

GLP compliance: Yes, **QA report:** yes (✓), no ()
Drug: Prasugrel HCl, **Vehicle:** Tragacanth 0.5% w/v
CAC concurrence: Yes, 7/22/2003 (Appendix/Attachments)
Doses: 30, 100 and 300 mg/kg/day
Basis of dose selection: MTD
Species/strain: Crj;B6C3F₁ mice
Number/sex/group (main study): n=55/sex/group
Route: Oral gavage

Frequency of dosing: The dosing suspensions were administered daily by oral gavage using a flexible stomach tube, at the dosage volume of 10 mL/kg body weight.

Satellite groups for toxicokinetics: Concentrations of two metabolites, R-138727 (active metabolite) and R-106583 (major human metabolite), in plasma of satellite animals were determined (n=60/sex/group).

Age: Started at 6 weeks of age (weight: 22 - 26 g males, 17 - 22 g females).

Animal housing: Animals were housed individually in cages under conditions of temperature at 23±3°C, relative humidity at 50±20%, air ventilation at 10-15 times/hour and 12-hour illumination. CRF-1 powdered diet and drinking water were provided *ad libitum*.

Drug stability/homogeneity: A suspension of prasugrel HCl in 0.5% w/v tragacanth solution at 250 mg/mL was stable in a refrigerator for 72 hours.

Mortality: The moribund animals were necropsied after collecting blood samples under ether anesthesia for hematology. The animals found dead were necropsied as soon as they were discovered, and then subjected to histopathological examination.

Clinical signs: All animals were observed daily for clinical signs, including external appearance, nutritional condition, posture, behavior and excretions. Palpation was done once a week to detect superficial masses.

Body weights: In the first week of administration, all animals were weighed twice: on days 1 and 7. Then, body weight was recorded once a week up to week 26 at 7-day intervals and every 2 weeks thereafter.

Food consumption: Food consumption was recorded twice in the first week of administration on days 1 and 7. Then, 7 day's cumulative consumption was recorded weekly up to week 26 at 7-day intervals and every 14 days thereafter, and one day's food consumption was calculated from the 7 day's cumulative consumption.

Histopathology: Peer review: yes (✓), no ()

Toxicokinetics: Collection of blood samples was conducted 3 times; in week 2 (8th dose), month 6 (176th dose) and month 18 (540th dose) of administration.

Results:

Survival rate: No treatment-related effects on the survival rate were observed in either sex. In the males, total number of deaths in the 0, 30, 100 and 300 mg/kg groups was 24, 19, 28 and 28, respectively, the survival rate was 56, 66, 49 and 49%, respectively (Table 29). In the females, total number of deaths in the 0, 30, 100 and 300 mg/kg groups was 20, 22, 23 and 24, respectively, the survival rate was 64, 60, 58 and 56%, respectively, and no effect of the test article on the survival rate was observed.

Table 29. Summary of mortality and survival rate

Sex	Male				Female			
	0	30	100	300	0	30	100	300
Dose (mg/kg/day)	0	30	100	300	0	30	100	300
No. of animals used	55	55	55	55	55	55	55	55
No. of deaths								
1-26 week	0 ^{a)}	0	0	0	0	0	0	0
1-52 week	0	1	1	1	2	1	0	2
1-78 week	2	6	8	8	4	6	5	8
1-104 week	24	19	28	28	20	22	23	24
No. of survivors	31	36	27	27	35	33	32	31
Survival rate (%)	56.4	65.5	49.1	49.1	63.6	60.0	58.2	56.4

Clinical signs: No obvious treatment-related abnormalities in the clinical signs were observed at relatively high incidence (> 5 animals) in any dose group, although incidence of emaciation appeared to be increased in the mid and high dose groups (Table 30). No treatment-related superficial masses were observed in any dose group.

Table 30. Incidence summary of major clinical signs

Sex	Male				Female			
	0	30	100	300	0	30	100	300
Dose (mg/kg/day)	0	30	100	300	0	30	100	300
No. of animals used	55	55	55	55	55	55	55	55
No. of deaths	24	19	28	28	20	22	23	24
Decrease, spontaneous movement	12 ^{a)} (12) ^{b)}	7(7)	12(12)	6(6)	8(8)	6(6)	9(9)	12(11)
Bradypnea	13(13)	10(10)	15(15)	9(9)	13(13)	9(9)	13(13)	13(13)
Hypothermia	11(11)	7(7)	15(15)	8(8)	6(6)	5(5)	7(7)	10(10)
Emaciation	3(3)	0(0)	10(10)	7(4)	0(0)	0(0)	1(1)	4(1)
Pale, skin	3(3)	3(2)	4(4)	2(2)	5(5)	4(4)	6(6)	5(5)
Excoriation	11(6)	7(6)	8(8)	4(3)	4(1)	4(2)	2(1)	4(2)
Abdominal distention	8(6)	5(4)	2(2)	8(4)	10(9)	9(7)	9(7)	9(9)

Number in parentheses indicate the number of animals that died or sacrificed as moribund

Body weights: In the males (100 mg/kg), significantly lower values were observed from week 2 to week 90 of administration, but no differences were recorded thereafter (Table 31). In the females (30 and 100 mg/kg), no treatment-related changes were observed (Table 31). In the high dose group (300 mg/kg), significantly ($p < 0.01$) lower values were observed at all time points from week 2 and the mean body weight at the end of the administration period was lower (males by 11%, and females by 9%) than that of the control group. Body weight gain from the start to the end of the administration period was also lower than that of the control group.

Table 31. Summary of body weight at termination of administration period

Sex	Male			Female		
	30	100	300	30	100	300
Dose (mg/kg/day)	30	100	300	30	100	300
No. of animals	36	28	28	34	32	31
Mean body weight (week 104)	N	N	-11%**	N	N	-9%**
Body weight gain (week 0-104)	N	N	-28%	N	N	-19%

Values in the table indicate percentage of change against the mean control value (-: decrease).

N: No remarkable changes

**: $p < 0.01$ (significantly different from the control group)

Food consumption: No treatment-related changes were observed throughout the administration period in either sex.

Gross pathology: The gross lesions observed at relatively high incidence (> 5 animals/group) in the liver was a tendency for an increase in the incidence of nodules in females in the mid-dose group (100 mg/kg) and both sexes in the high dose group (300 mg/kg) (Table 32). A tendency for an increase in the incidence of raised focus was observed in males in the 100 mg/kg group and both sexes in the 300 mg/kg group. A tendency for an increase in the incidence of white foci was observed in males in the mid- and high dose groups (100 and 300 mg/kg). A tendency for an increase in the incidence of dark red foci was observed in females in the 100 and 300 mg/kg groups.

Table 32. Incidence summary of major gross lesions

Sex	Male				Female			
	0	30	100	300	0	30	100	300
Dose (mg/kg/day)								
No. of animals used	55	55	55	55	55	55	55	55
General description								
Discoloration, skin, pale	2	2	4	2	5	3	6	5
Undernourishment	5	0	10	10	4	3	1	3
Excoriation	11	7	7	3	4	4	2	4
Abdominal cavity								
Excess fluid	2	4	0	2	4	7	9	4
Harderian gland								
Nodule	3	7	2	2	6	4	5	5
Liver								
Large	0	3	1	0	1	2	5	2
Nodule	25	28	30	42	8	16	21	36
Focus, raised	1	1	9	11	2	4	5	8
Focus, dark red	15	8	10	20	10	13	21	30
Focus, white	12	16	24	25	9	7	13	16
Lung (bronchus)								
Nodule	11	10	12	13	3	6	5	5
Lymph node, mesenteric								
Large	7	9	1	4	5	11	6	9
Lymph node, submandibular								
Large	2	5	3	2	5	9	3	8
Lymph node, nos⁹								
Large	2	7	4	3	7	13	11	10
Ovary								
Cyst	/	/	/	/	16	17	20	10
Seminal vesicle								
Small	1	1	2	6	/	/	/	/
Skin								
Nodule	2	1	2	3	6	1	2	2
Spleen								
Large	3	9	5	2	11	15	15	15
Stomach								
Focus, dark red, glandular stomach	3	3	8	4	4	2	2	1
Focus, raised, forestomach	3	3	4	8	2	2	3	5
Urinary bladder								
Distention	5	3	2	1	1	0	0	2
Uterus								
Nodule	/	/	/	/	3	4	7	2
Distention	/	/	/	/	6	0	2	2
Cyst, endometrial	/	/	/	/	33	35	41	26

Number in the Table indicates the number of animals with lesion.

Histopathology: In the mid-dose group (100 mg/kg), a tendency for increase in the number of benign tumors and number of benign tumor bearers were observed in females (Table 33). In the high dose group (300 mg/kg), a tendency for increase in the number of benign tumors, number of tumors, and number of multiple tumor bearers were observed in both sexes.

Table 33. Number of tumors and tumor bearers

Sex	Male				Female			
	0	30	100	300	0	30	100	300
Dose (mg/kg/day)	0	30	100	300	0	30	100	300
No. of animals used	55	55	55	55	55	55	55	55
No. of benign tumors	59	42	74	153	25	30	53	154
No. of malignant tumors	23	33	32	37	35	44	28	32
No. of tumors	82	75	106	190	60	74	81	186
No. of benign tumor bearers	33	22	29	45	17	24	32	45
No. of malignant tumor bearers	19	26	25	25	29	32	27	28
No. of multiple tumor bearers	20	19	28	39	14	25	20	40
No. of tumor bearing animals	42	36	39	52	37	42	44	50

Number in the table indicates the number of animals.

Non-neoplastic: Treatment-related non-tumor lesions observed in the liver were minimal to moderate hypertrophy of the centrilobular hepatocytes in males in the mid and high dose groups (100 and 300 mg/kg) (Table 34). A tendency for an increase in the incidence of eosinophilic altered cell foci was observed in both sexes in the 100 and 300 mg/kg groups. In the thyroid, a tendency for an increase in the incidence of minimal hypertrophy of the follicular cells was observed in both sexes in the 300 mg/kg group (Table 34). A tendency for an increase in the incidence of minimal to moderate pigmentation of the follicular cells was observed in both sexes in the 300 mg/kg group.

Table 34. Incidence summary of treatment-related non-tumor lesions

Sex	Male				Female				
	0	30	100	300	0	30	100	300	
Dose (mg/kg/day)	0	30	100	300	0	30	100	300	
No. of animals used	55	55	55	55	55	55	55	55	
Liver									
Hypertrophy, hepatocytic, central	(total)	0	0	9	22	0	0	0	0
	(minimal)	0	0	7	6	0	0	0	0
	(mild)	0	0	2	9	0	0	0	0
	(moderate)	0	0	0	7	0	0	0	0
Altered cell focus, eosinophilic	9	17	23	24	6	6	18	36	
Thyroid									
Hypertrophy, follicular cell	(total)	0	0	1	19	1	1	1	9
	(minimal)	0	0	1	19	1	0	0	9
	(mild)	0	0	0	0	0	1	1	0
Pigmentation, follicular cell	(total)	0	1	5	28	1	3	7	30
	(minimal)	0	1	5	23	1	2	6	25
	(mild)	0	0	0	5	0	1	1	4
	(moderate)	0	0	0	0	0	0	0	1

Number in the Table indicates the number of animals with lesion.

Neoplastic: Tumors observed at relatively high incidence (incidence of tumors of > 5% in any test groups) include hepatocellular adenoma commonly observed in both sexes in each test group, but the incidence in males in the high dose group (300 mg/kg) and in females in the mid and high dose groups (100 and 300 mg/kg) was significantly higher than that in the control group (Table 35). In addition, hepatoblastoma was observed in 1 male in the 300 mg/kg group and in 1 female in the 100 mg/kg group.

Table 35. Incidence summary of major tumors

Sex	Male				Female			
	0	30	100	300	0	30	100	300
Dose (µg/kg/day)	55	55	55	55	55	55	55	55
No. of animals used								
Bone + bone marrow, femoral								
Hemangioma	1	0	1	0	0	2	0	0
Hemangiosarcoma	0	1	0	0	1	1	0	0
Harderian gland (n=54)^b								
Adenoma, acinar cell	5	8	2	2	5	3	6	6
Carcinoma, acinar cell	0	0	0	0	0	0	0	1
Hemolymphoreticular (all sites)								
Lymphoma, multifocal	4	9	3	5	14	22	13	12
Sarcoma, histiocytic	1	3	1	1	5	2	7	4
Liver								
Adenoma, hepatocellular	205 ^{b)}	11	26	44 ^{b)}	55 ^{b)}	5	20 ^{b)}	39 ^{b)}
Carcinoma, hepatocellular	11	12	13	16	1	4	2	5
Hepatoblastoma	0	0	0	1	0	0	1	0
Hemangioma	6	3	1	1	1	2	0	0
Hemangiosarcoma	0	3	1	0	1	2	0	0
Lung (bronchus) (n=54)								
Adenoma, bronchiolo-alveolar	5	5	5	6	1	2	4	3
Carcinoma, bronchiolo-alveolar	3	3	8	4	2	2	1	2
Pituitary (n=54)								
Adenoma, anterior	0	0	0	0	1	3	1	0
Adenoma, intermediated	1	0	0	0	1	0	3	3
Skin (n=54)								
Sarcoma, spindle cell	0	0	0	0	3	0	0	0
Spleen								
Hemangioma	4	0	1	0	2	3	0	1
Hemangiosarcoma	0	0	1	0	1	3	0	1
Uterus								
Polyp, endometrial, stromal	/	/	/	/	1	2	3	2

Number in the table indicates the number of animals with respective tumor.

/: Not applicable

S: p<0.005 (significantly different from the control group for tumors with high incidence by Peto's positive trend test of all groups)

*: p<0.01 (significantly different from the control group for common tumors in pairwise comparison between each dose group and control group by Peto's test)

Toxicokinetics: The AUC_{0-24h} for R-106583 and R-138727 analyte increased with increasing dose levels at 2 weeks of administration, and these parameters did not indicate major gender differences even though those of R-138727 in females were slightly higher than those in males at 30 and 100 mg/kg (Table 36). With the progress of the administration period, the AUC_{0-24h} for R-106583 increased slightly in males at 30 mg/kg and in females in each dose group.

Table 36. Summary of TK parameters of R-106583 and R-138727

Sex	Male (n=3)			Female (n=3)		
	30	100	300	30	100	300
R-106583						
AUC _{0-24h} (µg·h/mL)						
Week 2	10.75	92.50	249.06	12.40	65.60	132.10
Month 6	22.59	116.77	244.07	21.14	67.95	173.42
Month 18	23.06	86.55	205.72	23.12	85.34	200.77
R-138727						
AUC _{0-24h} (µg·h/mL)						
Week 2	1.88	15.3	71.1	5.41	25.2	63.8
Month 6	1.50	11.3	40.4	6.44	21.9	61.8
Month 18	2.28	15.7	40.9	6.38	26.3	67.9

Discussion (mouse study):

The mouse carcinogenicity study was conducted at doses up to 300 mg/kg which yielded systemic exposures of R-138727 and R-106583, about 500-fold greater than the anticipated human exposures. The doses were adequately high in that an MTD was achieved in the 300 mg/kg groups as indicated by body weight decreases of 9 - 11% of controls. An increased incidence of hepatocellular adenoma was observed in male mice in the high dose group (300 mg/kg) and in females in the mid and high dose groups (100 and 300 mg/kg). Increase in liver weight, centrilobular hepatocellular hypertrophy, increased smooth endoplasmic reticulum and increase in the incidence of eosinophilic altered cell foci were also observed. Hepatoblastoma was observed in 1 male at the high dose (300 mg/kg) and 1 female in the mid dose (100 mg/kg). Altered cell foci are considered to be progenitor lesions from which hepatocellular neoplasia might arise and some of the benign hepatocellular neoplasia may progress to malignant hepatocellular neoplasia. Other non-tumors include hypertrophy of the thyroid follicular cells observed at the high dose (300 mg/kg). In the lung, the incidence of foamy cell accumulation tended to increase in both sexes at 30 or 100 mg/kg, and corresponded to the increased incidence of white foci at necropsy, but there were no apparent differences in morphological features between the treated and control groups. In the trachea, the incidence of globule leukocytes in the epithelium tended to increase in males at 100 mg/kg and females at 30 or 100 mg/kg, but there were no degenerative changes in the tracheal epithelium. In the mice, prasugrel enhanced the incidence of hepatocellular tumors at doses ≥ 100 mg/kg (300 mg/m²) which is approximately 190-fold greater than the anticipated human exposure levels of the major metabolite.

FDA's Statistical Analysis: This analysis showed statistically significant positive dose-response relationship in the incidence of hepatocellular adenoma, and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in both sexes. Pairwise comparisons showed statistically significantly increased incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in high dose group in males, and mid and high dose groups in females compared to their respective control.

Summary (rat and mice carcinogenicity):

In the rat, there was no evidence of treatment-related tumors in a 2 year study at dosages up to 100 mg/kg (R-106583: AUC_{0-24h} 22 μ g.h/ml), at which exposure to the primary human metabolite is about 50 times higher than that in patients receiving a daily dose of 10 mg (R-106583: AUC_{0-last} 450 ng.h/ml). In the mice, prasugrel enhanced the incidence of hepatocellular adenomas (at 100 mg/kg, R-106583: AUC_{0-24h} 85 μ g.h/ml), where exposure to the major human metabolite is about 190 times higher than the exposure at daily dose of 10 mg prasugrel (R-106583: AUC_{0-last} 450 ng.h/ml) (Section 2.6.7.: Tables 43 and 44). The sponsor considers the hepatocellular adenoma to be secondary to prasugrel-induced hepatic metabolizing enzyme-induction. However, this is unlikely because there was induction of hepatic metabolizing enzymes in the rat but no adenomas were present in the two year study. In the rat and mouse, there were incidence of spontaneous liver adenomas and carcinomas but were not enhanced by treatment with prasugrel, which rules out tumor promoter effects.

The CAC also concluded that there were no evidence of carcinogenicity.

- Appendix/Attachments: - Exec-CAC meeting minutes for protocol dose selections.
- Exec-CAC final study minutes.

2.6.6.6 Reproductive and developmental toxicology

Prasugrel on fertility and early embryonic development in rat:

Key findings: There was no significant effect of prasugrel on male or female fertility, or on early embryonic development at 300 mg/kg. At doses \geq 100 mg/kg, decrease adrenal gland, seminal vesicle/prostate gland and epididymal weights, and reduction in mean fetal weight was observed. This dosages provides 150 times higher than the major metabolite in humans (Section 2.6.7. Tabulated Summary: Table 45).

Study no.:	TRC142-024	
Conducting laboratory:	_____	
Date of study initiation:	December 21, 1994	Report date: Aug 30, 1995
GLP compliance:	Yes,	QA reports: yes (✓), no ()
Drug:	Prasugrel free base	
Doses:	30, 100 and 300 mg/kg/day,	Vehicle: Tragacanth, 0.5%
Species/strain:	— CD BR VAF rat	
Number/sex/group:	24/sex/dose group	
Route:	Oral gavage	

b(4)

Study design: Males were treated for 4 weeks prior to, and through mating, to termination. Females were treated for 2 weeks prior to, and through mating, up to Day 7 of presumed pregnancy.

Parameters and endpoints evaluated: On Day 15 of presumed pregnancy, females were sacrificed, and subjected to post mortem examination.

Results:

Mortality: There was one mortality in the male 300 mg/kg male group, and was cannibalised at Day 16 having received 15 consecutive daily doses.

Clinical signs: Bright yellow staining of the tray paper was observed under all cages of males and females treated at 100 or 300 mg/kg throughout the pre-mating treatment period. At 30 mg/kg, yellow staining was observed under all cages of females; and no yellow staining was observed under cages holding males. At 100 and 300 mg/kg, females showed dilated pupils following administration of the first dose. Pupil dilation was not apparent among males. At doses 100 and 300 mg/kg, bleeding was observed from either damaged toenails or from a small cut on the right hindlimb.

Body weight: In males, there was a significant reduction in bodyweight gain in the 100 and 300 mg/kg dose groups during the pre-mating treatment period. Among males at 30 mg/kg, there was no obvious adverse effect on bodyweight gain. In the females, there was a significant reduction in bodyweight gain in the 100 and 300 mg/kg groups compared with the control, during the two-week pre-mating treatment period and during the initial eight days of pregnancy.

Food consumption: At 300 mg/kg, cumulative food consumption of males and females during the pre-mating treatment period was significantly lower than in controls. At 100 or 30 mg/kg, there was no apparent effect of treatment on food consumption in either sex.

Necropsy: For both sexes at 30, 100 and 300 mg/kg the incidence and distribution of occasional macroscopic changes at autopsy did not indicate any obvious adverse effect of treatment.

Fertility parameters: There were no obvious adverse effects of treatment on sperm counts and motility in the left *vas deferens* and left epididymides. There were no difference in the number of dams with live young on Day 15 in all test groups and control. For all pregnant females, there were no obvious adverse effects of treatment in any of the litters. There was no adverse effect observed on parental fertility, or the early embryonic development of the conceptus.

Summary: At doses ≥ 100 mg/kg, decrease body weight and food consumption, and among males decrease adrenal gland, seminal vesicle/prostate gland, and epididymal weights were observed. There was no adverse effect on fertility or early embryonic development to implantation at 150 times higher exposure to major metabolite in humans (Section 2.6.7.: Table 45).

Prasugrel on embryo-fetal development in the rat:

Key findings: At the high dose (300 mg/kg), a dose associated with maternal toxicity, decreases in mean fetal weight were observed. However, there were no adverse effects on *in utero* survival or morphological development of the conceptus at the high dose which affords 150 times the clinical exposure (Section 2.6.7. Tabulated Summary: Table 46).

Study no.:	TRC142-025	
Conducting laboratory:	_____	
Date of study initiation:	December 22, 1994	Report date: Sept 30, 1995
GLP compliance:	Yes,	QA reports: yes (<input checked="" type="checkbox"/>) , no ()
Drug:	Prasugrel free base	
Doses:	30, 100 and 300 mg/kg/day, Vehicle tragacanth 0.5%	
Species/strain:	— CD BR VAF rat	
Number/sex/group:	24 female/dose group	
Route:	Oral gavage	

Study design: Prasugrel was administered by gavage to time-mated female rats from Day 7 to 17 of presumed pregnancy.

Parameters and endpoints evaluated: Rats were sacrificed at Day 20 of presumed pregnancy, and fetal weight and *in utero* survival was observed.

Results:

Mortality (dams): There was one death in the 100 mg/kg group on Day 20 of pregnancy with a large amount of blood in the cage.

Clinical signs (dams): At 300 mg/kg, 22/24 animals showed dilation of the pupils following administration of the first dose on Day 7 *post coitum*. Occasional instances of

clear or red/brown salivation were apparent for 11/24 animals during the last 3 days of treatment (Days 15 to 17). Bright yellow staining was apparent under all cages of animals from the morning of Day 8 until the morning following administration of the last dose (Day 18). Five animals in the high dose showed bleeding from toe, perioral region and an ulceration on the ear.

Body weight (dams): Treatment at 300 mg/kg was associated with a mean loss of 5.2 g of body weight during the first day of treatment (Days 7 to 8 of pregnancy), compared with a mean gain of 4.7 g of body weight in the control group. Thereafter, it was significantly lower than in controls to Day 14 of pregnancy. At 100 mg/kg, a marginal mean loss of body weight was recorded during the first day of treatment. At 30 mg/kg, there were no obvious adverse effects of treatment on body weight gain during pregnancy.

Food consumption (dams): At 300 mg/kg, food consumption was significantly lower than the controls during the first seven days of treatment (Days 7 to 13 *post coitum*). Thereafter, food intake was similar to the control during the remaining treatment period. At 100 mg/kg, food consumption was slightly but significantly lower than the controls during the first five days of treatment (Days 7 to 11 *post coitum*). At 30 mg/kg, there was no obvious adverse effect of treatment on food consumption.

Terminal and necroscopic evaluations: There were 2/281, 0/332, 9/299 and 1/343 malformed fetuses (2/23, 0/24, 3/23 and 1/24 litters affected) in the 0, 30, 100 and 300 mg/kg groups, respectively. Neither the type, incidence or distribution of malformations indicated any obvious adverse effect of treatment. There were no obvious effects of treatment on the number or distribution of litters or fetuses with skeletal anomalies or, on the incidence of fetuses with skeletal variants.

Offspring (malformations, variations): At 300 mg/kg, it was noted that 12 fetuses (6/24 litters) showed abnormal lobation of the liver compared with 6 fetuses (4/23 litters) in the control group. At 30 and 100 mg/kg, the number and distribution of litters and fetuses with visceral anomalies was comparable to controls. At 300 mg/kg, there was a slight but significant reduction in mean fetal weight compared with the controls which indicate maternal toxicity. The *in utero* survival and morphological development of the conceptus was unaffected. Prasugrel did not adversely affect the maintenance of pregnancy.

Summary: In rats sacrificed at Day 20 of presumed pregnancy, reduction in mean fetal weight was observed at doses > 100 mg/kg; however, there were no adverse effects on *in utero* survival. At 30 mg/kg, there were no significant adverse effects in the pregnant female or on *in utero* development of the conceptus. At 300 mg/kg, although *in utero* survival and morphological development of the conceptus appeared unaffected, there was a slight but significant reduction in mean fetal weight. The no effect level for *in utero* development of the conceptus is 100 mg/kg/day (150 times the human metabolite exposure). Prasugrel did not adversely affect the maintenance of pregnancy. The NOAEL for general toxicity to the pregnant female is considered to be 30 mg/kg/day (Section 2.6.7. Tabulated Summary: Table 46).