

In this study target organ of toxicity was thymus. Highest tested dose (30/20/25/30 mg/kg/day) also produced CNS toxicities and death. Mid dose level (5.5 mg/kg/day) could be considered as well tolerated dose since it only produced minimal involution of the thymus in 1 out of 3 male dogs.

6-Month Oral Toxicity Study in Dogs  
(Study # D11865)

Testing Laboratories: Pathology and Toxicology Division  
Glaxo Group Research Ltd.,  
Hertfordshire, UK.

Study Started: August 22, 1989

Study Completed: March 27, 1990

GLP Requirements: A Statement of Compliance with GLP regulation was included.

Animals: Beagle dogs (18-28 weeks old; males = 7.0-10.6 kg and females = 5.7-9.4 kg).

Drug Batch No.: C1034/104/1, C1034/98/1, C1034/98/1, C1017/189/1 and C1034/102/1.

Methods: In this study dose selection was based on 35-day oral toxicity study in dogs (see above). Groups of dogs (4/sex/group) were given orally (gavage) GR 68755 at daily doses of 0 (vehicle: water), 1, 5.5 and 20 (days 1-3)/30 (days 4-8)/25 (day 9 onwards) mg/kg/day for 28 weeks. The volume of administration was fixed at 2 ml/kg. Additionally, 2 dogs/sex were included in control and high dose group for 21-day recovery study. All dogs were observed for clinical signs twice daily. Body weights were recorded weekly. Food intakes were recorded weekly until day 70 of the study (food and water was available at all times). Due to clinical reaction, from day 71 onwards, food was withdrawn overnight and replaced following morning prior to dose administration. This regimen was implemented in order to reduce clinical reaction and mortality. Ophthalmic examinations and ECG recordings were performed on all dogs once pre-test, days 92, 94, 95, 96 and 183, 185, 186, 187 and 192 of the study. Hearing acuity tests were performed on 1 dog/sex each of control and high dose groups on day 191 of the study. Blood samples were collected from jugular vein during pre-test, weeks 4, 13 and 26 of the study for hematology and serum chemistry tests. Blood samples were also collected at pre-dose, 45 min, 2 hr and 24 hr after drug administration on days 1, 4, 9, 21, 98, 189 and 193 of the study for measuring drug absorption according to

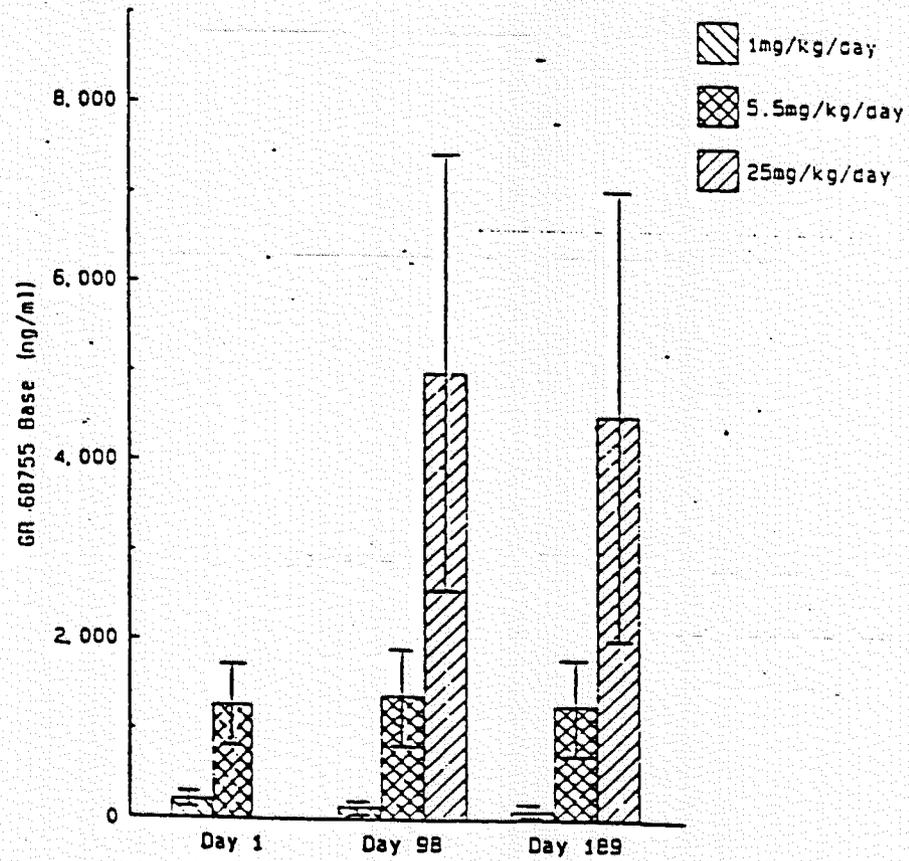
methods. Twenty-four hours urine samples during days 30/31, 93/94 and 184/185 were collected for urinalysis. At end of study period/recovery period all surviving dogs were sacrificed and subjected to complete necropsy and histopathological examinations.

Results:

1. Observed Effects: Highest tested dose produced CNS toxicities (subdued behavior, salivation, vocalizing, partly closed eyes, open mouth, ataxia and tremor) in dogs.
2. Mortality: One male (# 87960) and 2 females (# 87968 and 87984) from high dose group died during the course of study. Prior to death, two dogs (one male and one female) showed severe CNS toxicities, therefore, death of these two dogs were treatment related. No clinical signs were seen prior to the death of dog # 87984 and microscopic examination could not establish the cause of death of this dog.
3. Body Weights/Food Consumptions/Water Consumptions: The initial and final mean body weights of control males were 8.82 kg and 14.54 kg and the corresponding mean weights of control females were 7.81 kg and 11.39 kg respectively. Food consumptions in control males and females were \_\_\_\_\_ g/kg/day and \_\_\_\_\_ g/kg/day respectively. At the end of treatment period, body weight gains were reduced by 6% and 13.7% in high dose treated males and females respectively, when compared to control values. There was also an indication of decreased food consumptions in high dose treated dogs.
4. Hematology/Coagulation/Bone Marrow: No treatment related effects were seen.
5. Blood Chemistry/Coagulation/Bone Marrow: At the end of treatment period plasma alkaline phosphatase levels were increased by 68% and 112% in mid and high dose treated male dogs, while in females the corresponding increases were 34% and 42% when compared to their respective control values. At the end of recovery period plasma alkaline phosphatase levels were still high in high dose treated dogs (males: 175% and females: 38% [only high dose group were used for recovery study]). Additionally, plasma alanine aminotransferase activity was increased by 38% in high dose treated males, compared to control values. No treatment related effects were seen in urinalysis.
6. Vital Signs/Physical Examination/Ophthalmic Examination/ECG/Hearing Test: No treatment related effects were seen.
7. Organ Weights: No treatment related effects were seen.

- 8. Gross Pathology: No treatment related effects were seen.
- 9. Histopathology: No treatment related effects were seen.
- 10. Plasma Level of GR 68755 (Report # WPT/90/188): At 45 min (supposedly  $C_{max}$ , based on study # WBP/89/62) after drug administration plasma levels of GR 68755 increased with increasing dosages. Drug was not detected at 24 hr after drug administration, indicating no accumulation of drug after repeat administration.

Mean Plasma GR 68755 Base Concentrations (ng/ml)  
45 Minutes After a Daily Oral Dose of  
GR 68755C to the Dog. (Study D11865).



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Error bars indicate +/- 1 standard deviation.

Fig. 1, Pg. 318, Vol. 1.23

Highest tested dose (20/30/25 mg/kg/day) produced CNS toxicities, increases in serum alkaline phosphatase (both sexes) and alanine aminotransferase activities (in males) without accompanying histopathological changes in liver and deaths. Mid dose level (5.5 mg/kg/day) could be considered as well tolerated dose since it only produced increases in plasma alkaline phosphatase levels (males: 68% and females: 34%).

12-Month Oral Toxicity Study in Beagle Dogs  
(Study # D12561)

Testing Laboratories: Glaxo Spa,  
Verona, Italia

Study Started: June 10, 1991

Study Completed: July 5, 1995

GLP Requirements: A Statement of Compliance with GLP regulations was included.

Animals: Beagle dogs (about 4 months old, males = 5.5-8.1 kg and females = 5.1-7.2 kg).

Drug Batch No.: M91/025, M91/026 and M91/027.

Methods: Groups of dogs (4/sex/group) were given orally (capsules) GR 68755 at daily doses of 0 (placebo in gelatin capsules), 1, 5 and 20 (day 1-3)/25 (day 4 onward) mg/kg/day for 12 months. Additionally, dogs were included in control (2/sex) and high (2 males and 1 female) dose group for 6-week recovery study. Dosing was carried out at approximately 1 hr after feeding. During the first half of the study dogs were given 45 g of food per kg and 25-35 g food per kg subsequently. All dogs were observed for clinical signs 3-4 times daily. Body weights were recorded weekly and food intakes daily. Ophthalmic examinations and ECG recordings were performed on all dogs once pre-test, during weeks 14, 25 and 54 of the study. Hearing acuity tests were performed on all dogs during weeks 49, 53 (including otoscopic examination), 55, 56, 57 and 58 of the study. Blood samples were collected from jugular vein at pre-test and during week 14, 26, 52 and 59 of the study for hematology and serum chemistry tests. Overnight urine samples were also collected at pre-test, during week 14, 26, 52 and 59 of the study for urinalysis. Blood samples were also collected from jugular vein on days 1 (0, 0.25, 0.5, 0.75, 1, 1.5, 2 and 24 hr after drug administration), 37 (0, 2 and 3 hr after dosing) and at 0 and 2 hr after dosing on days 100, 184, 198 and 352 of the study for measuring drug absorption according to \_\_\_\_\_ methods.

At the end of study/recovery period all surviving dogs were sacrificed and subjected to complete necropsy and histopathological examinations. Additionally, right cochlea were also examined by electron microscopy.

**Results:**

1. **Observed Effects:** Highest tested dose produced CNS toxicities (salivation, chewing, blinking, a rotating motion of the head, ataxia, stiff limbs and walking on tip-toe, abnormalities of movement and respiration, emesis and subdued behavior) in dogs.
2. **Mortality:** Two out of 6 females from high dose group died on days 37 and 39 of the study. Prior to death, these dogs showed severe CNS toxicities (tremors, convulsions, cyanosis and mydriasis) and these deaths were treatment related.
3. **Body Weights/Food Consumptions/Water Consumptions:** The initial and final mean body weights of control males were 6.70 kg and 13.71 kg and the corresponding mean weights of control females were 6.42 kg and 11.86 kg respectively. Food consumptions in control males and females were \_\_\_\_\_ g/kg/day during the first half of the study and \_\_\_\_\_ g/kg/day last half of the study. No treatment related effects were seen in treated males. In females body weight gains were reduced by 8.6%, 0% and 5.4% in low, mid and high dose respectively, compared to control values (final body weights were 9%, 2% and 7% lower than the final body weights of the control group dogs). Food intakes were not significantly affected by the treatment.
4. **Hematology/Coagulation/Bone Marrow:** No treatment related effects were seen.
5. **Blood Chemistry/Urinalysis:** No treatment related effects were seen. At the end of treatment period, urinary volumes were increased by 158% and 186% in mid and high dose treated females respectively, without any significant changes in specific gravity. At the end of recovery period no such changes were evident.
6. **Vital Signs/Physical Examination/Ophthalmic Examination/ECG/Hearing Tests:** No treatment related effects were seen. Hearing test were conducted by the sponsor (Glaxo Group Research Ltd., Hertfordshire, UK). Brainstem auditory evoked response tests indicated that hearing threshold at high dose level was "increased". At the end of recovery period hearing threshold returned to normal.
7. **Organ Weights:** No treatment related effects were seen.

8. Gross Pathology: No treatment related effects were seen.
9. Histopathology: No treatment related effects were seen.
10. Electron Microscopic Examination of Cochlea: No treatment related effects were seen.
11. Plasma Level of GR 68755 (Report # WPT/92/325): Levels of GR 68755 were measured by At  
2 hr after drug administration, plasma levels of GR 68755 increased with increasing dosages. At 24 hr after drug administration plasma levels of GR 68755 were below detection limit (ng/ml). Hence, there was no accumulation of drug after repeat dosing.

Table 1 Mean Plasma Concentrations (ng/mL) and (SD) in dog plasma, two hours after doses of 1, 5 or 25mg/kg daily (D12561)

Dose	Week 1	Day 37	Day 100	Day 198	Day 352
1mg/kg	68 (27)	65 (13)	80 (24)	86 (41)	89 (35)
5mg/kg	411 (71)	465 (97)	550 (172)	577 (225)	637 (214)
25mg/kg	3030 (1030)	4090 (316)	4520 (497)	4810 (646)	4530 (1130)

Table 1, Pg. 352, Vol. 1.24

Highest tested dose (20/25 mg/kg/day) produced CNS toxicities, "increased hearing threshold" (which at the end of recovery period returned to normal) and deaths. Mid dose level (5 mg/kg/day) could be considered as well tolerated dose since it only produced increase urinary volumes (158%) in females without any significant changes in specific gravity.

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CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC)  
STUDY PROPOSAL COVER SHEET

APPLICATION (IND) NUMBER: \_\_\_\_\_  
DIVISION: HFD-180  
DRUG NAME: Alosetron (GR 68755) CAS #:  
SPONSOR/APPLICANT: Glaxo Wellcome Inc.  
PHARMACOLOGICAL CLASSIFICATION: 5-HT<sub>3</sub> Receptor Antagonist  
DATE SUBMITTED: 8/4/95  
REVIEW COMPLETED: 3/21/96  
DATE OF CAC REVIEW: \_\_\_\_\_  
CAC MEMBERS: \_\_\_\_\_

**SUMMARY OF PROPOSAL FOR REVIEW**

SPECIES/STRAIN: Mouse/B6C3F<sub>1</sub>  
NUMBER/SEX/DOSE: 15  
ROUTE: Via drinking water

	MALE	FEMALE
DOSES SELECTED (mg/kg/day):	1, 5.5 & 30	1, 5.5 & 30
BASIS OF DOSE SELECTION:		
MTD	_____ X _____	_____ X _____
AUC RATIO	_____	_____
SATURATION	_____	_____
MFD	_____	_____

KINETICS SUBMITTED:	RODENT	HUMAN
PHARMACOKINETICS		
METABOLISM		
PROTEIN BINDING		

NOTABLE DESIGN FEATURES: \_\_\_\_\_

**SUMMARY OF RECOMMENDATIONS TO CAC**

	MALE	FEMALE
DOSES RECOMMENDED		
BASIS FOR RECOMMENDATION:		
CAC CONCURRENCE (Y/N):		
CAC RECOMMENDATIONS:		

COMMENTS: Two INDs (# \_\_\_\_\_ and # \_\_\_\_\_) for GR 68755 were previously submitted to the Division of Neuropharmacological Drug Products (HFD-120) for the treatment of \_\_\_\_\_ respectively. Both of these INDs are currently on inactive status. Subsequently on April 22, 1994 a third IND (# \_\_\_\_\_) was submitted in HFD-180 by \_\_\_\_\_ for the treatment of \_\_\_\_\_. In 13-week dose-ranging study sponsor selected dose levels on their own and no concurrence was obtained from the Division.

13-Week Oral (via drinking water) Toxicity Study in Mice  
(Study # M12419)

Testing Laboratories: Pathology and Toxicology Division  
Glaxo Group Research Ltd.  
Hertfordshire, UK

Study Started and Completed: September 17, 1990 and June 2, 1992

GLP Requirements: A Statement of Compliance with GLP regulations was included.

Animals: B6C3F<sub>1</sub> mice (males: 25.0-32.7 g and females: 18.4-25.3 G)

Drug Batch No.: C1026/120/1

Methods: In this study dose selection was based on the results of 14-day palatability study (# M12418) in which mice were given water containing 0 (acidified water, pH 5.5), 0.005-0.007 or 0.5 mg/ml of GR 68755 to drink. A concentration of 0.5 mg GR 68755/ml caused reduction in water consumptions by 16% and 29% in males and females respectively. Based on water consumption data males were exposed to 65 mg/kg of GR 68755 and females were exposed to 70.5 mg/kg of GR 68755. According to sponsor, "the maximum palatable concentration is defined as a concentration that causes a decrease in water consumption of approximately 20% compared to control data". Based on the above findings, a concentration of 0.5 mg R 68755/ml was considered to be maximum palatable in drinking water for B6C3F<sub>1</sub> mice.

Groups of mice (15/sex/group) were given (via drinking water) GR 68755 at daily doses of 20, 30 and 40 mg/kg/day (GR 68755 concentrations in drinking water were 0.11-0.13, 0.18-0.27 and 0.27-0.35 mg/ml respectively) for 13 weeks. The target dosages were achieved by varying the concentration of GR68755 in drinking water twice weekly, and the degree of adjustment depending on changes in mean body weight and water consumption during the previous measurement period. Control mice received acidified (pH 5.5) water. All animals were observed for clinical signs twice daily. Body weights were recorded weekly and water intakes were recorded twice weekly. Blood samples were collected from vena cava just before sacrifice to measure drug levels in plasma. At the end of study period, all surviving animals were sacrificed and subjected to complete necropsy. Only brain, kidneys, lungs, testes, heart, liver, spleen and ovaries from control and high dose groups were examined microscopically.

Results:

1. Observed Effects: None
2. Mortality: None

3. Body Weight/Food Consumption/Water Consumption: The initial and final mean body weights of control males were 28.9 g and 41.1 g and the corresponding mean weights of control females were 21.6 g and 27.8 g respectively. Food consumptions were not reported. Treatment had no consistent effect on body weight gains. In males, body weight gains were reduced by 6.3%, 1.4% and 3.5% at low, mid and high dose respectively, when compared to control values. In females, body weight gains were not affected by the treatment. Water consumptions in males were not affected by the treatment except in low dose group significant increase (8-37%) in water intakes were recorded. However, in treated females water intakes were decreased steadily over the treatment period such that, by the end of treatment period, water intakes were 12%, 11% and 22% lower than the control values in low, mid and high dose groups respectively.

4. Hematology/Coagulation/Bone Marrow: Not done.

5. Blood Chemistry/Urinalysis: Not done.

6. Vital Signs/Physical Examination/Ophthalmic Examination: Not done.

7. Organ Weights: No treatment related effects were seen.

8. Histopathology: No treatment related effects were seen.

9. Levels of GR 68755 in Plasma (Report # WBP/91/044): Levels of GR 68755 in plasma samples were measured at

At the end of treatment period, plasma concentrations of GR 68755 were  $21.4 \pm 9.1$ ,  $30.1 \pm 8.5$  and  $47.1 \pm 34.7$  ng/ml in low, mid and high dose treated males and the corresponding levels in females were  $9.9 \pm 1.3$ ,  $14.2 \pm 11.4$  and  $22.3 \pm 4.4$  ng/ml. Thus, levels of GR 68755 in plasma increased with increasing dosage and levels in males were generally higher than that seen in females.

In this study, data indicated that GR68755 was unpalatable in females when given via drinking water. In females, water intakes were 12%, 11% and 22% lower than the control values in low, mid and high dose groups respectively. During the study period, GR 68755 concentration in water was adjusted twice weekly, hence animal did received the intended dosages. Based on this finding, sponsor selected 30 mg/kg (via drinking water) as the maximum tolerated dose in mouse carcinogenicity study.

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CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC)  
STUDY PROPOSAL COVER SHEET

APPLICATION (IND) NUMBER: \_\_\_\_\_  
DIVISION: HFD-180  
DRUG NAME: Alosetron (GR 68755) CAS #:  
SPONSOR/APPLICANT: Glaxo Wellcome Inc.  
PHARMACOLOGICAL CLASSIFICATION: 5-HT<sub>2</sub> receptor antagonist

DATE SUBMITTED: 8/4/95  
REVIEW COMPLETED: 3/21/96  
DATE OF CAC REVIEW:  
CAC MEMBERS:

**SUMMARY OF PROPOSAL FOR REVIEW**

SPECIES/STRAIN: Rat/Wistar  
NUMBER/SEX/DOSE: 10  
ROUTE: Via diet

	MALE	FEMALE
DOSES SELECTED:	1, 6.5 & 40	1, 6.5 & 40
BASIS OF DOSE SELECTION:		
MTD		
AUC RATIO	X	X
SATURATION		
MFD		

	RODENT	HUMAN
KINETICS SUBMITTED:		
PHARMACOKINETICS	X	X
METABOLISM	X	None
PROTEIN BINDING	X	X

NOTABLE DESIGN FEATURES:

**SUMMARY OF RECOMMENDATIONS TO CAC**

	MALE	FEMALE
DOSES RECOMMENDED		
BASIS FOR RECOMMENDATION:		

CAC CONCURRENCE (Y/N):  
CAC RECOMMENDATIONS:

COMMENTS:

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3-Month Oral (via diet) Dose-Ranging Study in Wistar Rats  
(Study # R12457)

Testing Laboratories:

Study Started and Completed: October 25, 1990 and March 24, 1992

GLP Requirements: A Statement of Compliance with GLP regulations was included.

Animals: Male and female Wistar rats (29-36 days old; 82-112 g).

Drug Batch No.: C1026/120/1

Methods: In this study dose selection was based on the results of 21-day palatability study (# R12495) in which 100 mg/kg/day caused lethality and reductions in body weight gains (males: 12% and females: 4%) were seen at 30 mg/kg/day dose levels. Based on these findings, sponsor selected 10, 20 and 40 mg/kg/day for the present study. Groups of rats (10/sex/group) were given GR 68755 via diet at daily doses of 10, 20 and 40 mg/kg/day for 3 months. The control group animals were given unmedicated diet. Additionally, 6 rats/sex/group were included as satellite animals for toxicokinetics study. All animals were observed for clinical signs twice daily. Body weights and food intakes were recorded weekly. Blood samples were collected from tail vein on day 8/9 from satellite rats and on days 90/91 from main study rats. The blood collection time points were 0800, 1200, 1600, 2000, 0400 and 0800 hours and 3 rats/sex/group/time points were used. All surviving animals were sacrificed at the end of study period and subjected to complete necropsy. Only tissues from control and high dose groups were examined histopathologically. Liver from low and mid dose groups, pituitary from low and mid dose treated females and gross abnormal tissues from all animals were also examined histopathologically.

Results: The intakes of the drug were within 2% of the intended doses (low dose = \_\_\_\_\_ mg/kg/day, mid dose = \_\_\_\_\_ mg/kg/day and high dose = \_\_\_\_\_ mg/kg/day). There were no deaths and no treatment related signs were seen. Treatment had no significant effect on food consumptions and body weights. Only in high dose treated females, absolute as well as relative, weights of pituitary were reduced by 27-28% compared to control values. No treatment related histopathological abnormalities were evident in this study.

Levels of GR 68755 in plasma were measured at \_\_\_\_\_  
increased with increasing dosages. Levels seen on day 90/91 of \_\_\_\_\_  
Levels of GR 68755

the study were higher than that seen on days 8/9 of the study. Throughout the study period, plasma concentrations in males were lower than that seen in females.

AUC <sub>0-24 hr</sub> (ng.hr/ml)				
Dose (mg/kg/day)	Day 8/9		Day 90/91	
	Male	Female	Male	Female
10	1660	2520	2410	4090
20	2260	3790	7510	11600
40	9460	19500	21400	35500

In this study only in high dose treated females, absolute as well as relative, weights of pituitary were reduced by 27-28% compared to control values. No treatment related histopathological abnormalities were evident in this study. The systemic exposure of GR 68755 at 40 mg/kg/day dose level was about 24-89 fold higher than the anticipated human exposure (AUC<sub>0-24 hr</sub> = 396.4 ng.hr/ml, 0.32 mg/kg/day [8 mg b.i.d.], 50 kg body wt. assumed). Based on multiple of human exposure, sponsor selected 40 mg/kg/day as the top dose for the carcinogenicity study in rat and the mid and low doses were set at 6.5 and 1.0 mg/kg/day respectively.

3-Month Oral (gavage) Dose-Ranging Study in Wistar Rats  
 (Study # 12569)

Testing Laboratories:

Study Started and Completed: October 29, 1990 and June 29, 1995

GLP Requirements: A Statement of Compliance with GLP regulations was included.

Animals: Male and Female Wistar Rats (33-40 days old, 82-113 g)

Drug Batch No.: C1026/120/1

Methods: Groups of rats (10/sex/group) were given orally (gavage) GR 68755 at daily doses of 10, 20 and 20/40 (20 mg/kg/day for the first seven days) mg/kg/day for 3 months. The volume

of administration was fixed at 10 ml/kg. Control group animals received vehicle (water) in similar fashion. Additionally, 7 rats/sex/group were included as satellite animals for toxicokinetic study. All animals were observed for clinical signs and mortality twice daily. Body weights and food consumptions were recorded weekly. Blood samples from tail vein were collected on days 1/2 from low and mid dose groups, on days 8/9 from control and high dose group and on days 92/93 from all groups. The collection time points were 10, 20 and 30 min, 1, 2, 4 and 24 hr after drug administration. All surviving rats were killed at the end of study period and subjected to complete necropsy. Only tissues from control and high dose groups were examined microscopically. Liver from low and mid dose groups and all gross abnormal tissues from all groups were also examined histopathologically.

**Results:** Transient noisy respiration was seen in mid and high dose treated rats. One mid dose treated female died on day 28 of the study and the cause of death was not treatment related. Treatment had no significant effect on body weight gains and food consumptions. In high dose treated females, liver weights were increased by 28% while a 10-13% increase in liver weights were seen in all treated males. Histopathological examinations revealed periacinar hepatocytic hypertrophy in 6/10 high dose treated females (and none in the control group) and foci of "pre-basophilic" hepatocytes in 3/10 high dose treated females (and none in the control).

Levels of GR 68755 in plasma were measured at

Levels of GR 68755 increased with increasing dosages. In low and mid dose groups, levels seen on day 92 were higher than that seen on day 1 of the study. Furthermore, there is an indication that a given dose level of GR 68755 in males were less than that seen in females (may be due to higher clearance of GR 68755 in male rats). In all treated rats, GR 68755 levels at 24 hr after drug administration were  $\leq 3.1\%$  of  $C_{max}$  values.

AUC <sub>0-4 hr</sub> (ng.hr/ml)				
Dose (mg/kg/day)	Day 1		Day 92	
	Male	Female	Male	Female
10	2970	5130	6340	10500
20	6520	12100	13700	17600
20*/40	13600**	18900**	20700	24400

\* = given during the first 7 days of the study  
 \*\* = levels were measured on day 8 of the study

In this study, increase in liver weights were seen in all treated males (10-13%) and in high dose treated females (28%). Histopathological examinations revealed periacinar hepatocytic hypertrophy and foci of "pre-basophilic" hepatocytes in some of the high dose treated females (and none in the control).

In both dietary and gavage 3-month dose ranging study in rats, the systemic exposure of GR 68755 at 40 mg/kg/day dose level was at least 24 fold higher than the anticipated human exposure ( $AUC_{0-24hr} = 396.4$  ng.hr/ml, 0.32 mg/kg/day [8 mg b.i.d.], 50 kg body wt. assumed). Based on multiple of human exposure, sponsor selected 40 mg/kg/day as the top dose for the carcinogenicity study in rat and the mid and low doses were set at 6.5 and 1.0 mg/kg/day respectively. The selection of top dose is appropriate (see the result of main carcinogenicity study in rat).

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