomolgus monkey, with a somewhat greater than dose-proportion increase in dose from 12.5 to 25 mg/kg. At 5 mg/kg p.o., absolute oral bioavailability was 5-8%. The $t_{1/2}$ was 3-4 hrs following i.v. and p.o.dosing. The V_d following an acute i.v. dose was consistent with some tissue distribution, but was considerably lower than the V_d in either mouse or rat. The Cl rate [846 mL/hr/kg], ≈60% of hepatic plasma flow in monkey, was lower than in mouse or rat. The major route of elimination was via the feces. OPC-3733 and DM-1451 were the major drug-related compounds in urine and feces, respectively. Metabolism studies indicated the presence of the same three primary metabolic pathways as identified in mouse and rat: (a) N-dealkylation, (b) hydroxylation, and (c) dehydrogenation. Following an acute oral dose, OPC-3373 was the major circulating drug-related material, accounting for 62% of total radioactivity at T_{max}. Aripiprazole, DM-1451, DM-1454, and DM-1451 sulfate were also detected in plasma. Aripiprazole accounted for 30% of total radioactivity at T_{max}. Interestingly, the T_{max} for OPC-3373 was earlier than that for aripiprazole [2 vs 8 hrs postdosing]. DM-1451, DM-1454, and DM-1451 sulfate accounted for 2, 10, and 4% of total radioactivity at their T_{max}. Peak levels of these compounds were 10, 82, and 35%, respectively, of the peak level for aripiprazole. The C_{max} for OPC-3373 was ≈5 times the C_{max} for aripiprazole. In a separate acute oral dose study, OPC-3373, DM-1451, DM-1454, DM-1452, DCPP, and OPC-14857 were found to circulate at levels 400% [5-fold], <1, 56, 30, 32, and 56% of circulating aripiprazole levels. Following chronic dosing [26-39 wks], aripiprazole and OPC-1487 were the major circulating drug-related materials and were present [based on AUC] at fairly similar levels. In monkey, N-dealkylation appears to be a major metabolic pathway. *In vitro* metabolism studies conducted in monkey hepatocytes identified the presence of the three primary pathways. Conjugation of DM-1451 was detected in both monkey and human hepatocytes, although in monkey it was primarily sulfate conjugation whereas in human formation of sulfate and glucuronide conjugates occurred to a fairly similar extent. Analyses of drug-related material in bile and gallstones/gall sand samples obtained in the 39-wk oral toxicity study in monkey indicated the presence of three conjugates, BMS-337041 [DM-

1454], BMS-337042 [DM-1458], and BMS-511426 [DM-1460]. BMS-337042 and BMS-511426 accounted for 36 and 6% of the conjugate present [on a per wt basis], respectively. BMS-337041 accounted for <2%. [BMS-337-42 was confirmed to be a major component of "sludgy" substance present in bile collected from 2 monkeys treated at high doses of aripiprazole (500-2000 mg/kg).] BMS-337042 and BMS-511426 were also detected in plasma collected during the 39-wk study; metabolite-to-parent ratios were ≈0.1-0.15 and 0.01-0.02, respectively. It is of note that the proposed metabolic pathways for aripiprazole based on these analyses included the formation of an epoxide intermediate [formed during conversion of BMS-511429 (DM-1459) to M1 (trihydroxysulfate conjugate)]; it was noted that M1 was a minor component of bile. A similar pathway was not noted in the proposed metabolic scheme for human. Instead, it appears that BMS-511429 [aka DM-1459, a minor metabolite (1-3% of plasma radioactivity)] is sulfate conjugated [BMS-511426, DM-1460] in humans and presumably excreted as such.

The PK/ADME data provided for mouse, rat, monkey, and human indicate that (a) absolute oral bioavailability is highest in humans [F = 46, 16-54 (10-30 mg/kg p.o.), 8, and 87%, respectively, (b) the clearance rate is lowest in humans [$t_{1/2}$ = 3, 1, 3-4, and 99 hrs, respectively; Cl ≈ 20, 83-120, 14, and 0.72 mL/min/kg, respectively], and that (c) the metabolic pathways proposed for aripiprazole are qualitatively similar in mouse, rat, monkey, and human, although the relative contribution of these pathways differs somewhat among species. Notable from a toxicological standpoint is the relatively greater extent of sulfate conjugation in monkey, with elimination of the conjugates via the bile.

The metabolic pathways for aripiprazole in humans were summarized in the following sponsor's figure:

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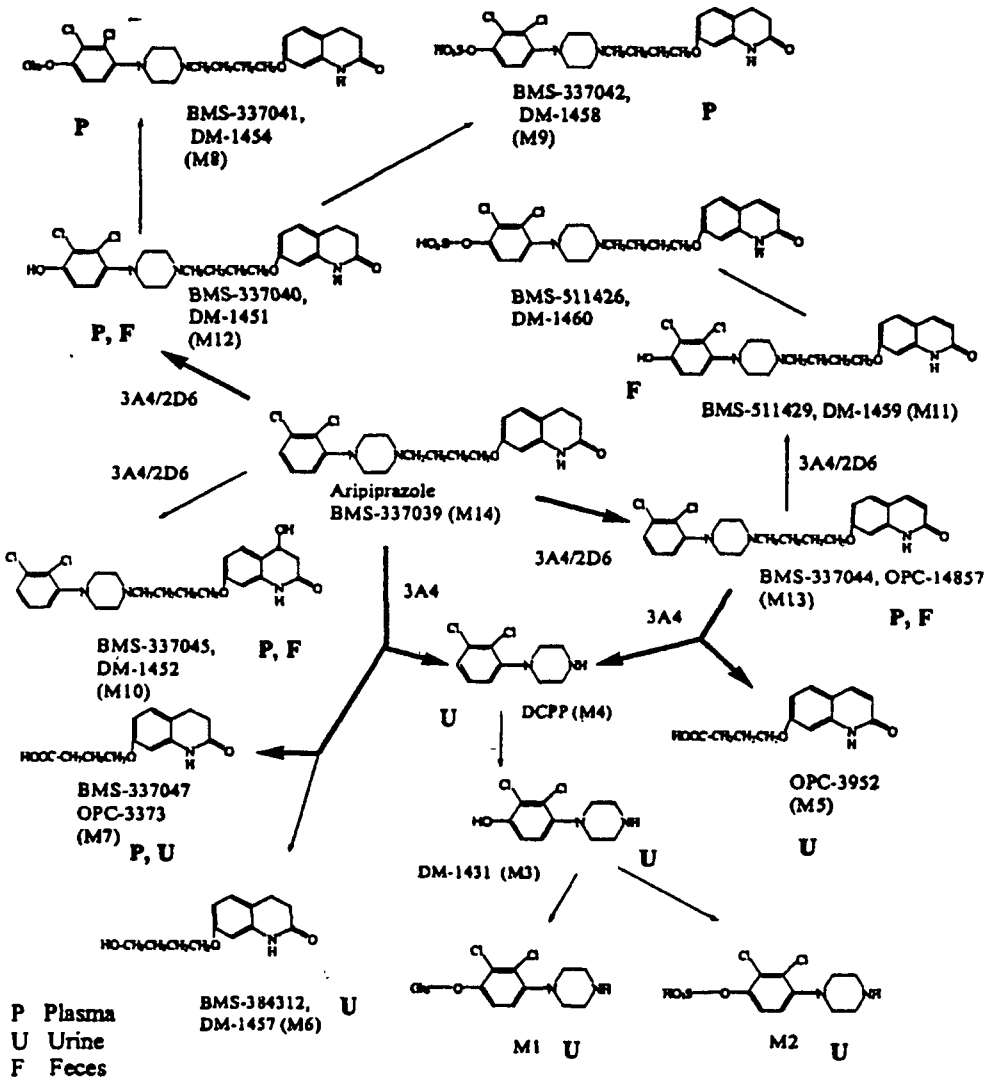
Figure 8: Proposed metabolic pathways of aripiprazole in humans



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IV. GENERAL TOXICOLOGY

A number of toxicology studies have been previously reviewed [Steven Sparenborg, Ph.D.]; a brief summary of these studies [based on the previous reviews] is provided. A number of acute and subchronic studies have been conducted but not previously reviewed. Data from these studies are summarized only as needed. Chronic studies that have not previously been reviewed are reviewed in detail.

Acute studies

Mouse

An acute oral toxicity study was conducted in ICR mice [3/sex/grp] at doses of 93, 327, 1143, and 4000 mg/kg. No C grps were included. All animals receiving doses >LD died, and 1 LDF died. There were no deaths in LDM. Drug-related clinical signs were evident at all doses in both males and females [e.g., decreased spontaneous motor activity, ptosis, prone position, hypothermia (i.e., cool to touch), convulsions]. Body wt was transiently reduced at the LD. In animals found dead, unabsorbed drug was detected in the GI tract. No macroscopic findings were detected in survivors. No histopathology was performed.

Rat

1. an acute oral toxicity study was conducted in Sprague-Dawley rat [5/sex/grp] at doses of 395, 593, 889, 1333, 2000 mg/kg. The LD_{50}'s were 965 mg/kg in males and 705 mg/kg in females. Clinical signs [doses not specified in the review] included decreased spontaneous motor activity, crouching, prone posture, ataxia, tremor, convulsions, Straub tail, catalepsy, ptosis, lacrimation, chromodacryorrhea, cold to touch, read urine, and wetness around the urogenital area. Gross findings at necropsy in animals that died prematurely consisted of remains of unabsorbed drug in stomach and GI tract, gastric mucosal hemorrhage, and adrenal enlargement. No histopathology was performed.

2. an acute i.v. toxicity study was conducted in Sprague-Dawley rat [12/sex/grp] at doses of 0, 0.1, 0.4, and 2 mg/kg. There were no unscheduled deaths, or any drug-related effects on any parameter assessed [including body wt, clinical pathology, gross and histopathology] except for some signs of irritation at the injection site. The C_{max} and AUC values were as follows: LD: 57.3-34.4 ng/mL and 33.1-25.7 ng•hr/mL, respectively; MD: 153-103 ng/mL and 176-74.2 ng•hr/mL, respectively; HD: 451-277 ng/mL and 738-327 ng•hr/mL, respectively.

Monkey

1. an acute oral toxicity study was conducted in cynomolgus monkey at doses of 500 and 1000 mg/kg in 2 male monkeys and at a dose of 2000 mg/kg in 2/sex. There were no drug-related deaths. Clinical signs were evident at all doses and consisted of reduced spontaneous motor activity and reactivity to external stimuli, catalepsy, crouching, prone/lateral position, tremor, and/or ptosis. Adverse effects on body wt and food consumption were observed at all doses. No drug-related gross pathology findings were detected. Histopathology was not performed.

2. an acute i.v. toxicity study was conducted in cynomolgus monkey [3/sex/grp] at doses of 0, 0.05, 0.2, and 1 mg/kg. There were no unscheduled sacrifices. There were also no drug-related effects on the parameters assessed, including body wt, clinical pathology, gross and histopathology. The only microscopic finding was irritation at the injection site, detected in both C and dosed grps. C_{max} and AUC at the HD were 466-470 ng/mL and 769-924 ng•hr/mL, respectively.

Subchronic studies

Rat

1. a 13-wk oral (gavage) toxicity study [with a 4-wk recovery period] was conducted in Sprague-Dawley rat at doses of 0, 2, 6, and 20 mg/kg [n = 10/sex/grp; 6/sex for C and HD recovery]. [OPC-14597 batch 8K84M was used.] Observations consisted of clinical signs, body wt, food consumption, clinical pathology [including urinalysis], and terminal studies [organ wt, gross and histopathology]. There were no drug-related deaths or clinical signs. Body wt gain was reduced in HDM [10-20%], with final body wt 94% of CM. Body wt was increased in MDF and HDF, with final body wts being 13 and 8% greater, respectively, than in CF. The only hematological finding of note was a slightly increased [3-4%] hgb and hct values in MDM and HDM. On clinical chemistry parameters, the primary drug-related findings were as follows: (a) a decrease in TG in HDM (36%) [this finding was not noted in HDM-R], and (b) a decrease in PL in HDF (12%); this finding persisted in HDF-R. No drug-related effects were observed on urinalysis parameters. Organ wt changes were as follows: (a) decrease in liver wt in HDM [18%, absolute and relative], (b) a decrease in ovary and uterus wts in MDF and HDF [only the decrease in relative uterus wt in HDF (24%) was significant]; there were no clear drug-related findings in recovery animals. Microscopic findings were detected in mammary gland [lobular hyperplasia in all HDF and 1 MDF, dilatation of the acini and ducts with secretion in 2 HDF] and vagina [mucification of the epithelium in 5 HDF and 1 MDF].

2. a 4-wk oral (gavage) toxicity study [with a 4-wk recovery period; GLP] was conducted in Sprague-Dawley rat [10/sex/grp for main study, 4/sex C and HD animals were used for recovery] at doses of 0, 60, and 100 mg/kg. [OPC-14597 lot no. 98A91M was used.] An additional 21/sex were treated at a dose of 100 mg/kg in order to assess TK. Observations consisted of clinical signs, body wt, food consumption, ophthalmology, clinical pathology [hematology, clinical chemistry, urinalysis], terminal studies [gross pathology, organ wts, histopathology; EM (liver, kidney form 2/sex/grp)], and TK. There were no unscheduled deaths. The primary drug-related clinical sign at the LD was sedation [all animals]. At the HD, additional clinical signs observed included abdominal wetness, lacrimation, hypothermia [1 M, 2 F], and tremors [F]. Body wt was reduced [compared to Cs] at both doses in males and females. Final mean body wts were reduced by 19 and 34% in LDM and HDM, respectively, compared to CM, and by 15 and 25% in LDF and HDF, respectively, compared to CF. Mean body wt tended to normalize in HD-R animals; however, at the end of the recovery period, mean body wt was still reduced in HDM-R [17%] compared to CM-R. Overall mean body wt gain was reduced by 43 and 77% in LDM and HDM, respectively, and by 50 and 83% in LDF and HDF, respectively. Food consumption was reduced throughout the dosing period at both doses in males and females, and in HDM-R during the first 2 wks of the recovery period. At the HD, the effect was greatest during the first few days of dosing. There were no ophthalmology findings. On urinalysis parameters, significant decreases in water consumption [50-70 and 78-71% at LD and HD, respectively], urine volume [56-74 and 74-68% at LD and HD, respectively], and Na , K, and Cl concentrations [50-80%; similar at both doses], and creatinine [42-50 and 58-52%] were observed at both doses in males and females. All parameters normalized by the end of the recovery period, except that creatinine remained reduced in HDM-R [15%]; water consumption was significantly increased in HDF-R [28%]. On hematology parameters, the following were noted: (a) small, but significant decreases in MCV in HDM [4%], LDF [3%], and HDF [5%], (b) a decrease in platelet ct in LDM [18%], HDM [25%], and LDF and HDF [9%], decreases in PT [7-6%] and APTT [8%] in LDM and HDM. (c) decreases in wbc ct [30%], basophil ct [50%], and large unnucleated cells [65%] in HDM. (d) reticulocyte ct was reduced at both doses in females [46 and 50% at LD and HD, respectively]. Findings upon examination of the bone marrow smears consisted of the following: (a) decreases in bone marrow nucleated cells at both doses in males [≈30%] and females [17 and 28% at LD and HD, respectively, (b) 75 and 100% reductions in proerythroblasts/orthochromatic erythroblasts in males and females at both doses [M: 32 and 29% at LD and HD, respectively; F: 38-42% at LD and HD,

respectively]. (c) decreases in neutrocytes at both doses in males and females [M: 37%; F: 21 and 30% at LD and HD, respectively. (d) decreases in megakaryoctes in LDM [45%] and HDM [52%]. (e) a decrease in mitotic cells in HDM [89%]. There were no significant hematology findings in recovery animals. [Regarding bone marrow smears, only data on bone marrow nucleated cells were provided in recovery animals.] On clinical chemistry parameters, the following were notable: (a) increases in LDH in HDF [76%], (b) marked, dose-related increases in SGOT [2.3 and 3.7-fold at LD and HD, respectively] and SGPT [3.6 and 5.4-fold at LD and HD, respectively] in females, (c) increases in GTP in LDF [43%] and HDF [70%], (d) decreases in cholesterol, PL, and TG in HDF [23, 20, and 58%, respectively] and in TG in males [65 and 75% at LD and HD, respectively], (e) decreases in glucose at both doses in males [15-13%], (f) small, but significant increases in albumin and A/G ratio in HDM [8 and 16%, respectively], (g) decreases in Ca in males [5 and 9% at LD and HD, respectively] and females [7 and 12% at LD and HD, respectively]. (h) decreases in selected globulins [α_1 and β; 15-10%] and total globulins [9%] in HDM; α_1 globulin was also reduced in HDF [17%]. (i) small, but significant increases in Cl in HD animals [3%], (j) an increase in K [14%] in HDM. An increase in alkaline phosphatase in HDM-R [52%] and decreases in glucose HDM-R and HDF-R [15-9%] were observed in recovery animals.

At necropsy, the primary drug-related gross findings were soiled fur [LD (1/sex), HD] and reduced adipose tissue [HD]. No macroscopic findings were noted in recovery animals. On organ wts, the following were notable: (a) increases in absolute and relative adrenal wt at both doses in males [13-36 and 18-82% at LD and HD, respectively] and females [23 (relative only) and 32-78% at LD and HD, respectively], (b) decreases in pituitary wt in females [19-4 and 33-10% at LD and HD, respectively], (c) a decrease in ovary wt at the HD [42-23%], (d) decreases in seminal vesicle and prostate wts in HDM [38-9 and 40-12%, respectively]; prostate wt was also reduced in LDM [21-4%]. These findings were not noted in recovery animals. Histopathology findings are summarized in the following table:

TISSUE	FINDING	MALES			FEMALES		
		0	60	100	0	60	100
adrenal	hypertrophy of z. fasciculata/reticularis						
	very slight	0/10	4/10	1/10	0/10	5/10	0/10
	slight	0/10	0/10	7/10	0/10	0/10	2/10
	moderate	0/10	0/10	0/10	0/10	0/10	8/10
pituitary	atrophy, pars intermedia						
	very slight	0/10	0/10	0/10	0/10	0/10	0/10
	slight	0/10	10/10	10/10	0/10	10/10	8/10
lung/bronchus	foamy cells in alveoli						
	very slight	1/10	7/10	3/10	1/10	8/10	4/10
	slight	0/10	1/10	7/10	0/10	1/10	6/10
mammary gland	lobular hyperplasia [very slight]	0/10	0/10	0/10	0/10	8/10	2/10
	milk secretion						
	very slight	0/10	0/10	0/10	0/10	6/10	3/10
	slight	0/10	0/10	0/10	0/10	2/10	0/10
bone marrow	hypocellularity						
	very slight	0/10	0/10	2/10	0/10	4/10	2/10
	slight	0/10	0/10	4/10	0/10	0/10	3/10
submaxillary gland	hypertrophy, acinar cells [very slight]	0/10	2/10	6/10	0/10	0/10	0/10
sublingual gland	hypertrophy, acinar cells [very slight]	0/10	6/9	5/10	0/10	-	1/10
prostate	flattening of glandular epithelium [v. slight]	2/10	3/10	4/10			
	decreased secretion						
	very slight	1/10	5/10	3/10			
	slight	2/10	5/10	7/10			
ovary	decreased CL						
	very slight				0/10	0/10	0/10
	slight				1/10	3/10	6/10
uterus	atrophy						
	very slight				0/10	0/10	0/10
	slight				0/10	1/10	2/10
vagina	mucification of epithelium [very slight]				0/10	0/10	2/10

The sponsor considered the adrenal gland findings secondary to "aggravated general conditions", and a number of clinical chemistry [e.g., decreases in serum lipids, increased BUN] and organ wt effects to decreases in body wt/food consumption. The hypocellularity of bone marrow was also attributed to body wt/food consumption effects. Microscopic findings in male and female reproductive organs were attributed to alterations in serum prolactin [not measured in this study]. Atrophy of the pars intermedia was attributed to direct D_2 agonist effects. The sponsor noted that bromocriptine has been shown to "...reduce the number of cell layers, and D_2 antagonist, haloperidol increased their number". The sponsor also noted that microscopic findings in adrenal gland, lung alveoli [foamy cells], submaxillary and sublingual glands [acinar cell hypertrophy], and ovary [decreased corpora lutea] had not been observed in previously conducted toxicity studies in rat [i.e., 5-, 13-, and 52-wk studies].

TK parameters in satellite animals [100 mg/kg] were as follows:

C_{max}: 4603 and 6021 ng/mL in males and females, respectively.
T_{max} : 2 and 8 hrs in males and females, respectively.
$AUC_{(0\text{-}24\ hr)}$: 72223 and 95389 ng•hr/mL, respectively.

3. a 5-week "screening" study was conducted in Sprague-Dawley rats [8/sex/grp]. OPC-14597 was administered by gavage at doses of 2, 6, 20, and 60 mg/kg. Observations consisted of clinical signs, body wt, food consumption, clinical pathology [hematology, clinical chemistry], TK, and terminal studies [gross pathology, organ wts, histopathology]. There were no unscheduled deaths, and no drug-related clinical signs were evident at doses of 2-20 mg/kg. At 60 mg/kg, sedation, lacrimation, piloerection, tremor, and "loss of vigor" were observed throughout the dosing period. HDF appeared emaciated from Day 25 on. Decreases in body wt [relative to Cs] were observed in HDM and HDF throughout the dosing period; final mean body wts were 19-17% lower in HD animals compared to Cs. Food consumption was reduced at the HD, particularly in HDM. Small, but significant, decreases in MCV and MCH [5-4%] were noted in HDF. The following were noted on clinical chemistry parameters: (a) increased SGOT [22%] in HDF, (b) increases in cholinesterase and cholesterol in HDM [41 and 32%, respectively], (c) decreases in glucose in HDM and HDF [15-20%], (d) decreases in total protein at the HD [6%] and a decrease in albumin in HDF [5%], (e) increased BUN in HDF [25%], (f) decreased creatinine in HDM [12%], (g) reduced serum Ca in HDM [4%], MDF [4%], and HDF [36%], (h) small, but significant increase in Cl in HD animals [2-1%]. Organ wt findings consisted of the following: (a) decrease in absolute and relative liver wt in HDM [27-9%], (b) increases in relative, but not absolute, adrenal wt in HD animals [33%], (c) an increase in relative, but not absolute, lung wt in HDF [23%], (d) decreased absolute and relative ovary wt in HDF [35-22%]. [Other organ wt changes appeared to reflect body wt effects.] Gross findings consisted of 'atrophy of the spleen and decrease in abdominal fat" in HD animals, and small liver in 1 HDF. Microscopic findings are summarized in the following table:

TISSUE	FINDING	MALES					FEMALES				
		0	2	6	20	60	0	2	6	20	60
liver	atrophy [hepatocytes] [slight]	0/8	0/8	0/8	0/8	6/8	0/8	0/8	1/8	2/8	5/8
spleen	extramedullary hematopoiesis [slight]	8/8	8/8	8/8	8/8	8/8	8/8	8/8	8/8	8/8	5/8
	atrophy [white pulp] [slight]	0/8	0/8	0/8	0/8	3/8	0/8	0/8	0/8	0/8	3/8
bone marrow	vacuolar degeneration										
	slight	0/8	0/8	0/8	3/8	4/8	0/8	0/8	1/8	4/8	1/8
	moderate	0/8	0/8	0/8	1/8	3/8	0/8	0/8	0/8	2/8	6/8
	severe	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	1/8
	decreased hematopoiesis										
	slight	0/8	0/8	0/8	3/8	4/8	0/8	0/8	1/8	4/8	1/8
	moderate	0/8	0/8	0/8	1/8	3/8	0/8	0/8	0/8	2/8	6/8
	severe	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	1/8
ovary	degeneration of gmnulose cells [slight]						0/8	0/8	0/8	0/8	5/8
uterus	endometrial atrophy [slight]						0/8	0/8	0/8	0/8	6/8

Plasma levels of OPC-14597 were <LOQ [redacted], and near the LOQ [redacted] 'C_{max}" at 20 and 60 mg/kg were as follows:

Day 0: 105.3 and 196 ng/mL in males and females, respectively, at 20 mg/kg.
514.1 and 531.7 ng/mL in males and females, respectively, at 60 mg/kg.
Wk 5: 107.5 and 314.4 ng/mL in males and females, respectively, at 20 mg/kg.
787.2 and 1133.2 ng/mL in males and females, respectively, at 60 mg/kg.

Monkey

1. a 4-wk oral (gavage) dose-range finding study was conducted in cynomolgus monkey [n = 1/sex/grp] at doses of 1, 5, 25, and 125 mg/kg. [OPC-31 batch 8K84M was used.] Observations consisted of the following: clinical signs, body wt, food consumption, clinical pathology [including urinalysis], bone marrow examination, TK [at 2, 4, 8, and 24 hrs after the 1st and last doses], terminal studies [organ wt, gross pathology, selected histopathology (liver, spleen, bone marrow)]. There was no statement made regarding unscheduled deaths. Clinical signs were observed at all doses. Impaired motor activity was observed at all doses [only in the male at the LD]. Ptosis, tremors, and catalepsy were observed at all but the LD. At the higher doses, abnormal posture and hyporeactivity were also observed. A transient decrease in body wt was observed at 25 and 125 mg/kg; however, body wt remained reduced (11-12% compared to baseline) in the HDM. Changes in food consumption were fairly consistent with body wt effects. No drug-related effects were noted on bone marrow examination or on urinalysis parameters, and a clear drug-related effect was not observed on hematology parameters. A decrease in serum K was noted at all doses; at the HD, a "slight" decrease in Cl, and increases in ALT and BUN (female only). The following organ wt findings were of note: (a) a decrease in thymus wt [absolute, relative]at all doses, (b) decreases in seminal vesicle, prostate gland, and testis wts [absolute, relative] at all but the LD. The prominent gross finding was the presence of "gall sand" in the liver of both animals at 25 and 125 mg/kg. Microscopic findings were observed at all doses. At the LD, findings were noted in liver [fatty change in hepatocytes, single cell or focal necrosis of hepatocytes (observed in both animals), "dark brownish pigment deposition in enlarged Kupffer cells" and a small granuloma, hepatocytes with enlarged nuclei] and spleen ["moderately" enlarged germinal centers of splenic nodule (M only), neutrophilic leukocytes "slightly" increased in red pulp (F only)]. At 5 mg/kg, findings were also noted in liver ["slight" fatty changes in hepatocytes (F only)] and spleen ["moderately" enlarged splenic nodule (M only), neutrophilic leukocytes "slightly" increased in the red pulp]. At 25 mg/kg, liver [dark brownish pigment deposition in hepatocytes (M only), fatty change in hepatocytes, "atrophy of hepatocytes and proliferation of sinusoidal fibers" (F only)] and bone marrow [hypocellularity (F only), eosinophilic myelocytes (M only)] were noted. At the HD, liver [fatty change in hepatocytes, increase in fat-storing cells, "Moderate single cell necrosis and slight focal necrosis of hepatocytes" (F only)] and spleen [neutrophilic leukocytes increased in red pulp (M only)].

Plasma levels of OPC-31 were not detectable at the LD. The apparent C_{max} was 51-86, 123-403, and 247-395 ng/mL at 5, 25, and 125 mg/kg, respectively, on Day 1, and 51-90, 207-441, and 839-1123 ng/mL at 5, 25, and 125 mg/kg, respectively, on last day of dosing. The apparent T_{max} was 2-4 hrs.

2. a 13-wk oral (gavage) toxicity study [+ 4-wk recovery period] was conducted in cynomolgus monkey [n = 3/sex/grp; 1/sex for C and 2/sex for HD recovery grps] at doses of 0, 0.5, 1, 5, and 25 mg/kg. [OPC-31 batch 8K84M was used.] Observations consisted of the following: clinical signs, body wt, food consumption, clinical pathology [including urinalysis], ophthalmology, ECG [HD: Wks 5 and 12], TK [Day 1, Wk 11; 2, 4, 8, and 24 hrs postdosing], terminal studies [organ wts, gross and histopathology]. There were no unscheduled deaths during the study. Clinical signs were observed at all doses, although only 1 LD animal was affected [tremor]. Tremor was observed at all doses. Additional clinical signs observed at the 2 highest doses included reduced spontaneous motor activity and catalepsy; ptosis was

noted at the HD. There were no drug-related effects on body wt. Food consumption was markedly, but transiently reduced at the HD. There were no drug-related effects on clinical pathology or ECG parameters, upon ophthalmology examination, or on organ wts. There were also no clear drug-related microscopic findings, although there was sporadic evidence of parasitic infestation in dosed animals.

[According to the sponsor's summary, at necropsy "moderate to severe muddy substance" was detected in bile at 25 mg/kg. According to the study report, muddy substance in the bile was detected in 2/3 males and 2/3 females at 25 mg/kg. The finding was also detected in recovery animals.]

Aripiprazole was not detectable in plasma at 0.5 and 1 mg/kg. C_{max} was 40-60 and 200-450 ng/mL at 5 and 25 mg/kg, respectively; plasma levels were higher in females than in males. [AUC values were not reported.]

Chronic studies

Rat

1. a 52-wk oral (gavage) toxicity study was conducted in Sprague-Dawley rat [20/sex/grp] at doses of 0, 1, 3, and 10 mg/kg. [OPC-14597 batch 8K89M was used.] This study was performed at [redacted] from 9/25/00 to 7/7/92. Observations consisted of the following: clinical signs, body wt, food consumption, hematology [hgb, hct, rbc ct, MCH, MCHC, MCV, thrombocytes, wbc ct (total, differential), PT, APTT], clinical chemistry [BUN, ALT, "AFOS", "ASAT", CPK, albumin, "LD", Ca Na, K, Cl, bilirubin, globulin, glucose, creatinine, cholesterol, P_i, total protein, TG, PL, cholinesterase], urinalysis [pH, protein, glucose, volume, microscopic analysis of sediment, bilirubin, turbidity, Hb, osmolality, specific gravity, leukocytes, ketone bodies, urobilinogen, erythrocytes], ophthalmology, terminal studies [organ wt, gross and histopathology (adrenals, aorta, bone/femur, bone marrow, brain, colon, duodenum, epididymides, esophagus, eyes, Harderian gland, heart, ileum, jejunum, kidney, liver, lung, lymph nodes (mesenteric, submandibular), mammary gland, ovary, pancreas, parathyroids, pituitary, prostate, rectum, salivary gland, seminal vesicle, skeletal muscle, skin, spinal cord, spleen, sternum (with marrow), stomach, testes, thymus, thyroid, trachea, urinary bladder, uterus, vagina].

There were 4 unscheduled deaths (moribund sacrifices), however, "...the signs were not related to OPC-14597 treatment". There were no drug-related clinical signs. Body wt was not affected in males. In females, body wt was increase at the MD and HD; however, the effect was transient at the HD. Final body wt was increased (19%) only in MDF. There were no drug-related effects on ophthalmology or hematology parameters. TG was decreased (37%), and γ-globulin [14%] and creatinine [30%] were increased in HDM. ALT, LD, AST, and CPK were increased in individual animals; however, there were no histopathology correlates in any of the affected animals. Urine osmolality was increased in HDF [38%]. Organ wt changes were as follows: (a) ovary wt (absolute, relative) wt was increased, whereas uterus wt (absolute, relative) was decreased in MDF and HDF, (b) decrease in liver wt (relative) in HDM, and (c) increased brain wt (absolute) in HDF. The prominent gross finding was dose-dependent development of the mammary glands in females. Microscopic findings consisted of the following: (a) "Slight to very slight lobular hyperplasia and milk secretion...in mammary gland" in females at all doses, (b) "atrophy of the uterus and mucification of the vaginal epithelium...in treated rats but not controls".

2. Study title: **Twenty-six-week oral toxicity study in rats** [Study no: 99353,Volume #: 1.51-1.55, Conducting laboratory and location: Bristol-Myers Squibb Pharmaceutical Research Institute, Mt. Vernon, Indiana, Date of study initiation:11/29/99, GLP, QA report:Y].

The study report was poorly organized. The material and methods were presented in two separate reports [Toxicology and Pathology reports] and the parameters assessed were not specified in the Methods section of the Pathology report.

Drug, lot #, and % purity: BMS-337039, batch C99G74M, purity not stated.
Formulation/vehicle: suspension/5% gum arabic in sterile water

Methods
Dosing:

Species/strain: Sprague-Dawley rat [redacted]
#/sex/group or time point (main study): 20/sex/grp
Satellite groups used for toxicokinetics or recovery: 5/sex for C and HD recovery [13-wk]
Age: ≈7 wks
Weight: 171-242 gm in males, 139-185 gm in females
Doses in administered units: 0, 10, 30, 60 mg/kg
Route, form, volume, and infusion rate: oral, suspension, 5 mL/kg.

Observations and times:

Clinical signs: animals were observed twice daily. A videotape of "...a representative number of female animals was made to record clinical observations".
Body weights: body wts were recorded prior to the start of dosing, on Day 1, and weekly during the dosing period.
Food consumption: food intake was "determined" prior to the start of dosing and weekly during the dosing period.
Water consumption: water intake was determined over an 18-hr period in 10/sex/grp during Wk 14 and in all survivors during Wk 27 (not recovery animals) and Wk 40 (recovery animals).
Ophthalmoscopy: an ophthalmologic examination was performed on all rats prior to the start of dosing and postdosing during Wks 13 and 26.
ECG: no.
Clinical Pathology: blood samples were collected during Wks 12, 25, and 40 for analysis of hematology and clinical chemistry parameters. Blood samples were collected during Wks 27 and 40 for analysis of coagulation parameters. In addition, blood samples were collected from 4 HD animals [1410, 1422, 2404, 2413] prior to moribund sacrifice. Urine samples were collected during Wks 14, 27, and 40. The following parameters were assessed:

- Hematology: hct, hgb, rbc ct, MCH, MCHC, MCV, reticulocytes, platelets, wbc [total, differential], large unstained cells, rbc morphology, PT, APTT, fibrinogen. [Bone marrow smears were to have been collected; however, there was no indication that they were or that they were but not examined.
- Clinical chemistry: Na, K, Cl, Ca, P_i, urea N, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, globulins, A/G ratio, total cholesterol, TG.
- Urinalysis: volume, specific gravity, pH, glucose, protein, ketones, bilirubin, urobilinogen, clarity, microscopic examination of sediment.

Gross pathology: a complete necropsy was performed on all animals.
Organs weights: wts of the following organs were recorded: adrenal, brain, heart, kidney, liver, lung, pituitary, prostate, salivary gland, spleen, testis, thymus, thyroid.
Histopathology: the following tissues were examined microscopically in all C and HD animals:

In addition, pituitary adrenal, lungs, mammary gland, testes, epididymides, prostate, seminal vesicles, ovaries, uterus, cervix, vagina, and gross lesions from the lower dose grps were examined microscopically.

In addition to the routine methods used [not specified], sections

Toxicokinetics: blood samples were collected on Day and during Wk 26 from 3/sex/grp/time point at 1, 2, 4, 8, and 24 hrs postdosing. Blood samples from C animals were discarded. BMS-227039, BMS-337040, BMS-337045, BMS-337047, and DCPP were quantitated in plasma.

Results

Mortality: there were 4 unscheduled deaths, all in HD animals. M1410 was sacrificed moribund on Day 51; prior to death the following clinical signs were observed: "...atonia, red material around muzzle, tremors, hypoactivity, labored respiration, salivation, urogenital staining, lacrimation, and ptosis". Morbidity was attributed to urolithiasis based on clinical signs and histopathology findings. M1422 was sacrificed moribund on Day 81; clinical signs consisted of "...hunched posture, red material around muzzle, hypoactivity, labored respiration, salivation, urogenital staining, and ptosis. Morbidity was attributed to dosing trauma. Two HDF were sacrificed moribund on Days 18 [F2404] and 32 [F2413] due to tail sores/sloughing off. The sponsor did not attribute any premature deaths to drug.

Clinical signs: the primary drug-related clinical signs observed in MD and HD animals were hypoactivity, hyperactivity, and ptosis. The incidence and duration [i.e., no. of days observed] of these findings were dose-related. Hyperactivity was noted during the recovery period in HDM-R [4/5, the 1st 9 days of recovery] and HDF-R [4/5, the entire recovery period]. Clonic convulsions were observed in 1/20 MDM [one occurrence on Day 25]. Upon physical examinations, unkempt appearance and scabs were noted primarily at the HD (M and F). Scabs were also noted in HDM-R and HDF-R, and unkempt appearance was noted in HDF-R during the recovery period.

Body weights: in males, mean body wt was reduced throughout the dosing period [from Wk 2 on] at the MD and HD, and from Wk 9-12 on at the LD; final mean body wt was reduced by 8, 21, and 39% (compared to CM) at the LD, MD, and HD, respectively. Mean body wt remained reduced in HDM-R (compared to CM-R) throughout the 13-wk recovery period; final mean body wt was reduced by 25% in HDM-R. In females, mean body wt was reduced in HDF throughout the dosing period, and in MDF from Wk 3 on. Mean body wt was elevated in LDF from Wk 5 on. Final mean body wts were 8% higher in LDF, and 9 and 24% lower in MDF and HDF, respectively, compared to CF. Mean body wt remained reduced in HDF-R throughout the recovery period; final mean body wt was reduced 17% compared to CF-R. Body wt gain data were not provided.

In both HDM-R and HDF-R, there appeared to be some degree of catch-up growth, although final mean body wts in both grps were still lower than comparable C grps.

Food consumption: food consumption was consistently reduced in MDM and HDM throughout the dosing period, and in HDM-R relative to CM-R during the recovery period. Food intake was reduced throughout most of the dosing period in HDF, whereas food intake in MDF was similar to CF. Food intake was increased compared to CF during most of the dosing period. During the recovery period, food intake tended to be higher in HDF-R compared to CF-R, although the differences were not statistically significant.

Water consumption: water intake was reduced in MDM and HDM at Wks 14 and 27 [58-45 and 79-66%, respectively], and in MDF and HDF [71-21 and 50-20%, respectively] during the same sampling times. In LDF, water intake was reduced [52%] at Wk 14, but was 87% higher at Wk 27. At the end of the recovery period, water intake was elevated in both HDM-R [5.8 fold] and HDF-R [59%].

Ophthalmoscopy: the sponsor reported no drug-related effects.

Hematology: in males, the primary drug-related effect was a decrease in wbc ct [32-29%] in HDM, observed at Wks 12 and 25. The decrease in total wbc ct was due to a decrease in absolute cts of neutrophils [37-11%], lymphocytes [30-31%], monocytes [56-54%], esoinophils [49-38%], and basophils [43-58%]. Although decreases were noted in one or more of these parameters at the lower doses, the effects were not consistent or consistently dose-related. On coagulation parameters, PT was increased in HDM [4%], and in a dose-related manner in females [4, 6, and 8% at LD, MD, and HD, respectively], and fibrinogen was reduced [11%] in HDM at Wk 27. There were no differences grps observed during the recovery period.

Clinical chemistry: in males, the following drug-related findings were noted: (a) a small (1%), but significant increase in Na and an increase in K [17%] in HDM at Wk 12; no increases noted at Wk 27, (b) serum Ca was decreased at the MD [3%] and HD [8%] at Wk 12, and at all doses at Wk 27 [2, 4, and 10% at LD, MD, and HD, respectively], (c) an increase in P_i at the HD at both Wks 12 and 27 [20-8%], (d) an increase in BUN at Wk 12 [19%] and Wk 27 [33%], (e) an increase in creatinine at all doses during Wks 12 [29, 25, and 46% at LD, MD, and HD, respectively] and 27 [35, 30, and 35% at LD, MD, and HD, respectively], (f) decreases in glucose at the MD and HD at Wks 12 [13 and 27%, respectively] and 27 [13 and 21%, respectively], (g) decrease in total protein [5%]and globulin [15%], resulting in an increased A/G ratio [19%] at Wk 12, and a decrease in total protein, albumin, and globulin [6, 4, and 8%, respectively] with no significant effect on A/G ratio at Wk 27, (h) a decrease [22%] in cholesterol at Wk 27, and (i) decreases in TG at all doses during Wks 12 [23, 49, and 62% at LD, MD, and HD, respectively] and 27 [23, 49, and 62% at LD, MD, and HD, respectively]. There were no significant differences between grps at the end of the recovery period.

In females, the following drug-related findings were noted: (a) small, but significant decreases in Cl at the HD at both Wk 12 [2%] and 27 [4%], (b) decreases in Ca at all doses during Wks 12 [3, 5, and 9% at LD, MD, and HD, respectively] and 27 [5,4, and 9% at LD, MD, and HD, respectively], (c) an increase in P_i at all doses at Wk 27 [4, 20, and 21% at LD, MD, and HD, respectively; significant only at the 2 highest doses], (d) increases in BUN at the HD [23%] during Wk 12 and at all doses during Wk 27 [14, 14, and 46% at LD, MD, and HD, respectively], (e) decreases in glucose at the MD and HD during Wks 12 [12 and 8, respectively] and 27 [17 and 21%, respectively], (f) decreases in total protein at the HD [6%] at Wk 12 and at all doses during Wk 27 [4-7%, not dose-related], (g) decreases in albumin at all doses during Wks 12 [7-8%, not dose-related] and 27 [11-14%, not dose-related], (h) a non-dose-related increase in globulin at all dose during Wk 27 [7-14%], (i) non dose-related decreases in A/G ratio during Wks 12 [4-

14%] and 27 [18-22%], (j) decreases in cholesterol during Wks 12 [22, 22, and 40% at LD, MD, and HD, respectively] and 27 [26, 27, and 50% at LD, MD, and HD, respectively], and (k) decreases in TG during Wks 12 [14-21%, not dose-related] and 27 [42, 45, and 52% at LD, MD, and HD, respectively]. There were no significant differences between grps at the end of the recovery period.

The sponsor attributed the following to reduced food and/or water intake: (a) decreased glucose in MD and HD animals, (b) increased P_i in MD and HD animals, and (c) increases in Na, K, Cl, and A/G ratio and decreases in globulins in HDM, and (d) decreases in Cl in HDF.

The sponsor noted that there were no clear drug-related changes in clinical pathology in the 4 animals sacrificed moribund; however, such effects (if any) may have been masked by the general effects of their moribund state.

Urinalysis: in males, urinary volume was reduced at the MD [35-40%] and HD [64-56%] during Wks 14 and 26, specific gravity was slightly but significantly at the HD [2%], and urinary pH was increased at the MD [13-8%, 1-0.5 units] and HD [10-17%, 0.8-1 units]. In HDM-R, urinary volume was 3-fold higher than in CM-R; however, the difference was not significant due to large interanimal variability in the HDM-R grp. In females, urinary volume was reduced during Wk 14 at all doses [25-70%], but not in a dose-related manner, and urinary pH was increased at the HD [11-17%, 0.65-1 units] at Wks 14 and 26. In LDF, urinary volume was increased [2.4 fold] and specific gravity was decreased during Wk 26 [2%]. In HDF-R, urinary volume was increased 2-fold compared to CF-R; however, as in males, the difference was not significant due to large interanimal variability in the HDF-R grp. The sponsor considered the urinary effects due to changes in water consumption.

Organ weights: organ wt data were somewhat difficult to evaluate due to the body wt effects in both males and females. In a number of organs, absolute wt decreased and relative wt increased secondary to decrease in body wt gain accompanied by a compensatory effect in the affected organs. However, of note were the following: (a) an increase in relative adrenal wt in HDM [60%] and HDF [87%]; absolute wt was also elevated in HDF [42%], (b) an increase in relative lung wt in HDM [51%] and HDF [64%]; absolute wt was also elevated in HDF [24%], (c) a decrease in absolute testis wt at the HD [24%] [relative wt was increased 25%], (d) a non-dose-related decrease in absolute and relative uterus wt. [absolute: 44, 22, and 30% at LD, MD, and HD, respectively; relative: 48, 10, and 9% at LD, MD, and HD, respectively].

In recovery animals, an increase in relative lung wt in HDM [21%] and HDF [16%] was still evident; relative wt was increased in HDF [30%].

Gross pathology: according to the sponsor, there were no remarkable findings in the animals sacrificed moribund. Selected findings in terminally sacrificed animals are summarized in the following table:

TISSUE	FINDING	MALES				FEMALES			
		C	LD	MD	HD	C	LD	MD	HD
MAIN STUDY									
adrenal	dark discoloration	0/20	0/20	0/20	9/20	0/20	0/20	0/20	15/20
	increased size	0/20	0/20	0/20	2/20	0/20	0/20	0/20	0/20
ovary	dark discoloration					0/20	0/20	0/20	6/20
	decreased size, L					0/20	0/20	0/20	1/20
lung	pale discoloration, multifocal	0/20	1/20	2/10	14/20	0/20	0/20	0/20	17/20
testis	decreased, bilateral	0/20	0/20	0/10	2/20				
RECOVERY									
adrenal	dark discoloration	0/5			2/5	0/5			0/5
lung	pale discoloration, multifocal	0/5	--	--	4/5	0/5	--	--	4/5

The sponsor noted that, in main-study animals, the severity of the lung finding was increased at the HD. In recovery animals, the lung finding was characterized as minimal in HDM-R and mild in HDF-R; the adrenal gland finding was characterized as minimal severity.

Histopathology: microscopic findings detected in animals that were sacrificed moribund that wer considered drug-related by the sponsor consisted of the following: (a) atrophy of the pituitary [pars intermedia] in 2 M and 1 F, (b) lung histiocytosis in both M, (c) mammary gland atrophy and hyperplasia in 1 M and 2 F, respectively, (d) uterine atrophy in 1 F. Selected findings in main-study and recovery animals are summarized in the following table:

TISSUE	FINDING	MALES				FEMALES			
		C	LD	MD	HD	C	LD	MD	HD
heart	ventricular necrosis	0/20	0/20	0/20	1/20	0/20	0/20	0/20	0/20
	subacute inflammation	2/20	0/20	0/20	7/20	0/20	0/20	0/20	2/20
liver	necrosis	0/20	0/20	0/20	2/20	0/20	0/20	0/20	0/20
adrenal ctx	diffuse hypertrophy	0/20	0/20	0/20	2/20	0/20	0/20	3/20	10/20
	lipofuscin pigment								
	minimal	12/20	13/20	10/20	11/20	15/20	18/20	13/20	15/20
	mild	0/20	0/20	0/20	3/20	0/20	0/20	2/20	2/20
pituitary	pars intermedia - atrophy								
	minimal/mild	0/20	4/20	18/20	7/20	0/20	5/20	12/20	16/20
	moderate	0/20	0/20	0/20	13/20	0/20	0/20	0/20	0/20
tail	chronic inflammation	0/20	0/20	0/20	3/20	0/20	1/20	0/20	11/20
	necrosis	0/20	0/20	0/20	0/20	0/20	0/20	0/20	2/20
ovary	mean % large CL					24.6	48.1	49.1	56.6
	mean total CL					17.3	20.6	16.2	12.1
	lipofuscin pigment								
	minimal					19/20	19/20	17/20	12/20
	mild					0/20	0/20	0/20	5/20
vagina	diestrus					4/20	19/20	13/20	8/20
	persistent diestrus					1/20	19/20	12/20	7/20
	mucification					2/20	20/20	14/20	8/20
uterus	atrophy (minimal/mild)					0/20	5/20	2/20	2/20
epididymis	spermatogenic epithel. [exfoliative]	0/20	0/20	0/20	11/20				
prostate	ampullary gland								
	subchronic inflammation								
	minimal	4/20	0/20	9/20	11/20				
	mild	0/20	0/20	0/20	1/20				
testis	bilateral atrophy								
	minimal/mild	0/20	0/20	0/20	2/20				
	moderate	0/20	0/20	0/20	2/20				
mammary gland	hyperplasia								
	minimal/mild	0/20	0/20	0/20	0/20	7/20	17/20	18/20	16/20
	moderate	0/20	0/20	0/20	0/20	0/20	3/20	2/20	3/20
	secretion (minimal/mild)	0/20	0/20	0/20	0/20	3/20	5/20	10/20	13/20
lung	histiocytosis								
	minimal	2/20	2/20	6/20	10/20	0/20	2/20	9/20	2/20
	mild	0/20	2/20	1/20	9/20	0/20	0/20	0/20	9/20
	moderate	0/20	0/20	0/20	1/20	0/20	0/20	0/20	7/20
eye	retinal degeneration	0/20	0/20	0/20	1/20	0/20	0/20	0/20	2/20
RECOVERY									
lung	histiocytosis	0/5	--	--	4/5	0/5	--	--	4/5
adrenal ctx	lipofuscin pigment								
	minimal	5/5			1/5	0/5			0/5
	mild	0/5			4/5	0/5			5/5
ovary	interstitium - lipofuscin pigment								
	minimal					5/5			1/5
	mild					0/5			4/5

All findings listed in the above table, except for tail and eye, were considered drug-related by the sponsor. Further characterization of selected findings was provided by the sponsor as follows: (a) adrenal cortex: the lipofuscin pigment detected in the adrenal cortex was present in reticulum cells located "in the inner cortex of the adrenal glands". (b) lung: the increase in histiocytes was consistent with the increase in lung wt and the pale lung noted upon gross examination and "...microscopically, consisted of intra-alveolar accumulations of foamy macrophages in one or more subpleural and/or peribronchiolar locations that were frequently accompanied by minimal mononuclear cell infiltration." (c) testis: the atrophy was further characterized as reflecting complete.