

**Body weights:** No noticeable changes were recorded in both sexes of any experimental group including the control throughout the treatment and recovery period.

**Food consumption:** No noticeable changes were recorded in both sexes of any experimental group including the control throughout the treatment and recovery period.

**Hematology:** Low MCHC value for males of the 4 mg/kg group in month 6 of treatment, and low APTT values for males of the 4 and 20 mg/kg groups were observed.

**Clinical chemistry:** Animals receiving 20 mg/kg showed increased ALP (> 2-fold), decreased total cholesterol levels (by 20%) and proliferation of the smooth surfaced endoplasmic reticulum in hepatocytes.

**Urinalysis:** Positive occult blood reaction was recorded in 1 to 3 females of any group (except 4 mg/kg group) including the control. Red blood cells in the urinary sediment were a concomitant finding.

**Gross pathology:** Examination of hepatocytes revealed proliferation of smooth-surfaced endoplasmic reticulum which may be due to an activation of drug metabolism enzymes induced by prasugrel.

**Histopathology:** Adequate battery: yes (√), no ( ); Peer review: yes (√), no ( ). Treatment-related changes were seen in the liver of animals in the high dose group (20 mg/kg). 2 males in the 20 mg/kg group exhibited slight to mild centrilobular hepatocytic hypertrophy and hypertrophic cells with ground glass appearance.

**Toxicokinetics:** The AUC of the human major metabolite R-106583 was about 1.5-fold higher than that of metabolite in human (Table 16).

Table 16: Prasugrel metabolites in the dog and projected human plasma exposure multiples

Species Dose	R-138727		R-106583		Prasugrel	
	AUC <sub>0-24</sub> µg•h/mL	MOS <sup>a</sup>	AUC <sub>0-24</sub> µg•h/mL	MOS <sup>a</sup>	Dose mg/m <sup>2</sup>	MOS <sup>a</sup>
Human <sup>b</sup> 10 mg/day	0.0545	-	0.299	-	7.4	-
Dog <sup>d</sup> 4 mg/kg, M	1.01	19	0.445	1.5	80	11
4 mg/kg, F	1.42	26	0.650	2.2	80	11

<sup>a</sup> AUC<sub>0-24</sub> in animals at the NOAEL/AUC<sub>0-24</sub> in humans, <sup>b</sup> mean AUC<sub>0-last</sub>

<sup>d</sup> Toxicokinetics determined on Day 28 at the NOAEL for chronic toxicity.

**Summary:** In the dog, treatment-related changes were observed in the liver consisting of centrilobular hepatocytic hypertrophy, ground glass-like appearance change of cytoplasm, proliferation of smooth surfaced endoplasmic reticulum and elevation of ALP activity. Histopathological liver changes were thought to be a phenomenon accompanying the induction of drug metabolizing enzymes. The NOAEL of prasugrel in the dog study was considered to be 4 mg/kg, which affords about 1.5-fold higher exposure of the circulating metabolite of R-106583 in human dosed 10 mg/day (Section 2.6.7. Tabulated Summary: Table 42).

## 2.6.6.4 Genetic toxicology

### In vitro bacterial mutation assay (Ames):

**Key findings:** Prasugrel was non-mutagenic in an *in vitro* bacterial reverse mutation assay.

**Study no.:** 93-0067; TR140-103  
**Conducting laboratory:** \_\_\_\_\_  
**Date of study initiation:** June 11, 1993      **Report date:** Aug 10, 1999  
**GLP compliance:** Yes,      **QA reports:** yes (√), no ( )  
**Drug:** Prasugrel free base

b(4)

#### **Methods:**

**Strains/cell line:** *Salmonella typhimurium* tester strains (TA1535, TA1537, TA98, TA100) and *E. Coli* (WP2uvrA).

**Doses used in study:** 200, 500, 1000, 2000 and 5000 µg/plate

**Negative control:** DMSO vehicle

**Positive control:** Bezo(a)pyrene (BaP 5 µg/plate), 2-aminoanthracene (2AA, 2 µg/plate)

**Incubation and sampling times:** The agar pate was cultivated for 48 hrs at 37° C, the resulting revertant colonies were scored by an automated colony counter.

**Results:** No cytotoxic effects were observed at 5000 µg/plate. Prasugrel was non-mutagenic in the bacterial reverse mutation assay (Table 17). Positive controls (benzo(a)pyrene, 5 µg/plate) showed increase in revertant colony incidence.

Table 17. Bacterial mutation assay with (+S9) and without (-S9) metabolic activation.

Prasugrel (µg/plate)	- S9					+ S9				
	TA98	TA100	TA1535	TA1537	WP2uvrA	TA98	TA100	TA1535	TA1537	WP2uvrA
200	13	111	6	2	23	19	142	6	3	30
500	12	114	6	1	25	23	129	7	3	28
1000	13	109	6	2	22	14	123	7	4	32
2000	11	95	6	3	32	23	111	7	4	26
5000	17	100	5	1	28	16	104	7	2	31
Vehicle Control	13	119	6	3	22	16	113	8	5	33
Positive Control	488*	540*	152*	1551*	329*	176*	649*	234*	139*	660*

Revertant cells: \* = p<0.05

### In vitro chromosome aberration assay:

**Key findings:** Prasugrel was non-clastogenic in an *in vitro* Chinese hamster lung chromosomal aberration assay.

**Study no.:** 94-0002; TR141-009  
**Conducting laboratory:** \_\_\_\_\_  
**Date of study initiation:** Dec 16, 1993      **Report date:** Aug 10, 1999  
**GLP compliance:** Yes,      **QA reports:** yes (√), no ( )  
**Drug:** Prasugrel free base

b(4)

#### **Methods:**

**Strains/species/cell line:** Chinese hamster lung cell line

**Concentrations:** up to 0.488 mM (+ S9) and 0.833 mM (-S9).

**Basis of dose selection:** Prasugrel concentrations were based on reduction in mitotic indices in cells with and without metabolic activation (Table 18).

Table 18. Percent reduction/increase in mitotic index in CHL cells treated for 6 - 18 hrs

+ S9 mix		- S9 mix	
Prasugrel (mM)	Mitotic index (%)	Prasugrel (mM)	Mitotic index (%)
0	100	0	100
0.191	96	0.247	179
0.305	99	0.370	188
0.488	40	0.556	96
0.781	43	0.833	59
1.25	36	1.25	0
BaP	35	BaP	79
		MMC (24 h)	163

**Negative controls:** DMSO vehicle

**Positive controls:** Mitomycin C (MMC, 5 µg/ml) or benzo(a)pyrene (BaP, 10 µg/ml)

**Incubation and sampling times:** Treatment periods were 24 hours in the absence of metabolic activation (-S9), and 6-18 hours in the presence of metabolic activation (+S9).

**Results:** There were no increased incidence of cells with abnormal chromosomes in the presence or absence of metabolic activation at concentrations of 0.488 and 0.833 mM of prasugrel, respectively, which caused mitotic reduction by about 50% (Table 17). The positive control groups treated with mitomycin C (MMC, 5 µg/ml) or benzo(a)pyrene (BaP, 10 µg/ml) showed marked clastogenic responses (Table 19).

Table 19. Percent increase in chromosomal aberration in CHL cells treated with prasugrel

+ S9 mix			- S9 mix		
Incubation (hr)	Prasugrel (mM)	Aberrant cells (%)	Incubation (hr)	Prasugrel (mM)	Aberrant cells (%)
6-18	0	0.5	24	0	0.5
6-18	0.122	0	24	0.062	0.5
6-18	0.244	1	24	0.122	0
6-18	0.488	0.5	24	0.244	0
6-18	BaP	18*	6-18	0.417	0
			6-18	0.833	1.5
			6-18	BaP	0
			24	MMC	20*

\* = p<0.05, vs. control

### In vivo micronucleus assay in mice:

**Key findings:** No significant increase in the incidence of micronucleated polychromatic erythrocytes were observed in the *in vivo* mouse micronucleus assay

**Study no.:** 95-0023; TR142-054

**Conducting laboratory:** \_\_\_\_\_

**Date of study initiation:** March 15, 1995

**Report date:** Aug 10, 1999

**GLP compliance:** Yes,

**QA reports:** yes (✓), no ( )

**Drug:** Prasugrel free base

**Strains/species:** ICR mice, male

**Doses used in definitive study:** 400, 800 and 1600 mg/kg *i.p.* injection

b(4)

Basis of dose selection: MTD.

Negative controls: Tragacanth gum/saline 0.5%

Positive controls: Mitomycin C (MMC)

Incubation and sampling times: Blood was collected from the mouse tail 48 hours after *i.p.* injection to assess micronucleated polychromatic erythrocytes. 4/6 animals at 1600 mg/kg died, and were replaced with a group of 1000 mg/kg.

**Results:** On autopsy at 72 hours after the administration, no residual material was observed within the intraperitoneal cavity. There was no significant increase in the incidence of micronucleated polychromatic erythrocytes in comparison with that of vehicle treated mice (Table 20). The micronucleus incidence in the MMC treatment group as a positive control markedly increased to as high as 1.44% in comparison to 0.14% in the vehicle control group.

Table 20. Micronucleated reticulocytes in blood after 48 hrs of *i.p.* injection of prasugrel to mice

<u>Treatment</u>	<u>Dose (mg/kg)</u>	<u>Polychromatic erythrocytes (%)</u>	<u>Micronucleated reticulocytes (%)</u>
Vehicle	-	3.7 ± 0.6	0.14 ± 0.12
Prasugrel	400	3.0 ± 0.4	0.16 ± 0.09
"	800	2.7 ± 0.3	0.14 ± 0.12
"	1600	2.6 ± 0.2	0.18 ± 0.04
<u>Mitomycin C</u>	<u>0.5</u>	<u>2.8 ± 0.4</u>	<u>1.44 ± 0.36*</u>

\* = p<0.05, vs. control

Summary (Genetic toxicology):

No genetic toxicity was observed for prasugrel in standard tests for mutagenicity or clastogenicity that included an *in vitro* bacterial mutation test, and Chinese hamster lung chromosomal aberration assay, and an *in vivo* mouse micronucleus assay for clastogenicity.

## 2.6.6.5 Carcinogenicity

### 24-month carcinogenicity study of prasugrel in rats:

**Key findings:** Both the primary reviewer and the carcinogenicity Assessment Committee (CAC) concluded that there was no evidence of treatment-related tumors in a 2 year rat study with prasugrel exposures ranging to about 50 times the recommended therapeutic exposures of primary human metabolite (Section 2.6.7. Tabulated Summary: Table 43).

Adequacy of carcinogenicity study and appropriateness of test model: All organs and tissues were fixed and preserved in phosphate buffered 10% formalin. All organs/tissues were embedded in paraffin, sectioned, stained with hematoxylin and eosin (H&E), and examined histopathologically. Dosages and survival rates were judged to be adequate.

Evaluation of tumor findings: Dose-related trend as well as pairwise comparison between the control group and each treated group was evaluated using survival-adjusted test for tumors with high incidence or using exact test for those with low incidence. For

incidental tumors, the analysis intervals were: weeks 0 through 52, 53 through 78, 79 through 92, and 93 until sacrifice. Analysis of positive trend in incidence were conducted at the significance levels of 0.005 (one tailed-level) for common tumors and 0.025 (one tailed-level) for rare tumors. Pairwise comparison were conducted at the significance levels of 0.01 (one tailed-level) for common tumors and 0.05 (one tailed-level) for rare tumors. Common tumors were defined as those with a historical incidence in controls of  $\geq 1\%$  and rare tumors as  $< 1\%$ .

<b>Study no.:</b>	B-5166	
<b>Conducting laboratory:</b>	_____	
<b>Date of study initiation:</b>	9/12/2003	<b>Report date:</b> 8/23/2006
<b>GLP compliance:</b>	Yes,	<b>QA report:</b> yes ( <input checked="" type="checkbox"/> ) , no ( <input type="checkbox"/> )
<b>Drug:</b>	Prasugrel HCl	
<b>CAC concurrence:</b>	Yes, 7/22/2003 (Appendix/Attachments)	
<b>Doses:</b>	10, 30 and 100 mg/kg/day, Vehicle: Tragacanth 0.5%	
<b>Basis of dose selection:</b>	MTD	
<b>Species/strain:</b>	F344 _____ Fisher) rat	
<b>Number/sex/group (main study):</b>	n=55/sex/group	
<b>Route:</b>	Oral gavage	

**Frequency of dosing:** The dosing suspensions were administered daily by oral gavage using a flexible stomach tube, at the dosage volume of 5 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=5/sex/group).

**Age:** Started at 4 weeks of age (weight: 107 - 130 g males, 89 - 109 g females).

**Animal housing:** Animals were housed individually in cages under conditions of temperature at  $23\pm 3^{\circ}\text{C}$ , relative humidity at  $50\pm 20\%$ , 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.

b(4)

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

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

## Results

**Survival rate:** In males, total number of deaths in the 0, 10, 30 and 100 mg/kg groups was 9, 11, 12 and 6, respectively, the survival rate was 83, 80, 78 and 89%, respectively (Table 21). In the females, total number of deaths in the 0, 10, 30 and 100 mg/kg groups was 17, 15, 12 and 10, respectively, the survival rate was 69, 73, 78 and 82%, respectively, and no effect of the test article on the survival rate was observed.

Table 21. Summary of mortality and survival rate

Sex	Male				Female			
	0	10	30	100	0	10	30	100
Dose (mg/kg/day)								
No. of animals used	55	55	55	55	55	55	55	55
No. of deaths								
1-26 week	0 <sup>a)</sup>	0	0	0	0	0	0	0
1-52 week	0	0	0	0	0	1	0	0
1-78 week	2	1	4	2	0	2	1	1
1-104 week	9	11	12	6	17	15	12	10
No. of survivors	46	44	43	49	38	40	43	45
Survival rate (%)	83.6	80.0	78.2	89.1	69.1	72.7	78.2	81.8

a): Cumulative number of animals that died including the animals that were sacrificed as moribund.  
There were no statistically significant differences between the control group and any dose group.

**Clinical signs:** Excretion of fluorescent yellow urine was observed in both sexes in the high dose group (100 mg/kg), but no toxic signs were observed. No obvious treatment-related abnormalities in the clinical signs were observed at relatively high incidence (> 5 animals) in any dose group (Table 22). The excretion of colored urine was considered to be due to excretion of metabolites of the test article into the urine.

Table 22. Summary of major clinical signs incidence

Sex	Male				Female			
	0	10	30	100	0	10	30	100
Dose (mg/kg/day)								
No. of animals used	55	55	55	55	55	55	55	55
No. of deaths	9	11	12	6	17	15	12	10
Fluorescent yellow urine	0 <sup>a)</sup> (0) <sup>b)</sup>	0(0)	0(0)	55(6)	0(0)	0(0)	0(0)	55(10)
Decrease, spontaneous movement	5(5)	5(4)	6(6)	3(3)	12(12)	12(12)	9(9)	7(7)
Bradypnea	5(5)	9(9)	7(7)	5(5)	11(11)	11(11)	9(9)	7(7)
Hypothermia	2(2)	5(5)	1(1)	5(5)	3(3)	4(4)	3(3)	4(4)
Pale, skin	1(0)	8(5)	4(4)	4(4)	10(9)	7(6)	8(6)	8(6)
Opacity, eyeball	6(1)	10(1)	5(1)	12(2)	4(0)	6(0)	6(1)	4(0)
Hemorrhage, vagina	/	/	/	/	5(4)	7(4)	9(3)	7(4)

a): Total number

b): Numbers in parentheses indicate the number of animals that died or were sacrificed as moribund with respective signs.

**Body weights:** In the males and females (10 and 30 mg/kg), no treatment-related changes were observed (Table 23). In the high dose group (100 mg/kg), significantly lower values were observed throughout the administration period and the mean body weight at the end of the administration period was lower (males by 11%, females by 13%) than that of the control group.

Table 23. Summary of body weight at termination

Sex	Male			Female		
	10	30	100	10	30	100
Dose (mg/kg/day)	10	30	100	10	30	100
No. of animals	45	43	49	41	43	45
Mean body weight (week 104)	N	N	-11%**	N	N	-13%**
Body weight gain (week 0-104)	N	N	-16%	N	N	-21%

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 dark red foci in males in the high dose group (100 mg/kg) (Table 24). In the lung, a tendency for an increase in the incidence of white foci was observed in males in the 100 mg/kg and in females in the mid and high dose groups (30 and 100 mg/kg).

Table 24. Summary of incidence of major gross lesions

Sex	Male				Female			
	0	10	30	100	0	10	30	100
Dose (mg/kg/day)	55	55	55	55	55	55	55	55
No. of animals used	55	55	55	55	55	55	55	55
General description								
Discoloration, skin, pale	1	6	4	4	7	6	5	6
Undernourishment	4	1	5	4	5	4	4	6
Eye								
Opacity	6	10	5	12	4	6	6	4
Liver								
Large	5	3	0	0	1	1	0	0
Focus, dark red	23	24	33	42	31	36	39	40
Focus, white	9	13	5	12	14	11	17	16
Irregular surface	6	5	2	0	5	6	1	0
Hepatodiaphragmatic nodule	10	6	6	5	12	11	6	10
Lung (bronchus)								
Nodule	2	4	4	3	0	0	4	5
Focus, dark red	1	7	2	1	0	1	2	1
Focus, white	0	5	3	14	3	7	13	29
Pancreas								
Nodule	7	10	6	7	0	1	2	2
Pituitary								
Nodule	7	7	5	5	9	12	15	11
Focus, dark red	10	8	9	4	12	4	9	12
Skin								
Nodule	6	8	10	10	5	8	8	6
Spleen								
Large	9	8	3	2	14	11	6	5
Stomach								
Focus, dark red, glandular stomach	6	5	6	2	6	8	1	5
Focus, raised, glandular stomach	2	5	3	2	0	0	1	1
Testis								
Focus, white	45	43	43	45	/	/	/	/
Thyroid								
Nodule	5	1	8	2	4	2	3	5
Uterus								
Nodule	/	/	/	/	9	5	11	7
Polyp	/	/	/	/	17	16	15	23
Cyst, endometrial	/	/	/	/	11	11	7	14

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

/: Not applicable

**Histopathology:** There were no obvious treatment-related increase in the number of tumors or tumor bearers observed in either sex group (Table 25).

Table 25. Number of tumors and tumor bearers

Sex	Male				Female			
	0	10	30	100	0	10	30	100
Dose (mg/kg/day)	0	10	30	100	0	10	30	100
No. of animals used	55	55	55	55	55	55	55	55
No. of benign tumors	147	148	142	128	66	65	62	81
No. of malignant tumors	20	23	21	10	36	27	30	17
No. of tumors	167	171	163	138	102	92	92	98
No. of benign tumor bearers	52	52	51	52	37	39	37	44
No. of malignant tumor bearers	18	21	19	9	31	21	25	15
No. of multiple tumor bearers	48	48	45	47	30	30	28	30
No. of tumor bearing animals	54	54	55	55	43	44	46	47

Number in the Table indicates the number of animals

**Non-neoplastic:** Treatment-related non-tumor lesions observed in the liver were minimal diffuse hypertrophy of the hepatocytes in both sexes in the high dose group (100 mg/kg) (Table 24). The number of animals with eosinophilic altered cell foci graded mild tended to be slightly higher in males in the 100 mg/kg group. In the lung, a tendency for an increase in the incidence of minimal or mild accumulation of foamy cells was observed in both sexes in the 30 and 100 mg/kg groups (Table 26). In the trachea, a tendency for an increase in the incidence of minimal or mild globule leukocytes in the epithelium was observed in males in the 100 mg/kg group, and females in the 30 and 100 mg/kg groups. Other lesions were considered to be incidental from their incidence and pathological characteristics.

Table 26. Summary of incidence of treatment-related non-tumor lesions

Sex	Dose (mg/kg/day)	No. of animals used	Male				Female				
			0	10	30	100	0	10	30	100	
<b>Liver</b>											
Hypertrophy, hepatocytic, diffuse			(total)	0	0	0	20	0	0	0	15
			(minimal)	0	0	0	20	0	0	0	15
Altered cell focus, eosinophilic			(total)	43	41	44	51	27	31	31	36
			(minimal)	43	39	42	40	26	30	30	35
			(mild)	0	2	2	11	1	0	1	1
			(moderate)	0	0	0	0	0	1	0	0
<b>Lung</b>											
Accumulation, foamy cell			(total)	0	3	8	15	7	9	15	35
			(minimal)	0	3	7	15	7	9	14	32
			(mild)	0	0	1	0	0	0	1	3
<b>Trachea</b>											
Globule leukocyte, epithelial			(total)	0	0	1	15	1	3	9	22
			(minimal)	0	0	1	12	1	3	9	21
			(mild)	0	0	0	3	0	0	0	1

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

**Neoplastic:** There were no treatment-related tumors observed at relatively high incidence (incidence of > 5%) (Table 27).

Table 27. Summary of incidence of major tumors

Sex	Male				Female			
	0	10	30	100	0	10	30	100
Dose (mg/kg/day)								
No. of animals used	55	55	55	55	55	55	55	55
<b>Adrenal</b>								
Pheochromocytoma	3	2	3	0	3	0	2	3
Pheochromocytoma, malignant	2	2	2	2	2	0	0	0
<b>Hemolymphoreticular (all sites)</b>								
Leukemia, large granular lymphocytic	8	8	3	2	14	13	6	1
<b>Liver</b>								
Adenoma, hepatocellular	2	4	0	1	0	0	0	0
<b>Lung</b>								
Adenoma, bronchiolo-alveolar	2	3	1	1	1	0	3	3
Carcinoma, bronchiolo-alveolar	0	1	1	1	0	0	0	0
<b>Mammary gland</b>								
Adenoma	0	0	0	0	1	1	0	0
Adenocarcinoma	0	1	0	0	1	2	2	1
Fibroadenoma	1	0	1	0	2	4	6	3
<b>Pancreas</b>								
Adenoma, islet cell	8	8	8	9	1	2	2	2
Carcinoma, islet cell	0	0	1	0	0	0	0	0
<b>Mesothelium</b>								
Mesothelioma, malignant	4	3	1	1	0	0	0	0
<b>Pituitary</b>								
Adenoma, anterior	11	13	18	7	17	15	17	17
Carcinoma, anterior	0	0	0	0	0	0	1	1
<b>Prostate</b>								
Adenoma	11	9	6	4	/	/	/	/
<b>Skin</b>								
Fibroma	4	2	4	5	1	0	1	2
Fibrosarcoma	0	0	0	0	0	1	0	0
<b>Testis</b>								
Leydig cell tumor	48	50	45	47	/	/	/	/
<b>Thyroid</b>								
Adenoma, C cell	13	9	11	10	7	7	4	9
Carcinoma, C cell	2	1	5	0	4	5	3	4
<b>Uterus</b>								
Polyp, endometrial, stromal	/	/	/	/	15	19	18	27
Adenoma	/	/	/	/	2	2	1	2
Adenocarcinoma	/	/	/	/	7	4	11	8

Number in the table indicates the number of animals with respective tumor. There were no significant differences in the incidence of any tumor by positive trend test of all groups using Peto's or exact test. Also there were no significant differences in the incidence of any tumor by pairwise comparison between the control group and each dose group using Peto's or exact test.

**Toxicokinetics:** The AUC<sub>0-24h</sub> for R-106583 and R-138272 analyte increased with increasing dose levels at one month, and these parameters did not indicate gender differences even though those in females were slightly higher than those in males except at dose level of 10 mg/kg (Table 28). With the progress of the administration period, the AUC<sub>0-24h</sub> for both analytes increased slightly.

Table 28. Summary of TK parameters of R-106583 and R-138272

Sex	Male (n=3)			Female (n=3)		
	10	30	100	10	30	100
Dose (mg/kg/day)						
<b>R-106583</b>						
AUC <sub>0-24h</sub> (µg·h/mL)						
Month 1	3.62	9.48	16.54	2.79	11.15	29.75
Month 6	2.78	6.71	22.82	5.24	9.59	47.55
Month 18	4.09	7.33	22.17	4.22	18.34	43.34
<b>R-138272</b>						
AUC <sub>0-24h</sub> (µg·h/mL)						
Month 1	1.65	4.57	17.5	3.99	11.5	34.3
Month 6	1.85	8.39	29.1	5.89	14.8	51.7
Month 18	5.05	13.8	57.9	6.76	28.1	58.9

Number in the table indicates the mean value.

**Discussion (rat study):**

The rat carcinogenicity study was conducted at doses up to 100 mg/kg which yielded systemic exposures of R-138727 and R-106583 up to 1000- and 50-fold, respectively, higher than the anticipated human exposures from daily dose of 10 mg prasugrel (100-fold on a mg/m<sup>2</sup> basis). The doses were adequately high in that an MTD was achieved in the 100 mg/kg groups as indicated by body weight decreases of 11 - 13% of controls. Prasugrel neither decreased the survival rate nor induced any excess specific tumor or non-tumor death. Necropsy revealed treatment-related non-tumor lesions in the liver, lung and trachea. In the liver, diffuse hypertrophy of the hepatocytes was observed in both sexes in the high dose group (100 mg/kg) and increased severity of eosinophilic foci in the liver was observed in males in the 100 mg/kg group, however there was no evidence of malignant tumors. In the lung, the incidence of foamy cell accumulation tended to increase in both sexes in the mid and high dose groups (30 and 100 mg/kg), and the incidence of globule leukocytes in the tracheal epithelium tended to increase in males in the 100 mg/kg group and females in the 30 and 100 mg/kg groups. Prasugrel did not induce treatment-related excess tumors in any of the organs/tissues at dosages up to 100 mg/kg/day (600 mg/m<sup>2</sup>).

*FDA's Statistical Analysis:* Reviewer's findings indicate that the tests showed no statistically significant dose-response relationship or differences between the control and any of the treated groups in survivals across treatment groups in either sex.

**24-month carcinogenicity study of prasugrel in mice:**

**Key findings:** There was an increased incidence of tumors (hepatocellular adenomas) in mice exposed for 2 years to high doses (190 times human exposure) (Section 2.6.7.: Table 44).

**Adequacy of carcinogenicity study and appropriateness of test model:** All organs and tissues were fixed and preserved in phosphate buffered 10% formalin. All organs/tissues were embedded in paraffin, sectioned, stained with hematoxylin and eosin (H&E), and examined histopathologically. Dose-range tested was considered adequate based on the exposure levels and body weight reductions.

**Evaluation of tumor findings:** Increasing trend of incidence to dose level and pairwise comparison between the control group and each dose group was evaluated using survival-adjusted test for tumors with high incidence or using exact test for those with low incidence. For incidental tumors, the analysis intervals were: weeks 0 through 52, 53 through 78, 79 through 92, and 93 till termination of the live phase. Analysis of positive trend in incidence were conducted at the significance levels of 0.005 for common tumors and 0.025 for rare tumors (one tailed-level). Pairwise comparison were conducted at the significance levels of 0.01 for common tumors and 0.05 for rare tumors (one tailed-level). Common tumors were defined as those with a historical incidence in controls of  $\geq 1\%$ , and rare tumors as  $< 1\%$ .

Study no.: B-5167

Conducting laboratory: \_\_\_\_\_

Date of study initiation: 10/1/2003

Report date: 8/23/2006

b(4)