4. Hematology Changes: A decrease of eosinophils counts were seen in treatment related manner in animals included in palonosetron treatment groups (eosinophil counts were 0.17 to $0.22X10^9$/l in males and were 0.12, 0.14, 0.13, 0.14 and $0.06X10^9$/l in females belonging 2 control and 3 treatment study groups. The differences were only of statistical importance.

5. Toxicokinetic/Plasma concentration Estimation: The peak plasma concentrations on day 1 were less than the concentrations seen on week 26, 52, 78 and 104. The steady state was not reached on day 1. The increase in peak plasma concentrations of the compound was linear but non-dose proportional. The plasma concentrations of the compound were more in females than males. On week 26, the plasma concentrations (AUC values) were 136.9 and 308.2 times the AUC value in man reported by sponsor in a study at the suggested clinical dose of 5 ug/kg. The pharmacokinetic data of the study animals are shown in the following tables. The half-lives of the palonosetron in males included in high dose treatment group were estimated to be 1.5, 2.2 and 2.1 hr on study weeks 26, 52 and 78 (not calculated for study day 1 and week 104). The half-life of the compound in females was more variable as it was 0.8 to 4.2 hr on study week 26, 0.8 to 2.4 hr on week 52 and 78. The plasma concentrations (Cmax and AUC values) of the compound in male and female rats are shown below (sponsor's table)

TABLE 21

Pharmacokinetic parameters of Palonosetron on Day 1 and during Weeks 26, 52, 78 and 104 of 104-Week Rat Carcinogenicity Study[1]

a. Cmax (ng/ml)

Sex	Doses	Cmax				
M	(mg/kg/day)	Day 1	Wk26	Wk 52	Wk 78	WK 104
	15	19.48	253.2	99.8	119.6	120.3
	30	153.4	593.3	212.8	557.8	276.9
	60	427.3	1744.7	1293.7	1521.2	1117.5
F	15	25.90	119.7	392.7	350.6	181.4
	45	141.2	718.7	1224.6	1180.7	662.8
	90	702.8	1645.2	2349.7	1288.0	2014.0

b. $AUC_{(0\text{-}24hr)}$ (ng.h/ml)

Sex	Doses	$AUC_{(0\text{-}24hr)}$ (ng.h/ml)				
M	(mg/kg/day)	Day 1	Wk26	Wk 52	Wk 78	WK 104
	15	38.8	195.0	215.3	462.6	311.5[a]
	30	361.7	372.1	1088.5[a]	1606.6	1766.8
	60	1402.0	4078.4	6139.5	6294.8	4968.0[b]
F	15	39.3	211.3	662.4	624.8	275.0[a]
	45	479.6	2758.8	3308.4	3391.4	4162.3[a]
	90	2511.2	9185.3	14933.3	6441.7	9537.2[a,c]

Cmax values calculated from 3 animals; except [a]2 animals; $AUC_{(0\text{-}24hr)}$ values calculated from 18 samples, except [a]17 samples, [b]15 samples, c = samples taken during week 103; [1] = 65 of rats/group

At the peak levels, the metabolite RS-17825-007 levels were present in a linear but in a non-dose proportional manner within 0.25 to 1 hr post dosing of palonosetron in mid and high dose treatment groups. AUC values of the metabolite from study week 26 to 104 were similar indicating that the compound and metabolite were not accumulated after the repeat administration of the compound. The metabolite to compound ratio was higher after repeat dosing than the single dose of the compound and the half life of the compound at different intervals were not estimated from the data. The pharmacokinetic profile of the metabolite is tabulated below (tables taken from sponsor submission):

TABLE 22

Pharmacokinetic parameters of Rs-17825-007 on Day 1 and during Week 26, 52, 78 and 104 of 104-Week carcinogenicity Study in Rats[1]

Sex	Doses	Cmax (ng/ml)				
	(mg/kg/day)	Day 1	Wk26	Wk 52	Wk 78	WK 104
M	15	BLQ	BLQ	11.5	14.0	BLQ
	30	BLQ	43.1	43.9	55.4	18.7
	60	32.4	117.8	55.5	60.5	53.2
F	15	BLQ	BLQ	22.4	18.4	BLQ
	45	BLQ	53.1	77.3	91.2	38.4
	90	56.33	93.8	96.3	55.9	59.3

b. $AUC_{(0\text{-}24hr)}$ (ng.h/ml)

Sex	Doses	$AUC_{(0\text{-}24hr)}$ (ng.h/ml)				
	(mg/kg/day)	Day 1	Wk26	Wk 52	Wk 78	WK 104
M	15	a	a	a	a[a]	a
	30	19.4	234.6	208.8	80.5	50.7
	60	90.2	669.3	353.4	360.4	258.3
F	15	a	a	a	a	a
	45	15.5[b]	200.7	157.4	292.9	160.2[b]
	90	298.6	630.9	671.7	305.4	337.4[bc]

Cmax values calculated from 3 animals; except [a]2 animals; [b]sample taken during week 103, [a] $AUC_{(0\text{-}24hr)}$ values not calculated, $AUC_{(0\text{-}24hr)}$ values calculated from 18 samples, except [b]17 samples, c = samples taken during week 103; [1] = 65 of rats/group

Orally administered palonosetron produced a dose related but non-proportional plasma peak concentration from low to high doses of the study. The estimated half lives was short, i.e., from 1.5 to 2.2 hr in males and 0.8 to 4.2 hr in females during the study as shown in the table above. There was no evidence of accumulation of the compound during the study. The study indicated that the exposure of the compound in female was higher than male animals during the study.

6. **Organ Weights Changes**: The absolute weight of liver was increased by 24.0 and 23.0% in males and females and, adrenal weight was increased by 37.5% and 30.9% in males and females included in high dose treatment group. The mean absolute weight of lung/bronchi and spleen were increased by 8.4 and 46.0% among males of high dose treatment group. The absolute weight of spleen of the animals of high dose treatment group was increased by 33.1 and 21.3% in males and females, respectively. The absolute weights of salivary glands and testes in males of high dose treatment group testes were lower than control animals by 12.2 and 56.3%, respectively. The absolute weight of ovaries was decreased in a treatment related manner, i.e., 70.5, 72.5 and 71.6% among females of low, mid and high dose treatment groups, respectively. The mean relative weight (in relation to body weight) of liver was increased by 36.8 and 56.1% in male and female of high dose treatment group and, uterus + cervix relative weight was reduced by 1.7, 2.32 and 2.5 times than the weight of the tissues of the control group animals.

7. **Physical Examination/Ophthalmoscopic Changes**: These changes were not observed during the study.

8. **Gross Pathology Changes**: At sacrifice, an increase in the incidences of dark areas in adrenals was seen in 2, 0, 1, 4 and 8 males and, 9, 11,15, 19 and 15 females included in 0, 0, low, mid and high dose treatment groups, respectively. Enlarged adrenal was seen in 2 males of high dose treatment group. Small epididymides was seen in 0, 0, 2, 1 and 11 males of control 1, control 2, low, mid and high dose treatment groups, respectively. The enlarged kidneys were reported in only 2, 0, 0, 1 and 5 males of control 1, control 2, low, mid and high dose treatment groups, respectively. The flaccid testes were seen in 7, 10, 6, 5 and 42 males, testicular fluid in subscapsular region in 2, 0, 0, 1 and 11 males, small testes in 0, 0, 3, 0 and 18 in males and, blue colored testes in 0, 0, 2, 3 and 9 males were reported in of control 1, control 2, low, mid and high dose treatment groups, respectively. Enlarged and swollen liver was seen 15 males and 16 females of high dose treatment group. Only a trend of an increase of mammary masses wee seen in both sees of animals. These and the other pathological findings noted in the animals are shown in the following table.

TABLE: Pathological Changes in Organs/Tissues of Rats*

Abnormality		Treatment Groups (male/female;mg/kg/day)				
		0/0	0/0	15/15	30/45	60/90
Dark Adrenal	M	2	0	1	4	8
	F	9	11	15	19	15
Enlarged Adrenal	M	0	0	0	0	6
	F	1	0	2	1	1
Epididymides small	M	0	0	2	1	11
Epididymides swollen	M	0	0	0	0	3
Enlar. Kidneys	M	2	1	2	1	7
	F	0	0	0	0	2
Liver Swollen	M	6	4	5	4	15
	F	11	7	13	11	16
Mammary Gland Mass	M	4	2	6	6	9
	F	25	21	24	31	33

Testes Flaccid		7	10	6	5	42
Testes Subscap. Fluid		2	0	0	1	11
Axill.Lymph Node Mass	M	5	3	8	6	15
	F	1	3	1	2	1
Mandibulr Lymph Node	M	1	1	0	1	4
	F	1	0	1	1	6
Pancreat. Lymph Node	M	0	1	2	3	8
Masses	F	0	0	1	1	0
Skin Masses Present	M	8	5	13	12	17
	F	4	5	1	10	12

*= 65/sex/group

9. **Histopathological Changes**:

a. **Non-Neoplastic Changes**: a. Males: Epididymal hypospermia, the absence of colloid from seminal vesicle and testicular tubular germinal epithelial degeneration were seen in higher incidences ($p<0.05 - 0.005$) than in control group animals. A significant increase in the incidences of progressive senile renal nephropathy ($p<0.05$) were seen in males of high dose treatment group (see table). Sinus erythrocytes and erythrophagocytosis in mesenteric lymph node were present in slightly higher incidences in males of the high dose group than control group. A dose related increase in the incidents of accumulation of alveolar macrophages of lung was seen in treatment groups males. The degeneration of testicular tubular germinal epithelium was noted in high dose treatment group (60 Vs 14-16 in control group). The incidences of epithelial hyperplasia of thymus and thymus cysts were high among males of high dose group animals. The epidermal hyperplasia of slight to moderate nature was present in mid and high dose treatment groups (see table below).

b. Females: Increased incidences of adrenal cortical vacuolation were seen in females of mid and high dose treatment groups animals, i.e., 6 males in each of mid and high dose treatment group, respectively (Vs 2 in control group). The incidences of adrenal medullary hyperplasia, chronic renal nephropathy (senile) were higher than control in females of high dose treatment group. The focal medullary hyperplasia was noted in 8 and 11 males and females of high dose treatment group. In mesenteric lymph nodes, sinus erythrocytes and erythrophagocytosis were reported in higher incidences in high dose treated animals than control females. The accumulation of alveolar macrophages in lung was noted in higher incidences, i.e., 26 females in high dose treatment group animals. The islet cell hyperplasia of pancreas was noted in 0, 1, 1, 1 and 3 females of study groups. The diffuse hyperplasia of pituitary was found in 0, 1, 0, 1 and 5 females. The incidences of scabs on tail were 7, 6, 10, 23, and 30 females and the observed epidermal hyperplasia was of slight to moderate nature in animals (see table below). Clear cell foci in liver were seen in 9, 13, 21, 20 and 25 females. Follicular abscess was in a dose-related manner.

TABLE: Incidences of Non-Neoplastic Lesions in Control and Treatment groups Rats[1]

Histopathological Lesion		Treatment Groups (N = 65/sex/group)				
		Control 1	Control 2	Low Dose	Mid Dose	High Dose
Adrenal						
Cortical Vacuolation	M	9	16	15	12	11
	F	2	2	0	6	6
Medullary Hyperplasia Focal	M	7	4	6	12	8
	F	2	3	5	3	11
Male Reproductive Organs:						
Epididymal Hypospermia		9	11	6	5	58
Absence of Colloid Seminal Vesicle		1	5	3	1	8
Test. Tubular Germ Epithel. Degen.		14	16	14	10	60
Progressive Senile	M	15	19	19	15	34
Nephropathy	F	8	9	7	10	18
Liver						
Focal Congestion	M	4	12	19	13	16
	F	11	8	15	15	6
Lungs						
Accumul. Alveolar Macroph.	M	14	10	23	25	30
	F	13	13	8	13	26
Perivasc. Lymphoid Aggreg.	M	2	4	3	5	6
Lungs	F	0	1	4	4	3
Mammary Gland						
Caudal Secretory Activity	M	6	2	8	11	10
	F	31	31	29	35	16
Acinar Hyperplasia	F	11	15	12	18	22
S. Muscle Thigh						
Myofibre Degeneration	M	4	5	10	8	8
	F	0	0	0	0	1
Spleen						
Extramedullary Haematopiesis	M	2	1	1	2	6
	F	6	4	8	10	11
Hemosiderosis	M	4	8	8	6	9
	F	31	29	36	29	50
Thymus						
Epithelial Hyperplasia	M	0	0	0	0	4
	F	6	5	4	5	19
Thymus Cysts	M	2	0	3	4	7
	F	15	20	27	27	24
Tail						
Epidermal Hyperplasia	M	5	9	10	17	21
	F	5	3	13	14	11
Follicular Abscess	M	4	5	10	9	19
	F	1	4	8	10	13
Scabs	M	7	10	10	17	23
	F	7	6	10	23	30

[1] = 65 of rats/group

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