In each rat, 6 nonoverlapping areas of the ROI were examined in each adrenal [i.e., 12 areas per animal]; this accounted for ≈20% of the "total target proliferative region of each adrenal section".

The data were summarized in the following sponsor's Table 1:

Table 1: Group mean of Ki-67 immunopositive adrenocortical cells per standard image field in the outer zona fasciculata

	Male	Female
Controls: (Groups 1 and 2 combined)	**11.5 ± 5.7 [12]**	**10.3 ± 6.0 [12]**
Group 5: 40 mg/kg BMS-337039	**11.2 ± 6.6 [10]** ***p = 0.496***	**9.7 ± 6.7 [10]** ***p = 0.482***
Group 6: 60 mg/kg BMS-337039	**17.4 ± 7.8 [10]** ***p = 0.043***	**15.5 ± 4.0 [10]** ***p = 0.036***

Data expressed as mean ± standard deviation; [number of animals]; One-tailed Dunnett's test

An examination of the individual data indicated that only a few HD values were outside of the C range (combined).

Toxicokinetics: Wk 26 data [4-hr postdosing] are summarized in the following table [data expressed as means [SD]; data were expressed to 3 places, but were rounded down].

CPND	TIME (hr)	MALES				FEMALES			
		LD	MD-1	MD-2	HD	LD	MD-1	MD-2	HD
aripiprazole	4	99 [51]	677[318]	1659[270]	1607[452]	225[96]	1401[544]	1881[602]	3490[1458]
DM-451		14[4]	12[2]	8[7]	11[10]	8[3]	8[2]	2[5]	5[7]
OPC-14857		19[8]	58[7]	142[20]	135[34]	26[8]	72[20]	233[132]	293[93]
D1452		3[2]	7[0.8]	19[3]	18[4]	5[2]	12[5]	23[10]	46[18]
OPC-3373		8[6]	32[5]	81[12]	92[14]	8[4]	28[11]	60[42]	152[48]
DCPP		4[2]	21[4]	75[18]	88[25]	2[0.7]	10[4]	32[12]	82[48]
aripiprazole	24	0.2[0.5]	17[14]	533[287]	479[208]	0.8[1.3]	23[18]	909[421]	1355[236]
DM-451		<LLOQ	3[2]	2[6]	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
OPC-14857		<LLOQ	4[5]	104[38]	106[44]	<LLOQ	7[6]	176[69]	240[57]
D1452		<LLOQ	<LLOQ	7[4]	5[4]	<LLOQ	<LLOQ	8[5]	12[10]
OPC-3373		<LLOQ	<LLOQ	11[10]	19[13]	6[13]	<LLOQ	23[13]	54[14]
DCPP		<LLOQ	<LLOQ	39[24]	39[25]	<LLOQ	<LLOQ	14[5]	30[7]

The Wk 65 data were summarized in the following sponsor's table:

Dose (mg/kg/day)	Study Week	BMS-337039		BMS-337040		BMS-337044	
		Males	Females	Males	Females	Males	Females
		Cmax (ng/mL)					
10	65	291	917	50.3	18.5	41.1	93.5
20		1329	3407	65.8	13.6	107	162
40		3672	5270	29.3	20.4	396	232
60		7337	8476	27.8	30.0	445	352
		AUC[a] (ng·h/mL)					
10		2109	8899	273	223	322	1268
20		20167	26057	530	300	1827	1952
40		55322	76335	558	433	4927	4120
60		89352	102366	512	485	6590	6448
Dose Ratio 1:2:4:6		Cmax ratio					
		1:5:13:25	1:4:6:9	1:1:0.6:0.6	1:0.7:1:2	1:3:10:11	1:2:2:4
		AUC ratio					
		1:10:26:42	1:3:9:12	1:2:2:2	1:1:2:2	1:6:15:20	1:2:3:5

[a] Calculated from time zero to the time of last measurable concentration, ranging between 8 and 24h

Summary of Individual Carcinogenicity Study Findings

In the first mouse carcinogenicity study, aripiprazole was administered to CD-1 [ICR] mice at doses of 0, 1, 3, and 10 mg/kg as a drug/diet admixture for 104 wks. As originally reported, there was no significant effect on mortality in either males or females; however, in a re-analysis report, the sponsor reported a significant negative trend on mortality in males [i.e., better survival] and a positive trend [not statistically significant] in females [i.e., reduced survival]. There were no clear drug-related clinical signs. In males, body wt was transiently increased at 1 mg/kg, but transiently decreased at 3 and 10 mg/kg [compared to CM]; final mean body wts were similar among grps. In females, body wt was significantly increased at 1 and 3 mg/kg, and tended to be higher at 10 mg/kg [compared to CF]. Food intake was significantly reduced in males and females at all doses during the early part of the dosing period; overall daily food intake was similar among grps for both males and females. There were no apparent drug-related findings on hematology parameters. Organ wt effects consisted primarily of decreases in seminal vesicles and prostate [3 and 10 mg/kg], decreases in ovary and uterus wts at all doses, and a marked increase in pituitary wt in females at all doses. The primary non-neoplastic findings were (a) atrophy of the pituitary gland pars intermedia in males and females, (b) increases in mammary gland acinar proliferation in females, and (c) an increase in uterine atrophy; these findings were observed at doses of 3 and 10 mg/kg. Drug-related tumor findings were observed only in females; anterior pituitary adenoma and mammary gland adenocarcinoma and adenoacanthoma were increased at 3 and 10 mg/kg [0.5 and 1.6 times the maximum recommended human dose on a mg/m^2 basis]. [These tumor findings are consistent with FDA's independent analysis of the data, cf. Statistical Review and Evaluation: Review of Mouse Carcinogenicity Studies. NDA #21-436, Roswitha Kelly, M.S., HFD-710.] TK data were collected in satellite animals at Wks 2 and 52 [at 9:00 a.m.] and in main-study animals at the end of the 104-wk dosing period. The 52-wk data [only aripiprazole was quantitated] are summarized in the following table, along with estimated AUC data ["C_{ss}" x 24 hrs; calculated by the reviewer].

DOSE [mg/kg]	"C_{ss}" [ng/mL]		"AUC" [ng•hr/mL]	
	MALES	FEMALES	MALES	FEMALES
1	19.0 ± 4.4	13.5 ± 2.3	456	324
3	51.6 ± 4.4	32.6 ± 5.7	1238	782
10	169.3 ± 7.2	89.2 ± 34.2	4063	2141

TK data were also collected in a separate 4-wk TK study in ICR mouse. The data from that study are provided in the following sponsor's table:

Text Table 4 Mean AUC(0-24 h) of aripiprazole and its principal pharmacologically active metabolite, OPC-14857, after dietary administration of aripiprazole to mice for 4 weeks

Dose (mg/kg/day)	AUC(0-24 h) (ng·h/ml)			
	Aripiprazole		OPC-14857 (BMS-337044)	
	Males	Females	Males	Females
1	387	292	143	118
3	1104	818	390	298
10	3797	2472	1279	848
30	10714	6872	3437	2123

The AUCs estimated from the 52-wk "C_{ss}" data are fairly similar to the AUC data quantitated in the 4-wk study. Based on the 4-wk data, the AUCs associated with pituitary and mammary gland tumors in female mice are 0.1 and 0.3 times [at 3 and 10 mg/kg, respectively] the AUC in humans at the maximum recommended clinical dose [7600 ng•hr/mL, based on 30-mg/day data from two 14-15 day clinical studies].

In a second mouse carcinogenicity study, aripiprazole was administered to CD-1[ICR] mice at a dose of 30 mg/kg [controls grps were included] as a drug/diet admixture for 104 [males] or 100 [females] wks. According to the original report and the re-analysis report, the mortality rate was significantly increased in DTF and significantly decreased in DTM. There were no significant effects on clinical signs. Body wt was reduced throughout the dosing period in DTM [compared to CM], but was unaffected in DTF. Food intake was reduced in DTM throughout most of the dosing period, with the greatest effect occurring during the first wk of dosing. Overall mean daily intake was 10% lower in DTM compared to CM. Food intake was only transiently reduced in DTF, with the overall mean daily intake being similar to CF. There were no drug-related effects on hematology parameters. The primary effects on organ wts were marked decreases in testis and ovary wts in DT grps. The primary non-neoplastic findings were (a) atrophy of the pituitary gland pars intermedia in DT grps, (b) an increase in mammary gland acinar proliferation in DTF, and (c) uterine atrophy and persistent diestrus [vagina] in DTF. No drug-related tumor findings were detected in DTM. The incidences of anterior pituitary gland adenoma and mammary gland adenocarcinoma and adenoacanthoma were increased in DTF [the 30 mg/kg dose is ≈5 times the maximum recommended human dose on a mg/m^2 basis]. The onset of mammary gland tumors and, to a lesser extent, pituitary adenomas was earlier in DTF compared to CF. [These tumor findings are consistent with FDA's independent statistical analysis of the data, cf. Statistical Review and Evaluation: Review of Mouse Carcinogenicity Studies. NDA#21-436, Roswitha Kelly, M.S., HFD-170.] TK data were collected in satellite animals at Wks 2 and 52 [9:00 a.m.] in satellite animals and in main-study animals at the end of the dosing period [104-100 wks]. The 52- and 104-100-wk data [only aripiprazole was quantitated] are summarized in the following table, along with estimated AUC data ["C_{ss}" x 24 hrs; calculated by the reviewer].

M/F	"C_{ss}" [ng/mL]		"AUC" [ng•hr/mL]	
	WK 52	WK 104	WK 52	WK 100
M	713.4 ± 280.1	405.9 ± 112.4	17123	9742
F	723.0 ± 37.6	354.1 ± 176.8	17352	8498

dose = 30 mg/kg

As previously noted, TK data were also collected in a separate 4-wk TK study in ICR mouse. The data from that study were provided in the sponsor's table above. Comparing those data with the AUC estimated based on the C_{ss} data from the carcinogenicity study, it is apparent that the AUC data from the 4-wk study more closely agrees with the Wk 104-100 AUC estimates. Therefore, based on the 4-wk AUC

data [at 30 mg/kg], the plasma AUC estimated to have been achieved at 30 mg/kg in the 2nd carcinogenicity study are ≈1 times the AUC in humans at the maximum recommended clinical dose [7600 ng•hr/mL, based on 30-mg/day data from two 14-15 day clinical studies].

Regarding comparisons of plasma AUC between mice and humans, the data suggest that such comparisons are reasonable since (a) plasma kinetics appear to be fairly linear within the dose range tested in mice, and up to 30 mg/day in humans and (b) since the AUC for the active metabolite, OPC-14857 [as quantitated in the 4-wk TK study], was ≈30-40% of the AUC for the parent in mice and was reported to be ≈40% of the AUC for the parent in humans [cf. Office of Clinical Pharmacology and Biopharmaceutics Review, Hong Zhao, Ph.D., HFD-860]. [No plasma exposure data were available for OPC-14857.]

In the first rat carcinogenicity study, aripiprazole was administered to Fischer 344 rats in the diet at doses of 0, 1, 3, and 10 mg/kg. There were no drug-related effects on mortality in either males or females. There were no significant drug-related effects on behavior; however, the incidence of reduced spontaneous motor activity was greater at 3 and 10 mg/kg in females [not dose-related]. Body wt was slightly, but significantly reduced at 3 [3-4%] and 10 [6-7%] mg/kg in males. In females, body wt was significantly increased at all doses. Food intake was consistently reduced during the dosing period at 10 mg/kg in males and females; overall daily food intake was reduced by 9% at 10 mg/kg. On hematological parameters, the only finding was an increase in wbc ct in males [all doses, but significantly only at 10 mg/kg]. This increase was due to increases in lymphocyte and segmented neutrophil cts. In females, lymphocyte and segmented neutrophil cts were elevated at the HD; wbc ct was elevated at all doses, but not in a dose-related manner. Organ wt findings consisted of changes in pituitary wt in males [decrease] and females [increase], a decrease in liver and in testis wts in males, an increase in seminal vesicle wt, and a decrease in uterus wt, all at 10 mg/kg; pituitary gland wt tended to be affected [males and females] at 3 mg/kg; however, the effects were not significant. The primary non-neoplastic findings were noted in pituitary gland [atrophy of the pars intermedia; at 3 and 10 mg/kg in males, 10 mg/kg in females], testis [interstitial cell hyperplasia, 10 mg/kg], and uterus [atrophy; 3 and 10 mg/kg, significant only HD]. Other non-neoplastic findings [e.g., atrophy/fibrosis of male reproductive organs, eosinophilic foci in liver (M), hypersteosis of bone (F)] were reduced in treated grps. Mammary gland acinar proliferation was not significantly increased in males or females. Drug-related tumor findings were not detected in males. The only drug-related tumor finding in females was an increase in mammary gland fibroadenoma [at 10 mg/kg, or 3 times the maximum recommended human dose on a mg/m^2 basis]. [This finding is consistent with FDA's independent statistical analysis, cf. Statistical Review and Evaluation: Review of Mouse Carcinogenicity Studies. NDA#21-436, Roswitha Kelly, M.S., HFD-170.] TK data were collected in satellite animals at Wks 2 and 52 [9:00 a.m.] and in main-study animals at the end of the 104-wk dosing period. The 52-wk data [only aripiprazole was quantitated] are summarized in the following table, along with estimated AUC data ["C_{ss}" x 24 hrs; calculated by the reviewer]:

DOSE [mg/kg]	"C_{ss}" [ng/mL]		"AUC" [ng•hr/mL]	
	MALES	FEMALES	MALES	FEMALES
1	0.47 ± 0.0	0.87 ± 0.06	11	21
3	2.07 ± 0.15	4.03 ± 1.36	49	96
10	42.87 ± 12.81	77.47 ± 17.79	1028	1859

TK data were also collected in a separate 4-wk TK study in Fischer 344 rats. The data from that study are provided in the following sponsor's table:

Text Table 6 Mean AUC(0-T) of aripiprazole and its pharmacologically active metabolites, OPC-14857 and DM-1451, after dietary administration of aripiprazole to rats for 4 weeks

Dose (mg/kg/day)	AUC(0-24 h) (ng.h/ml)					
	Aripiprazole		OPC-14857 (BMS-337044)		DM-1451 (BMS-337040)	
	Male	Female	Male	Female	Male	Female
1	NC	NC	NC	NC	NC	NC
3	24	48	NC	NC	27	41
10	261	465	87	160	138	170

NC = Not calculated since all values were below lower limit of quantification (2 ng/ml).

The AUCs estimated from the 52-wk "C_{ss}" data are notably higher than those quantitated in the 4-wk study. Based on the 4-wk data, the AUC associated with mammary gland fibroadenomas in female rats is ≈1 times the AUC at the MRHD.

In the second rat carcinogenicity study, aripiprazole was administered to Sprague-Dawley rats by gavage at doses of 0, 0, 10, 20, 40, and 60 mg/kg. There were no adverse effects on survival; survival rates were higher in drug-treated grps [all but the LD in females]. [According to the FDA's statistical analysis, there was a highly significant increase in survival in both males and females.] However, deaths in 5 HDF [1 spontaneous death, 4 moribund sacrifices] were considered drug-related by the sponsor, although the cause(s) of death were not determined. Body wt was reduced at all doses in males [8, 17, 34, and 44% at 10, 20, 40, and 60 mg/kg, respectively, at Wk 102]. In females, body wt was reduced at 20, 40, and 60 mg/kg [11, 28, and 43%, respectively, at Wk 106], but increased at 10 mg/kg [20%] compared to CF. Food consumption was reduced at all doses in males and at all but the LD in females. There were no notable drug-related findings on hematology parameters. Effects on organ wts included an increase in adrenal wt [males and females at 40 and 60 mg/kg], increased lung wt [males and females at 40 and 60 mg/kg], decreased pituitary wt [in males at 20, 40, and 60 mg/kg], and decreased testis wt at 60 mg/kg. Drug-related non-neoplastic findings were detected in a number of organs, i.e., eye [retinal degeneration], skeletal muscle [atrophy], sciatic nerve [degeneration], lung [histiocytosis], liver [lipofuscin deposition, Kupffer cells], mesenteric lymph node [pigmented macrophage infiltrate, hemorrhage], pituitary [atrophy of the pars intermedia], testis [atrophy/degeneration], epididymides [hypospermia, degenerate/multinuclear spermatogenic cells], ovary [interstitial cell hyperplasia, lipofuscin pigment]. Decreases in other findings [e.g., chronic progressive nephropathy, thyroid C-cell hyperplasia, hepatocellular vacuolation] were considered secondary to body wt effects. No drug-related tumors were detected in males. In females, the only drug-related finding was an increase in adrenocortical tumors [carcinoma, adenoma and carcinoma combined] observed at the HD. [This dose, 60 mg/kg, is 19 times the maximum recommended human dose (MRHD) on a mg/m^2 basis.] This tumor finding is consistent with the FDA's independent statistical analysis, cf. cf. Statistical Review and Evaluation: Review of Mouse Carcinogenicity Studies. NDA#21-436, Roswitha Kelly, M.S., HFD-170.] The sponsor analyzed sections of adrenal cortex for evidence of cellular proliferation using immunohistochemistry. The "adrenocortical proliferation index" was significantly increased in males and females at 60 mg/kg. TK data were collected at Wks 26 and 65. The Wk 65 data were summarized in the sponsor's table provided on [or near] pg. 143. Based on these data, the C_{max} and AUC in females at the dose associated with adrenocortical tumors are 20 and 13 times, respectively, the C_{max} and AUC at the MRHD. At the highest dose not associated with adrenocortical tumors, the C_{max} and AUC were 12-10 times the C_{max} and AUC at the MRHD.

Palatability issue: due to the use of dietary dosing and the fact that reduced body wt gain and food consumption were primary adverse effects, the palatability of the drug/diet admixture was an important issue to be considered in assessing the adequacy of the dietary carcinogenicity studies. Therefore, the

data from the 4-wk dietary/gavage studies were re-examined. In mice, following 4 wks of dosing, body wt was reduced by 4, 4, and 11% at doses of 10, 30, and 100 mg/kg in the gavage study, and by 2, 6, and 8% at doses of 10, 30, and 100 mg/kg in the dietary study. However, plasma $AUC_{(0\text{-}24\ hr)}$ with gavage doses of 10, 30, and 100 mg/kg were 1, 1.9, and 1.5 times, respectively, the plasma $AUC_{(0\text{-}24\ hr)}$ with the same doses administered via the diet. The data are summarized in the following table:

ROUTE	FINAL BODY WEIGHT (gm)					$AUC_{(0\text{-}24\ hr)}$ [ng•hr/mL]			
	0	10	30	60	100	10	30	60	100
gavage	32.19 ± 1.98	31.00 ± 1.55	31.06 ± 1.68	29.90 ± 1.59	28.58 ± 1.79	3443	14573	22084	44906
diet	34.03 ± 2.19	33.46 ± 1.84	31.93 ± 1.30		31.33 ± 2.27	3259	7604		30638

Therefore, it would appear that there might be both a drug-related effect and an effect of palatability on body wt in mice. These data also suggest that higher plasma exposures [to parent compound] could have been achieved with gavage dosing.

In rats, aripiprazole was administered for 4 wks at doses of 10, 30, and 100 mg/kg by gavage and by drug/diet admixture. The final body wt and plasma exposure data are summarized in the following table:

ROUTE	FINAL BODY WEIGHT (gm)				$AUC_{(0\text{-}24\ hr)}$ [ng•hr/mL]		
	0	10	30	100	10	30	100
gavage	213.0 ± 8.2	219.9 ± 13.3	205.4 ± 10.2	143.7 ± 5.4	377.52	12274.24	60644.19
diet	231.5 ± 7.9	224.6 ± 5.6	198.0 ± 5.5	149.8 ± 11.3	253.53	4278.76	49302.42

As observed in mice, similar body wt effects were observed with gavage and dietary administration; however, plasma exposure [to parent compound] was higher with gavage, particularly at 30 mg/kg. The kinetics of aripiprazole was markedly greater-than dose-proportional with both routes in rat.

Carcinogenicity Summary and Conclusions

A number of drug-related non-neoplastic findings were observed in both mouse and rat. Many were consistent with drug-related effects on hormonal status [discussed further below]. Of note, however, were several findings observed in the carcinogenicity study in Sprague-Dawley rat [gavage dosing]. These include retinal degeneration, skeletal muscle atrophy, sciatic nerve degeneration, lung histiocytosis, and pigment [lipofuscin] deposition in liver, ovary, and mesenteric lymph node. The sponsor did not discuss any of these findings in any detail, but did indicate that, in general, the drug-related non-neoplastic findings observed were "either pharmacologically mediated or represented exacerbations of spontaneous age-related lesions". Sciatic nerve degeneration and pigment deposition in mesenteric lymph node were detected in a majority of animals in all grps, including controls. The severity of both was increased in a dose-related manner. The most notable effect on sciatic nerve was an increase in severity in males at 60 mg/kg. An increase in the severity of the lymph node effect was increased at 60 mg/kg in males and at doses of 20-60 mg/kg in females. Therefore, these findings are consistent with exacerbation of spontaneous lesions. Both the incidence and severity of lipofuscin deposition in liver [Kupffer cells] was increased in a dose-related manner [40 and 60 mg/kg]. Although liver necrosis was reported in the 26-wk study [2/20 males at 60 mg/kg], there was no indication of hepatocellular damage in the carcinogenicity study. According to Greaves [Greaves P. *Histopathology of Preclinical Toxicity Studies*, 2nd Ed., New York: Elsevier Science B.V., pg. 466, 2000], increased deposition of "lipochrome", detected in Kupffer cells in dogs treated with bromocriptine, was attributed to "general adverse changes such as shown by body weight loss and diminished food intake at exaggerated dose levels..." The skeletal muscle atrophy was not further characterized, but it may have also been the result of body wt/food consumption effects. Retinal degeneration and lung histiocytosis

[characterized as phospholipidosis] were detected in the chronic toxicity study; therefore, these findings were discussed in some detail in the summary of the toxicology data.

Aripiprazole was negative for neoplasms in male mice and rats. Assessment of carcinogenic potential was adequate in male mice based on a ≥10% decrease in body wt relative to controls at the highest dose tested [i.e., 30 mg/kg]. In male rats, the HD in the 2nd study [i.e., 60 mg/kg] exceeded the MTD based on excessive effects on body wt. This raises a concern that the sensitivity of the assay was reduced, as there are published studies demonstrating that dietary restriction inhibits spontaneous and drug-induced neoplasms. However, complete histopathology data were provided for lower doses [in the 1st study] at which body wt was not as markedly affected. When the carcinogenicity studies were originally proposed, there was concern that body wt effects observed with dietary administration were due to unpalatability of the drug/diet admixture. The sponsor conducted special 4-wk studies in mice and rats comparing gavage and dietary administration. The data from those studies clearly demonstrated a drug-related effect on body wt and food consumption; however, they also suggested the possibility that unpalatability may have had some role in the adverse effects on body wt and food consumption. However, in the single-dose level carcinogenicity study in mice, food intake was not affected in females. This would suggest a direct drug-related effect rather than an effect of unpalatability on body wt. In rats, food intake was reduced in both males and females. It is possible, although unlikely, that the drug/diet admixture palatability would be an issue in rats, but not mice.

The assessment of carcinogenic potential was adequate in female mice and rats. In female mice, there was a drug-related increase in mortality at 30 mg/kg [2nd study], indicating that higher doses could not have been used. In female rats, body wt effects were marked [as observed in males]. In female mice, the results of the two studies [in terms of tumor findings] were consistent. Drug-related increases in anterior pituitary adenoma and mammary gland tumors [adenocarcinoma, adenoacanthoma] were observed in both studies [i.e., at doses of 3, 10, and 30 mg/kg]. These doses are ≈0.5, 1.6, and 5 times the maximum recommended human dose [MRHD, 30 mg/day] on a mg/m^2 basis. Plasma AUCs at these doses were determined to be 0.1, 0.3, and 1 times the AUC at the MRHD.

The sponsor attributed these findings to hyperprolactinemia [serum prolactin was not measured in the carcinogenicity studies]. A series of special toxicity studies [1-, 4-, 13-wk dietary] was, however, conducted in order to investigate the effects of aripiprazole on serum prolactin in CD-1 [ICR] mice at the doses used in the carcinogenicity studies. [The results of these studies were summarized in the Special Toxicology section of this review.] Briefly, serum prolactin levels were not significantly increased in females following 1 [30 mg/kg] and 4 wks [3, 10, 30 mg/kg] of dosing. However, in the 1-wk study, the mean serum prolactin level was increased at 30 mg/kg, although the effect was not statistically significant due to large interanimal variability in the DT grp [SD ≈ 17 in CF, 208 in DT]. In the 13-wk study, serum prolactin was significantly elevated at doses of 10 and 30; however, the magnitude of the effect was similar at these doses. Serum prolactin was not significantly elevated at 3 mg/kg. In all three special studies, there was evidence of persistent diestrus in females at all doses [3-30 mg/kg]. Persistent diestrus could theoretically be caused by factors other than serum prolactin; however, it does suggest drug-related disruption of hormonal balance. In males, consistent effects on serum prolactin were not observed. In the 4-wk study, serum prolactin was significantly reduced in males at 30 mg/kg. In the 13-wk study, serum prolactin was not significantly affected at that dose, but was consistently reduced at 10 mg/kg; at 3 mg/kg, serum prolactin was significantly reduced at Wk 4, but significantly increased at Wk. 13. While the serum prolactin data are not strongly correlated with the incidence of mammary gland tumors, they do indicate that, in general, serum prolactin was elevated in females following prolonged administration of aripiprazole at doses of 10 and 30 mg/kg. While serum prolactin was not significantly elevated at 3 mg/kg, a similar disruption of the estrus cycle was observed a 3 mg/kg as noted at the higher doses.

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice, and SD and F344 rats. Aripiprazole was administered for two years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats [**0.2 to 5** and 0.3 to 3 **3** times the maximum recommended human dose (MRHD) on a mg/m^2 basis, respectively]. In addition, SD rats were dosed orally for two years at 10, 20, 40, and 60 mg/kg/day [**3 to 19** times the MRHD on a mg/m^2 basis). **Aripiprazole did not induce tumors in male mice or rats.** In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.5 to 5 times the MRHD on a mg/m^2 basis). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day [**3** times the MRHD on a mg/m^2 basis); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day [**19** times the MRHD on a mg/m^2 basis).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. **Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However,** increases in serum prolactin levels were observed **in female mice** in a 13-week dietary **study** [**at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mammary gland tumors.**

[**The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.**

Mammary gland adenocarcinomas and pituitary gland adenomas are tumors that have been observed in carcinogenicity studies of other antipsychotic drugs [e.g., risperidone, ziprasidone], and have been presumed to be prolactin-mediated. The only tumor finding not observed with other recently approved antipsychotic drugs is mammary gland adenoacanthoma. The sponsor was asked to provide data to support a relationship between this tumor type and elevations in serum prolactin. In response, the sponsor provided one reference directly relevant to this issue [McGrath CM *et al. JNCI* 67(4):841-852, 1981] and several other references relevant to an association between mammary tumors in general and hyperprolactinemia. McGrath *et al.* [1981] reported that prolonged "hormonal imbalance" in female BALB/c mice induced by hypophyseal implants resulted in the development of mammary gland tumors. Of the tumors detected during months 7-14, all were "adenoacanthomatous tumors". [Adenoacanthomatous tumors were defined as "composed of carcinomatous tissue intermixed with tissue undergoing squamous differentiation...".] Adenocarcinomas ["with no evidence of squamous differentiation"] developed later [≥14 mo post implant]. The authors noted that another published study [Medina D. *JNCI* 53:213-221, 1974] "observed a similar preponderance of adenoacanthomatous tumors early after chemical carcinogen treatment and a later change in tumor type to adenocarcinomas". Measurement of serum prolactin, estradiol, and progesterone indicated increases in all three hormones in female receiving hypophyseal implants, to levels similar to those in normal pregnancy. The authors also noted a state of continuous diestrus in all females receiving the implants.

In addressing the evidence for the notion that the mammary gland adenoacanthomas are related to elevations in serum prolactin, the sponsor made the following points: (a) adenoacanthomas are "a common variant of mammary carcinoma", (b) the "morphologic distinction" between adenocarcinomas and adenoacanthomas "has no biological or toxicological significance", (c) "Both mammary adenoacanthomas and adenocarcinomas have been described in experimental models of hyperprolactinemia, and (d) other antipsychotic drugs increase mammary tumors. From the information provided, it would appear that, although adenoacanthomas are essentially carcinomas containing a certain percentage of squamous metaplasia, the distinction between adenoacanthomas and adenocarcinomas may not be an unimportant one. McGrath *et al.* [1981] reported differences in the temporal development of the two tumors, and stated that "...the difference between the two types of tumor [i.e., adenocarcinoma, adenoacanthoma] may be more important than the quantitative differences in squamous tissue between different adenoacanthomatous tumors". The authors further stated that "The significance of the two tumor types has not been established". According to the abstract [article not available] of a published article by Imai S *et al.* [Imai S *et al. JNCI* 73(4):935-941, 1984], mammary gland adenoacanthomas induced by urethane were "very different from hyperplastic alveolar nodules, the preneoplastic lesions for adenocarcinomas". None of the references provided by the sponsor documented that adenoacanthomas were common mammary gland tumors. Seely and Boorman [Seely JC, Boorman GA. Mammary gland and specialized sebaceous glands. In: Maronpot RR, ed. *Pathology of the Mouse* Vienna, Illinois: Cache River Press, 1999; 613-635] described adenoacanthomas as "essentially carcinomas with at least 25% or more of the tumor consisting of squamous metaplasia", and noted that there are marked strain differences in the spontaneous rate of adenoacanthomas in mice. The authors summarized data on the rates of spontaneous mammary tumors in untreated female B6C3F$_1$ mice from 6 published studies. Only one of the 6 studies reported any incidence of an adenoacanthoma-type tumor; in that report, the incidence of "squamous cell carcinomas" was 0.1%. According to the database maintained by [redacted], [dated March, 1995], the incidence of mammary gland adenoacanthomas in CD-1 mice in 24-mo studies is 3 tumors detected upon examination of 549 tissues [11 study groups; mean % = 0.55, range %: 0-4.23]. That adenoacanthomas may result from elevations in pituitary hormones [sufficient to induce persistent diestrus] was supported by the findings of McGrath *et al.* [1981], even though the data from that study did not provided evidence of a specific relationship between serum prolactin and adenoacanthomas. Considering that McGrath *et al.* [1981] reported "a....preponderance" of adenoacanthomas following hypophyseal implantation, it is interesting that this

tumor type has not been previously reported in carcinogenicity studies of recently approved antipsychotic drugs.

In female rats, tumor findings differed between studies. In the 1st study, the only drug-related tumor finding was an increase in mammary gland fibroadenomas at the high dose [10 mg/kg]. This dose is ≈3 times the MRHD on a mg/m^2 basis. In the 2nd study, the only drug-related tumor finding was an increase in adrenocortical tumors [adenoma, adenoma and carcinoma combined] at the high dose [60 mg/kg]. This dose is 19 times the MRHD on a mg/m^2 basis. The difference between the two studies may be due to differences in method of drug administration [dietary vs gavage] or differences in strain. It was presumed that the mammary gland tumors were secondary to hyperprolactinemia. Serum prolactin was not measured in the carcinogenicity studies. However, a series of special toxicity studies was conducted in order to investigate the effects of aripiprazole on serum prolactin. In Fischer 344 rats administered aripiprazole in the diet, no effect was observed on serum prolactin at doses of 1, 3, and 10 mg/kg for 4 wks or at doses of 3, 10, and 25 mg/kg for 13 wks. No effects on the estrus cycles were observed in the 4-wk study, whereas in the 13-wk study, the incidence of persistent diestrus was increased at all doses. The plasma levels achieved in the 13-wk study at 3 mg/kg and 10 mg/kg were similar to and 6 times lower, respectively, than those achieved at the same doses in the carcinogenicity study in Fischer 344 rats. However, the plasma levels at 25 mg/kg in the 13-wk study were ≈4 times the level achieved at 10 mg/kg in the carcinogenicity study. As noted, serum prolactin was not elevated at the 25-mg/kg dose. In males, serum prolactin was significantly decreased at 10 mg/kg in the 4-wk study, and at all doses in the 13-wk study. Therefore, there is no evidence that serum prolactin levels were elevated at 10 mg/kg in the carcinogenicity study, the dose associated with mammary gland fibroadenomas. It is of note that serum prolactin was markedly elevated in a 13-wk special study in Sprague-Dawley rats at the same doses used in the carcinogenicity study conducted in this strain, but that "prolactin-mediated" tumors, e.g., mammary gland tumors, were not observed in that study. Taken together, the data minimize the concern regarding the mammary gland fibroadenomas due to the following: (a) although there is no evidence that serum prolactin levels were elevated in female Fischer 344 rats, there was evidence of "hormonal imbalance" as noted by the incidences of persistent diestrus at 3 and 10 mg/kg in the special toxicology study, (b) mammary gland tumors were not evident in male Fischer 344 rats or in male or female Sprague-Dawley rats at plasma exposures exceeding those achieved in female Fischer 344 rats, and (c) mammary gland fibroadenomas are tumors that have been observed in carcinogenicity studies of other antipsychotic drugs [e.g., risperidone].

Regarding the adrenocortical tumors, the sponsor was asked to provide information relevant to any proposed mechanism underlying these tumors. In response, the sponsor provided a number of published articles in support of the position that these tumors are "...epigenetic and likely a consequence of increased adrenocortical cell proliferation secondary to chronic drug-related adrenocortical cytotoxicity". The sponsor based this conclusion primarily on two microscopic findings in adrenal gland [i.e., lipofuscin pigment accumulation and adrenocortical cell loss] and evidence of cellular proliferation in the adrenal cortex [zona faciculata]. The data for the two microscopic findings were summarized in the following sponsor's table:

Table 1 - Aripiprazole: Oral Carcinogenicity Study in Rats - Summary of Drug-Related Adrenocortical Cell Loss and Lipofuscin Pigment Accumulation

Dose (mg/kg/day):	0	0	10	20	40	60
Sex:	M/F	M/F	M/F	M/F	M/F	M/F
No. Examined (Adrenals)	54/55	55/55	55/55	55/55	55/55	55/55
Cortical cell loss, mid/inner cortex	0	0	0	0	11/13	24/39
Minimal	0	0	0	0	5/3	5/6
Slight	0	0	0	0	4/2	9/8
Moderate	0	0	0	0	1/5	8/15
Moderately Severe	0	0	0	0	0/3	2/9
Severe	0	0	0	0	1/0	0/1
Pigment, lipofuscin (cortical)	42/55	42/52	40/52	47/54	52/55	52/50
Minimal	34/19	35/19	29/18	20/8	4/0	0/0
Slight	8/29	7/29	11/32	27/27	21/5	6/2
Moderate	0/7	0/4	0/2	0/19	26/13	35/2
Moderately Severe	0	0	0	0	1/19	11/11
Severe	0	0	0	0	0/18	0/35

The sponsor noted that the response in females was greater than in males. [Adrenocortical tumors [carcinomas, adenomas and carcinomas combined] were significantly increased only in females.] The sponsor also made the following points: (a) aripiprazole-induced adrenocortical cell injury [of which the underlying mechanism(s) is unknown] leads to loss of cells and an accumulation of lipofuscin pigment, (b) tissue accumulation of lipofuscin pigment is recognized as an indicator of lipid peroxidation; the female adrenal gland [particularly the zona fasciculata and zona reticularis] is more susceptible to oxidative injury than the male due to its greater volume and rate of steroidogenesis, (c) human adrenal gland is at lower risk of oxidative injury since "the available experimental data support the fact that cellular resistance to oxidative and non-oxidative stresses is positively correlated with mammalian life span..and that production of reactive oxygen species per unit weight of total oxygen consumed is much less in longer-lived species than in shorter-lived species", (d) the nongenotoxic nature of the toxicity is evidenced by the fact that tumors occur only in females even though plasma drug exposure is similar in males, the effect is clearly dose-related, and the tumors are late-onset. In general, the published articles submitted by the sponsor support the processes proposed by the sponsor. Colby [Colby HD. The adrenal cortex as a toxicological target organ. In: *The Adrenal in Toxicology*. Harvey PW (Ed.), London: Taylor and Francis 1996:131-164] noted that lipofuscin itself is not thought to induce cellular damage unless, perhaps, accumulation were to be so extensive that cellular function were compromised. Regarding the relative risk to humans, published studies provided by the sponsor do support the notion that the risk of oxidative injury to adrenal gland may be less in humans than in rat, related to the difference in life-span. According to Floyd *et al.* [Floyd RA *et al. Exp Gerontol* 36:619-640, 2001], "limited experimental comparative results available implicate that ROS [reactive oxygen species] production per unit weight of total oxygen consumed is much less in the longer-lived species than in shorter-lived species". However, it does necessarily follow from this observation that humans would not be equally susceptible to drug-induced injury [involving free radical reactions] if treated chronically. Floyd *et al.* [2001] also noted that "...long-lived species appear to have less antioxidant defense enzymatic activity" than short-lived species.

Drug-related effects on adrenal gland were noted in the 4-wk [+ 4-wk recovery] and the 26-wk toxicity studies in Sprague-Dawley rat and in the 2-yr carcinogenicity studies in ICR mouse. In all of these studies, females were more affected than males. In the 4-wk study, the incidence of adrenocortical [z. fasciculata/reticularis] hypertrophy was only slightly higher in females than in males at 100 mg/kg; however, the severity was greater in females. In the 26-wk study, there was no effect on lipofuscin

pigment deposition; however, diffuse hypertrophy of the adrenal cortex was increased in females at 30 and 60 mg/kg. In the 2-yr studies in mouse, in adrenal gland, increased "brown pigment" deposition was noted in females [deposition was decreased in males], and the incidence of subcapsular cell hyperplasia was increased in DT females in the single-dose level study. [Adrenal gland was not affected in cynomolgus monkey.] Quantitation of cell proliferation in the 26-wk toxicity study indicated decreases in cell proliferation in both males and females. However, in the 2-yr study in Sprague-Dawley rat, the sponsor demonstrated a significant increase in cell proliferation [as quantitated by K_i-67 nuclear antigen expression] in both males and females at 60 mg/kg. The sponsor also submitted a 4-wk interim report for a 13-wk study [a study report for the 13-wk study could not be found]. According to the interim report, circulating levels of ACTH and corticosterone were significantly increased and adrenal gland hypertrophy was detected in females at 60 mg/kg; no effects were detected in males. The sponsor attributed the effects in females to $5HT_{1A}$ partial agonist properties of aripiprazole. $5HT_{1A}$ agonists have been reported to increase serum ACTH levels [Bluet PMT *et al. Neuroendrocrinology* 61(2):159-166, 1995; Di Sciullo A *et al. Endocrinol* 127(2):567-572, 1990 (only abstracts available)] and chronic elevations in ACTH have be associated with adrenocortical hypertrophy. However, the relationship between elevated ACTH levels and adrenocortical tumors is unclear. A recent study published by Imazawa *et al.* [Imazawa T *et al. Toxicol Pathol* 28(4):535-539, 2000] reported ACTH-induced promotion of adrenocortical adenomas. In female Sprague-Dawley rats treated with 4HAQO ["a long-acting synthetic ACTH"] and ACTH, there was an increase in the incidence of adenocortical adenomas/adenomatous nodules after 30-40 wks of treatment. However, ACTH alone did not induce tumors by Wk 40. The data provided for aripiprazole was insufficient to determine a possible relationship between $5HT_{1A}$, ACTH, and the adrenocortical tumors observed.

The fact that aripiprazole was shown to be genotoxic *in vitro* [*in vivo* genotoxicity cannot be entirely ruled out] makes it particularly important to carefully assess the tumors observed in the carcinogenicity studies. The data from these studies would be more consistent with a nongenotoxic mechanism for aripiprazole-induced tumors. That is, the mammary tumors in female mice and female Fischer 344 rats reasonably appear to be related to elevations in serum prolactin or other hormonal effects. The adrenocortical tumors in female Sprague-Dawley rats reasonably appear to be related to aripiprazole-induced cytotoxicity [mechanism unknown], resulting in increased cellular proliferation. The adrenocortical tumors were evident in only one sex and one species, with a clear dose-response and an established no-effect level. The dose associated with adrenocortical tumors [60 mg/kg] is 19 times the maximum recommended human dose on a mg/m^2 basis. The C_{max} and AUC in females at the dose associated with adrenocortical tumors are 20 and 13 times, respectively, the C_{max} and AUC at the MRHD. At the highest dose not associated with adrenocortical tumors, the C_{max} and AUC were 12-10 times the C_{max} and AUC at the MRHD. The highest dose not associated with adrenocortical cell loss [20 mg/kg] is 6.5 times the MRHD on a mg/m^2 basis. Plasma C_{max} and AUC at that dose are 8 and 3 times, respectively, the C_{max} and AUC at the MRHD. As noted previously, safety margins for exposure based on mean AUC data for the parent compound in humans may be overestimates due to the possibility that higher plasma levels of parent compound may be achieved in poor metabolizers.

In conclusion, base on the data and additional information provided by the sponsor, the tumor findings in mouse and rat would not preclude approving aripiprazole for the treatment of schizophrenia. However, the relevance of these tumor findings [the adrenocortical tumors in particular] to humans cannot be dismissed.

Labeling Recommendations: the following revisions to the sponsor's proposed labeling are recommended:

Number of Pages Redacted 1

❖❖❖

Draft Labeling
(not releasable,

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

I. SEGMENT I: REPRODUCTION STUDIES IN RATS

I.1. Study title: Fertility and general reproductive performance study of OPC-14957 administered orally to rats

Key study findings: Upon oral administration (by gavage) of aripiprazole (OPC-14957) to male and female rats during pre-mating (for 9 and 2 weeks in males and females, respectively), mating, and first week of gestation at dose levels of 2, 6, and 20 mg/kg, the maximum no-effect doses were estimated to be 2 mg/kg/day for parental male and female general toxicity in view of the effects on body weight and food consumption; 20 mg/kg/day for male fertility and reproductive performance in view of lack of effect up to the highest tested dose; less than 2 mg/kg/day for female fertility and reproductive performance in view of the disturbances in estrus cycle at 2 mg/kg/day or higher; and 6 mg/kg/day for fetal toxicity in view of the decrease in fetal body weight at 20 mg/kg/day.

Study No.: 005437
NDA Volume #, page #: 1.109, p. 220
Conducting laboratory and location: Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan
Date of study initiation: May 15, 1989
GLP compliance: Yes
QA reports: Yes
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 8K84M; ———
Formulation/ vehicle: suspension 0.4% (w/v) in 5% gum arabic/distilled water

Methods:
Species/strain: Rat, Sprague-Dawley
Doses employed: 0 (vehicle control, 5% gum arabic), 2, 6 and 20 mg/kg/day
(Individual dosage volumes adjusted at a rate of 5 ml/kg)
The highest dose was shown to cause a decrease in body weight and food consumption in preceding sub-chronic oral experiments on adult female and male rats (for 5 and 13 weeks, respectively).
Route of administration: Oral (by gavage)

Study design: Male and female rats (6 and 8 weeks old, respectively), were randomly distributed among the experimental groups and treated for 63 days prior to mating in the males, and for 14 days prior to mating, through mating and until day 7 of gestation in the females. In an additional experiment, treated males were paired with untreated females to determine male fertility. The effects of the compound on male and female fertility and reproductive performance, on dams, and on fetal development were determined. The results were statistically analyzed.

Number/sex/group: 25 males and 25 females per group; Mating ratio: 1/1

Parameters and endpoints evaluated: General condition, body weight and food consumption, estrus cycle, duration of pairing, copulation, fertility, cesarean and fetal data (numbers of corpora lutea, implantations, resorptions, live and dead fetuses, fetal body weight, sex ratio, external abnormalities, and placental weight); sperm and male reproductive organ specimens were examined only in infertile males.

Results

Parameter	Observed Effect	NOAEL (mg.kg/day)		LOAEL (mg.kg/day)	
		Males	Females	Males	Females
A. Treated males + treated females					
- Pre-mating: Parental (F_0) General toxicity					
Body weight	Increase (mid*- and high† dose)	2	2	6	6
Body weight gain	Increase* (mid-dose only)	2	2	6	6
Food consumption	Increase*	2	2	6	6
Clinical signs	No (Note: Ptosis & sedation in 1 female, low dose group)	20	20	>20[1]	>20[1]
- Mating: Fertility endpoints					
Estrus cycle	Prolonged estrus, irregular cycles*	NA	<2[2]	NA	2
Mating time	Increase	20	6	>20[1]	20
% Fertilized	No effect	20	20	>20[1]	>20[1]
% Pregnant	No effect	20	20	>20[1]	>20[1]
Gross pathology	No (Note: Testicular & epididymal hypoplasia found in 1 control male and in 1 male from the low dose group)				
- Gestation					
Maternal weight gain	Decrease (mid*- and high* dose; Not statistically significant but well defined at the lowest dose)	NA	2	NA	6
Maternal food consum.	Decrease*	NA	6	NA	20
N Corpora lutea	Increase*	NA	2	NA	6
Pre-implantation loss	Increase*	NA	2	NA	6
Post-implantation loss	No effect	NA	20	NA	>20[1]
Fetal weight	Decrease* (slight)	NA	6	NA	20
Placental weight	No effect	NA	20	NA	>20[1]
Congenital anomalies	No effect (Note: 1 fetus (0.5%) of the mid-dose group with multiple anomalies – rate similar to historical control)	NA	20	NA	>20[1]
B. Treated males + untreated females (*male fertility test*)					
Mating time	No effect	20	NA	>20[1]	NA
% Fertilized	No effect	20	NA	>20[1]	NA
% Pregnant	No effect	20	NA	>20[1]	NA
N Corpora lutea	No effect	20	NA	>20[1]	NA
Pre-implantation loss	No effect	20	NA	>20[1]	NA
Post-implantation loss	No effect	20	NA	>20[1]	NA
Fetal weight	No effect	20	NA	>20[1]	NA
Placental weight	No effect	20	NA	>20[1]	NA
Congenital anomalies	No effect (Note: 1 fetus (0.3%) of the mid-dose group with exencephaly - rate similar to historical control)	20	NA	>20[1]	NA
SUMMARY					
F_0 General toxicity	Altered body weight & food consumption*	2	2	6	6
F_0 Maternal toxicity	Decreased weight gain in pregnancy	NA	2	NA	6
Fertility & repro performance	Effect in females only: Estrus cycle prolongation & irregularities*; Hyperovulation*	20	<2	>20[1]	2
Embryo toxicity	Increased pre-implantation lethality*	20	2	>20[1]	6
Fetotoxicity	Decreased fetal weight*	20	6	>20[1]	20

*Statistically significant; † At the high dose, the initial increase in body weight was followed by a decrease by the end of the treatment period; [1]LOAEL not reached (highest dose tested: 20 mg/kg/day); [2] NOAEL not reached (lowest dose tested: 2 mg/kg/day); NA= not applicable

Summary of findings, study # 005437:

Exposure: Oral application (gavage) of aripiprazole (suspension in 5% gum arabic) to male and female Sprague Dawley rats, at doses of 2, 6, and 20 mg/kg/day for 9 weeks prior to and during mating (males) and for 2 weeks prior to mating through gestation day 7 (females).

General toxicity upon pre-mating exposure: Except for increased food consumption and accelerated body weight gain in both males and females (LOAEL = 6 mg/kg/day), no other general effects were observed. At the highest tested dose (20 mg/kg/day), the weight was increased initially but decreased subsequently during the course of exposure, so that by the end of the treatment period it was not different from control. Thus, at the highest dose level, there was no overall increase in body weight gain despite the higher food consumption.

Fertility, reproductive performance and embryo/fetal toxicity: The tested dose levels did not result in impairment of fertility or congenital anomalies in the progeny up to the highest dose. However, significant and dose-dependent estrus cycle irregularities were induced in the females at all dose levels, including the lowest tested dose (LOAEL = 2 mg/kg/day), along with hyperovulation (slight but significant increase in the number of corpora lutea), increased pre-implantation embryonic losses (LOAEL = 6 mg/kg/day), and decreased fetal weight (LOAEL= 20 mg/kg/day). Maternal weight gain in pregnancy was slightly but significantly decreased in a dose-dependent manner (LOAEL=6 mg/kg/day). These effects were associated with the female exposure because when treated males were paired with untreated females, similar effects did not occur. No effect on male fertility parameters was observed as well.

The above listed findings were attributed to endocrine changes associated with accelerated prolactin release (literature data), characteristic for the pharmacological effect of antipsychotic drugs in the rat through blocking of central dopaminergic neurotransmission. No prolactin measurements were performed in this study.

I.2. Study title: Male fertility study of OPC-14957 administered orally to rats

Key study findings: Exposure of male Sprague-Dawley rats to aripiprazole (OPC-14957) by gavage for 9 weeks prior to and during mating at dose levels of 20, 40, and 60 mg/kg/day, resulted in general toxicological effect (significant weight decrease), as well as in reduced organ weight and histopathological changes in reproductive organs at the mid- and high dose (atrophy of the prostate at the mid- and high dose, disturbances of spermatogenesis, atrophy of seminiferous tubule and decrease of sperm in the epididymal duct at the high dose). Upon pairing with untreated females, however, no changes in fertility, reproductive capacity, or prenatal development of the F_1 generation were observed. The maximum no-effect doses were estimated to be 20 mg/kg/day for parental male general toxicity and histopathological changes in male reproductive organs, and 60 mg/kg/day for male fertility and embryo-fetal development.

Study No.: 05707
NDA Volume #, page #: 1.110, p. 1
Conducting laboratory and location: Tokushima Research Institute, Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan
Date of study initiation: December 15, 1999
GLP compliance: Yes
QA reports: Yes
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 98A91M; [redacted]
Formulation/ vehicle: suspension in 5% gum arabic/ distilled water

Methods:
Species/strain: Rat, Sprague-Dawley

Doses employed: 0 (vehicle control, 5% gum arabic), 20, 40 and 60 mg/kg/day
(Individual dosage volumes adjusted on the basis of body weight at a rate of 5 ml/kg)

Route of administration: Oral (by gavage)

Study design: This study was designed to examine the compound's effect on male fertility at dose levels higher than those in the former fertility study (No.005437) because, in that study, no definite male toxicity was observed even at the highest dose of 20 mg/kg/day. Male rats (6 to 7 weeks old) were randomly distributed among the experimental groups and treated for 63 days prior to and through mating with untreated healthy females of the same strain, aged 10 to 11 weeks. The effects of the compound on male reproductive organs, fertility, reproductive performance and embryo-fetal development were determined. The results were statistically analyzed.

Number/sex/group: 25 males and 25 females per group; Mating ratio: 1/1

Parameters and endpoints evaluated: General condition, body weight and food consumption, estrus cycle, duration of pairing, copulation, fertility, cesarean and fetal data (numbers of corpora lutea, implantations, resorptions, live and dead fetuses, fetal body weight, sex ratio, external abnormalities, placental weight); male reproductive organs weights and histopathology (testis, epididymis, prostate and seminal vesicles).

Results

Parameter	Observed Effect	NOAEL (mg/kg/day)		LOAEL (mg/kg/day)	
		Males	Females†	Males	Females†
Treated males + untreated females					
Parental (male) general toxicity					
Body weight	Decrease*	<20[2, 3]	NA	20	NA
Body weight gain	Decrease*	<20[2, 3]	NA	20	NA
Food consumption	Decrease*	<20[2, 3]	NA	20	NA
Clinical signs	Partially closed eyes, hypoactivity	20	NA	40	NA
Male reproductive organs					
Organ weight:					
Prostate	Decrease* of absolute, but not relative weight	20	NA	40	NA
Testis	Decrease* of absolute, but not relative weight	40	NA	60	NA
Histopathology:					
Prostate	Atrophy	20	NA	40	NA
Seminiferous tubule	Atrophy; decrease of sperm in epididymal duct	40	NA	60	NA
Spermatogenesis	Disturbed spermatogenesis: Exfoliation of spermatids in the seminiferous tubule; Retention of step 19 spermatids; Exfoliation of germ cells in the epididymal duct	40	NA	60	NA
Fertility endpoints					
Estrus cycle, females	Normal (Note: females not treated with aripiprazole)	NA	NA	NA	NA
Mating time	No effect	60	NA	>60[1]	NA
% Fertilized females	No effect	60	NA	>60[1]	NA
% Pregnant females	No effect	60	NA	>60[1]	NA
Embryo-fetal data					
Pre-implantation loss	No effect	60	NA	>60[1]	NA
Post-implantation loss	No effect	60	NA	>60[1]	NA
Fetal weight	No effect	60	NA	>60[1]	NA
Sex ratio	No effect	60	NA	>60[1]	NA
Placental weight & morphology	No effect	60	NA	>60[1]	NA
Congenital anomalies	No effect (Note: 1 fetus (0.2%) from the control group with anophtalmia; 2 fetuses (0.7%) from the low-dose group with brachydactyly and short tail each)	60	NA	>60[1]	NA
SUMMARY					
Male general toxicity	Decreased body weight *	<20	NA	20	NA
Male reproductive organs	Prostate atrophy	20	NA	40	NA
Spermatogenesis	Disturbed	40	NA	60	NA
Fertility & reproductive performance	No effect	60	NA	>60[1]	NA
Embryo-fetal effects	No effect	60	NA	>60[1]	NA

* Statistically significant; †Females not treated; [1]LOAEL not reached (highest dose tested : 60 mg/kg/day); [2] NOAEL not reached (lowest dose tested . 20 mg/kg/day); [3] Not significant at the lowest tested dose, but consistent and well defined; NA= not applicable

Summary of findings, study # 05707:

Exposure of male rats to aripiprazole at oral doses of 20, 40, and 60 mg/kg/day for 9 weeks prior to and during mating with untreated females causes signs of general toxicity in the males (significant body weight decrease) down to the lowest dose tested (LOAEL= 20 mg/kg/day). Pathological changes in male reproductive organs morphology (e.g. prostate atrophy) and function (e.g. spermatogenesis disturbances) are seen at LOAELs of 40 and 60 mg/kg/day, respectively – i.e. at dose levels that are generally toxic. Despite of these effects, no changes in male fertility or prenatal development of the progeny upon mating with untreated females are seen up to the highest exposure level.

2. SEGMENT II: TERATOLOGY STUDIES IN RATS

2.1. Study title: Preliminary teratogenicity study of OPC-14957 administered orally to rats

Key study findings: Oral administration of aripiprazole at doses of 2, 6, 20 and 30 mg/kg/day to pregnant Sprague-Dawley rats during the period of organogenesis (gestation day 7 to 17) resulted in maternal toxicity (decrease in body weight) and clinical signs (ptosis) at 20 mg/kg/day and higher; these doses also suppressed the fetal growth causing a decrease in fetal weight and retarded ossification, but no congenital abnormalities or embryo-fetal lethality. Slight decrease in placental weights and in F1 male: female ratios were seen at maternally non-toxic doses. The adverse fetal effects appear to be gender-dependent, more expressed in the female fetuses. LOAEL for maternal toxicity: 20 mg/kg/day; LOAEL for fetal toxicity: 6 mg/kg/day

Study No.: 006642
NDA Volume #, page #: 1.110, p. 124
Conducting laboratory and location: Tokushima Research Institute, Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan
Date of study initiation: August 23, 1990
GLP compliance: No data
QA reports: No
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 8K89M; [redacted]
Formulation/ vehicle: 0.6% (w/v) suspension in 5% gum arabic/distilled water

Methods:
Species/strain: Rat, Sprague-Dawley

Doses employed: 0 (vehicle control, 5% gum arabic), 2, 6, 20, and 30 mg/kg/day
(Individual dosage volumes adjusted on the basis of body weight at a rate of 5 ml/kg)

Route of administration: Oral (by gavage)

Study design: This is a preliminary, dose-finding teratology study that was designed to determine the high dose for the scheduled rat Segment 2 teratogenicity study. Four dose levels were employed. The highest dose was presumed to affect maternal body weight gain and food consumption on the basis of a previous 5-week subacute toxicity study in adult non-pregnant females. Aripiprazole was administered to pregnant females during the period of organogenesis (gestation day 7-17). Cesarean section was performed on gestational day 20. Relevant endpoints were measured to assess maternal and embryo-fetal toxicity. The data were analyzed statistically.

Number/sex/group: 10 pregnant females per group

Parameters and endpoints evaluated: Maternal general condition, body weight and food consumption, clinical signs, cesarean and fetal data (numbers of corpora lutea, implantations, resorptions, live and dead fetuses, fetal body weight, sex ratio, external, visceral and skeletal abnormalities, placental weight).

Results

Study 006642: Preliminary teratogenicity study of OPC-14957 administered orally to rats

Parameter	Observed Effect	NOAEL *(mg/kg/day)*	LOAEL *(mg/kg/day)*
Maternal Toxicity			
Body weight	Decrease (n.s., but dose-dependent, consistent)	6	20
Body weight gain during gestation	Decrease*	6	20
Food consumption	Decrease (*at 30 mg/kg/day; n.s. but consistent at 20 mg/kg/day)	6	20
Clinical signs	Yes (Drooping eyelids in 100% of dams at 20 & 30 mg/kg/day , reversible at 24 hrs post-dosing)	6	20
Mortality	No effect	30	>30[1]
N Corpora lutea	NA (treatment started after implantation)	.	.
Embryo/fetal Toxicity (Prenatal developmental toxicity)			
Pre-implantation lethality	NA (treatment started after implantation)	.	.
Post-implantation lethality (resorptions, dead fetuses)	No effect	30	>30[1]
Fetal weight	Decrease* , female fetuses Decrease* , male fetuses	6 20	20 30
Placental weight	Decrease (n.s. but dose-dependent and consistent. Up to 5% decrease in the fetal female - not male - placental weight)	2	6
Fetal sex ratio (male:female)	Decrease (n.s. but present in all dose groups except the lowest one)	2	6
Congenital anomalies, incl.:			
Malformations			
- External	No effect (hydrocephaly in 1 fetus at 6 mg/kg/day)	30	>30[1]
- Visceral	No effect (ventricular septal defect in 3 control & 1 high dose fetuses)	30	>30[1]
- Skeletal	No effect	30	>30[1]
Variations		30	>30[1]
- Visceral	No effect	30	>30[1]
- Skeletal	No effect	30	>30[1]
Other			
Skeletal ossification	Retarded (moderately)	6	20
SUMMARY			
Maternal toxicity	Decreased food cosumption & weight gain in pregnancy	6	20
Embryo/fetal toxicity	Decreased placental weight (female fetuses), Decreased male to female sex ratio	2	6
	Retarded skeletal ossification, Decreased fetal weight (female)	6	20

*Statistically significant; n.s. = Not statistically significant; [1]LOAEL not reached (highest dose tested: 30 mg/kg/day); NA= not applicable

Summary of findings, study # 006642:

Post-implantation exposure of pregnant rats to aripiprazole at oral doses of 2, 6, 20 and 30 mg/kg/day during the period of organogenesis (gestation day 7-17) is maternally toxic at levels of 20 mg/kg/day and higher, as demonstrated by a significant decrease in maternal weight gain and food consumption during pregnancy, as well as a presence of clinical signs (ptosis). Such dose levels also affect the fetal intrauterine growth, as demonstrated by fetal weight decrease and retarded skeletal ossification (LOAEL = 20 mg/kg/day). However, some signs of adverse embryo/fetal effect (slightly decreased placental weight and male: female offspring ratio) are present at lower, non-maternally toxic doses (LOAEL = 6 mg/kg/day). It should be noted that the embryo/fetal effects (e.g. placental and fetal weight reduction) appear to be gender-related, being significantly more expressed in the female than in the male fetuses.

2.2. Study title: Teratogenicity study of OPC-14957 administered orally to rats

Key study findings: Oral exposure (by gavage) of pregnant rats to aripiprazole at dose levels of 3, 10, and 30 mg/kg/day during the period of major organogenesis (day 7 to17 of gestation) causes *maternal* toxicity at 10 mg/kg/day and higher. Prolongation of gestation, and signs of *prenatal* developmental toxicity (reduction in placental weight, retarded fetal skeletal ossification, visceral abnormalities) are seen at maternally toxic levels. LOAEL for most of these effects is 30 mg/kg/day, and 10 mg/kg/day for retarded skeletal ossification. However, disturbances in the *postnatal* development of the progeny (deviations in postnatal weight gain, delayed sexual maturation in the female offspring) (LOAEL = 3 mg/kg/day) are observed at lower, maternally non-toxic dose levels. Impaired *reproductive capacity of F1* generation (decreased number of corpora lutea and implantations, slightly increased pre- and post-implantation F2 embryolethality) is observed upon mating of male and female F1 animals that had been prenatally exposed to aripiprazole at levels of 10 mg/kg/day and higher. The impaired reproductive capacity of the F1 generation is most probably mediated through the F1 prenatally treated females, because such impairment is not seen when untreated females are mated with the prenatally treated F1 males.

The higher sensitivity of the female animals is supported by the findings in the preceding fertility studies.

Study No.: 006939
NDA Volume #, page #: volume 1.110, p. 250; volume 1.111. p. 1
Conducting laboratory and location: Tokushima Research Institute, Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan
Date of study initiation: March 4, 1991
GLP compliance: Yes
QA reports: Yes
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 8K89M; [redacted]
Formulation/ vehicle: 0.6% (w/v) suspension in 5% gum arabic/distilled water

Methods:

Species/strain: Rat, Sprague-Dawley

Doses employed: 0 (vehicle control, 5% gum arabic), 3, 10, and 30 mg/kg/day
(Individual dosage volumes adjusted on the basis of body weight at a rate of 5 ml/kg)

Route of administration: Oral (by gavage)

Study design: This is a pre- and postnatal developmental toxicity study of aripiprazole upon oral administration to pregnant rats from day 7 to 17 of gestation, at dose levels of 3, 10, and 30 mg/kg/day. The highest dose was presumed to cause some maternal toxicity on the basis of a preliminary teratology study in the same strain (Study No. 006642). Out of the total of 40 pregnant females per group, 25 were subjected to Cesarean section on gestational day 20; the rest were allowed to deliver spontaneously. Relevant endpoints were measured to assess maternal, pre- and postnatal toxicity. On postnatal day 4, all litters were culled to a standard number of 8 offspring (4 per sex per group where possible). Postnatal viability, physical and neurobehavioral development of F1 generation were followed until maturity (42 days of age). The pups were weaned on postnatal day 21. To assess F1 reproductive capacity, F1 males were mated with F1 (non-sibling) females within the treatment groups. F1 males of the highest dose group were subsequently mated again (second pairing at 19-20 weeks of age) with untreated females to

assess independently the effect on the male reproductive function. F1 fertility and F2 prenatal toxicity parameters were studied. The data were analyzed statistically.

Number/sex/group: 40 pregnant females per group (25 for Cesarean and 15 for spontaneous delivery)

Parameters and endpoints evaluated: Maternal general condition, body weight and food consumption, clinical signs, cesarean and fetal data (numbers of corpora lutea, implantations, resorptions, live and dead fetuses, fetal body weight, sex ratio, external, visceral and skeletal abnormalities, placental weight); postnatal developmental parameters: viability, body weight gain, physical developmental landmarks (pinna detachment, hair emergence, incisor eruption, eyelid opening, testes descend on postnatal day 28, vaginal opening on postnatal day 35), neurobehavioral development (reflexes, sensory-motor coordination, learning ability –conditioned avoidance response); F1 reproductive capacity (copulation, fertility, and F2 prenatal embryo/fetal indices as above). The testes, epidydimides, and accessory reproductive organs were fixed in formalin and stored. At the highest dose level, necropsies were performed on neonatal F1 animals (postnatal day 4), as well as at 6 weeks of age to assess visceral abnormalities in comparison to the control group.

Results (See table page 13)

Summary of findings and comments

Oral administration of aripiprazole at doses of 3, 10 and 30 mg/kg/day to pregnant Sprague-Dawley rats during the period of organogenesis (gestation day 7 to 17) resulted in *maternal toxicity* at 10 mg/kg/day and higher (decreased food consumption and suppressed weight gain at 10 and 30 mg/kg/day; clinical signs at 30 mg/kg/day - ptosis, disappearance of touch response, attributed to a central inhibitory action of the drug). The gestation period was slightly but significantly prolonged at the highest dose.

Adverse prenatal fetal effects were observed at maternally toxic doses (at and above 10 mg/kg/day) and included decreased placental weight, decreased fetal weight, retarded ossification, increased incidence of visceral abnormalities (abnormal shape of the liver, diaphragmatic hernia, sporadic cases of undescended testes). Undescended testes were noted in a small number of 30 mg/kg/day fetuses at term, but not postnatally; thus, this appears to be a transient delay, unlikely to continue after birth. Among the visceral abnormalities, *abnormal shape of the liver* (with a nodule on the diaphragmatic side of the liver, sometimes protruding into thoracic cavity) was the most prevalent. It was observed in about 14% of the examined F1 neonatal animals from the 30 mg/kg group on postnatal day 4, as well as in some of the F1 progeny from the same group at the age of 6 weeks. Because this change was seen only at the highest exposure level, its relation to aripiprazole treatment cannot be excluded. However, it is not likely to be an abnormality specific for the agent because it was reported to occur genetically or spontaneously (e.g. was also noted in some untreated adult females used in the fertility study of this experiment, as well as in a control male animal in the Segment III study). These data, as well as the fact that this abnormality did not interfere with the growth and survival (e.g., the offspring with abnormal shape of the liver did not die during the course of the study and showed no marked difference in body weight compared with other animals at 30 mg/kg/day), suggest that the abnormal shape of the liver can be classified as a variation rather than a malformation.

No embryo-fetal lethality or changes in the male: female ratio were observed.

Postnatally, body weight gain was suppressed dose-dependently in both male and female offspring at 10 and 30 mg/kg/day (significant at the latter). At 3 mg/kg/day, pup body weight was significantly increased. The latter is consistent with the accelerated weight gain seen in adult animals at aripiprazole oral doses of up to 6 mg/kg/day. A dose-dependent delay in vaginal opening was seen in female offspring

(significant at 10 mg/kg/day and higher). No changes in other developmental landmarks, and behavior, and no significant changes in cognitive development of the progeny were found. However, impaired reproductive capacity of the progeny, most likely mediated through the F1 females, was induced by prenatal exposures of 10 mg/kg/day and higher.

LOAEL for maternal toxicity: 10 mg/kg/day; LOAEL for fetal toxicity: 10 mg/kg/day; LOAEL for postnatal developmental effects: 3 mg/kg/day.

Results Study No. 006939: Teratogenicity study of OPC-14957 administered orally to rats

Parameter	Observed Effect	NOAEL *(mg/kg/day)*	LOAEL *(mg/kg/day)*
Maternal Toxicity			
Body weight	Decrease (dose-dependent, *at 30 mg/kg/day)	**3**	**10**
Body weight gain	Decrease (dose-dependent, *at 30 mg/kg/day)	**3**	**10**
Food consumption	Decrease (dose-dependent, *at 30 mg/kg/day)	**3**	**10**
Clinical signs	Yes (Drooping eyelids in 100% and disappearance of touch response in 18% of the animals at 30 mg/kg/day)	**10**	**30**
Mortality	No effect	30	>30[1]
Duration of gestation	Prolonged*(slightly)	**10**	**30**
F1 Prenatal developmental toxicity			
Pre-implantation loss	NA (treatment started after implantation)	.	.
Post-implantation loss (resorptions, dead fetuses)	No effect	30	>30[1]
Fetal weight	Decrease* (both sexes)	**10**	**30**
Placental weight	Decrease* (both sexes)	**10**	**30**
Fetal sex ratio	No effect	30	>30[1]
Abnormalities			
- External	No effect	30	>30[1]
- Visceral	Increase[2] ("abnormal shape" of liver (14%) Slight increase[2] (diaphragmatic hernia, 1.3- 1.6%) Slight increase* (undescended testis, incidence 2.2%)	<30 (ND) <30 (ND) **10**	**30** **30** **30**
- Skeletal	No effect	30	>30[1]
Other			
Skeletal ossification	Retarded (dose-dependent, *at 30 mg/kg/day)	**3**	**10**
F1 Postnatal developmental effects			
Survival Rate	No effect	30	>30[1]
Altered body weight	Increase* (3 mg/kg/day); Decrease (10, 30* mg/kg/day)	<3	**3**
Physical development landmarks	No effect (pinna detachment, hair coat, incisor eruption, eye-lid opening , testes descent	30	>30[1]
Vaginal opening	Delayed (dose-dependent, *at 10 and 30 mg/kg/day)	<3	**3**
Neurobehavioral - Reflexes - Learning ability	 No effect No effect	 30 30	 >30[1] >30[1]
F1 Reproductive capacity			
A) Prenatally Treated F1 males + prenatally treated F1 females			
Fertility (% pregnant)	Decrease (20% n.s.)	10	30
F1maternal weight	Decrease (10, 30* mg/kg/day)	**3**	**10**
N corpora lutea	Decrease (10, 30* mg/kg/day)	**3**	**10**
N implants	Decrease (10, 30* mg/kg/day)	**3**	**10**
F2 pre-implantation loss	Increase (n.s.10, 30 mg/kg/day)	**3**	**10**
F2 post-implantation loss	Increase (early resorptions, 30* mg/kg/day)	10	30
F2 N live fetuses	Decrease (30* mg/kg/day)	10	30
B) F1 Male fertility test (Prenatally Treated F1 males (30 mg/kg/day)+ untreated females			
Fertility (% pregnant)	Decrease (11% n.s.)	**ND**	**30**
Maternal weight	No effect	30	>30[1]

N corpora lutea	No effect	30	>30[1]
N implants	No effect	30	>30[1]
F2 pre-implantation loss	Increase (n.s.)	**ND**	**30**
F2 post-implantation loss	No effect	30	>30[1]
F2 N live fetuses	No effect	30	>30[1]
SUMMARY			
F0 Maternal toxicity	Decreased food consumption & weight gain in pregnancy	**3**	**10**
F1Prenatal toxicity	Decreased placental weight , fetal weight, increased visceral anomalies (abnormal liver shape, diaphragmatic hernia, undescended testes)	**10**	**30**
	Retarded skeletal ossification	**3**	**10**
F1Postnatal developmental effects	Altered body weight & weight gain, Delayed vaginal opening	**<3**	**3**
F1 Reproductive capacity (prenatally treated males & females)	Decreased N corpora lutea (10, 30* mg/kg/day); Decreased N implantations (10, 30* mg/kg/day) Decreased maternal weight gain in pregnancy (10, 30* mg/kg/day)	**3**	**10**
	Decreased fertility (n.s.) Increased pre- and post-implantation loss (n.s.)	**10**	**30**
F1 Male fertility test (prenatally treated males & untreated females)	Decreased fertility (n.s.) Increased pre- and post-implantation loss (n.s.)	**ND**	**30**

*Statistically significant; n.s. = Not statistically significant; [1]LOAEL not reached (highest dose tested: 30 mg/kg/day); [2] Seen in progeny on postnatal day 4 or 6, but not in fetuses at term; NA= not applicable; ND = not determined

2.3. Study title: Supplemental teratogenicity study of OPC-14957 administered orally to rats

Key study findings: Oral exposure (by gavage) of pregnant rats to aripiprazole at a dose level of 30 mg/kg/day from day 7 to17 of gestation causes no apparent maternal toxicity, but results in a retardation in F1 postnatal physical development (consistently lower body weight of both the male and female offspring through maturity) as well as in retardation in sexual maturation of F1 females (delayed vaginal opening). F1 fertility was not impaired, but some adverse effect was seen in F1 reproductive performance, as shown by the decreased number of implantations and live fetuses, and the increased (pre-implantation) embryonic loss. These effects did not reach statistical significance.

Study No.: 011358
NDA Volume #, page #: volume 1.112, p. 1
Conducting laboratory and location: Tokushima Research Institute, Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan
Date of study initiation: September 22, 1995
GLP compliance: Yes
QA reports: Yes
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 93H80M1; [redacted]
Formulation/ vehicle: 0.6 % (w/v) suspension in 5% gum arabic/distilled water

Methods:

Species/strain: Rat, Sprague-Dawley

Doses employed: 0 (vehicle control, 5% gum arabic); 30 mg/kg/day
(The dose was set at a level that affected reproductive capacity and delayed the vaginal opening in the previous Segment II experiment).

Route of administration: Oral (by gavage)

Study design: Fo pregnant rats, treated with aripiprazole at a dose of 30 mg/kg/day from day 7 to 17 of gestation, were allowed to deliver spontaneously. The numbers of live and dead offspring, sex, and external abnormalities were determined at birth. On postnatal day 4, all litters were culled to a standard number of 8 offspring (4 per sex per group where possible). The pups weight was measured weekly until maturity (42 days of age). The female animals were observed daily for vaginal opening from postpartum day 29 onwards. At the age of 11-12 weeks, F1 males were mated with F1 (non-sibling) females within the experimental groups to assess F1 reproductive capacity. The pregnant F1 females were subjected to cesarean section on day 13 of gestation, and the numbers of corpora lutea, implantations, live fetuses, and early and late resorptions were determined. The data were analyzed statistically.

Number/sex/group: 20 pregnant Fo females per group; 20 F1 animals from each sex for F1 reproductive capacity study

Parameters and endpoints evaluated: Maternal body weight (measured but not evaluated), length of gestation, parturition, number of live and dead offspring at birth, pup weight, sex, external, abnormalities; postnatal body weight gain, vaginal opening, reproductive capacity (copulation rate, gestation rate, fertility, corpora lutea, implantations, live fetuses, early and late resorptions, pre- and post-implantation losses). The F1 dams were necropsied after the cesarean section.

Results

Parameter	Observed Effects at 30 mg/kg/day	
	Description	Effect: Present (+) Absent (-) Uncertain (±)
Fo Maternal Toxicity		
Body weight (g. d. 20)	Slight decrease (about 4%, n.s.)	(±)
Body weight gain	ND	ND
Food consumption	ND	ND
Clinical signs	ND	ND
Mortality	No effect	(-)
Duration of gestation	No effect	(-)
F1 Litter data at birth		
N implants	No effect	(-)
N live neonates	No effect	(-)
N dead neonates	No effect	(-)
Viability rate (n live neonates/n implantations)	No effect	(-)
Birth weight	Slight decrease (about 4%, for males and 2.5% for females, n.s.)	(±)
Male: female ratio	No effect	(-)
F1 Postnatal developmental effects		
Survival Rate	No effect	(-)
Altered body weight	Decrease, n.s. (on day 4 postpartum, but also present consistently, although n.s. through adulthood in both males and females)	(+)
Vaginal opening	Delayed (by postnatal day 35, vaginal opening completed in 84% of control litters and in 96% of control animals versus 58% of the treated litters and 84% of the treated animals. The difference is n.s.	(+)
F1 Reproductive capacity		
Fertility (% pregnant)	No effect	(-)
F1maternal weight	No effect	(-)
N corpora lutea	Decrease (- 6% , n.s.)	(±)
N implants	Decrease (- 14%, n.s.)	(+)
F2 pre-implantation loss	Increase (2-fold, n.s.)	(+)
F2 post-implantation loss	No effect	(-)
F2 N live fetuses	Decrease (- 15%, n.s.)	(+)
SUMMARY		
Fo Maternal toxicity	No apparent maternal toxicity (not enough data)	(±)
F1 prenatal development (Litter data at birth)	No effect	(-)
F1Postnatal development:	Decreased body weight through maturity, Delayed vaginal opening,	(+)
F1 Reproductive capacity (prenatally treated males & females)	No effect on fertility, but consistently decreased n implantations, live fetuses, and increased pre-implantation embryonic loss.	(+)

Statistically significant; n.s. = Not statistically significant; ND = not determined

Summary of findings

This supplemental Segment II teratogenicity study was conducted to determine if the decrease in reproductive capacity and the retardation of sexual maturation (vaginal opening), seen in the F1 offspring in the previous teratogenicity study (# 006939), occur reproducibly. Only one treatment dose was employed (30 mg/kg/day); this dose corresponds to the highest dose in the previous study which was associated with significant changes in the above parameters. The route of administration (gavage) and the period of exposure (gestation day 7 to 17) were identical to the previous experiment, but a different lot of the compound of slightly higher purity was used in this study. The present study (which was performed in a different year and season than the previous one) showed less maternal toxicity, and the fetal effects were also slightly lower. However, it confirmed the retardation in F1 vaginal opening, as well as the retardation in F1 physical development as demonstrated by the consistently lower body weight of both the male and female offspring through maturity. Although F1 fertility was not impaired, some adverse effect was seen in the reproductive performance of F1 generation, as shown by the decreased number of implantations and live fetuses, and the increased pre-implantation embryonic loss. These effects did not reach statistical significance.

2A. SEGMENT II: TERATOLOGY STUDIES IN RABBITS

2A.1. Study title: Preliminary study (I) to oral teratogenicity study of OPC-31 (OPC-14957) in rabbits

Key study findings: This is a dose-finding study in non-pregnant rabbits to determine the highest dose to be used in the teratogenicity study. Oral administration of aripiprazole at doses of 10, 30 and 60 mg/kg/day to adult female New Zealand White rabbits for a period of 13 days caused a marked but transitory decrease in food consumption at the highest dose level, and no other signs of toxicity. General condition, mortality, body weight, and pathological examination showed no treatment-related abnormalities.
LOAEL for female adult toxicity: 60 mg/kg/day

Study No.: M-68P I
NDA Volume #, page #: 1.112, p. 88
Conducting laboratory and location: [redacted]
Date of study initiation: July 8, 1989
GLP compliance: Yes
QA reports: Yes
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 8K84M: [redacted]
Formulation/ vehicle: suspension in 5% gum arabic/distilled water

Methods:
Species/strain: KBL New Zealand White rabbits (SPF)

Doses employed: 0 (vehicle control), 10, 30, and 60 mg/kg/day
(Individual dosage volumes adjusted on the basis of body weight at a rate of 5 ml/kg)

Route of administration: Oral (by gavage)

Study design: This is a preliminary, dose-finding study on non-pregnant adult female rabbits (5 weeks of age), that was designed to determine the high dose for the scheduled Segment 2 teratogenicity study in the same species and strain. Three dose levels were employed. The highest dose was presumed to affect food consumption on the basis of a previous single oral administration study in the same species. The route (gavage) and duration of administration (13 days) were identical with those planned in the scheduled main study. The animals were observed daily during treatment, and necropsied one day after the last administration.

Number/group: 4 animals

Parameters and endpoints evaluated: General condition, body weight, food consumption, clinical signs, mortality, gross pathology.

Results:

Study No.M-68P I. P̃reliminary study (I) to oral teratogenicity study of OPC-31 (OPC-14957) in rabbits

Parameter	Observed Effect	NOAEL *(mg/kg/day)*	LOAEL *(mg/kg/day)*
Body weight	No effect	60	>60[1]
Food consumption	Decrease, transient (*on day 2 of treatment)	**30**	**60**
Clinical signs	No effect	60	>60[1]
Gross pathology	No effect	60	>60[1]
Mortality	No drug-related effect[2]	60	>60[1]

* Statistically significant
[1]Highest tested dose
[2] One animal from the 10 mg/kg group died because of mishandling of catheter insertion, confirmed by necropsy.

2A.2. Study title: Preliminary study (II) to oral teratogenicity study of OPC-31 (OPC-14957) in rabbits

Key study findings: This is a dose-finding study in pregnant rabbits to determine the highest dose to be used in the teratogenicity study. Oral administration of aripiprazole at doses of 10, 30 and 100 mg/kg/day to pregnant New Zealand white rabbits during the period of organogenesis (days 6-18 of gestation) caused a marked, dose-dependent decrease in maternal food consumption at 30 mg/kg/day (g. day 22) and 100 mg/kg/day (throughout gestation, statistically significant at the beginning of treatment (g. day 7, 8) and at late gestation (g. day 22). However, maternal body weight was not affected, except for a slight and non-significant decrease at the highest exposure during the 2nd and 3rd week of gestation. General condition and mortality showed no treatment-related effects, but, on gross examination, liver atrophy and yellowish discoloration of the liver were found in 1 animal each at the highest dose (liver discoloration was also observed in one control animal). Signs of fetal toxicity are seen at maternally toxic dose: an entire litter from the highest dose group was aborted in late gestation (day 21). No other cases of embryo/fetal death were seen in the test groups, neither any significant differences in fetal and placental weight and sex ratio. Congenital anomalies were found in 1 fetus from the 30 mg/kg/day group (spina bifida); 2 fetuses from the 100 mg/ kg/day group (ventricular septal defect; pulmonary atresia); and 3 fetuses from the control group (retrocaval ureter). Because these anomalies are sporadic, not dose-dependent, and do not show a consistent pattern, they are most likely spontaneous.
LOAEL for maternal toxicity: 30 mg/kg/day (in view of decreased food consumption); LOAEL for fetal toxicity: 100 mg/kg/day (in view of spontaneous abortion)

Study No.: M-68P II
NDA Volume #, page #: 1.112, p. 129
Conducting laboratory and location: [redacted]
Date of study initiation: August 25, 1989
GLP compliance: Yes
QA reports: Yes
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 8K84M; [redacted]
Formulation/ vehicle: suspension in 5% gum arabic/distilled water
Methods:
Species/strain: KBL New Zealand White rabbits (SPF)

Doses employed: 0 (vehicle control), 10, 30, and 100 mg/kg/day
(Individual dosage volumes adjusted on the basis of body weight at a rate of 5 ml/kg)
Route of administration: Oral (by gavage)

Study design: This is a preliminary, dose-finding study on pregnant rabbits, that was designed to determine the high dose for the scheduled Segment 2 teratogenicity study in the same species and strain. Three dose levels were employed. The highest dose was set at a level higher than the one used in the preceding study in non-pregnant females (60 mg/kg/day, a dose that had caused a transient decrease in food consumption), in order to produce a definite decrease in this parameter. The route (by gavage) and period of administration (g.day 6-17) were identical with those planned in the scheduled main study. The animals were observed daily during treatment, and subjected to caesarean and necropsied on gestation day 28.
Number/group: 7

Parameters and endpoints evaluated: Maternal general condition, body weight, food consumption, clinical signs, mortality, gross pathology, corpora lutea, implantations, embryo/fetal death, placental and fetal weight, fetal external and visceral anomalies, gender.

Results:

Study # M-68P II: Preliminary study (II) to oral teratogenicity study of OPC-14957 in rabbits

Parameter	Observed Effect	NOAEL *(mg/kg/day)*	LOAEL *(mg/kg/day)*
Maternal Toxicity			
Body weight	Slight decrease, n.s.	**30**	**100**
Food consumption	Decrease * (dose-dependent)	**10**	**30**
Clinical signs	No effect	100	>100[1]
Gross pathology	- Liver atrophy (1 animal at 100 mg/kg/day)	**30**	**100**
	- Yellow discoloration of liver (1 control animal & 1 animal at 100 mg/kg/day)	.	.
Mortality	No drug-related effect[2]	100	>100[1]
Prenatal developmental toxicity			
Pre-implantation loss	NA (treatment started after implantation)	.	.
Fetal death	One complete litter aborted at 100 mg/kg/day[3]	**30**	**100**
Fetal weight	No effect	100	>100[1]
Placental weight	Slight decrease, n.s. (males) at 100 mg/kg/day	30	100
Fetal sex ratio	No effect	100	>100[1]
Abnormalities			
- External	No effect (1 spina bifida at 30 mg/kg/day)	100	>100[1]
- Visceral	No effect (1 cardiovascular & 1 pulmonary at 100 mg/kg/day; 3 ureteral in control)	100	>100[1]
- Skeletal	ND	.	.
SUMMARY			
Maternal Toxicity		**10**	**30**
Food consumption	Decrease * (dose-dependent)	10	30
Gross pathology	Liver atrophy (?) (1 animal at 100 mg/kg/day)	30	100
Fetal Toxicity		**30**	**100**
Fetal death	Abortion, 1 of 8 litters, 100 mg/kg/day[3]	30	100
Placental weight	Slight decrease (?), n.s. (males), 100 mg/kg/day	30	100

* Statistically significant
[1]Highest tested dose
[2] One animal from the 10 mg/kg group died because of mishandling of catheter insertion, confirmed by necropsy.
[3] This litter was not included in the calculations of fetal lethality
NA= not applicable; ND= no data

2A. 3. Study title: Teratological study of OPC-31 administered orally to rabbits

Key study findings: Oral administration of aripiprazole at doses of 10, 30 and 100 mg/kg/day to pregnant New Zealand white rabbits during the period of organogenesis (days 6-18 of gestation) caused: 1. A significant, dose-dependent decrease in maternal food consumption at all dose levels and a tendency to a decrease in maternal body weight at the highest dose; 2. A significant increase in embryo/fetal mortality, and a marked rise in spontaneous abortions rate at 100 mg/kg/day (7 of 18 dams aborted their entire litters in late pregnancy); 3. Placental weight decrease, significant at the highest dose; 4. Fetal weight decrease at 30 mg/kg/day (males only) and 100 mg/kg/day (significant in both males and females); 5. Dose-dependent increase in both skeletal variations and skeletal abnormalities (fused sternebrae). The latter were significantly increased at the highest dose (involving 30% of fetuses and 60% of the litters examined), but were also present in the 30 and 10 mg/kg/day groups at rates of 3% and <1% of fetuses, respectively. Although such anomalies are reported to occur spontaneously (literature data), none were found in the control group. Their dose-dependence and high incidence support their relationship to treatment.

Sporadic visceral anomalies were found in the lowest and highest dose group (aberrant subclavian artery in one fetus at 10 mg/kg/day, and ventricular septal defect in combination with aortic stenosis in another fetus at 100 mg/kg/day). Because these anomalies were seen in single fetuses, were not dose-dependent, and known to occur spontaneously in the rabbit, they are considered not treatment-related.

Based on these findings, the maximum no-effect doses with repeated oral administration during organogenesis were estimated to be less than 10 mg/kg/day in the general toxicological effect in the dams, and 10 mg/kg/day in the embryo/fetal development. LOAEL for maternal toxicity: 10 mg/kg/day (in view of decreased food consumption); LOAEL for fetal toxicity: 30 mg/kg/day (in view of fetal weight decrease and skeletal anomalies).

Study No.: M-68; **NDA Volume #, page #:** 1.112, p. 194
Conducting laboratory and location: [redacted]
Date of study initiation: December 28, 1989
GLP compliance: Yes; **QA reports:** Yes
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 8K89M: [redacted]
Formulation/ vehicle: suspension in 5% gum arabic/distilled water
Methods:
Species/strain: KBL New Zealand White rabbits (SPF)
Doses employed: 0 (vehicle control), 10, 30, and 100 mg/kg/day
(Individual dosage volumes adjusted on the basis of body weight at a rate of 5 ml/kg)
Route of administration: Oral (by gavage)

Study design: This is a Segment 2 teratogenicity study to determine maternal and embryofetal effects of aripiprazole in the rabbit upon repeated oral administration during the period of major organogenesis (g. day 6–18, copulation day designated as day 0). Three dose levels were employed, administered by a route corresponding to the intended route in humans. The highest dose was set at a level shown in a preliminary study to produce signs of maternal toxicity (a decrease in maternal food consumption). The animals were observed daily during treatment, and subjected to caesarean on gestation day 28. Fetuses were removed for observation, and dams were examined pathomorphologically. Animals that died or aborted during the study were promptly necropsied and abnormal organs preserved in formalin fixative.
Number dams/group: 16 - 18

Parameters and endpoints evaluated: Maternal general condition, body weight, food consumption, clinical signs, mortality, gross pathology, corpora lutea, implantations, embryo/fetal death, placental and fetal weight of live fetuses, fetal external, visceral and skeletal anomalies, gender.

Results:

Study # M-68 Teratological study of OPC-31 administered orally to rabbits

Parameter	Observed Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
Maternal Toxicity			
Body weight	Slight decrease, n.s.	**30**	**100**
Food consumption	Marked decrease * (dose-dependent)	**<10**	**10**
Clinical signs	Abortion spontaneous*	**30**	**100**
Gross pathology	No effect[1]	100	>100†
Mortality	No effect[2]	100	>100†
Prenatal developmental toxicity			
Pre-implantation loss	NA (treatment started after implantation)	.	.
Fetal death	Increase (*at 100 mg/kg/day, and n.s. at 10 & 30 mg/kg/day) (1 of 16 litters aborted at 10 mg/kg/day[3] and 7 of 18 litters aborted at 100 mg/kg/day[3])	**10**	**30**
Fetal weight	Decrease * (dose-dependent)	**10**	**30**
Placental weight	Decrease (*at 100 mg/kg/day, and n.s. at 10 & 30 mg/kg/day)	**30**	**100**
Fetal sex ratio	No effect	100	>100†
Abnormalities			
- External	No effect	100	>100†
- Visceral	No effect (1 cardiovascular at 100 mg/kg/day; 1 vascular variation in control)	100	>100†
- Skeletal anomalies	Increased rates of sternebral fusion (30% of fetuses and 60% of litters at 100 mg/kg/day*, and 3% of fetuses and 24% of litters at 30 mg/kg/day, ns) versus 0 in control	**10**	**30**
- Skeletal variations	Increased rates of extra or rudimentary ribs and extra thoracic & lumbar vertebrae (*at 100 mg/kg/day, and n.s. at 30 mg/kg/day)	**10**	**30**
SUMMARY			
Maternal Toxicity		**<10**	**10**
Food consumption	Marked decrease * (dose-dependent)	<10	10
Clinical signs	Abortion spontaneous*	30	100
Body weight	Slight decrease, n.s.	30	100
Fetal Toxicity		**10**	**30**
Fetal weight	Decrease * (dose-dependent)	10	30
Fetal death	Increase (*at 100 mg/kg/day, and n.s. at 10 & 30 mg/kg/day)	10	30
Skeletal anomalies	Increased (*at 100 mg/kg/day, and n.s. at 30 mg/kg/day)	10	30
Placental weight	Decrease (*at 100 mg/kg/day)	30	100

* Statistically significant; n.s. = non-significant

† Highest dose tested

[1]Sporadic, no dose-dependent gross pathology: Cyst in fallopian tubes (1animal at low & high dose; 2 animals at mid dose); Yellow discoloration of liver (control, low dose & mid dose: 1 animal each ; 2 animals at 100 mg/kg/day)

[2] One animal of 10 mg/kg group died after spontaneous abortion on day 26 of pregnancy; no deaths in mid- and high dose groups.

[3] These litters were not included in the calculations of fetal lethality

NA= not applicable; ND= no data

3. SEGMENT III: PERI-/ POSTNATAL STUDIES IN RATS

3.1. Study title: Preliminary perinatal and postnatal study of OPC-14597 administered orally to rats

Key study findings: Aripiprazole (OPC-14957) administered by gavage to female rats in the perinatal and postnatal periods (gestation day 17 – post-parturition day 21) at dose levels of 1, 3, 10, and 20 mg/kg/day, caused signs of maternal general toxicity (ptosis and sedation) at 10 mg/kg or higher, but no notable effect on body weight or food consumption. No notable effects on parturition, lactation, or offspring were observed. A slight delay in the completion of vaginal opening in the female generation was seen at the highest dose (100% completed on postnatal day 42 versus day 38 in control), but not statistically significant. LOAEL for maternal toxicity = 10 mg/kg/day; LOAEL for effect on progeny: 20 mg/kg/day (?).

Study No.: 008316
NDA Volume #, page #: 1.113, p. 55
Conducting laboratory and location: Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan
Date of study initiation: October 12, 1992
GLP compliance: No data
QA reports: Not attached
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 1E79M; [redacted]
Formulation/ vehicle: suspension in 5% gum arabic/distilled water

Methods:
Species/strain: Rat, Sprague-Dawley
Doses employed: 0 (vehicle control, 5% gum arabic), 1, 3, 10, and 20 mg/kg/day
(Individual dosage volumes adjusted at a rate of 5 ml/kg)
The highest dose was expected to cause a decrease in maternal body weight and food consumption based on the results previously obtained in study No 006939 (Teratogenicity study of OPC-14597 administered orally to rats)

Route of administration: Oral (by gavage)

Study design: Pregnant female rats (10 weeks old at the start of the mating) were treated with aripiprazole perinatally and postnatally (from gestation day 17 to post-parturition day 21). The animals were allowed to deliver spontaneously and nurse the progeny up to postnatal day 21. On postnatal day 4, the litters were culled to a standard number of 8 (4 per sex where possible). Maternal animals were sacrificed on p.n. day 22 and necropsied after the number of implantation scars was counted; the progeny was examined at birth and at weekly intervals until day 35 of life (for body weight) and daily from day 28 for sexual maturation (until opening of vagina and onset of estrus cycle was confirmed). The results were statistically analyzed.

Number/sex/group: 10 females per group

Parameters and endpoints evaluated: Maternal general condition, body weight, food consumption, parturition and nursing, live and dead newborns, pup body weight, external abnormalities, postnatal

physical development of progeny (body weight gain), and sexual maturation of female offspring (day of positive result for vaginal opening and first estrus day as determined by vaginal smears).

Results

Parameter	Observed Effect	NOAEL *(mg/kg/day)*	LOAEL *(mg/kg/day)*
Maternal (F_0) Effects			
Body weight gain	Slight decrease during the1st week post-partum (n.s.);	**10**	**20**
	Increase in the 2nd and particularly 3rd week postpartum (marked –x 2, but n.s.)	**1**	**3**
Food consumption	Slight decrease during the first week after delivery at the highest dose (n.s.)	**10**	**20**
Clinical signs	Yes (Ptosis in 30% at 10 mg/kg and 100% at 20 mg/kg and sedation in 90% of the animals at 10 and 20 mg/kg/day)	**3**	**10**
Mortality	No effect	20	>20[1]
Duration of gestation	No effect	20	>20[1]
Necropsy	No drug-related findings		
F1 Developmental effects			
External anomalies at birth	No effect	20	>20[1]
Sex ratio	No effect (2x decrease* in M:F ratio at 10 mg/kg, but no change at the highest dose)	20	>20[1]
Survival Rate	No effect	20	>20[1]
Altered body weight	No effect	20	>20[1]
Vaginal opening	Slight delay (n.s.) in the age of attainment in 100% of female offspring: day 42 of life at the highest dose vs. d. 38 in control	**10**	**20**
Onset of estrus cycle	No effect	20	>20[1]
SUMMARY			
F0 Maternal effects	Slight decrease in food consumption & weight gain in the 1st week post partum, n.s.	**10**	**20**
	Clinical signs	**3**	**10**
F1 developmental effects	Slight delay in vaginal opening, n.s.	**10**	**20**

[1]Not reached (maximal dose + 20 mg/kg/day); * statistically significant; n.s. = not statistically significant

3.2. Study title: Preliminary perinatal and postnatal study of OPC-14597 administered orally to rats (II)

Key study findings: Aripiprazole (OPC-14957) administered by gavage to pregnant rats in the perinatal and postnatal periods (gestation day 17 – post-parturition day 21) at a dose level of 30 mg/kg/day, causes significant changes in maternal general condition: inhibition of body weight gain and food consumption, clinical signs (ptosis, sedation), and prolongation of gestation, as well as abnormalities in parturition (unsuccessful and/ or prolonged delivery). Adverse effects on the offspring (increased stillbirths, decreased postnatal survival, and inhibition of body weight) are observed. No significant differences in sexual maturation of female offspring (completion of vaginal opening), or in reproductive capacity of the progeny were found. It is concluded that at a dose level of 30 mg/kg/day, applied peri/postnatally, aripiprazole is toxic to the mother, fetus and the neonate, but does not appear to affect the reproductive capacity of the progeny. However, it should be taken into account that, because of excessive perinatal mortality (e.g., 100% stillbirths in 4 of the 10 dosed F0 maternal animals), the number of F1 offspring available for evaluation of vaginal opening and reproduction was much smaller in the treated group (13 F1 females from 5 litters) in comparison to control (39 from 10 litters); this number is insufficient to allow a definitive conclusion applicable to the entire F1 progeny in the 30 mg/kg group .

Study No.: 009491
NDA Volume #, page #: 1.114, p. 1
Conducting laboratory and location: Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan
Date of study initiation: August 25, 1993
GLP compliance: No data
QA reports: Not attached
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 93H80M1 [redacted]
Formulation/ vehicle: suspension in 5% gum arabic/distilled water

Methods:
Species/strain: Rat, Sprague-Dawley
Doses employed: 30 mg/kg/day
The selected dose was expected to inhibit maternal body weight and food consumption based on the results previously obtained in the Teratogenicity study of OPC-14597.
Route of administration: Oral (by gavage)

Study design: Pregnant female rats (12 weeks old at the start of the mating) were treated with aripiprazole perinatally and postnatally (from gestation day 17 to post-parturition day 21). The animals were allowed to deliver spontaneously and nurse the progeny up to postnatal day 21. On postnatal day 4, the litters were culled to a standard number of 8 (4 per sex where possible). Maternal animals were sacrificed on p.n. day 22 and necropsied after the number of implantation scars was counted; the progeny was examined at birth and at weekly intervals until day 75 of life (for body weight) and daily from day 28 until opening of vagina was confirmed in the females. Reproductive performance of the progeny was examined at the age of 12 weeks, when F1 males and females were paired to produce F2 generation. Cesarean section was performed at end gestation (day 20), and indices of prenatal development of F2 were measured. The results were statistically analyzed.
Number/sex/group: 10 maternal F0 animals per group and 20 F1 animals per sex per group for the F1 reproduction study (Note: The latter number was smaller (12 females and 13 males) in the dosed group because less F1 animals were available due to the reduced F1 survival).

Parameters and endpoints evaluated: Maternal general condition, body weight, food consumption, parturition and nursing, live and dead newborns, pup body weight, external abnormalities, postnatal physical development of progeny (body weight gain), and sexual maturation of female offspring (day of

positive result for vaginal opening), F1 fertility, presence of sperm in the epididymis of non-fertile or non-copulated males, gestation, corpora lutea, placental weight, F2 pre- and post-implantation lethality, external abnormalities.

Results

Parameter	Observed Effects at 30 mg/kg/day	
	Description	Effect: Present (+) Absent (-) Uncertain (±)
Maternal (F_0) Effects		
Body weight gain	Decrease •	(+)
Food consumption	Decrease •	(+)
Clinical signs	Yes (Ptosis and sedation in 30% of the animals at 30 mg/kg/day)	(+)
Mortality	1 moribund animal sacrificed on postpartum day 2	(±)
Duration of gestation	Prolonged*	(+)
Delivery	Unsuccessful labor and delivery (40% of animals)	(+)
Necropsy	Performed on 4 animals that delivered dead neonates: Maternal emaciation, enlarged adrenals, dark spots on gastric mucosa, dead fetuses retained in the uterus.	(+)
F1 Developmental effects		
Fetal death	Increase, marked*	(+)
Liveborn rate	Decrease •	(+)
External anomalies at birth	No effect (Note: determined only in the liveborn pups)	(-)
Sex ratio	Effect unknown - gender not determined in dead offspring (out of a total of 133 neonates at 30 mg/kg, 53 dead)	(?)
Survival Rate (postnatal)	Decrease, marked • (3-fold, p.n. day 4)	(+)
Altered body weight	Decrease* postnatally	(+)
Vaginal opening	No effect (?) Note: Insufficient number observations (only 13 surviving F1 females examined at 30 mg/kg)	(?)
Onset of estrus cycle	No effect (?) Note: (as above)	(?)
F1 Reproductive capacity		
Fertility	No effect	(-)
Maternal weight gain in pregnancy	No effect	(-)
N Corpora Lutea	No effect	(-)
F2 Embryo/fetal death	No effect	(-)
F2 Fetal weight	No effect	(-)
F2 External anomalies	No effect	(-)
Placental weight	No effect	(-)
SUMMARY		
F0 maternal toxicity	Marked	(+)
F1 developmental tox.	Marked: ↑fetal death, ↓weight, ↓postnatal survival	(+)
F1 reproductive capacity	No effect	(-)

* Statistically significant

3.3. Study title: Perinatal and postnatal study of OPC-14597 administered orally to rats

Key study findings: Aripiprazole (OPC-14957) administered by gavage to pregnant rats in the perinatal and postnatal periods (gestation day 17 – post-parturition day 21) at dose levels of 0, 3, 10, and 30 mg/kg/day, causes maternal toxicity at the highest dose level (continuously suppressed food consumption from gestation day 18 through post partum day 21, and decreased body weight at end pregnancy), slightly but significantly prolonged gestation and increased stillbirths. Post-partum deviations in the maternal "nursing behavior", qualitatively described by the sponsor as "incomplete post-partal care" and "poor lactation" occur in 16% (4/25) of the high-dose dams, resulting in decreased survival of the progeny in the early postnatal period (e.g. death of the entire litters of 2 dams within the first 4 days after birth). The same dose level results in significant adverse effects in the offspring (increased fetal death, decreased postnatal survival, and inhibition of body weight through adolescence). However, the surviving progeny show no significant differences in physical development, learning ability, and reproductive performance except for lower F1 maternal body weight at the highest dose. The slight delay in some developmental landmarks seen in F1 at the highest dose is most likely a consequence of the lower F1 body weight. The maximal no adverse effect level (NOAEL) is 10 mg/kg/day for both mothers and offspring.

Study No.: 010337
NDA Volume #, page #: 1.114, p. 113
Conducting laboratory and location: Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan
Date of study initiation: August 30, 1994
GLP compliance: Yes
QA reports: Yes
Drug, lot #, % purity: OPC-14597 (Aripiprazole), lot No. 93H80M1: [redacted]
Formulation/ vehicle: suspension in 5% gum arabic/distilled water
Methods:
Species/strain: Rat, Sprague-Dawley
Doses employed: 0, 3, 10, and 30 mg/kg/day
The highest dose was shown to inhibit maternal body weight and food consumption in a preliminary study of a similar timing and duration of exposure (# 009491).
Route of administration: Oral, gavage (corresponds to the clinically intended route)
Study design: Pregnant female rats (10 weeks old at the start of mating) were treated with aripiprazole peri- and postnatally (from gestation day 17 to post-parturition day 21). The animals were allowed to deliver spontaneously and nurse the progeny up to postnatal day 21. Animals in which parturition did not occur by day 26 of gestation were sacrificed on that day. On postnatal day 4, the litters were culled to a standard number of 8 (4 per sex where possible). Maternal animals were sacrificed on p.n. day 22; the number of implantation sites was counted. The progeny was examined at birth and at weekly intervals until day 42 of life (for body weight). F1 offspring were necropsied at the age of 6 weeks, except for those used in learning and reproduction tests. F1 reproductive performance was examined at the age of 11-13 weeks, when F1 males and (non-sibling) females were paired to produce F2 generation. Cesarean section was performed on F1 pregnant females at end gestation (day 20), and indices of F2 prenatal development were measured. The results were statistically analyzed.
Number/sex/group: 25 maternal F0 animals per group and 20 F1 animals per sex per group for the F1 reproduction study.
Parameters and endpoints evaluated: F0 maternal general condition, body weight, food consumption, observations on the "course of parturition" and qualitative description of maternal "nursing behavior" and "post-partal care", as well as the number of live and dead newborns, pup body weight, external abnormalities, F1 postnatal physical development (weight, developmental milestones), neurobehavioral development (reflex function, learning (males); sexual maturation and reproductive performance; F1 maternal weight and food consumption during gestation, N corpora lutea, placental weight, and F2 pre-