2. Developmental Toxicity Study of Irbesartan in Rats (Segment II)

Study No: 311/518 (Ter225)

Performing Laboratory:

Sponsor: Sanofi Recherche, Montpellier Cedex, France

Initiation of Treatment: 9/14/92

Quality Assurance: A statement of conformance to GLPs is included.

Test Animals: OFA SD (IOPS Caw) RATS, supplied by IFFA Credo (France). Twenty five females per group were 10 to 12 weeks old and weighed 211-265 g when mated.

Procedure: SR 47436 (batch no. 92.02) was administered in 10% aqueous gum Arabic solution at doses of 0, 50, 150 and 450 mg/kg/day, once daily, by gastric intubation, from gestation day (GD) 6 to GD 15. The dose volume was 5 ml/kg for each group. Dams were observed daily for physical condition and mortality; body weight and food consumption measurements were made on GD 0, 6, 11, 16 and 20. Dams were C-sectioned on GD 20 and examined for number of corpora lutea in each ovary; numbers of implantation and resorption sites; and numbers of live and dead fetus. Fetal and placental weights were determined. Live fetuses were examined for determination of sex and external anomalies; half were examined for soft tissue abnormalities by free hand sectioning (modified Wilson-Barrow technique), the remaining half were first internally examined by dissection, and then cleared with KOH and stained with Alizarin-red (modification of Dawson method) for determination of skeletal abnormalities.

Justification of Dosage: Not provided. It was noted that no toxicity had been observed in dams or fetuses in a dose range study with doses of 0, 50, 150, and 450 mg/kg/day (6 pregnant rats per group).

Definitions: The following definitiions were used by the sponsor to define fetal abnormalities found in this and in subsequent developmental toxicity studies in the rat and rabbit.

> Malformations: Structural defects that are rare in the control population and are thought to be life-threatening or of major physiological consequence.
>
> Variations: Minor abnormalities or defects that are relatively rare in the control population and/or are not considered to be of major physiological consequence.

Incidental findings: Minor abnormalities, defects or alternative forms that are either common in the control population or are of no known physiological consequence.

Drug Associated Findings:

Dams: After initiation of treatment, decreases in mean body weight and body weight gain, compared to control, were observed in the mid and high dose groups (not dose related). A decrease in body weight gain was observed at low dose only during the initial 5 days of dosing. Decreases in food intake were observed in all 3 treated groups (not dose related). All dams survived to scheduled C-section.

Fetuses: There was an absence of malformations or other structural anomalies in any (test or control group) fetus, with the exception of a few external variations which showed no relationship to treatment. There were no effects on fetal weight or postimplantation loss.

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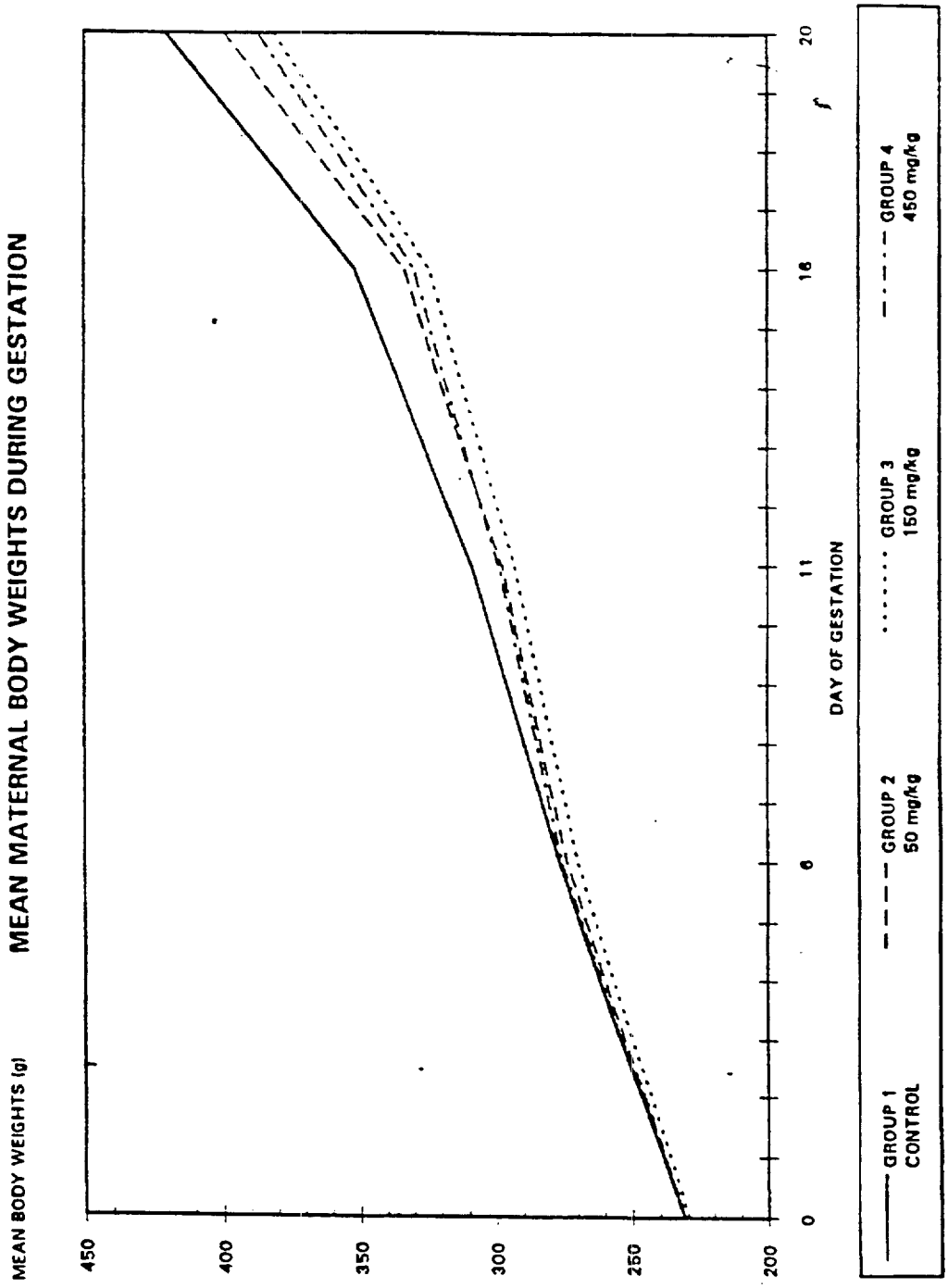
STUDY NUMBER 311/518 - FIGURE 1 -
MEAN MATERNAL BODY WEIGHTS DURING GESTATION



SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RAT (SEGMENT II).
MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- grams

DOSE LEVEL		CONTROL	50 mg/Kg	150 mg/Kg	450 mg/Kg
DAY 0	MEAN	231.1	230.7	229.4	230.8
	S.D.	12.5	14.0	9.8	12.7
	N	21	21	24	25
DAY 6	MEAN	276.8	274.0	270.0	275.9
	S.D.	15.6	14.6	13.7	15.3
	N	21	21	24	25
DAY 11	MEAN	308.8	297.7	293.1**	298.9
	S.D.	17.7	16.4	13.8	19.5
	N	21	21	24	25
DAY 16	MEAN	351.7	333.6*	324.1**	329.8**
	S.D.	24.2	17.8	20.8	27.1
	N	21	21	24	25
DAY 20	MEAN	420.6	399.7	381.7**	387.6**
	S.D.	35.5	23.5	32.7	34.6
	N	21	21	24	25

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.
Means calculated excluding dams with no viable embryos/fetuses or with no pups delivered.

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RAT (SEGMENT II).
MEAN MATERNAL BODY WEIGHT CHANGES DURING GESTATION -- grams

	DOSE LEVEL	CONTROL	50 mg/Kg	150 mg/Kg	450 mg/Kg
DAYS 0 TO 6	MEAN	45.69	43.34	40.65*	45.14
	S.D.	6.90	5.91	6.98	6.52
	N	21	21	24	25
DAYS 6 TO 11	MEAN	32.01	23.65**	23.10**	22.95**
	S.D.	7.07	5.41	6.79	7.21
	N	21	21	24	25
DAYS 11 TO 16	MEAN	42.91	35.88	31.01**	30.88**
	S.D.	10.79	8.47	9.96	12.09
	N	21	21	24	25
DAYS 16 TO 20	MEAN	68.87	66.15	57.56	57.86
	S.D.	14.14	13.05	19.57	19.76
	N	21	21	24	25

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P<0.05$; ** = $P<0.01$.
Means calculated excluding dams with no viable embryos/fetuses or with no pups delivered.

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RAT (SEGMENT II).
MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- SUMMARY

	DOSE LEVEL	CONTROL	50 mg/Kg	150 mg/Kg	450 mg/Kg
MATERNAL FOOD CONSUMPTION -- grams/ANIMAL/DAY					
DAYS 0 TO 6	MEAN	24.5	23.9	23.8	24.1
	S.D.	1.7	2.1	1.9	2.0
	N	21	21	24	25
	SPILLED	0	0	0	0
DAYS 6 TO 11	MEAN	27.9	24.8**	24.4**	24.3**
	S.D.	2.4	2.4	2.8	2.7
	N	21	21	24	25
	SPILLED	0	0	0	0
DAYS 11 TO 16	MEAN	30.5	27.8*	26.4**	26.0**
	S.D.	2.9	2.1	3.2	3.6
	N	21	21	24	25
	SPILLED	0	0	0	0
DAYS 16 TO 20	MEAN	34.3	32.6	30.9**	30.2**
	S.D.	3.5	2.6	3.7	3.2
	N	21	21	24	25
	SPILLED	0	0	0	0

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.
Means calculated excluding dams with no viable embryos/fetuses or with no pups delivered.

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RAT (SEGMENT II).
SUMMARY OF CESAREAN SECTION DATA

HF 311518

DOSE LEVEL		CONTROL	50 mg/Kg	150 mg/Kg	450 mg/Kg
Females Mated	N	25	25	25	25
Pregnant	N	21	22	25	25
	%	84	88	100	100
Aborted	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Died	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Delivered Early	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Pregnant at C-section	N	21	22	25	25
Dams with Viable Fetuses	N	21	21	24	25
	%	100	95	96	100
Dams with no Viable Fetuses	N	0	1	1	0
	%	0.0	4.5	4.0	0.0
Corpora Lutea	MEAN	16.5	15.8	14.6	15.4
	S.D.	3.5	2.5	3.2	2.7
	N	21	22	25	25
	TOTAL	347	348	364	386
Implantation Sites	MEAN	14.1	12.4	11.8	12.6
	S.D.	4.1	4.2	4.3	4.3
	N	21	22	25	25
	TOTAL	296	272	294	316
Preimplantation Loss	MEAN%	15.7	21.9	20.7	18.5
	S.D.	15.8	24.8	22.6	24.5

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RAT (SEGMENT II).
SUMMARY OF CESAREAN SECTION DATA

	DOSE LEVEL	CONTROL	50 mg/Kg	150 mg/Kg	450 mg/Kg
Pregnant at C-section	N'	21	22	25	25
Resorptions: Total	MEAN	1.0	0.9	1.5	1.0
	S.D.	1.2	0.8	1.3	1.0
	N	21	22	25	25
	TOTAL	20	19	37	26
	MEAN%	7.0	10.3	17.4	9.6
	S.D.	9.6	20.9	23.3	11.4
Early	MEAN	1.0	0.8	1.4	0.9
	S.D.	1.2	0.8	1.3	0.8
	N	21	22	25	25
	TOTAL	20	17	34	22
	MEAN%	7.0	5.7	15.4	8.1
	S.D.	9.6	6.1	22.5	10.9
Late	MEAN	0.0	0.1	0.1	0.2
	S.D.	0.0	0.4	0.6	0.4
	N	21	22	25	25
	TOTAL	0	2	3	4
	MEAN%	0.0	4.5	2.0	1.5
	S.D.	0.0	21.3	10.0	3.9
Dead Fetuses	TOTAL	0	0	0	0
Postimplantation Loss	MEAN%	7.0	10.3	17.4	9.6
	S.D.	9.6	20.9	23.3	11.4

Table 4 (cont'd)

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RAT (SEGMENT II).
SUMMARY OF CESAREAN SECTION DATA

	DOSE LEVEL	CONTROL	50 mg/Kg	150 mg/Kg	450 mg/Kg
Pregnant at C-section	N'	21	22	25	25
Live Fetuses	MEAN	13.1	11.5	10.3	11.6
	S.D.	4.0	4.3	4.7	4.2
	N	21	22	25	25
	TOTAL	276	253	257	290
	MEAN%	93.0	89.7	82.6	90.4
	S.D.	9.6	20.9	23.3	11.4
Females	MEAN	6.6	5.8	5.2	6.1
	S.D.	2.6	2.5	2.8	2.7
	N	21	21	24	25
	TOTAL	139	121	124	152
	MEAN%	50.6	46.9	44.6	51.8
	S.D.	11.6	18.2	21.5	21.7
Males	MEAN	6.5	6.3	5.5	5.5
	S.D.	2.6	2.3	2.9	2.7
	N	21	21	24	25
	TOTAL	137	132	133	138
	MEAN%	49.4	53.1	55.4	48.2
	S.D.	11.6	18.2	21.5	21.7
Sex Ratio M:F		50:50	52:48	52:48	48:52

Table 4 (cont'd)

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RAT (SEGMENT II).
SUMMARY OF CESAREAN SECTION DATA

DOSE LEVEL		CONTROL	50 mg/Kg	150 mg/Kg	450 mg/Kg
Pregnant at C-section	N'	21	22	25	25
Dams with Viable Fetuses	N	21	21	24	25
Resorptions: Total	MEAN	1.0	0.8	1.5	1.0
	S.D.	1.2	0.8	1.4	1.0
	N	21	21	24	25
	TOTAL	20	17	35	26
	MEAN%	7.0	6.0	14.0	9.6
	S.D.	9.6	6.2	16.0	11.4
Early	MEAN	1.0	0.8	1.3	0.9
	S.D.	1.2	0.8	1.3	0.8
	N	21	21	24	25
	TOTAL	20	17	32	22
	MEAN%	7.0	6.0	11.9	8.1
	S.D.	9.6	6.2	14.3	10.9
Late	MEAN	0.0	0.0	0.1	0.2
	S.D.	0.0	0.0	0.6	0.4
	N	21	21	24	25
	TOTAL	0	0	3	4
	MEAN%	0.0	0.0	2.1	1.5
	S.D.	0.0	0.0	10.2	3.9
Dead Fetuses	TOTAL	0	0	0	0
Postimplantation Loss	MEAN%	7.0	6.0	14.0	9.6
	S.D.	9.6	6.2	16.0	11.4

Means calculated excluding dams with no viable fetuses.

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RAT (SEGMENT II). HF 311518

SUMMARY OF CESAREAN SECTION DATA

	DOSE LEVEL	CONTROL	50 mg/Kg	150 mg/Kg	450 mg/Kg
Pregnant at C-section	N'	21	22	25	25
Dams with Viable Fetuses	N	21	21	24	25
Live Fetuses	MEAN	13.1	12.0	10.7	11.6
	S.D.	4.0	3.5	4.3	4.2
	N	21	21	24	25
	TOTAL	276	253	257	290
	MEAN%	93.0	94.0	86.0	90.4
	S.D.	9.6	6.2	16.0	11.4
Females	MEAN	6.6	5.8	5.2	6.1
	S.D.	2.6	2.5	2.8	2.7
	N	21	21	24	25
	TOTAL	139	121	124	152
	MEAN%	50.6	46.9	44.6	51.8
	S.D.	11.6	18.2	21.5	21.7
Males	MEAN	6.5	6.3	5.5	5.5
	S.D.	2.6	2.3	2.9	2.7
	N	21	21	24	25
	TOTAL	137	132	133	138
	MEAN%	49.4	53.1	55.4	48.2
	S.D.	11.6	18.2	21.5	21.7
Sex Ratio M:F		50:50	52:48	52:48	48:52

Means calculated excluding dams with no viable fetuses.

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RAT (SEGMENT II).
MEAN FETAL NUMERICAL DATA

DOSE LEVEL		CONTROL	50 mg/Kg	150 mg/Kg	450 mg/Kg
PLACENTAL WEIGHT UNITS: grams					
of all Viable Fetuses	MEAN	0.58	0.55	0.63	0.59
	S.D.	0.06	0.05	0.15	0.16
	N	21	21	24	25
Covariate Adjusted	MEAN	0.61	0.55	0.61	0.59
of Male Fetuses	MEAN	0.59	0.56	0.63	0.58
	S.D.	0.06	0.06	0.15	0.15
	N	21	21	24	24
Covariate Adjusted	MEAN	0.61	0.56	0.61	0.58
of Female Fetuses	MEAN	0.57	0.54	0.59	0.56
	S.D.	0.08	0.06	0.09	0.10
	N	21	20	22	23
Covariate Adjusted	MEAN	0.59	0.54	0.58	0.56
FETAL WEIGHTS UNITS: GRAMS					
of all Viable Fetuses	MEAN	4.11	4.02	4.04	4.07
	S.D.	0.24	0.50	0.47	0.29
	N	21	21	24	25
Covariate Adjusted	MEAN	4.08	4.01	4.08	4.08
of Male Fetuses	MEAN	4.21	4.14	4.12	4.26
	S.D.	0.22	0.57	0.50	0.28
	N	21	21	24	24
Covariate Adjusted	MEAN	4.19	4.14	4.14	4.26
of Female Fetuses	MEAN	4.00	3.90	3.94	3.95
	S.D.	0.32	0.45	0.53	0.27
	N	21	20	22	23
Covariate Adjusted	MEAN	3.97	3.90	3.97	3.95

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$; ** = $P \leq 0.01$.

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3. Developmental Toxicity Study of Irbesartan/HCTZ Combination in Rats (Segment II)

Study No: 94017

Performing Laboratory:

Sponsor: Bristol-Myers Squibb
New Brunswick, NJ 08903

Initiation of Treatment: 5/31/94

Quality Assurance: A statement of conformance to GLPs is included.

Test Animals: Crl:CD BR Sprague-Dawley rats (from Charles River in Portage, MI), 25 mated females per group, 12-13 weeks of age, were assigned to each of 5 groups.

Dose Levels

Group Number	Irbesartan (mg/kg/day)	Hydrochlorothiazide (mg/kg/day)
1	0	0
2	50	50
3	150	150
4	150	0
5	0	150

Procedure: Irbesartan (batch no. 3SNP006)and hydrochlorothiazide (HCTZ)(lot 48192) were administered in 1% sodium carboxymethylcellulose suspension as a combination. All rats on test were dosed once daily, by gastric intubation, from gestation day (GD) 6 to GD 15. The dose volumes were 2.5 (low dose combination) or 7.5 ml/kg (all other groups). Dams were observed twice daily for physical signs and mortality; body weight and food consumption measurements were made on GD 0, daily between GD 6 and GD 16, and on GD 20. Gravid uterine weight was obtained at C-section on GD 20. Dams were examined for number of corpora lutea in each ovary, numbers of implantation and resorption sites, live and dead fetal counts, fetal weights and crown-rump measurements; live fetuses were examined for determination of sex and external anomalies. All fetuses were examined for visceral anomalies by a fresh dissection technique. The heads from half of the fetuses in each litter were examined for soft tissue abnormalities by free hand sectioning (Wilson technique); the

remaining half were examined by a mid-coronal slice. All fetuses were examined for skeletal anomalies after clearing with KOH and staining with Alizarin-red S (modification of Dawson method).

Justification of Dosage: These dosages were based on the Segment II study with Irbesartan (study no. 311/518) where "slight, transient reductions in weight gain and food consumption were evident at 50 mg/kg/day, and greater reductions were observed at the two higher doses. (150 and 450 mg/kg/day)". A 1:1 ratio of BMS-186295 and HCTZ was selected "to provide the maximum exposure of the animals to the two drugs when they were administered in combination."

Mortality: One animal receiving the high dose combination died on GD 19 (considered to be compound related).

Drug Associated Findings:

Dams: After the initial 3 days of treatment, a statistically significant decrease in mean body weight (body weight loss) occurred for the high dose combination drug treated group. Throughout the treatment period, dose related and statistically significant decreases in mean body weight and body weight gain, compared to control, were observed in the combination drug treated groups (GD 8 to GD 16). Slight decreases in mean body weight and body weight gain were observed in the group treated with Irbesartan alone ($P < 0.05$ on GD 16). Dose-related decreases in food consumption were observed in the 2 combination drug treated groups, but there was no decrease in food intake for the groups treated with Irbesartan or HCTZ alone.

Fetuses: Mean fetal weight for the high dose combination group was slightly but significantly lower than control for females and for males and females combined, but it is claimed that the high dose mean value matches the mean value for historical controls, based on 108 data sets. It was suggested that the fetal growth retardation was "secondary to the poor condition of the dams".

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TABLE 1
BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS
SUMMARY OF MATERNAL SURVIVAL AND PREGNANCY STATUS

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

DOSE GROUP :	1		2		3		4		5	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
FEMALES ON STUDY	25		25		25		25		25	
FEMALES THAT ABORTED OR DELIVERED	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES THAT DIED	0	0.0	0	0.0	1	4.0	0	0.0	0	0.0
FEMALES THAT ABORTED	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0
FEMALES THAT WERE EUTHANIZED	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES EXAMINED AT SCHEDULED NECROPSY	25	100.0	25	100.0	24	96.0	25	100.0	25	100.0
NONGRAVID	3	12.0	3	12.0	4	16.7	4	16.0	2	8.0
GRAVID	22	88.0	22	88.0	20	83.3	21	84.0	23	92.0
WITH RESORPTIONS ONLY	0	0.0	0	0.0	0	0.0	1	4.8	0	0.0
WITH VIABLE FETUSES	22	100.0	22	100.0	20	100.0	20	95.2	23	100.0
TOTAL FEMALES GRAVID	22	88.0	22	88.0	21	84.0	21	84.0	23	92.0

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG

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TABLE 2 (DAILY EXAMINATIONS)
BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

----- F E M A L E -----

TABLE RANGE:	05-31-94 TO 06-27-94				
GROUP:	1	2	3	4	5
NORMAL					
-NO SIGNIFICANT CLINICAL OBSERVATIONS	452/ 24	400/ 25	448/ 24	409/ 24	466/ 25
DISPOSITION					
-FOUND DEAD	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
-SENT TO LAB FOR SCHEDULED LAPAROHYSTERECTOMY	25/ 25	25/ 25	24/ 24	25/ 25	25/ 25
BODY/INTEGUMENT					
-HAIR LOSS RIGHT FORELIMB	41/ 5	94/ 9	55/ 6	86/ 6	47/ 8
-HAIR LOSS LEFT FORELIMB	28/ 3	75/ 7	55/ 5	80/ 5	39/ 8
-RIGHT HINDLIMB APPEARS SWOLLEN	0/ 0	19/ 1	0/ 0	0/ 0	0/ 0
-HAIR LOSS RIGHT HINDLIMB	0/ 0	0/ 0	0/ 0	26/ 2	2/ 1
-HAIR LOSS LEFT HINDLIMB	13/ 1	0/ 0	0/ 0	26/ 2	0/ 0
-HAIR LOSS VENTRAL ABDOMINAL AREA	8/ 1	0/ 0	8/ 1	29/ 2	0/ 0
-HAIR LOSS RIGHT INGUINAL AREA	0/ 0	0/ 0	0/ 0	29/ 2	0/ 0
-HAIR LOSS LEFT INGUINAL AREA	0/ 0	0/ 0	0/ 0	19/ 3	7/ 1
-HAIR LOSS VENTRAL NECK	9/ 1	0/ 0	0/ 0	4/ 1	0/ 0
-HAIR LOSS VENTRAL THORACIC AREA	8/ 2	0/ 0	0/ 0	26/ 2	0/ 0
-HAIR LOSS LEFT LATERAL ABDOMINAL AREA	0/ 0	9/ 1	0/ 0	0/ 0	0/ 0
-SCABBING RIGHT FORELIMB	0/ 0	17/ 3	0/ 0	0/ 0	4/ 2
-SCABBING LEFT FORELIMB	0/ 0	11/ 3	0/ 0	0/ 0	3/ 1
-HAIR LOSS BASE OF TAIL	3/ 1	0/ 0	0/ 0	3/ 1	0/ 0

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG

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TABLE 2 (DAILY EXAMINATIONS)
BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

----- F E M A L E -----

TABLE RANGE:	05-31-94 TO 06-27-94				
GROUP:	1	2	3	4	5
BODY/INTEGUMENT					
-BLACK STAINING UROGENITAL AND ANOGENITAL AREA	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
-BLACK STAINING OF TAIL	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
-HAIR LOSS RIGHT LATERAL ABDOMINAL AREA	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
EYES/EARS/NOSE					
-DRIED RED MATERIAL AROUND NOSE	3/ 1	4/ 3	3/ 3	1/ 1	0/ 0
EXCRETA					
-SOFT STOOL	1/ 1	0/ 0	0/ 0	3/ 1	0/ 0

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG

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TABLE 3
BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS
MEAN BODY WEIGHTS (GRAMS) DURING GESTATION

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

	GROUP :	1	2	3	4	5
DAY 0	MEAN	265.	263.	267.	263.	266.
	S.D./N	19.4/22	14.0/22	15.7/21	14.6/21	10.4/23
DAY 6	MEAN	309.	301.	306.	303.	308.
	S.D./N	20.5/22	18.0/22	18.5/21	17.2/21	13.8/23
DAY 7	MEAN	310.	297.	298.	304.	300.
	S.D./N	19.4/22	15.2/22	17.0/21	17.0/21	13.7/23
DAY 8	MEAN	314.	298.*	297.**	305.	303.
	S.D./N	20.2/22	15.8/22	16.7/21	17.1/21	14.5/23
DAY 9	MEAN	320.	302.**	299.**	310.	310.
	S.D./N	21.4/22	17.3/22	16.5/21	16.0/21	15.7/23
DAY 10	MEAN	327.	306.**	299.**	313.	319.
	S.D./N	22.2/22	17.4/22	19.5/21	16.2/21	16.2/23
DAY 11	MEAN	334.	313.**	301.**	320.	327.
	S.D./N	22.4/22	19.1/22	17.6/21	16.9/21	18.2/23
DAY 12	MEAN	337.	317.**	302.**	326.	331.
	S.D./N	21.6/22	20.1/22	16.8/21	18.6/21	19.1/23
DAY 13	MEAN	345.	321.**	306.**	331.	338.
	S.D./N	23.0/22	18.3/22	19.8/21	20.8/21	19.9/23
DAY 14	MEAN	353.	331.**	313.**	340.	347.
	S.D./N	24.6/22	21.1/22	23.5/21	21.0/21	19.1/23

1- 0:0 MG/KG 2- 50:150 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

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TABLE 3
BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS
MEAN BODY WEIGHTS (GRAMS) DURING GESTATION

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

	GROUP :	1	2	3	4	5
DAY 15	MEAN	361.	337.**	318.**	344.	357.
	S.D./N	24.6/22	21.1/22	25.8/21	23.8/21	20.0/23
DAY 16	MEAN	374.	348.**	326.**	355.*	369.
	S.D./N	25.7/22	21.5/22	26.2/21	26.9/21	18.4/23
DAY 20	MEAN	439.	433.	415.*	432.	441.
	S.D./N	30.2/22	23.3/22	22.2/20	31.7/21	27.7/23

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1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

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TABLE 4

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS
MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

GROUP :	1	2	3	4	5
DAY 0- 6 MEAN	44.	38.	39.	40.	41.
S.D./N	7.6/22	8.6/22	9.4/21	9.0/21	7.9/23
DAY 6- 7 MEAN	1.	-4.*	-8.**	1.	-7.**
S.D./N	4.7/22	7.3/22	6.8/21	4.8/21	6.1/23
DAY 7- 8 MEAN	4.	2.	-1.**	2.	2.
S.D./N	3.7/22	5.4/22	5.0/21	4.0/21	6.1/23
DAY 8- 9 MEAN	6.	3.	2.*	4.	8.
S.D./N	5.1/22	5.8/22	5.3/21	6.5/21	5.0/23
DAY 9- 10 MEAN	7.	4.	1.**	3.	9.
S.D./N	5.1/22	7.3/22	5.9/21	6.0/21	4.7/23
DAY 10- 11 MEAN	7.	7.	1.**	7.	8.
S.D./N	3.9/22	6.5/22	6.1/21	3.7/21	4.4/23
DAY 11- 12 MEAN	3.	4.	2.	6.	3.
S.D./N	4.1/22	6.7/22	5.9/21	6.6/21	4.7/23
DAY 12- 13 MEAN	8.	5.	4.	5.	7.
S.D./N	4.3/22	5.9/22	6.8/21	7.9/21	5.3/23
DAY 13- 14 MEAN	8.	10.	7.	8.	10.
S.D./N	5.8/22	6.8/22	7.5/21	5.1/21	4.7/23
DAY 14- 15 MEAN	8.	6.	5.	4.	9.
S.D./N	4.8/22	5.6/22	6.1/21	4.5/21	4.2/23

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

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TABLE 4
BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS
MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

GROUP :	1	2	3	4	5
DAY 15- 16 MEAN	13.	11.	8.	11.	13.
S.D./N	5.2/22	5.3/22	7.2/21	5.2/21	7.5/23
DAY 16- 20 MEAN	65.	85.**	86.**	76.*	72.
S.D./N	10.8/22	13.3/22	12.6/20	10.5/21	16.6/23
DAY 6- 9 MEAN	12.	1.**	-7.**	7.	3.**
S.D./N	5.9/22	8.8/22	8.7/21	6.7/21	9.5/23
DAY 9- 12 MEAN	16.	15.	4.**	16.	20.
S.D./N	4.9/22	13.5/22	8.1/21	10.0/21	8.0/23
DAY 12- 16 MEAN	37.	32.	23.**	29.	39.
S.D./N	7.8/22	8.9/22	17.4/21	12.6/21	7.3/23
DAY 6- 16 MEAN	65.	47.**	20.**	52.	62.
S.D./N	10.1/22	16.4/22	26.6/21	21.1/21	12.8/23
DAY 0- 20 MEAN	174.	170.	148.**	168.	175.
S.D./N	19.9/22	16.4/22	16.2/20	28.5/21	22.8/23

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

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TABLE 5

BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

MEAN GRAVID UTERINE WEIGHTS AND NET BODY WEIGHT CHANGES (GRAMS)

	GROUP:	1	2	3	4	5
INITIAL BODY WT.	MEAN	265.	263.	267.	263.	266.
	S.D.	19.4	14.0	16.1	14.6	10.4
	N	22	22	20	21	23
TERMINAL BODY WT.	MEAN	439.	433.	415.*	432.	441.
	S.D.	30.2	23.3	22.2	31.7	27.7
	N	22	22	20	21	23
GRAVID UTERINE WT.	MEAN	85.1	95.5	82.3	87.3	88.3
	S.D.	19.85	12.49	13.21	22.77	10.89
	N	22	22	20	21	23
NET BODY WT.	MEAN	353.9	337.6*	332.8**	344.2	353.0
	S.D.	22.27	14.21	18.44	19.86	23.57
	N	22	22	20	21	23
NET BODY WT. CHANGE	MEAN	89.3	74.9**	65.7**	81.2	86.7
	S.D.	10.46	12.32	13.83	17.88	19.18
	N	22	22	20	21	23

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST

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TABLE 6

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS
MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

GROUP :	1	2	3	4	5
DAY 0- 6 MEAN	25.	25.	25.	24.	25.
S.D./N	2.3/22	2.1/22	2.9/21	2.2/20	1.5/23
DAY 6- 7 MEAN	26.	21.**	19.**	24.	22.**
S.D./N	2.7/22	3.3/22	3.8/21	2.0/21	3.1/23
DAY 7- 8 MEAN	26.	22.**	21.**	23.	24.
S.D./N	3.6/22	3.9/22	2.5/21	3.0/21	4.6/23
DAY 8- 9 MEAN	27.	25.	21.**	25.	26.
S.D./N	3.6/22	3.8/22	4.6/21	4.2/21	3.6/23
DAY 9- 10 MEAN	26.	24.	20.**	26.	28.
S.D./N	2.5/22	5.2/22	6.9/21	3.2/21	4.1/23
DAY 10- 11 MEAN	27.	26.	20.**	25.	29.
S.D./N	3.0/22	6.4/22	5.3/21	4.3/21	3.8/23
DAY 11- 12 MEAN	26.	25.	20.**	27.	27.
S.D./N	3.1/22	6.2/22	5.5/21	4.7/21	5.0/23
DAY 12- 13 MEAN	29.	26.	22.**	27.	29.
S.D./N	2.7/22	6.7/22	6.9/21	5.5/21	4.9/23
DAY 13- 14 MEAN	28.	29.	23.*	28.	29.
S.D./N	3.6/22	6.3/22	8.2/21	5.1/21	3.6/23
DAY 14- 15 MEAN	28.	26.	21.**	25.	29.
S.D./N	3.0/22	4.9/22	8.3/21	5.0/21	3.7/23

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

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TABLE 6

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS
MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

GROUP :		1	2	3	4	5
DAY 15- 16	MEAN	31.	28.	24.**	29.	31.
	S.D./N	3.0/22	5.0/22	8.1/21	5.4/21	3.5/23
DAY 16- 20	MEAN	31.	31.	33.	32.	32.
	S.D./N	1.9/22	2.6/22	2.6/20	3.0/21	4.5/23
DAY 6- 9	MEAN	26.	23.**	20.**	24.*	24.*
	S.D./N	2.9/22	2.7/22	2.9/21	2.3/21	3.2/23
DAY 9- 12	MEAN	27.	25.	20.**	26.	28.
	S.D./N	2.3/22	4.9/22	4.8/21	3.0/21	4.0/23
DAY 12- 16	MEAN	29.	27.	23.**	27.	30.
	S.D./N	2.3/22	4.3/22	6.6/21	4.4/21	3.1/23
DAY 6- 16	MEAN	28.	25.	21.**	26.	27.
	S.D./N	2.2/22	3.4/22	4.6/21	3.0/21	3.2/23
DAY 0- 20	MEAN	27.	26.	25.**	27.	28.
	S.D./N	1.9/22	1.8/22	2.7/20	2.4/21	2.2/23

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

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TABLE 7

BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS

SUMMARY OF MEAN FETAL DATA AT THE SCHEDULED NECROPSY

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

GROUP	SEX M	SEX F	VIABLE FETUSES	DEAD FETUSES	RESORPTIONS EARLY	RESORPTIONS LATE	POST IMPLANTATION LOSS	IMPLANTATION SITES	CORPORA LUTEA	PRE IMPLANTATION LOSS	FETAL WEIGHTS IN GRAMS	NO. OF GRAVID FEMALES
1 TOTAL	167	165	332	0	24	1	25	357	386	29	NA	22
MEAN	7.6	7.5	15.1	0.0	1.1	0.0	1.1	16.2	17.5	1.3	3.7	
S.D.	2.82	2.43	3.65	0.00	1.95	0.21	1.93	2.98	2.82	1.21	0.23	
2 TOTAL	176	204	380	0	18	0	18	398	432	34	NA	22
MEAN	8.0	9.3	17.3	0.0	0.8	0.0	0.8	18.1	19.6	1.5	3.6	
S.D.	2.27	3.03	2.31	0.00	0.80	0.00	0.80	2.37	2.80	1.79	0.20	
3 TOTAL	150	157	307	0	26	0	26	333	404	71	NA	20
MEAN	7.5	7.9	15.4	0.0	1.3	0.0	1.3	16.7	20.2*	3.5	3.5*	
S.D.	2.54	1.79	2.70	0.00	0.98	0.00	0.98	2.25	3.33	3.85	0.26	
4 TOTAL	172	154	326	0	22	0	22	348	368	20	NA	21
MEAN	8.2	7.3	15.5	0.0	1.0	0.0	1.0	16.6	17.5	1.0	3.7	
S.D.	3.30	3.54	4.18	0.00	1.24	0.00	1.24	3.87	3.30	0.97	0.34	
5 TOTAL	152	198	350	0	21	9	30	380	434	54	NA	23
MEAN	6.6	8.6	15.2	0.0	0.9	0.4	1.3	16.5	18.9	2.3	3.7	
S.D.	1.75	2.27	2.21	0.00	0.90	1.67	1.74	2.13	2.88	2.77	0.32	

* = SIGNIFICANTLY DIFFERENT FROM CONTROL AT 0.05 LEVEL
NA = NOT APPLICABLE

MEAN NUMBER OF VIABLE FETUSES COMPARED USING DUNNETT'S TEST;
TOTAL NUMBER OF DEAD FETUSES COMPARED USING MANN-WHITNEY TEST;
TOTAL NUMBER OF EARLY RESORPTIONS COMPARED USING MANN-WHITNEY TEST;
TOTAL NUMBER OF LATE RESORPTIONS COMPARED USING MANN-WHITNEY TEST;
SEX RATIO COMPARED USING CHI SQUARE TEST
TOTAL POST IMPLANTATION LOSS COMPARED USING MANN-WHITNEY TEST
MEAN NUMBER OF IMPLANTATION SITES COMPARED USING DUNNETT'S TEST
MEAN NUMBER OF CORPORA LUTEA COMPARED USING DUNNETT'S TEST
FETAL WEIGHTS COMPARED USING DUNNETT'S TEST

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG

TABLE 8

BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

GROUP NUMBER:	1	2	3	4	5
CORPORA LUTEA					
MEAN	17.5	19.6	20.2*	17.5	18.9
S.D.	2.82	2.80	3.33	3.30	2.88
N	22	22	20	21	23
IMPLANTATION SITES					
MEAN	16.2	18.1	16.7	16.6	16.5
S.D.	2.98	2.37	2.25	3.87	2.13
N	22	22	20	21	23
VIABLE FETUSES (%)					
MEAN	92.7	95.5	91.8	89.7	92.5
S.D.	14.58	4.33	6.43	21.78	9.72
N	22	22	20	21	23
DEAD FETUSES (%)					
MEAN	0.0	0.0	0.0	0.0	0.0
S.D.	0.00	0.00	0.00	0.00	0.00
N	22	22	20	21	23
EARLY RESORPTIONS (%)					
MEAN	7.0	4.5	8.2	10.3	5.4
S.D.	14.67	4.33	6.43	21.78	5.15
N	22	22	20	21	23
LATE RESORPTIONS (%)					
MEAN	0.3	0.0	0.0	0.0	2.2
S.D.	1.43	0.00	0.00	0.00	9.28
N	22	22	20	21	23

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG

PROPORTIONAL (%) DATA COMPARED USING THE KRUSKAL-WALLIS TEST
CORPORA LUTEA AND IMPLANTATION SITES COMPARED USING DUNNETT'S TEST
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP AT THE 0.05 LEVEL

TABLE 8

BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS

SPONSOR:BRISTOL-MYERS SQUIBB SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

SPONSOR NO.:94017

GROUP NUMBER:	1	2	3	4	5
TOTAL RESORPTIONS (%)					
MEAN	7.3	4.5	8.2	10.3	7.5
S.D.	14.58	4.33	6.43	21.78	9.72
N	22	22	20	21	23
PRE-IMPLANTATION LOSS (%)					
MEAN	7.8	7.4	15.8	7.4	11.3
S.D.	7.43	8.08	15.96	14.05	12.18
N	22	22	20	21	23
POST-IMPLANTATION LOSS (%)					
MEAN	7.3	4.5	8.2	10.3	7.5
S.D.	14.58	4.33	6.43	21.78	9.72
N	22	22	20	21	23
MALES (%)					
MEAN	50.2	46.9	48.0	53.4	43.7
S.D.	12.54	14.19	11.06	17.70	10.68
N	22	22	20	20	23
FEMALES (%)					
MEAN	49.8	53.2	52.0	46.7	56.3
S.D.	12.55	14.19	11.06	17.70	10.67
N	22	22	20	20	23
MALE FETAL WEIGHTS (g)					
MEAN	3.8	3.7	3.6	3.8	3.8
S.D.	0.32	0.21	0.30	0.34	0.37
N	22	22	20	20	23

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG

PROPORTIONAL (%) DATA COMPARED USING THE KRUSKAL-WALLIS TEST
FETAL WEIGHTS COMPARED USING DUNNETT'S TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP

TABLE 8

BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

GROUP NUMBER:	1	2	3	4	5
FEMALE FETAL WEIGHTS (g)					
MEAN	3.6	3.5	3.4*	3.6	3.6
S.D.	0.20	0.17	0.26	0.32	0.27
N	22	22	20	20	23
COMBINED FETAL WEIGHTS (g)					
MEAN	3.7	3.6	3.5*	3.7	3.7
S.D.	0.23	0.20	0.26	0.34	0.32
N	22	22	20	20	23

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG

FETAL WEIGHTS COMPARED USING DUNNETT'S TEST

* = SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP AT THE 0.05 LEVEL

TABLE 9

BMS-186295/NCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS

NUMBER OF FETUSES AND LITTERS WITH MALFORMATIONS - SUMMARY

SPONSOR:BRISTOL-MYERS SQUIBB

SPONSOR NO.:94017

DAY 20

DOSE GROUP:	FETUSES 1	2	3	4	5	LITTERS 1	2	3	4	5
NUMBER EXAMINED EXTERNALLY	332	380	307	326	350	22	22	20	20	23
SHORT TAIL	1	0	0	0	0	1	0	0	0	0
MICROPHTHALMIA AND/OR ANOPHTHALMIA	1	0	1	0	0	1	0	1	0	0
MANDIBULAR MICROGNATHIA	1	0	0	0	0	1	0	0	0	0
OMPHALOCELE	0	0	1	0	0	0	0	1	0	0
EXOPHTHALMIA	0	0	1	0	0	0	0	1	0	0
MANDIBULAR AGNATHIA	0	0	1	0	0	0	0	1	0	0
MICROGNATHIA (MAXILLAE)	0	0	1	0	0	0	0	1	0	0
CLEFT PALATE	1	0	1	0	0	1	0	1	0	0
MICROSTOMIA	0	0	1	0	0	0	0	1	0	0
ADACTYLY	1	0	0	0	0	1	0	0	0	0
BRACHYDACTYLY	1	0	0	0	0	1	0	0	0	0
FETAL ANASARCA	1	0	0	0	0	1	0	0	0	0
AGLOSSIA	0	0	1	0	0	0	0	1	0	0
ABLEPHARIA	0	0	1	0	0	0	0	1	0	0
VERTEBRAL AGENESIS	1	0	0	0	0	1	0	0	0	0
NUMBER EXAMINED VISCERALLY	332	380	307	326	350	22	22	20	20	23
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0	0	0
NUMBER EXAMINED SKELETALLY	332	380	307	326	350	22	22	20	20	23
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY	1	0	1	0	1	1	0	1	0	1
BENT LIMB BONE(S)	1	0	0	0	0	1	0	0	0	0
TOTAL NUMBER WITH MALFORMATIONS										
EXTERNAL :	1	0	1	0	0	1	0	1	0	0
SOFT TISSUE:	0	0	0	0	0	0	0	0	0	0
SKELETAL :	1	0	1	0	1	1	0	1	0	1
COMBINED :	1	0	1	0	1	1	0	1	0	1

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG

NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING FISHER'S EXACT TEST

TABLE 10
(Sponsor's TABLE 12)

SPONSOR:BRISTOL-MYERS SQUIBB
SPONSOR NO.:94017

BMS-186295/HCTZ: SEGMENT II ORAL TERATOLOGY STUDY IN RATS
NUMBER OF FETUSES AND LITTERS WITH VARIATIONS - SUMMARY

DAY 20

DOSE GROUP:	FETUSES 1	2	3	4	5	LITTERS 1	2	3	4	5
NUMBER EXAMINED EXTERNALLY	332	380	307	326	350	22	22	20	20	23
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0	0	0
NUMBER EXAMINED VISCERALLY	332	380	307	326	350	22	22	20	20	23
MAJOR BLOOD VESSEL VARIATION	1	0	0	0	0	1	0	0	0	0
RENAL PAPILLA(E) NOT DEVELOPED AND/OR DISTENDED URETER(S)	0	0	2	0	0	0	0	1	0	0
HEMORRHAGIC RING AROUND THE IRIS	0	0	1	0	0	0	0	1	0	0
NUMBER EXAMINED SKELETALLY	332	380	307	326	350	22	22	20	20	23
14TH RUDIMENTARY RIB(S)	27	41	11	30	3	14	14	6*	5*	3*
CERVICAL CENTRUM #1 OSSIFIED	52	89	81	92	64	18	16	17	17	18
STERNEBRA(E) #5 AND/OR #6 UNOSSIFIED	20	28	51	34	37	7	10	9	10	10
STERNEBRA(E) #1,#2,#3 AND/OR #4 UNOSSIFIED	1	2	0	2	4	1	2	0	2	4
7TH CERVICAL RIB(S)	2	5	3	2	2	2	4	3	2	2
REDUCED OSSIFICATION OF THE 13TH RIB(S)	2	7	1	2	4	2	4	1	1	3
27 PRESACRAL VERTEBRAE	0	1	0	0	0	0	1	0	0	0
BENT RIB(S)	1	1	5	6	0	1	1	4	5	0
HYOID UNOSSIFIED	7	1	0	2	4	4	1	0	2	3
REDUCED OSSIFICATION OF THE RIB(S)	0	1	0	0	0	0	1	0	0	0
14TH FULL RIB(S)	0	2	0	0	0	0	2	0	0	0
REDUCED OSSIFICATION OF THE VERTEBRAL ARCHES	0	1	1	0	0	0	1	1	0	0
STERNEBRA(E) MALALIGNED(SLIGHT OR MODERATE)	0	0	0	1	1	0	0	0	1	1
PUBIS UNOSSIFIED	1	0	1	0	0	1	0	1	0	0
ENTIRE STERNUM UNOSSIFIED	1	0	1	0	0	1	0	1	0	0
REDUCED OSSIFICATION OF THE SKULL	0	0	1	0	0	0	0	1	0	0

1- 0:0 MG/KG 2- 50:50 MG/KG 3- 150:150 MG/KG 4- 150:0 MG/KG 5- 0:150 MG/KG

* = SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

4. Developmental Toxicity Study of Irbesartan in Rabbits (Segment II)

Study No: 311/519 (TER226)

Performing Laboratory:

Sponsor: Sanofi Recherche
Montpellier Cedex, France

Initiation of Treatment: 10/11/92

Quality Assurance: A statement of conformance to GLPs is included.

Test Animals: New Zealand white rabbits (from a supplier in France), 18 females per group, were 16-18 weeks old and weighed 3.15-3.89 kg when mated.

Procedure: SR 47436 (batch 92.02) in 10% aqueous gum Arabic solution, was administered once daily by oral gavage at doses of 0, 3, 10 and 30 mg/kg, from GD 6 to GD 18. The dose volume was 5 ml/kg for each group. Mated females were observed each day for mortality and physical condition; body weight and food consumption were measured GDs 0, 6, 9, 13, 19, 24 and 29. C-sections were performed on GD 29 for a corpora lutea count, evaluation of the uterus (dead and live fetal counts, resorptions), determination of fetal and placental weights and determination of sex. All live and dead fetuses were examined for external anomalies; live fetuses were examined for visceral anomalies by a dissection technique, but the heads from half the fetuses were removed, fixed in Harrison's fluid and serially sectioned. All fetuses were cleared with KOH and stained with alizarin red for skeletal evaluation of anomalies and variations.

Justification of Dosage: An oral range-finding study was performed with 6 pregnant rabbits/group (same strain and same supplier) that received oral doses of 0, 50, 150 and 450 mg/kg/day. All 6 does/group that received doses of 150 and 450 mg/kg and 2 in the 50 mg/kg/day group were found dead or were sacrificed in moribund state before scheduled necropsy; an additional doe at 50 mg/kg/day aborted completely by GD 26 Therefore, a top dose of 30 mg/kg/day was chosen for the definitive study.

Compound Related Effects

Does:

Mortality and Clinical Signs: At 30 mg/kg/day, 3 does died between GD 17 and GD 22 (a 4th one died on GD 6 due to an

intubation error); two others were sacrificed in moribund condition on GD 23 and GD 24, and an additional 3 aborted on GDs 19, 22 and 28 (including 1 that was subsequently found dead on GD 22). Only the 2 moribund animals that were killed on GD 23 and GD 24 had clinical signs; thin, "subdued behavior" and slow breathing in one of them, red/black vaginal discharge in the other. No clinical signs were noted for the 3 high dose does that aborted. There were no other deaths or moribund sacrifices in this study. One female at 3 mg/kg/day had a dark red vaginal discharge during the last 6 days before C-section, and had no viable fetuses at C-section.

Other compound related effects: At high dose, there was a decrease in body weight and body weight gain compared to control (weight loss between GDs 9 and 19), but an apparent rebound in body weight vs control by GD 29, after discontinuation of treatment. At mid dose, there was a lower than control body weight gain from GD 9 to GD 13 ($P< 0.01$), but a greater than control body weight gain at low and mid doses from GD 13 to GD 19 ($P< 0.01$ for both groups). Between days 9 and 19 of treatment, there was a lower than control food intake at the high dose, which was statistically significant only from GD 9 to GD 13. A decrease in food intake was also observed at the mid dose between GD 9 and GD 13 ($P< 0.01$).

Fetuses: At the high dose, an increased incidence of early resorptions and a decreased number of live female fetuses were evident. Neither of these effects reached statistical significance, but cannot be ignored because the number of surviving dams with viable fetuses was low and standard deviations were high.

One of the nine high dose treated does with surviving litters had seven fetuses, all of which had vertebral malformations; five with acaudia (lack of a tail), which in this species may be considered a vertebral malformation. All of the vertebral (and soft tissue) malformations found at this dose were confined to the litter of this doe. The investigators claim there was no compound related effect on malformations, but with the low number of surviving fetuses and litters, it does not seem possible to rule out such a possibility at high dose.

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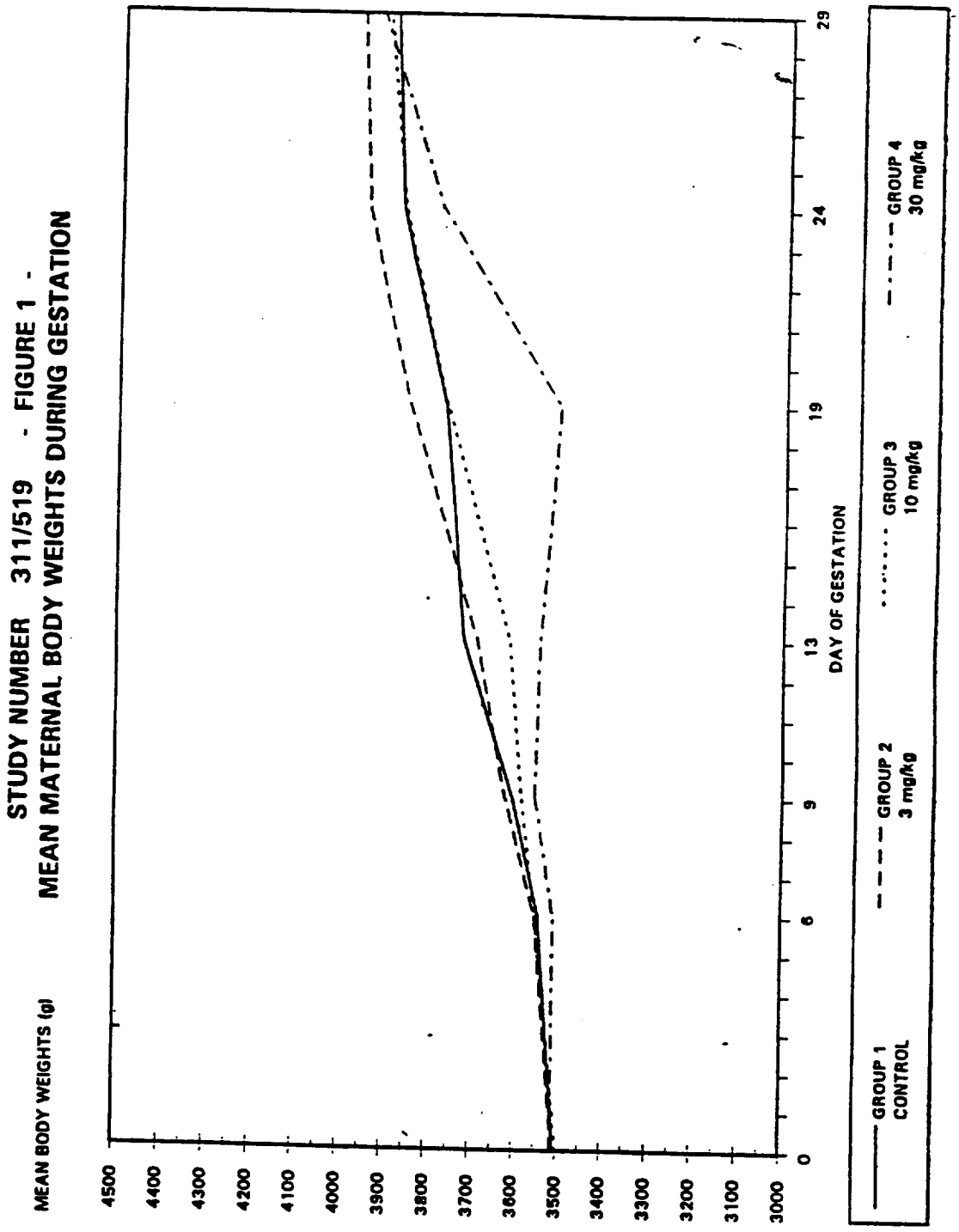
STUDY NUMBER 311/519 - FIGURE 1 -
MEAN MATERNAL BODY WEIGHTS DURING GESTATION
MEAN BODY WEIGHTS (g)
4500
4400
4300
4200
4100
4000
3900
3800
3700
3600
3500
3400
3300
3200
3100
3000
0
6
9
13
19
24
29
DAY OF GESTATION
GROUP 1
CONTROL
GROUP 2
3 mg/kg
GROUP 3
10 mg/kg
GROUP 4
30 mg/kg

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RABBIT (SEGMENT II). MF 311519

MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- grams

	DOSE LEVEL	CONTROL	3 mg/Kg	10 mg/Kg	30 mg/Kg
DAY 0	MEAN	3504.3	3507.5	3497.6	3511.3
	S.D.	186.2	220.2	212.9	218.8
	N	14	16	17	16
DAY 6	MEAN	3544.7	3553.2	3552.9	3509.8
	S.D.	192.8	168.3	218.4	220.8
	N	14	16	17	16
DAY 9	MEAN	3607.4	3624.2	3586.1	3555.6
	S.D.	192.8	182.3	213.6	212.6
	N	14	16	17	16
DAY 13	MEAN	3718.9	3688.8	3615.9	3545.5
	S.D.	186.5	182.6	217.8	253.8
	N	14	16	17	16
DAY 19	MEAN	3766.6	3848.1	3764.0	3505.5
	S.D.	195.5	188.6	194.1	394.5
	N	14	16	17	15
DAY 24	MEAN	3869.1	3945.9	3864.9	3779.3
	S.D.	217.7	227.9	199.3	274.8
	N	14	16	17	11
DAY 29	MEAN	3888.1	3963.8	3905.8	3919.9
	S.D.	231.9	221.3	205.8	185.7
	N	14	16	17	9

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.
Means calculated excluding dams with no viable embryos/fetuses or with no pups delivered.

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Table 1

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RABBIT (SEGMENT II). HF 311519

MEAN MATERNAL BODY WEIGHT CHANGES DURING GESTATION -- grams

	DOSE LEVEL	CONTROL	3 mg/Kg	10 mg/Kg	30 mg/Kg
DAYS 0 TO 6	MEAN	40.43	45.69	55.29	-1.44
	S.D.	97.94	93.43	92.05	130.59
	N	14	16	17	16
DAYS 6 TO 9	MEAN	62.64	71.00	33.12	45.81
	S.D.	43.13	42.66	47.43	66.38
	N	14	16	17	16
DAYS 9 TO 13	MEAN	111.57	64.56	29.82**	-10.13**
	S.D.	42.25	60.57	53.14	95.53
	N	14	16	17	16
DAYS 13 TO 19	MEAN	47.64	159.31**	148.12**	-27.27
	S.D.	71.72	69.42	91.18	234.69
	N	14	16	17	15
DAYS 6 TO 19	MEAN	221.86	294.88	211.06	22.40
	S.D.	104.47	97.93	111.34	338.99
	N	14	16	17	15
DAYS 19 TO 24	MEAN	102.57	97.81	100.94	77.82
	S.D.	65.95	86.89	50.65	156.12
	N	14	16	17	11
DAYS 24 TO 29	MEAN	19.00	17.88	40.82	44.78
	S.D.	57.83	75.81	69.57	82.54
	N	14	16	17	9

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.
Means calculated excluding dams with no viable embryos/fetuses or with no pups delivered.

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RABBIT (SEGMENT II). MF 311519

MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- SUMMARY

DOSE LEVEL		CONTROL	3 mg/Kg	10 mg/Kg	30 mg/Kg
MATERNAL FOOD CONSUMPTION -- grams/ANIMAL/DAY					
DAYS 0 TO 6	MEAN	134.5	145.4	138.8	129.0
	S.D.	29.6	21.8	18.3	38.1
	N	14	16	17	16
	SPILLED	0	0	0	0
DAYS 6 TO 9	MEAN	167.4	174.5	159.2	162.0
	S.D.	31.5	12.4	21.5	26.7
	N	14	16	17	16
	SPILLED	0	0	0	0
DAYS 9 TO 13	MEAN	173.9	163.0	142.2**	135.5*
	S.D.	20.6	25.2	33.2	51.3
	N	14	16	17	16
	SPILLED	0	0	0	0
DAYS 13 TO 19	MEAN	126.7	142.8	122.4	86.3
	S.D.	39.9	46.7	49.4	67.1
	N	14	16	17	15
	SPILLED	0	0	0	0
DAYS 6 TO 19	MEAN	150.6	156.3	137.0	120.4
	S.D.	28.2	29.9	31.3	48.4
	N	14	16	17	15
	SPILLED	0	0	0	0
DAYS 19 TO 24	MEAN	121.4	150.6	140.0	137.0
	S.D.	36.4	32.7	32.4	71.9
	N	14	16	17	11
	SPILLED	0	0	0	0
DAYS 24 TO 29	MEAN	95.5	107.9	101.6	108.0
	S.D.	19.3	31.4	26.2	30.8
	N	14	16	17	9
	SPILLED	0	0	0	0

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.
Means calculated excluding dams with no viable embryos/fetuses or with no pups delivered.

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RABBIT (SEGMENT II).
SUMMARY OF CESAREAN SECTION DATA

DOSE LEVEL		CONTROL	3 mg/Kg	10 mg/Kg	30 mg/Kg
Females Mated	N	18	18	18	18
Pregnant	N	14	18	17	16
	%	78	100	94	89
Aborted	N	0	0	0	2 [a]
	%	0.0	0.0	0.0	11
Died	N	0	0	0	5 [b]
	%	0.0	0.0	0.0	28
Delivered Early	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Pregnant at C-section	N	14	18	17	9
Dams with Viable Fetuses	N	14	16	17	9
	%	100	89	100	100
Dams with no Viable Fetuses	N	0	2	0	0
	%	0.0	11	0.0	0.0
Corpora Lutea	MEAN	12.5	12.2	12.3	12.6
	S.D.	3.4	3.3	3.9	3.0
	N	14	18	17	9
	TOTAL	175	219	209	113
Implantation Sites	MEAN	11.6	10.9	10.9	10.9
	S.D.	3.5	3.1	3.5	3.6
	N	14	18	17	9
	TOTAL	162	197	186	98
Preimplantation Loss	MEAN%	8.0	8.9	10.8	16.7
	S.D.	6.2	14.4	12.8	11.4

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$; ** = $P \leq 0.01$.

a excluding a 3rd female aborted which died

b excluding one dead female which was not pregnant

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RABBIT (SEGMENT II).
SUMMARY OF CESAREAN SECTION DATA

	DOSE LEVEL	CONTROL	3 mg/Kg	10 mg/Kg	30 mg/Kg
Pregnant at C-section	N	14	18	17	9
Resorptions: Total	MEAN	0.6	1.5	0.9	1.7
	S.D.	0.7	2.9	1.1	2.1
	N	14	18	17	9
	TOTAL	9	27	15	15
	MEAN%	5.2	16.2	6.9	13.2
	S.D.	6.1	31.1	8.3	16.8
Early	MEAN	0.4	0.5	0.3	1.1
	S.D.	0.6	1.0	0.6	1.5
	N	14	18	17	9
	TOTAL	5	9	5	10
	MEAN%	3.3	8.2	2.5	9.8
	S.D.	6.0	23.3	4.8	15.4
Late	MEAN	0.3	1.0	0.6	0.6
	S.D.	0.6	2.8	0.9	1.3
	N	14	18	17	9
	TOTAL	4	18	10	5
	MEAN%	2.8	8.0	4.4	3.3
	S.D.	4.8	23.5	6.6	7.5
Dead Fetuses	TOTAL	1	0	0	0
Postimplantation Loss	MEAN%	6.3	16.2	6.9	13.2
	S.D.	6.4	31.1	8.3	16.8

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.

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Table 4 (cont'd)

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RABBIT (SEGMENT II).
SUMMARY OF CESAREAN SECTION DATA

	DOSE LEVEL	CONTROL	3 mg/Kg	10 mg/Kg	30 mg/Kg
Pregnant at C-section	N	14	18	17	9
Live Fetuses	MEAN	10.9	9.4	10.1	9.2
	S.D.	3.3	4.1	2.9	2.6
	N	14	18	17	9
	TOTAL	152	170	171	83
	MEAN%	93.7	83.8	93.1	86.8
	S.D.	6.4	31.1	8.3	16.8
Females	MEAN	5.4	5.6	5.1	4.2
	S.D.	2.4	2.8	1.9	2.8
	N	14	16	17	9
	TOTAL	76	89	86	38
	MEAN%	49.1	51.9	51.0	42.9
	S.D.	14.2	18.5	13.6	20.8
Males	MEAN	5.4	5.1	5.0	5.0
	S.D.	2.1	2.2	2.0	1.9
	N	14	16	17	9
	TOTAL	76	81	85	45
	MEAN%	50.9	48.1	49.0	57.1
	S.D.	14.2	18.5	13.6	20.8
Sex Ratio M:F		50:50	48:52	50:50	54:46

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.

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Table 4 (cont'd)

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RABBIT (SEGMENT II).
SUMMARY OF CESAREAN SECTION DATA

DOSE LEVEL		CONTROL	3 mg/Kg	10 mg/Kg	30 mg/Kg
Pregnant at C-section	N	14	18	17	9
Dams with Viable Fetuses	N	14	16	17	9
Resorptions: Total	MEAN	0.6	0.7	0.9	1.7
	S.D.	0.7	0.9	1.1	2.1
	N	14	16	17	9
	TOTAL	9	11	15	15
	MEAN%	5.2	5.7	6.9	13.2
	S.D.	6.1	6.5	8.3	16.8
Early	MEAN	0.4	0.3	0.3	1.1
	S.D.	0.6	0.5	0.6	1.5
	N	14	16	17	9
	TOTAL	5	5	5	10
	MEAN%	3.3	1.8	2.5	9.8
	S.D.	6.0	4.7	4.8	15.4
Late	MEAN	0.3	0.4	0.6	0.6
	S.D.	0.6	0.8	0.9	1.3
	N	14	16	17	9
	TOTAL	4	6	10	5
	MEAN%	2.0	2.7	4.4	3.3
	S.D.	4.0	5.2	6.6	7.5
Dead Fetuses	TOTAL	1	0	0	0
Postimplantation Loss	MEAN%	6.3	5.7	6.9	13.2
	S.D.	6.4	6.5	8.3	16.8

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.
%Dams calculated excluding dams with no viable fetuses.

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ON ORIGINAL

SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RABBIT (SEGMENT II).
SUMMARY OF CESAREAN SECTION DATA

	DOSE LEVEL	CONTROL	3 mg/Kg	10 mg/Kg	30 mg/Kg
Pregnant at C-section	N	14	18	17	9
Dams with Viable Fetuses	N	14	16	17	9
Live Fetuses	MEAN	10.9	10.6	10.1	9.2
	S.D.	3.3	2.4	2.9	2.6
	N	14	16	17	9
	TOTAL	152	170	171	83
	MEAN%	91.7	94.3	93.1	86.8
	S.D.	6.4	6.5	8.3	16.8
Females	MEAN	5.4	5.6	5.1	4.2
	S.D.	2.4	2.8	1.9	2.8
	N	14	16	17	9
	TOTAL	76	89	86	38
	MEAN%	49.1	51.9	51.0	42.9
	S.D.	14.2	18.5	13.6	20.8
Males	MEAN	5.4	5.1	5.0	5.0
	S.D.	2.1	2.2	2.6	1.9
	N	14	16	17	9
	TOTAL	76	81	85	45
	MEAN%	50.9	48.1	49.0	57.1
	S.D.	14.2	18.5	13.6	20.8
Sex Ratio M:F		50:50	48:52	50:50	54:46

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.
Means calculated excluding dams with no viable fetuses.

APPEARS THIS WAY
ON ORIGINAL

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SR 47436 - TERATOLOGY STUDY BY ORAL ROUTE (GAVAGE) IN THE RABBIT (SEGMENT II).
MEAN FETAL NUMERICAL DATA

DOSE LEVEL		CONTROL	3 mg/Kg	10 mg/Kg	30 mg/Kg
PLACENTAL WEIGHT UNITS: grams					
of all Viable Fetuses	MEAN	5.23	5.29	5.18	5.47
	S.D.	0.73	0.86	0.67	1.22
	N	14	16	17	9
Covariate Adjusted	MEAN	5.37	5.38	5.15	5.27
of Male Fetuses	MEAN	5.48	5.37	5.25	5.61
	S.D.	0.84	0.95	0.92	1.29
	N	14	16	17	9
Covariate Adjusted	MEAN	5.64	5.46	5.22	5.39
of Female Fetuses	MEAN	5.07	5.26	5.06	5.15
	S.D.	0.74	0.89	0.66	1.04
	N	14	16	17	9
Covariate Adjusted	MEAN	5.19	5.34	5.04	4.98
FETAL WEIGHTS UNITS: GRAMS					
of all Viable Fetuses	MEAN	38.02	39.37	39.63	40.83
	S.D.	6.01	5.36	5.88	7.29
	N	14	16	17	9
Covariate Adjusted	MEAN	39.12	40.08	39.41	39.24
of Male Fetuses	MEAN	38.79	40.35	39.63	41.66
	S.D.	6.47	5.17	6.09	7.64
	N	14	16	17	9
Covariate Adjusted	MEAN	39.87	41.06	39.42	40.06
of Female Fetuses	MEAN	37.84	37.88	39.12	39.12
	S.D.	6.33	6.06	5.58	6.28
	N	14	16	17	9
Covariate Adjusted	MEAN	38.90	38.49	38.91	37.58

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$; ** = $P \leq 0.01$.

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SR 47436 - TERATOLOGY STUDY IN RABBITS (Segment II)

RESULTS OF EXTERNAL, VISCERAL AND SKELETAL EXAMINATIONS OF FETUSES

Summary of External Anomalies	***(Study 311/519)***			
Dose Level (mg/kg/day)	00	03	10	30
Litters Evaluated	14	16	17	9
Fetuses Evaluated	153	170	71	83
Fetal Incidence of Malformations	1	0	1	5
Litter Incidence of Malformations	1	0	1	1
Fetal Incidence of Variations	1	0	1	0
Litter Incidence of Variations	1	0	1	0
Fetal Incidence of Incidentals	0	0	0	0
Litter Incidence of Incidentals	0	0	0	0

Malformations *consisted of gastroschisis (1 fetus @ 10 mg/kg), acaudia (1 fetus @ 10 mg/kg, 5 (from 1 litter) @ 30 mg/kg, and open eyes (1 control fetus).* ***Variations*** *consisted of slightly flexed forelimbs (1 control fetus) and slightly flexed hindlimbs (1 fetus @ 10 mg/kg).*

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Summary of Soft Tissue Anomalies of Body (Study 311/519)

Dose Level (mg/kg/day)	00	03	10	30
Litters Evaluated	14	16	17	9
Fetuses Evaluated	152	170	171	83
Fetal Incidence of Malformations	0	0	0	0
Litter Incidence of Malformations	0	0	0	0
Fetal Incidence of Variations	1	0	1	0
Litter Incidence of Variations	1	0	1	0
Fetal Incidence of Incidentals	1	12	3	1
Litter Incidence of Incidentals	1	4	3	1

Summary of Soft Tissue Anomalies of Head (Study 311/519)

Dose Level (mg/kg/day)	00	03	10	30
Litters Evaluated	14	16	17	9
Fetuses Evaluated	72	81	81	39
Fetal Incidence of Malformations	1	0	1	0
Litter Incidence of Malformations	1	0	1	0
Fetal Incidence of Variations	4	4	3	2
Litter Incidence of Variations	2	2	3	2
Fetal Incidence of Incidentals	0	0	0	0
Litter Incidence of Incidentals	0	0	0	0

Malformations *consisted of malformed eyes (1 control fetus) and internal hydrocephaly of brain (1 fetus @ 10 mg/kg).* ***Variations*** *consisted of incompletely inflated lungs (1 control fetus and 1 @ 10 mg/kg), vacuole in the medulla of the brain (2 fetuses/1 litter from control group, 2 fetuses/1 litter @ 3 mg/kg, and 3 fetuses/3 litters @ 10 mg/kg) and dilated ventricles of brain (2 fetuses/1 litter from control group, 2 fetuses/1 litter @ 3 mg/kg and 2 fetuses/2 litters @ 30 mg/kg. (The ventricular and medullary variations at the high dose occurred in the same 2 fetuses.)* ***Incidentals*** *consisted of dark lungs (1 fetus/1 litter for all groups but 3 mg/kg group where incidence was 10 fetuses/2 litters) and reduced or absent azygous lobe of lung (2 additional fetuses/2 additional litters @ 3 mg/kg, 2 additional fetuses/2 additional litters @ 10 mg/kg).*

Summary of Skeletal Anomalies of Body (Study 311/519)

Dose Level (mg/kg/day)	00	03	10	30
Litters Evaluated	14	16	17	9
Fetuses Evaluated	152	170	171	83
Fetal Incidence of Malformations	1	2	1	7
Litter Incidence of Malformations	1	2	1	1
Fetal Incidence of Variations	106	119	94	66
Litter Incidence of Variations	14	16	16	9
Fetal Incidence of Incidentals	58	55	65	37
Litter Incidence of Incidentals	13	14	15	8

Summary of Skeletal Anomalies of Head (Study 311/519)

Dose Level (mg/kg/day)	00	03	10	30
Litters Evaluated	14	16	17	9
Fetuses Evaluated	80	89	90	44
Fetal Incidence of Malformations	0	0	0	0
Litter Incidence of Malformations	0	0	0	0
Fetal Incidence of Variations	11	3	5	4
Litter Incidence of Variations	6	2	4	2
Fetal Incidence of Incidentals	0	0	0	0
Litter Incidence of Incidentals	0	0	0	0

Malformations *consisted of malformed vertebrae (1 control fetus, 2 fetuses from 2 litters @ 3 mg/kg, 1 fetus @ 10 mg/kg, and 4 fetuses from 1 litter @ 30 mg/kg), acaudia (1 fetus @ 3mg/kg and 5 from 1 litter @ 30 mg/kg) and malformed ribs (1 fetus @ 3 mg/kg and 2 fetuses from 1 litter @ 30 mg/kg).* ***Variations*** *involved vertebra (incomplete ossification, misshapen, minor displacement or minor fusion), scapulae (irregular ossification), limbs (incomplete ossification of tarsals or phalanges), sternebrae (bipartite or asymetric or incomplete ossification), pelvis (incomplete or absence of ossification), ribs (bifid), hyoid (misshapen or incompletely ossified), zygomatic arch (incompletely ossified) and cranium (depressed). None of the variations showed incidence related to drug treatment.* ***Incidentals*** *consisted of incomplete or unossified sternebrae and incompletely ossified metacarpals. None of the incidentals showed incidence related to drug treatment.*

5. Late Gestation and Lactation Study of Irbesartan in Rats (Segment III)

Study Reference: LSR:SNF034 - Sanofi:DPN235

Performing Laboratory:

Sponsor: Sanofi Recherche
Montpellier Cedex, France

Initiation of Treatment: 6/14/93

Quality Assurance: A statement of conformance to GLPs is included.

Test Animals: Charles River CD rats (from Charles River, UK), 22 mated females per group, were 10-11 weeks old and weighed 226-293 g at initiation of the study.

Procedure: SR 47436 (Batch 93.04) in 10% gum Arabic (w/v) vehicle, was administered once daily by oral gavage between GD 15 and PPD 24 at doses of 0 (vehicle control), 50, 180 and 650 mg/kg/day. The dose volume was 10 ml/kg for each group. Prenatal observations of F_0 dams included mortality, physical signs, body weight and feed consumption measurements. Neonatal and postnatal observations included parturition, duration of pregnancy, body weight and feed consumption of dams, mortality, litter size, weight, sex and appearance of pups. On PPD 4, litters were randomly culled to 8 (4/sex if possible). F_1 pup weights were obtained on PPDs 1, 4, 7, 14, 18, 21 and 25. Post weaning, pups were examined on day 25 for visual and auditory function; on days 26-27 for activity, on day 27 for learning in a water filled maze, on day 28-30 for neuromuscular function (6 different tests). Pups were further examined for physical developmental signs (time to pinna unfolding, hair growth, eye opening, tooth eruption, testes descent and vaginal opening). F_0 females were killed and macroscopically examined after weaning.

At 9 to 10 weeks of age 20 F_1 males and 20 F_1 females (1 male and 1 female per litter where possible) were paired (1 male to 1 female within treatment groups) for mating. Mated females were killed on GD 20 for corpora lutea count and examination of uterine contents, including implantation and resorption sites; fetal and placental weights, and sex and external abnormalities of fetuses were determined. Males were also killed at around the time of C-section, and both the males and C-sectioned females were examined for macroscopic abnormalities. F_1 offspring not selected for evaluation of reproductive performance were weighed at weekly intervals, killed at 8 weeks of age and examined for macroscopic abnormalities.

Evaluation of F_0 Dams

One dam at 650 mg/kg/day was found dead on PPD 13, and one dam at 180 mg/kg/day was found dead just after parturition on PPD 1. Although cause of death was not determined, neither death was considered to be compound related.

During gestation, there were no treatment related effects on mean body weight, although mean food consumption was slightly (significantly) less than control in all 3 treated groups on GDs 18 and 19 (not dose related). During lactation, mean body weight of high dose dams tended to be slightly lower than control between PPDs 4 and 18 ($P< 0.05$ only on PPDs 4 and 5). Mean food consumption during lactation was slightly but significantly decreased at mid and high doses between PPDs 7 and 10 and PPDs 11 and 14, but there was no dose-relationship. There were no cases of dystocia reported in this study and gestation length appeared to be unaffected by treatment.

Evaluation of F_1 Pups

Body weights of F_1 male and female pups in all three treated groups were slightly lower than control on PPD 1 (n.s.) and remained slightly lower throughout lactation; the differences became statistically significant and dose related for both sexes on PPD 25. In animals selected for observation of mating performance (sacrificed at 15 weeks of age), body weights of males in the 3 treated groups tended to be lower than control, but there was no dose relationship. Postnatal survival, physical and functional development (including reproductive function) were unaffected by treatment.

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TABLE 1

Summary of mortality (F_0)

Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group and sex	Animal number	History and circumstances of death	Summary of necropsy findings
3 F	1060	Found dead on Day 22 of gestation, after parturition, before Day 1 of lactation.	External: Fur stained red around mouth and urogenital area. Internal: Stomach contents slightly gaseous. All abdominal organs slightly autolysed.
4 F	1071	Found dead on Day 13 of lactation.	External: Both pupils constricted, cyanosis of all extremities and all nipples reddened. Internal: Large amount of red serous fluid and small amount of pale caseous materal free in thoracic cavity. All lung lobes severely congested. Stomach contents gaseous. All internal organs slightly autolysed.

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TABLE 2

Group mean bodyweights (g) of females during gestation (F_0-F_1)

Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group		Day of gestation									
		0	5	10	15	16	17	18	19	20	21
1	Mean	253	293	326	365	375	390	407	426	447	460
	SD	17	17	21	23	24	23	24	27	30	33
	n	22	22	22	22	22	22	22	22	22	22
2	Mean	253	292	324	365	375	388	403	419	437	454
	SD	13	13	15	18	18	19	17	18	18	18
	n	22	22	22	22	22	22	22	22	22	22
3	Mean	251	290	325	364	376	390	404	422	441	458
	SD	14	19	18	22	21	21	19	22	23	25
	n	22	22	22	22	22	22	22	22	22	22
4	Mean	248	287	321	361	373	387	401	416	436	453
	SD	15	17	22	26	26	27	27	28	28	31
	n	22	22	22	22	22	22	22	22	22	22

SD Standard deviation.
n Number of animals.

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TABLE 3

Group mean food consumption
(g/rat/day) of females during gestation (F_0-F_1)

Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group		Days of gestation					
		0-2	3-6	7-10	11-14	15-17	18-19
1	Mean	28	30	32	33	35	33
	SD	3	3	3	3	3	4
	n	22	22	22	22	22	22
2	Mean	27	29	31	33	32[a]	29[c]
	SD	2	3	3	3	2	2
	n	22	22	22	22	22	22
3	Mean	27	30	32	32	33	30[a]
	SD	3	3	3	4	3	4
	n	22	22	22	22	22	22
4	Mean	28	30	33	34	34	29[c]
	SD	3	3	3	3	3	3
	n	22	22	22	22	22	22

SD Standard deviation.
n Number of pregnant animals.
Significantly different from Controls: a - $p<0.05$; c - $p<0.001$, (t-test following one-way analysis of variance).

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TABLE 4

Gestation length and gestation index (F_0-F_1)

Group	: 1	2	3	4
Compound	: Control	----	SR 47436	----
Dosage (mg/kg/day)	: 0	50	180	650

Group	Number of pregnant animals		Gestation length (days) 22	22½	23	23½	Number of live litters born	Gestation index (%)
1	22	n (%)	2 (9)	11 (50)	7 (32)	2 (9)	22	100
2	22	n (%)	3 (14)	13 (59)	5 (23)	1 (5)	22	100
3	22	n (%)	3 (14)	18 (82)	1 (5)	0	22[α]	100
4	22	n (%)	1 (5)	14 (64)	6 (27)	1 (5)	22	100

n Number of animals in category.
α Includes one female found dead after parturition before Day 1 of lactation.

Gestation index was calculated as:

$$\frac{\text{Number of live litters born}}{\text{Number pregnant}} \times 100$$

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TABLE 5

Group mean bodyweights (g) of females during lactation (F_0-F_1)

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Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group		Day of lactation												
		1	2	3	4	5	6	7	8	9	10	11	12	13
1	Mean	337	336	341	346	352	350	350	356	361	366	370	373	378
	SD	28	25	26	26	27	26	23	25	26	28	29	29	28
	n	22	22	22	22	22	22	22	22	22	22	22	22	22
2	Mean	337	339	340	344	349	347	348	350	357	362	366	369	373
	SD	21	20	17	18	18	20	18	17	18	19	19	17	17
	n	22	22	22	22	22	22	22	22	22	22	22	22	22
3	Mean	339	344	346	350	356	354	352	357	361	364	368	371	376
	SD	19	22	23	22	22	24	23	24	23	22	20	21	21
	n	21	21	21	21	21	21	21	21	21	21	21	21	21
4	Mean	338	342	338	338[a]	342[a]	342	342	346	349	355	357	362	368
	SD	28	26	24	24	24	23	22	24	23	23	25	22	24
	n	22	22	22	22	22	22	22	22	22	22	22	22	21

SD - Standard deviation.
n Number of animals.
Significantly different from Controls: a - $p<0.05$, (t-test following one-way analysis of variance).

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TABLE 5 - continued

Group mean bodyweights (g) of females during lactation (F_0-F_1)

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Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group		Day of lactation											
		14	15	16	17	18	19	20	21	22	23	24	25
1	Mean	381	380	382	379	386	375	375	372	365	362	355	353
	SD	31	29	29	28	27	32	28	27	29	27	26	27
	n	22	22	22	22	22	22	22	22	22	22	22	22
2	Mean	374	376	376	376	383	380	383	377	368	361	356	352
	SD	19	20	20	20	21	21	18	22	18	17	18	17
	n	22	22	22	22	22	22	22	22	22	22	22	22
3	Mean	379	378	381	378	386	382	381	380	376	369	363	359
	SD	23	23	23	19	19	22	23	22	24	21	23	23
	n	21	21	21	21	21	21	21	21	21	21	21	21
4	Mean	372	371	374	372	378	378	377	374	368	360	355	355
	SD	24	23	24	23	26	26	29	28	26	26	25	29
	n	21	21	21	21	21	21	21	21	21	21	21	21

SD Standard deviation.
n Number of animals.

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ON ORIGINAL

TABLE 6

Group mean food consumption
(g/rat/day) of females during lactation (F_0-F_1)

Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group		Days of lactation						
		1-3	4-6	7-10	11-13	14-17[A]	18-20[A]	21-24[A]
1	Mean	38	45	61	71	75	87	106
	SD	8	7	8	9	10	15	18
	n	22	22	22	22	22	22	22
2	Mean	37	44	58	68	72	86	102
	SD	6	4	8	5	6	8	8
	n	22	22	22	22	22	22	22
3	Mean	37	42	56[a]	65[b]	72	86	102
	SD	4	5	4	8	7	9	9
	n	21	21	21	21	21	21	21
4	Mean	34	41	55[b]	66[a]	71	84	104
	SD	5	4	4	5	4	8	8
	n	22	22	22	21	21	21	21

A Includes diet consumed by offspring.
SD Standard deviation.
n Number of animals.
Significantly different from Controls: a - $p<0.05$; b - $p<0.01$, (t-test following one-way analysis of variance).

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TABLE 7

Group mean litter sizes (F_1)

Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group		Implantation sites	Total at Day 1	Day of age: Before culling 1	Before culling 4	After culling 4	After culling 7	After culling 11	After culling 14	After culling 18	After culling 21	After culling 25
1	Mean	17.6	15.6	15.6	15.1	7.8	7.6	7.6	7.6	7.6	7.6	7.6
	SD	1.8	2.3	2.3	3.5	1.1	1.1	1.1	1.1	1.1	1.1	1.1
	n	22	22	22	22	22	22	22	22	22	22	22
2	Mean	16.7	15.5	15.4	15.3	8.0	8.0	8.0	8.0	8.0	8.0	8.0
	SD	2.1	2.3	2.3	2.3	0.0	0.0	0.0	0.0	0.0	0.2	0.2
	n	22	22	22	22	22	22	22	22	22	22	22
3	Mean	17.4	16.0	16.0	15.7	8.0	7.9	7.9	7.9	7.9	7.9	7.9
	SD	1.6	1.4	1.4	1.6	0.0	0.3	0.3	0.5	0.5	0.5	0.5
	n	22	21	21	21	21	21	21	21	21	21	21
4	Mean	16.8	14.7	14.7	14.6	8.0	8.0	8.0	8.0	8.0	8.0	8.0
	SD	1.9	2.4	2.4	2.4	0.0	0.2	0.2	0.0	0.0	0.0	0.0
	n	22	22	22	22	22	22	22	21	21	21	21

SD Standard deviation.
n Number of litters.

TABLE 8

Offspring survival indices (F_1)

Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group	Post-implantation survival index (%)	Live birth index (%)	Viability index (%) Day 4	Lactation index (%) on Day of age					
				7	11	14	18	21	25
1	89	100	97	98	98	98	98	98	98
2	92	99	100	100	100	100	100	99	99
3†	92	100	98	99	99	98	98	98	98
4α	87	100	99	99	99	100	100	100	100

† Excludes one litter for which the dam was found dead.
α Lactation indices on Days 14-25 exclude one litter for which the dam was found dead.

Post-implantation survival index was calculated as:

$$\frac{\text{Number of offspring at Day 1 of age}}{\text{Number of uterine implantation sites}} \times 100$$

Live birth index was calculated as:

$$\frac{\text{Number of live offspring at Day 1 of age}}{\text{Total number of offspring at Day 1 of age}} \times 100$$

Viability index was calculated as:

$$\frac{\text{Number of live offspring at Day 4 before culling}}{\text{Number of live offspring at Day 1 of age}} \times 100$$

Lactation index was calculated for each group on Days 7, 11, 14, 18, 21 and 25 of age as:

$$\frac{\text{Number of live offspring at day of examination}}{\text{Number of live offspring at Day 4 after culling}} \times 100$$

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TABLE 9

Sex ratios (F_1)

Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group	Total at Day 1 of age			Number alive at Day 1 of age			Number alive at Day 4 of age: Before culling			Number alive at Day 4 of age: After culling			Number alive at Day 25 of age		
	M	F	Ratio	M	F	Ratio	M	F	Ratio	M	F	Ratio	M	F	Ratio
1	151	193	1:1.28	151	193	1:1.28	145	188	1:1.30	84	87	1:1.04	82	86	1:1.05
2	165	175	1:1.06	164	174	1:1.06	163	174	1:1.07	88	88	1:1.00	87	88	1:1.01
3	172	164	1:0.95	172	164	1:0.95	168	162	1:0.96	84	84	1:1.00	82	83	1:1.01
4	176	147	1:0.84	176	147	1:0.84	176	145	1:0.82	88	88	1:1.00	84	84	1:1.00

TABLE 10

Group mean bodyweights (g) of male offspring (F_1)

Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group		Day of age: Before culling		After culling						
		1	4	4	7	11	14	18	21	25
1	Mean	7.0	10.0	10.1	16.6	27.4	36.2	47.5	59.3	83.7
	SD	0.6	1.1	1.1	2.0	2.9	3.2	3.9	4.9	6.4
	n	22	21	21	21	21	21	21	21	21
2	Mean	6.7	9.3	9.4	15.1	24.5	32.2	42.2	52.4	76.2[b]
	SD	0.6	1.1	1.0	1.7	2.6	3.1	3.9	4.9	6.5
	n	22	22	22	22	22	22	22	22	22
3	Mean	6.5	8.7	8.9	14.5	23.6	31.7	42.5	52.5	73.9[c]
	SD	0.6	1.0	1.0	2.1	3.1	3.5	3.8	5.5	9.4
	n	21	21	21	21	21	21	21	21	21
4	Mean	6.8	9.3	9.5	15.0	24.1	31.7	41.7	50.7	73.2[c]
	SD	0.6	1.1	1.0	1.8	2.4	2.7	3.4	5.1	6.9
	n	22	22	22	22	22	21	21	21	21

SD Standard deviation.
n Number of litters.
Bodyweight gain from Day 1 significant when compared with Controls: b - $p<0.01$; c - $p<0.001$, (t-test following one-way analysis of variance).

TABLE 11

Group mean bodyweights (g) of female offspring (F_1)

Group	:	1	2	3	4
Compound	:	Control	----	SR 47436	----
Dosage (mg/kg/day)	:	0	50	180	650

Group		Day of age								
		Before culling		After culling						
		1	4	4	7	11	14	18	21	25
1	Mean	6.6	9.5	9.6	15.9	26.4	35.0	45.7	56.8	78.9
	SD	0.6	1.1	1.1	2.1	2.7	3.1	3.8	5.0	6.5
	n	22	22	22	22	22	22	22	22	22
2	Mean	6.5	8.9	9.1	14.6	23.9	31.7	41.5	51.5	73.8[a]
	SD	0.6	1.1	1.1	1.6	2.4	2.9	3.7	5.1	6.7
	n	22	22	22	22	22	22	22	22	22
3	Mean	6.1	8.3	8.4	13.6	22.6	30.2	40.3	49.9	70.5[c]
	SD	0.5	1.1	1.1	2.0	3.4	4.0	4.5	6.2	8.1
	n	21	21	21	21	21	21	21	21	21
4	Mean	6.5	9.0	9.0	14.3	23.0	30.3	39.7	48.5	69.6[c]
	SD	0.7	1.1	1.0	1.6	2.3	2.5	3.4	5.1	7.5
	n	22	22	22	22	22	21	21	21	21

SD Standard deviation.
n Number of litters.
Bodyweight gain from Day 1 significant when compared with Controls: a - $p<0.05$; c - $p<0.001$, (t-test following one-way analysis of variance).

B. TISSUE DISTRIBUTION STUDIES

1. Tissue Distribution of Irbesartan in Pregnant Rats

In this tissue distribution study at Sanofi Research Laboratories in France, performed between 12/94 and 7/95 (Study No. DIS0174, Report No. RS0005951108/01), a single oral dose of 150 mg/kg ^{14}C-labeled Irbesartan (batch no. 4SNP017) as a suspension in 10% gum arabic solution, was administered to 12 overnight fasted female Sprague-Dawley rats on GD 11 (embryo-organogenesis stage) and another 12 on GD 18 (fetal stage). Animals weighed between 261 and 325 g on GD 11, and between 320 and 369 g on GD 18. Blood samples were obtained at 2, 8, 24 and 48 hours after dosing (3 rat/sampling time). Whole body sagittal sections were obtained from the same animals, sacrificed and deep frozen, for determination of tissue distribution by means of qualitative and quantitative autoradioluminography. During sectioning, aliquots of selected organs were excised. Quantitative determinations of radioactivity in blood, plasma and the selected excised tissues were performed by liquid scintillation counting. Quantitative tissue distribution data shown below is based on qualitative and quantitative radioluminography.

Although tissue levels in virtually all organs were lower on GD 18 than on GD 11, the investigators concluded that there were no major differences in maternal tissue concentrations between these two days of gestation. Highest concentrations in maternal tissues and fetus (including fetal organs on GD 18), on both days of pregnancy, were found at the 2 hour sampling time. The level of radioactivity at all time periods was higher in maternal tissues and placenta than in the embryo, fetus or fetal tissues, except for fetal gut at 48 hours. Substantial levels of radioactivity persisted, in maternal liver and in fetal gut, to 48 hours after dosing.

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Qualitative tissue distribution in embryo area (3 animals/sampling time)

. Day 11 of gestation

Time	Organs in embryonic area
2 h	maternal blood > placenta, uterus and/or embryonic appendices> embryo, amniotic fluid
8 h	placenta, uterus and/or embryonic appendices ≡ maternal blood > embryo
24 h	not detected
48 h	not detected

Radioactivity levels at 2 hours were superior to those at 8 hours

. Day 18 of gestation

Time	Organs in fetal area
2 h	placenta, maternal blood > fetus (fetal liver > fetal brain)
8 h	placenta, uterus > fetus > amniotic fluid
24 h	not detected
48 h	fetal gut

Quantitative tissue distribution (mean values expressed as mg Eq./kg of tissue ± standard deviations ; n = 3 animals per time point excepted when indicated between brackets)

. Day 11 of gestation

Tissue	Ct_1	Ct_2	Ct_1/Cp	Ct_2/Cp
Plasma	133.76 ± 18.10	10.46 ± 10.13	1.00 ± 0.00	1.00 ± 0.00
Blood	78.46 ± 15.49	7.05 ± 5.82	0.59 ± .010	0.74 ± 0.15
Brain	2.46 (n = 2)	UDL	0.02(n =2)	
Kidney	86.67 ± 1.58	23.91 ± 8.52	0.66 ± 0.08	3.32 ± 1.81
Liver	179.81 ± 24.44	96.98 ± 16.09	1.35 ±0.13	14.74 ± 8.89
Muscle	15.71 ± 3.04	2.56 (n = 1)	0.12 ± 0.01	0.32 (n = 2)
Mammary gland	30.28 ± 2.33	5.38 ± 2.46	0.23 ± .01	0.79 ± 0.66
Ovary	43.10 ± 1.74	6.30 ± 2.20	0.33 ± 0.04	0. 0.59
Uterus	68.13 (n = 2)	9.26 (n = 2)	055 (n = 2)	0.68 (n = 2)
Placenta	51.80 ± 7.83	7.78 (n = 2)	0.39 ± 0.01	0.81 (n = 2)
Embryo	7.64 ± 3.21	3.74 (n = 2)	0.06 ± 0.02	0.53 (n = 2)

. Day 18 of gestation

Tissue	Ct_1	Ct_2	Ct_1/Cp	Ct_2/Cp
Plasma	70.95 ± 16.59	17.91 ± 18.47	1.00 ± 0.00	1.00 ± 0.00
Blood	48.82 ± 15.68	14.48 ± 11.93	0.68 ± 0.16	1.04 ± 0.39
Brain	3.27 (n = 2)	2.76 (n = 1)	0.05 (n = 2)	0.07 (n = 1)
Kidney	62.66 ± 16.62	31.54 ± 16.06	0.88 ± 0.13	3.20 ± 2.59
Liver	175.92 ± 29.91	134.46 ± 32.42	2.54 ± 0.57	15.97 ± 14.25
Muscle	12.06 ± 5.59	5.02 (n = 1)	0.16 ± 0.04	0.13 (n = 1)
Mammary gland	17.55 ± 4.30	7.22 (n = 1)	0.25 ± 0.00	0.19 (n = 1)
Ovary	30.23 ± 10.33	20.38 (n = 1)	0.42 ± 0.05	0.53 (n = 1)
Uterus	46.97 ± 9.18	14.61 ± 7.11	0.67 ± 0.07	1.99 ± 2.43
Amniotic fluid	2.88 (n = 2)	UDL	0.04 (n = 2)	
Placenta	34.47 ± 7.85	7.97 ± 5.23	0.49 ± 0.08	0.72 ± 0.51
Fetal brain	3.19 (n = 1)	UDL	0.05 (n = 1)	
Fetal liver	11.62 (n = 2)	6.89 (n = 2)	0.15 (n = 2)	0.32 (n = 1)
Fetus	6.85 ± 1.60	5.39 ± 2.11	0.10 ± 0.01	0.61 ± 0.55

LOD : 2.63 mg Eq./kg
LOQ : 8.77 mg Eq./kg
UDL : under detection limit

Ct_1 = 2 hours after dosing
Ct_2 = 8 hours after dosing
Cp = maternal plasma concentration

2. Tissue Distribution of Irbersartan in Pregnant Rabbits

In this tissue distribution study at Sanofi Research Laboratories in France, performed between 3/95 and 11/95 (Study No. DIS0175, Report No. RS0005951204/01), a single oral dose of 10 mg/kg ^{14}C-labeled Irbesartan (batch no. 93-06) as a suspension in 10% gum arabic solution, was administered to 12 overnight fasted New Zealand rabbits (body weights of 3.3-4.9 kg) on GD 28 (fetal stage). Blood samples were obtained from the marginal ear vein at 2, 8, 24 and 48 hours after dosing (3 rabbits/sampling time). Whole body sagittal sections were obtained from the same animals, sacrificed and frozen after blood sampling, for qualitative and quantitative determination of tissue distribution by means of autoradioluminography. Quantitative determinations of radioactivity in blood, plasma and blood cells, were performed by liquid scintillation counting.

Radioactivity levels in maternal tissues, at all time periods after dosing, were often only slightly above the limit of quantification (stated as 1.002 mg Eq/kg). With the exception of blood, plasma and uterus, maternal tissue levels were determined only by qualitative nuclear image analysis. For the whole fetus, radioactivity at 2 to 24 hours after dosing was around the limit of detection (stated as 0.3 mg Eq/kg) and under the limit of quantification. Also fetal data at 2 and 24 hours after dosing are based on only one fetus.

At 2 hours after dosing, concentrations in the whole fetus and in fetal organs were lower than in maternal blood, plasma and uterus, and lower than in the placenta and chorion. In maternal tissues (blood and uterus) and plasma, the concentrations of radioactivity were highest at 2 hours and became progressively lower with increasing time. In contrast, the concentrations found in the whole fetus, fetal gall bladder, liver, gastric and gut contents persisted or became even higher at 8 and 24 hours after dosing. By 48 hours, fetal gall bladder concentrations were remarkably high, and radioactivity derived from the drug was still present in fetal gastric and gut contents.

The investigators claimed that the high concentrations in the fetal gall bladder and gut resulted from accumulation due to biliary excretion. Nevertheless, the sponsor concluded that the transfer of drug to fetal tissue was small; "Only trace amounts of Irbesartan were found in the fetus", and the radioactivity was mainly present in the digestive tract and liver.

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• **Qualitative nuclear image analysis**

Time	Tissues
2 hours	gastric, gut contents > bile > liver > myocardium > lung > kidney > adrenals > blood > salivary glands > bone marrow, mammary gland > placenta > fetus > brain
8 hours	gut content > gastric content > bile > liver > kidney > blood > lung > placenta > myocardium > mammary gland > fetuses > brain
24 hours	gastric, gut contents > bile > kidney > liver > lung > blood > fetuses
48 hours	gastric, gut contents > bile > liver > fetuses

• **Quantitative tissue distribution**

* *Maternal tissue concentrations in pregnant rabbits on day 28 of pregnancy*
(results expressed as mg Eq. SR 47436/kg of tissue ± standard deviations ; n = 3 animals per time point excepted when indicated between brackets)

Tissue	2h	8h	24h	48h
Plasma	3.62 ± 0.91	1.27 ± 0.13	0.09 ± 0.06	0.04 ± 0.01
Blood	2.15 ± 0.58	0.86 ± 0.17	0.15 ± 0.06	0.08 ± 0.00
Blood cells	0.88 ± 0.12	0.59 ± 0.25	0.51 ± 0.11	0.37 ± 0.16
Uterus	2.44 (n = 2)	0.79 ± 0.11	ND	ND

ND : Not Detectable

* *Placental and fetal unit concentrations in fetuses on day 28 of pregnancy*
(results expressed as mg Eq. SR 47436/kg of tissue ± standard deviations ; n = 3 animals per time point excepted when indicated between brackets)

Tissue	2h	8h	24h	48h
Placenta	1.77 ± 0.60	0.82 ± 0.29	UDL	UDL
Chorion	1.79 (n = 2)	1.48 ± 0.40	0.47 (n = 1)	ND
Whole fetus	0.37 (n = 1)	0.40 (n = 2)	0.32 (n = 1)	UDL
Brain	UDL	UDL	UDL	UDL
Fetal gall bladder	ND	5.33 (n = 1)	17.21 ± 6.78	43.53 ± 16.37
Fetal gastric content	UDL	0.94 ± 0.38	0.86 ± 0.23	0.54 (n = 2)
Fetal gut content	ND	2.67 ± 1.97	4.03 (n = 2)	1.26 ± 0.96
Fetal liver	0.40 ± 0.04	0.50 ± 0.05	0.42 ± 0.02	UDL
Fetal lung	UDL	UDL	UDL	UDL

LOD : 0.30 mg Eq./kg ; LOQ : 1.00 mg Eq./kg ; UDL : under detection limit
ND : Not Detectable

* *Ratio of concentrations fetal tissue to maternal plasma*

Tissue	2h	8h	24h	48h
Whole fetus	0.10 (n = 1)	0.30 (n = 2)	5.71 (n = 1)	-
Liver	0.12 ± 0.02	0.39 ± 0.01	6.27 ± 3.19	-
Gastric content	-	0.74 ± 0.33	11.54 ± 3.84	17.67 (n = 2)
Gut content	-	2.01 ± 1.26	40.90 (n = 2)	36.91 ± 32.43
Gall bladder	-	4.43 (n = 1)	225 ± 84	1310 ± 780
Placenta	0.50 ± 0.13	0.63 ± 0.16	-	-

3. Excretion of Irbesartan into Milk of Rats

In a study designed to determine the transfer of drug to nursing pups (performed at Sanofi Research Laboratories in France between 1/96 and 3/96), a single oral dose of 180 mg/kg ^{14}C-labeled Irbesartan (batch 4SNP017) in 10% aqueous gum arabic solution was administered to 9 non-fasted lactating Sprague-Dawley rats (276-344 g) on PPD 11 (Study No DIS0245, Report No. RS0005960226/01). Maternal blood was obtained at 1, 4 and 24 hours after dosing (3 rats/sampling time) for quantitative measurements of radioactivity in plasma and blood by liquid scintillation counting. In nursing pups (6 from each dam), liquid scintillation was used for quantitative determination of radioactivity in gastric tract and contents (3 pups from each of 3 dams/sampling time), and qualitative radioluminography was used for whole body autoradiography (3 pups from each of 3 dams/sampling time).

In the dams, the highest levels of drug were found at 4 hours after dosing, and by 24 hours the blood or plasma levels were about 1% or less of that observed at 4 hours. The level of radioactivity found in the gastric content in pups (based on percent of administered dose) indicated that the total amount of drug transferred to the neonate pups via the milk was very low. Based on radioluminography, drug was found to be present mainly in the gastric and intestinal contents during all 3 time periods after dosing, but was also found in the esophagus, liver and in urine.

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STUDY TITLE : Milk excretion of radioactivity after single oral administration (180mg/kg) of [Cyclopentane-1-^{14}C] SR 47436 (IRBESARTAN, BMS-186295) in the lactating female rat.

RESULTS :

Qualitative whole body radioluminography

SAMPLING TIMES (hours)	TISSUES OR ORGANS
1	gastric content > gut content > liver > oesophagus
4	gastric content > gut content > liver
24	gut content > gastric content > urine > liver

Liquid scintillation counting

. Quantitative evaluation of gastric content in pups : mean values ± standard deviation
(results expressed as % of the administered dose; n = 9 animals/sampling time except where indicated between brackets)

SAMPLING TIMES		
1 hour	4 hours	24 hours
UDL	0.006 ± 0.005 (n = 6)	0.002 ± 0.003

UDL = Under Detection Limit

. Blood and plasma concentrations in dams : mean values ± standard deviation
(results expressed as mg Eq. of SR 47436/kg of tissue; n = 3 animals/sampling time)

SAMPLING TIMES (hours)	BLOOD	PLASMA
1	12.4 ± 0.8	20.9 ± 1.5
4	76.7 ± 69.5	122.8 ± 102.8
24	0.7 ± 0.1	1.0 ± 0.2

Comments

Following a single oral (180 mg/kg) administration of [Cyclopentane-1-^{14}C] SR 47436 (IRBESARTAN, BMS186295) to the lactating Sprague Dawley rat, radioactivity was mainly located in gastric and gut contents of pups at times 1, 4 and 24 hours after drug intake in dams.
Radioactivity was detected in liver and in oesophagus 1 hour after administration, in liver 4 hours after administration and in urine and in liver 24 hours after intake.
Radioactivity was also detected in blood and plasma of dams at times 1, 4 and 24 hours after administration.
From these data, milk excretion of radioactivity could be postulated in the lactating Sprague Dawley rat.

C. SUMMARY AND EVALUATION

Irbesartan is an angiotensin II receptor antagonist that is being proposed for use, alone (NDA 20-757) or in fixed combination with hydrochlorothiazide (NDA 20-758) for the treatment of hypertension. The recommended initial dose is 150 mg once daily, but doses as high as 300 mg once daily may be used. Reproduction toxicology studies were performed according to the FDA "three segment" guidelines rather than the newer ICH guidelines. Doses administered to rats were 0, 50, 180 and 650 mg/kg/day, except for the Irbesartan/HCTZ study in which the doses of Irbesartan were 50 and 150 mg/kg/day. In the rabbit study, the doses were 0, 3, 10 and 30 mg Irbesartan/kg/day.

In the Segment I study of the effects of Irbesartan on fertility and general reproductive performance, which included fetal evaluation after C-section on GD 20, increased incidences (dose related) of hydroureter, renal pelvic cavitation and absence of renal papilla were observed in fetuses of all drug treated groups (in free-hand serial sectioned and/or dissected fetuses), and increased incidences (dose related) of subcutaneous edema (only in free hand sectioned fetuses) were observed in mid and high dose groups. The kidney effects, commonly associated with fetal immaturity (usually reversible), may have resulted from C-section on GD 20 instead of GD 21 or GD 22. The greater prevalence in treated groups may have been a consequence of a dose-related retardation of fetal growth (lower fetal weights); significantly decreased mean fetal weight, relative to concurrent control weight, however, was observed only at the high dose.

The sponsor attributes the renal effects and subcutaneous edema observed in the GD 20 fetuses to drug exposure during late gestation as these kidney effects were not observed in the Segment II developmental toxicity study in which there was no exposure to drug during the last trimester of gestation.

The sponsor also claims in the report and in their proposed labeling that the kidney and subcutaneous effects were transient. Although the veracity of this claim has not been established, similar effects were not observed at gross necropsy of 4 day old (culled) F_1 pups or pups that died, or pups sacrificed at 6 weeks of age.

In F_0 females, Irbesartan was associated with slight but statistically significant decreases in mean body weights (not dose related) before mating and during pregnancy, but not during lactation. Decreased food intake was observed only at the high dose. In F_0 males, Irbesartan was associated with a dose related decrease in mean body weight at all 3 doses and decreased food intake at the highest dose. In females allowed to litter, a reduced gestation index [(number of females with live born/number

of females with confirmed pregnancy) X 100] at the high dose was attributed to 3 females that were killed *in extremis* on GD 21 or GD 22, at the time of expected parturition. During the postnatal phase of this study, group mean body weights of male and female offspring were lower than control on PPD 25, but not on PPDs 1 or 4 (before culling), nor between PPD 4 and PPD 21 (after culling).

In the Segment II rat study of the effects of Irbesartan on *in utero* development, the only effects noted were significant decreases (non-dose related) in mean body weight gain and mean food intake of treated dams. Fetal visceral effects noted in the Segment I study (kidney anomalies and subcutaneous edema) were not observed in this study, even though examination for soft tissue anomalies included both free hand sectioning (for half of the fetuses of each dam) and dissection (for the remaining half of the fetuses). The Segment I study included treatment with this angiotensin II receptor antagonist during the periods of fetal and neonatal development; i.e. beyond GD 15, the last day of treatment in the Segment II study.

Although each tablet of the fixed combination proposed for marketing contains 150 mg of Irbesartan and 12.5 mg of hydrochlorothiazide (ratio of 12:1), the ratio tested in the Segment II combination study was 1:1. The combination drug treatment, even at 50/50 mg/kg/day, caused a greater decrease in maternal body weight gain in pregnant rats than did either drug alone at 150 mg/kg/day. In spite of this increase in toxicity to the dams with the drug combination, there did not appear to be an increase in developmental toxicity with the combination when compared to treatment with Irbesartan or hydrochlorothaizide alone.

In the Segment III rat study of the effects of Irbesartan on peri-postnatal development, the only effect noted in the offspring was a slightly lower than control mean body weight for both the male and female pups on PPD 25, as was also noted in the Segment I study. Although there were no effects of treatment on mean maternal body weight, a statistically significant, but non-dose related, decrease in food intake was noted for all treated groups.

In the Segment II rabbit study of the effects of Irbesartan on *in utero* development, severe maternal toxicity was observed at the high dose, manifested by a high incidence of deaths and abortions; decreased maternal body weight gain was seen in all Irbesartan treated groups. In the high dose group, there was a suggestion of an increased incidence of early resorptions and a concomitant decrease in number of live female fetuses. The investigators claimed there was no compound related effect on malformations, but with the low number of surviving fetuses and litters, such a possibility at the high dose could not be ruled out.

DOSAGE THRESHOLDS FOR ADVERSE FINDINGS IN IRBESARTAN REPRODUCTION STUDIES

Study Type & Species	Segment I, Rat	Segment III, Rat	Segment II, Rat	Segment II, Rabbit
Strain	Sprague-Dawley[1]	Sprague-Dawley[1]	Sprague-Dawley[2]	New Zealand White[2]
Doses (mg/kg/day)	0, 50, 180, 650	0, 50, 180, 650	0, 50, 150, 450	0, 3, 10, 30
Days Administered	[3]	GD 15 - PPD 24	GD 6 - GD 15	GD 6 - GD 18
Day of C-Section	GD 20	NA	GD 20	GD 29
No. Mated/Group	36/sex[4]	22	25	18
Mortality, Dams	>180<650[10]	>650	>650	>10<30[11]
↓Dam Weight Gain	<50[6]	>650	>50<180[12]	>3<10
↓Dam Food Intake	>180<650[5]	<50[8]	<50[9]	>10<30
↑Postimplantation loss	NA	NA	NA	>10<30[13]
↓Fetal Weight	>180<650	↓Dam Food Intake	>650	>30
↓Placental Weight	>180<650	NA	>650	>30
Fetal Kidney Anomalies[7]	≤50	NA	>650	>30
Fetal Subcut. Edema	>50<180	NA	>650	>30
↓Gestation Index	>180<650	>650	NA	NA
↓Pup Wt on PPD 25	<50[9]	<50[9]	NA	NA

[1] From Charles River
[3] Females from 15 days pre-mating to PPD 24; males from 71 days pre-mating until littering of all females.
[4] Treated females were mated with treated males. 23 dams in each group were C-sectioned, the remainder were allowed to litter.
[5] Only during the first 2 weeks of treatment.
[6] Not dose related; evident before mating and during pregnancy, but not during lactation.
[7] Increased incidences of (unilateral and bilateral) hydroureter and (unilateral and bilateral) renal pelvic cavitation.
[8] Slightly (significantly) decreased during gestation but not dose related. Decreased at mid and high dose between PPD 7 and PPD 13.
[9] Not dose related.
[10] Three deaths associated with digestive disorders, and one of those deaths was associated with prolonged vaginal bleeding.
[11] At the 30 mg/kg/day dose, four were found dead, 2 were killed moribund and 2 were sacrificed after they aborted.
[12] Statistically significant only on GD 16 @ low dose, but significant throughout treatment @ mid and high dose.
[13] Associated with an increase in early resorptions.

Toxicokinetic (TK) studies were not performed with the reproduction toxicity tests. Relative exposures (animals vs. human) could be estimated only from toxicokinetic data from repetitive dosing studies in males and non-pregnant females. Those TK studies did not include sampling following the initial dose of irbesartan, so that single dose exposure ratios were estimated from animal exposures following multiple dosing (steady state). The sponsor claims that "this extrapolation is supported by a single-dose and multiple-dose pharmacokinetic study in rats (Study No. TPK0009, Report No. RS0005920618/01), which demonstrated similar pharmacokinetics following single and multiple irbesartan doses of 10 mg/kg with no accumulation of drug."

The following table, submitted by the sponsor, summarizes relative exposures at doses evaluated in repeat-dose toxicology studies with irbesartan in rats.

	Dose	Sex	AUC (µg x h/ml)		Ratio[a]	
			Single dose	Steady state	Single dose	Steady state
Human	300 mg/day	M	18.3[b]	20.6		
		F	18.8[b]	23.4		
Sprague Dawley Rat	10 mg/kg/day	M		17.3[c]	0.95	0.84
		F		16.1[c]	0.86	0.69
	30 mg/kg/day	M		16.3[c]	0.89	0.79
		F		15.0[c]	0.80	0.64
	90 mg/kg/day	M		23.6[c]	1.29	1.15
		F		39.9[c]	2.12	1.71
	250 mg/kg/day	M		24.9[d]	1.36	1.21
		F		68.7[d]	3.65	2.94
	500 mg/kg/day	M		47.3[d]	2.58	2.30
		F		126.0[d]	6.70	5.38
	1000 mg/kg/day	M		178.4[d]	9.75	8.66
		F		202.2[d]	10.76	8.64

[a] Relative exposure of rats when compared with mild-moderate hypertensive patients.

[b] AUC following single dose of 300 mg/day not determined. An estimated value was obtained by multiplying the ratio of the single dose/multiple dose AUCs at the 100 mg dose (from study CV131-004) by the multiple dose AUC value at the 300 mg dose (from study CV131-057).

[c] Mean SR47436 AUC value obtained after 5 and 26 weeks from the 6-month oral toxicity study TXC 0857-RS0006930712/01.

[d] Mean SR47436 AUC value obtained after 5, 13, and 26 weeks from the 6-month oral toxicity study TXC 0949-RS0006960118/01.

The above data were used in interpolating estimates of steady-state exposure and exposure ratios (animal vs human) at doses used in reproductive toxicology studies in rats. The following table summarizes this information.

	Dose	Sex	AUC (µg x h/ml)		Ratio[a]	
			Single dose	Steady state	Single dose	Steady state
Human	300 mg/day	M	18.3[b]	20.6		
		F	18.8[b]	23.4		
Sprague Dawley Rat	50 mg/kg/day	M			1.02	0.91
		F			1.23	1.00
	150 mg/kg/day	M			1.32	1.17
		F			2.69	2.17
	180 mg/kg/day	M			1.68	1.18
		F			2.98	1.86
	450 mg/kg/day	M			2.34	2.08
		F			6.09	4.89
	650 mg/kg/day	M			4.73	4.21
		F			7.92	6.36

[a] Interpolated from ratios determined on the basis of mean exposures in repeat dose toxicity studies.

[b] AUC following single dose of 300 mg/day not determined. An estimated value was obtained by multiplying the ratio of the single dose/multiple dose AUCs at the 100 mg dose (from study CV131-004) by the multiple dose AUC value at the 300 mg dose (from study CV131-057).

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The Segment II study with irbesartan/HCTZ in rats did not include toxicokinetic measurements. However, exposures can be compared using toxicokinetic data from the 6-month repeat-dose toxicology study with irbesartan/HCTZ. The following table summarizes relative exposures to Irbesartan in that study.

	Dose	Sex	AUC (µg x h/ml)		Ratio[a]	
			Single dose	Steady state	Single dose	Steady state
Human	300 mg/day	F[b]	18.8[c]	23.4		
Sprague Dawley Rat	10:10[d] mg/kg/day	F	16.2	46.0	0.86	1.97
	90:90[d] mg/kg/day	F	27.2	57.4	1.45	2.45
	90:0[d] mg/kg/day	F	33.6	54.6	1.79	2.33

[a] Relative exposure of rats when compared with mild-moderate hypertensive patients.
[b] Only female data are relevant to the Segment II reproductive evaluation.
[c] AUC following single dose of 300 mg/day not determined. An estimated value was obtained by multiplying the ratio of the single dose/multiple dose AUCs at the 100 mg dose (from study CV131-004) by the multiple dose AUC value at the 300 mg dose (from study CV131-057).
[d] Dose expressed as ratio of irbesartan to HCTZ (irbesartan:HCTZ).

These pharmacokinetic data were used in estimating the exposure ratios (animal vs. human) following single and multiple-doses of 50:50 mg (irbesartan:HCTZ)/kg in pregnant rats. These estimates are 1.15 and 2.11, respectively. The ratios at the highest dose (150:150 mg/kg) would be >1.45 and >2.45 for the single-dose and multiple doses, respectively.

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No specific pharmacokinetic parameters were measured during the rabbit reproduction study and no data are available after repeated administration to non-pregnant rabbits. Extrapolation for comparisons of exposure can only be done using data from a single dose pharmacokinetic study in non-pregnant females using radiolabeled compound (Study No. ABS0100, Report No. RS0005920902/01).

The following table summarizes the estimated exposure and exposure ratio for the intermediate dosage level (10 mg/kg/day, the NOEL for fetuses) in the rabbit developmental toxicity study.

	Dose	Sex	AUC observed (µg equiv. x h/ml)	SR 47436 AUC (µg x h/ml)		Ratio[a]	
				Single dose	Steady state	Single dose	Steady state
Human	300 mg	F		18.8[b]	23.4		
Rabbit	10 mg/kg	F	10.8	≈0.5[c]		0.03	

[a] Relative exposure of rats when compared with mild-moderate hypertensive human.
[b] AUC following single dose of 300 mg/day not determined. An estimated value was obtained by multiplying the ratio of the single dose/multiple dose AUCs at the 100 mg dose (from study CV131-004) by the multiple dose AUC value at the 300 mg dose (from study CV131-057).
[c] Value extrapolated using metabolism data: irbesartan accounting for 68 to 40% of radioactivity up to 8h.

This estimate suggests that exposures of pregnant rabbits to irbesartan in the developmental toxicity study were lower than exposures expected in humans following a therapeutic dose.

In a tissue distribution study in pregnant rats that received single oral doses of 150 mg/kg ^{14}C-Irbesartan on GD 11 (embryo-organogenesis stage) or GD 18 (fetal stage), the highest drug concentrations (based on radioactivity) in maternal plasma and tissues, in the placenta and in the fetus, were found at 2 hours (the first sampling), and they progressively decreased with time up to 48 hours post-dosing. With the exception of maternal brain, the level of drug concentration found in maternal tissues was considerably higher than that found in the whole embryo or fetus, with the possible exception of the fetal gut (GD 18), which tended to retain radioactivity even after 48 hours. When considering the whole fetus, radioactivity was found to be below the limit of detection (0.3 mgEq/kg) by 24 hours after dosing, whether the drug was administered on GD 11 or GD 18.

In a similar tissue distribution study in pregnant rabbits which received a single oral dose of 10 mg/kg, the level of radioactivity in the administered drug was low, resulting in low levels in maternal tissues, and trace amounts that were below quantifiable limits in whole fetuses. Although the levels in

fetuses were below quantifiable limits, detectable levels persisted to 24 hours post dosing. The highest drug concentrations in maternal plasma and tissues were found at 2 hours (the first sampling), and then progressively decreased with time up to 48 hours post-dosing. The data indicate preferential accumulation or retention by specific organs of the fetus, particularly the gall bladder and gastrointestinal tract, which the investigators attributed to biliary excretion by the fetus. The data also suggest retention of the drug by the whole fetus. Although the effect of repeated doses on transfer of drug to the fetus was not tested, the rabbit data suggest that if given as repeated oral daily doses during pregnancy, there is the possibility of a preferential accumulation by the fetus.

From the results of a study in rats on excretion of Irbesartan into milk, it can be postulated that excretion into milk of rats is low following a single oral dose of Irbesartan.

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