CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-866

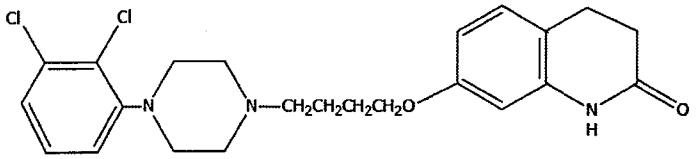
PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: **21-866**
Review number: 1
Sequence number/date/type of submission: N000/11.29.2005/ Original application
Information to sponsor: No
Sponsor and/or agent: Otsuka Pharmaceutical Co., Ltd.
Second Tokushima Factory 224-18, Hiraishi Ebisuno, Kawauchi-cho
Tokushima-shi, Tokushima 771-0182, Japan
Manufacturer for drug substance:
Otsuka Pharmaceutical Co., Ltd.
Reviewer name: Sonia Tabacova.
Division name: Psychiatric Drug Products
Review completion date: September 6, 2006

Drug:

Trade name: ABILIFY®
Generic name: Aripiprazole
Code name: OPC-14597, OPC-31, BMS-337039-01
Chemical name: *7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone*
CAS registry number: 129722-12-9
Molecular formula/molecular weight: $C_{23}H_{27}Cl_2N_3O_2$/ 448.38
Structure:



Aripiprazole

Relevant INDs/NDAs/DMFs: IND 60-158 (Aripiprazole i.m), IND 42-776; NDA 21-436 (ABILIFY Tablets); NDA 21-713; DMF [redacted]

Drug class: Psychotropic (partial D_2 and $5HT_{1A}$ agonist, $5HT_2$ antagonist)

Indication: Treatment of agitation in schizophrenia and bipolar mania patients

Clinical formulation: Injection drug product for intramuscular (IM) use, a sterile ready-to-use solution formulated to deliver 7.5 mg/mL of aripiprazole. The drug substance (aripiprazole anhydrous) is the same as that used in aripiprazole oral tablets approved in the USA in the treatment of schizophrenia.

Route of administration: Intramuscular

Proposed use: Prescription product

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: Approvable

B. Recommendation for Nonclinical Studies: None

C. Recommendations on Labeling:

Under subtitle "Pregnancy":

In pregnant rats receiving aripiprazole injection intravenously (3, 9, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose, which also caused some maternal toxicity.

In pregnant rabbits receiving aripiprazole injection intravenously (3, 10, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The no-effect dose was 10 mg/kg, which produced 15 times the human exposure at the MRHD based on AUC, and is 6 times the MRHD based on mg/m^2.

In rats receiving aripiprazole injection intravenously (3, 8, and 20 mg/kg/day) from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8 and 20 mg/kg, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg, but there were no effects on postnatal behavioral and reproductive development. These doses produced some maternal toxicity. The no-effect dose was 3 mg/kg which produced plasma exposure equal to the human exposure at the MRHD based on AUC.

II. Summary of Nonclinical Findings

An abbreviated nonclinical testing strategy for IM aripiprazole was employed by the sponsor since it was supported, in part, by results from previous in vitro and in vivo nonclinical studies conducted to support the aripiprazole oral tablet that characterized the pharmacology and safety pharmacology, oral pharmacokinetics and metabolism, genetic toxicity, oral toxicity including carcinogenicity, and oral toxicokinetics. The studies that were conducted with the IM aripiprazole formulation assessed its PK/TK, repeat-dose toxicity, reproductive and developmental toxicity and local irritation potential. This testing strategy was approved by the Division (6/9/2004, Pre-NDA Meeting Minutes). Toxicologic evaluation of the excipient Captisol® is not included in this application since Captisol® has been used in 2 approved marketed products, Geodon® (ziprasidone hydrochloride) and Vfend®IV (voriconazole) for Injection, and is considered not to be a novel excipient.

A. Brief Overview of Nonclinical Findings:

PK/TK:

Absorption of aripiprazole from the injection site upon IM administration in rats, dogs, and monkeys was rapid (Cmax for aripiprazole following a single intramuscular dose was observed at approximately 10 min in dogs and monkeys, and 15 min in rats) and extensive (the absolute

bioavailability of aripiprazole following a single IM dose was 99.5% in dogs and about 87% in monkeys, indicating essentially complete absorption of aripiprazole from the injection site, as compared to a much lower bioavailability (12% in dogs) upon oral administration of the same dose; the bioavailability in rats "could not be calculated due to loss of the data resulting from bioanalytical discrepancies".

Specific studies to examine the distribution, metabolism, and excretion of aripiprazole following IM administration have not been conducted by the sponsor. Aripiprazole metabolites upon IM and/or IV administration of aripiprazole were determined in PK or TK studies in rats, rabbits, dogs, and monkeys. The metabolites identified after IM administration were the same as those identified after IV and oral administration. The available data suggest that the metabolism of aripiprazole is qualitatively similar across the tested species (rats, rabbits, dogs, and monkeys) and humans.

The systemic exposure to aripiprazole and the active metabolite (as assessed by Cmax and AUC values upon repeat IM or IV administration of the IM formulation in 1-month toxicity studies in monkeys and rats) increased in a dose-related manner. Accumulation of systemic exposures to aripiprazole and its active metabolite was observed in rats and monkeys after 1 month of repeated daily administration of aripiprazole by IV (rats) or IM (monkeys) injection as compared to day 1. The accumulation was much more pronounced in rats. There were no apparent sex-related exposure differences in the tested animal species.

Toxicology:

The toxicity studies conducted with IM aripiprazole included: 2-week and 1-month repeat-dose toxicity studies in rats and monkeys, studies of embryo-fetal development in rats and rabbits, a study of pre- and postnatal development in rats, a single-dose IM irritation study in rats and rabbits, and a 2-week IM irritation study in rats. These studies are reviewed for the present application. Additional range-finding studies in pregnant rats and rabbits were conducted as a basis for dose selection for the definitive embryo-fetal development studies.

Genotoxicity, carcinogenicity, and reproductive (fertility) studies for IM aripiprazole were not performed by the sponsor. These toxicological studies [namely, genetic toxicity studies, carcinogenicity studies in mice and rats, fertility and early embryonic development upon oral administration in rats and rabbits, as well as some special toxicology studies (ocular and dermal irritation studies in rabbits, an immunotoxicity study in rats, studies of serum prolactin in mice and rats, an in vitro phototoxicity study, and investigational studies on the mechanism of the adrenocortical tumorigenic response in female rats] had been previously performed and reviewed in conjunction with the approval of aripiprazole oral tablet formulation (NDA 21-436).

General toxicology: The definitive general toxicology studies are the 1-month repeat-dose toxicity studies in rats (employing the IV route in order to achieve sufficient systemic exposures) and monkeys (IM administration). The dose selection for these studies was based on preliminary 2-week range-finding studies in the same species/strain by the same route of administration as that to be used in the corresponding main study.

The repeat-dose IV daily administration of IM aripiprazole formulation at doses of 3, 10, and 30 mg/kg/day for 1 month to rats (10/sex/group) resulted in pharmacologically-related clinical signs (dose-related decreased activity) at all doses, and morphologic changes in the adrenals at HD and in female reproductive and mammary tissues at all doses. In the females, the morphologic changes included (at all doses): decrease in the total number of corpora lutea in the ovary with increased proportion of large corpora lutea, dose-related persistent diestrus with excessive vaginal mucification and mildly decreased uterine weights, and hyperplasia of mammary glandular tissue. In the males, atrophy of mammary glandular tissue was observed at all doses. Adrenal gland weights were increased at the HD (30 mg/kg/day) in both sexes, in correlation

with the microscopic finding of hypertrophy of the zona fasciculata in the adrenal cortex (F). There was no direct target organ toxicity at any dose level; the observed changes were a likely manifestation of exaggerated pharmacological effect. A NOEL was not reached, but aripiprazole was well tolerated at 3 mg/kg/day. Systemic exposures to aripiprazole at 3 mg/kg/day were 7 to 8 times (Cmax) and 0.5 to 0.6 times (AUC) human exposures at the MRHD of 30 mg IM. Systemic exposures to aripiprazole at 10 and 30 mg/kg/day were 18 to 51 times based on Cmax and 2 to 15 times based on AUC human exposures at the MRHD.

The repeat-dose IM administration of aripiprazole to monkeys (5/sex/dose) at daily doses of 2, 4, 7.5 mg/kg/day (and a vehicle control group) for 1 month resulted in the following effects at all doses: pharmacologically mediated CNS clinical signs (decreased activity and tremors), decreased food consumption during the dosing period (22-28% lower than control at 2 mg/kg/day, and 51-59% lower than control at 4 and 7.5 mg/kg/day), and increased frequency of scabbing and reversible muscle injury in injection sites. The daily injection volumes were 0.26, 0.53, and 1 ml/kg, for LD, MD and HD, respectively, and 1 ml/kg for control, but not exceeding 1.5 ml at a time to any one injection site; the injection sites were alternated daily between the right and left posterior thigh muscles. Microscopically, injection site changes observed in Captisol (vehicle) control group were slight and less pronounced than the injection site changes at 2, 4, and 7.5 mg/kg/day, suggestive of a drug-related effect. Injection site changes attributed to aripiprazole included increased incidence and/or severity of skeletal muscle necrosis (minimal to mild), degeneration (mild to moderate), and regeneration (mild to moderate) at all doses; increased severity of subacute inflammation (mild) at 4 and 7.5 mg/kg/day; and increased incidence and severity of fibroplasia/fibrosis (minimal to mild) at 7.5 mg/kg/day. Drug-related clinical chemistry changes at 4 and 7.5 mg/kg/day included slightly decreased serum GGT in males, and increased serum AST (means approximately 2x the control mean values in MDF and HDF, and approximately 3 times the control in one male HD animal). The increases in serum AST observed at MD and HD (4 and 7.5 mg/kg/day) were likely a consequence of the skeletal muscle injury at injection sites. Systemic exposures to aripiprazole and BMS-337044 were dose-proportional with no apparent sex-related differences. There was no appreciable accumulation after 1 month of dosing. Following a 1-month post-dose recovery period, all aripiprazole-related clinical pathology changes were reversible.

NOAEL: Not reached (<2 mg/kg/day). At the lowest tested IM dose of 2 mg/kg/day, plasma AUC exposures for aripiprazole and its active metabolite, dehydroaripiprazole, were 1x and 6x, respectively, the human AUC exposures at MRHD (30 mg IM aripiprazole).

Reproductive and developmental toxicology

The IV route of administration of aripiprazole IM formulation was used in the reproductive and developmental toxicity studies to ensure that multiples of clinically relevant systemic exposures to aripiprazole were achieved. Embryo-fetal development studies were conducted in rats and rabbits with IM aripiprazole administered intravenously from implantation to closure of the hard palate to detect potential adverse effects on the pregnant female and on development of the embryo and fetus. In addition, an IV study of pre- and postnatal development in rats was conducted to evaluate the potential adverse effects of IM aripiprazole on gestation, parturition, lactation, and maternal behavior and on the development and reproductive function of F_1-generation offspring. In this study, drug administration to F_0-generation females was from implantation through lactation and weaning. Other aspects of reproductive and developmental toxicity (fertility and early embryonic development) had been previously studied and reviewed in conjunction with the approval of aripiprazole oral tablet formulation. Fertility studies were not repeated with IM aripiprazole because of, as stated by the sponsor, the recommended short

duration of use for this product, lack of effect on fertility upon oral aripiprazole administration in rats, and assessment of reproductive organ endpoints in the 1-month IV toxicity study in rats.

Effect on Embryo-Fetal Development

Rats: IM aripiprazole administered intravenously to pregnant rats on gestation days 6 through 15 at doses of 3, 9, or 27 mg/kg, produced dose-dependent maternal clinical signs related to exaggerated pharmacologic activity (ptosis, lacrimation, decreased motor activity) at all doses, and maternal toxicity at 9 and 27 mg/kg/day (demonstrated by dose-dependent decrease in body weight gain and food consumption). Drug-related effects in the fetuses (growth retardation, characterized by reductions in fetal body weight with associated decreases in ossification) occurred only at 27 mg/kg/day. Thus, in the rat, aripiprazole affected fetal development (causing intrauterine growth retardation) at a dose level that also caused maternal toxicity.

Rabbits: IM aripiprazole formulation, administered intravenously at doses of 3, 10, or 30 mg/kg to pregnant rabbits once daily on gestation days 7 through 19, caused maternal toxicity at all dose levels (manifested as clinical signs, weight and/or weight gain reduction, and decreased food consumption) at all tested doses with dose-dependent frequency and severity. Drug-related clinical signs included decreased motor activity, tachypnea, and soft or liquid feces at all dose levels, and ataxia, convulsions, hyperpnea, nystagmus, altered righting reflex, and prostration at 30 mg/kg/day. Maternal body-weight gain was reduced at 10 mg/kg/day (67% and 50% less than saline and Captisol controls, respectively) and body-weight loss was noted at 30 mg/kg/day (20 g loss compared with a gain of 30 g and 20 g in saline and Captisol controls, respectively) during the first several days of dosing (gestation days 7 to 10). During the post-dosing period (g.d. 20 to 29), body-weight gain was reduced at 3, 10, and 30 mg/kg/day (33% and 27%, 46% and 41%, and 54% and 50% less than the saline and Captisol controls, respectively). Reductions in maternal food consumption paralleled the reductions in maternal body-weight gain at all doses. Drug-related changes in the fetuses occurred only at the HD of 30 mg/kg/day and included decreased fetal body weights (15% and 16% less than saline and Captisol controls, respectively) with associated reductions in ossification, as well as congenital malformations, including absence of the intermediate lobe of the lungs, split ribs, fused sternal ossification centers, and irregularly shaped scapulae. In conclusion, IM aripiprazole administered intravenously to pregnant rabbits on g.days 7 through 19 produced maternal toxicity (manifested in reduction in body weight and/ or weight gain as well as clinical signs) at all doses, and drug-related fetal effects (growth retardation and congenital abnormalities, predominantly skeletal) at 30 mg/kg/day, a dose that induced a pronounced maternal toxicity. Thus, aripiprazole affected fetal development in the rabbit at a dose that caused pronounced maternal toxicity.

Effect on Pre- and Postnatal Development

Aripiprazole IM formulation administered intravenously at doses of 3, 8, and 20 mg aripiprazole /kg/day to pregnant/lactating rats from gestation day 6 (implantation) through lactation day 20 (weaning) produced maternal clinical signs (hypoactivity, ptosis, lacrimation) at 8 and 20 mg/kg/day, attributable to aripiprazole pharmacologic activity, and maternal toxicity at 20 mg/kg/day (demonstrated by reduction in body weight, weight gain, and food consumption). Adverse effects on the F1-generation offspring were induced at 8 mg/kg/day (increased rate of stillbirths) and 20 mg/kg/day (increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life). No effects on dams or progeny were induced at the dose of 3 mg/kg/day (NOAEL). Thus, aripiprazole induced increased stillbirth rates at the dose of 8 mg/kg/day that caused maternal clinical signs attributable to exaggerated pharmacologic activity, but no other manifestations of maternal toxicity, except for a slight transient decrease in body weight gain on gestation days 6 through 9. The higher, maternally toxic dose (20 mg/kg/day) affected pronouncedly the pre- and postnatal development of F1

generation, causing increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life, but no drug-related changes were observed in the tested post-weaning developmental endpoints of F1 generation (sensory perception, motor activity, learning, memory, sexual maturation, or reproductive function).

Special toxicology studies

Local tolerance studies in 2 animal species (rats and rabbits) showed that aripiprazole IM formulation has a mild and reversible local irritation effect upon IM administration.

Rats: Repeated IM administration of aripiprazole to rats for 2 weeks at concentrations of 2 or 7.5 mg/ml in a dose volume of 0.5 ml/kg resulted in clinical and morphologic evidence of a reversible muscle injury. At both tested dose levels, there was increased incidence of swelling and discoloration at the injection site; microscopically, degeneration, necrosis, and regeneration of skeletal muscle and subacute inflammation, hemorrage, edema, and fibroplasias/fibrosis of skeletal muscle and surrounding connective tissue were found in all groups (including vehicle control), with dose-dependent severity. In addition to the local injection-site effects, there were slight increases in body weight and food consumption in females at both tested dose levels, and slight increase in serum AST in HDF. The clinical and clinical pathology changes were reversible; microscopically, at the injection sites, only minimal late-stage muscle regeneration and fibrosis were present in vehicle- and drug-treated groups after the 2-week recovery period.

Rabbits: Reversible muscle irritation was observed in rabbits (6F/group) upon a single intramuscular injection of aripiprasole IM formulation at concentrations of 2, 4 or 7.5 mg/ml in a dose volume of 1 ml/kg; two control groups received IM the same volume of either vehicle [redacted] or saline. Microscopically, muscle degeneration/regeneration and inflammation with a dose-related severity were observed on day 4 post-dose in all test and control groups (minimal severity in the saline control group); hemorrhage and mineralization of degenerated muscle fibres were present in vehicle control and aripiprazole-treated groups. In addition to the local injection-site effects, there was an increase in serum creatininephosphokinase (CPK) values in the vehicle control and all dose groups (statistically significant vs. saline control values); when compared to vehicle control, only CPK increase at HD was statistically significant. These changes were reversible; after a 2-week recovery period, there was only slight edema and minimal muscle regeneration, inflammation, mineralization, or fibrosis at the injection site in the HD group.

B. Pharmacologic Activity: Pharmacology studies were not performed for this application

C. Nonclinical Safety Issues Relevant to Clinical Use:

In pregnant rabbits receiving aripiprazole IM formulation intravenously (3, 10, and 30 mg/kg/day) during the period of organogenesis (gestation day 6 through 19), aripiprazole induced maternal toxicity (manifested as reduction in body weight and/ or weight gain as well as clinical signs) at all doses in a dose-dependent manner, and drug-related fetal effects [growth retardation and congenital abnormalities (predominantly skeletal) at the highest tested and pronouncedly maternally toxic dose of 30 mg/kg/day, equivalent to maternal exposure (AUC) 62 times human exposure at the MRHD. No adverse embryo/fetal developmental effects were induced at the dose of 10 mg/kg/day, equivalent to maternal exposure (AUC) 29 times human exposure at the MRHD.

Aripiprazole IM formulation administered intravenously at doses of 3, 8, and 20 mg aripiprazole /kg/day to pregnant/lactating rats from gestation day 6 (implantation) through postpartum day 20 (weaning), resulting in maternal plasma exposures 1, 2, and 6 times, respectively, the human AUC exposure at the maximum recommended IM dose, produced maternal clinical signs (hypoactivity, ptosis, lacrimation) at 8 and 20 mg/kg/day, attributable to aripiprazole pharmacologic activity, and maternal toxicity at 20 mg/kg/day (demonstrated by reduction in body weight, weight gain, and food consumption); at 8 mg/kg/day, a transient reduction (-11%)in maternal weight gain occurred between gestation days 6 and 9 only. Adverse effects on the progeny were induced at 8 mg/kg/day (increased rate of stillbirths) and 20 mg/kg/day (increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life). Thus, aripiprazole induced increased stillbirth rates in the rat at the IV dose of 8 mg/kg/day that caused maternal clinical signs attributable to exaggerated pharmacologic activity, but no other manifestations of maternal toxicity except for a transient decrease (-11%) in maternal weight gain beween gestation days 6 and 9. The higher, maternally toxic dose (20 mg/kg/day) affected pronouncedly the pre- and postnatal development of the progeny, causing increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life, but no drug-related changes were observed in the tested post-weaning developmental endpoints of the offaspring (sensory perception, motor activity, learning, memory, sexual maturation, or reproductive function). At the IV doses of 8 and 20 mg/kg/day, aripiprazole systemic maternal plasma exposures in rats were 2x and 6x respectively (based on AUC) the corresponding values in humans at the MRHD (30 mg IM aripiprazole). No effects on dams or progeny were induced at the IV dose of 3 mg/kg/day (aripiprazole systemic exposure 1x (based on AUC) the corresponding values in humans at the MRHD.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Nonclinical pharmacology studies with IM aripiprazole were not performed by the sponsor since the pharmacology studies completed for the oral tablet submission were "sufficient to characterize aripiprazole with regard to its proposed indication". All pharmacology assessments were reviewed for the oral tablet application (NDA 21-436).

Pharmacology summary:

Pharmacology conclusions:

II. SAFETY PHARMACOLOGY:

Safety pharmacology studies with IM aripiprazole were not carried out because safety pharmacology testing to assess aripiprazole potential for adverse pharmacodynamic effects on major organ systems was performed for aripiprazole oral tablet application (reviewed for NDA 21-436).

Safety pharmacology summary:

Safety pharmacology conclusions:

III. PHARMACOKINETICS/TOXICOKINETICS:

The submitted nonclinical PK and TK studies to characterize the pharmacokinetics of aripiprazole upon IM or IV administration (as shown in the sponsor's table on the next page) included: a single-dose IM aripiprazole pharmacokinetic study in dogs; a single and repeat-dose IM aripiprazole PK in monkeys collected as a part of toxicological assessments; a 1-month toxicology study in rats and reproductive toxicology studies in rats and rabbits using intravenous administration of the proposed commercial IM formulation ——————————————————— to achieve higher systemic exposure to aripiprazole and the excipients used in the formulation than could be achieved by the IM route alone where the volume of formulation that could be administered was limited.

No additional metabolism, tissue distribution, or drug interaction studies were performed to support specifically the IM route because "the data generated for the ABILIFY® (aripiprazole) oral tablet submission were applicable to the IM route of administration". Summaries of relevant in vitro and in vivo nonclinical studies from aripiprazole oral tablet application are provided by the sponsor in the present application.

PK/TK studies submitted to support IM Aripiprazole Pharmacokinetics

Overview				
Test Article:				Aripiprazole (OPC-14597, OPC-31, BMS-337039)
Type of Study	Test System	Method of Administration	Testing Facility	Study No./ Document Control Number
Absorption				
Single dose IM exploratory irritation	Rats	Single IM	BMS	99328 / 920003720
Plasma concentrations	Dogs	Single IV, IM, SC, PO	BMS	DM00026 / 920010397
Distribution				
No additional distribution studies were performed				
Metabolism				
No addition metabolism studies were performed				
Excretion				
No additional excretion studies were performed				
Pharmacokinetic Drug Interactions				
No additional non-clinical studies were performed.				
Toxicokinetics				
Toxicokinetics - 10-day dose range finding	Pregnant Rats	Multiple IV	BMS	DN04018 / 930008662
Toxicokinetics - 10-day embryo-fetal development	Pregnant Rats	Multiple IV	BMS	DN04039 / 930009018
Toxicokinetics - 2-week tolerance	Rats	Multiple IM	BMS	DM00005 / 920007291
Toxicokinetics - 18- to 20-days pre- and postnatal development	Lactating Rats	Multiple IV	BMS	DN04046/ 930011278
Toxicokinetics - 1-month toxicity	Rats	Multiple IV	BMS	DM04011 / 930008946
Toxicokinetics - 13-day dose range finding	Pregnant rabbits	Multiple IV	BMS	DN04017 / 930008584
Toxicokinetics - 13-day embryo-fetal development	Pregnant rabbits	Multiple IV	BMS	DN04038 / 930009017
Toxicokinetics - 2-week toxicity	Monkeys	Multiple IM	BMS	99351 / 920007292
Toxicokinetics - 1-month toxicity	Monkeys	Multiple IM	BMS	DS04063 / 930009043

Note: As stated by the sponsor, the analytical method for aripiprazole and 5 of its metabolites in dog plasma "was not validated according to the US Food and Drug Administration guidance for bioanalytical method validation." Due to the lack of a validated analytical method for analysis of for aripiprazole and 5 of its metabolites in dog plasma, the sponsor included the results of the PK study (DM 00026) in female dogs following single-dose IV, IM, SC, and oral administration "for information only".

Some PK/TK studies were affected by analytical problems. As stated by the sponsor, "A review of the bioanalytical data revealed some irregularities associated with manual integration of chromatographic peaks which could not be scientifically justified. After thorough evaluation, these data discrepancies were found to be limited to the work of a

single analyst whose contribution to the current submission included 5 nonclinical studies. In all of these studies plasma samples were analyzed for aripiprazole and 5 of its metabolites." To correct the discrepancies, the sponsor "reintegrated chromatographic peaks for all analytes (aripiprazole and its metabolites) using pre-specified criteria, and, where possible revised the plasma concentration-time data for these studies". The toxicokinetic parameters were "also recalculated, where possible, for all analytes (aripiprazole and its metabolites)". The data discrepancies with the revised toxicokinetic data along with its assessment were documented as an amendment to the individual study report for the five affected studies.

The following sponsor's table (expanded by this reviewer based on sponsor's data) lists the nonclinical studies affected by analytical data discrepancies.

PK/TK Studies with Bioanalytical Discrepancies

Species	**Study Title**	**Study Number**	**BMS DCN**	Note*
Rat	Pharmacokinetic evaluation of BMS-337039 (aripiprazole) and metabolites after single intravenous and intramuscular administration of BMS-337039 to male rats	178/337039/001A	920003842	No valid data recovered. Study not included in this submission
	Pharmacokinetic evaluation of BMS-337039 (aripiprazole) and five metabolites in a single-dose intramuscular exploratory irritation study of prototype formulations in rats	99328	920003720	Recalculated on the basis of recovered valid data. Study data included in this submission
	Toxicokinetic evaluation of BMS-337039 (aripiprazole) and five metabolites in a two-week intramuscular tolerance study	DM00005	920007291	Recalculated on the basis of recovered valid data. Study data included in this submission
Monkey	Pharmacokinetic evaluation of BMS-337039 (aripiprazole) and metabolites after single intravenous and intramuscular administration of BMS-337039 to male cynomolgus monkeys	178/337039/002	920003843	No valid data recovered
	Toxicokinetic analysis of BMS-337039 (aripiprazole) and five metabolites in a two-week intramuscular toxicity study in monkeys	99351	920007292	Recalculated on the basis of recovered valid data. Study data included in this submission

*Column added by this reviewer based on sponsor's evaluation

Because "no valid data were recovered for the rat and monkey aripiprazole single-dose IV and IM pharmacokinetic studies (178/337039/001A and 178/337039/002) following the reintegration of chromatographic data", these studies are not reviewed. For the remaining toxicokinetic studies affected by bioanalytical discrepancies in rats (99328 and DM00005) and monkeys (99351), "some valid concentration data were recovered following reintegration of chromatograms using acceptance criteria for standards and quality control samples established a priori for the original analysis". The available TK data from these studies are reviewed. There were no bioanalytical discrepancies in TK data derived from toxicology studies in which only aripiprazole and its pharmacologically active metabolite, dehydro-aripiprazole, were determined in plasma.

PK parameters:

Absorption:

Rats: A single-dose, non-GLP study, entitled "Pharmacokinetic evaluation of BMS-337039 (aripiprazole) and metabolites in a single dose intramuscular irritation study of prototype formulations in rats" (Study No/Document Control Number 99328 / 920003720) was carried out in Sprague-Dawley rats to determine the irritation potential of prototype IM formulations. The rats received a single 3.75 mg/kg IM dose of aripiprazole in a solution of ——————————— PK data are shown in the table on next page (sponsor's table abbreviated by this reviewer). The absorption of aripiprazole from the injection site was rapid: peak plasma concentrations of aripiprazole were observed at the first pharmacokinetic sampling time point - 15 min following dosing in female rats (Tmax in males not available due to loss of data resulting from bioanalytical discrepancies).

Table **Pharmacokinetics: Absorption After a Single IM Dose to Rats (Study 99328)**

Study No./Document Control Number 99328 / 920003720 Location in Dossier	**Study Title: Pharmacokinetic evaluation of BMS-337039 (aripiprazole) and metabolites in a single dose intramuscular irritation study of prototype formulations in rats (Non-GLP)**							
Test Article:			**Aripiprazole** (OPC-14597, OPC-31, BMS-337039)					
Method of Administration, Dose			**Single IM 3.75 mg/kg**					
Species: Rats (M/F) / Number of Animals	4 M / 4 F Fasted		4 M / 4 F Fasted		4 M / 4 F Fasted		4 M / 4 F Fasted	
Vehicle/Formulation	7.5 mg/mL aripiprazole in 20% HPBCD [redacted] 0.05 M tartrate buffer		7.5 mg/mL aripiprazole in [redacted]		7.5 mg/g aripiprazole in benzyl alcohol / medium chain triglyceride (10:90)		10 mg/mL aripiprazole in [redacted]	
PK parameters in plasma (means) Assay: LC/MS/MS								
Sex	Male	Female	Male	Female	Male	Female	Male	Female
Analyte: Aripiprazole								
Cmax (ng/mL)	-	-	-	920	-	-	-	-
AUC_{0-24}(ng•h/mL)	-	-	-	1470	-	-	-	-
Tmax (h)	-	-	-	0.25	-	-	-	-
Analyte: BMS-337040	-	-	-	-	-	-	-	-
Analyte: Dehydro-aripiprazole								
Cmax (ng/mL)	-	-	1.46	5.62	-	-	-	-
AUC0-24(ng•h/mL)	-	-	3.85	8.89	-	-	-	-
Ratio of Metabolite AUC to aripiprazole	ND	ND	ND	0.6	ND	ND	ND	ND
Tmax (h), median:	-	-	1.5	0.75	-	-	-	-

Table: Pharmacokinetics: Absorption After a Single IM Dose to Rats (Study 99328) - continued

Sex	Male	Female	Male	Female	Male	Female	Male	Female
Analyte: DM-1452	-	-	-	-	-	-	-	-
Analyte: OPC-3373								
Cmax (ng/mL)	-	-	6.82	4.93	-	-	-	-
AUC0-24(ng•h/mL)	-	-	14.2	5.87	-	-	-	-
Ratio of Metabolite AUC to aripiprazole	ND	ND	ND	0.4	ND	ND	ND	ND
Tmax (h), median:	-	-	0.75	0.75	-	-	-	-
Analyte: DCPP	-	-	-	-	-	-	-	-

(-): The pharmacokinetic parameters could not be calculated due to loss of data resulting from the bioanalytical discrepancies
ND: Not Determined
Additional Information: The Cmax and AUC(0-24) values were determined based on composite pharmacokinetic profiles collected from 3 pharmacokinetic samples from 2 rats/sex/treatment.

Dogs: Aripiprazole was rapidly and extensively absorbed following IM administration to dogs. One single-dose crossover PK study in Beagle dogs (n=3 F) was conducted to support the development of IM aripiprazole [BMS-337039 (aripiprazole): Single-dose intravenous, intramuscular, subcutaneous, and oral pharmacokinetic study in female dogs (Study No/ Document Control No DM00026/ 920010397)]. Because the analytical method for aripiprazole and 5 of its metabolites in dog plasma "was not validated according to the US Food and Drug Administration guidance for bioanalytical method validation", the sponsor presented the results of this study in this document "for information only". This study assessed the single-dose pharmacokinetics of aripiprazole and 5 of its metabolites following IM, oral (PO), subcutaneous (SC) and intravenous (IV) administration. A single 15 mg dose of aripiprazole was administered on separate occasions to 3 F dogs by each of the 4 routes (with a washout period of at least 3 days between the consecutive administrations, and 6 days after the IM injection). An intramuscular injection formulation (Aripiprazole, 7.5 mg/ml in [redacted]) was used for IV, IM, and SC routes, and the 15 mg aripiprazole oral tablets were used for oral dose. Blood samples were collected over 24 to 72 h after dosing for determination of aripiprazole and 5 metabolites (BMS-337040, BMS-337044, BMS-337045, BMS-337047, and 1-(2,3-dichlorophenyl) piperazine (DCPP) in plasma using a LC/MC/MC method with a lower limit of quantification 1 ng/ml for each analyte. The mean PK values for aripiprazole following dosing via various administration routes are presented in the sponsor's table reproduced below.

Mean (SD) PK values for aripiprazole in Beagle dogs (N=3F) after a single 15 mg dose via various administration routes (Study DM00026)

	BMS-337039			
	IV	PO	IM	SC
CMAX (ng/mL)	1445 (813)	28.8 (32.1)	565 (173)	88.7 (24.4)
TMAX[a] (h)	0.08*(0.08, 0.08)	2.00*(0.50, 2.00)	0.17*(0.17, 0.50)	0.50*(0.17, 1.00)
AUC(0-T) (ng.h/mL)	1028 (159)	118 (121)	1028 (98.7)	1002 (160)
AUC(INF) (ng.h/mL)	1048 (157)	285[b]	1036 (97.6)	1021 (160)
MRT(INF) (h)	4.04 (0.57)	4.23[b]	4.25 (0.54)	9.6 (2.15)
T-HALF (h)	4.84 (0.90)	2.21[b]	5.09 (1.68)	6.01 (1.66)
CLT (mL/min/kg)	21.2 (3.01)	[c]	[c]	[c]
VSS (L/kg)	5.14 (1.08)	[c]	[c]	[c]
F (%)	[d]	12.2 (11.9)[e]	99.5 (6.8)	97.3 (1.00)

[a]: reported as median (minimum, maximum)
[b]: N = 1, the AUC(INF) values were not obtained in two animals because the terminal phases of plasma concentration-time profiles were not well-defined in these two animals.
[c]: not determined.
[d]: not applicable.
[e]: F was calculated based on AUC(0-T) in Dogs 2102 and 2103 as AUC(INF) values were not obtainable in these two animals and based on AUC(INF) in one animal.

Following the IM administration of 15 mg aripiprazole, the peak plasma concentrations for aripiprazole (Cmax range of 375 to 711 ng/ml) occurred at 0.2 to 0.5 h after dosing, indicating a rapid absorption from the injection site (absorption much faster and higher in comparison to the oral route, where Cmax values ranging from 5 to 65 ng/ml occurred at 0.5 to 2 h. after the same dose taken orally). The mean and individual aripiprazole $AUC_{(0-T)}$ values were similar among the IM, IV, and SC routes, and much lower for PO route

(see sponsor's table above). The absolute bioavailability of aripiprazole following the IM dose was 99.5% (range 94%-107%), indicating essentially complete absorption of aripiprazole from the injection site, as compared to 12% (range 1.9% to 25%) upon oral administration of the same dose (indicative of extensive first-pass of aripiprazole after PO dose). The terminal half-life upon a single IM dose of 15 mg was 5 h., similar to T1/2 following IV and SC administration of the same dose (4.8 h. and 6 h, respectively), but longer than T1/2 following oral administration of the same dose (2.2 h).

Monkeys: The absorption of aripiprazole from the injection site was rapid with peak plasma concentrations observed 10 minutes following aripiprazole single IM dose (3.75 mg/kg) (study 920003843, see sponsor's table below). The same Tmax was observed in the 1-month repeat-dose toxicity study in monkeys (Study DS04063) using the proposed commercial IM formulation at aripiprazole doses of 2, 4, and 7.5 mg/kg/day (TK data from the 1-month study shown under "Toxicokinetics in monkeys", on page 21). The absolute bioavailability of aripiprazole after IM administration was high (87%, based on a comparison of the mean AUC values after IV and IM administration of the IM formulation).

Aripiprazole PK parameters in monkeys (n=3 M) after a single IV and IM dose (3.75 mg/kg) of aripiprazole IM formulation (study 920003843)

Route	CMAX (ng/mL)	TMAX[a] (h)	AUC(INF) (ng.h/mL)	T-HALF (h)	MRT (h)	CLT (mL/min/kg)	VSS (L/kg)	F (%)
iv	4097	0.17	4684	3.80	3.88	14.0	3.06	d
im	3626	0.17	4061[b]	5.56[b]	3.75[b]	c	c	86.7

a reported as median; b N=2
c not reported for intramuscular administration; d not applicable

Distribution:

Specific studies on distribution of aripiprazole and its metabolites following IM administration were not conducted. The sponsor states that "the tissue distribution of aripiprazole has been characterized in studies following oral administration of radiolabeled aripiprazole; the details of these studies are included in the ABILIFY oral tablet submission, and these data also support the development of IM aripiprazole. These studies showed that aripiprazole is highly bound to serum protein but distributes extensively into tissues, including brain". The sponsor's summary of the pertinent results of these studies is reproduced below.

"Aripiprazole is extensively bound to serum proteins. The mean binding of aripiprazole in mouse, rat, rabbit, dog, monkey, and human sera determined by equilibrium dialysis was 99.8, 99.7, 99.7, 99.7, 99.4, and 99.8%, respectively (In vitro determination of protein binding of BMS-337039 in mouse, rat, rabbit, monkey, dog, and human sera and of BMS-337044 in human serum. May 30, 2001. BMS Document Control No. 930000112, as cited by the sponsor). The extent of serum protein binding of aripiprazole was independent of the concentration over the concentration range tested (500 to 5000 ng/mL). The ex vivo plasma protein binding of aripiprazole was similar to the plasma protein binding determined by equilibrium dialysis in vitro, indicating that the presence of metabolites in the plasma did not affect the binding of aripiprazole (Phase I single-dose evaluation of the pharmacokinetics of aripiprazole in normal and hepatically-impaired subjects. Report for Otsuka study 31-98-205. July 3, 2001. BMS Document Control No. 930000294, as cited by the sponsor). Dehydro-aripiprazole was also extensively bound to human plasma proteins (99.8% bound by equilibrium dialysis). Aripiprazole-related radioactivity was minimally distributed into or associated with

mouse, rat, rabbit, monkey or human red blood cells (The blood-plasma partition ratio of OPC-14597 in rat, mouse, rabbit, and human. Otsuka Report No. 013277. May 24, 2000. BMS Document Control No. 920007069; The blood-plasma partition ratio of OPC-14597 in cynomolgus monkeys. Otsuka Report No. 013353. May 25, 2000. BMS Document Control No. 920007071, as cited by the sponsor).

Aripiprazole has a large volume of distribution. [Reviewer's Note: A single-dose crossover PK study conducted in Beagle dogs (n=3 F) to support the development of IM aripiprazole [BMS-337039 (aripiprazole): Single-dose intravenous, intramuscular, subcutaneous, and oral pharmacokinetic study in female dogs (Study No/ Document Control No DM00026/ 920010397)] showed that aripiprazole was extensively distributed to extravascular tissues (mean steady-state volume of distribution (Vss) =5.14 l/kg) following IV administration of aripiprazole IM injection formulation (15 mg aripiprazole in a single IV bolus dose)]. The estimated total body clearance (blood) was 74-88% of the hepatic blood flow, suggesting a high hepatic drug extraction in dogs. The Vss value for aripiprazole observed following IV administration to dogs (5.14 L/kg) was larger than the volume of total body water (0.60-0.69 L/kg) (Davis B, Morris T. Physiological parameters in laboratory animals and humans. Pharm. Res. 10(7) 1993; p 1093-1095, as cited by the sponsor) suggesting extensive extravascular distribution of aripiprazole and/or preferential binding to tissue proteins. The mean Vss value in humans was also high (4.94 L/kg), and was comparable to the value observed in dogs (Open-label, randomized, three-way crossover study of the absolute bioavailability of aripiprazole 5 mg commercial tablet and aripiprazole 5 mg IM injection with reference to 2 mg IV infusion in healthy subjects (Study CN138016). July 20, 2001. BMS Document Control No. 930000380, as cited by the sponsor).

The volume of distribution of aripiprazole in rats and monkeys after single IV administration could not be determined due to loss of pharmacokinetic data resulting from the bioanalytical discrepancies.

Aripiprazole and/or its metabolites distribute extensively into tissues. After oral administration of [^{14}C] aripiprazole to male and female rats, drug-related radioactivity was extensively distributed to all tissues examined (Tissue distribution of total radioactivity following oral administration of [^{14}C] BMS-337039 to male and female Sprague-Dawley rats (Study 178/337039/006). June 1, 2001. BMS Document Control No. 930000152; Limited tissue distribution of total radioactivity following a single oral administration of dual-label [^{14}C]-BMS-337039 to male Long-Evans rats (Study 178/337039/003). October 23, 2000. BMS Document Control No. 920008794, as cited by the sponsor). The highest levels of radioactivity were associated with the dosing/absorption site(s) along the gastrointestinal tract (stomach, small intestine, and large intestine) and liver. Drug-related radioactivity was also rapidly distributed to the brain.

The high serum protein binding and extensive tissue distribution of aripiprazole from the systemic circulation following IM administration are expected to be similar to those after an IV or oral dose." (End citation)

Metabolism:

As stated by the sponsor, "specific studies designed to examine the metabolism of aripiprazole following its IM administration have not been conducted". Plasma exposure to aripiprazole metabolites upon i.m. administration of aripiprazole was determined in TK studies in rats, dogs, and monkeys.

Rat: Aripiprazole and 5 of its metabolites [BMS-337044 (dehydro-aripiprazole), BMS-337040, BMS-337045, BMS-337047, and 1-(2, 3-dichlorophenyl) piperazine (DCPP)], were determined in plasma upon a repeat-dose IM administration of 1 and 3.75

mg/kg/day aripiprazole for 10 days. The systemic exposures of rats to aripiprazole and its metabolites were dose related. At LD, the plasma concentrations for dehydro-aripiprazole were measurable for up to 3 h after dosing, whereas plasma concentrations for the other 4 metabolites were below LLQ. At HD, the AUC values of BMS-337040, dehydro-aripiprazole, and BMS-337045 compared to aripiprazole were 3.0%, 0.3%, and 0.2% in males and 1.4%, 0.6%, and 0.4% in females, respectively.

Dog: The predominant metabolite in plasma following a single-dose IM (as well as IV and SC) administration of 15 mg aripiprazole to Beagle dogs (3F) was the active metabolite dehydroaripiprazole (BMS-337044); the other four determined metabolites (BMS-337040, BMS-337045, BMS-337047, and DCPP) were minor. The mean AUC_{0-T} of the active metabolite BMS-337044 was 21% of the mean AUC_{0-T} of the parent compound; for the other 4 metabolites, the individual metabolite to parent AUC_{0-T} ratios were: 8.6% for BMS-337045, 1.9% for BMS-337047, 1.2% for DCPP, and 0.2% for BMS-337040. The individual metabolite to parent ratios were essentially similar among IM, IV and SC routes of administration, while after PO administration, the individual metabolite to parent AUC_{0-T} ratios were much higher in comparison to either IM, IV, or SC routes. Thus, after administration of the same single dose via the oral route, individual to parent AUC_{0-T} ratios for BMS-337044, BMS-337045 and BMS-337047 were 169%, 80%, and 43%, respectively. PK values for five metabolites after administration of a single aripiprazole dose (15 mg) by different routes are presented in the following sponsor's table.

Mean (SD) PK values for aripiprazole metabolites in Beagle dogs (N=3F) after a single 15 mg dose via various administration routes (Study DM00026)

Metabolite	Route	CMAX (ng/mL)	TMAX[a] (h)	AUC (0-T) (ng.h/mL)	$\frac{AUC(metabolite)}{AUC(parent)}$
BMS-337040 (DM-1451)	IV	2.14 (0.62)	0.33* (0.50, 1.00)	2.98 (1.44)	0.30 (0.12)
	PO	1.98[b]	0.75* (0.50, 1.00)	[c]	[c]
	IM	1.85 (0.27)	1.00* (0.33, 2.00)	1.69[b]	0.18[b]
	SC	[c]	[c]	[c]	[c]
BMS-337044 (OPC-14587)	IV	30.8 (11.7)	2.00* (1.00, 4.00)	269 (191)	25.1 (15.7)
	PO	28.8 (29.5)	2.00* (1.00, 2.00)	221 (266)	169 (41.3)
	IM	29.3 (18.2)	2.00* (0.33, 4.00)	222 (202)	21.3 (18.8)
	SC	19.2 (14.0)	8.00* (8.00, 8.00)	277 (198)	26.7 (17.2)
BMS-337045 (DM-1452)	IV	17.7 (4.59)	1.00* (0.33, 2.00)	86.9 (30.6)	8.43 (2.33)
	PO	19.0 (18.7)	2.00* (0.50, 2.00)	83.4 (72.7)	80.1 (14.0)
	IM	16.2 (7.58)	1.00* (0.50, 2.00)	88.6 (43.3)	8.59 (3.95)
	SC	8.99 (4.86)	8.00* (8.00, 8.00)	129 (67.8)	12.6 (5.61)
BMS-337047 (OPC-3373)	IV	9.52 (1.88)	1.00* (0.50, 1.00)	31.2 (17.8)	3.00 (1.47)
	PO	16.2 (9.05)	1.00* (0.50, 2.00)	29.5 (13.6)	42.9 (29.6)
	IM	6.66 (1.79)	1.00* (0.50, 4.00)	18.8 (13.9)	1.88 (1.44)
	SC	2.12 (0.81)	2.00* (2.00,4.00)	23.6[b]	1.07[b]
DCPP	IV	1.97 (0.28)	1.00* (1.00, 4.00)	10.5 (4.12)	1.05 (0.45)
	PO	2.56 (1.27)	2.00* (0.50, 2.00)	11.6[b]	6.12[b]
	IM	1.96 (0.32)	2.00* (1.00, 8.00)	12.5 (1.53)	1.23 (0.27)
	SC	1.76 (0.39)	8.00* (8.00, 8.00)	[c]	[c]

[a] reported as median (minimum, maximum).
[b] N = 2.
[c] Not reported because only two or less than two plasma concentrations were above LLQ in all individual animals.

Thus, in the dog, plasma exposure to five metabolites [BMS-337044 (the active metabolite), BMS-337040, BMS-337045, BMS-337047, and 1-(2, 3-dichlorophenyl) piperazine (DCPP)], was minor after IM (as well as IV and SC) administration of aripiprazole IM formulation at a single 15 mg dose ($AUC_{0-T} \leq 25\%$ of that for the parent compound), while after oral administration of the same single dose, exposure to BMS-337044 and BMS-337045 was 'substantial' [AUC_{0-T} =169% and 80%, respectively of AUC_{0-T} for the parent compound]. Overall, the exposure of the dogs to the metabolites was in the following order: BMS-337044 (the active metabolite)> BMS-337045> BMS-337047> DCPP> BMS-337040.

Monkey: Plasma concentrations of aripiprazole, and 5 of its metabolites, BMS-337040, BMS-337044 (dehydro-aripiprazole), BMS-337045, BMS-337047, and DCPP, were determined after IV and IM administration of a single dose of 3.75 mg/kg aripiprazole (in IM formulation) to male cynomolgus monleys (3 per treatment) (Study 920003843). Serial blood samples were collected over 24 hours post-dose; the results are shown in sponsor's table below. Following IV and IM administration of aripiprazole, peak plasma concentrations of all metabolites occurred between 0.5 and 4 h. after dosing. The predominant metabolites in plasma were BMS-337044 (dehydro-aripiprazole) and BMS-337047. The mean AUC_{0-T} values were about 7-15% and 10-19% that of the parent for dehydro-aripiprazole and BMS-337047, respectively. Plasma concentrations of metabolites BMS-337040, BMS-337045, and DCPP each were < 3% that of the parent. These results suggested that aripiprazole "was not extensively metabolized after IV and IM administration to monkeys and that the extent of metabolism for these routes of administration was essentially similar".

Mean (SD) plasma concentration vs. time data for aripiprazole and metabolites BMS-337040, BMS-337044, BMS-337045, BMS-337047, and DCPP after a single IV and IM administration of 3.75 mg/kg aripiprazole to monkeys

Aripiprazole

			MEAN PLASMA CONCN OF ARIPIPRAZOLE (BMS-337039) (NG/ML)					
TIME			Intravenous			Intramuscular		
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	10	3	4096.70	2173.22	53.05	3	3625.63	988.24	27.26
.	.	20	3	1519.62	451.94	29.74	3	2002.10	554.05	27.67
.	.	30	3	1166.77	377.14	32.32	3	1337.92	219.82	16.43
.	1	0	3	798.56	171.35	21.46	3	949.74	12.51	1.32
.	2	0	3	572.32	139.23	24.33	3	607.35	184.11	30.31
.	4	0	3	329.96	147.98	44.85	3	177.40	31.14	17.56
.	8	0	3	114.99	73.69	64.09	3	52.99	18.55	35.01
1	0	0	3	10.96	11.61	105.93	3	7.39	6.90	93.40

NOTE: VALUES <LLQ = 0

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Mean (SD) plasma concentration vs. time data for aripiprazole metabolites BMS-337040, BMS-337044, BMS-337045, BMS-337047, and DCPP after a single IV and IM administration of 3.75 mg/kg aripiprazole to monkeys (continued)

BMS-337040

MEAN PLASMA CONCN OF BMS-337040 (DM-1451) (NG/ML)									
TIME			Intravenous				Intramuscular		
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	10	3	0.00	0.00	.	3	0.00	0.00	.
.	.	20	3	0.00	0.00	.	3	0.00	0.00	.
.	.	30	3	1.97	3.42	173.21	3	0.00	0.00	.
.	1	0	3	6.36	7.07	111.19	3	6.29	5.48	87.07
.	2	0	3	7.84	4.73	60.36	3	8.04	7.48	93.09
.	4	0	3	2.06	3.56	173.21	3	4.05	3.78	93.54
.	8	0	3	0.00	0.00	.	3	0.00	0.00	.
1	0	0	3	0.00	0.00	.	3	0.00	0.00	.

NOTE: VALUES <LLQ = 0

BMS-337044 (Dehydroaripiprazole)

MEAN PLASMA CONCN OF BMS-337044 (OPC-14857) (NG/ML)									
TIME			Intravenous				Intramuscular		
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	10	3	6.84	4.48	65.47	3	2.89	0.74	25.69
.	.	20	3	9.72	2.78	28.61	3	4.00	1.50	37.56
.	.	30	3	17.93	7.19	40.08	3	8.79	2.79	31.74
.	1	0	3	38.12	13.42	35.21	3	19.70	9.81	49.79
.	2	0	3	56.89	19.22	33.79	3	31.49	12.43	39.47
.	4	0	3	60.01	28.26	47.09	3	24.95	10.88	43.59
.	8	0	3	43.76	26.37	60.27	3	14.42	13.51	93.69
1	0	0	3	12.44	12.10	97.25	3	1.62	2.81	173.21

NOTE: VALUES <LLQ = 0

BMS-337045

MEAN PLASMA CONCN OF BMS-337045 (DM-1452) (NG/ML)									
TIME			Intravenous				Intramuscular		
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	10	3	2.13	1.88	88.52	3	0.00	0.00	.
.	.	20	3	5.41	1.95	36.05	3	0.73	1.27	173.21
.	.	30	3	9.34	4.27	45.71	3	3.82	1.30	34.10
.	1	0	3	16.06	6.46	40.20	3	8.37	3.19	38.05
.	2	0	3	21.59	6.71	31.07	3	12.70	3.30	26.00
.	4	0	3	20.40	6.16	30.17	3	10.34	1.92	18.59
.	8	0	3	10.28	2.88	28.03	3	4.26	1.61	37.67
1	0	0	3	0.00	0.00	.	3	0.00	0.00	.

NOTE: VALUES <LLQ = 0

Mean (SD) plasma concentration vs. time data for aripiprazole metabolites BMS-337040, BMS-337044, BMS-337045, BMS-337047, and DCPP after a single IV and IM administration of 3.75 mg/kg aripiprazole to monkeys (continued)

BMS-337047

MEAN PLASMA CONCN OF BMS-337047 (OPC-3373) (NG/ML)

TIME			Intravenous				Intramuscular			
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	10	3	14.89	9.65	64.78	3	18.97	22.30	117.57
.	.	20	3	63.92	31.13	48.70	3	95.20	108.74	114.22
.	.	30	3	112.71	74.72	66.30	3	147.41	134.15	91.01
.	1	0	3	82.67	9.89	11.97	3	198.15	147.88	74.63
.	2	0	3	72.46	41.57	57.37	3	205.33	191.94	93.48
.	4	0	3	33.11	20.19	60.97	3	73.48	66.45	90.43
.	8	0	3	12.49	2.78	22.25	3	13.26	9.41	70.98
1	0	0	3	1.50	1.30	87.12	3	1.04	1.80	173.21

DCPP

MEAN PLASMA CONCN OF DCPP (NG/ML)

TIME			Intravenous				Intramuscular			
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	10	3	0.00	0.00	.	3	0.00	0.00	.
.	.	20	3	0.00	0.00	.	3	0.00	0.00	.
.	.	30	3	1.55	1.38	88.99	3	0.00	0.00	.
.	1	0	3	4.92	3.03	61.58	3	5.33	4.92	92.26
.	2	0	3	3.48	3.70	106.31	3	9.14	8.31	91.00
.	4	0	3	6.46	6.44	99.69	3	10.22	9.17	89.71
.	8	0	3	3.30	3.76	113.84	3	4.21	4.23	100.52
1	0	0	3	0.00	0.00	.	3	0.00	0.00	.

NOTE: VALUES <LLQ = 0

MEAN PLASMA CONCN OF DCPP (NG/ML)

TIME			Intravenous				Intramuscular			
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	10	3	0.00	0.00	.	3	0.00	0.00	.
.	.	20	3	0.00	0.00	.	3	0.00	0.00	.
.	.	30	3	1.55	1.38	88.99	3	0.00	0.00	.
.	1	0	3	4.92	3.03	61.58	3	5.33	4.92	92.26
.	2	0	3	3.48	3.70	106.31	3	9.14	8.31	91.00
.	4	0	3	6.46	6.44	99.69	3	10.22	9.17	89.71
.	8	0	3	3.30	3.76	113.84	3	4.21	4.23	100.52
1	0	0	3	0.00	0.00	.	3	0.00	0.00	.

NOTE: VALUES <LLQ = 0

Plasma exposures to aripiprazole, and 5 of its metabolites, dehydro-aripiprazole, BMS-337044, BMS-337045, BMS-337047, and DCPP, were determined in a 2 week IM toxicity study (Study 99351, BMS DCN 920007292) in monkeys (4/sex/dose) at i.m. doses of 2, 4, and 7.5 mg/kg/day of aripiprazole. Toxicokinetic data discrepancies were identified in this study; the bioanalytical discrepancies "resulted in inaccurate determination of plasma concentrations of aripiprazole (BMS-337039) and 4 of the 5 metabolites from the samples collected. These discrepancies were caused by manual integration of chromatographic peaks that could not be scientifically justified". Toxicokinetic parameters for aripiprazole could not be calculated "due to the lack of any complete plasma concentration-time profiles at all doses following reintegration of chromatograms". Some concentration-time profiles were recovered for dehydro-aripiprazole, BMS-337040, and BMS-337045, but the information is insufficient to characterize the exposure to aripiprazole metabolites. Although there are "reliable toxicokinetic data for the same doses (2, 4, and 7.5 mg/kg/day) from a 1-month intramuscular toxicity study in monkeys, a study with no bioanalytical discrepancies", the 1-month study does not provide information on aripiprazole metabolites, since only the main metabolite (dehydro-aripiprazole) was determined (BMS-337039: One-Month Intramuscular Toxicity Study in Monkeys, Study DS04063, BMS DSN 930009043).
Thus, there is insufficient information to characterize the exposure to aripiprazole metabolites upon repeat-dose aripiprazole i.m. administration in the monkey.

The sponsor states that "several metabolic studies conducted to support the development of the ABILIFY (aripiprazole) oral tablet are directly relevant to the IM route of administration. *In vivo* and *in vitro* biotransformation studies of aripiprazole were conducted for the purposes of metabolic profiling and structural elucidation of metabolites and to investigate the underlying metabolic pathways of aripiprazole in humans and in various animal species. The systemic clearance of aripiprazole has been studied following IV administration of aripiprazole to rats, dogs, and monkeys. The details of these studies are included in the ABILIFY oral tablet submission, and these data support the development of IM aripiprazole."
The results of relevant biotransformation and pharmacokinetic studies are summarized by the sponsor as follows:
"The primary biotransformation pathways of aripiprazole in humans are cytochrome P450-mediated metabolic reactions [In vitro metabolism of OPC-14597 by microsomes from human lymphoblastoid cell line transformed with human cytochrome P450 cDNAs. Otsuka Report Number 010498. December 5, 1996. BMS Document Control No. 920001393. NDA 21-436, 31-Oct-2001 (as cited by the sponsor)]. Based on *in vitro* studies with recombinant human cytochrome P-450 isoforms, CYP3A4 and CYP2D6 are responsible for dehydrogenation and hydroxylation, and N-dealkylation is catalyzed by CYP3A4. These 3 pathways give rise to a number of metabolites that have been identified in animals and humans in both *in vitro* and *in vivo* biotransformation studies. These include (1) aromatic hydroxylation to form BMS-337040; (2) N-dealkylation to form DCPP and BMS-337047; and (3) dehydrogenation to form dehydro-aripiprazole, which is the predominant metabolic pathway. Hydroxylation at the benzylic carbon to form BMS-337045 was a minor metabolic pathway. Some of the primary metabolites were either directly excreted into urine (BMS-337047) or underwent secondary metabolic reactions catalyzed by either cytochrome P450 enzymes

or Phase II enzymes. BMS-337040 was further converted to glucuronide and sulfate conjugates in human hepatocytes and in humans *in vivo* [Comparative biotransformation of [14C]-aripiprazole in mouse, rat, monkey and human hepatocytes. May 22, 2001. BMS Document Control No. 930000129.; Biotransformation of dual label [14C]-aripiprazole in humans after oral administration. July 27, 2001. BMS Document Control No. 930000409. NDA 21-436, 31-Oct-2001 (as cited by the sponsor)].

All these primary biotransformation reactions of aripiprazole and the conjugation reactions of BMS-337040 were also observed in mice, rats, and monkeys *in vitro* and/or *in vivo*. The major circulating metabolite in human plasma is dehydro-aripiprazole, which is also pharmacologically active. The other metabolites have little, if any, pharmacological activity, and hence, do not substantially contribute towards the pharmacological effects observed following administration of aripiprazole.

The mean systemic clearance value of aripiprazole after IV administration to dogs was 21 mL/min/kg [BMS-337039 (aripiprazole): Single-dose intravenous, intramuscular, subcutaneous, and oral pharmacokinetic study in female dogs (Study No/ Document Control No DM00026/ 920010397) NDA 21-436, 31-Oct-2001 (as cited by the sponsor)], whereas the total clearance in humans (0.72 mL/min/kg) after a 2 mg IV dose of aripiprazole was much lower [Open-label, randomized, three-way crossover study of the absolute bioavailability of aripiprazole 5 mg commercial tablet and aripiprazole 5 mg IM injection with reference to 2 mg IV infusion in healthy subjects (Study CN138016). July 20, 2001. BMS Document Control No. 930000380 (as cited by the sponsor)].

The systemic clearance of aripiprazole in rats and monkeys after single IV administration could not be determined due to loss of pharmacokinetic data resulting from the bioanalytical discrepancies.

Overall, the biotransformation data suggest that the metabolism of aripiprazole was qualitatively similar in mice, rats, monkeys, and humans. Metabolism is the major mechanism for aripiprazole clearance. The metabolic profile of aripiprazole following IM administration is expected to be similar to other routes of administration." (End citation)

Excretion:

Specific studies designed to examine the excretion of aripiprazole and its metabolites following IM administration of aripiprazole were not conducted by the sponsor. According to the sponsor, mass-balance studies administering radiolabeled aripiprazole by the oral route were conducted in rats and monkeys to support the development of the ABILIFY (aripiprazole) oral tablet and showed that in these species, similarly to humans, "renal and biliary excretion of aripiprazole played a relatively minor role in the clearance of parent aripiprazole relative to the contribution of metabolism." The details of these studies are included in the ABILIFY oral tablet submission. The results of these studies are summarized by the sponsor as follows:

"Following oral administration, aripiprazole was mainly eliminated via metabolic clearance in rats, monkeys, and humans. In bile-duct cannulated male rats administered a single oral 3 mg/kg dose of [^{14}C]-aripiprazole, 82% of the administered dose was recovered in the bile (Absorption, distribution and excretion of radioactivity in male rats after single oral administrations of [^{14}C]-OPC-14597 at 3 mg/kg (Otsuka Report Number 005520. November 16, 1990. BMS Document Control No. 920001344. NDA 21-436, 31-Oct-2001, as cited by the sponsor). Since male rats have a low oral bioavailability of aripiprazole (16%) due to potential extensive pre-systemic metabolism, the majority of the radioactivity in bile and also in urine was presumed to be [^{14}C]-aripiprazole metabolites. In monkeys administered 5 mg/kg [^{14}C]-aripiprazole, urinary and fecal excretion of total radioactivity were 34.0 and

59.7% of the administered dose, respectively (High-performance liquid chromatographic analysis of radioactivity in plasma, urine, and feces after single oral administration of [14C]-OPC-14597 in cynomolgus monkeys. Otsuka Report Number 010127. April 17, 1996. BMS Document Control No. 920001388. NDA 21-436, 31-Oct-2001, as cited by the sponsor). In both monkey urine and feces, unchanged aripiprazole was not detected or was present in very small amounts in each matrix. Metabolites of [^{14}C]-aripiprazole were eliminated predominantly by the biliary route in rats, and by both the renal and biliary routes in monkeys and humans (Biotransformation of dual label [^{14}C]-aripiprazole in humans after oral administration. July 27, 2001. BMS Document Control No. 930000409. NDA 21-436, 31-Oct-2001, as cited by the sponsor). Biliary and renal excretion is a relatively minor clearance mechanism for aripiprazole in rats, monkeys, and humans. The systemic excretion of aripiprazole and its metabolites following IM administration is expected to be similar to that after an IV or oral dose." (End citation)

Other studies:
TK studies

Toxicokinetic data for rats, rabbits, and monkeys were collected in a series of repeat-dose toxicology studies designed to support the development of the IM formulation of aripiprazole (see table below). The IM route of administration was employed in the monkey studies, while in most of the rodent and rabbit studies the IV route was used to deliver the IM formulation in order to achieve suitably high systemic exposures, since the volume of the IM formulation that could be administered to rats and rabbits was limited due to their relatively small muscle mass.

Species	Toxicokinetic Studies	Route	Study Number
Rat	2 week tolerance	IM	DM00005/920007291
	1- month toxicity	IV	DM04011/930008946
	10-day dose range finding (Pregnant rats)	IV	DN04018/930008662
	10-day embryo-fetal development (Pregnant rats)	IV	DN04039/930009018
	18 to 20 days pre- & postnatal development (Lactating rats)	IV	DN04046/930011278
Rabbit	13-day dose range finding (Pregnant rabbits)	IV	DN04017/930008584
	13-day embryo-fetal development (Pregnant rabbits)	IV	DN04038/930009017
Monkey	2-week toxicity	IM	99351/920007292
	1-month toxicity	IM	DS04063/930009043

TK studies in rats

TK in 2-week IM tolerance study in rats

Aripiprazole at i.m. doses of 1 and 3.75 mg/kg [2 and 7.5 mg/mL in _____ was administered once daily for 2 weeks to 12 rats/sex/dose. Aripiprazole and 5 of its metabolites (dehydro-aripiprazole, BMS-337040, BMS-337045, BMS-337047, and DCPP), were determined in plasma collected at 10 and 30 min and at 1, 3, 8, and 24 h (2 samples per rat) after dosing on day 10 of the study. The systemic exposures of rats to aripiprazole and its metabolites were dose related. For doses increasing in the ratio of 1:3.75, the Cmax for aripiprazole at 10 min after the dosing increased in the ratio of 1:4.6 (M) and 1:4 (F). The corresponding ratios for AUC values were 1:5 and 1:4.2. The exposures of aripiprazole in females appeared to be lower than in males. At LD, the plasma concentrations for dehydro-aripiprazole were measurable for up to 3 h after dosing, whereas plasma concentrations for the other 4

metabolites were below LLQ. At HD, the AUC values of BMS-337040, dehydro-aripiprazole, and BMS-337045 compared to aripiprazole were 3.0%, 0.3%, and 0.2% in males and 1.4%, 0.6%, and 0.4% in females, respectively.

Study Description or Title:	Toxicokinetic evaluation of aripiprazole (BMS-337039) and five metabolites in a two-week intramuscular tolerance study in rats.								
Test Article:		Aripiprazole (OPC-14597, OPC-31, BMS-337039)							
Dose (mg/kg)		1				3.75			
Analyte		Aripiprazole (BMS-337039)		DM-1451 (BMS-337040)		Aripiprazole (BMS-337039)		DM-1451 (BMS-337040)	
Parameter / Sex	Study Day	M	F	M	F	M	F	M	F
Cmax (ng/mL)	Day 10	198	182	5.50	3.05	911	719	12.3	5.92
AUC_{0-T} (ng•h/mL)[b]	Day 10	365	272	10.6	c	1850	1131	55.5	15.3
Tmax (h)[d]	Day 10	0.17	0.17	0.5	0.5	0.17	0.17	0.5	3.0

[a] The PK parameter values are reported as means

[b] T = 8 to 24 h for aripiprazole, and 3 to 8 h for DM1451 (BMS-337040)

[c] AUC value was not reported since there were less than 3 measurable concentrations in the composite plasma concentration-time profiles.

[d] Tmax values are reported as medians

Analyte		OPC-14857 (BMS-337044)		DM-1452 (BMS-337045)		OPC-14857 (BMS-337044)		DM-1452 (BMS-337045)	
Parameter / Sex	Study Day	M	F	M	F	M	F	M	F
Cmax (ng/mL)	Day 10	b	b	b	c	2.21	2.62	1.76	1.86
AUC_{0-T} (ng•h/mL)[d]	Day 10	b	b	b	c	5.48	6.60	4.52	4.35
Tmax (h)[e]	Day 10	b	b	b	c	3.0	1.0	1.0	0.5

[a] The PK parameter values are reported as means

[b] All plasma concentrations were below LLQ of 1 ng/mL

[c] All plasmas concentrations were below LLQ except one rat at 24 h (2.984 ng/mL), which is considered as an outlier.

[d] T = 3 h for OPC-14857 (BMS-337044), and DM-1452 (BMS-337045)

[e] Tmax values are reported as medians

Additional Information : All plasma concentrations of other two metabolites, OPC-3373 (BMS-337047) and DCPP were below LLQ, therefore none of the pharmacokinetic parameters were calculated.

TK in 1-month IV toxicity study in rats

Aripiprazole at i.v. doses of 3, 10 and 30 mg/kg (7.5 mg/mL aripiprazole, 150 mg/mL Captisol, 7.8 mg/mL tartaric acid in Sterile Water for Injection US, pH approximately 4.3) was administered once daily as a bolus injection to 10 rats/sex/dose for 28 days. Aripiprazole and dehydro-aripiprazole were determined in plasma collected at 5 and 30 min and at 1, 2, 4, 8, 12, and 24 h post-dosing on days 1 and 27 of the study (3 rats per sampling time and 2 samples per rat). For aripiprazole, the AUC values increased dose-proportionally between 3 and 10 mg/kg/day, but greater than dose-proportionally between 10 and 30 mg/kg/day; Cmax values were dose-proportional between 3 and 10 mg/kg/day, but less than dose-proportional between 10 and 30 mg/kg/day. For dehydro-aripiprazole, the AUC values appeared to increase greater than dose-proportionally between 3, 10 and 30 mg/kg/day; Cmax increased dose-proportionally between 3 and 10 mg/kg/day, and greater than dose increment between 10 and 30 mg/kg/day. Accumulation in the systemic exposure of aripiprazole and dehydro-aripiprazole was observed upon repeated dosing for 1 month. No apparent sex-related differences in toxicokinetics of aripiprazole and dehydro-aripiprazole were observed.

Toxicokinetic analysis of Aripiprazole (BMS-337039) in a one-month intravenous toxicity study in rats

Dose of aripiprazole		3 mg/kg/day		10 mg/kg/day		30 mg/kg/day	
Analyte		Aripiprazole					
PK parameters[a]:							
Parameter / Sex	Study Day	M	F	M	F	M	F
Cmax (ng/mL)	Day 0	755	866	1591	2126	4649	5301
	Day 27	1210	985	2939	2597	6488	7237
AUC_{0-T} (ng•h/mL)[b]	Day 0	871	864	2436	2969	8973	18823
	Day 27	1376	1097	4489	4514	30700	35210
Tmax (h)[c]	Day 0	0.083	0.083	0.083	0.083	0.083	0.083
	Day 27	0.083	0.083	0.083	0.083	0.083	0.083
Analyte		OPC-14857 (BMS-337044, dehydro-aripiprazole)					
Parameter / Sex	Study Day	M	F	M	F	M	F
Cmax (ng/mL)	Day 0	2.1	3.3	5.5	9.1	32.7	60.1
	Day 27	2.8	4.1	13.9	18.7	119	117
AUC_{0-T} (ng•h/mL)[b]	Day 0	3.4	8.3	29.0	75.5	257	916
	Day 27	8.8	18.6	84.9	166	1859	1796
Tmax (h)[c]	Day 0	1.0	1.0	1.0	12.0	4.0	8.0
	Day 27	1.0	1.0	2.0	8.0	8.0	8.0

[a] The PK parameter values are reported as means

[b] T ranged from 2 to 24 h post-dose

[c] Tmax values are reported as medians

TK in Embryo-fetal development study in rats (i.v.)

In a definitive embryo-fetal development study, pregnant rats (9/dose group) were given daily aripiprazole intravenous doses of 3, 9 and 27 mg/kg (7.5 mg/mL aripiprazole, 150 mg/mL Captisol, 7.8 mg/mL tartaric acid in Sterile Water for Injection USP, pH adjusted to approximately 4.3) for 10 days (from day 6 through 15 of gestation). Blood samples for determination of aripiprazole and dehydro-aripiprazole were collected on day 15 of gestation at 5 and 30 min and at 1, 2, 4, 8, 12, and 24 h post-dosing from 3 rats per sampling time. The exposures of aripiprazole and dehydro-aripiprazole appeared to be dose-related. "For doses increasing in the ratio of 1:3:9, the Cmax and AUC values of aripiprazole increased in the ratio of 1:4:8 and 1:3:26, respectively. The Cmax and AUC values for dehydro-aripiprazole increased in the ratio of 1:2:11 and 1:4:86, respectively. Thus, between the 3 and 9 mg/kg/day dose levels, the AUC values for aripiprazole and dehydro-aripiprazole generally appeared to increase approximately equal to the dose increment, whereas between the 9 and 27 mg/kg/day dose levels, the AUC values appeared to increase greater than the dose increment".

Toxicokinetic analysis of Aripiprazole (BMS-337039) in an intravenous study of embryo-fetal development in rats

Analyte		Aripiprazole (BMS-337039)			OPC-14857 (BMS-337044) (dehydro-aripiprazole)		
PK parameters:							
Dose (mg/kg/day)		3[a]	9	27	3[a]	9	27
Parameter[b]	Study Day[c]						
Cmax (ng/mL)	Day 10	821	2976	6426	7.7	13.9	84.1
AUC_{0-T} (ng•h/mL)[d]	Day 10	1293	3366	34065	17.7	69.2	1522
Tmax (h)[e]	Day 10	0.083	0.083	0.083	1.0	2.0	8.0

[a] N = 8

[b] The PK parameter values are reported as means

[c] Study Day 10 was day 15 of presumed gestation in the rats.

[d] T ranges from 8 to 24 h post-dose

[e] Tmax values are reported as medians

TK in Pre- and postnatal development study in rats (i.v.)

Aripiprazole at daily intravenous doses of 3, 8 and 20 mg/kg (7.5 mg/mL aripiprazole, 150 mg/mL Captisol, 7.8 mg/mL tartaric acid in Sterile Water for Injection USP pH adjusted to approximately 4.3) was administered to 9 pregnant rats/dose on day 6 of gestation through day 4 postpartum. Blood samples were collected on day 4 of lactation at 5 and 30 min, and at 1, 2, 4, 8, 12, and 24 h post-dosing (3 rats per sampling time and 2 or 3 samples per rat) for toxicokinetic evaluation of aripiprazole and dehydro-aripiprazole (BMS-337044),. The systemic exposure of the female rats to aripiprazole and dehydro-aripiprazole between doses 3 and 20 mg/kg/day appeared to be dose-related. "For doses increasing in the ratio of 1:2.7:6.7, the Cmax and AUC values of aripiprazole increased in the ratio of 1:1.1:1.7 and 1: 2.1: 5, respectively. For dehydro-aripiprazole, the Cmax and AUC values increased in the ratio of 1:3.1:10.6 and 1: 9: 31.8, respectively. Thus,

between the 3 and 20 mg/kg/day dose levels, the AUC values for aripiprazole appeared to increase less than the dose increment, whereas values for dehydro-aripiprazole generally appeared to increase greater than the dose increment."

Toxicokinetic analysis of Aripiprazole (337039) in an intravenous study of pre-and postnatal development in Rats (Study DN04046)

Analyte		Aripiprazole (BMS-337039)			OPC-14857 (BMS-337044, dehydro-aripiprazole)		
Assay		LC/MS/MS			LC/MS/MS		
PK parameters[a]:							
Dose of aripiprazole (mg/kg)		3	8	20	3	8	20
Parameter / Sex	Lactation Day[b]						
Cmax (µg/mL)	4	4103	4685	6801	4.9	15.4	52.1
AUC_{0-T} (µg•h/mL)[c]	4	2556	5358	12863	14.6	132	464
Tmax (h)[d]	4	0.083	0.083	0.083	1.0	4.0	4.0

[a] The parameters are summarized as means

[b] The rats were administered with aripiprazole doses from day 6 of the gestation to day 4 post partum. The derived number of days of dosing ranged from 18 to 20 days for all dose levels.

[c] T ranged from 4 to 12 h post-dose

[d] Tmax is summarized as median

Toxicokinetics in Rabbits

TK parameters of aripiprazole and the active metabolite dehydroaripiprazole were determined in a definitive embryo-fetal developmental study in rabbits. Aripiprazole IM formulation (7.5 mg/ml aripiprazole, 150 mg/ml Captisol, 7.8 mg/ml tartaric acid in Sterile Water for Injection, pH approximately 4.3) was administered intravenously, as a slow bolus or by injection pump, at doses of 3, 10, and 30 mg/kg/day for 13 days to pregnant rabbits (6/dose group) from Day 7 through Day 19 of gestation. Aripiprazole and dehydroaripiprazole were determined in blood samples collected at 5 min, 30 min, and at 1, 2, 4, 8, 12, and 24 h. post-dose on Day 19 of gestation. The systemic exposure parameters for aripiprazole and dehydroaripiprazole (as assessed by Cmax and AUC in plasma) were dose-related. Thus, for doses increasing in the ratio of 1: 3: 10, the Cmax and AUC for aripiprazole increased in the ratio of 1: 3: 5 and 1: 4: 7, respectively; both the Cmax and AUC for dehydroaripiprazole increased in the ratio of 1: 4: 9. Therefore, between LD and HD, the exposure parameters for aripiprazole and dehydroaripiprazole increased approximately equally to the dose increment, with the exception of the Cmax for aripiprazole that increased less than the dose increment at the HD.

TK analysis of aripiprazole upon repeated IV administration to pregnant rabbits (Study DN04038)

Study Description or Title:	Toxicokinetic analysis of Aripiprazole (BMS-337039) in an intravenous study of embryo-fetal development in rabbits						
Test Article:	Aripiprazole (OPC-14597, OPC-31, BMS-337039)						
Study Type:	GLP						
Species	Rabbits						
Study No./Document Control Number	DN04038 / 930009017						
Location in Dossier							
Analyte		Aripiprazole (BMS-337039)			OPC-14857 (BMS-337044) (dehydro-aripiprazole)		
Assay		LC/MS/MS			LC/MS/MS		
PK parameters:							
Dose (mg/kg/day)		3	10	30	3	10	30
Parameter[a]	Study Day[b]						
Cmax (ng/mL)	Day 13	1868	5377	9941	37.4	165	329
AUC_{0-T} (ng•h/mL)[c]	Day 13	9262	35329	66559	610	2699	5671
Tmax (h)[d]	Day 13	0.083	0.083	0.083	6.0	8.0	12.0

[a] The PK parameter values are reported as means

[b] Study Day 13 was day 19 of presumed gestation in the rats.

[c] Calculated from time zero to 24 h post-dose.

[d] Tmax values are reported as medians

Toxicokinetics in monkeys

TK parameters of aripiprazole and the active metabolite dehydroaripiprazole were determined in a pivotal 1-month toxicity study in monkeys (5/sex/dose group). Aripiprazole was administered IM at daily doses of 2, 4, and 7.5 mg/kg/day for 29 days. Aripiprazole and dehydroaripiprazole were determined in blood samples collected at 10 min, 30 min, and at 1, 3, 8, and 24 h. post-dose on Days 1 and 29. The systemic exposure parameters for aripiprazole and dehydroaripiprazole (as assessed by Cmax and AUC in plasma) were dose-related over the studied dose range, increasing approximately equally to the dose increment on days 1 and 29. Thus, for doses increasing in the ratio of 1: 2: 4, the Cmax and AUC for aripiprazole on Day 29 increased in the ratio of 1: 2: 5 without apparent sex differences; for dehydro-aripiprazole the Cmax values on Day 29 increased in the ratio of 1: 3: 4 (M) and 1: 2: 3.5 (F), and the corresponding AUC increased in the ratio of 1: 3: 5 (M) and 1: 2: 4 (F). Compared to Day 1, there was some accumulation in systemic exposure upon repeated daily dosing on Day 29 (see sponsor's table on the next page).

TK analysis of aripiprazole and dehydroaripiprazole in a 1-month IM toxicity study in monkeys (Study DS04063)

Study Description or Title:	**Toxicokinetic analysis of Aripiprazole (BMS-337039) in a one-month intramuscular toxicity study in monkeys**
Test Article:	**Aripiprazole (OPC-14597, OPC-31, BMS-337039)**
Study Type:	**GLP**
Species	**Monkeys**
Study No./Document Control Number	
DS04063 / 930009043	

Vehicle/Formulation 7.5 mg/mL aripiprazol

Analyte		Aripiprazole (BMS-337039)					
Assay		LC/MS/MS					
Dose of aripiprazole		**2 mg/kg/day**		**4 mg/kg/day**		**7.5 mg/kg/day**	
PK parameters[a]:							
Parameter / Sex	**Study Day**	**M**	**F**	**M**	**F**	**M**	**F**
Cmax (ng/mL)	Day 1	637	691	1096	2065	2559	2931
	Day 29	697	767	1159	1586	3733	3763
AUC_{0-T} (ng•h/mL)[b]	Day 1	1746	1934	3678	4627	9272	9471
	Day 29	2263	2189	5600	4809	11070	9718
Tmax (h)[c]	Day 1	0.17	0.5	0.17	0.5	0.5	0.5
	Day 29	0.17	0.17	0.5	0.17	0.17	0.17

[a] The PK parameter values are reported as means

[b] Calculated from time zero to 24 h post-dose.

[c] Tmax values are reported as medians

Analyte		OPC-14857 (BMS-337044, dehydro-aripiprazole)					
Assay		LC/MS/MS					
Dose of aripiprazole		**2 mg/kg/day**		**4 mg/kg/day**		**7.5 mg/kg/day**	
PK parameters[a]:							
Parameter / Sex	**Study Day**	**M**	**F**	**M**	**F**	**M**	**F**
Cmax (ng/mL)	Day 1	40	47	79	75	167	135
	Day 29	43[b]	49	121	91	183	172
AUC_{0-T} (ng•h/mL)[c]	Day 1	329	477	878	924	2097	1716
	Day 29	554[b]	688	1799	1445	2703	2587
Tmax (h)[d]	Day 1	3.0	3.0	3.0	3.0	3.0	3.0
	Day 29	3.0[b]	3.0	3.0	3.0	3.0	3.0

[a] The PK parameter values are reported as means

[b] N = 4

[c] T ranged from 8 to 24 h post-dose

[d] Tmax values are reported as medians

PK/TK summary:

The absorption of IM aripiprazole from the injection site is rapid and extensive. Following a single intramuscular dose of aripiprazole, peak plasma concentrations for aripiprazole were observed at the first pharmacokinetic sampling time point (approximately 10 min in dogs and monkeys, and 15 min in rats). The absolute bioavailability of aripiprazole following a single IM dose of 15 mg was 99.5% in dogs and about 87% in monkeys, indicating essentially complete absorption of aripiprazole from the injection site, as compared to a much lower bioavailability (12% in dogs) upon oral administration of the same dose (indicative of extensive first-pass of aripiprazole after PO dose); the bioavailability in rats "could not be calculated due to loss of the data resulting from bioanalytical discrepancies". Specific studies on the distribution of aripiprazole and its metabolites following IM administration were not conducted by the sponsor. Following IV administration of the IM injection formulation in dogs (15 mg single bolus dose), aripiprazole was extensively distributed to extravascular tissues (VSS =5.14 l/kg). According to the sponsor, the tissue distribution of aripiprazole was "characterized in studies following oral administration of radio-labeled aripiprazole; the details of these studies are included in the ABILIFY oral tablet submission. These studies showed that aripiprazole is highly bound to serum protein but distributes extensively into tissues, including brain."

Specific studies to examine the metabolism of aripiprazole following IM administration were not conducted by the sponsor. Plasma exposure to aripiprazole metabolites upon IM administration of aripiprazole was determined in TK studies, as a part of toxicology studies, in rats, dogs, and monkeys. In *rats*, upon repeat-dose IM administration of aripiprazole at doses of 1 and 3.75 mg/kg/day for 2 weeks, the plasma exposures to aripiprazole and 5 of its metabolites [the active metabolite dehydro-aripiprazole (BMS-337044), BMS-337040, BMS-337045, BMS-337047, and 1-(2, 3-dichlorophenyl) piperazine (DCPP)] were dose related. The AUC values of BMS-337040, dehydro-aripiprazole, and BMS-337045 compared to aripiprazole were 3.0%, 0.3%, and 0.2% in males and 1.4%, 0.6%, and 0.4% in females, respectively. In *dogs*, the predominant metabolite in plasma following a single-dose IM (as well as IV and SC) administration of 15 mg aripiprazole was the active metabolite BMS-337044; the other four determined metabolites [BMS-337040, BMS-337045, BMS-337047, and DCPP] were minor. The mean AUC_{0-T} of the active metabolite BMS-337044 was 21% of the mean AUC_{0-T} of the parent compound; for the other 4 metabolites, the individual metabolite to parent AUC_{0-T} ratios were: 8.6% for BMS-337045, 1.9% for BMS-337047, 1.2% for DCPP, and 0.2% for BMS-337040. The individual metabolite to parent ratios were essentially similar among IM, IV and SC routes of administration, while after PO administration, the individual metabolite to parent AUC_{0-T} ratios were much higher in comparison to either IM, IV, or SC routes. Thus, after administration of the same single dose via the oral route, individual to parent AUC_{0-T} ratios for BMS-337044, BMS-337045 and BMS-337047 in dogs were 169%, 80%, and 43%, respectively. In *monkeys,* the predominant metabolites in plasma were BMS-337044 (dehydro-aripiprazole) and BMS-337047. The mean AUC_{0-T} values were about 7-15% and 10-19% that of the parent for dehydro-aripiprazole and BMS-337047, respectively. Plasma concentrations of metabolites BMS-337040, BMS-337045, and DCPP each were < 3% that of the parent. These results suggested that aripiprazole was not extensively metabolized after IV and IM administration to monkeys and that the extent of metabolism for these routes of administration was essentially similar.

Metabolism is the major mechanism for aripiprazole clearance. The estimated total body clearance in dogs was 74-88% of the hepatic blood flow, suggesting a high hepatic drug extraction in this species. The mean systemic clearance value of aripiprazole after IV administration to dogs was 21 mL/min, whereas the total clearance in humans was much lower (0.72 mL/min/kg after a 2 mg IV dose of aripiprazole) [Open-label, randomized, three-way crossover study of the absolute bioavailability of aripiprazole 5 mg commercial tablet and aripiprazole 5 mg IM injection with reference to 2 mg IV infusion in healthy subjects (Study CN138016). July 20, 2001. BMS Document Control No. 930000380 (as cited by the sponsor)]. The systemic clearance of aripiprazole in rats and monkeys after a single IV administration could not be determined due to loss of pharmacokinetic data resulting from the bioanalytical discrepancies. Specific preclinical studies to examine the excretion of aripiprazole and its metabolites following IM administration of aripiprazole were not conducted.

The available data suggest that the metabolism of aripiprazole is qualitatively similar in the tested animal species and humans. The active metabolite in animals and humans is dehydro-aripiprazole, which is also a major circulating metabolite in humans, dogs, and monkeys. The other metabolites have little, if any, pharmacological activity, and do not substantially contribute towards the pharmacological effects of aripiprazole.

The systemic exposure to aripiprazole was assessed in rats, rabbits and monkeys on the basis of TK data collected in single- and repeat-dose IM and IV toxicology studies (pivotal studies in rats and rabbits employed the IV instead of IM route to deliver the IM formulation in order to achieve acceptable multiples of human exposure, because the volume of the IM formulation that could be administered to rats and rabbits was limited due to their small muscle mass, and acceptable multiples of human exposure could not be reached by the IM route in these species). The systemic exposure to aripiprazole and the active metabolite upon a repeat IM or IV administration of the IM formulation (in 1-month toxicity studies in rats and monkeys) increased in a dose-related manner; accumulation of systemic exposures to aripiprazole and its active metabolite was observed in rats and monkeys (much more pronounced in the former) after 1 month of repeated daily IV (rats) or IM (monkeys) administration as compared to day 1. There were no apparent sex-related exposure differences.

PK/TK conclusions:

Absorption of aripiprazole from the injection site upon IM administration in rats, dogs, and monkeys is rapid (Cmax for aripiprazole following a single intramuscular dose was observed at approximately 10 min in dogs and monkeys, and 15 min in rats) and extensive (the absolute bioavailability of aripiprazole following a single IM dose was 99.5% in dogs and about 87% in monkeys, indicating essentially complete absorption of aripiprazole from the injection site, as compared to a much lower bioavailability (12% in dogs) upon oral administration of the same dose; the bioavailability in rats "could not be calculated due to loss of the data resulting from bioanalytical discrepancies".

Specific studies to examine the distribution, metabolism, and excretion of aripiprazole following IM administration have not been conducted by the sponsor. Aripiprazole metabolites upon IM and/or IV administration of aripiprazole were determined in PK or TK studies in rats, rabbits, dogs, and monkeys. The metabolites identified after IM administration were the same as those identified after IV and oral administration. The available data suggest that the metabolism of aripiprazole is qualitatively similar across the tested species (rats, rabbits, dogs, and monkeys) and humans.

The systemic exposure to aripiprazole and the active metabolite (as assessed by Cmax and AUC values upon repeat IM or IV administration of the IM formulation in 1-month toxicity studies in monkeys and rats) increased in a dose-related manner. Accumulation of systemic exposures to aripiprazole and its active metabolite was observed in rats and monkeys after 1 month of repeated daily administration of aripiprazole by IV (rats) or IM (monkeys) injection as compared to day 1. The accumulation was much more pronounced in rats. There were no apparent sex-related exposure differences in the tested animal species.

IV. GENERAL TOXICOLOGY:

The toxicity studies conducted with IM aripiprazole included: 2-week and 1-month repeat-dose toxicity studies in rats and monkeys, studies of embryo-fetal development in rats and rabbits, a study of pre- and postnatal development in rats, a single-dose IM irritation study in rats and rabbits, and a 2-week IM irritation study in rats. These studies are reviewed for the present application. Additional range-finding studies in pregnant rats and rabbits were conducted as a basis for dose selection for the definitive embryo-fetal development studies.

Study title: Study **DM04011 - One-Month Intravenous Toxicity Study in Rats**

Key study findings: A repeat-dose IV daily administration of IM aripiprazole formulation at doses of 3, 10, and 30 mg/kg/day for 1 month to rats (10/sex/group) resulted in pharmacologically-related clinical signs (dose-related decreased activity) at all doses, and morphologic changes in the adrenals at HD and in female reproductive and mammary tissues at all doses. In the females, the morphologic changes included (at all doses): decrease in the total number of corpora lutea in the ovary with increased proportion of large corpora lutea, dose-related persistent diestrus with excessive vaginal mucification and mildly decreased uterine weights, and hyperplasia of mammary glandular tissue. In the males, atrophy of mammary glandular tissue was observed at all doses. Adrenal gland weights were increased at the HD (30 mg/kg/day) in both sexes, in correlation with the microscopic finding of hypertrophy of the zona fasciculata in the adrenal cortex (F). There was no direct target organ toxicity at any dose level; the observed changes were a likely manifestation of exaggerated pharmacological effect. A NOEL was not reached, but aripiprazole was well tolerated at 3 mg/kg/day. Systemic exposures to aripiprazole at 3 mg/kg/day were 7 to 8 times (Cmax) and 0.5 to 0.6 times (AUC) human exposures at the MRHD of 30 mg IM. Systemic exposures to aripiprazole at 10 and 30 mg/kg/day were 18 to 51 times based on Cmax and 2 to 15 times based on AUC human exposures at the MRHD.

Study no: DM04011
Volume # 1
Conducting laboratory and location: [redacted]
Date of study initiation: April 20, 2004
GLP compliance: Yes
QA report: yes
Drug, lot #, radiolabel, and % purity: BMS-337039, Batch # R4217; [redacted] purity

Formulation/vehicle: [redacted]

Methods (unique aspects):
Dosing:

Species/strain: Rat [redacted]
#/sex/group or time point (main study): 10/sex/group.

Group	Daily Doses			Number of Animals									
				Toxicity Group		Toxicokinetic Group		Clinical Pathology		Necropsy			
				Total		Day 0 and Term		Termination Week 5		Termination Week 5		Microscopic Pathology	
	Dose[a] (mg/kg)	Volume (mL/kg)	Conc. (mg/mL)	M	F	M	F	M	F	M	F	M	F
1	0	4	0	10	10	-	-	10	10	10	10	10	10
2	3	0.4	7.5	10	10	12	12	10	10	10	10	X	X
3	10	1.33	7.5	10	10	12	12	10	10	10	10	X	X
4	30	4	7.5	10	10	12	12[b]	10	10	10	10	10	10

[a]Doses represent active ingredient [b]Only 11 animals were present at termination. M = Male F = Female
mg/kg = milligrams of test article per kilogram of body weight
X = microscopic pathology was conducted on target tissues in groups 2 and 3, see section 2.18.4.

Satellite groups used for toxicokinetics: TK (12/sex/dose group). TK samples were collected at 8 time points (5 min, 30 min, 1, 2, 4, 8, 12 and 24 h. post-dose) on Days 0 and at termination of the study (3 animals/sex/group/time point)
Age (initial): 9 weeks
Weight:

	Mean	Range
Male:	309	285 – 335
Female:	222	205 – 248

Doses in administered units: 3, 10, 30 mg/kg/day
Dose selection: The doses were selected on the basis of a 10-day range-finding study in pregnant rats (BMS Study No. DN04018) at aripiprazole IV doses of 1, 3, 10 and 30 mg/kg/day (7.5 mg/ml in ————). Ptosis and lacrimation were observed at 10 and 30 mg/kg/day; at HD (30 mg/kg/day), decrease in, body weight (8% relative to control) and food consumption were seen. No drug-related clinical signs or changes in body weight and/or food consumption were seen at the lower doses (1 and 3 mg/kg/day).

Route, form, volume, and infusion rate: IM aripiprazole formulation as a solution (7.5 mg/ml) in ———— was administered intravenously by bolus injection once daily for 28 days at doses of 3, 10, or 30 mg/kg (dose volumes of 0.4, 1.33, or 4 mL/kg, respectively). The control group was administered 4 mL/kg of the vehicle: ————

Observations and times: Evaluation criteria included: survival, clinical signs including injection site observations, body weight, food consumption, ophthalmology, clinical pathology parameters, organ weights, and macroscopic and microscopic pathology.

Clinical signs:

> Observations for mortality and general condition were made for all animals at least twice daily (once in the morning and once in the afternoon). Animals in poor health or in a possible moribund condition were identified for further monitoring and possible euthanasia.
>
> Observations for signs of toxic or pharmacologic effects were made at least once daily for each animal in the Toxicity group only.

Body weights:

Non-fasted body weights for Toxicity group animals were recorded twice pretest, three times during Week 1 (to monitor health status) and weekly (over a 7-day period) during the remainder of the study. Only the last body weights recorded during Week 1 are reported.

Food consumption:

Feed consumption was measured (weighed) for all Toxicity group animals during the week prior to treatment initiation and weekly throughout the study.

Ophthalmoscopy:

Toxicity group animals were examined pretest and at the end of the dosing period. Eyelids, lacrimal apparatus and conjunctiva were examined visually; cornea, anterior chamber, iris, lens, vitreous humor, retina and optic disc were examined by indirect ophthalmoscopy. The eyes were examined after instillation of the mydriatic, atropine sulfate, USP 1%.

EKG: Not performed

Hematology:

Number of Animals	10/sex/group at termination
Parameters Evaluated	

HCT (hematocrit)
RBC (red blood cell count)
HGB (hemoglobin)
MCH (mean corpuscular hemoglobin)
MCHC (mean corpuscular hemoglobin concentration)
MCV (mean cell volume)
RDW (red cell distribution width)
absolute reticulocyte count
% reticulocytes
red blood cell morphology
WBC (white blood cell count)
leukocyte count (total and differential)
white blood cell morphology
platelet count
platelet morphology

A bone marrow differential count was not performed as it was not deemed necessary by the Study Director based on other hematology and pathology results.

Coagulation:

prothrombin time
activated partial thromboplastin time
fibrinogen

Clinical chemistry:

Aspartate aminotransferase (*Kinetic - Modified IFCC Technique*)
Alanine aminotransferase (*Kinetic - Modified IFCC Technique*)
Alkaline phosphatase (*Kinetic – Modified AMP Buffer*)
Sorbitol dehydrogenase (*Sigma Diagnostics NADH*)
Blood urea nitrogen (*Kinetic - Modified Urease*)
Creatinine (*Kinetic –Modified Jaffe Method*)
Glucose (*Hexokinase Method*)

Cholesterol (*Enzymatic – Modified Trinder Method*)
Triglycerides (*GPO Triglyceride-lipase Method*)
Total protein (*Biuret Technique*)
Albumin (*Bromocresol Green Method*)
Total bilirubin (*Modified Wahlefield et al.*)
Sodium (*Ion Selective Electrode*)
Potassium (*Ion Selective Electrode*)
Chloride (*Ion Selective Electrode*)
Calcium (*Cresolphthalein Complexone Method*)
Inorganic phosphorus (*Phosphomolybdate - UV Method*)
Bicarbonate - CO_2 content (*UV/PEPC Method*)

Other
Globulin (*calculated value; total protein - albumin*)
Albumin/globulin ratio (*calculated value; albumin ÷ globulin*)

Urinalysis:

Number of Animals/Intervals 10/sex/group at termination

Protein
Glucose
Ketones
Occult blood
pH
Bilirubin
Urobilinogen

Other
Appearance
Specific gravity (*Clinical Refractometer, Atago Uricon-N*)
Volume

Gross pathology:

Necropsy was performed on 10 toxicity animals/sex/group after animals had been treated for at least 28 days. Animals were fasted overnight prior to necropsy (and terminal blood collections). A complete macroscopic examination was performed on all toxicity group animals. All abnormal observations were recorded. The necropsy consisted of an external examination, including identification of all clinically-recorded lesions, as well as a detailed internal examination.

Organs weighed:

adrenals	prostate
brain	spleen
heart	testes
kidneys	thymus
liver	thyroid/parathyroids
ovaries	uterus (with cervix)
pituitary	

Histopathology: The tissues listed in sponsor's table below were obtained from all toxicity animals at the scheduled necropsies. Tissue samples and gross lesions from all control and HD animals and target organs from LD and MD animals (Table) were processed and stained (hematoxylin and eosin stain). Tissue sections and gross lesions from control and HD animals were examined microscopically. Tissue sections of target organs from LD and MD groups were also examined microscopically.

List of organs processed and examined microscopically

ORGAN NAME	PRESERVED	EXAMINED MICROSCOPICALLY
adrenal glands	X	X[b]
aorta (thoracic)	X	X
bone marrow smear (rib)	X	[c]
bone (sternum, femur with joint)	X	X
bone marrow (sternum, femur)	X	X[a]
brain (medulla, pons, cerebrum and cerebellum)	X	X
epididymides	X	X
esophagus	X	X
eyes (with optic nerve)	X	X
Harderian glands	X	X
heart	X	X
injection site (tail)	X	X[b]
kidneys	X	X
lacrimal glands	X	X
large intestine (cecum, colon)	X	X
liver	X	X
lungs (with mainstem bronchi)	X	X
lymph nodes (mesenteric, mediastinal)	X	X
mammary gland (inguinal)	X	X[b]
nerve (sciatic)	X	X
ovaries	X	X[b]
pancreas	X	X
pituitary gland	X	X
prostate gland	X	X
salivary glands (submandibular)	X	X
seminal vesicles	X	X
skeletal muscle (*Biceps femoris*)	X	X
skin (right inguinal)	X	X
small intestine (duodenum, ileum, jejunum)	X	X
spinal cord (cervical, thoracic, lumbar)	X	X
spleen	X	X[b]
stomach	X	X
testes	X	X
thymus	X	X
thyroid/parathyroid glands	X	X
tongue	X	X
trachea	X	X
urinary bladder	X	X
uterus (body/horns) with cervix	X	X[b]
vagina	X	X[b]
tissues with macroscopic findings including tissue masses	X	X

[a]Qualitative examination was performed. (There was no need to evaluate bone marrow smears).
[b]Target organs were also examined microscopically in groups 2 and 3.
[c]Tissue not examined.

Toxicokinetics: Plasma concentrations of aripiprazole and its pharmacologically active metabolite BMS-337044 (dehydro-aripiprazole) were measured after dosing on Day 0 (initial dose) and during Week 4 in corresponding satellite groups of 12 male and 12 female rats at each dose level.

Results: The results are summarized in sponsor's tables on next pages.

Mortality: There was no drug-related mortality.

Clinical signs: At 3, 10, and 30 mg/kg/day, drug-related clinical signs included dose-related decreased activity after dosing in both sexes, that was considered to be pharmacologically mediated. At the LD, animals had decreased activity after dosing on Days 1 and 3, while at the higher doses, animals were affected on most (10 mg/kg/day) or all days (30 mg/kg/day) after dosing.

Body weights:

Drug-related, statistically significant decreases in mean body weight (7 to 10% lower than control) were observed in HDM beginning at week 2, and increases in mean body weight (9 to 13% greater than control) were observed in LDF beginning at week 1, attributable, at least in part, to increased food consumption.

Food consumption:

Drug-related, significant increases in food consumption were observed in LDF during weeks 1 to 3 (11 to 14% higher than controls).

Ophthalmoscopy: No notable findings.

Hematology: No notable findings

Clinical chemistry:

At all doses, serum triglycerides were mildly to moderately decreased (28 to 53%, compared to controls) in males. Additional test article-related clinical chemistry changes at 30 mg/kg/day included minimally decreased calcium (3%, compared to controls) in both sexes; mildly decreased glucose (22%, compared to controls) in males; minimally or mildly decreased total cholesterol (41%), alkaline phosphatase (25%, compared to controls), and bicarbonate (6%, compared to controls) in females. None of these test article-related changes were considered to be toxicologically significant.

Urinalysis: Moderately decreased urine volumes at HD in both males and females (-50% and -33% vs.control means, respectively), with associated increases in specific gravity.

Organ weights:

Administration of BMS-337039 at all doses was associated with mildly decreased absolute and relative uterus weights (27 to 39% absolute) in females. Additionally, there were drug-related mild decreases in absolute and relative thymus weights (23 to 34% absolute) at 10 and 30 mg/kg/day in males. Further drug-related organ weight changes at 30 mg/kg/day included a minimal increase in absolute and relative adrenal gland weights (13 to 17% absolute) in both sexes and a minimal decrease in absolute and relative thymus weights (17% absolute) in females.

There were no microscopic correlates for the decreased thymus weight changes of males at 10 mg/kg/day and both sexes at 30 mg/kg/day.

The statistically significant decreases in absolute and relative uterine weights in females at all doses likely were a consequence of the higher number of treated females with persistent diestrus.

Gross pathology: No notable findings

Histopathology: In the females, the morphologic changes included (at all doses): decrease in the total number of corpora lutea in the ovary with increased proportion of large corpora lutea, dose-related persistent diestrus with excessive vaginal mucification and mildly decreased uterine weights, and hyperplasia of mammary glandular tissue. In the males, atrophy of mammary glandular tissue was observed at all doses. Minimal to mild hypertrophy of cortical cells of the zona fasciculata in adrenal glands of females at HD.

One-Month Intravenous Toxicity Study in Rats (Study No. DM04011)

Daily Dose (mg/kg):	(0) Control		3		10		30	
Number of Animals:	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (g) (%[c]) Week 4	410	258	+1	+13**	-5	+2	-10**	-6
Food Consumption (g/kg/day) (%[c]) Week 1	--	73	--	+14**	--	+8	--	-4
Clinical Observations								
Decreased activity	--	--	+	+	++	++	+++	+++
Ophthalmoscopy	--	--	--	--	--	--	--	--
Hematology	--	--	--	--	--	--	--	--
Serum Chemistry	--	--	--	--	--	--	--	--
Urinalysis								
Urine Volume (mL)	18.1	12.2	12.2	11.3	11.8	10.2	6.5	7.6
Organ Weights (g) (%[d])								
Adrenal Glands	0.0746	0.0787	+7	-3	+2	-12	+12	+17
Thymus	0.4946	0.4398	-14	+17*	-23**	-4	-34**	-17*
Uterus		0.7819		-27**		-39**		-33**
Gross Pathology	--	--	--	--	--	--	--	--

One-Month Intravenous Toxicity Study in Rats (Study No. DM04011) - continued

Daily Dose (mg/kg):	(0) Control		3		10		30	
Number of Animals:	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Histopathology								
Adrenal Cortex								
Hypertrophy, zona fasciculata	0/10	0/10	0/10	0/10	0/10	0/10	0/10	9/10
Minimal severity	0/10	0/10	0/10	0/10	0/10	0/10	0/10	7/10
Mild severity	0/10	0/10	0/10	0/10	0/10	0/10	0/10	2/10
Ovary								
Mean total CL/female		34.1		24.8		17.7		19.6
Mean percent large, presumed functional CL[e]		36		59		60		60
Vagina/Uterus								
Number of females in persistent diestrus[f]		0/10		2/10		3/10		5/10
Vagina								
Mucification (excessive)		0/10		6/10		4/10		5/10
Minimal severity		0/10		5/10		3/10		2/10
Mild severity		0/10		1/10		1/10		3/10

Abbreviations: -- No noteworthy findings, ND = not determined, CL = Corpora lutea, + Mild, ++ Moderate, +++ Marked
* p≤0.05, ** p≤0.01, Statistical analysis - see table endnotes
All footnotes are available as table end notes.

Histopathology (Continued)								
Mammary Gland								
Hyperplasia, glandular tissue	0/10	0/10	0/10	7/10	0/10	6/10	0/10	6/10
Minimal severity	0/10	0/10	0/10	6/10	0/10	4/10	0/10	1/10
Mild severity	0/10	0/10	0/10	1/10	0/10	2/10	0/10	4//10
Moderate severity	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10
Atrophy, glandular tissue	0/10	0/10	4/10	0/10	8/10	0/10	7/10	0/10
Minimal severity	0/10	0/10	3/10	0/10	2/10	0/10	3/10	0/10
Mild severity	0/10	0/10	0/10	0/10	4/10	0/10	1/10	0/10
Moderate severity	0/10	0/10	1/10	0/10	1/10	0/10	1/10	0/10
Marked severity	0/10	0/10	0/10	0/10	1/10	0/10	2/10	0/10

[b] Day 0 = initial dose

[c] For controls, group means are shown. For treated groups, percent differences from controls are shown (treated value - control value ÷ control value × 100). Statistical significance is based on actual data (not on the percent differences).

[d] For controls, group means are shown. For treated groups, percent differences from controls are shown for absolute weights (treated value - control value ÷ control value × 100). Statistical significance is based on actual data (not on the percent differences). Both absolute and relative weights differed from controls in the direction indicated.

[e] The percent presumed functional CL was determined by dividing the number of active CL by the total number of CL.

[f] Based on vaginal and uterine morphology.

Concentration of IM aripiprazole administered to all drug-treated groups: 7.5 mg/mL.

Toxicokinetics: Toxicokinetic evaluations demonstrated that exposures to aripiprazole and BMS-337044were dose related and, in general, no sex-related differences were apparent. Exposures (Cmax and AUC) between 3 and 10 mg/kg/day generally increased in a dose-proportional manner. Between 10 and 30 mg/kg/day, the majority of exposure values (Cmax and AUC) increased greater than dose proportionally (both sampling intervals), particularly AUC values for BMS-337044. With repeated dosing, accumulation in systemic exposures to aripiprazole (up to 3.4-fold) and BMS-337044 (up to 7.2-fold) was observed. The Cmax and AUC values for aripiprazole and BMS-337044 are listed in the following sponsor's table:

TK parameters, 1-month IV toxicity study in rats

Dose (mg/kg/day)	Study Day	Cmax (ng/mL)				AUC[a] (ng•h/mL)			
		Aripiprazole		BMS-337044		Aripiprazole		BMS-337044	
		Male	Female	Male	Female	Male	Female	Male	Female
3	0	755	866	2.1	3.3	871	864	3.4	8.3
	27	1210	985	2.8	4.1	1376	1097	8.8	19
10	0	1591	2126	5.5	9.1	2436	2969	29	76
	27	2939	2597	14	19	4489	4514	85	166
30	0	4649	5301	33	60	8973	18823	257	916
	27	6488	7237	119	117	30700	35210	1859	1796
Dose Ratio	**Day**	**Cmax Ratios**				**AUC Ratios**			
1:3.3:10	0	1:2.1:6	1:2.5:6	1:2.6:16	1:2.7:18	1:2.8:10	1:3.4:22	1:8.5:75	1:9.1:111
	27	1:2.4:5	1:2.6:7	1:5.0:43	1:4.5:28	1:3.3:22	1:4.1:32	1:9.7:211	1:8.9:97

[a] Calculated from time zero to the time of the last quantifiable plasma concentration, ranging from 2 to 24 hours.

Multiples of human systemic exposures for aripiprazole and dehydroaripiprazole in 1-Month IV Toxicity Study in Rats

Species (Study)	Type of Study	Sex	Aripiprazole Dose (mg/kg/day)	Cmax (ng/mL)	Cmax multiples[a]	AUC(0-T) (ng•h/mL)	AUC(0-T) multiples[a]
Aripiprazole							
Rat (DM04011)	1-Month IV Toxicity (Day 27)[b]	M	3	1210	8	1376	0.6
			10	2939	21	4489	2
			30	6488	45	30700	13
		F	3	985	7	1097	0.5
			10	2597	18	4514	2
			30	7237	51	35210	15
Dehydroaripiprazole							
Rat (DM04011)	1-Month IV Toxicity (Day 27)[b]	M	3	2.8	0.4	8.8	0.1
			10	14	2	85	0.9
			30	119	16	1859	20
		F	3	4.1	0.6	19	0.2
			10	19	3	166	2
			30	117	16	1796	20

Summary of individual study findings:

IM aripiprazole as a solution (7.5 mg/mL) in [redacted] was administered intravenously by bolus injection once daily for 1 month to groups of 10 male and 10 female rats each at doses of 3, 10, or 30 mg/kg (dose volumes of 0.4, 1.33, or 4 ml/kg, respectively). A control group of 10 rats/sex was administered 4 ml/kg of the vehicle [redacted] Evaluation criteria included: survival, clinical signs including injection site observations, body weight, food consumption, ophthalmology, clinical pathology parameters, organ weights, and macroscopic and microscopic pathology. Plasma concentrations of aripiprazole and its pharmacologically active metabolite BMS-337044

(dehydro-aripiprazole) were measured after dosing on Day 0 (initial dose) and during Week 4 in corresponding satellite groups of 12 male and 12 female rats at each dose level.
Drug-related changes observed only at 3 mg/kg/day were minimal increases in body weight and food consumption in females. At 3, 10, and 30 mg/kg/day, drug-related changes included dose-related decreased activity after dosing in both sexes, that was considered to be pharmacologically mediated. At the low dose of 3 mg/kg/day, animals had decreased activity after dosing on Days 1 and 3, whereas at the higher doses, animals were affected on most (10 mg/kg/day) or all days (30 mg/kg/day) after dosing. Other findings at all doses included mildly decreased uterine weights, increased mean percentage of large corpora lutea and associated decreases in the total number of CL in the ovaries, atrophy of mammary glandular tissue in males, hyperplasia of mammary glandular tissue in females, excessive vaginal mucification; and dose-related persistent diestrus. At 10 and 30 mg/kg/day, mild decreases in thymus weights were observed in males with no microscopic correlates. Additional drug-related changes at 30 mg/kg/day included minimally decreased body weight in males, moderately decreased urine volumes with associated increases in specific gravity and minimally increased adrenal gland weights in both sexes, minimally decreased thymus weight in females with no microscopic correlates, and minimal to mild hypertrophy of cortical cells of the zona fasciculata in adrenal glands of females.
There was no direct target organ toxicity at any dose level. A NOEL was not reached, but aripiprazole was well tolerated at 3 mg/kg/day. Systemic exposures to aripiprazole at 3 mg/kg/day were 7 to 8 times (Cmax) and 0.5 to 0.6 times (AUC) human exposures at the MRHD of 30 mg IM. Systemic exposures to aripiprazole at 10 and 30 mg/kg/day were 18 to 51 times based on Cmax and 2 to 15 times based on AUC human exposures at the MRHD.

Study title: Study DS04063 - **One-Month Intramuscular Toxicity Study in Monkeys**

Key study findings: Repeated intramuscular administration of aripiprazole IM formulation [redacted] to monkeys (5/sex/dose) at daily doses of 2, 4, 7.5 mg/kg/day (and a vehicle control group) for 1 month resulted in the following effects at all doses: pharmacologically mediated CNS clinical signs (decreased activity and tremors), decreased food consumption during the dosing period (22-28% lower than control at 2 mg/kg/day, and 51-59% lower than control at 4 and 7.5 mg/kg/day), and increased frequency of scabbing and reversible muscle injury in injection sites. The daily injection volumes were 0.26, 0.53, and 1 ml/kg, for LD, MD and HD, respectively, and 1 ml/kg for control, but not exceeding 1.5 ml at a time to any one injection site; the injection sites were alternated daily between the right and left posterior thigh muscles). Microscopically, injection site changes observed in Captisol (vehicle) control group were slight and less pronounced than the injection site changes at 2, 4, and 7.5 mg/kg/day, suggestive of a drug-related effect. Injection site changes attributed to aripiprazole included increased incidence and/or severity of skeletal muscle necrosis (minimal to mild), degeneration (mild to moderate), and regeneration (mild to moderate) at all doses; increased severity of subacute inflammation (mild) at 4 and 7.5 mg/kg/day; and increased incidence and severity of fibroplasia/fibrosis (minimal to mild) at 7.5 mg/kg/day. Drug-related clinical chemistry changes at 4 and 7.5 mg/kg/day included slightly decreased serum GGT in males, and increased serum AST (means approximately 2x the control mean values in MDF and HDF, and approximately 3 times the control in one male HD animal). The increases in serum AST observed at MD and HD (4 and 7.5 mg/kg/day) were likely a consequence of the skeletal muscle injury at injection sites. Systemic exposures to aripiprazole and BMS-337044 were dose-proportional with no apparent sex-related differences. There was no appreciable accumulation

after 1 month of dosing. Following a 1-month post-dose recovery period, all aripiprazole-related clinical pathology changes were reversible.
NOAEL: Not reached (<2 mg/kg/day). At the lowest tested IM dose of 2 mg/kg/day, plasma AUC exposures for aripiprazole and its active metabolite, dehydroaripiprazole, were 1x and 6x, respectively, the human AUC exposures at MRHD (30 mg IM ariupiprazole).
Study no: DS04063
Volume # 1
Conducting laboratory and location:
Bristol-Myers Squibb
Pharmaceutical Research Institute
Departments of Toxicology and Pathology
Syracuse, New York USA
Date of study initiation: April 6, 2004
GLP compliance: Yes
QA report: yes
Drug, lot #, radiolabel, and % purity: BMS-337039, Batch # R4217; [redacted] purity
Formulation/vehicle: [redacted]
Methods (unique aspects): Administration: Daily dose volumes that exceeded 2 ml were divided and administered at separate sites in the muscle so that no more than 1.5 ml was delivered to any one site. In addition, the injection sites were alternated daily between the right and left posterior thigh muscles. Examinations of injection sites included gross and microscopic pathology. Necropsies were performed after 1 month of dosing [in 2 or 3 monkeys/sex/group (depending on survival) and after a 1-month post-dose recovery period (in the remaining animals).
Dosing:
Species/strain: Monkey/Cynomolgus
#/sex/group or time point (main study): 5/ sex/group
Age: Approximately 2-3 years
Weight (initial): between 2.0 and 2.8 kg (males) and 2.0 and 2.6 kg (females)
Doses in administered units: 2, 4, 7.5 mg/kg/day
Dose selection: The doses were selected on the basis of a two-week intramuscular toxicity study in monkeys (4/sex/group) at IM aripiprazole doses of 2, 4, and 7.5 mg/ml, with a 2-week post-dose recovery period. At all doses, dose-related clinical signs (increased incidences of tremors and hypoactivity) and reduced food consumption were found in both genders. At 7.5 mg/kg/day, aripiprazole administration was associated with minimal increases in reticulocyte count as well as in serum ALT (in HDM and HDF) and serum AST (in HDF). In addition, serum GGT was mildly decreased, and urine pH was minimally increased in HDM. Microscopic findings at the injection sites were present in all groups, including controls, and consisted of degeneration, necrosis, and regeneration of skeletal muscle and subacute inflammation, hemorrhage, edema, and fibroplasia/fibrosis in skeletal muscle and adjacent connective tissues. Microscopic changes at the injection sites were "generally minimal" in the Captisol (vehicle) control and 2 and 4 mg/kg/day groups and "generally mild" in the 7.5 mg/kg/day group. Following a 2-week post-dose period, recovery from the aripiprazole-related clinical and clinical pathology changes was complete, and there was nearly complete reversibility of injection site changes.
Route, form, volume, and infusion rate: IM aripiprazole formulation as a solution (7.5 mg/ml) in [redacted] was administered intramuscularly once daily for 1 month at doses of 2, 4, and 7.5 mg/kg (dose volumes of

0.26, 0.53, or 1 ml/kg, respectively). The control group was administered 1 ml/kg of the vehicle [redacted] "Daily dose volumes that exceeded 2 ml were divided and administered at separate sites in the muscle so that no more than 1.5 ml was delivered to any one site. In addition, the injection sites were alternated daily between the right and left posterior thigh muscles".

Observations and times: Evaluation criteria included: survival; clinical signs and injection site observations; body weight; food consumption; physical, neurologic, ophthalmologic, and electrocardiographic examinations; clinical pathology parameters, organ weights; and macroscopic and microscopic pathology. Plasma concentrations of aripiprazole and its pharmacologically active metabolite BMS-337044 (dehydro-aripiprazole) were measured after dosing on Days 1 and 29.

- Clinical signs: Observations for clinical signs and mortality were made twice daily.
- Physical examinations were conducted by a veterinarian prior to study inception and on days 23 and 57. Physical examinations included an assessment of general health status, neurologic function and status, heart and lung auscultation, temperature, pulse rate, and respiratory rate.
- Body weights: Pretest and at least once each week thereafter.
- Food consumption: Measured daily, including 4 days pretest.
- Ophthalmoscopy: Ophthalmologic examinations were performed in conjunction with physical examinations and included examination of external structures of the eye as well as a fundus examination by direct ophthalmoscopy.
- EKG: Performed prior to study inception and on days 23 and 49 or 50.

Electrocardiograms were analyzed for: heart rate, durations of the P wave, PR interval, QRS complex, QT interval, QTc interval (Fridericia method for correction1), and ST segment, and amplitudes of the P, R and T waves.

- Hematology: Hemoglobin, hematocrit, erythrocyte count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, absolute reticulocyte count, relative reticulocyte count, red cell distribution width, absolute total and differential leukocyte counts, platelet count, and evaluation of cell morphology in peripheral blood smears.
- Coagulation: Prothrombin time, activated partial thromboplastin time, and plasma fibrinogen.
- Clinical chemistry: Blood samples for scheduled clinical pathology tests were obtained from the femoral vein from fasted, anesthetized animals, prior to the first dose and prior to a daily dose during week 4, and during week 3 of the postdose period. Urea nitrogen, creatinine, glucose, total cholesterol, total protein, albumin, globulins, albumin/globulin ratio, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, triglycerides, gamma glutamyltransferase, sodium, potassium, bicarbonate, calcium, chloride, and phosphorus.
- Urinalysis: Performed on urine collected over an approximate 18-hour period pretest, during week 4, and during week 3 of the postdose period. The determinations included: urinary sediments; output, specific gravity, pH, color and appearance, and qualitative determinations of protein, glucose, ketones, bilirubin, occult blood, and urobilinogen.
- Gross pathology: Two or 3 monkeys/sex/group (depending on survival) were necropsied after 1 month of dosing, and the remaining animals were necropsied after a 1-month post-dose recovery period. A complete necropsy was conducted on all animals and included gross examination and collection of the following organs and tissues: adrenal glands, aorta, bone and bone marrow (sternum, rib, femur), brain, cervix, epididymides, esophagus, eyes (with optic nerve), gallbladder, heart, injection sites (muscle), kidneys, large intestine (cecum, colon), liver,

lung, lymph nodes (mandibular and mesenteric), mammary gland, ocular accessory gland (lacrimal gland), ovaries, pancreas, parathyroid gland, peripheral nerve (sciatic and axillary), pituitary gland, prostate gland, salivary gland (mandibular), seminal vesicles, skeletal muscle (psoas), skin (dorsal thorax), small intestine (duodenum, jejunum, ileum), spinal cord (cervical, lumbar), spleen, stomach (cardia, fundus, pylorus), testes, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus, and vagina.

- Organs weighed: The following organs were weighed for all animals that survived to the scheduled necropsies: adrenal glands, brain, heart, kidneys, liver, ovaries, pituitary, prostate (with seminal vesicles), spleen, testes, and thyroid gland (with parathyroids). Bone-marrow smears of rib were collected from all animals at scheduled necropsies but were not examined.

- Histopathology: The following tissues were obtained from all toxicity animals at the scheduled necropsies: adrenal glands, aorta, bone and bone marrow (sternum, rib, femur), brain, cervix, epididymides, esophagus, eyes (with optic nerve), gallbladder, heart, injection sites (muscle), kidneys, large intestine (cecum, colon), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, ocular accessory gland (lacrimal gland), ovaries, pancreas, parathyroid gland, peripheral nerve (sciatic and axillary), pituitary gland, prostate gland, salivary gland (mandibular), seminal vesicles, skeletal muscle (psoas), skin (dorsal thorax), small intestine (duodenum, jejunum, ileum), spinal cord (cervical, lumbar), spleen, stomach (cardia, fundus, pylorus), testes, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus, and vagina. Representative samples of each organ and tissue listed above and all suspected gross lesions were collected and fixed in 10% neutral buffered formalin (except eyes which were fixed in 5% glutaraldehyde).

All tissues from the monkey that died during the study and those from the scheduled end-of-dose necropsies were sectioned, stained with hematoxylin and eosin, and examined by light microscopy. For post-dose recovery animals, only injection sites and gross lesions were sectioned, stained, and examined. The pathology data were reviewed by a second pathologist, the Peer-Review Pathologist.

- Toxicokinetics: Plasma concentrations of BMS-337039 and BMS-337044 were determined at each dose level on days 1 and 29. Approximately 1.2-ml blood samples were collected from all drug-treated animals at approximately 10 and 30 min and 1, 3, 8, and 24 hr after dosing.

Results: The results are summarized in sponsor's tables below and on next page.

Mortality: There was no drug-related mortality. A low-dose male monkey (Animal No. 2103) had an emetic episode immediately after being given its daily oral dose of liquid dietary supplement on day 15 and died shortly thereafter. Gross and histopathology findings were consistent with death due to aspiration of the nutritional supplement.

Clinical signs: Decreased activity occurred in all animals, at all dose levels, with higher frequency in the MD and HD groups. Tremors occurred with low incidence at LD, and with higher incidence and frequency at MD and HD. Tremors and decreased activity were not observed in any animals during the 1-month recovery period. One MD male had a tonic convulsion on day 2, but as no other convulsions were observed in the study, this single event was considered to be unrelated to BMS-337039 in view of the lack of relationship to dose and that it was observed prior to dosing.

Redness, swelling, and scabbing at the injection site occurred in all groups, including controls. The frequency of swelling at the injection site correlated with the volume of material injected, which was highest in the vehicle-control and high-dose groups. Scabbing at the injection site occurred with a dose-related frequency. Injection-site findings were generally reversible during the first week of the 1-month recovery phase.

Food consumption: A drug-related decrease of food consumption, which was likely secondary to the pharmacologic activity of BMS-337039, occurred in all drug-treated animals except for 2 LD males. During the dosing period (days 1-29), the mean food consumption of males was 22%, 59%, and 51% lower than control, at LD, MD, and HD, respectively. The corresponding values in the females were28%, 54%, and 58% lower than control at LD, MD, and HD, respectively., A liquid nutritional supplement was given as a single daily 30 ml oral dose to each animal (including controls), beginning on day 4 (females) or day 5 (males) "to provide additional liquid- and caloric-intake and to prevent possible deterioration of the animals' condition secondary to the reduced food consumption". The daily dose of the supplement was increased to 45 ml 2 days later, and that volume was administered once daily until discontinuation during the first week of the recovery period. Food consumption recovered to pretest values during the first week of recovery period.

Body weights: Due to the nutritional supplementation that was provided, there was no adverse effect on body weight, despite the relatively large drug-related decreases of food consumption.

One-Month Intramuscular Toxicity Study in Monkeys Study No. DS04063

Daily Dose (mg/kg):	(0) Control		2		4		7.5	
Number of Animals (End-of-Dose):	M: 3	F 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Number of Animals (Post Dose):	M: 2	F 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	1[b]	0	0	0	0	0
Body Weight	--	--	--	--	--	--	--	--
Food Consumption[c]	121 g/day	121 g/day	-22%	-28%	-59%	-54%	-51%	-58%
Clinical Observations								
Decreased activity (hypoactivity)[d]	0	0	5	5	5	5	5	5
Tremors[d]	0	0	3	1	5	4	4	5
Dehydration[e]	0	0	0	0	3	2	4	2
Thin appearance[e]	0	0	0	0	2	3	0	2
Redness at the injection site[f]	10 (6)		8 (8)		10 (7)		10 (11)	
Scabbing at the injection site[f]	10 (4)		10 (7)		10 (12)		10 (19)	
Serum Chemistry (%)								
Aspartate aminotransferase (U/L)	46	37	60	44	48	73*	69[g]	73*
Urinalysis	--	--	--	--	--	--	--	--
Organ Weights	--	--	--	--	--	--	--	--
Gross Pathology[h]								
Injection sites, red or dark discoloration	0	0	0	0	1	2	0	2
Histopathology[h] at Injection Sites:								
Necrosis, skeletal muscle	2/3	1/3	0/3	2/3	1/3	3/3	3/3	3/3
Minimal	2/3	1/3	0/3	0/3	1/3	1/3	3/3	3/3
Mild	0/3	0/3	0/3	2/3	0/3	2/3	0/3	0/3
Degeneration, skeletal muscle	3/3	3/3	2/3	3/3	3/3	3/3	3/3	3/3
Minimal	3/3	2/3	1/3	1/3	1/3	2/3	2/3	2/3
Mild	0/3	1/3	1/3	2/3	2/3	1/3	0/3	1/3
Moderate	0/3	0/3	0/3	0/3	0/3	0/3	1/3	0/3

Histopathology[a] at Injection Sites: (Continued)								
Regeneration, skeletal muscle	3/3	2/3	0/3	3/3	2/3	3/3	3/3	3/3
Minimal	3/3	2/3	0/3	2/3	0/3	1/3	0/3	0/3
Mild	0/3	0/3	0/3	1/3	2/3	1/3	3/3	3/3
Moderate	0/3	0/3	0/3	0/3	0/3	1/3	0/3	0/3
Subacute inflammation	2/3	3/3	2/3	2/3	2/3	3/3	3/3	2/3
Minimal	2/3	3/3	2/3	2/3	1/3	1/3	2/3	1/3
Mild	0/3	0/3	0/3	0/3	1/3	2/3	1/3	1/3
Fibroplasia/fibrosis	2/3	2/3	0/3	2/3	0/3	1/3	3/3	3/3
Minimal	2/3	2/3	0/3	1/3	0/3	1/3	1/3	3/3
Mild	0/3	0/3	0/3	1/3	0/3	0/3	2/3	0/3
Hemorrhage	2/3	2/3	2/3	3/3	3/3	3/3	3/3	3/3
Minimal	2/3	2/3	1/3	3/3	2/3	3/3	3/3	3/3
Mild	0/3	0/3	1/3	0/3	0/3	0/3	0/3	0/3
Moderate	0/3	0/3	0/3	0/3	1/3[i]	0/3	0/3	0/3
Post-Dose Evaluation								
Histopathology[h,j,k] at Injection Sites:								
Degeneration, skeletal muscle, minimal	0/2	0/2	0/2	1/2	1/2	0/2	0/2	1/2
Regeneration, skeletal muscle, minimal	1/2	1/2	1/2	0/2	0/2	0/2	1/2	0/2
Subacute inflammation, minimal	0/2	0/2	0/2	2/2	0/2	0/2	1/2	0/2

Abbreviations: -- = No noteworthy findings; ND = Not determined
* p<0.05, ** p<0.01, Statistical analysis - see table end notes
All footnotes are available as table endnotes.

[b] The death of the low-dose male monkey was not drug related. Due to reduced food consumption (secondary to the pharmacologic activity of aripiprazole), all animals were administered a daily oral dose of [redacted] liquid dietary supplement; immediately after being administered its daily oral dose of [redacted] on Day 15, the affected monkey had an emetic episode and apparently aspirated the liquid into its lungs. The monkey died shortly thereafter, and necropsy revealed that the lungs did not collapse and abundant white fluid (dietary supplement) in the lungs and stomach. Histopathologic examination revealed pulmonary fluid. These pathology findings were consistent with death due to aspiration of the nutritional supplement.

[c] Values shown are average food consumption during the dosing phase (Days 1-29). For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical analyses were not performed on these data, but statistical analyses were conducted on daily food consumption data. Statistically significant decreases in daily food consumption were evident on 1 day at 2 mg/kg/day and on most days at 4 and 7.5 mg/kg/day. Beginning on Day 4 (females) or Day 5 (males), each animal (including controls) was given a single daily 30 mL oral dose of "[redacted]" a liquid nutritional supplement - to provide additional liquid- and caloric-intake and prevent deterioration of the animals' condition. The daily dose of "[redacted]" was increased to 45 mL 2 days later, and that volume was administered once daily until discontinuation during the first week of the recovery period. Also during the first week of the study, each animal was offered additional fruit (generally a whole banana or a whole orange) to provide additional dietary supplement; this supplementation was discontinued during the 1-month recovery period. Due to the nutritional supplementation that was provided, there was no adverse effect on body weight, despite the relatively large drug-related decreases of food consumption.

[d] Decreased activity and tremors were considered extensions of pharmacologic activity; dehydration and thin appearance were secondary to these effects. All noteworthy clinical signs were reversible during the first 3 days of the 1-month recovery phase.

[e] Attributed to decreased activity and food consumption.

[f] Data are tabulated as the number of males and females affected (10/group) at least once during the dosing phase (Days 1-29) with the average number of days in which the finding was observed in parentheses.

[g] Only 1 high-dose male was affected; AST in this animal was 40 U/L at pretest, 118 U/L (195% increase) at week 4, and 37 U/L (full reversibility) during the post-dose recovery phase. Elevations of AST in males and females were reversible during the 1-month recovery phase.

[h] Data shown are the number of animals having the indicated change.

[i] Attributed to hemorrhage due to mechanical trauma associated with intramuscular injections. Although not observed in vehicle controls, a comparable incidence and severity of hemorrhage was noted microscopically in control and treated groups.

[j] Considered to be likely due to the administration of anesthetic "[redacted]" at the injection site prior to necropsy.

[k] All other drug-related effects were completely reversible during the first few days of the 1-month recovery phase.

Concentration of IM aripiprazole administered to all drug-treated groups: 7.5 mg/mL.

Mortality: There was no drug-related mortality. A low-dose male monkey (Animal No. 2103) had an emetic episode immediately after being given its daily oral dose of liquid dietary supplement on day 15 and died shortly thereafter. Gross and histopathology findings were consistent with death due to aspiration of the nutritional supplement.

Ophthalmoscopy: No abnormal findings

EKG: No abnormal findings

Hematology: There were no direct drug-related effects on hematology or coagulation parameters. There were statistically significant minimal increases in mean absolute (110%) and relative (124%) reticulocyte counts in HD males, and comparable increases in females at all doses and in 1 MD male. These alterations were considered to be likely a consequence of hemorrhage associated with the IM dosing procedure. Similar increases in reticulocytes were seen in a prior 2-week IM toxicity study in monkeys at the same doses. The statistically significant minimal increase in mean neutrophil count (128%) in HD males was considered not to be drug-related because the mean and individual values were comparable to pretest.

Clinical chemistry: Drug-related serum chemistry changes included statistically significant minimal decreases in serum gamma glutamyl transferase (GGT) in MDM and HDM (37 and 29%, respectively) and increases in serum aspartate aminotransferase (AST) in MDF and HDF (99 and 98%, respectively) and in one HDM animal (195% in Animal No. 4105). The increases in serum AST were attributed to skeletal muscle injury at the injection sites. Similar changes in these serum chemistry parameters were seen at the same dose levels in the previous 2-week IM toxicity study in monkeys. Following a 1-month recovery period, the mean and individual values of serum chemistry parameters were comparable in animals from control and treated groups.

Urinalysis: No drug-related changes.

Organ weights: No drug-related changes.

Gross pathology: Red or dark discoloration in the region of the injection site, interpreted to be hemorrhage, occurred in 1 MD male and 2 females each at MD and HD. Microscopic evaluation demonstrated hemorrhage at the injection site that was generally comparable in incidence and severity in control and treated groups.

Histopathology: Injection site changes in control and treated groups included skeletal muscle necrosis, degeneration, and regeneration; subacute inflammation, fibroplasia/fibrosis, hemorrhage, and edema. These changes were generally minimal in severity in the control group. There was evidence of drug-related exacerbation of these changes as indicated by: increased incidences and/or severity of minimal to mild skeletal muscle necrosis at all doses; and degeneration (mild to moderate) and regeneration (mild to moderate). Mild subacute inflammation at the injection sites was observed at MD and HD, and an increased incidence and severity of fibroplasia/fibrosis was seen at HD.

TK: Systemic exposures to aripiprazole and BMS-337044 were dose-related with no apparent sex-related differences. There was no appreciable accumulation after 1 month of dosing. Systemic exposures to aripiprazole and BMS-337044 were generally similar after 2 weeks and 1 month of dosing. The Cmax and AUC values for aripiprazole and BMS-337044 are listed in the following sponsor's table.

TK summary 1-Month IM Toxicity Study in Monkeys

Dose (mg/kg/day)	Study Day	Cmax (ng/mL)				AUC[a] (ng•h/mL)			
		Aripiprazole		BMS-337044		Aripiprazole		BMS-337044	
		Male	Female	Male	Female	Male	Female	Male	Female
2	1	637	691	40	47	1746	1934	329	477
	29	697	767	43	49	2263	2189	554	688
4	1	1096	2065	79	75	3678	4627	878	924
	29	1159	1586	121	91	5600	4809	1799	1445
7.5	1	2559	2931	167	135	9272	9471	2097	1716
	29	3733	3763	183	172	11070	9718	2703	2587
Dose Ratio	Day	Cmax Ratios				AUC Ratios			
1:2:3.75	1	1:1.7:4.0	1:3.0:4.2	1:2.0:4.2	1:1.6:2.9	1:2.1:5.3	1:2.4:4.9	1:2.7:6.4	1:1.9:3.6
1:2:3.75	29	1:1.7:5.4	1:2.1:4.9	1:2.8:4.3	1:1.8:3.5	1:2.5:4.9	1:2.2:4.4	1:3.3:4.9	1:2.1:3.8

a Calculated from time zero to the time of the last quantifiable plasma concentration, ranging from 8 to 24 hours.

Multiples of human systemic exposures for aripiprazole and dehydroaripiprazole in 1-Month IM Toxicity Study in Monkeys

Species (Study)	Type of Study	Sex	Aripiprazole Dose (mg/kg/day)	Cmax (ng/mL)	Cmax multiples[a]	AUC(0-T) (ng•h/mL)	AUC(0-T) multiples[a]
Aripiprazole							
Monkey (DS04063)	1-Month IM Toxicity (Day 29)[b]	M	2	697	5	2263	1
			4	1159	8	5600	2
			7.5	3733	26	11070	5
		F	2	767	5	2189	1
			4	1586	11	4809	2
			7.5	3763	26	9718	4
Dehydroaripiprazole							
Monkey (DS04063)	1-Month IM Toxicity (Day 29)[b]	M	2	43	6	554	6
			4	121	17	1799	20
			7.5	183	25	2703	29
		F	2	49	7	688	7
			4	91	12	1445	16
			7.5	172	24	2587	28

[a] Based on mean Cmax and AUC(0-24 h) values obtained following a 30 mg IM dose of aripiprazole (MRHD) on Day 1 in a multiple ascending dose study in schizophrenia patients (CN138017): 143 ng/mL (Cmax) and 2297 ng•h/mL (AUC)

[b] Denotes the study day on which the toxicokinetic samples were collected.

Summary of individual study findings:

The results are adequately summarized by the sponsor as reproduced below:

Repeated intramuscular administration of aripiprazole IM formulation [redacted] to monkeys (5/sex/dose) at daily doses of 2, 4, 7.5 mg/kg/day for 1 month (and a vehicle control group) resulted in "findings at all doses of BMS-337039 that included 1) reversible and dose-related decreased activity and tremors, attributed to the pharmacology of BMS-337039, 2) a drug-related increase in the frequency of scabbing at the injection site, 3) a reversible decrease of food consumption, likely secondary to decreased activity; mean food consumption during the dosing phase (days 1-29) was 22-28% lower than control at 2 mg/kg/day, and 51-59% lower than control at 4 and 7.5 mg/kg/day, and 4) microscopically, increased incidence and/or severity of skeletal muscle necrosis (minimal to mild), degeneration (mild to moderate), and regeneration (mild to moderate) at injection sites. Additional drug-related findings at 4 and 7.5 mg/kg/day included 1) reversible and generally

dose-related incidences of dehydration and thin appearance (likely secondary to decreased activity and food consumption), 2) minimally increased aspartate aminotransferase in females (98-99%) and in 1 male (195%) at 7.5 mg/kg/day, and 3) microscopically, increased severity of subacute inflammation (mild) at the injection sites. Additional drug-related findings at 7.5 mg/kg/day included 1) an increased incidence of red discoloration at the injection site, and 2) microscopically, increased incidence and/or severity of fibroplasia/fibrosis (minimal to mild) at the injection sites.

Red discoloration, swelling, and scabbing at injection sites were completely reversible following 1-month postdose recovery period, and there was evidence of recovery for all control article- and BMS-337039-related injection site changes. In conclusion, intramuscular administration of BMS-337039 to monkeys for 1 month was associated with pharmacologically mediated CNS-related clinical signs and evidence of reversible skeletal muscle injury in injection sites at all doses. Additionally, minimal increases in serum aspartate aminotransferase at 4 and 7.5 mg/kg/day were considered a consequence of injection site injury. Microscopically, injection site changes associated with the control article and/or intramuscular injection procedure were generally minimal in severity, whereas, injection site changes at 2, 4, and 7.5 mg/kg/day were generally mild in severity and considered in part, drug related."

Systemic exposures to aripiprazole and BMS-337044 were dose-proportional with no apparent sex-related differences. There was no appreciable accumulation after 1 month of dosing.

NOAEL: Not reached (<2 mg/kg/day). At the lowest tested IM dose of 2 mg/kg/day, plasma AUC exposures for aripiprazole and its active metabolite, dehydroaripiprazole, were 1x and 6x, respectively, human AUC exposures at MRHD.

Toxicology summary:

The toxicity studies conducted with IM aripiprazole included: 2-week and 1-month repeat-dose toxicity studies in rats and monkeys, studies of embryo-fetal development in rats and rabbits, a study of pre- and postnatal development in rats, a single-dose IM irritation study in rats and rabbits, and a 2-week IM irritation study in rats. These studies are reviewed for the present application. Additional range-finding studies in pregnant rats and rabbits were conducted as a basis for dose selection for the definitive embryo-fetal development studies.

Genotoxicity, carcinogenicity, and reproductive (fertility) studies for IM aripiprazole were not performed by the sponsor. These toxicological studies [namely, genetic toxicity studies, carcinogenicity studies in mice and rats, fertility and early embryonic development upon oral administration in rats and rabbits, as well as some special toxicology studies (ocular and dermal irritation studies in rabbits, an immunotoxicity study in rats, studies of serum prolactin in mice and rats, an in vitro phototoxicity study, and investigational studies on the mechanism of the adrenocortical tumorigenic response in female rats] had been previously performed and reviewed in conjunction with the approval of aripiprazole oral tablet formulation (NDA 21-436).

General toxicology: Definitive general toxicology studies are the 1-month repeat-dose toxicity studies in rats (employing the IV route in order to achieve sufficient systemic exposures) and monkeys (IM administration). The dose selection for these studies was based on preliminary 2-week range-finding studies in the same species/strain by the same route of administration as that to be used in the corresponding main study.

The repeat-dose IV daily administration of IM aripiprazole formulation at doses of 3, 10, and 30 mg/kg/day for 1 month to rats (10/sex/group) resulted in pharmacologically-related clinical signs (dose-related decreased activity) at all doses, and morphologic changes in the adrenals at HD and in female reproductive and mammary tissues at all doses. In the females, the morphologic changes included (at all doses): decrease in the total number of corpora lutea in the ovary with

increased proportion of large corpora lutea, dose-related persistent diestrus with excessive vaginal mucification and mildly decreased uterine weights, and hyperplasia of mammary glandular tissue. In the males, atrophy of mammary glandular tissue was observed at all doses. Adrenal gland weights were increased at the HD (30 mg/kg/day) in both sexes, in correlation with the microscopic finding of hypertrophy of the zona fasciculata in the adrenal cortex (F). There was no direct target organ toxicity at any dose level; the observed changes were a likely manifestation of exaggerated pharmacological effect. A NOEL was not reached, but aripiprazole was well tolerated at 3 mg/kg/day. Systemic exposures to aripiprazole at 3 mg/kg/day were 7 to 8 times (Cmax) and 0.5 to 0.6 times (AUC) human exposures at the MRHD of 30 mg IM. Systemic exposures to aripiprazole at 10 and 30 mg/kg/day were 18 to 51 times based on Cmax and 2 to 15 times based on AUC human exposures at the MRHD.

The repeat-dose IM administration of aripiprazole to monkeys (5/sex/dose) at daily doses of 2, 4, 7.5 mg/kg/day (and a vehicle control group) for 1 month resulted in the following effects at all doses: pharmacologically mediated CNS clinical signs (decreased activity and tremors), decreased food consumption during the dosing period (22-28% lower than control at 2 mg/kg/day, and 51-59% lower than control at 4 and 7.5 mg/kg/day), and increased frequency of scabbing and reversible muscle injury in injection sites. The daily injection volumes were 0.26, 0.53, and 1 ml/kg, for LD, MD and HD, respectively, and 1 ml/kg for control, but not exceeding 1.5 ml at a time to any one injection site; the injection sites were alternated daily between the right and left posterior thigh muscles. Microscopically, injection site changes observed in Captisol (vehicle) control group were slight and less pronounced than the injection site changes at 2, 4, and 7.5 mg/kg/day, suggestive of a drug-related effect. Injection site changes attributed to aripiprazole included increased incidence and/or severity of skeletal muscle necrosis (minimal to mild), degeneration (mild to moderate), and regeneration (mild to moderate) at all doses; increased severity of subacute inflammation (mild) at 4 and 7.5 mg/kg/day; and increased incidence and severity of fibroplasia/fibrosis (minimal to mild) at 7.5 mg/kg/day. Drug-related clinical chemistry changes at 4 and 7.5 mg/kg/day included slightly decreased serum GGT in males, and increased serum AST (means approximately 2x the control mean values in MDF and HDF, and approximately 3 times the control in one male HD animal). The increases in serum AST observed at MD and HD (4 and 7.5 mg/kg/day) were likely a consequence of the skeletal muscle injury at injection sites. Systemic exposures to aripiprazole and BMS-337044 were dose-proportional with no apparent sex-related differences. There was no appreciable accumulation after 1 month of dosing. Following a 1-month post-dose recovery period, all aripiprazole-related clinical pathology changes were reversible.

NOAEL: Not reached (<2 mg/kg/day). At the lowest tested IM dose of 2 mg/kg/day, plasma AUC exposures for aripiprazole and its active metabolite, dehydroaripiprazole, were 1x and 6x, respectively, the human AUC exposures at MRHD (30 mg IM ariupiprazole).

The following sponsor's tables show interspecies comparisons of systemic exposures and multiples of human systemic exposures for aripiprazole and dehydro-aripiprazole in pivotal repeat-dose toxicology studies with IM or IV administration of IM aripiprazole formulation.

Interspecies comparisons of multiples of human systemic exposures for aripiprazole (30 mg IM aripiprazole) in pivotal toxicity and developmental studies with IM aripiprazole formulation

Species (Study) 930009149	Type of Study	Sex	Aripiprazole Dose (mg/kg/day)	Cmax (ng/ml)	Cmax multiples[a]	AUC(0-T) (ng.h/ml)	AUC(0-T) multiples[a]
Rat (DM04011) 930008946	1 Month IV Toxicity (Day 27)[b]	M	3	1210	8	1376	0.6
			10	2939	21	4489	2
			30	6488	45	30700	13
		F	3	985	7	1097	0.5
			10	2597	18	4514	2
			30	7237	51	35210	15
Monkey (DS04063) 930009043	1 Month IM Toxicity (Day 29)[b]	M	2	697	5	2263	1
			4	1159	8	5600	2
			7.5	3733	26	11070	5
		F	2	767	5	2189	1
			4	1586	11	4809	2
			7.5	3763	26	9718	4
Pregnant Rat (DN04039) 930009018	IV Embryo-Fetal Development (Gestation Day 15)[b]	F	3	821	6	1293	0.6
			9	2976	21	3366	1
			27	6426	45	34065	15
Pregnant Rabbit (DN04038) 930009017	IV Embryo-Fetal Development (Gestation Day 19)[b]	F	3	1868	13	9262	4
			10	5377	38	35329	15
			30	9941	70	66559	29
Lactating Rat (DN04046) 930011278	IV Pre- and Postnatal Development (Lactation Day 4)[b]	F	3	4103	29	2556	1
			8	4685	33	5358	2
			20	6801	48	12863	6

[a] Based on mean Cmax and AUC(0-24 h) values obtained following a 30 mg IM dose of aripiprazole on Day 1 in a multiple ascending dose study in schizophrenia patients (CN138017)[43]: 143 ng/mL (Cmax) and 2297 ng.h/mL (AUC)

[b] Denotes the study day on which the toxicokinetic samples were collected.

Interspecies comparisons of multiples of human systemic exposures for dehydro-aripiprazole (30 mg IM aripiprazole) in pivotal toxicity and developmental studies with IM aripiprazole formulation

Species (Study)	Type of Study	Sex	Aripiprazole Dose (mg/kg/day)	Cmax (ng/ml)	Cmax multiples[a]	AUC(0-T) (ng.h/ml)	AUC(0-T) multiples[a]
Rat (DM04011) 930008946	1 Month IV Toxicity (Day 27)[b]	M	3	2.8	0.4	8.8	0.1
			10	14	2	85	0.9
			30	119	16	1859	20
		F	3	4.1	0.6	19	0.2
			10	19	3	166	2
			30	117	16	1796	20
Monkey (DS04063) 930009043	1 Month IM Toxicity (Day 29)[b]	M	2	43	6	554	6
			4	121	17	1799	20
			7.5	183	25	2703	29
		F	2	49	7	688	7
			4	91	12	1445	16
			7.5	172	24	2587	28
Pregnant Rat (DN04039) 930009018	IV Embryo-Fetal Development (Gestation Day 15)[b]	F	3	7.7	1	18	0.2
			9	14	2	69	0.8
			27	84	12	1522	17
Pregnant Rabbit (DN04038) 930009017	IV Embryo-Fetal Development (Gestation Day 19)[b]	F	3	37	5	610	7
			10	165	23	2700	29
			30	329	45	5671	62
Lactating Rat (DN04046) 930011278	IV Pre- and Postnatal Development (Lactation Day 4)[b]	F	3	4.9	0.7	15	0.2
			8	15	2	132	1
			20	52	7	464	5

[a] Based on mean Cmax and AUC(0-24 h) values obtained following a 30 mg IM dose of aripiprazole on Day 1 in a multiple ascending dose study in schizophrenia patients (CN138017)[43]: 7.3 ng/mL (Cmax) and 92 ng.h/mL (AUC)

[b] Denotes the study day on which the toxicokinetic samples were collected.

Toxicology conclusions:

1. The repeat-dose IV daily administration of IM aripiprazole formulation at doses of 3, 10, and 30 mg/kg/day for 1 month to rats (10/sex/group) resulted in pharmacologically-related clinical signs (dose-related decreased activity) at all doses, and morphologic changes in the adrenals at HD and in female reproductive and mammary tissues at all doses. In the females, the morphologic changes included (at all doses): decrease in the total number of corpora lutea in the ovary with increased proportion of large corpora lutea, dose-related persistent diestrus with excessive vaginal mucification and mildly decreased uterine weights, and hyperplasia of mammary glandular tissue. In the males, atrophy of mammary glandular tissue was observed at all doses. Adrenal gland weights were increased at the HD (30 mg/kg/day) in both sexes, in correlation with the microscopic finding of hypertrophy of the zona fasciculata in the adrenal cortex (F). There was no direct target organ toxicity at any dose level; the observed changes were a likely manifestation of exaggerated pharmacological effect. A NOEL was not reached, but aripiprazole was well tolerated at 3 mg/kg/day. Systemic exposures to aripiprazole at 3 mg/kg/day were 7 to 8 times (Cmax) and 0.5 to 0.6 times (AUC) human exposures at the MRHD of 30 mg IM. Systemic exposures to aripiprazole at 10 and 30 mg/kg/day were 18 to 51 times based on Cmax and 2 to 15 times based on AUC human exposures at the MRHD.

2. The repeat-dose IM administration of aripiprazole to monkeys (5/sex/dose) at daily doses of 2, 4, 7.5 mg/kg/day (and a vehicle control group) for 1 month resulted in the following effects at all doses: pharmacologically mediated CNS clinical signs (decreased activity and tremors), decreased food consumption during the dosing period (22-28% lower than control at 2 mg/kg/day, and 51-59% lower than control at 4 and 7.5 mg/kg/day), and increased frequency of scabbing and reversible muscle injury in injection sites. The daily injection volumes were 0.26, 0.53, and 1 ml/kg, for LD, MD and HD, respectively, and 1 ml/kg for control, but not exceeding 1.5 ml at a time to any one injection site; the injection sites were alternated daily between the right and left posterior thigh muscles. Microscopically, injection site changes observed in Captisol (vehicle) control group were slight and less pronounced than the injection site changes at 2, 4, and 7.5 mg/kg/day, suggestive of a drug-related effect. Injection site changes attributed to aripiprazole included increased incidence and/or severity of skeletal muscle necrosis (minimal to mild), degeneration (mild to moderate), and regeneration (mild to moderate) at all doses; increased severity of subacute inflammation (mild) at 4 and 7.5 mg/kg/day; and increased incidence and severity of fibroplasia/fibrosis (minimal to mild) at 7.5 mg/kg/day. Drug-related clinical chemistry changes at 4 and 7.5 mg/kg/day included slightly decreased serum GGT in males, and increased serum AST (means approximately 2x the control mean values in MDF and HDF, and approximately 3 times the control in one male HD animal). The increases in serum AST observed at MD and HD (4 and 7.5 mg/kg/day) were likely a consequence of the skeletal muscle injury at injection sites. Systemic exposures to aripiprazole and BMS-337044 were dose-proportional with no apparent sex-related differences. There was no appreciable accumulation after 1 month of dosing. Following a 1-month post-dose recovery period, all aripiprazole-related clinical pathology changes were reversible.

NOAEL: Not reached (<2 mg/kg/day). At the lowest tested IM dose of 2 mg/kg/day, plasma AUC exposures for aripiprazole and its active metabolite, dehydroaripiprazole, were 1x and 6x, respectively, the human AUC exposures at MRHD (30 mg IM ariupiprazole).

Histopathology Inventory for NDA #

Study	1-month i.v. study in rats	1-month i.m. study in monkeys
Species	Rat	Monkey
Adrenals	X*	X*
Aorta	X	X
Bone Marrow smear	X	X
Bone (femur)	X	X
Brain	X*	X*
Cecum	X	X
Cervix	X*	X
Colon	X	X
Duodenum	X	X
Epididymis	X	X
Esophagus	X	X
Eye	X	X
Fallopian tube		
Gall bladder		X
Gross lesions	X	X
Harderian gland	X	
Heart	X*	X*
Ileum	X	X
Injection site	X	X
Jejunum	X	X
Kidneys	X*	X*
Lachrymal gland	X	X
Larynx		
Liver	X*	X*
Lungs	X	X
Lymph nodes, cervical		
Lymph nodes mandibular		X
Lymph nodes, mesenteric	X	X
Mammary Gland	X	X
Nasal cavity		
Optic nerves	X	X
Ovaries	X*	X*
Pancreas	X	X
Parathyroid	X*	X*
Peripheral nerve	X	X

Pharynx		
Pituitary	X*	X*
Prostate	X*	X*
Rectum		
Salivary gland	X	X
Sciatic nerve	X	X
Seminal vesicles	X	X*
Skeletal muscle	X	X
Skin	X	X
Spinal cord	X	X
Spleen	X*	X*
Sternum	X	X
Stomach	X	X
Testes	X*	X*
Thymus	X*	X
Thyroid	X*	X*
Tongue	X	X
Trachea	X	X
Urinary bladder	X	X
Uterus	X*	X
Vagina	X	X
Zymbal gland		
Standard List		

X, histopathology performed
*, organ weight obtained

V. GENETIC TOXICOLOGY:

Genetic toxicity studies were not performed

VI. CARCINOGENICITY:

Carcinogenicity studies were not performed

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Study title: Intravenous Study of Embryo-Fetal Development in Rats
Key study findings: IM aripiprazole administered intravenously to pregnant rats on gestation days 6 through 15 at doses of 3, 9, or 27 mg/kg, produced dose-dependent clinical signs related to exaggerated pharmacologic activity (ptosis, lacrimation, decreased motor activity) at all doses, and maternal toxicity at 9 and 27 mg/kg/day (demonstrated by dose-dependent decrease in body weight gain and food consumption). Drug-related effects in the fetuses (growth retardation, characterized by reductions in fetal body weight with associated decreases in ossification)

occurred only at 27 mg/kg/day. Thus, aripiprazole affected fetal development (causing intrauterine growth retardation) at a dose level that also caused maternal toxicity.
TK: Cmax values within the tested dose range and AUC values between 3 and 9 mg/kg/day for aripiprazole and BMS-337044 generally increased dose-proportionally. AUC values between 9 and 27 mg/kg/day for both the parent compound and metabolite increased in an increment substantially greater than dose.

Study no.: DN 04039
Volume # 1
Conducting laboratory and location: [redacted]

Date of study initiation: 1 April 2004
GLP compliance: Yes
QA reports: yes
Drug, lot #, radiolabel, and % purity: BMS-337039, Batch No. R4217; [redacted] purity
Formulation/vehicle: [redacted]

Methods:

Species/strain: Rat [redacted] CD

Doses employed: 3, 9, or 27 mg/kg IM aripiprazole as a solution (7.5 mg/mL) in [redacted] (dose volumes of 0.4, 1.2, and 3.6 mL/kg).

[The dose selection was based on a dose-range finding study at aripiprazole IV doses of 1, 3, 10, and 30 mg/kg/day on gestation days 6 through 15 (8 pregnant rats/group). In that study, there were no drug-related changes in dams at 1 or 3 mg/kg/day or in fetuses at 1, 3, or 10 mg/kg/day. In dams, drug-related ptosis, lacrimation, red perivaginal substance, urine-stained abdominal fur, and soft or liquid feces occurred at 10 and 30 mg/kg/day and decreased motor activity, reductions in maternal bodyweight gain (including body-weight losses) and reduced food consumption, at 30 mg/kg/day. Drug-related changes in the fetuses were limited to reductions in fetal body weight at 30 mg/kg/day.]

Route of administration: Intravenous

Study design: The test agent was administered intravenously by bolus injection once daily on DG 6 through 15 to groups of 25 pregnant rats each. Two control groups (25 pregnant rats each) were similarly administered either the vehicle [redacted] or saline (0.9% sodium chloride for injection, USP) at 3.6 ml/kg (see "Parameters and endpoints evaluated" below).
Number/sex/group: 25 pregnant females
Parameters and endpoints evaluated: survival; clinical observations; body weight; food consumption; and macroscopic examination of thoracic, abdominal, and pelvic viscera of the dams; maternal and litter observations at cesarean-sectioning on DG 20; and fetal observations. Plasma concentrations of aripiprazole and its pharmacologically active metabolite BMS-337044 (dehydro-aripiprazole) were measured on DG 15 in corresponding satellite groups of 9 pregnant rats at each dose level.

Results: The study results are summarized in the sponsor's table below and on the next 2 pages.

Dams:

Drug-related findings in the dams occurred at 3, 9, and 27 mg/kg/day (clinical signs of ptosis, lacrimation, decreased motor activity at all doses, with a dose-related frequency; and chromorhinorrhea, urine-stained abdominal fur, and soft or liquid feces at 27 mg/kg/day). Maternal toxicity, demonstrated by reduction in body weight and/or weight gain, was seen at MD and HD. At MD (9 mg/kg/day), a transient reduction in maternal body weight gain occurred during gestation days 9 to 12 (15% and 18% less than saline and Captisol controls, respectively), while at HD (27 mg/kg/day) body weight gain was reduced during g.days 6 to 9 (76% and 72% lower than saline and Captisol controls, respectively) and also during g.days 9 to 12 (41% and 43% lower than the saline and Captisol controls, respectively). Additional maternal toxicity at 27 mg/kg/day included reduced food consumption throughout the dosing period (11% and 10% lower than saline and Captisol controls, respectively). In all aspects of this study, the Captisol controls were comparable to the saline controls.

NOAEL dams: < 3 mg/kg/day

Fetuses:

Drug-related effects in fetuses occurred only at the HD (27 mg/kg/day), demonstrated as growth retardation, characterized by reductions in fetal body weight (9% and 13% lower than saline and Captisol controls, respectively) with associated decreases in ossification of the sternal centra, caudal vertebrae, and forelimb metacarpals.

NOAEL fetuses: 9 mg/kg/day

Intravenous Study of Embryo-Fetal Development in Rats
Study No. DN04039

Daily Dose (mg/kg)	0 (Saline)	0 (Captisol®)	3	9	27
Dams:					
No. Pregnant/No. Assigned to Study - N/N (%)	24/25 (96.0)	22/25 (88.0)	24/25 (96.0)	25/25 (100)	25/25 (100)
No. Died or Sacrificed Moribund	0	1[b]	0	0	0
No. Aborted or with Total Resorption of Litter	0	0	0	0	0
Clinical Observations[c,d]	--	--	+	++	+++
Body Weight (%[e]) Gestation Day 15	295.4 g	0	0	-1%	-7%**
Body Weight Change (%[e]) Gestation Days 6-9	16.2 g	-15%	-12%	-17%	-76%**
Body Weight Change (%[e]) Gestation Days 9-12	20.2 g	+4%	-5%	-15%*	-41%**
Body Weight Change (%[e]) Gestation Days 6-16	62.2 g	0	-1%	-2%	-35%**
Food Consumption (%[e]) Gestation Day 6-16	21.9 g/day	-1%	+1%	+3%	-11%**
Mean No. Corpora Lutea	15.2	15.3	17.0	15.4	15.3
Mean No. Implantations	13.7	14.0	13.8	13.6	13.2
Litters (Cesarean-Delivered on Gestation Day 20):					
No. Evaluated	24	21	24	25	25
No. Live Fetuses	317	274	320	314	312
Mean No. Resorptions	0.4	1.0	0.4	1.1	0.8
No. of Litters with Dead Fetuses	0	0	0	0	0
Mean % Preimplantation Loss[f]	9.0	7.2	16.8	11.1	13.5
Mean % Postimplantation Loss[g]	3.2	7.2	2.7	7.5	5.3
Mean Fetal Body Weight/Litter (g)	3.70	3.88	3.84	3.70	3.37**
Fetal Sex Ratios (% male fetuses)	43.2	49.1	47.3	52.5	49.0

Abbreviations: -- No noteworthy findings, ♦ = Not performed, + Mild, ++ Moderate, +++ Marked; N = Number
* p≤0.05, ** p≤0.01, Statistical analysis - see table endnotes
All footnotes are available as table end notes.

Intravenous Study of Embryo-Fetal Development in Rats (Study No. DN04039) - Continued

Daily Dose (mg/kg)	0 (Saline)	0 (Captisol®)	3	9	27
Summary of Gross External, Visceral & Skeletal Anomalies:[n,z]					
Total Affected Fetuses/Total Fetuses Evaluated - N/N (%)	27/317 (8.5)	20/274 (7.3)	19/320 (5.9)	24/314 (7.6)	34/312 (10.9)
Total Affected Litters/Total Litters Evaluated - N/N (%)	14/24 (58.3)	9/21 (42.8)	11/24 (45.8)	12/25 (48.0)	17/25 (68.0)
Percent Affected Fetuses/Litter (Mean %)	8.6	7.8	5.8	8.4	11.3
Fetal Visceral Anomalies:[1]					
No. Fetuses Examined/ No. Litters Examined	153/24	132/21	155/24	152/25	149/25
Brain: Irregular shape					
Fetal Incidence N (%)	2 (1.3)	1 (0.8)	1 (0.6)	1 (0.6)	0 (0.0)
Litter Incidence N (%)	2 (8.3)	1 (4.8)	1 (4.2)	1 (4.0)	0 (0.0)
Eyes: Microphthalmia					
Fetal Incidence N (%)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Litter Incidence N (%)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Eyes: Folded retina					
Fetal Incidence N (%)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Litter Incidence N (%)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Vessels: Umbilical artery descended to the left of the urinary bladder					
Fetal Incidence N (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Litter Incidence N (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)
Fetal Skeletal Anomalies:[1]					
No. Fetuses Examined/ No. Litters Examined	164/24	142/21	166/24	162/25	163/25
Ribs: Short					
Fetal Incidence N (%)	1 (0.6)	0 (0)	1 (0.6)	3 (1.9)	1 (0.6)
Litter Incidence N (%)	1 (4.2)	0 (0)	1 (4.2)	2 (8.0)	1 (4.0)
Sternal Centra: Incompletely ossified					
Fetal Incidence N (%)	19(11.6)	13 (9.2)	9 (5.4)	8 (4.9)*	27 (16.6)
Litter Incidence N (%)	9 (37.5)	5 (23.8)	6 (25.0)	6 (24.0)	14 (56.0)
Sternal Centra: Not ossified					
Fetal Incidence N (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.2)
Litter Incidence N (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	1 (4.0)
Sternal Centra: Asymmetric					
Fetal Incidence N (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)
Litter Incidence N (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (12.0)	0 (0.0)
Pelvis: Pubes, incompletely ossified					
Fetal Incidence N (%)	2 (1.2)	2 (1.4)	3 (1.8)	9 (5.6)	9 (5.5)
Litter Incidence N (%)	2 (8.3)	2 (9.5)	2 (8.3)	3 (12.0)[k]	4 (16.0)[k]
Pelvis: Ishium, incompletely ossified					
Fetal Incidence N (%)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)
Litter Incidence N (%)	0 (0.0)	0 (0.0)	1 (4.2)	1 (4.0)	0 (0.0)
Skull: Zygomatic, incompletely ossified					
Fetal Incidence N (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)
Litter Incidence N (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)
Cervical Vertebrae: Cervical rib present at 7th cervical vertebrae					
Fetal Incidence N (%)	3 (1.8)	2 (1.4)	0 (0.0)	0 (0.0)	2 (1.2)
Litter Incidence N (%)	3 (12.5)	2 (9.5)	0 (0.0)	0 (0.0)	2 (8.0)

Intravenous Study of Embryo-Fetal Development in Rats (Study No. DN04039) - Continued

Daily Dose (mg/kg)		0 (Saline)	0 (Captisol®)	3	9	27
Thoracic Vertebrae: Centrum, bifid						
Fetal Incidence	N (%)	2 (1.2)	2 (1.4)	4 (2.4)	2 (1.2)	2 (1.2)
Litter Incidence	N (%)	2 (8.3)	1 (4.8)	3 (12.5)	2 (8.0)	2 (8.0)

[a] Data are presented as aripiprazole/BMS-337044 (dehydro-aripiprazole, the pharmacologically active metabolite).

[b] One rat was found dead on Gestation Day 15 due to a restraint injury sustained during dosing.

[c] No inferential statistical analyses were conducted on clinical observation data.

[d] At 3, 9, and 27 mg/kg/day, drug-related clinical observations included ptosis, lacrimation, decreased motor activity, and perivaginal substance. At 27 mg/kg/day drug-related clinical observations also included chromorhinorrhea, urine-stained abdominal fur, and soft or liquid feces.

[e] For saline controls, group means are shown. For Captisol® controls and treated groups, percent differences from saline controls are shown. Statistical significance is based on actual data (not on the percent differences).

[f] Preimplantation loss calculated as: [(Corpora lutea - implantations)/Corpora lutea] x 100.

[g] Postimplantation loss calculated as: [(Dead + resorbed conceptuses)/Implantations] x 100.

[h] Anomalies noted exclusively in control fetuses (situs inversus) are omitted from the listings below, but are included in the total incidence of affected fetuses and litters and percent affected fetuses/litter.

[i] All percentages were calculated on the basis of the number of live fetuses in each group.

[j] Includes values for a fetus that was inadvertently included in skeletal examinations as well as visceral examinations.

Toxicokinetic evaluation: Systemic exposures to aripiprazole and BMS-337044 were dose related. Exposures to BMS-337044 were 1.4% to 4.5% relative to the parent (based on AUC). Cmax values between 3 and 27 mg/kg/day and AUC values between 3 and 9 mg/kg/day for aripiprazole and BMS-337044 generally increased dose-proportionally. AUC values between 9 and 27 mg/kg/day for both parent and metabolite increased in an increment substantially greater than dose. The Cmax and AUC values for aripiprazole and BMS-337044 are listed in the following sponsor's table.

Toxicokinetic Summary

Dose (mg/kg/day)	Cmax (ng/mL)		AUC[a] (ng•h/mL)	
	Aripiprazole	BMS-337044	Aripiprazole	BMS-337044
3	821	7.7	1293	18
9	2976	14	3366	69
27	6426	84	34065	1522
Dose Ratio	**Cmax Ratio**		**AUC Ratio**	
1:3:9	1:4:8	1:2:11	1:3:26	1:4:85

[a] Calculated from time zero to the time of the last quantifiable plasma concentration, ranging from 8 to 24 hours.

Summary of individual study findings:

IM aripiprazole as a solution (7.5 mg/mL) in [redacted] was administered intravenously by bolus injection once daily on gestation days 6 through 15 to groups of 25 pregnant rats each at doses of 3, 9, or 27 mg/kg (dose volumes of 0.4, 1.2, and 3.6 ml/kg). Two control groups (25 pregnant rats each) were administered either the control article [redacted] or saline (0.9% sodium chloride forinjection, USP) at 3.6 mL/kg. Criteria for evaluation included survival; clinical observations; body weight;

food consumption; and macroscopic examination of thoracic, abdominal, and pelvic viscera of the dams; maternal and litter observations at cesarean-sectioning on DG 20; and fetal observations. Plasma concentrations of aripiprazole and its pharmacologically active metabolite BMS-337044 (dehydro-aripiprazole) were measured on DG 15 in corresponding satellite groups of 9 pregnant rats at each dose level. IM aripiprazole administered intravenously during the period of major organogenesis produced maternal dose-dependent clinical signs related to exaggerated pharmacologic activity (decreased motor activity, ptosis, lacrimation,) at all tested doses, and maternal toxicity at 9 and 27 mg/kg/day (demonstrated by dose-dependent decrease in body weight gain and food consumption). Drug-related effects in the fetuses (growth retardation, characterized by reductions in fetal body weight with associated decreases in ossification) occurred only at 27 mg/kg/day. Thus, aripiprazole affected fetal development (causing intrauterine growth retardation) at a dose level that also caused maternal toxicity.

Study title: Intravenous Study of Embryo-Fetal Development in Rabbits

Key study findings: IM aripiprazole formulation, administered intravenously at doses of 3, 10, or 30 mg/kg to pregnant rabbits (22/group) once daily on gestation days 7 through 19, caused maternal toxicity at all dose levels (manifested as clinical signs, weight and/or weight gain reduction, and decreased food consumption) at all tested doses with dose-dependent frequency and severity. The clinical signs included decreased motor activity, tachypnea, and soft or liquid feces at all dose levels, and ataxia, convulsions, hyperpnea, nystagmus, altered righting reflex, and prostration at HD (30 mg/kg/day). Maternal body-weight gain was reduced at MD, 10 mg/kg/day (67% and 50% less than saline and Captisol controls, respectively) and body-weight loss was noted at 30 mg/kg/day (20 g loss compared with a gain of 30 g and 20 g in saline and Captisol controls, respectively) during the first several days of dosing (gestation days 7 to 10). During the post-dosing period (g.d. 20 to 29), body-weight gain was reduced at 3, 10, and 30 mg/kg/day (33% and 27%, 46% and 41%, and 54% and 50% less than the saline and Captisol controls, respectively). Reductions in maternal food consumption paralleled the reductions in maternal body-weight gain at all doses. Drug-related changes in the fetuses occurred only at the HD of 30 mg/kg/day and included decreased fetal body weights (15% and 16% less than saline and Captisol controls, respectively) with associated reductions in ossification, as well as congenital malformations, including absence of the intermediate lobe of the lungs, split ribs, fused sternal ossification centers, and irregularly shaped scapulae. In conclusion, IM aripiprazole administered intravenously to pregnant rabbits on g.days 7 through 19 produced maternal toxicity (manifested in reduction in body weight and/ or weight gain as well as clinical signs) at all doses, and drug-related fetal effects (growth retardation and skeletal malformations) at 30 mg/kg/day. Thus, aripiprazole affected fetal development in the rabbit at a dose that caused pronounced maternal toxicity. Toxicokinetic evaluation demonstrated that systemic exposures to aripiprazole and BMS-337044 were dose related, the Cmax and AUC values generally increased dose-proportionally.
Study No.: DN 04038
Volume # 1
Conducting laboratory and location: [redacted]

Date of study initiation: 11 April 2004
GLP compliance: Yes
QA reports: yes
Drug, lot #, radiolabel, and % purity: BMS-337039, Batch No. R4217; [redacted] purity

Formulation/vehicle: [redacted]

Methods:

Species/strain: Rabbit/[redacted](NZW)

Doses employed: 3, 10, or 30 mg/kg (dose volumes of 0.4, 1.3, and 4 ml/kg)

Rationale for dose selection: The doses were selected on the basis of a range-finding study in pregnant rabbits of the same strain at aripiprazole daily doses of 3, 9, 15 and 30 mg/kg/day, administered intravenously from gestation day 7 through g.d. 19. In the range-finding study, the maternal drug-related effects included: clinical signs of decreased motor activity, hyperpnea, and tachypnea (at all doses); ptosis at 15 mg/kg/day, and prostration and ataxia at 30 mg/kg/day. Drug-related changes in the fetuses were limited to reductions in fetal body weight at 30 mg/kg/day. There were no drug-related changes in fetuses at 3, 9, or 15 mg/kg/day.

Route of administration: Intravenous

Study design: IM aripiprazole as a solution (7.5 mg/ml) in [redacted] was administered intravenously once daily on gestation days 7 through 19 to groups of 22 pregnant rabbits each at doses of 3, 10, or 30 mg/kg (dose volumes of 0.4, 1.3, and 4 ml/kg). Two control groups (22 pregnant animals each) were similarly administered the vehicle [redacted] or saline (0.9% sodium chloride for injection, USP) at 1.3 ml/kg on the first day of dosing (g.d. 7) and 4 ml/kg on g.d. 8 through the remainder of the dosing period to control for potential effects of the Captisol vehicle, volume administered, and rate of administration. For the 3 and 10 mg/kg/day groups and on g.d. 7 for the control article and saline groups, dose volumes were administered as bolus injections. Beginning on g.d. 8 for the control article and saline groups and for the 30 mg/kg/day group, dose volumes were administered at a rate of 3 ml/minute using a calibrated syringe injection pump. Cesarean section was performed on g.d. 29. Plasma concentrations of aripiprazole and its pharmacologically active metabolite BMS-337044 (dehydro-aripiprazole) were measured on g.d. 19 in corresponding satellite groups of 6 pregnant rabbits at each dose level.

Number/sex/group: 22 pregnant females

Parameters and endpoints evaluated: Survival; clinical observations; body weights; food consumption; macroscopic examination of thoracic, abdominal, and pelvic viscera of the does; maternal and litter observations at cesarean section on g.d. 29; and fetal observations. Plasma concentrations of aripiprazole and its pharmacologically active metabolite BMS-337044 (dehydro-aripiprazole) were measured on g.d. 19 in corresponding satellite groups of 6 pregnant rabbits at each dose level.

Results: In-life observations:

Dams: Aripiprazole caused maternal toxicity (manifested as clinical signs, weight and/or weight gain reduction, and decreased food consumption) at all tested doses. Drug-related clinical signs in the does occurred intermittently during the dosing period with a frequency that was generally dose related, and included decreased motor activity, tachypnea, and soft or liquid feces at 3, 10 and 30 mg/kg/day; and ataxia, convulsions, hyperpnea, nystagmus, altered righting reflex, and prostration at 30 mg/kg/day. Maternal body-weight gain was reduced at 10 mg/kg/day (67% and 50% less than saline and Captisol controls, respectively), and body-weight loss was noted at 30 mg/kg/day (20 g loss compared with a gain of 30 g and 20 g in saline and Captisol controls,

respectively) during the first several days of dosing (g.days 7 to 10). During the post-dosing period (g. days 20 to 29), body-weight gain was reduced at 3, 10, and 30 mg/kg/day (33% and 27%, 46% and 41%, and 54% and 50% less than the saline and Captisol controls, respectively). Reductions in maternal food consumption generally paralleled the reductions in maternal body-weight gain at all doses. Maternal food consumption was reduced at 10 and 30 mg/kg/day (14% and 16%, and 22% and 24% less than the saline and Captisol controls, respectively) during the first several days of dosing (g.days 7 to 10); in addition, at 30 mg/kg/day, food consumption was decreased during g.days 7 to 20 (14% and 16% less than the saline and Captisol controls, respectively). During the post-dosing period (DG 20 to 29), food consumption was decreased at 3, 10, and 30 mg/kg/day (13% and 10%, 17% and 14%, and 18% and 15% lower than the saline and Captisol controls, respectively).

Maternal NOAEL: Not reached (<3 mg/kg/day)

Fetuses

Drug-related changes in the fetuses occurred only at the HD (30 mg/kg/day) and included abortion of 1 litter on gestation day 28; growth retardation, demonstrated in decreased fetal body weight (15% and 16% less than saline and Captisol controls, respectively) with associated reductions in ossification site counts for forelimb metacarpals and hindpaw phalanges; and fetal malformations, including absence of the intermediate lobe of the lungs, split ribs, fused sternal ossification centers, and irregularly shaped scapulae.

Fetal NOAEL: 10 mg/kg/day

In all aspects of this study, the Captisol controls were comparable to the saline controls.

The results are summarized in the sponsor's table below and on the next 2 pages.

Intravenous Study of Embryo-Fetal Development in Rabbits (Study No.: DN 04038)

Daily Dose (mg/kg)	0 (Saline)	0 (Captisol®)	3	10	30
Does					
No. Pregnant/No. Assigned to Study N/N (%)	21/22 (95.5)	22/22 (100)	21/22 (95.5)	22/22 (100)	20/22 (90.9)
No. Died or Sacrificed Moribund	0	0	0	0	0
No. Aborted or with Total Resorption of Litter	0	0	0	0	1[b]
Clinical Observations[c,d]	--	--	+	++	+++
Body Weight (%[e]) Gestation Day 19	3.63 kg	+1%	+3%	+1%	-1%
Body Weight Change (%[e]) Gestation Days 7-10	0.03 kg	-33%	0%	-67%	Loss of 20 grams
Body Weight Change (%[e]) Gestation Days 7-20	0.23 kg	-4%	+17%	+13%	-13%
Body Weight-Change (%[e]) Gestation Day 20-29	0.24 kg	-8%	-33%*	-46%*	-54%**
Food Consumption (%[e]) Gestation Days 7-10	160.7 g/day	+3%	-2%	-14%	-22%**
Food Consumption (%[e]) Gestation Days 7-20	159.6 g/day	+2%	+5%	-2%	-14%**
Food Consumption (%[e]) Gestation Days 20-29	148.5 g/day	-4%	-13%	-17%*	-18%**

Abbreviations: -- No noteworthy findings, ♦ = Not performed, + Mild, ++ Moderate, +++ Marked; N = Number,
* p≤0.05, ** p≤0.01, Statistical analysis - see table endnotes
All footnotes are available as table end notes.

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Intravenous Study of Embryo-Fetal Development in Rabbits (Study No.: DN 04038) **(Continued)**

Daily Dose (mg/kg)	0 (Saline)	0 (Captisol®)	3	10	30
Mean No. Corpora Lutea	9.4	10.2	10.3	10.0	10.8
Mean No. Implantations	8.8	9.1	9.5	8.8	9.7
Litters (Cesarean-Delivered on Gestation Day 29):					
No. Evaluated	21	22	21	22	19
No. Live Fetuses	178	183	188	180	168
Mean No. Resorptions	0.4	0.8	0.3	0.6	0.8
No. of Litters with Dead Fetuses	0	0	1	0	0
Mean % Preimplantation Loss[♦]	5.9	12.0	7.9	13.8	12.4
Mean % Postimplantation Loss[♣]	4.3	8.6	5.5	6.0	7.5
Mean Fetal Body Weight/Litter (g)	44.54	45.17	42.72	42.36	38.08**
Fetal Sex Ratios (% male fetuses)	51.1	52.9	49.2	50.2	59.3
Summary of Gross External, Visceral, & Skeletal Anomalies:[n,1]					
Total Affected Fetuses/Total Fetuses Evaluated - N/N (%)	19/178 (10.7)	17/183 (9.3)	37/188 (19.7)*	21/180 (11.7)	44/168 (26.2)**
Total Affected Litters/Total Litters Evaluated - N/N (%)	12/21 (57.1)	10/22 (45.4)	15/21 (71.4)	14/22 (63.6)	14/19 (73.7)
Percent Affected Fetuses/Litter (Mean %)	10.0	8.7	19.5	12.8	25.3
Fetal Visceral Anomalies:[1]					
No. Fetuses Examined/No. Litters Examined	178/21	183/22	188/21	180/22	168/19
Eyes: Circumcorneal Hemorrhage					
Fetal Incidence N (%)	0	1 (0.5)	0	0	1 (0.6)
Litter Incidence N (%)	0	1 (4.5)	0	0	1 (5.3)
Brain: Dilated Ventricles, moderate					
Fetal Incidence N (%)	0	0	0	1 (0.6)	0
Litter Incidence N (%)	0	0	0	1 (4.5)	0
Lungs: Intermediate Lobe, absent					
Fetal Incidence N (%)	3 (1.7)	0	3 (1.6)	0	9 (5.4)
Litter Incidence N (%)	1 (4.8)	0	1 (4.8)	0	3 (15.8)
Intestines: Portion protruded through umbilicus					
Fetal Incidence N (%)	1 (0.6)	0	1 (0.5)	0	0
Litter Incidence N (%)	1 (4.8)	0	1 (4.8)	0	0
Fetal Skeletal Anomalies:[1]					
No. Fetuses Examined/No. Litters Examined	178/21	183/22	188/21	180/22	168/19
Skull: Nasals, midline suture displaced					
Fetal Incidence N (%)	9 (5.0)	9 (4.9)	19 (10.1)	9 (5.0)	12 (7.1)
Litter Incidence N (%)	7 (33.3)	7 (31.8)	11 (52.4)	8 (36.4)	9 (47.4)
Skull: Frontals, contained an interfrontal					
Fetal Incidence N (%)	0	0	0	0	3 (1.8)
Litter Incidence N (%)	0	0	0	0	2 (10.5)
Cervical Vertebrae: Centra, fused					
Fetal Incidence N (%)	0	0	0	0	1 (0.6)
Litter Incidence N (%)	0	0	0	0	1 (5.3)
Thoracic Vertebrae: Arches, fused					
Fetal Incidence N (%)	0	0	0	0	1 (0.6)
Litter Incidence N (%)	0	0	0	0	1 (5.3)
Thoracic Vertebrae: Centra, fused					
Fetal Incidence N (%)	0	1 (0.5)	0	0	1 (0.6)
Litter Incidence N (%)	0	1 (4.5)	0	0	1 (5.3)
Caudal Vertebrae: Misaligned					
Fetal Incidence N (%)	1 (0.6)	0	1 (0.5)	1 (0.6)	0
Litter Incidence N (%)	1 (4.8)	0	1 (4.8)	1 (4.5)	0

Abbreviations: -- No noteworthy findings, ♦ = Not performed, + Mild, ++ Moderate, +++ Marked; N = Number,
* p≤0.05, ** p≤0.01, Statistical analysis - see table endnotes
All footnotes are available as table end notes.

Intravenous Study of Embryo-Fetal Development in Rabbits (Study No.: DN 04038) **(Continued)**

Daily Dose (mg/kg)	0 (Saline)	0 (Captisol®)	3	10	30
Fetal Skeletal Anomalies:[1] (Continued)					
Caudal Vertebrae: Fused					
Fetal Incidence N (%)	0	0	0	0	1 (0.6)
Litter Incidence N (%)	0	0	0	0	1 (5.3)
Ribs: Fused					
Fetal Incidence N (%)	1 (0.6)	0	4 (2.1)	0	1 (0.6)
Litter Incidence N (%)	1 (4.8)	0	2 (9.5)	0	1 (5.3)
Ribs: Split				0	
Fetal Incidence N (%)	0	0	1 (0.5)	0	3 (1.8)
Litter Incidence N (%)	0	0	1 (4.8)	0	2 (10.5)
Sternal Centra: Fused					
Fetal Incidence N (%)	3 (1.7)	1 (0.5)	5 (2.6)	4 (2.2)	13 (7.7)*
Litter Incidence N (%)	3 (14.3)	1 (4.5)	2 (9.5)	2 (9.1)	6 (31.6)
Sternal Centra: Incompletely Ossified					
Fetal Incidence N (%)	0	0	9 (4.8)**	1 (0.6)	5 (3.0)
Litter Incidence N (%)	0	0	5 (23.8)*	1 (4.5)	3 (15.8)
Scapulae: Ala, irregularly shaped					
Fetal Incidence N (%)	0	0	0	0	2 (1.2)
Litter Incidence N (%)	0	0	0	0	2 (10.5)
Pelvis: Pubes, not ossified					
Fetal Incidence N (%)	0	0	0	0	5 (3.0)
Litter Incidence N (%)	0	0	0	0	1 (5.3)

[a] Toxicokinetic evaluations reported as aripiprazole/BMS-337044 (dehydro-aripiprazole, the pharmacologically active metabolite).

[b] One 30-mg/kg doe was euthanatized on Day 28 of gestation following abortion.

[c] No inferential statistical analyses were conducted on clinical observation data.

[d] At 3, 10, and 30 mg/kg/day, clinical observations of decreased motor activity, tachypnea, clear perinasal substance, and soft or liquid feces occurred intermittently during the dosing period. Scant feces was observed at 10 and 30 mg/kg/day and ataxia, convulsions, hyperpnea, nystagmus, altered righting reflex and prostration occurred intermittently during the dosing period at 30 mg/kg/day.

[e] For saline controls, group means are shown. For Captisol® control and treated groups, percent differences from saline controls are shown, unless otherwise indicated. Statistical significance is based on actual data (not on the percent differences).

[f] Preimplantation loss calculated as: [(Corpora lutea - implantations)/Corpora lutea] x 100.

[g] Postimplantation loss calculated as: [(Dead + resorbed conceptuses)/Implantations] x 100.

TK evaluations:

Within the tested dose range, the Cmax and AUC values for aripiprazole and dehydroaripiprazole generally increased dose-proportionally, with the exception of Cmax for aripiprazole at 30 mg/kg/day, which increased less than dose-proportionally. The Cmax and AUC values for aripiprazole and BMS-337044 are listed in the following sponsor's table.

Toxicokinetic Summary

Dose (mg/kg/day)	Cmax (ng/mL)		AUC[a] (ng•h/mL)	
	Aripiprazole	BMS-337044	Aripiprazole	BMS-337044
3	1868	37	9262	610
10	5377	165	35329	2700
30	9941	329	66559	5671
Dose Ratio	**Cmax Ratio**		**AUC Ratio**	
1:3.3:10	1:2.9:5.3	1:4.5:8.9	1:3.8:7.2	1:4.4:9.3

[a] Calculated from time zero to the time of the last quantifiable plasma concentration at 24 hours.

Multiples of human systemic exposures in developmental study in rabbits

Species (Study)	Type of Study	Sex	Aripiprazole Dose (mg/kg/day)	Cmax (ng/mL)	Cmax multiples[a]	AUC(0-T) (ng•h/mL)	AUC(0-T) multiples[a]
Aripiprazole							
Pregnant Rabbit (DN04038)	IV Embryo-Fetal Development (Gestation Day 19)[b]	F	3	1868	13	9262	4
			10	5377	38	35329	15
			30	9941	70	66559	29
Dehydroaripiprazole							
Pregnant Rabbit (DN04038)	IV Embryo-Fetal Development (Gestation Day 19)[b]	F	3	37	5	610	7
			10	165	23	2700	29
			30	329	45	5671	62

[a] Based on mean Cmax and AUC(0-24 h) values obtained following a 30 mg IM dose of aripiprazole (MRHD) on Day 1 in a multiple ascending dose study in schizophrenia patients (CN138017): 7.3 ng/mL (Cmax) and 92 ng•h/mL (AUC)

[b] Denotes the study day on which the toxicokinetic samples were collected.

Summary of individual study findings:

IM aripiprazole as a solution (7.5 mg/ml) in [redacted] administered intravenously once daily on gestation days 7 through 19 to groups of 22 pregnant rabbits each at doses of 3, 10, or 30 mg/kg (with two control groups: a vehicle- and a saline control), caused maternal toxicity at all dose levels (manifested as clinical signs, weight and/or weight gain reduction, and decreased food consumption) at all tested doses with dose-dependent frequency and severity. Drug-related clinical signs included decreased motor activity, tachypnea, and soft or liquid feces at all dose levels, and ataxia, convulsions, hyperpnea, nystagmus, altered righting reflex, and prostration at 30 mg/kg/day. Maternal body-weight gain was reduced at 10 mg/kg/day (67% and 50% less than saline and Captisol controls, respectively) and body-weight loss was noted at 30 mg/kg/day (20 g loss compared with a gain of 30 g and 20 g in saline and Captisol controls, respectively) during the first several days of dosing (gestation days 7 to 10). During the post-dosing period (g.d. 20 to 29), body-weight gain was reduced at 3, 10, and 30 mg/kg/day (33% and 27%, 46% and 41%, and 54% and 50% less than the saline and Captisol controls, respectively). Reductions in maternal food consumption paralleled the reductions in maternal body-weight gain at all doses. Drug-related changes in the fetuses occurred only at the HD of 30 mg/kg/day and included decreased fetal body weights (15% and 16% less than saline and Captisol controls, respectively) with associated reductions in ossification, as well as congenital malformations, including absence of the intermediate lobe of the lungs, split ribs, fused sternal ossification centers, and irregularly-shaped scapulae. In conclusion, IM aripiprazole administered intravenously to pregnant rabbits on g.days 7 through 19 produced maternal toxicity (manifested in reduction in body weight and/ or weight gain as well as clinical signs) at all doses, and drug-related fetal effects (growth retardation and congenital abnormalities) at 30 mg/kg/day. Thus, aripiprazole affected fetal development in the rabbit at a dose that caused pronounced maternal toxicity. Toxicokinetic evaluation demonstrated that systemic exposures to aripiprazole and BMS-337044 were dose related; the Cmax and AUC values generally increased dose-proportionally.

Study title: Intravenous Study of Pre- and Postnatal Development in Rats

Key study findings: Aripiprazole IM formulation administered intravenously at doses of 3, 8, and 20 mg aripiprazole /kg/day to pregnant/lactating rats from gestation day 6 (implantation) through lactation day 20 (weaning) produced maternal clinical signs (hypoactivity, ptosis, lacrimation) at 8 and 20 mg/kg/day, attributable to aripiprazole pharmacologic activity, and maternal toxicity at 20 mg/kg/day (demonstrated by reduction in body weight, weight gain, and food consumption). Adverse effects on the F1-generation offspring were induced at 8 mg/kg/day (increased rate of stillbirths) and 20 mg/kg/day (increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life). No effects on dams or progeny were induced at the dose of 3 mg/kg/day (NOAEL). Thus, aripiprazole induced increased stillbirth rates at the dose of 8 mg/kg/day that caused maternal clinical signs attributable to exaggerated pharmacologic activity, but no other manifestations of maternal toxicity, except for a transient decrease in weight gain (-11%) on gestation days 6 through 9. The higher, maternally toxic dose (20 mg/kg/day) affected pronouncedly the pre- and postnatal development of F1 generation, causing increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life, but no drug-related changes were observed in the tested post-weaning developmental endpoints of F1 generation (sensory perception, motor activity, learning, memory, sexual maturation, or reproductive function).

Study no.: DN 04046

Conducting laboratory and location: [redacted]

Date of study initiation: 29 April 2004

GLP compliance: Yes

QA reports: yes

Drug, lot #, radiolabel, and % purity: BMS-337039, Batch No. R4217; [redacted] % purity

Formulation/vehicle: [redacted]

Methods:

Species/strain: Rat/[redacted]CD (SD)IGS BR VAF/Plus

Doses employed: 3, 8, or 20 mg Aripiprazole /kg/day (dose volumes of 0.4, 1.07, and 2.67 mL/kg, respectively). Two control groups administered either the vehicle [redacted] or saline (0.9% sodium chloride for injection, USP) at 2.67 mL/kg. The rationale for dose selection is described by the sponsor as follows:

> Doses were selected based on the results of previous oral and intravenous toxicity studies in rats with BMS-337039.
>
> In a ten-day intravenous range-finding study[4] in pregnant rats, BMS-337039 was administered at doses of 1, 3, 10, or 30 mg/kg/day on DGs 6 to 15. Drug-related maternal toxicity at 10 and 30 mg/kg/day included clinical observations (ptosis, lacrimation, perivaginal substance, urine-stained abdominal fur, soft or liquid feces, and/or decreased motor activity) and reductions in body-weight gain throughout the dosing period (approximately 15 and 67% less than controls, respectively, including body-weight loss during DGs 6 to 9 at 30 mg/kg/day). Additional evidence of maternal toxicity at 30 mg/kg/day included reductions in food consumption over the entire dosing period (19% less than controls during gestation days 6 to 16). Drug-related changes in cesarean-delivered fetuses on DG 20 were limited to reductions in fetal body weight (15% less than controls) at 30 mg/kg/day.

Route of administration: Intravenous

Study design: The test agent was administered IV once daily to pregnant Fo females (n=25/group) from Gestation day 6 through Lactation day 20 at doses of 3, 8, or 20 mg/kg (dose volumes of 0.4, 1.07, and 2.67 mL/kg, respectively). There were 2 control groups (25 pregnant rats each) administered either the vehicle or saline (0.9% sodium chloride for injection, USP) at 2.67 mL/kg. The dams were allowed to litter spontaneously and were continued on aripiprazole dosing through lactation (postnatal day 20). The F1 progeny was evaluated from birth through pre-weaning, post-weaning and sexual maturity (see "Parameters and endpoints evaluated" below).

Number/sex/group: 25 pregnant females

Parameters and endpoints evaluated: In Fo-generation dams: survival, clinical observations, body weights, and food consumption during gestation and lactation; clinical signs during parturition, duration of gestation, maternal behavior during lactation, and gross pathology at the end of lactation. In F1-generation: pre-weaning litter observations (viability, clinical signs, and body weight on days 1, 7, 14 and 21) (litters not culled); and post-weaning survival, clinical observations, body weight (twice weekly), food consumption, physical and neurobehavioral development [auditory startle (p.n. day 50), sexual maturation (vaginal patency or preputial separation), open field and locomotor activity testing (p.n. day 58-62), water maze testing (p.n. day 67), and reproductive capacity (mating and fertility, p.n. day 98-112)], and gross pathology of male and female F1-generation animals. Plasma concentrations of aripiprazole and its pharmacologically active metabolite BMS-337044 (dehydro-aripiprazole) were measured on Lactation Day 4 in corresponding groups of 9 F_0 rats at each dose level.

Necropsies – dams and F1 pups

After completion of the 21-day lactation period, all surviving female rats were euthanatized by carbon dioxide asphyxiation and a gross necropsy of the thoracic, abdominal, and pelvic viscera was performed. The number and distribution of implantation sites were recorded. Gross lesions were retained in 10% NBF for

Pups found dead were examined for gross lesions and for the cause of death. Pups with gross lesions found between PNDs 1 to 4 were preserved in Bouin's solution for possible future evaluation; gross lesions of pups found dead between PNDs 5 to 21 were preserved in 10% NBF.

Pups not assigned to continue on study were euthanatized by carbon dioxide asphyxiation and examined for gross lesions. Gross lesions were preserved in 10% NBF. All other tissues were discarded without further evaluation.

Necropsies – F1 Post-weaning

Male rats were euthanatized by carbon dioxide asphyxiation after completion of the 17-day cohabitation period. A gross necropsy of the thoracic, abdominal, and pelvic viscera was performed. Gross lesions were retained in 10% NBF. Testes and epididymides were excised and paired organ weights were recorded. The epididymides were retained in 10% NBF. The testes were fixed in Bouin's solution for 48 to 96 hours and then retained in 10% NBF.

On DG 20, female rats were euthanatized by carbon dioxide asphyxiation, and a gross necropsy of the thoracic, abdominal, and pelvic viscera was performed. Gross lesions were retained in 10% NBF. Uteri of apparently nonpregnant rats were stained with 10% ammonium sulfide to confirm the absence of implantation sites[6] and retained in 10% NBF. The rats were examined for number and distribution of corpora lutea, implantation sites (placentae that appear abnormal were noted in the raw data), live and dead fetuses, and early and late resorptions. Each fetus was weighed and examined for sex and gross external alterations. Representative photographs of fetal alterations were taken. Fetuses were tagged with identification noting study number, litter number, uterine distribution and fixative, and retained for possible future evaluation. Approximately one-half of the fetuses in each litter were retained in Bouin's solution; the remaining fetuses were retained in isopropyl alcohol.

Results:

In-life observations:

Dams (Fo): At LD, no maternal effects were observed. At MD and HD, drug-related clinical signs (ptosis, decreased motor activity, lacrimation) during gestation and/or lactation, occurred at dose-dependent frequency. At HD, on gestation days 6 through 21, reductions in maternal body weight gain (31 and 33% less than saline and Captisol® controls, respectively) and in maternal food consumption (13 and 11% less than saline and Captisol® controls, respectively); food consumption was also reduced at HD during lactation days 1 to 14 (16 and 18% less than saline and Captisol® controls, respectively) resulting in reduced maternal body weights from gestation day 9 through lactation day 21. These findings are indicative of maternal toxicity at HD. At MD, there were clinical signs related to aripiprazole pharmacologic activity (hypoactivity, ptosis, lacrimation), but no effect on body weight, weight gain (except for a transient decrease in weight gain (-11%) on gestation days 6 through 9), food consumption, nor indications of systemic or organ toxicity. Maternal MTD: 8 mg/kg/day; NOAEL: 3 mg/kg/day

The following sponsor's table summarizes the maternal findings (Fo dams)

Maternal Fo findings

Table 2.6.7.14 Reproductive and Developmental Toxicity - Effects on Pre- and Postnatal Development, Including Maternal Function

Document Control Number: 9300011278 **(Continued)** **Test Article:** BMS-337039 **Study No.** DN04046

Daily Dose (mg/kg)	0 (Saline)	0 (Captisol®)	3	8	20
Fo Females: (Continued)					
No. Pregnant/No. Assigned to Pre- and Postnatal Study - N/N (%)	25/25 (100.0)	24/25 (96.0)	25/25 (100.0)	25/25 (100.0)	26/26[c] (100.0)
No. Died or Sacrificed Moribund	1[a]	1[b]	0	0	1[c]
No. Aborted or with Total Resorption of Litter	0	0	0	0	0
No. Sacrificed Due to No Surviving Pups	0	0	0	0	1[d]
Clinical Observations[e]	--	--	--	++	+++
Necropsy Observations	--	--	--	--	--
Body Weight (%[f]) - Gestation Day 6[g]	249.0 g	-1%	0%	+1%	-1%
Body Weight (%[f]) - Gestation Day 9[g]	264.6 g	-1%	0%	0%	-4%*
Body Weight (%[f]) - Gestation Day 12[g]	281.8 g	0%	0%	0%	-5%**
Body Weight (%[f]) - Gestation Day 15[g]	299.9 g	-1%	0%	0%	-5%**
Body Weight (%[f]) - Gestation Day 18[g]	331.1 g	0%	+1%	-1%	-8%**
Body Weight (%[f]) - Gestation Day 21[g]	367.6 g[h]	+1%[h]	+1%	-1%	-11%**

Body-Weight Change (%)[i] - Gestation Days 6-9	15.5 g	-1%	0%	-11%	-45%**
Body-Weight Change (%)[f] - Gestation Days 6-21	118.7 g[h]	+3%[h]	+3%	-4%	-31%**
Body-Weight Change (%)[f] - Gestation Days 0-21	152.2 g[h]	+1%[h]	+2%	-2%	-26%**
Body Weight (%)[f] - Lactation Day 4[g]	283.8 g	0%	+1%	+1%	-6%**
Body Weight (%)[f] - Lactation Day 7[g]	299.5 g	+2%	+2%	0%	-7%**
Body Weight (%)[f] - Lactation Day 14[g]	319.5 g	+1%	0%	+2%	-5%**
Body Weight (%)[f] - Lactation Day 21[g]	310.2 g	+3%	+1%	+1%	-5%*
Food Consumption (%)[f] - Gestation Days 6-21	23.3 g/day[h]	-2%[h]	+2%	+1%	-13%**
Food Consumption (%)[f] - Lactation Days 1-14	47.3 g/day	+2%	-3%	-3%	-16%**
Mean Duration of Gestation (days)	22.6	22.4	22.4	22.5	22.9
Abnormal Parturition	--	--	--	--	--

bbreviations: -- No noteworthy findings, ◆= Not performed, + Mild, ++ Moderate, +++ Marked, N = Number
p<0.05, ** p<0.01, Statistical analysis - see table end notes
ll footnotes are available as table end notes.

Offspring (F1 generation): At HD, drug-related increase in neonatal mortality (18% during postnatal days 1 to 4, compared to 2% and 5% for the saline and Captisol® controls, respectively), with associated reductions in litter size (mean of 9.4 pups/litter on p.n. day 4, compared to 11.9 and 12.5 pups/litter in saline and Captisol® controls, respectively); clinical observations in pups of coldness to touch and absence of milk in the stomach during this same period; decreased pup body weights throughout 1st week of life (14 to 16% less than saline and Captisol® controls); and increased incidence of dilated renal pelvis in males and females at scheduled post-weaning necropsies. No drug-related changes were observed for the post-weaning developmental endpoints of sensory perception, motor activity, learning, memory, sexual maturation, or reproductive function at any of the tested dose levels.

At MD and HD, dose-dependent increases in stillbirths (stillbirths registered in 28 and 44% of litters at 8 and 20 mg/kg/day respectively, compared to 4% in saline controls and 8% in Captisol® controls). At LD (3 mg/kg/day), no adverse effects in F1 progeny were observed.

Note: As stated by the sponsor,

Although the incidence of dams with 1 or more stillbirths at 3 mg/kg/day (16%) was elevated as compared with the saline and Captisol® controls (4% and 8.3%, respectively), this observation was considered not to be drug-related because: 1) the value was within the range of those observed historically at the test facility (0 to 20.8%)[(8)]; 2) the difference was not statistically significant; and 3) the average number of stillbirths per litter (a more quantitatively valid index of a drug-related effect on this parameter) at 3 mg/kg/day (0.3 stillbirths/litter) was comparable to the saline and Captisol® controls (0 and 0.2 stillbirths/litter, respectively).

(End of citation).

F1 offspring NOAEL: 3 mg/kg/day

The following sponsor's table summarizes the pre- and post-weaning findings in F1 offspring.

F1 Offspring findings

Table 2.6.7.14 Reproductive and Developmental Toxicity - Effects on Pre- and Postnatal Development, Including Maternal Function

Document Control Number: 930011278 **(Continued)** **Test Article:** BMS-337039

Study No. DN04046

Daily Dose (mg/kg)	0 (Saline)	0 (Captisol®)	3	8	20
F_1 Litters: Preweaning					
No. Litters Evaluated	25	24	25	25	25
No. of Implantations - Mean	13.0	13.8	12.6	13.5	13.3
No. Delivered Pups/Litters - Mean	12.2	12.8	11.6	12.0	12.4
No. Liveborn Pups/Litter - Mean	12.1	12.6	11.2	11.3	11.4
Litters with One or More Stillborn Pups - N/N (%)	1/25 (4.0)	2/24 (8.3)	4/25 (16.0)	7/25 (28.0)*	11/25 (44.0)**
Pup Survival to Postnatal Days 1 to 4[i]	98.0%	95.0%	98.2%	95.7%	82.4%
Pup Survival to Postnatal Days 4 to 21[j]	96.0%	99.3%	100.0%	99.6%	98.7%
No. of Total Litter Losses - N	0	0	0	0	1
Litter Size on Postnatal Day 4 - Mean	11.9	12.5	11.0	10.8	9.4
Litter Size on Postnatal Day 21 - Mean	11.9	12.4	11.0	10.8	9.2
Pup Body Weights on Postnatal Day 1 - Mean (g)	6.4	6.4	6.5	6.3	5.4
Pup Body Weights on Postnatal Day 7 - Mean (g)	12.5	12.3	13.2	12.8	10.6
Pup Body Weights on Postnatal Day 21 - Mean (g)	37.4	38.0	39.6	40.7	36.5
F_1 Litters: Preweaning (Continued)					
Pup Sex Ratios (% Males/Litter on Postnatal Day 1) - Mean	50.7	48.1	47.3	45.4	49.0
Pup Clinical and Necropsy Signs[k]	--	--	--	--	+
F_1 Males: Postweaning					
No. Evaluated Postweaning - N	25	25	25	25	25
No. Died or Sacrificed Moribund - N	1[l]	0	0	0	2[m]
Clinical and Necropsy Observations[n]	--	--	--	--	++
Paired epididymal weights - Mean (g)	1.60	1.67	1.61	1.63	1.51
Paired testis weights - Mean (g)	3.54	3.70	3.60	3.74	3.53
Body Weight (%[f]) - End of Postweaning Period	528.3 g	-1%	+7%*	+3%	-1%
Body-Weight Change (%[f]) - Weaning to Cohabitation	398 g	+1%	+6%*	+3%	-1%
Food Consumption (%[f]) - Weaning to Cohabitation	26.5 g/day	+1%	+4%	0%	-1%
Age of Preputial Separation - Mean (days)	46.8	46.5	46.4	46.8	47.8
Motor Activity	--	--	--	--	--
F_1 Males: Postweaning (Continued)					
Sensory Function - Auditory Startle	--	--	--	--	--
Learning and Memory	--	--	--	--	--
No. of Days in Cohabitation Prior to Mating - Mean	2.6	3.3	3.0	2.5	3.4
Males that Mated (No. Mated/No. Cohabited) - N/N (%)	25/25 (100.0)	24/25 (96.0)	24/24[o] (100.0)	25/25 (100.0)	22/22[o] (100.0)
Fertile Males (No. Fertile/No. Mated) - N/N (%)	23/25 (92.0)	22/24 (91.7)	22/24 (91.7)	20/25 (80.0)	20/22 (90.9)
F_1 Females: Postweaning					
No. Evaluated Postweaning Per Litter - N	25	25	25	25	25
No. Died or Sacrificed Moribund - N	0	0	0	0	0
Clinical and Necropsy Observations[n]	--	--	--	--	+
Body-Weight Change (%[f]) - Premating	206.0 g	+3%	+6%	+6%	+3%
Body-Weight Change (%[f]) - Gestation Days 0-20	142.8 g	+4%	+5%	+0%	-6%
Premating Food Consumption (%[f]) Weaning to Cohabitation	18.8 g/day	+4%	+3%	+3%	0%
Food Consumption (%[f]) - Gestation Days 0-20	26.6 g/day	+3%	+5%	+2%	-3%

F_1 Females: Postweaning (Continued)					
Vaginal Patency - Mean (days)	32.5	32.9	32.9	33.3	33.5
Motor Activity	--	--	--	--	--
Sensory Function - Auditory Startle	--	--	--	--	--
Learning and Memory	--	--	--	--	--
No. Days in Cohabitation Prior to Mating - Mean	2.6	3.4	3.0	2.5	3.2
Females Sperm Positive (No. Mated/No. Cohabited) - N/N%	25/25 (100.0)	25/25 (100.0)	24/24[o] (100.0)	25/25 (100.0)	24/24[o] (100.0)
Pregnant Females (No. Pregnant/No. Mated) - N/N%	23/25 (92.0)	23/25 (92.0)	22/24 (91.7)	20/25 (80.0)	21/24 (87.5)
No. with Total Resorption of Litter - N	0	0	0	0	0
No. Corpora Lutea - Mean	16.4	17.3	17.6	17.4	16.7
No. Implantations - Mean	15.3	16.0	15.9	15.6	14.3

[a] Dam 10007 was found dead shortly after dosing on Day 11 of Lactation; death was attributed to a dosing accident (presumed air embolism from air bubbles in the injection line).

[b] Dam 10028 died during dosing on Day 1 of Lactation; death was attributed to a dosing accident (presumed air embolism from air bubbles in the injection line).

[c] Dam 10109 died immediately after dosing of Day 8 of Gestation; death was attributed to a dosing accident (presumed air embolism from air bubbles in the injection line). Dam 10109 was replaced by Dam 8850. Dam 10109 was excluded from data summarization.

[d] Dam 10113 was euthanatized on Day 2 of Lactation due to no surviving pups in its litter.

[e] Drug-related clinical observations included ptosis, decreased motor activity, lacrimation, and urine-stained abdominal fur noted during gestation and/or lactation.

[f] For saline controls, group means are shown. For Captisol® controls and treated groups, percent differences from saline controls are shown. Statistical significance is based on actual data (not on the percent differences).

[g] At 20 mg/kg/day, reduced maternal body-weight gains during Gestation Days 6-21 resulted in reduced maternal body weights from Gestation Day 9 through Lactation Day 21. Representative intervals have been included in the table.

[h] Excludes 1 saline and 2 Captisol® control dams, which delivered litters prior to body weight and food consumption evaluations on Gestation Day 21.

[i] Calculated as: the number of live pups on Postnatal Day 4 divided by the number of liveborn pups.

[j] Calculated as: the number of live pups on Postnatal Day 21 divided by the number of live pups on Postnatal Day 4.

[k] Drug-related clinical observations included coldness to touch and absence of milk in the stomach during the first week of lactation. There were no drug-related necropsy findings in any group.

[l] During handling procedures at weaning on Postnatal Day 21, male 13023 convulsed and died. Since this death was attributed to traumatic injury, male 13023 was replaced by male 8845. Male 13023 was excluded from data summarization.

[m] Male rat 13109 was found dead on Postnatal Day 58. Male rat 13120 died (traumatic injury) after being caught in a cage opening during transfer to its home cage on Postnatal Day 28.

[n] Drug-related necropsy observations in males (Postnatal Days 133 to 136) and females (Gestation Day 20) included an increased incidence of dilated renal pelvis.

[o] Excludes rats that did not have a confirmed date of mating.

Abbreviations: -- No noteworthy findings, ♦ = Not performed, + Mild, ++ Moderate, +++ Marked, N = Number
* $p \leq 0.05$, ** $p \leq 0.01$, Statistical analysis - see table end notes

Terminal and necroscopic evaluations:

[see sponsor's tables (best available from sponsor's submission) on next 2 pages]

Dams: No drug-related gross lesions were identified at scheduled necropsy of the Fo-generation dams. Slight or moderate dilatation of the renal pelvis was observed in single animals at MD (1/25) and HD (1/25), but this finding was not considered to be drug-related because the incidence was not dose-dependent and the rates were within the range of test facility historical values. No other necropsy findings were registered in Fo dams.

Offspring: There were no drug-related necropsy findings in F1 generation at LD and MD. At HD, an increased incidence of "slight to extreme" dilatation of renal pelvis was observed in 5/25 F1 males and 3/25 F1 females at scheduled post-weaning necropsies (on postnatal days 133 to 136 in males and gestation day 20 in females). This finding was considered "a drug-related exacerbation of a necropsy observation seen in control animals at the testing facility". No other drug-related necropsy findings were registered in the F1-generation rats.

TABLE 2 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F_0 GENERATION FEMALE RATS

DOSE GROUP		I	II	III	IV	V
DOSE (MG/KG/DAY)a		0(SALINE)	0(CAPTISOL®)	1	6	20
RATS EXAMINED b	N	25	25	25	25	25
DOSING ACCIDENT	N	1c	1d	0	0	0
EUTHANIZED DUE TO NO SURVIVING PUPS	N	0	0	0	0	1f
APPEARED NORMAL	N	23c	23d	25	24	24f
KIDNEYS: RIGHT, PELVIS, SLIGHT TO MODERATE DILATION	N	0	0	0	1e	1g

a. Dose occurred on Day 6 of Presumed Gestation through Day 20 of Lactation.
b. Refer to the individual clinical observations table (Table A1) for external observations confirmed at necropsy.
c. Observed in dam 10007 which was found dead shortly (approximately 30 minutes) after dose administration on Day 11 of Lactation; death was attributed to a dosing accident (presumed air embolism from air bubbles in the injection line).
d. Observed in dam 10028 which died during dose administration on Day 1 of lactation; death was attributed to a dosing accident (presumed air embolism from air bubbles in the injection line).
e. Observed in dam 10076.
f. Observed in dam 10113 which was euthanized due to no surviving pups in the litter on Day 2 of Lactation.
g. Observed in dam 10102.

TABLE 11 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F_1 GENERATION PUPS

DOSE GROUP		I	II	III	IV	V
DOSE (MG/KG/DAY)a		0(SALINE)	0(CAPTISOL®)	1	6	20
LITTERS EXAMINED	N	25	23	24	25	22
TOTAL PUPS STILLBORN OR FOUND DEAD, b,c,d,e	N	4	4	7	10	28g
STILLBORN	N	1	3	5	5	17
FOUND DEAD	N	3	1	2	4	11
NO MILK IN STOMACH	N	2	0	2	4	9
PUPS SACRIFICED AND NECROPSIED ON DAY 21 POSTPARTUM a						
LITTERS EVALUATED	N	23f	23g	24	25	21h
PUPS EVALUATED	N	221e	219	219	219	174
KIDNEYS: RIGHT OR BILATERAL, PELVIS, SLIGHT DILATION						
LITTER INCIDENCE	N(%)	3(4.3)	0(0.0)	1(4.2)	2(8.0)	0(0.0)
PUP INCIDENCE	N(%)	3(0.4)	0(0.0)	1(0.4)	3(1.4)	0(0.0)
LEFT, PELVIS, MODERATE DILATION						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
PUP INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	0(0.0)
BRAIN: LEFT LATERAL VENTRICLE, SLIGHT DILATION						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
PUP INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	0(0.0)

a. Dose occurred on Day 6 of Gestation through Day 20 of Lactation.
b. Excludes litters for which all necropsy observations were inadvertently not recorded or documentation was misplaced.
c. Excludes pups for which necropsy observations were inadvertently not recorded or documentation was misplaced.
d. Restricted to pups in which complete necropsies were performed. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation.
e. Refer to the individual pup clinical observations table (Appendix A11) for external clinical observations confirmed at necropsy.
f. Dam 10107 was found dead shortly (approximately 30 minutes) after dose administration on Day 11 of lactation; death attributed to a dosing accident (presumed air embolism from air bubbles in the injection line); surviving pups in the litter were euthanized.
g. Dam 10028 died during dose administration on Day 1 of lactation; death attributed to a dosing accident (presumed air embolism from air bubbles in the injection line); surviving pups in the litter were euthanized.
h. Dam 10113 had no surviving pups on Day 2 of lactation.

TABLE 34 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F1 GENERATION MALE RATS

DOSE GROUP DOSE (MG/KG/DAY)		I 0(SALINE)	II 0(CARTISOL®)	III 3	IV 6	V 20
RATS EXAMINED a	N	26b	25	25	25	25
FOUND DEAD	M	0	0	0	0	1c
HANDLING ACCIDENT	M	1b	0	0	0	1c
APPEARED NORMAL	M	24	24	23	23	18d
EPIDIDYMIDES:						
BILATERAL OR RIGHT, SMALL	M	1	1	1	0	0
TESTES:						
BILATERAL, SMALL, FLACCID	M	0	0	1	0	0
RIGHT, LARGE	M	0	0	0	1	0
KIDNEYS:						
PELVIS, RIGHT, LEFT, OR BILATERAL						
DILATION, TOTAL	M	0	0	0	0	6**
DILATION, SLIGHT	M	0	0	0	0	3
DILATION, MODERATE	M	0	0	0	0	2
DILATION, MARKED	M	0	0	0	0	1c
BILATERAL, PALE, MOTTLED						
TAN AND RED	M	0	0	0	0	1c
CALCULI PRESENT	M	0	0	0	0	1c
BLADDER:						
THICK AND RED,						
CALCULI PRESENT	M	0	0	0	0	1c
SITUS INVERSUS	M	0	1	0	0	0
STOMACH						
CONTAINED RED SUBSTANCE	M	0	0	1	0	0

a. Refer to the individual clinical observations table (Appendix 13) for external observations confirmed at necropsy.
b. During handling procedures at weaning on Postnatal Day 21, male 13023 convulsed and died. Since this death was attributed to traumatic injury, male 13623 was replaced by male 8845 and was excluded from data summarization.
c. Male rat 13109 was found dead on Postnatal Day 58.
d. Male rat 13180 died (traumatic injury) after being caught in a cage opening during transfer to its home cage on Postnatal Day 28.
** Significantly different from the control group value (P≤0.01).

TABLE 35 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS

DOSE GROUP DOSE (MG/KG/DAY)		I 0(SALINE)	II 0(CARTISOL®)	III 3	IV 6	V 20
RATS EXAMINED a	N	25	25	25	25	25
MORTALITY	M	0	0	0	0	0
APPEARED NORMAL	M	23	25	24	24	22
KIDNEYS:						
PELVIS, RIGHT, LEFT, OR BILATERAL						
DILATION, TOTAL	M	1	2	1	1	3
DILATION, SLIGHT	M	0	0	0	0	1
DILATION, MODERATE	M	1	0	1	1	1
DILATION, MARKED	M	0	0	0	0	1b
DILATION, EXTREME	M	0	0	0	0	1b
UTERUS: CERVIX CONSTRICTED	M	1	0	0	0	0
URETER: RIGHT, MODERATE DILATION	M	0	0	0	0	1

a. Refer to the individual clinical observations table (Appendix 14) for external observations confirmed at necropsy.
b. Observed in Rat 13203.

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TK: Maternal systemic exposures to aripiprazole and the active metabolite BMS-337044, measured on lactation day 4, were dose- related. BMS-337044 exposures were 4% or less relative to aripiprazole. Within the tested dose range, aripiprazole exposure values (Cmax and AUC) increased slightly less than dose-proportionally, while the corresponding BMS-337044 plasma exposure values generally increased in an increment greater than the dose increment (listed in the following sponsor's table).

TK: Maternal systemic exposure parameters (lactation day 4)

Dose (mg/kg/day)	Cmax (ng/mL)		AUC (ng•h/mL)[a]	
	Aripiprazole	BMS-337044	Aripiprazole	BMS-337044
3	4103	5	2556	15
8	4685	15	5358	132
20	6801	52	12863	464
Dose Ratio	**Cmax Ratio**		**AUC Ratio**	
1:2.7:6.7 Dose Ratio	1:1.1:1.7	1:3.1:10.6	1:2.1:5.0	1:9.0:31.8

[a] Calculated from time zero to the time of the last quantifiable plasma concentration, ranging from 4 to 12 hours post dose.

Doses of 3, 8, and 20 mg/kg/day evaluated in this study resulted in aripiprazole plasma exposures that were approximately equivalent, 2, and 6 times, respectively, human AUC exposure at the maximum recommended human IM dose (MRHD), as shown in the following sponsor's table.

Multiples of human systemic exposure following IM dose of 30 mg aripiprazole

Species (Study) 930009149	Type of Study	Sex	Aripiprazole Dose (mg/kg/day)	Cmax (ng/ml)	Cmax multiples[a]	AUC(0-T) (ng.h/ml)	AUC(0-T) multiples[a]
Aripiprazole							
Lactating Rat (DN04046) 930011278	IV Pre- and Postnatal Development (Lactation Day 4)[b]	F	3	4103	29	2556	1
			8	4685	33	5358	2
			20	6801	48	12863	6

[a] Based on mean Cmax and AUC(0-24 h) values obtained following a 30 mg IM dose of aripiprazole on Day 1 in a multiple ascending dose study in schizophrenia patients (CN138017)[43]: 143 ng/mL (Cmax) and 2297 ng.h/mL (AUC)

Dehydroaripiprazole

Lactating Rat (DN04046) 930011278	IV Pre- and Postnatal Development (Lactation Day 4)[b]	F	3	4.9	0.7	15	0.2
			8	15	2	132	1
			20	52	7	464	5

[a] Based on mean Cmax and AUC(0-24 h) values obtained following a 30 mg IM dose of aripiprazole on Day 1 in a multiple ascending dose study in schizophrenia patients (CN138017)[43]: 7.3 ng/mL (Cmax) and 92 ng.h/mL (AUC)

[b] Denotes the study day on which the toxicokinetic samples were collected.

Summary of individual study findings:

Aripiprazole IM formulation [a solution (7.5 mg/mL) in [redacted])] was administered intravenously once daily to groups of pregnant rats (n=25/group) on Gestation day 6 through Lactation day 20 at doses of 3, 8, or 20 mg/kg (dose volumes of 0.4, 1.07, and 2.67 mL/kg, respectively. There were 2 control groups (25 pregnant rats each) administered either the vehicle ([redacted]) or saline (0.9% sodium chloride for injection, USP) at 2.67 mL/kg. Criteria for evaluation included survival, clinical observations, body weights, and food consumption in Fo-generation dams during gestation and lactation; clinical signs during parturition, duration of gestation, maternal behavior during lactation, and gross pathology at the end of lactation in the Fo-generation dams; F1-generation pre-weaning litter observations (viability, clinical signs, and body weight); and post-weaning survival, clinical observations, body weight, food consumption, physical and neurobehavioral development (auditory startle, sexual maturation, open field and locomotor activity testing , water maze testing, and reproductive capacity), and gross pathology of male and female F1-generation animals. Plasma concentrations of aripiprazole and its pharmacologically active metabolite BMS-337044 (dehydro-aripiprazole) were measured on LD 4 in corresponding groups of 9 pregnant rats at each dose level. TK: systemic exposures to aripiprazole and active metabolite were dose related; BMS-337044 exposures were 4% or less relative to aripiprazole. Within the tested dose range, Cmax and AUC values for active metabolite increased in an increment greater than the dose increment, while the parent compound generally increased in an increment slightly less than dose-proportionally.

Aripiprazole IM formulation administered intravenously at doses of 3, 8, and 20 mg aripiprazole /kg/day to pregnant/lactating rats from gestation day 6 (implantation) through lactation day 20 (weaning) produced maternal clinical signs (hypoactivity, ptosis, lacrimation) at 8 and 20 mg/kg/day, attributable to aripiprazole pharmacologic activity, and maternal toxicity at 20 mg/kg/day (demonstrated by reduction in body weight, weight gain, and food consumption). Adverse effects on the F1-generation offspring were induced at 8 mg/kg/day (increased rate of stillbirths) and 20 mg/kg/day (increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life). Thus, aripiprazole induced increased stillbirth rates in the rat at the IV dose of 8 mg/kg/day that caused maternal clinical signs attributable to exaggerated pharmacologic activity, but no other manifestations of maternal toxicity. A higher, maternally toxic dose (20 mg/kg/day) affected pronouncedly the pre- and postnatal development of F1 generation, causing increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life, but no drug-related changes were observed in the tested post-weaning developmental endpoints of F1 generation (sensory perception, motor activity, learning, memory, sexual maturation, or reproductive function). At the doses of 8 and 20 mg/kg/day, aripiprazole systemic maternal plasma exposures in rats were 2x and 6x respectively (based on AUC) and 33x and 48x respectively (based on Cmax) the corresponding values in humans following a single 30 mg IM dose of aripiprazole. No effects on dams or progeny were induced at the dose of 3 mg/kg/day (NOAEL) (aripiprazole systemic exposure 1x (based on AUC) and 29x (based on Cmax) the corresponding values in humans following a single 30 mg IM dose of aripiprazole).

The sponsor's summary of the noteworthy drug-related changes is reproduced on the next page.

SUMMARY OF NOTEWORTHY DRUG-RELATED CHANGES

BMS-337039 - 3 mg/kg/day

No drug-related changes.

BMS-337039 - 8 and 20 mg/kg/day

1. In F_0-generation dams, increased incidences of ptosis, decreased motor activity, lacrimation, and urine-stained abdominal fur during the gestation and/or lactation periods.
2. In F_1-generation litters, increased stillbirths (28 and 44% of litters at 8 and 20 mg/kg/day had one or more stillborn pups, compared to 4 and 8% in saline and Captisol® controls, respectively; 5 and 8.1% of pups at 8 and 20 mg/kg/day were stillborn, compared with 0.3 and 1.6% in saline and Captisol® controls, respectively).

BMS-337039 - 20 mg/kg/day

1. In F_0-generation dams:
   - Reduced body-weight gains during Gestation Days 6 to 21 (31 and 33% less than saline and Captisol® controls, respectively), resulting in reduced maternal body weights from Gestation Day 9 through Lactation Day 21.
   - Decreased food consumption during Gestation Days 6 to 21 (13 and 11% less than saline and Captisol® controls, respectively) and Lactation Days 1 to 14 (16 and 18% less than saline and Captisol® controls, respectively).
2. In F_1-generation pups/rats:
   - Increased neonatal mortality (18% during Postnatal Days 1 to 4, as compared to 2 and 5% for the saline and Captisol® control groups, respectively), with associated pup clinical observations of coldness to touch and no milk in the stomach during this same period.
   - Reductions in litter size from Postnatal Day 4 through weaning on Postnatal Day 21, secondary to early pup mortality (mean of 9.4 pups/litter on Postnatal Day 4 compared with 11.9 and 12.5 pups/litter in saline and Captisol® controls, respectively).
   - Decreased pup body weights from birth (16% less than saline and Captisol® controls, respectively) through Postnatal Day 7 (15 and 14% less than saline and Captisol® controls, respectively).
   - Increased incidence of dilated renal pelvis at necropsy in males (Postnatal Days 133 to 136) and females (Gestation Day 20).

Reproductive and developmental toxicology summary:
The IV route of administration of aripiprazole IM formulation was used in the reproductive and developmental toxicity studies to ensure that multiples of clinically relevant systemic exposures to aripiprazole were achieved. Embryo-fetal development studies were conducted in rats and rabbits with IM aripiprazole administered intravenously from implantation to closure of the hard palate to detect potential adverse effects on the pregnant female and on development of the embryo and fetus. In addition, an IV study of pre- and postnatal development in rats was conducted to evaluate the potential adverse effects of IM aripiprazole on gestation, parturition, lactation, and maternal behavior and on the development and reproductive function of F1-generation offspring. In this study, drug administration to F0-generation females was from implantation through lactation and weaning. Other aspects of reproductive and developmental toxicity (fertility and early embryonic development) had been previously studied and reviewed in conjunction with the approval of aripiprazole oral tablet formulation. Fertility studies were not repeated with IM aripiprazole because of, as stated by the sponsor, the recommended short duration of use for this product (1 day), lack of effect on fertility upon oral aripiprazole administration in rats, and assessment of reproductive organ endpoints in the 1-month IV toxicity study in rats.

Reproductive and developmental toxicology conclusions:
1. Effect on Embryo-Fetal Development
Rats: IM aripiprazole administered intravenously to pregnant rats on gestation days 6 through 15 at doses of 3, 9, or 27 mg/kg, produced dose-dependent maternal clinical signs related to exaggerated pharmacologic activity (ptosis, lacrimation, decreased motor activity) at all doses, and maternal toxicity at 9 and 27 mg/kg/day (demonstrated by dose-dependent decrease in body weight gain and food consumption). Drug-related effects in the fetuses (growth retardation, characterized by reductions in fetal body weight with associated decreases in ossification) occurred only at 27 mg/kg/day. Thus, in the rat, aripiprazole affected fetal development (causing intrauterine growth retardation) at a dose level that also caused maternal toxicity.
Rabbits: IM aripiprazole formulation, administered intravenously at doses of 3, 10, or 30 mg/kg to pregnant rabbits once daily on gestation days 7 through 19, caused maternal toxicity at all dose levels (manifested as clinical signs, weight and/or weight gain reduction, and decreased food consumption) at all tested doses with dose-dependent frequency and severity. Drug-related clinical signs included decreased motor activity, tachypnea, and soft or liquid feces at all dose levels, and ataxia, convulsions, hyperpnea, nystagmus, altered righting reflex, and prostration at 30 mg/kg/day. Maternal body-weight gain was reduced at 10 mg/kg/day (67% and 50% less than saline and Captisol controls, respectively) and body-weight loss was noted at 30 mg/kg/day (20 g loss compared with a gain of 30 g and 20 g in saline and Captisol controls, respectively) during the first several days of dosing (gestation days 7 to 10). During the post-dosing period (g.d. 20 to 29), body-weight gain was reduced at 3, 10, and 30 mg/kg/day (33% and 27%, 46% and 41%, and 54% and 50% less than the saline and Captisol controls, respectively). Reductions in maternal food consumption paralleled the reductions in maternal body-weight gain at all doses. Drug-related changes in the fetuses occurred only at the HD of 30 mg/kg/day and included decreased fetal body weights (15% and 16% less than saline and Captisol controls, respectively) with associated reductions in ossification, as well as congenital malformations, including absence of the intermediate lobe of the lungs, split ribs, fused sternal ossification centers, and irregularly shaped scapulae. In conclusion, IM aripiprazole administered intravenously to pregnant rabbits on g.days 7 through 19 produced maternal toxicity (manifested in reduction in body weight and/ or weight gain as well as clinical signs) at all doses, and drug-related fetal

effects (growth retardation and congenital abnormalities, predominantly skeletal) at 30 mg/kg/day, a dose that induced a pronounced maternal toxicity. Thus, aripiprazole affected fetal development in the rabbit at a dose that caused pronounced maternal toxicity.

2. Effect on Pre- and Postnatal Development in Rats: Aripiprazole IM formulation administered intravenously at doses of 3, 8, and 20 mg aripiprazole /kg/day to pregnant/lactating rats from gestation day 6 (implantation) through lactation day 20 (weaning) produced maternal clinical signs (hypoactivity, ptosis, lacrimation) at 8 and 20 mg/kg/day, attributable to aripiprazole pharmacologic activity, and maternal toxicity at 20 mg/kg/day (demonstrated by reduction in body weight, weight gain, and food consumption). Adverse effects on the F1-generation offspring were induced at 8 mg/kg/day (increased rate of stillbirths) and 20 mg/kg/day (increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life). No effects on dams or progeny were induced at the dose of 3 mg/kg/day (NOAEL). Thus, aripiprazole induced increased stillbirth rates at the dose of 8 mg/kg/day that caused maternal clinical signs attributable to exaggerated pharmacologic activity, but no other manifestations of maternal toxicity, except for a slight transient decrease in body weight gain on gestation days 6 through 9. The higher, maternally toxic dose (20 mg/kg/day) affected pronouncedly the pre- and postnatal development of F1 generation, causing increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life, but no drug-related changes were observed in the tested post-weaning developmental endpoints of F1 generation (sensory perception, motor activity, learning, memory, sexual maturation, or reproductive function).

Labeling recommendations:

VIII. SPECIAL TOXICOLOGY STUDIES:

Study title: Two-week Intramuscular Study in Rats

Key study findings:.
Daily IM administration of aripiprazole to rats for 2 weeks at concentrations of 2 or 7.5 mg/ml in a dose volume of 0.5 ml/kg resulted in clinical and morphologic evidence of a reversible muscle injury. At both tested dose levels, there was increased incidence of swelling and discoloration at the injection site; microscopically, degeneration, necrosis, and regeneration of skeletal muscle and subacute inflammation, hemorrage, edema, and fibroplasias/fibrosis of skeletal muscle and surrounding connective tissue were found in all groups (including vehicle control), with dose-dependent severity. In addition to the local injection-site effects, there were slight increases in body weight and food consumption in females at both tested dose levels, and slight increase in serum AST in HDF. The clinical and clinical pathology changes were reversible; microscopically, at the injection sites, only minimal late-stage muscle regeneration and fibrosis were present in vehicle- and drug-treated groups after a 2-week recovery period.

Study no: DM00005/920007291
Volume # 1
Conducting laboratory and location: Bristol-Myers Squibb, Dept. of Toxicology and Pathology, Mt. Vernon, Indiana
Date of study initiation: January 11, 2000
GLP compliance: yes
QA reports: yes
Drug, lot #, radiolabel, and % purity: BMS-337039, Batch # C99G74M, [redacted] purity
Formulation/vehicle: [redacted]

Methods:
Dosing: Aripiprasole IM formulation was administered daily intramuscularly for 2 weeks to rats (12/sex/group) at concentrations of 2 or 7.5 mg/ml in a dose volume of 0.5 ml/kg (alternating daily between right and left leg muscle); the control group received the same volume of vehicle. Dose selection was based on a preceding single-dose study, as described by the sponsor:

> **In a single-dose intramuscular exploratory irritation study in rats (BMS Study No. 99328), administration of 7.5 mg/ml BMS-337039 in 15% Captisol® at a dose volume of 0.5 ml/kg resulted in minimal to mild focal muscle necrosis and inflammation. In that study, a concentration of 15 mg/ml BMS-337039 caused significantly greater muscle injury in association with precipitation of test article at the site of injection. Based on the above findings, concentrations of 2 and 7.5 mg/ml were assessed for local muscle changes and represent those that will be evaluated clinically.**

Observations and times: Survival, clinical signs, injection site observations, body weights, food consumption, serum CPK and AST, gross and microscopic pathology of the injection sites.

Plasma concentrations of aripiprasole, the active metabolite (dehydroaripiprazole) and 4 other metabolites (BMS-337040, BMS-337045, BMS-337047, and DCPP) were measured after dosing on day 10. Necropsies were performed at the end of dosing period (on 8 rats/sex/group) and after a 2-week post-dose recovery period (4 rats/sex/group).

Results: Daily IM administration of aripiprazole to rats for 2 weeks at concentrations of 2 or 7.5 mg/ml in a dose volume of 0.5 ml/kg resulted in clinical and morphologic evidence of a reversible muscle injury. At both tested dose levels, there was increased incidence of swelling and discoloration at the injection site; microscopically, degeneration, necrosis, and regeneration of skeletal muscle and subacute inflammation, hemorrage, edema, and fibroplasias/fibrosis of skeletal muscle and surrounding connective tissue were found in all groups (including vehicle control), with dose-dependent severity. In addition to the local injection-site effects, there were slight increases in body weight and food consumption in females at both tested dose levels, and slight increase in serum AST in HDF (see sponsor's table below and on next page). All clinical and clinical pathology effects were reversible upon discontinuation of dosing, and there was a "nearly complete" reversibility of injection site changes (only signs of muscle regeneration and fibrosis were still present in control and dose groups by the end of the 2-week recovery period.

Clinical chemistry data

Males

Serum Chemistry Group Mean Summary for Males
Study : DM00005 - BMS-337039: Two-Week Intramuscular Tolerance Study in Rats

Week: 3 relative to Start Date

Group Sex		AST U/L	CK U/L
1m	Mean	81.1	176.1
	S.D.	9.0	62.0
	N	8	8
2m	Mean	80.8	162.0
	S.D.	13.5	42.5
	N	8	8
3m	Mean	85.1	147.5
	S.D.	9.3	47.5
	N	8	8

Week: 5 relative to Start Date

Group Sex		AST U/L	CK U/L
1m	Mean	72.3	115.5
	S.D.	9.5	25.3
	N	4	4
2m	Mean	73.0	131.3
	S.D.	12.5	67.8
	N	4	4
3m	Mean	73.0	169.5
	S.D.	8.8	82.0
	N	4	4

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01

Nominal Dose: Group 1 - 0 mg/ml Group 2 - 2 mg/ml Group 3 - 7.5 mg/ml

Clinical chemistry data

Females

Serum Chemistry Group Mean Summary for Females
Study : DM00005 - BMS-337039: Two-Week Intramuscular Tolerance Study in Rats

Week: 3 relative to Start Date

Group Sex		AST U/L	CK U/L
1f	Mean	79.1	143.1
	S.D.	10.2	40.8
	N	8	8
2f	Mean	83.9	140.0
	S.D.	14.2	22.0
	N	8	8
3f	Mean	94.6*	128.8
	S.D.	10.8	21.6
	N	8	8

Week: 5 relative to Start Date

Group Sex		AST U/L	CK U/L
1f	Mean	71.3	121.3
	S.D.	4.3	31.9
	N	4	4
2f	Mean	75.0	138.5
	S.D.	7.6	23.3
	N	4	4
3f	Mean	69.3	114.5
	S.D.	5.9	37.6
	N	4	4

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01

Nominal Dose: Group 1 - 0 mg/ml Group 2 - 2 mg/ml Group 3 - 7.5 mg/ml

Histopathology findings: End of dosing

Study ID: DM00005 TWO-WEEK INTRAMUSCULAR TOLERANCE STUDY IN RATS Page: 1
Compound: BMS-337039 Date:02/24/00
Species: Rat Histopathology Group Incidence Summary Time: 13:31
Study Pathologist: W. M. Peden Pathology Table 3: End-of-Dose Necropsy ADP402 V3.0
Protocol Date: 01/03/00

Group	1		2		3	
Dose(mg/ml)	0		2		7.5	
Sex	M	F	M	F	M	F
Animals On Study	12	12	12	12	12	12
Animals Logged	8	8	8	8	8	8
General Body Sites						
Injection Site	8	8	8	8	8	8
Remarkable Observations	8	8	8	8	8	8
Degeneration; Muscle	8	7	7	7	8	8
Necrosis; Muscle	7	7	7	7	8	7
Regeneration; Muscle	8	8	8	8	8	8
Inflammation, Subacute	7	8	8	8	8	8
Edema	0	1	2	1	8 b	8 b
Hemorrhage	5	5	5	7	7	7
Fibroplasia/Fibrosis	6	8	7	8	8	8
Pigment	0	0	0	1	0	0

Histopathology findings: Post-recovery period

Study Pathologist: W. M. Peden Pathology Table 3: Postdose Necropsy ADP402 V3.0
Protocol Date: 01/03/00

	Group	1		2		3	
	Dose(mg/ml)	0		2		7.5	
	Sex	M	F	M	F	M	F
	Animals On Study	12	12	12	12	12	12
	Animals Logged	4	4	4	4	4	4
General Body Sites							
Injection Site		4	4	4	4	4	4
Remarkable Observations		4	4	4	4	4	4
Regeneration; Muscle		4	4	4	4	4	4
Fibroplasia/Fibrosis		2	3	4	3	4	4
Infiltration, Mononuclear Cell		4	2	3	2	4	1

The tissue incidence reflects the number of tissues that were processed:
Remarkable, Not Remarkable, Missing, Autolyzed or Notes Only.
The morphology incidence reflects the number of animals in which the morphology occurred.
Autolysis Only and Notes Only are tabulated if no diagnoses are rendered.
Fisher's Exact Test, a = p<0.05, b = p<0.01 *= Fisher's Not Calculated (Less than 4 tissues)

TK: The TK results and exposure parameters are adequately summarized by the sponsor as follows:

After once-daily intramuscular administrations of 2- and 7.5-mg/mL dosing solutions of BMS-337039 (1- and 3.75-mg/kg doses) to rats for 10 days, plasma concentrations for BMS-337039 were generally measurable up to 8 h after dosing at the 1-mg/kg/day dose level, and up to 24 h at the 3.75 mg/kg/day dose level. For nominal doses increasing in 1:3.75 proportion, the CMAX values at 10 min after dosing increased in the proportions of 1:4.1 in males and 1:3.6 in females. The corresponding proportions for AUC(0-T) values were 1:5.0 in males and 1:4.5 in females. A trend of slightly lower plasma concentrations in females compared to males was observed. At the 1-mg/kg/day dose level, plasma concentrations for metabolite BMS-337040 were measurable for up to 3 h after dosing; however, plasma concentrations for the other four metabolites were below LLQ. At the 3.75-mg/kg/day dose level, plasma concentrations for BMS-337047 and DCPP were below LLQ. At the 3.75- mg/kg/day dose level, the AUC(0-T) values of BMS-337040, BMS-337044, and BMS-337045 compared to the parent compound were 2.9%, 0.3%, 0.2% in males and 1.3%, 0.5%, 0.4% in females, respectively. Overall, systemic exposures of rats to BMS-337039 and metabolites were dose related and exposure to BMS-337039 appeared to be somewhat lower in females compared to males. BMS-337040 was the major circulating metabolite.

Daily Dose (mg/kg)	Concentration of dosing solution (mg/mL)	Sex	BMS-337039		BMS-337040		BMS-337044	
			CMAX (ng/mL)	AUC (0-T)[a] (ng.h/mL)	CMAX (ng/mL)	AUC(0-T)[a] (ng.h/mL)	CMAX (ng/mL)	AUC(0-T)[a] (ng.h/mL)
1	2	M	199	383	5.47	8.29	b	b
		F	183	287	1.49	c	b	b
3.75	7.5	M	821	1913	12.4	55.9	1.95	4.94
		F	661	1294	5.91	16.6	2.66	6.72

a T = 8 to 24 h for BMS-337039; and T= 3 to 8 h for BMS-337040 and BMS-337044.
b Plasma concentrations were below LLQ.
c AUC value was not reported since there were less than 3 measurable concentrations in the composite plasma concentration-time profile.

Summary of individual study findings:

In this local tolerance study, aripiprasole IM formulation was administered daily intramuscularly for 2 weeks to rats (12/sex/group) at concentrations of 2 or 7.5 mg/ml in a dose volume of 0.5 ml/kg (alternating daily between right and left leg muscle); the control group received the same volume of vehicle (———————————— . TK evaluation on day 10 of dosing showed that systemic exposures to aripiprazole and its metabolites were dose-related. Clinical and morphologic evidence of a reversible muscle injury was present at both tested dose levels, i.e., increased incidence of swelling and discoloration at the injection site; microscopically, degeneration, necrosis, and regeneration of skeletal muscle and subacute inflammation, hemorrage, edema, and fibroplasias/fibrosis of skeletal muscle and surrounding connective tissue

were found in all groups (including vehicle control), with dose-dependent severity. In addition to the local injection-site effects, there were slight increases in body weight and food consumption in females at both tested dose levels, and slight increase in serum AST in HDF. The clinical and clinical pathology changes were reversible; microscopically, at the injection sites, only minimal late-stage muscle regeneration and fibrosis were present in vehicle- and drug-treated groups after the 2-week recovery period.

Study title: Single-dose Intramuscular Irritation Study in Rabbits

Key study findings: Reversible muscle irritation was observed in rabbits (6F/group) upon a single intramuscular injection of aripiprasole IM formulation at concentrations of 2, 4 or 7.5 mg/ml in a dose volume of 1 ml/kg; two control group received IM the same volume of either vehicle [redacted] or saline. Microscopically, muscle degeneration/regeneration and inflammation with a dose-related severity were observed on day 4 post-dose in all test and control groups (minimal severity in the saline control group); hemorrhage and mineralization of degenerated muscle fibres were present in vehicle control and aripiprazole-treated groups. In addition to the local injection-site effects, there was an increase in serum CPK values in the vehicle control and all dose groups (statistically significant vs. saline control values); when compared to vehicle control, only CPK increase at HD was statistically significant. These changes were reversible; after a 2-week recovery period, there was only slight edema and minimal muscle regeneration, inflammation, mineralization, or fibrosis at the injection site in the HD group.

Study no: 99356/920003932
Volume # 1
Conducting laboratory and location: Bristol-Myers Squibb, Dept. of Toxicology and Pathology, Mt. Vernon, Indiana
Date of study initiation: December 6, 1999
GLP compliance: yes
QA reports: yes
Drug, lot #, radiolabel, and % purity: C99G74M, [redacted] purity
Formulation/vehicle: [redacted]

Methods:
Dosing: Aripiprasole IM formulation was administered as a single intramuscular injection to female New Zealand White rabbits (6/group) at concentrations of 2, 4 or 7.5 mg/ml in a dose volume of 1 ml/kg; two control groups (6 animals each) received the same volume of either vehicle [redacted], or saline (0.9% sodium chloride for injection).
The rationale for dose selection was stated as follows: "The concentrations selected span those to be administered clinically (2 and 7.5 mg/ml). Higher concentrations of the test article in [redacted] Captisol resulted in precipitation of test article at the site of injection (Bristol-Myers Squibb Study No. 99328)".

Observations and times: Survival, clinical signs, injection site observations, body weight, creatinine phosphokinase (CPK) and aspartate-aminotransferase (AST) (in serum samples collected prior to, and approximately 24 h. and 18 days post-dose), gross and microscopic

pathology of the injection sites. Necropsies were performed on day 4 (4 animals/group) and on day 18 (the remaining 2 animals/group).

Results: Slight edema at injection sites was seen in the vehicle control and all dose groups at comparable incidences. Increase in serum CPK values was seen in the vehicle control and all dose groups (statistically significant vs. saline control values); when compared to vehicle control, only CPK increase at HD was statistically significant (see sponsor's table below). Microscopically, muscle degeneration/regeneration and inflammation with a dose-related severity were observed on day 4 post-dose in all groups (minimal severity in the saline control group); hemorrhage and mineralization of degenerated muscle fibres were present in vehicle control and aripiprazole-treated groups. These changes were reversible: by day 18 post-dose, CPK levels were normal in all groups; at the injection site, there was only slight edema and minimal muscle regeneration, inflammation, mineralization, or fibrosis at the HD.

Clinical chemistry

SLI STUDY NO.: 3148.30 — AN INTRAMUSCULAR IRRITATION STUDY IN RABBITS — PAGE
CLIENT: BRISTOL-MYERS SQUIBB — SUMMARY OF BIOCHEMISTRY DATA
CLIENT NO.: 99356

----- FEMALE -----

	GROUP:	1	2	3	4	5
	LEVEL (MG/ML):	0	0	2	4	7.5
	TEST ARTICLE:	SODIUM CHLORIDE	VEHICLE	BMS-337039	BMS-337039	BMS-337039
AST IU/L						
DAY -4	MEAN	37	35	31	36	37
	S.D.	7.1	9.2	8.3	10.5	7.6
	N	6	6	6	6	6
DAY 2	MEAN	29	29	35	31	30
	S.D.	4.5	9.8	11.6	7.3	8.4
	N	6	6	6	6	6
DAY 18 (RECOVERY PHASE)	MEAN	36	30	29	21	36
	S.D.	--	--	--	--	--
	N	2	2	2	2	2
CREATINE KINASE IU/L						
DAY -4	MEAN	427	479	379	310	402
	S.D.	141.6	123.7	33.9	110.1	105.7
	N	6	6	6	6	6
DAY 2	MEAN	623(**)	2388**	2167*	3149#	6042# (#)
	S.D.	159.7	649.1	960.8	582.8	1139.3
	N	6	6	6	6	6
DAY 18 (RECOVERY PHASE)	MEAN	757	429	460	173	360
	S.D.	--	--	--	--	--
	N	2	2	2	2	2

SIGNIFICANTLY DIFFERENT FROM SODIUM CHLORIDE CONTROL (GROUP 1): * = P<0.05; ** = P<0.01; # = P<0.001
SIGNIFICANTLY DIFFERENT FROM VEHICLE CONTROL (GROUP 2): (**) = P<0.01; (#) = P<0.001
NOTE: THE MEANS AND STANDARD DEVIATIONS WERE CALCULATED USING NONROUNDED VALUES. STANDARD DEVIATION WAS NOT CALCULATED AND STATISTICAL ANALYSIS WAS NOT PERFORMED WHEN N ≤ 2.

Histopathology findings, day 4

AN INTRAOCULAR IRRITATION STUDY IN RABBITS
Incidence of Histopathologic Findings for Females
Table: 1A

PROJECT NUMBER: 3148.30 SPECIES: RABBIT

Tissue/ Diagnosis/ Modifier(s)	Group 1	Group 2	Group 3	Group 4	Group 5
CONTROL	(4)	(4)	(4)	(4)	(4)
WITHIN NORMAL LIMITS	4	4	4	4	4
INJECTION SITE	(4)	(4)	(4)	(4)	(4)
DEGENERATION/REGENERATION	1	4	4	4	4
MINIMAL	1	1	4	0	0
MILD	0	3	0	4	1
MODERATE	0	0	0	0	3
HEMORRHAGE	0	4	4	4	4
MINIMAL	0	3	4	3	1
MILD	0	1	0	1	3
INFLAMMATION	3	4	4	4	4
MINIMAL	3	0	1	0	0
MILD	0	4	3	4	1
MODERATE	0	0	0	0	3
MINERALIZATION	0	4	2	3	4
MINIMAL	0	4	2	1	1
MILD	0	0	0	2	3
WITHIN NORMAL LIMITS	1	0	0	0	0

Histopathology findings, day 18

Table: 1B

PROJECT NUMBER: 3148.30 SPECIES: RABBIT

Tissue/ Diagnosis/ Modifier(s)	Group 1	Group 2	Group 3	Group 4	Group 5
CONTROL	(2)	(2)	(2)	(2)	(2)
WITHIN NORMAL LIMITS	2	2	2	2	2
INJECTION SITE	(2)	(2)	(2)	(2)	(2)
DEGENERATION/REGENERATION	0	0	1	0	1
MINIMAL	0	0	1	0	1
FIBROSIS	0	0	0	0	2
MINIMAL	0	0	0	0	2
INFLAMMATION	0	0	0	0	2
MINIMAL	0	0	0	0	2
MINERALIZATION	0	0	1	0	1
MINIMAL	0	0	1	0	1
WITHIN NORMAL LIMITS	2	2	1	2	0

Titles:
Group 1 0.9% SODIUM CHLORIDE
Group 2 VEHICLE CONTROL
Group 3 TEST ARTICLE 2.0 MG/ML
Group 4 TEST ARTICLE 4.0 MG/ML
Group 5 TEST ARTICLE 7.5 MG/ML

() = Number Of Animals Examined For This Tissue

Only severities are printed. (501-504)

Microscopic Incidence Page: 1

Summary of individual study findings: (See Key study findings)

Conclusions (Special toxicology studies):
Local tolerance studies in 2 animal species (rats and rabbits) showed that aripiprazole IM formulation had a mild and reversible local irritation effect upon IM administration.
Rats: Repeated IM administration of aripiprazole to rats for 2 weeks at concentrations of 2 or 7.5 mg/ml in a dose volume of 0.5 ml/kg resulted in clinical and morphologic evidence of a reversible muscle injury. At both tested dose levels, there was increased incidence of swelling and discoloration at the injection site; microscopically, degeneration, necrosis, and regeneration of skeletal muscle and subacute inflammation, hemorrage, edema, and fibroplasias/fibrosis of skeletal muscle and surrounding connective tissue were found in all groups (including vehicle control), with dose-dependent severity. In addition to the local injection-site effects, there were slight increases in body weight and food consumption in females at both tested dose levels, and slight increase in serum AST in HDF. The clinical and clinical pathology changes were reversible; microscopically, at the injection sites, only minimal late-stage muscle regeneration and fibrosis were present in vehicle- and drug-treated groups after the 2-week recovery period.
Rabbits: Reversible muscle irritation was observed in rabbits (6F/group) upon a single intramuscular injection of aripiprasole IM formulation at concentrations of 2, 4 or 7.5 mg/ml in a dose volume of 1 ml/kg; two control group received IM the same volume of either vehicle [redacted] or saline. Microscopically, muscle degeneration/regeneration and inflammation with a dose-related severity were observed on day 4 post-dose in all test and control groups (minimal severity in the saline control group); hemorrhage and mineralization of degenerated muscle fibres were present in vehicle control and aripiprazole-treated groups. In addition to the local injection-site effects, there was an increase in serum CPK values in the vehicle control and all dose groups (statistically significant vs. saline control values); when compared to vehicle control, only CPK increase at HD was statistically significant. These changes were reversible; after a 2-week recovery period, there was only slight edema and minimal muscle regeneration, inflammation, mineralization, or fibrosis at the injection site in the HD group.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

1. An abbreviated non-clinical testing strategy for IM aripiprazole was employed by the sponsor since it was supported, in part, by results from previous in vitro and in vivo nonclinical studies conducted to support the aripiprazole oral tablet that characterized the pharmacology and safety pharmacology, oral pharmacokinetics and metabolism, genetic toxicity, oral toxicity including carcinogenicity, and oral toxicokinetics. The studies that were conducted with the IM aripiprazole formulation assessed its PK/TK, repeat-dose toxicity, reproductive and developmental toxicity and local irritation potential. This testing strategy was approved by the Division (6/9/2004, Pre-NDA Meeting Minutes). Toxicologic evaluation of the excipient Captisol® is not included in this application since Captisol® has been used in 2 approved marketed products, Geodon® (ziprasidone hydrochloride) and Vfend®IV (voriconazole) for Injection, and is considered not to be a novel excipient.

2. PK:

Absorption of aripiprazole from the injection site upon IM administration in rats, dogs, and monkeys was rapid (Cmax for aripiprazole following a single intramuscular dose was observed at approximately 10 min in dogs and monkeys, and 15 min in rats) and extensive (the absolute bioavailability of aripiprazole following a single IM dose was 99.5% in dogs and about 87% in monkeys, indicating essentially complete absorption of aripiprazole from the injection site, as compared to a much lower bioavailability (12% in dogs) upon oral administration of the same dose; the bioavailability in rats "could not be calculated due to loss of the data resulting from bioanalytical discrepancies".

Specific studies to examine the distribution, metabolism, and excretion of aripiprazole following IM administration have not been conducted by the sponsor. Aripiprazole metabolites identified upon IM and/or IV administration in PK or TK studies in rats, rabbits, dogs, and monkeys were the same as those identified after IV and oral administration. The available data suggest that the metabolism of aripiprazole is qualitatively similar across the tested species and humans.

3. TK:

The systemic exposure to aripiprazole and the active metabolite (as assessed by Cmax and AUC values upon repeat IM or IV administration of the IM formulation in 1-month toxicity studies in monkeys and rats) increased in a dose-related manner. Accumulation of systemic exposures to aripiprazole and its active metabolite was observed in rats and monkeys after 1 month of repeated daily administration of aripiprazole by IV (rats) or IM (monkeys) injection as compared to day 1. The accumulation was much more pronounced in rats. There were no apparent sex-related exposure differences in the tested animal species.

4. General toxicology:

Definitive general toxicology studies are the 1-month repeat-dose toxicity studies in rats (employing the IV route in order to achieve sufficient systemic exposures) and monkeys (IM administration).

- The repeat-dose IV daily administration of IM aripiprazole formulation at doses of 3, 10, and 30 mg/kg/day for 1 month to rats (10/sex/group) resulted in pharmacologically-related clinical signs (dose-related decreased activity) at all doses, and morphologic changes in the adrenals at HD and in female reproductive and mammary tissues at all doses. In the females, the morphologic changes included (at all doses): decrease in the total number of corpora lutea in the ovary with increased proportion of large corpora lutea, dose-related persistent diestrus with

excessive vaginal mucification and mildly decreased uterine weights, and hyperplasia of mammary glandular tissue. In the males, atrophy of mammary glandular tissue was observed at all doses. Adrenal gland weights were increased at the HD (30 mg/kg/day) in both sexes, in correlation with the microscopic finding of hypertrophy of the zona fasciculata in the adrenal cortex (F). There was no direct target organ toxicity at any dose level; the observed changes were a likely manifestation of exaggerated pharmacological effect. A NOEL was not reached, but aripiprazole was well tolerated at 3 mg/kg/day. Systemic exposures to aripiprazole at 3 mg/kg/day were 7 to 8 times (Cmax) and 0.5 to 0.6 times (AUC) human exposures at the MRHD of 30 mg IM. Systemic exposures to aripiprazole at 10 and 30 mg/kg/day were 18 to 51 times based on Cmax and 2 to 15 times based on AUC human exposures at the MRHD.

- The repeat-dose IM administration of aripiprazole to monkeys (5/sex/dose) at daily doses of 2, 4, 7.5 mg/kg/day (and a vehicle control group) for 1 month resulted in the following effects at all doses: pharmacologically mediated CNS clinical signs (decreased activity and tremors), decreased food consumption during the dosing period (22-28% lower than control at 2 mg/kg/day, and 51-59% lower than control at 4 and 7.5 mg/kg/day), and increased frequency of scabbing and reversible muscle injury in injection sites. The daily injection volumes were 0.26, 0.53, and 1 ml/kg, for LD, MD and HD, respectively, and 1 ml/kg for control, but not exceeding 1.5 ml at a time to any one injection site; the injection sites were alternated daily between the right and left posterior thigh muscles. Microscopically, injection site changes observed in Captisol (vehicle) control group were slight and less pronounced than the injection site changes at 2, 4, and 7.5 mg/kg/day, suggestive of a drug-related effect. Injection site changes attributed to aripiprazole included increased incidence and/or severity of skeletal muscle necrosis (minimal to mild), degeneration (mild to moderate), and regeneration (mild to moderate) at all doses; increased severity of subacute inflammation (mild) at 4 and 7.5 mg/kg/day; and increased incidence and severity of fibroplasia/fibrosis (minimal to mild) at 7.5 mg/kg/day. Drug-related clinical chemistry changes at 4 and 7.5 mg/kg/day included slightly decreased serum gamma-glutamyl transferase (GGT) in males, and increased serum aspartate aminotransferase (AST) (means approximately 2x the control mean values in MDF and HDF, and approximately 3 times the control in one male HD animal). The increases in serum AST observed at MD and HD (4 and 7.5 mg/kg/day) were likely a consequence of the skeletal muscle injury at injection sites. Systemic exposures to aripiprazole and the active metabolite, dehydroaripiprazole, were dose-proportional with no apparent sex-related differences. There was no appreciable accumulation after 1 month of dosing. Following a 1-month post-dose recovery period, all aripiprazole-related clinical pathology changes were reversible.

NOAEL: Not reached (<2 mg/kg/day). At the lowest tested IM dose of 2 mg/kg/day, plasma AUC exposures for aripiprazole and its active metabolite, dehydroaripiprazole, were 1x and 6x, respectively, the human AUC exposures at MRHD (30 mg IM ariupiprazole).

5. Reproductive and developmental toxicology

- The IV route of administration of aripiprazole IM formulation was used in the reproductive and developmental toxicity studies to ensure that multiples of clinically relevant systemic exposures to aripiprazole were achieved. Embryo-fetal development studies were conducted in rats and rabbits with IM aripiprazole administered intravenously from implantation to closure of the hard palate to detect potential adverse effects on the pregnant female and on development of the embryo and fetus. In addition, an IV study of pre- and postnatal development in rats was conducted to evaluate the potential adverse effects of IM aripiprazole on gestation, parturition, lactation, and maternal behavior and on the development and reproductive function of F_1-generation offspring. In this study, drug administration to F_0-generation females was from implantation through lactation and weaning. Other aspects of reproductive and developmental

toxicity (fertility and early embryonic development) had been previously studied and reviewed in conjunction with the approval of aripiprazole oral tablet formulation. Fertility studies were not repeated with IM aripiprazole because of, as stated by the sponsor, the recommended short duration of use for this product (1 day), lack of effect on fertility upon oral aripiprazole administration in rats, and assessment of reproductive organ endpoints in the 1-month IV toxicity study in rats.

- Effect on Embryo-Fetal Development

Rats: IM aripiprazole administered intravenously to pregnant rats on gestation days 6 through 15 at doses of 3, 9, or 27 mg/kg, produced dose-dependent maternal clinical signs related to exaggerated pharmacologic activity (ptosis, lacrimation, decreased motor activity) at all doses, and maternal toxicity at 9 and 27 mg/kg/day (demonstrated by dose-dependent decrease in body weight gain and food consumption). Drug-related effects in the fetuses (growth retardation, characterized by reductions in fetal body weight with associated decreases in ossification) occurred only at 27 mg/kg/day. Thus, in the rat, aripiprazole affected fetal development (causing intrauterine growth retardation) at a dose level that also caused maternal toxicity.

Rabbits: IM aripiprazole formulation, administered intravenously at doses of 3, 10, or 30 mg/kg to pregnant rabbits once daily on gestation days 7 through 19, caused maternal toxicity at all dose levels (manifested as clinical signs, weight and/or weight gain reduction, and decreased food consumption) at all tested doses with dose-dependent frequency and severity. Drug-related clinical signs included decreased motor activity, tachypnea, and soft or liquid feces at all dose levels, and ataxia, convulsions, hyperpnea, nystagmus, altered righting reflex, and prostration at 30 mg/kg/day. Maternal body-weight gain was reduced at 10 mg/kg/day (67% and 50% less than saline and Captisol controls, respectively) and body-weight loss was noted at 30 mg/kg/day (20 g loss compared with a gain of 30 g and 20 g in saline and Captisol controls, respectively) during the first several days of dosing (gestation days 7 to 10). During the post-dosing period (g.d. 20 to 29), body-weight gain was reduced at 3, 10, and 30 mg/kg/day (33% and 27%, 46% and 41%, and 54% and 50% less than the saline and Captisol controls, respectively). Reductions in maternal food consumption paralleled the reductions in maternal body-weight gain at all doses. Drug-related changes in the fetuses occurred only at the HD of 30 mg/kg/day and included decreased fetal body weights (15% and 16% less than saline and Captisol controls, respectively) with associated reductions in ossification, as well as congenital malformations, including absence of the intermediate lobe of the lungs, split ribs, fused sternal ossification centers, and irregularly shaped scapulae. In conclusion, IM aripiprazole administered intravenously to pregnant rabbits on g.days 7 through 19 produced maternal toxicity (manifested in reduction in body weight and/ or weight gain as well as clinical signs) at all doses, and drug-related fetal effects (growth retardation and congenital abnormalities, predominantly skeletal) at 30 mg/kg/day, a dose that induced a pronounced maternal toxicity. Thus, aripiprazole affected fetal development in the rabbit at a dose that caused pronounced maternal toxicity.

- Effect on Pre- and Postnatal Development

Aripiprazole IM formulation administered intravenously at doses of 3, 8, and 20 mg aripiprazole /kg/day to pregnant/lactating rats from gestation day 6 (implantation) through lactation day 20 (weaning) produced maternal clinical signs (hypoactivity, ptosis, lacrimation) at 8 and 20 mg/kg/day, attributable to aripiprazole pharmacologic activity, and maternal toxicity at 20 mg/kg/day (demonstrated by reduction in body weight, weight gain, and food consumption). Adverse effects on the F1-generation offspring were induced at 8 mg/kg/day (increased rate of stillbirths) and 20 mg/kg/day (increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life). No effects on dams or progeny were induced at the dose of 3 mg/kg/day (NOAEL). Thus, aripiprazole induced increased stillbirth rates at the

dose of 8 mg/kg/day that caused maternal clinical signs attributable to exaggerated pharmacologic activity, but no other manifestations of maternal toxicity, except for a transient decrease (-11%) in body weight gain on gestation days 6 through 9. The higher, maternally toxic dose (20 mg/kg/day) affected pronouncedly the pre- and postnatal development of F1 generation, causing increased rates of stillbirths, neonatal mortality, and reduction in pup body weight during the first week of life, but no drug-related changes were observed in the tested post-weaning developmental endpoints of F1 generation (sensory perception, motor activity, learning, memory, sexual maturation, or reproductive function).

6. Special toxicology studies
Local tolerance studies in 2 animal species (rats and rabbits) showed that aripiprazole IM formulation had a mild and reversible local irritation effect upon IM administration.

General Toxicology Issues: None

Recommendations: Approvable

Labeling with basis for findings:

Under subtitle "Pregnancy":

In pregnant rats receiving aripiprazole injection intravenously (3, 9, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose, which also caused some maternal toxicity.

In pregnant rabbits receiving aripiprazole injection intravenously (3, 10, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The no-effect dose was 10 mg/kg, which produced 15 times the human exposure at the MRHD based on AUC, and is 6 times the MRHD based on mg/m^2.

In rats receiving aripiprazole injection intravenously (3, 8, and 20 mg/kg/day) from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8 and 20 mg/kg, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg, [redacted] These doses produced some maternal toxicity [redacted]

X. APPENDIX/ATTACHMENTS:

Addendum to review: None

Other relevant materials (Studies not reviewed, appended consults, etc.): None

Any compliance issues: None

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/s/

Sonia Tabacova
9/7/2006 03:54:03 PM
PHARMACOLOGIST

Barry Rosloff
9/11/2006 04:06:21 PM
PHARMACOLOGIST

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