PHARMACODYNAMICS:

(GR68755 abbreviated "GR").

A) Learning/Memory Studies:

GR showed activity in the following paradigms:

1) Mouse Habituation Test

GR active at 0.01 ng/kg i.p. b.i.d. (only dose used); this dose also attenuated the disruption of habituation induced by scopolamine.

2) Spontaneous Alternation in Rats:

GR at 1 ng-100 ug/kg i.p. b.i.d. partially reversed scopolamine-induced performance deficit; all GR doses tested in this range produced quantitalively similar effect.

3) Morris Water Maze Test in Rats:

GR at 1 ng-10 ug/kg i.p. antagonized scopolamine-induced performance deficit; all GR doses tested in this range produced quantitatively similar effect.

4) Wisconsin General Test Apparatus (Marmosets):

GR at 0.01 and 10 ng/kg s.c. b.i.d. reduced number of trials needed to reach criterion; however a higher dose (1 ug/kg) had no effect.

B) Anti-Anxiety Studies:

1) Social Interaction in Rats:

GR increased social interaction (without effect on locomotor activity); the effective dosage range was said to be [redacted] ug/kg p.o. in one place and [redacted] ng/kg p.o. in another. In a separate study, GR was active at 0.1 and 10 (but not 0.001) ug/kg i.p. The magnitude of the effect was not dose-related. The effect of a single dose of 1 ug/kg p.o. lasted for 6 hours. Activity did not decrease with subacute treatment. Diazepam was effective in this paradigm; however, unlike GS, it produced a rebound decrease in social interaction after subacute treatment.

2) Light Aversion in Mice:

GR decreased light aversion at 0.1 ng/kg-10 mg/kg i.p. (No effect at 0.01 ng/kg; all doses tested in the active range produced quantitatively similar effects; 50% died at 10 mg/kg). Diazepam was active at 0.125 but not 0.063 mg/kg i.p. GR had a duration of action of 12-24 hours after a single dose of 1 ug/kg i.p. or p.o. Tolerance did not develop with subactue treatment with either GR or diazepam; a rebound effect (i.e. increased light aversion) was seen after cessation of treatment with diazepam only.

3) Elevated Plus Maze in Rats:

GR at 1 and 10 ug/kg i.p. increased the amount of time spent in the open arm section of the maze, which was interpreted as an anxiolytic effect.

C) Receptor Interaction Studies:

GR is a putative antagonist of 5-HT_3 receptors. The attached Table "2" summarizes the in vitro pharmacological and ligand binding studies performed to show that GR antagonizes 5-HT_3 receptors without effects on a variety of other receptor types. GR was also active in an in vivo model of 5-HT_3 antagonism: antagonism of the bradycardia induced by the putative 5-HT_3 agonist 2-methyl 5-HT (Bezold-Jarisch reflex) in anesthetized cat. In this model GR was active at 0.1-1 ug/kg i.v. and 3-10 (but not 1) ug/kg i.d. The duration action after i.d. dosing was at least 3 hours.

D) Cardiovascular Studies:

Data were extremely limited. In a single anesthetized cat, 0.1-1 mg/kg i.v. caused no clear change in heart rate, blood pressure, or EKG. A slight increase in QTc interval was seen at 1 mg/kg; a smaller increase was seen during saline infusion. GR was also given to 2 conscious monkeys at i.v. doses of 0.01-1 mg/kg. No effects on heart rate, blood pressure, or EKG were seen up to 0.3 mg/kg. At 1 mg/kg, a slight increase in QT interval was seen in 1 monkey; this monkey also had a single transient "dysrhythmia" (see tracing in fig. 5, attached) at 6 minutes after this dose. It was stated that isolated dysrhythmias are not uncommon in vehicle-treated monkeys, and thus may not have been due to drug in this case.

E) Miscellaneous Studies:

1) General Behavior in Mouse, Rat, and Dog:

a) Mouse - no effect at 3 mg/kg i.v.; 10 mg/kg i.v. caused convulsions and 5/5 deaths.

b) Rat - 2.5 and 5 mg/kg i.v., and 5 and 10 mg/kg p.o., caused no effects. A decrease in spontaneous activity lasting 45 minutes was seen after 10 mg/kg i.v.

c) Dog - no effect at 0.625 - 2.5 mg/kg i.v. or 1.25 - 5 mg/kg p.o.

2) Antagonism of Cisplatin - and Cyclophosphamide-Induced Emesis in the Ferret:

GR was active at 0.1 - 1 mg/kg i.p.

3) Effect on Phenobarbitone Sleeping Time in Mouse:

GR had no effect at 3 mg/kg i.v.

Table 2: Selectivity Of Action Of GR68755A In Isolated Tissue Preparations

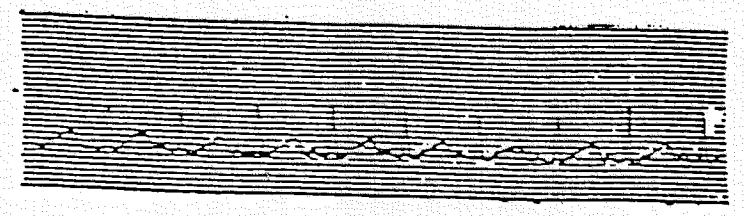
Receptor Type	Isolated Tissue	Agonist or Radioligand	Effect
5-HT_3	Rat vagus nerve (DEPOLARIZATION)	5-HT	$pK_B = 9.8$
	Rat entorhinal cortex	[^{3}H]GR65630B	$pK_i = 9.4$
	Guinea-pig ileum (CONTRACTION)	2-methyl-5-HT	$pA_2 = 7.7$
5-HT_2	Rat aorta	5-HT	$pA_2 = 5.2$
5-HT_1-like	Dog saphenous vein	5-HT	NSE 10mcM
	Rat striatum	[^{125}I]cyanopindolol	NSE 100mcM
	Rat hippocampus	[^{3}H]8OHDPAT	NSE 100mcM
α_1-adrenoceptor	Rabbit aorta	Noradrenaline	NSE 30mcM
α_1-adrenoceptor	Rat left atria	Isoprenaline	NSE 100mcM
β_2-adrenoceptor	Rat uterus	Isoprenaline	NSE 100mcM
Muscarinic M_1	Rat cortex	[^{3}H]pirenzepine	NSE 100mcM
Muscarinic M_2	Rat heart	[^{3}H]NMS	NSE 100mcM
Muscarinic M_3	Rat salivary gland	[^{3}H]NMS	NSE 100mcM
Nicotinic	Rat superior cervical ganglion	DMPP	NSE 10mcM
Histamine H_1	Guinea-pig ileum	Histamine	$pA_2 = 5.7$
$GABA_A$	Rat superior cervical ganglion	GABA	NSE 10mcM
Dopamine D_2	Rat striatum	[^{3}H]spiperone	NSE 10mcM
Opiate	Mouse vas deferens		NSE 0.1mcM

NSE = No significant effect
DMPP = 1,1-dimethyl-4-phenyl piperazinium iodide
[^{3}H]-NMS = [^{3}H]-N-methylscopolamine

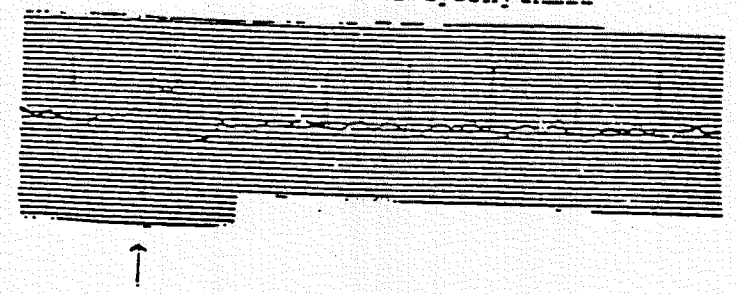
FIGURE 5 CXD/2673

Samples of ECG (lead I") recording from Monkey 39631 prior to and following GR 68755A administration

A Pre-dose



B 6 minutes following GR 68755A (1.0 mg/kg) administration showing single incidence of dysrhythmia



1 sec.

To aid interpretation, the above signal has been traced by hand to accentuate the dysrhythmia and subsequent waveforms.

[S]

4. Antipsychotic Activity:

A) GR68755 (hereafter abbreviated as GR) blocked the increased locomotor activity caused by amphetamine injection into the nucleus accumbens of rats. GR and ondansetron had similar effects at doses of 100 and 1 ng, respectively (injected into nucleus accumbens). GR was inactive at 1 and 10 ng.

B) GR partially blocked the increased locomotor activity caused by dopamine infused into the nucleus accumbens of rats. GR was active at doses of 1 ng/kg - 100 ug/kg given i.p. (inactive at 0.01 ng/kg); all doses tested within this active range produced a similar magnitude of effect.

C) Unilateral intrastriatal injection of GR (1 ug) in rats did not induce postural assymetries or circling behavior, either when given alone or when animals were subsequently challenged with systemic apomorphine. Fluphenazine, given at a higher dose (5 ug intra-striatal), did not have any effect when given alone but did cause assymetry in response to systemic apomorphine challenge.

D) GR at 0.5 - 5 mg/kg i.p. did not cause catalepsy in rats; haloperidol did so at 2 mg/kg i.p.

E) GR at 0.5 - 5 mg/kg i.p. did not antagonize apomorphine-induced stereotypy in rats; fluphenazine antagonized this at 0.1 mg/kg i.p.

F) GR partially antagonized the increased locomotor activity caused by the neurokinin receptor agonist DiMeC7 injected into the ventral tegmental area of rats. (It was stated that this procedure produces an increase in locomotor activity which is considered to be due to a selective increase in dopamine release in the mesolimbic and mesocortical dopaminergic systems, and can be abolished by haloperidol). GR was active at 1 - 1000 (but not 0.1) ug/kg s.c.; it was stated that these doses produced no effects on basal locomotor activity. (All doses within the active range produced a similar magnitude of effect). (Ondansetron had similar potency but lost activity at the highest dose). (This study was previously submitted to IND

It was concluded that GR could "potently antagonize the behavioural consequences of raised mesolimbic dopamine function" (i.e., # A, B, and F, above) while "failing to demonstrate activity in classical models designed to detect the liability of neuroleptic compounds to produce extrapyramidal side effects" (i.e., # C, D, E, above). (However, note that in one of the latter studies, #C, the positive control was given at a 5x higher dose, thus not clearly ruling out extrapyramidal liability of GR in this case). As previously noted regarding other behavioral studies submitted to IND [redacted], GR is unusual in that it was active at extremely low doses, i.e. at 1 ng/kg i.p. in #B, above, and produced similar magnitudes of effect across a dosage range spanning several orders of magnitude.

The hypothesized mechanism of action of currently used antipsychotic agents is a decrease in brain dopaminergic activity through a blockade of D_2 dopaminergic receptors. In the case of GR, the mechanism of its effects in blocking animal models of dopaminergic hyperactivity is not clear. It does not bind to D_2 receptors (IND [redacted]). In the models where GR blocked the increased locomotor activity due to agents which presumably work through dopamine, it cannot be concluded that GR acted through a specific effect on dopaminergic function; in fact in 2 of the 3 studies it was not stated if GR alone could decrease locomotor activity. There is some evidence that pathways involving $5HT_3$ receptors facilitate dopaminergic function (Barnes, et.al., Neuroscience and Biobehavioral Reviews 16:107, 1992), and thus the $5HT_3$ blocking activity of GR (see IND [redacted]) may be the mechanism for its potential antipsychotic effects, as implied by the sponsor. However, as discussed in my Original Summary of IND [redacted] it is unlikely that at the extremely low doses at which GR is active (e.g. 1 ng/kg i.p. in study #B, above), brain levels of drug will be high enough to block $5HT_3$ receptors. Furthermore, in one study (#A, above), ondansetron was 100x more potent than GR in blocking amphetamine-induced hyperactivity, yet according to the sponsor (vol. 1.3, p. 16) GR is approximately 10x more potent than ondansetron at $5\text{-}HT_3$ receptors in rat brain.

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION (ADME) STUDIES

The ADME studies were conducted in mouse, rat, rabbit and dog.

MOUSE:

Pharmacokinetics of GR 68755 in the Mouse Following a Single Oral Dose (Study # MET862, Report # WBP/92/021)

Methods: B6C3F$_1$ male mouse were given a single oral (gavage) dose of ^{14}C-GR 68755 (5.5 mg/kg). Volume of administration was fixed at 10 ml/kg. Blood samples were collected from abdominal vena cava at pre-test, 0.08, 0.17, 0.33, 0.5, 0.75, 1, 2, 3, 4, 6 and 8 hours after drug administration (5 mice/sampling time points were used). Levels of GR 68755 in plasma were measured by methods and total radioactivity was determined by methods. Various pharmacokinetic parameters were calculated.

Results: GR 68755 absorbed rapidly (T_{max} = 0.08 hr[first sampling point]). Plasma levels of GR 68755 decreased rapidly ($t_{½}$ = <0.25 hr) and at 2 hr post-dosing the levels were below detection limit (limit of detection = 25 ng/ml). Based on AUC values about 25 - 34% of the total radioactivity represented parent drug.

Pharmacokinetic Parameters in Mouse After A Single Oral Dose

Parameters	GR 68755	Radioactivity
C_{max} (ng/ml)	770 ± 536	1643 ± 271
T_{max} (hr)	0.08	0.33
AUC_{0-1} (ng.hr/ml)	481	1375
$AUC_{0-\infty}$ (ng.hr/ml)	<672*	2757
$t_{½}$ (hr)	<0.25*	0.63

* = Estimated because at 2 hr post-dose plasma levels were below detection limit.

Metabolism and Excretion in the Mouse After A Single Oral Dose of ^{14}C-GR 68755 (Study # BPW191, Report # WBP/91/019)

Methods: Male and female mice ($B6C3F_1$) were given a single oral (gavage) dose of ^{14}C-GR 68755 (5.5 mg/kg, 10 ml/kg) urine and feces were collected over 24 hr period for up to 144 hours after drug administration. In all samples, radioactivity was measured by

Results: About 47.4% and 47.5% of the administered radioactivity were excreted in urine and feces during 0-144 hr period respectively, and most of the radioactivity was cleared during the first 24 hr period. There were no sex differences in excretion pattern. About 13 and >15 radioactive peaks were seen in urine and feces samples. Only about 11% and 4% of the dose excreted in urine and feces respectively as unchanged drug. In urine, about 3 - 7% of the dose was glucuronide conjugate of GR 68755.

RAT:

Pharmacokinetics of GR 68755 in Pigmented (RH) Rats Following A Single Oral or I.V. Dose (Study # 541/579, Report # WBP/89/071)

Methods: Male and female Random-bred Hooded rats were given a single oral (gavage) or i.v. dose of ^{14}C-GR 68755 (3.5 mg/kg). The volumes of administration were 4 ml/kg for oral dose and 2 ml/kg for i.v. dose. Blood samples were collected from abdomina vena cava at 0, 0.08 (only post i.v. dose), 0.25, 0.5, 0.75 (only post oral dose), 1, 1.5, 2, 3 (only post oral), 4, 6, 8 and 24 hr after drug administration (2 rats/sex/time point were used). Levels of GR 68755 in plasma were measured by methods and total radioactivity was determined by methods. Various pharmacokinetic parameters were also calculated.

Results: The data indicated that GR 68755 rapidly absorbed when given orally (bioavailability is almost 100%). In the calculation of bioavailability it is generally assumed that plasma clearance is the same after i.v. or oral dose. Oral bioavailability of >100% may be due to the differences in Cl_p of the drug depending on route of administration. Irrespective of route of administration, based on AUC values, unchanged drug represented 57 - 59% and 76 - 78% of total plasma radioactivity in males and females respectively. Furthermore, systemic exposure to GR 68755 in females were about 2.5 fold higher than males. This conclusion was further supported by the lower Cl_p

values in females than males (16.4 vs 44.7 ml/min/kg). Since Vd is similar in both sexes, the difference in Clp may be due to shorter $t_{½}$ in males than in females (0.4 vs 1.1 hr). Both parent drug as well as total radioactivity levels reached to negligible levels at 24 hr after dosing (limit of detection: ng/ml). Plasma radioactivity declined in a biphasic manner ($t_{½}$ beta): i.v.: males = 2 hr and females = 9 hr; oral: males = 2 hr and females = 5 hr).

Mean Pharmacokinetic Parameters in Rats After A Single Oral or I.V. Dose (n=2)

	Male		Female	
	Oral	I.V.	Oral	I.V.
C_{max} (ng/ml)	2450	2240	3240	3400
T_{max} (hr)	0.25	0.08	0.25	0.08
$AUC_{0-\infty}$ (ng.hr/ml)	1980	1360	4880	3620
$t_{½}$ (hr)	0.6**	0.4*	1.0**	1.1*
Cl_p (ml/min/kg)	---	44.7	---	16.4
Bioavailability	139	---	123	---
Vd (L/kg)	---	1.6	---	1.6

Cl_p = plasma clearance
Vd = volume of distribution
* = $t_{½}$ calculation from 15 min-2 hr for males and 15-6 hr for female rats
** = $t_{½}$ calculation from 15 min-2 hr for both sexes

Pharmacokinetics of GR 68755 in AHA and Wistar Rats Following A Single Oral Dose
(Study # MET703, Report # WBP/90/073 and Study # BPW335, Report # WBP/94/012)

Methods: AHA rats were used in reproductive toxicity studies and Wistar rats were used in rat carcinogenicity study. Therefore, sponsor used these strains of rats for the present pharmacokinetic studies. Rats were given a single oral (gavage) dose of ^{14}C-GR 68755 (1 mg/kg). The volume of administration was fixed at 4 ml/kg. Blood samples were collected from dorsal aorta at 0, 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 24 hr after drug administration (2 rats/sex/time point were used). Levels of GR 68755 in plasma were measured by methods and total radioactivity was determined by methods. Various pharmacokinetic parameters were calculated.

Results: GR 68755 absorbed rapidly in AHA and Wistar rats (T_{max}: AHA rats = 0.08-0.25 hr and Wistar rats = 0.3-0.5 hr). The decline of GR 68755 and/or total radioactivity in plasma was linear with $t_{½}$ ranging from 0.9 - 1.6 hr depending upon strain and sex of rats. Irrespective of strain and sex, based on AUC values, unchanged drug in plasma represented about 33-53% of the total radioactivity. Furthermore, systemic exposure to GR 68755 in female AHA and Wistar rats were about 79% and 43% greater than corresponding males respectively. This trend of greater exposure of GR 68755 and/or radioactivity in females than males after a given dose is in line with the earlier findings (see above: report # WBP/89/071). At 4/6 hr after drug administration plasma levels of GR 68755 were close to detection limit (ng/ml) and at 24 hr post-dose radioactivity levels were negligible.

Mean Pharmacokinetic Parameters in Rats (AHA and Wistar) After A Single Oral Dose (n=2)

	AHA Rats		Wistar Rats	
	Male	Female	Male	Female
C_{max} (ng/ml)	198	328	320	450
T_{max} (hr)	0.25	0.08	0.3	0.5
$AUC_{0-\infty}$ (ng.hr/ml)	295	528	510	730
$t_{½}$ (hr)	1.6	1.1	0.9	0.9
$t_{½}$ (hr) [radioactivity]	1.6	1.3	1.4	1.5

In study BPW335 (Wistar rats), sponsor also collected urine and feces samples over 24 hr period for up to 144 hr after drug administration. About 52% and 47% of administered radioactivity were excreted in urine and feces during 0 - 144 hr period respectively, and most of the radioactivity was cleared during the first 24 hr period. There was no sex difference in excretion pattern. During the first 24 hr <10% of dose was excreted in the urine as unchanged drug. Ten unidentified radioactive peaks in urine and 8 unidentified peaks in feces were seen in 0 - 24 hr samples. Thus, indicating drug is extensively metabolized before elimination.

Distribution:

Distribution of Radioactivity Following A Single Oral (3.5 mg/kg) or I.V. (1 mg/kg) Administration of ^{14}C-GR 68755 to Male Albino (AHA) and Pigmented (RH) Rats
(Study # MET536/578, Report # WBP/89/101)

Methods: Male albino (AHA) and pigmented (RH) rats were given a single oral (gavage; 3.5 mg/kg) or i.v. (1 mg/kg) dose of ^{14}C-GR 68755. One pigmented rat per time point was sacrificed at 5, 15, 30 min., 1, 2, 4, 6, 24, 48, 72 and 168 hours after drug administration via oral route. Following oral administration, single albino rats were sacrificed at 1, 6, 24 and 168 hr. Following i.v. dose, one albino rat was sacrificed at 5, 15, 30 min., 1, 2, 4, 6, 24, 48, 72 and 168 hours and one pigmented rat was killed at 1, 24 and 168 hr.
Additionally, sagittal sections of 20 μm thick were obtained at various levels and radioactivity in various samples were measured by

Results: Irrespective of route of administration and strain, radioactivity was widely distributed throughout the body. Radioactivity levels in liver, kidneys and adrenals were significantly higher than the blood. Significant level of radioactivity was also seen in the eye of pigmented rats. Radioactivity from all tissues were cleared within 24 hr after drug administration except from adrenals, which was cleared by the end of 168 hr. Radioactivity in the eye of pigmented rat was still present at end of 168 hr after drug administration, indicating binding of drug and/or metabolites to melanin of the uveal tract.

Tissue	Concentrations (µg base equivalents/g of tissue) RH (po)*	AHA (po)†	RH (iv)†	AHA (iv)*
Blood	1.44 (0.25)	0.56 (1.0)	0.11 (1.0)	0.42 (0.08)
Adrenal	8.27 (1.0)	4.81 (1.0)	2.19 (1.0)	6.39 (0.08)
Bone	1.40 (1.0)	0.49 (1.0)	<LS (1.0)	1.07 (0.08)
Bone marrow	3.44 (0.25)	1.29 (1.0)	0.22 (1.0)	1.34 (0.08)
Testes	0.31 (1.0)	0.63 (1.0)	0.12 (1.0)	0.35 (1.0)
Heart	3.39 (0.25)	1.42 (1.0)	0.36 (1.0)	1.20 (0.08)
Kidney	12.67 (1.0)	5.64 (1.0)	1.23 (1.0)	4.93 (0.08)
Liver	9.59 (1.0)	3.61 (1.0)	1.39 (1.0)	4.65 (0.08)
Lung	4.44 (0.25)	2.30 (1.0)	0.40 (1.0)	1.32 (0.5)
Small intestine	6.44 (0.25)	2.23 (1.0)	0.65 (1.0)	1.05 (0.08)
Large intestine	3.49 (0.25)	3.57 (1.0)	0.21 (1.0)	0.79 (1.0)
Thyroid	2.75 (0.08)	0.94 (1.0)	0.30 (1.0)	1.32 (0.08)
Salivary gland	4.27 (0.25)	1.75 (1.0)	0.95 (1.0)	1.97 (0.5)
Pituitary	5.11 (0.25)	1.75 (1.0)	0.97 (1.0)	1.31 (0.25)
CNS	0.29 (0.25)	<LS (1.0)	<LS (1.0)	<LS (0.08)
Brown fat	3.60 (0.08)	1.42 (1.0)	-	-
Spleen	-	-	0.36 (1.0)	0.78 (0.25)
Eye	6.46 (4.0)	0.48 (1.0)	1.07 (1.0)	0.17 (0.08)
Eye	2.30 (168)	0.003 (168)	0.35 (168)	BKG (168)

Key:
RH = Random-bred Hooded rat.
AHA = Allen & Hanbury Albino
GR68755D = ^{14}C-GR68755 hydrochloride.
GR68755C = Non-radiolabelled GR68755 hydrochloride.

* = Values given are for peak concentrations
Values in parentheses are the sample time in hours.
† = Values given are concentrations observed at the first sampling time.
Values in parentheses are the sample time in hours.
<LS = Concentration lower than value of lowest visible standard on
BKG = Concentration not distinguishable from background.

Sponsor's Table, Page 198, Vol. 1.31

Placental Transfer of Radioactivity in Pregnant Albino (AHA) Rat
(Study # MET698, Report # WBP/90/055)

Methods: Pregnant albino (AHA) rats were given a single oral dose of ^{14}C-GR 68755 (1 mg/kg) on day 19 of gestation. At 1, 6 and 24 hr after drug administration, rats (1/time point) were sacrificed and Radioactivity levels in maternal blood, placenta and fetus were measured by

Results: Radioactivity crosses placental barrier and is widely distributed in fetuses. The levels of radioactivity in fetus at 1 hr post-dose were lower than that seen in maternal blood or placenta and the placental radioactivity was about 2-fold higher than that in maternal blood. Twenty-four hours after drug administration levels of radioactivity in maternal blood, placenta and fetus were below detection limit.

The Concentrations of Radioactive Drug-Related Material in Selected Tissues of Pregnant Albino Rats Following Oral Administration of ^{14}C-GR 68755 at 1mg Base/kg

Animal No.	805	807	808
Time (h)	1	6	24
	(Concentration Expressed as ng GR 68755 base/g tissue)		
Tissues			
Maternal blood	117	28.9	<13.0
Placenta	236	48.6	<13.0
Foetus	31.2	<13.0	<13.0

the value of the lowest visible standard measurable on the film

Sponsor's Table 1, Page 346, Vol. 1.32

Metabolism and Excretion of ^{14}C-GR 68755 in Rats After A Single Oral or I.V. Dose (Study # MET564/594, Report # WBP/89/060 and Study # MET533/711, Report # WBP/90/056)

Methods: Male and female rats (AHA and RH) were given a single oral (gavage) or i.v. dose of ^{14}C-GR 68755 (3.5 mg/kg or 1 ng/kg). The volumes of administration were 4 ml/kg for oral dose and 2 ml/kg for i.v. dose. Urine and feces samples were collected over 24 hr period for 144 hours after drug administration. In all samples radioactivity was measured by methods. Drug and its metabolites were identified by methods.

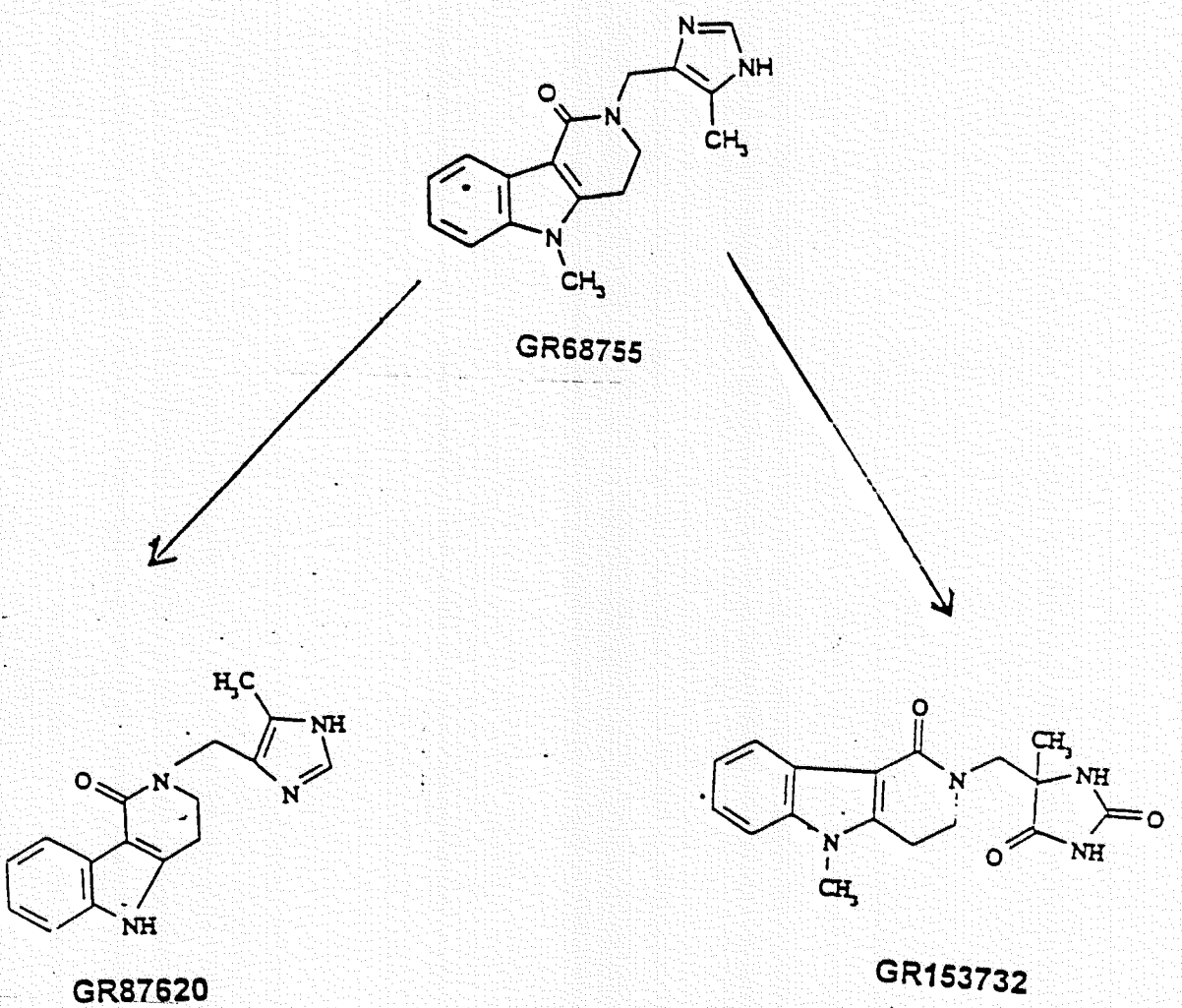
Results: Irrespective of route of administration, strain and sex, about 42-47% and 43-47% of the administered radioactivity were excreted in urine and feces during 0-144 hr period respectively, and most of the radioactivity was cleared during the first 24 hr period. Urinary excretion of radioactivity after

oral and i.v. dose were comparable which suggest that oral dose is completely absorbed and fecal excretion mainly represents biliary excretion. In both urine and feces samples (0-24 hr), about >10 radioactive peaks were seen and one of the peaks is identified as GR 87620 (N-desmethyl analogue of GR 68755). GR 87620 represented about 4% of the dose in urine. Furthermore, unchanged drug levels were less than 7% of the dose in urine and feces. Like in human urine, rat urine also contained bis-oxidized metabolite of GR 68755 (data presented as a peak and no quantitation was provided) (see fig 1.). Hence, the drug is metabolized rapidly in rats.

Percent of Dose Recovered (n-8)				
	RH Rats (3.5 mg/kg)		AHA Rats (1 mg/kg)	
	Oral	I.V.	Oral	I.V.
Urine				
0-24 hr	39.3 ± 9.6	38.9 ± 7.5	41.5 ± 8.1	38.2 ± 6.7
0-144 hr	42.9 ± 9.0	42.6 ± 7.6	47.4 ± 10.1	41.5 ± 7.3
Feces				
0-24 hr	37.5 ± 5.7	38.6 ± 7.2	33.4 ± 19.1	38.9 ± 10.0
0-144 hr	47.5 ± 6.1	43.9 ± 8.2	45.1 ± 9.7	46.8 ± 7.2

Proposed Metabolic Pathway

Fig. 1



(N-desmethyl GR68755)
(Rat and Dog)

(bis-Oxidation of GR6855)
(Rat, Dog and Man)

Note: On page 38, Vol. 1.1 (Investigator's Brochure) sponsor indicated the presence of GR 96105 (6-hydroxy-alosetron), a metabolite of GR 68755, in rat and dog urine sample. However, the presence of this metabolite (GR 96105) was not documented in the study reports.