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TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Primary pharmacodynamics: **SC-49483 = OGT 924 = Prodrug; SC-48334 = OGT 918 = Active metabolite**

STUDY TITLE	TEST SYSTEM	ROUTE	DOSES	RESULTS
N-Butyldeoxyroji -rimycin is a novel inhibitor of glycolipid Biosynthesis	Human myeloid cells HL-60, KS62. Human lymphoid cells MOLT-4 Hg. Murine myeloid cells P388 d-1, WEHI-3B	In vitro	50, 500 µM	OGT 918 was shown to have potent inhibitory activity of glucosyltransferase-catalysed biosynthesis of glucosylceramide (GlcCer). Both neutral glycolipids and gangliosides were depleted but the major phospholipid species and sphingomyelins were unaffected. The irreversible inhibitor of glucocerebrosid -ase, conduritol-B-epoxide (CBE), was used to mimic Gaucher disease in the murine macrophage cell line WEHI-3B. In the presence of CBE, cellular levels of GlcCer are raised and lipid accumulates in the lysosomes. When these cells were treated for 3 days with 50 µM OGT 918, GlcCer levels were reduced to control levels. At higher doses (500 µM), GlcCer is barely detectable by thin layer chromatography.
Inhibitors of glycosphingolipid biosynthesis	Human myeloid Cells HL-60	N/A	< 0.5-500 µM	A structure activity review was conducted of inhibitors of glycosphingolipid biosynthesis including the N-alkylated imino sugars. OGT 918's IC_{50} for glycolipid biosynthesis is 5-50 µM in vitro. This is virtually the same as the IC_{50} for production of surface G_{M1} ganglioside, indicating that intra-cellular concentrations of OGT 918 in the vicinity of the enzyme are the same or similar to the extracellular drug concentration.
Extensive glycosphingolipid depletion in the liver and lymphoid organs of mice treated with N-butyldeox -ynojirimycin.	C57BL/6, female mice (6 weeks old at the start of the study)	Diet Admixture	600, 1200, 1800 mg/kg/d as escalating dose for 118 days. Serum levels varied in a dose dependent manner.	Reduction in growth rate was only clinical sign observed. Modification of the diet to reduce complex carbohydrate and increase glucose did not abrogate the lower weight gain of the treated mice. Cell surface gangliosides were substantially reduced in the livers and spleens of OGT 918 treated mice indicating depletion of glycosphingolipids. There was no selective depletion of gangliosides. This is consistent with the proposed mechanism of OGT 918 as an inhibitor of the first step in glycosphingolipid biosynthesis. Shrinkage of the thymus and spleen occurred at all doses after 7 days. This was reflected in a reduced cellularity of both organs and a shift in the surface antigens of B and T lymphocytes. These changes were reversible on withdrawal of treatment.

Prevention of lysosonal storag -e in Tay-Sachs mice treated with N-Butyldeoxynoji -rimycin.	Tay-Sachs transgenic mouse.	Diet admixture	4800 mg/kg/d Serum levels ~ 50 μM	Tay-Sachs transgenic mice were dosed by diet admixture from immediately post-weaning for up to 12 weeks. Shrinkage of spleen and thymus was observed (50% ↓ cellularity relative to controls). The untreated transgenic mice accumulate G_{M2} progressively in the brain with increasing age. Following treatment with OGT 918 G_{M2} accumulation was reduced relative to the age-matched controls (50% ↓). This indicates that OGT 918 can cross the blood-brain barrier in mice.
SC-48334: Enzyme inhibitio-n profile	Isolated α-glucosi –dase from porcine liver, β-glucosidase from almond and hexokinase from yeast	In vitro	Not given.	OGT 918 was tested for its inhibitory activity against key enzymes in carbohydrate metabolism. Ki's for OGT 918 are 0.22 μM for α-glucosidase and 1125 μM for β-glucosidase. OGT 918 did not inhibit hexokinase.
In vitro and in vivo effects of SC-48334 and a related amino sugar inhibitor on PGE2 production.	Human fetal fibroblast and/or peritoneal macrophages	In vitro	0 to 6 mg/ml	To see if OGT 918 could alter PGE2 production and act as an anti-inflammatory agent, fetal fibroblast and/or peritoneal macrophages were incubated with OGT 918. OGT 918 did not inhibit PGE2 synthesis. It was concluded that OGT 918 does not demonstrate any anti-inflammator -y activity.
OGT 918/ Ceredase in vivo combination study.	Female BALB c/Mouse	Diet admixture	4800 mg/kg/d. Serum levels ~50 μM	To determine if OGT 918 would inhibit Ceredase activity or not, mice were treated with OGT 918 to achieve high steady state concentrations (50 μM) and subsequently IV injected with concentrations of Ceredase equivalent to low dose enzyme therapy in man (5-10 U/kg). Enzyme activity was measured in serum at various time intervals post injection and both peak activity and serum half-life were determined. Both mean peak serum activity and mean half-life was elevated in OGT 918/Ceredase combinatio -n treated mice compared with mice receiving Ceredase alone. Thus OGT 918 would not compromise Ceredase activity in combination therapy.
Delayed symptom onset and increased life expectancy in Sandhoff disease mice treated with N-butyldeoxynoji -rimycin	Sandhoff transgenic mice	Diet admixture	2400, 4800 mg/kg/d Serum levels ~ 50 μM	Sandhoff transgenic mice were dosed by diet admixture at 2400 and 4800 mg/kg/d at 3 and 6 weeks of age respectively. This resulted in serum levels of ~ 50μM and CSF levels of 5μM. The untreated transgen -ic mice accumulate G_{M2} progressively with increasing age. Following treatment with OGT 918 at 3 or 6 weeks of age, life expectancy was extended by 40%, correlating with reduced glycosphingolipid accumulation. CSF levels of OGT 918 were 10% (5μM) of the serum levels.

Mechanism of action: OGT 918 has been shown to inhibit glucosyltransferase, which is the enzyme responsible for the generation of glycosphinglipids. In patients with lysosomal storage disease, the enzymes required for the catabolism of glycosphingolipid are defective. The sponsor's approach to treating Gaucher and Fabry's disease (lysosomal storage diseases) is

one of "substrate deprivation", to balance the rate of glycosphingolipid biosynthesis such that the amount of substrate that the defective enzyme has to catabolize is reduced to a level which matches the residual enzyme activity. If this occurs, it is predicted that glycosphingolipid storage will be reduced which will result in a mitigation of the associated pathology.

Drug activity related to proposed indication: OGT 918 has been shown to reduce cellular glycosphingolipid (GSL) levels in splenocytes and hepatocytes, hence reducing the size of liver and spleen in treated patients and animal models. By reducing the cellular glycosphingolipid (GSL) levels in splenocytes and hepatocytes, OGT 918 mitigates the pathology associated with glycosphingolipid storage.

Secondary pharmacodynamics:
Cell surface gangliosides were substantially reduced in the livers and spleens of OGT 918 treated (600, 1200 and 1800 mg/kg/day as escalating doses for 118 days) mice, indicating depletion of glycosphingolipids. There was shrinkage of the thymus and spleen at all doses of OGT 918 after 7 days. This was reflected in a reduced cellularity of both organs and a shift in the surface antigens of B and T lymphocytes. These changes were reversible on withdrawal of treatment. Shrinkage of spleen and thymus which correlated with 50% reduction in cellularity were also observed in Tay-Sachs mice treated with OGT 918. OGT 918 did not alter PGE2 production in an in vitro study with fetal fibroblast and/or peritoneal macrophages suggesting a lack of anti-inflammatory activity.

Initial studies for the development of OGT 918 were conducted by G.D. Searle to support its use in an HIV treatment indication. These studies were conducted at high doses to support the high doses administered to HIV patients in the clinic. In the early phase clinical work, it was seen that the plasma levels of OGT 918 required for HIV therapy could not be achieved without unacceptable adverse GI effects. As a consequence, the perbutyrated prodrug, OGT 924, was developed by Searle and also placed on nonclinical testing. This compound is rapidly and quantitatively converted to OGT 918 on absorption from the gut and so studies performed on this compound also provide relevant data on the toxicological effects of OGT 918.

Pharmacology summary: OGT 918 has been shown to have potent inhibitory effective on glucosylceramide transferase in vitro and in vivo, resulting in a sharp reduction in the synthesis of glucosylceramides. Studies in animal models of other glycolipid storage disease (Tay-Sachs transgenic mice, C57BL/6 mice, Sandhoff disease transgenic mice) demonstrated that cell surface gangliosides were substantially reduced in the livers and spleens of OGT 918 treated animals, indicating depletion of glycosphingolipids. In untreated Tay-Sachs transgenic mice, GM_2 accumulate progressively with increasing age. Following treatment with OGT 918, GM_2 accumulation was reduced relative to the age-matched controls (~50%). This indicated that OGT 918 could cross the blood-brain barrier in mice sufficiently to inhibit storage of GM_2 at the doses tested. Similarly, untreated Sandhoff disease transgenic mice also accumulate GM_2 progressively with increasing age. This results in a life expectancy of 4 to 5 months. Following treatment with OGT 918 at 3 or 6 weeks of age, life expectancy was extended by 40%, correlating with reduced glycosphingolipid accumulation.

OGT 918 was tested for its inhibitory activity against selected key enzymes in carbohydrate metabolism: Isolated α-glucosidase from porcine liver, β-glucosidase from almond and hexokinase from yeast. OGT 918 inhibited α-glucosidase (Ki = 0.22 μM) and β-glucosidase (Ki = 1125 μM). OGT 918 did not inhibit hexokinase. OGT 918 did not inhibit PGE2 synthesis in fetal fibroblast and/or peritoneal macrophages suggesting a lack of anti-inflammatory activity.

Since a potential treatment for Gaucher disease could be a combination therapy of OGT 918 and Ceredase (an approved enzyme therapy for Gaucher disease), mice were treated with the combination therapy to determine if OGT 918 would inhibit Ceredase. The results showed that both mean peak serum activity and mean half-life of Ceredase was elevated in OGT 918/Ceredase combination treated mice compared with mice receiving Ceredase alone. This indicated that OGT 918 did not inhibit activity of the enzyme (Ceredase). This demonstrated that combination therapy could be used clinically and OGT 918 would not compromise this approach.

Pharmacology conclusions: OGT 918 has been shown to be an effective inhibitor of glucosylceramide transferase in vitro and in vivo.

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III. SAFETY PHARMACOLOGY:

STUDY TITLE	TEST SYSTEM	ROUTE	DOSES	RESULTS
CNS Evaluation of SC-48334 in Mice	Mouse, [redacted] CD-1 male	Intra-gastric	60, 300, 600 mg/kg single dose.	OGT 918 did not produce signs of neurotoxicity at any dose. There were no effects on motor co-ordination, forelimb grip strength and spontaneous locomotor activity. There was no analgesia produced by the treatment nor any antagonism of morphine induced analgesia. The 600 mg/kg dose of OGT 918 did reduce the duration of barbiturate-induced sleep by a small (4.7 minutes) but statistically significant amount.
Cardiovascular Effects of SC-48334 in the Anesthetized Dog.	Mongrel dogs, male and female.	Intravenou-s infusion	Plasma levels of 10, 20 and 50 µg/ml. Total dose of 27 mg/kg over 60 minutes.	OGT 918 did not alter HR, MAP, cardiac output, or peripheral resistance at any dose compared to pre-treatment values. Thus OGT 918 did not alter systemic hemodynamic or ventricular function in anesthetized dogs.
SC-48334: Effect on gastrointestin-al motility and gastric secretion in the rat.	Rat. [redacted] [Crl:COBS.CD(SD) BR], male.	Intra-gastric	60, 280, 700 mg/kg single dose	The charcoal meal model was used to determine GI transit time. OGT 918 had no effect on GI transit at any dose. Gastric secretion was determined by pylorus ligation 30 minutes after dosing with OGT 918. There was no effect on gastric secretion at 60 and 280 mg/kg but secretory volume was reduced at 700 mg/kg and consequently total acid was also reduced.
Contractile effects of high concentrations of SC-49483 on segments of unstimulated guinea pig Ileum, in vitro.	Isolated guinea pig ileal strips.	In vitro	10^{-6}, 10^{-5}, 10^{-4} M	Lower concentrations of OGT 924 caused a slow tonic increase in contractile tone at about 10% of the acetylcholine response. This was considered a weak response. The HD of OGT 924 caused an increase at 37.6% of the anetylcholine response. However, this dose was formulated in 100% DMSO and the solvent alone produced an effect at 30.2% of the acetylcholine response. The corrected response was 7.4% of the acetylcholine response at 10^{-4} M. Overall, there is no dose response to these contractile effects. The tissue was able to respond to an acetylcholine response following exposure to OGT 924 at 96.8% of the first acetylcholine response. This indicates that OGT 924 has no adverse effects on the contractile ability of the tissue. Pre-treatment of the ileal slices with atropine did not affect the response of the tissue to OGT 924. This indicates that the mechanism of the response does not involve activation of the muscarinic cholinergic receptors.

Safety pharmacology summary:

CNS evaluation of OGT 918 in mice did not produce symptoms of neurotoxicity or impair motor co-ordination or forelimb grip strength. OCT 918 did not produce analgesic effects, antagonize

opiate-Induced analgesia or affect spontaneous locomotor activity. OGT 918 did produce a small magnitude of reduction in the duration of sleep induced by the barbiturate, hexabarbitol.

The ability of OGT 918 to alter hemodynamic or ventricular function in the anesthetized dog was investigated. OGT 918 did not alter HR, MAP, cardiac output, or total peripheral resistance at any dose compared to the pre-treatment values. OGT 918 also did not alter left ventricular systolic and end diastolic pressures, maximum left ventricular dp/dt, and PR or QRS interval at any dose up to 50 µg/ml I.V. compared to the pre-treatment values.

Studies on GI motility and gastric secretion demonstrated that OGT 918 at 60, 280 and 700 mg/kg intragastrically had no significant effect on GI transit of a charcoal meal in the rat. OGT 918 had no significant effect on gastric secretory volume, acid concentration or total acid output at 60 and 280 mg/kg intragastrically. It had no effect on acid concentration at 700 mg/kg, but gastric secretory volume and consequently total acid output were reduced significantly.

OGT 924 (SC 49483) was examined for its ability to produce isotonic contractions in isolated segments of guinea pig ileum in vitro. OGT 924 displayed minimal ability to stimulate contractile activity in the guinea pig ileum relative to acetylcholine.

Safety pharmacology conclusions: OCT 918 did not display any secondary pharmacological effects in the central nervous system of mice, cardiovascular system of dogs or gastrointestinal tract of rats. OGT 924 displayed minimal ability to stimulate contractile activity in the guinea pig ileum.

III. PHARMACOKINETICS/TOXICOKINETICS:

PK parameters:

The active drug (OCT 918) and the prodrug (OGT 924) have both been investigated in a number of animal species including the mouse, rat, dog and monkey. OGT 914 is the perbutyrated derivative of OGT 918 developed in an attempt to avoid the GI side effects. In addition, in vitro studies have been conducted to determine protein binding, in vitro metabolism and inhibition of cytochrome P450 enzymes.

CONVERSION OF OGT 924 TO OGT 918

In Vivo Studies:

in a number of studies reported for OGT 924, the extent and site of conversion to OGT 918 has been monitored. In the rat (MRC-90B-0183, MRC-91S-0086) there was extensive hydrolysis of an oral dose of ^{14}C-OGT 924 to OGT 918 in the gastrointestinal tract followed by absorption of OGT 918, while there was no indication of absorption of OGT 924 or other metabolites of OGT 924 hydrolysis. —— profiling indicated that >87% of plasma radioactivity and 91% of urine radioactivity was associated with OGT 918.

In the monkey (MRC-91S-0088) there was also extensive hydrolysis of orally administered ^{14}C-OGT 924 to OGT 918 in the gastrointestinal tract followed by absorption of OGT 918, with no indication of absorption of OGT 924 or other metabolites of OGT 924 hydrolysis. —— profiles of plasma and urine indicated that 94% of plasma radioactivity and 53-70% of urinary radioactivity was associated with OGT 918.

In the dog (MRC-92S-0012), although there was extensive hydrolysis of orally administered ^{14}C -924 to OGT 918 in the gastrointestinal tract followed by absorption of OGT 918, this was not as

extensive as in the rat and monkey. In ——— profiles, >90% of plasma radioactivity and the majority of urinary radioactivity was associated with OGT 918. However, other peaks, not reported in the rat and monkey were also seen which indicated the absorption of OGT 924 or partially de-esterified intermediates of OGT 924.

Therefore, in the rat and monkey, the systemic effect of oral absorption would be comparable to the administration of OGT 918. This may not however be the case for the dog, where following oral administration of ^{14}C-OGT 924 the extent and rate of gastric hydrolysis was reduced, leading to a different profile of radioactivity in plasma and urine.

To support the use of OGT 918, the data generated following administration of OGT 924 to the rat and monkey is more representative of OGT 918 than that in the dog.

Plasma concentrations (µg SC-48334 equivalents/ml) of total radioactivity after oral administration of [^{14}C] SC-48334 and [^{14}C] SC-49483 to the dog (MRC-92S-0012) at doses of 80 and 183 mg/kg respectively.

[^{14}C] SC-48334 – 80 mg/kg		[^{14}C] SC-49483 – 183 mg/kg	
Time Interval (hr)	Mean Plasma concentration (µg SC-48334 equivalents/ml)	Time Interval (hr)	Mean Plasma concentration (µg SC-48334 equivalents/ml)
0.5	9.59	0.5	1.15
1.0	98.9	1.0	3.32
3.0	53.7	3.0	4.92
5.0	30.4	5.0	3.06
8.0	13.4	8.0	1.62
24.0	1.10	24.0	0.63

Cumulative percentage of doses excreted in urine as total radioactivity after oral administration of [^{14}C] SC-48334 and [^{14}C] SC-49483 to the dog (MRC-92S-0012) at doses of 80 and 183 mg/kg respectively.

[^{14}C] SC-48334 – 80 mg/kg		[^{14}C] SC-49483 – 183 mg/kg	
Time Interval (hr)	Mean % of dose excreted in urine (µg SC-48334 equivalents/ml)	Time Interval (hr)	Mean % of dose excreted in urine (µg SC-48334 equivalents/ml)
0 - 24	82.5	0 - 24	6.26
0 - 48	86.4	0 - 48	26.7

Comparative metabolism of [^{14}C] SC-48334 and [^{14}C] SC-49483 following oral administration to the monkey (MRC-91S-0088).

Plasma concentrations (µg SC-48334 equivalents/ml) of total radioactivity after oral administration of [^{14}C] SC-48334 and [^{14}C] SC-49483 to the monkey at doses of 55 and 125mg/kg respectively.

[^{14}C] SC-48334 – 55 mg/kg		[^{14}C] SC-49483 – 125 mg/kg	
Time Interval (hr)	Mean Plasma concentration (µg SC-48334 equivalents/ml)	Time Interval (hr)	Mean Plasma concentration (µg SC-48334 equivalents/ml)
1	34.7	1	2.13
8	4.24	8	4.38

Cumulative percentage of doses excreted in urine as total radioactivity after oral administration of [^{14}C] SC-48334 and [^{14}C] SC-49483 to the monkey at doses of 55 and 125 mg/kg respectively.

[^{14}C] SC-48334 – 55 mg/kg		[^{14}C] SC-49483 – 125 mg/kg	
Time Interval (hr)	Mean % of dose excreted in urine (µg SC-48334 equivalents/ml)	Time Interval (hr)	Mean % of dose excreted in urine (µg SC-48334 equivalents/ml)
0 - 24	72.3	0 - 24	29.5
0 - 48	73.9	0 - 48	41.4

Plasma and CSF concentrations (µg SC-48334 equivalents/ml) of total tritium after multiple oral doses (55 mg/kg) of [^{3}H]SC-48334 to the Rhesus monkey (MRC-89S-0070).

[^{3}H] SC-48334 – 55 mg/kg		[^{3}H] SC-48334 – 55 mg/kg	
Time Interval (hr)	Mean Plasma concentration (µg SC-48334 equivalents/ml)	Time Interval (hr)	Mean CSF concentration (µg SC-48334 equivalents/ml)
8 hr after 6th dose	11.5	8 hr after 6th dose	3.45
8 hr after 7th dose	13.6	8 hr after 7th dose	4.00

Plasma and CSF concentrations (µg/ml) of [^{3}H]SC-48334 after multiple oral doses (55 mg/kg) of [^{3}H]SC-48334 to the Rhesus monkey (MRC-89S-0070).

[^{3}H] SC-48334 – 55 mg/kg		[^{3}H] SC-48334 – 55 mg/kg	
Time Interval (hr)	Mean Plasma concentration (µg/ml)	Time Interval (hr)	Mean CSF concentration (µg/ml)
8 hr after 6th dose	8.08	8 hr after 6th dose	0.75
8 hr after 7th dose	9.75	8 hr after 7th dose	0.73

Plasma concentrations (µg SC-48334 equivalents/ml) of total radioactivity after IV and oral administration of [^{14}C] SC-49483 to the rat (MRC-91S-0086) at doses of 13.7 or 137 mg (6 or 60 mg SC-48334 equivalents)/kg respectively.

[^{14}C] SC-49483 – 13.7 mg/kg (IV)		[^{14}C] SC-49483 – 137 mg/kg (ORAL)	
Time Interval (hr)	Mean Plasma concentration (µg SC-48334 equivalents/ml)	Time Interval (hr)	Mean Plasma concentration (µg SC-48334 equivalents/ml)
0.08	7.03	-	-
0.25	4.44	0.25	3.03
0.50	2.70	0.50	4.41
1.0	1.67	1.0	5.97
2.0	0.93	2.0	3.45
4.0	0.40	4.0	1.14
8.0	0.098	8.0	0.49
24.0	0.030	24.0	0.07

Cumulative percentage of doses excreted in urine as total radioactivity after IV administration of [^{14}C] SC-49483 to the rat (MRC-91S-0086) at doses of 13.7 and 137 mg/kg respectively.

[^{14}C] SC-49483 – 13.7 mg/kg (IV)		[^{14}C] SC-49483 – 137 mg/kg (ORAL)	
Time Interval (hr)	Mean % of dose excreted in urine (µg SC-48334 equivalents/ml)	Time Interval (hr)	Mean % of dose excreted in urine (µg SC-48334 equivalents/ml)
0 - 24	88.1	0 - 24	73.2
0 - 48	90.6	0 - 48	74.0

To investigate the metabolic stability of OGT 924, ^{14}C-OGT 924 was incubated in buffer, whole blood, liver S9 fraction and sections of duodenum, jejunum, ileum and proximal and distal colon from rat, dog, cynomolgus monkey and man. The table below shows the amount of OGT 924 remaining after 30 minutes incubation.

Stability of OGT 924 following incubation for 30 minutes with various tissues from the rat, dog, cynomolgus monkey and man (MRC-93S-0028)

Tissue	% ^{14}C-OGT 924 remaining after 30 minutes incubation			
	Rat	Dog	Cyno. monkey	Man
Duodenum	0	97.5	86.7	90.7
Jejunum	0.12	98.0	85.8	82.9
Ileum	67.4	97.9	88.3	75.8
Proximal colon	92.8	97.5	96.9	Not determined
Distal colon	93.7	96.3	97.7	Not determined
Liver S9	8.81	44.4	0.26	2.80
Blood	27.9	60.4	50.5	

In the duodenum and jejunum mucosa hydrolysis was greatest in rat, followed by human and monkey, with limited hydrolysis in the dog. In ileum the order was the same but the extent of hydrolysis was reduced. In the colon, hydrolysis was minimal in all species. With the liver S9 fraction there was extensive hydrolysis in all species with greater than 90% hydrolyzed after 30 minutes incubation in rat, monkey and man and 53% hydrolyzed in the dog.

Overall it was concluded that in all tissues and species, ^{14}C-OGT 924 was hydrolyzed to ^{14}C-OGT 918. There was variation between species so that OGT 924 was least stable in rat blood and tissues and most stable in dog blood and tissues with the monkey and human results intermediate between.

Absorption:

Pharmacokinetic data was generated after single oral administration of 60 to 600 mg/kg ^{3}H-OGT 918 to mice and single and multiple dose administration of ^{3}H-OGT 918 to rats and monkeys at doses of 60-1400 mg/kg and 55-550 mg/kg, respectively. The data from these studies are summarized in the following tables.

Radiolabelled Studies

Pharmacokinetic parameters of non-volatile radioactivity following a single oral dose of ^{3}H-OGT 918 to male mice (MRC-88S-0051).

Dose (mg/kg)	$AUC_{0-\infty}$ (µg.h/ml)	C_{max} (µg/ml)	t_{max} (hours)	F (%)
60	31.6	29.4	0.25	75.7
160	77	51.3	0.25	69.2
300	172	101	0.5	82.4
600	422	230	0.5	101

AUC = Area under plasma concentration time curve; C_{max} = Maximum observed plasma concentration; t_{max} = Time occurrence of C_{max}; F = Extent of absorption;

Pharmacokinetic parameters of non-volatile radioactivity following three times daily oral doses of ^{3}H -OGT 918 to rats (MRC-88S-0059).

Dose	$AUC_{(0-8h)}$ (µg.h/ml)		C_{max} (µg/ml)		t_{max} (hours)		F (%)
(mg/kg)	1st dose	7th dose	1st dose	7th dose	1st dose	7th dose	
60	16.6	24.4	3.89	5.7	0.6	0.5	-
160	37.8	63.8	8.19	14	0.8	1	58.0
1400	239	509	50.3	108	0.4	0.4	-

Pharmacokinetic parameters of non-volatile radioactivity following three times daily oral doses of ^{3}H -OGT 918 to monkeys (MRC-88S-0060).

Dose	$AUC_{(0-8h)}$ (µg.h/ml)		C_{max} (µg/ml)		t_{max} (hours)		F (%)
(mg/kg)	1st dose	7th dose	1st dose	7th dose	1st dose	7th dose	
55	118	159	27.8	32.8	1	2	-
165	205	420	43.1	90.9	3	2	69.2
550	388	1130	80.4	214	3	2	-

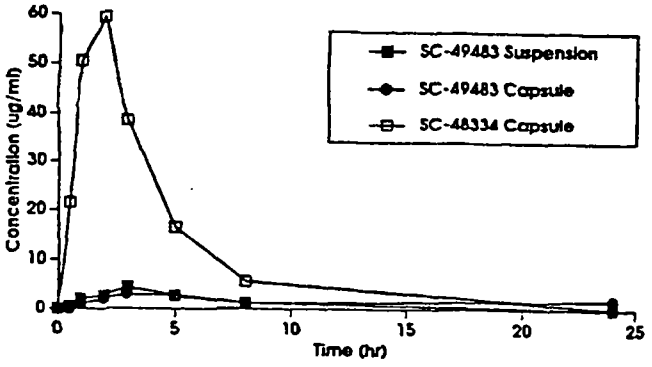
Pharmacokinetic parameters of non-volatile radioactivity (OGT 918) following a single intravenous dose of ^{3}H-OGT 918 (MRC-88S-0071).

Species	Dose (mg/kg)	CL (ml/min/kg)	CL_R (ml/min/kg)	GFR* (ml/min/kg)	V_d (l/kg)	$t_{1/2}$ (h)	Fe (% dose)
Mouse	160	24	NC#	15	2.1	1	93-96
Rat	160	17	NC#	7	1.8	1	89
Dog	40	3.4	NC#	4	0.8	3	89
Monkey	160	4.3 (5-6)	2.4	5	0.7 (0.7-0.8)	2-1	82

Values in parentheses were derived after intravenous administration of unchanged OGT 918
# Assumed to be equivalent to CL since ≥90% excreted in urine. *Approximated as 6.5 * BW $^{0.79}$
CL = Systemic plasma clearance; CL_R = Renal clearance, GFR = Glomerular Filtration Rate; V_d = Volume of distribution; $t_{1/2}$ = Apparent terminal rate half-life; Fe = Proportion of dose excreted in urine

Non-Radiolabelled Studies

Mean plasma concentrations of SC-48334 after oral administration of SC-49483 as neat chemical in gelatin capsules or 0.5% methylcellulose/0.1% polysorbate suspension and after oral administration of SC-48334 as a capsule. The dose for SC-49483 was 183 mg (80 mg SC-48334 equivalents)/kg and the dose for SC-48334 was 80 mg/kg (PSA-92S-3949).



Day 11 PK data from a Two-week oral capsule comparative study of SC-48334 and SC-49483 in the dog (PSA-92S-3905). Report # MRC-92S-0006.

Compound	Dose (mg/kg)	Sex	T_{max} (hr)	C_{max} (µg/ml)	AUC_{0-8hr} (µg.h/ml)
SC-48334	80	F	1.00	73.07	280.12
		M	1.67	60.30	264.40
		M + F	1.33	66.68	272.26
SC-49483	183	F	1.17	7.15	39.98
		M	3.67	5.36	30.98
		M + F	2.42	6.26	35.48

Pharmacokinetic parameters of OGT 918 following three times daily oral doses of OCT 918 to rats for 13 weeks (*DWV11007; +4MRC-89S-0047).

Dose	AUC_{0-8h} (µg.h/ml)			C_{max} (µg/ml)			t_{max} (hours)		
(mg/kg)	Week 1	Week 4	Week 13	Week 1	Week 4	Week 13	Week 1	Week 4	Week 13
6.7*	3.7	4.4	7	1.7	1.2	2.4	0.5	0.8	0.5
20*	11.7	12.8	18	3.1	2.6	3.5	0.5	0.5	0.5
60*	41.7	40.9	46.6	4.7	5.4	7.8	0.5	1	0.5
30+	NC	NC	17.5	3.2	NC	7.7	0.5	NC	0.5
60+	19.4	NC	45.7	5.1	NC	14.3	1	NC	1
140+	38.6	NC	82.8	9	NC	25.3	0.5	NC	0.5
280+	71.11	NC	168	19.4	NC	55.2	1.	NC	1

***DWV11007; +4MRC-89S-0047; #AUC0-24hr for DWV11OO7 and AUC for MRC-89S-0047; NC = not calculated**

Pharmacokinetic parameters of OGT 918 following three times daily oral doses of OGT 918 to rats for 52 weeks (MRC-90S-0086).

Dose	AUC_{0-8h} (µg.h/ml)			C_{max} (µg/ml)			t_{max} (hours)		
(mg/kg)	Week 1	Week 26	Week 52	Week 1	Week 26	Week 52	Week 1	Week 26	Week 52
60	16.5	NC	36.2	4.2	2.7	11.3	1	4	0.5
140	32.7	61.3	66.4	6.1	20.2	15.6	1	0.5	1
280	50.4	93.7	93.3	10.5	26.4	36.9	0.5	1	1
560	207	NC	NC	32	NC	NC	4	NC	NC

Mean plasma concentrations (µg/ml) of OGT 918 following three times daily oral doses of OGT 918 to juvenile rats for 10 weeks (DWVI1011).

Dose (mg/kg)	Day 21*	Day 35*	Day 70*
6.7	2.2	1.6	1.6
20	6.2	3.3	2.7
60	16.2	5.5	5.7

*Samples were taken 30 minutes post first daily dose

Pharmacokinetic parameters of OGT 918 following three times daily oral doses of OGT 924 to monkeys for 52 weeks (1514/9-D0142)

Dose	AUC_{0-8h} (µg.h/ml)			C_{max} (µg/ml)			t_{max} (hours)		
(mg/kg)	Week 1	Week 26	Week 52	Week 1	Week 26	Week 52	Week 1	Week 26	Week 52
750	24.4	36.5	43.7	4.5	7	8.5	1-5	1-1	1-3
2000	33.1	47.7	68.9	5.5	8.4	14	1-5	1-5	1-5

Pharmacokinetic parameters of OCT 918 after single intravenous administration of OGT 918 to cynomolgus monkeys (PSSA-94C-4142).

Dose (mg/kg)	$AUC_{0-\infty}$ (µg.h/ml)	$t_{1/2}$ (hours)
20	60.1	1.34
200	537	1.77

Pharmacokinetic parameters of OCT 918 after three times daily intravenous dosing of OGT 918 to cynomolgus monkeys for 28 days (PSA-94S-0180).

Dose (mg/kg)	$AUC_{0-\infty}$ (µg.h/ml)		$t_{1/2}$ (hours)	
	Day 1	Day 28	Day 1	Day 28
20	56	49.8	1.52	1.86
100	318	409	1.74	1.68
200	646	701	1.64	1.47

Distribution: The tissue distribution of total radioactivity was studied qualitatively (MCR-92B-0345) and quantitatively (MCR-92S-0008) by whole body autoradiography in the rat. The results of the 2 studies were in agreement and indicated that following an oral administration of ^{14}C-OGT 924 (137 mg/kg; equivalent to 60 mg/kg OGT 918), radioactivity was rapidly absorbed with peak concentrations measured at 1 hour post dose and then rapidly excreted with the majority of the dose (84.5%) excreted within 24 hours.

Highest concentrations were measured in GI tract, urinary bladder and kidney, consistent with an oral dose and subsequent excretion via urine. There was some penetration of radioactivity into tissues with tissue:plasma ratios >1 but no evidence of retention of radioactivity, with the longest elimination half lives in bone marrow (20.4 hours), eye (not lens, 18.0 hours) and brain (17.6 hours).

Blood and plasma concentrations of total radioactivity after oral administration of [^{14}C]-SC-49483 in the rat qualitatively (MCR-92B-0345).

RAT ID	TIME (hrs)	BLOOD (µg/mL)	PLASMA (µg/mL)
286-0001	1		
286-0008	1		
286-0003	8		
286-0010	8		
286-0004	24	BLQ	BLQ
286-0012	24	BLQ	BLQ

BLQ means that the concentration was below the limit of quantification (three times the background).

Pharmacokinetic parameters of total radioactivity in the plasma, red blood cells and tissues after oral administration of [^{14}C]-SC-49483 to male rats at a dose of 137 mg/kg (MCR-92S-0008).

Tissue	C_{max} (µg equiv/g)	t_{max} (hours)	AUC (µg equiv.h/g)	$t_{1/2}$ (hours)	Tissue/plasma ratio
Plasma	12.8	1	63.4	12.4	
Red blood cells	11.1	1	62.6	11.4	
Adrenals	11.9	1	84.5	14.9	
Bone marrow	5.91	4	68.1	20.4	
Brain	0.815	4	22.5	17.6	
Carcass	12.6	1	110	11.3	
Cecum	259	8	3310	5.87	
Eye	6.11	4	115	18.0	
Eye lens	1.02	4	16.7	11.6	
Heart	12.3	1	65.7	6.54	
Kidney	151	1	667	8.56	
L. intestine	137	8	1720	5.13	
Liver	36.1	1	207	10.8	
Lungs	14.5	1	78.7	9.79	
Salivary gland	27.5	4	304	5.50	
S. intestine	294	1	1030	5.46	
Spleen	13.6	1	116	7.29	
Stomach	248	4	1970	8.87	
Testes	2.69	1	46.0	12.9	
Urinary bladder	201	1	1500	7.97	

Metabolism: In the mouse following both i.v. and oral administration of ^{3}H-OGT 918 (MRC-88S-0051), plasma radioactivity was present mainly as parent material (87.1% and 96.2% at 0.5 hours following oral and intravenous administration). However, the presence of tritiated water, which increased with time, may indicate some metabolism, but this could also be due to simple exchange of the tritium radiolabel with body water. In urine, the majority of the excreted radioactivity was present as OGT 918 (93.0—95.6%) indicating that there was minimal metabolism of OGT 918.

In the rat following oral administration of ^{3}H-OGT 918 (MRC-88S-0059), plasma radioactivity was present mainly as parent material (>85% one hour after dosing and >62% eight hours after dosing), with the remaining radioactivity present mainly as tritiated water, indicating metabolism was limited.

In the dog following oral administration of ^{14}C-OGT 918 (MRC-92S-0012), plasma and urinary radioactivity was present mainly as parent material. In plasma, 5 hours after dosing, >90% of the radioactivity was associated with OGT 918. In urine collected 0-12 hours after dosing, a single component corresponding to OGT 918 was detected. Following intravenous infusion of OGT 918 to the dog, there was also no metabolism detected, with no component other than OGT 918 present in either plasma or urine.

In the rhesus monkey at 1 and 8 hours following intravenous and oral administration of ^{3}H-OGT 918 (MRC-88S-0060), plasma radioactivity was present mainly as parent material (>94%, except for 78.7% in oral eight hour plasma). Remaining radioactivity was associated with volatile tritiated water, indicating metabolism was limited.

In the mouse, rat, dog and monkey there appeared to be only a single major component seen in plasma and urine following administration of OGT 918. Sponsor stated that in some studies there were other minor components reported, both more and less polar than parent but these were not present in all samples and were considered to be of minor importance (no data).

A further in vitro study (DWVK1007) investigated the metabolic stability of OGT 918 during incubation with rat, monkey and human microsomes and did not detect any breakdown of OGT 918 during the 2 hour incubations, suggesting that OGT 918 was not metabolized by liver microsomes from the rat, monkey or man.

Overall, very little metabolism of OGT 918 was seen either in vivo or in vitro.

Excretion: Following administration of ^{3}H-OGT 918 to the mouse (MRC-88S-0051), radioactivity was rapidly cleared, mainly via urine with 93.0% of the administered dose excreted within 24 hours following intravenous administration and 70.7-83.6% recovered within 24 hours following oral administration. The excretion of radioactivity in the urine following oral administration was not affected by dose levels between 60-600 mg/kg. Excretion of radioactivity in feces was negligible after intravenous (1.8%) and low after oral administration (3.8-14.0%) at all doses.

Following either single oral or intravenous administration of ^{3}H-OGT 918 to the rat (MRC-88S-0059), the radioactivity was rapidly excreted, with the majority of the administered dose excreted in urine. In the 24 hours following oral administration, 63.2% and 73.5% of the total radioactivity was recovered in urine with 21.2% and 13.2% in the feces in males and females, respectively. This increased to 65.4% and 75.7% recovered in urine with 22.8% and 13.9% in the feces in males and females, respectively by 72 hours post-dose. Following intravenous

administration to male rats, 88.6% of the total radioactivity was recovered in urine and 2.6% in feces. Following oral and intravenous administration, the majority of the urinary radioactivity was present as non-volatile material.

In the dog, following an intravenous infusion of ^{14}C-OGT 918 (MRC-88S-0071), the radioactivity was rapidly excreted, with the majority of the administered dose excreted in urine. In the 72 hours following intravenous administration, 89.0% of the administered dose was recovered in urine, with the majority, 87.2% in the first 24 hours. Following single oral administration of ^{14}C-OGT 918 at 80 mg/kg the majority of the radioactivity was excreted in urine (86.4% within 48 hours).

Following either single oral or i.v. administration of ^{3}H-OGT 918 to the rhesus monkey (MRC-88S-0060), the majority of the administered dose was excreted in urine. In the 72 hours following oral administration, 61.5% of the total radioactivity was recovered in urine with 14.7% in the feces. Of this, the majority (58.1% and 9.7%. respectively) was recovered in the first 24 hours. In the 24 hours following intravenous administration, 82.3% of the total radioactivity was recovered in urine and <1.0% in feces.

Other studies:
Protein binding: The extent of binding of radioactivity from ^{14}C-OGT 918 to plasma proteins and red blood cells was investigated in the rat, monkey and man (DWVK1009). In all species there was no indication of binding of radioactivity to plasma proteins. There was some blood cell binding, which accounted for 36.0%, 39.2% and 38.8% of the radioactivity in the rat, monkey and man, respectively.

STUDY TITLE	TEST SYSTEM	RESULTS
Potential inhibitory effect of OGT 918 on the metabolism of cytochrome P450 model substr -ates (DWVK1000).	Model substrates of CYP1A2 (ethoxyresorufin), CYP2A6 (coumarin), CYP2C9 (tolbutamide), CYP2C19 (S-mephenytoin), CYP2-D6 (bufuralol), CYP2E1 (chlorzoxazone), CYP3A4 (testosterone), CYP4A11 (lauric Acid) were incubated with OGT 918 at a single concentration of 20 µg/ml in the presence of pooled hepatic microsome -s. Inhibition of enzyme activity by OGT 918 was expressed as percentage of control enzyme activity remaining.	OGT 918 slightly inhibited 7-ethoxyresorufin O-deethylase activity (CYP1A2) and chlorzoxazone 6-hydroxylase activity (CYP2E1) (91.6 and 91.0 % of control activity remaining, respectively). Negligible inhibition of S-mephenytoin 4-hydroxylase (CYP2C 19) was observed. A slight elevation in catalytic activity was observed with coumarin 7-hydroxylase (CYP2A6), tolbutamide 4-hydroxylase (CYP2C9), bufuralol 1-hydroxylase (CYP2D6), testosterone 6β-hydroxylase (CYP3A4) and lauric acid hydroxylase (CYP4A11). At a concentration of 20 µg/ml OGT 918 showed little or no inhibitory potential against CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP3A4 or CYP4A11 activity, and only slight potential to inhibit the activity of CYP1A2 and CYP2E1. As the concentration of OGT 918 screened is 10-fold higher than peak plasma concentrations, it is unlikely that OGT 918 would cause clinically relevant drug-drug interactions.

PK/TK summary: In all species, following administration of the prodrug, OGT 924, there was significant hydrolysis within the GI tract to form OGT 918, which was then absorbed. There was no absorption of OGT 924 or intermediaries except in the dog,.

The absorption of OGT 918 was rapid and extensive, with peak plasma measured at approximately 1 hour. There was a dose proportional increase in systemic exposure of mice, rats, dogs and monkeys at dose levels of 20-840 mg/kg/day. There were no apparent sex-related differences in systemic exposure to OGT 918.

Systemic clearance correlates with bodyweight of mice, rats, dogs and monkeys. The volume of distribution was similar to or greater than total body water volume in mice, rats, dogs and monkeys. There was distribution to the brain in mice and monkeys.

Elimination of OGT 918 was mainly by renal clearance. Fecal excretion was variable and likely due to non-absorbed dose material. From intravenous studies there was no indication of any biliary elimination.

——— profiling of plasma and urine samples indicated that the only component present following oral administration of radiolabelled OGT 918 to mouse, rat, dog and monkey had the same retention time as parent OGT 918, suggesting minimal or no metabolism of OGT 918.

In vitro incubations of OGT 918 with rat, monkey and human microsomes have also shown no metabolism of OGT 918. This supports the results of the in vivo studies in rat and monkey and indicates that in man the metabolism of OGT 918 is likely to be similar to that already seen in the nonclinical studies.

Tissue distribution of radioactivity following oral administration of radiolabelled OGT 924 indicated that there was penetration of radioactivity into tissues but that subsequent clearance from tissues was rapid ($t_{1/2}$ <20 hours) and that there was no indication of any retention in tissues.

PK/TK conclusions: In vivo and in vitro studies with OGT 924 have shown that it is rapidly converted to OGT 918 in the rat and monkey. Sponsor stated that studies conducted with OGT 924 in these species can be considered equivalent to studies conducted with OGT 918. OGT 918 was rapidly and extensively absorbed in a dose proportional manner across species with peak plasma concentration measured at approximately 1 hour. Elimination of OGT 918 was mainly by renal clearance. Overall, very little metabolism of OGT 918 was seen either in vivo or in vitro.

IV. GENERAL TOXICOLOGY:

Acute Toxicity Studies (Non GLP Studies)

STUDY NUMBER/TITLE	DOSES (mg/kg) /DURATION	KEY TREATMENT-RELATED TOXICOLOGIC FINDINGS
PSA-89S-3402: Range-finding acute oral toxicity study of SC-48334 in mice.	2800, 5000 mg/kg Single oral dose, animals were observed for 7 days post dose.	No deaths. Clinical signs of soft stool were observed on day 2 in 5/10 LD and 8/10 HD mice. LD_{50} > 5000 mg/kg.
PSA-90S-3493: Range-finding acute 24 hour infusion tolerance study of SC-48334 in male rats.	10.6, 31.8, 53 and 106 mg/kg/hr (13.5 ml/24 hr dose volume). IV infusion. Animals were observed for 8 days after dosing.	No deaths occurred. Swollen limbs were observed in 5/5 animals of the 106 mg/kg/hr group during the first four hours of dosing. The swelling was reversed. Mean body weight was significantly decreased in both the 53 and 106 mg/kg/hr animals. LD_{50} > 106 mg/kg/hr.
PSA-89S-3491: An exploratory range finding study of SC-48334 in mice.	1250, 2500, 5000 mg/kg. 24 h observation period.	All animals survived 24 h. All (3/3) HD animals appeared unkempt.

Subacute Toxicity Studies (Non GLP Studies)

STUDY NUMBER/TITLE	DOSES (mg/kg) /DURATION	KEY TREATMENT-RELATED TOXICOLOGIC FINDINGS
PSA-90S-3589: Five day oral comparative study of SC-48334 and SC-49483 in the rat.	OGT 918: 1680. OGT 924: 1680. 4/sex/group. Dosed daily by gavage for 5 consecuti - ve days.	No deaths. Watery stool was observed in 7/8 animals dosed with SC-48334 but not in animals dosed with SC-49483. Feces of control animals were not different from those of animals dosed with SC-49483.
PSA-90S-3610: Five day oral comparative study of SC-48334 and SC-49483 in the rat.	OGT 918: 1200, 1680 OGT 924: 2740, 3830 5/sex/group. Dosed daily by gavage for 5 consecuti -ve days.	There were no deaths in the study. Watery stool was observed in 9/10 and 8/10 animals dosed with 1200 and 1680 mg/kg/day OGT 918, respectively. In rats dosed with OGT 924, watery stool was observed in 1/10 animals in each of the 2740 and 3830 mg/kg/day groups. Swollen limbs and face were observed in 1/10 animals dosed with OGT 918 at 1200 mg/kg/day. Swollen limbs and/or faces were also observed in 8/10

		animals dosed with OGT 924 at 2740 mg/kg/day and 6/10 at 3830 mg/kg/day. OGT 924 demonstrated significantly less diarrhea activity when compared to equimolar doses of OGT 918.
PSA-90S-3578: Eight day oral toxicity study of SC-48334 in the rat.	OGT 918: 840, 1680, 3400. Gavage. 5/sex/group. Dosed daily by gavage for 8 consecutiv –e days.	1/10 animals in the 3400 mg/kg/d group died. 7/10 animals given 840 mg/kg/day exhibited watery stool at least once during the treatment phase of the study. 10/10 animals in both the 1680 and 3400 mg/kg/day groups exhibited diarrhea. Consistent results were achieved at both the 1680 mg/kg/day and the 3400 mg/kg/day dosage, however, due to the death of one 3400 mg/kg animal, this dosage is considered excessively high. It is recommended that 1680 mg SC-48334/kg administered once daily be used in the future repeated dose studies for eliciting diarrhea in rats.
PSA-91S-3609: Oral comparative study of SC-48334 and SC-49483 in the dog.	OGT 918: 120 OGT 924: 275 Doses were administered in gelatin capsules to 2/sex/group in three divided doses for 11 days.	No animals died. Sporadic findings of vomitus and soft stools or watery stools were observed with about equal frequency with both test compounds. There were no toxicologically meaningful changes seen in physical examinations, body weights, or food consumption from either test article. AST levels were markedly increased over baseline levels in all dogs of both groups on Days 5 and 12. The values of dogs given OGT 918 were statistically significantly higher, but the differences between compounds were not toxicologically meaningful. No gross lesions of the GI tract were observed at necropsy. Histologically, the only treatment-related change was slight to mild atrophy (lymphoid depletion) of Peyer's patches in the ileum of the two males treated with OGT 918. Sponsor stated that the Peyer's patches of the males treated with OGT 924, may also have been affected, but this was equivocal. Sponsor stated that there was no evidence of enteritis in the treated animals as seen in previous dog studies of OGT 918.
PSA-89C-3394: Two week oral range-finding study of SC-48334 in the dog.	OGT 918: 85, 165, 495, 825. Doses were administered orally (capsules) to 2/sex/group in three divided doses for 2 weeks.	Treatment with OGT 918 for 8 days caused ataxia, bloody discharge, hypoactivity, anorexia, vomiting and death. Changes (elevated heart rate, decreased body temperature, labored breathing, pale mucous membranes, diminished or absent pupillary, palpebral or patellar reflexes) were noted as the animals treated with 495 or 825 mg/kg/day became moribund on Days 6 and 8. Mortality: ¼, 4/4 and 4/4 for for LD, MD & HD. Due to high mortality, dosing was discontinued for all surviving animals after the third dose on day 7. On day 8, all surviving animals in the MD and HD groups were sacrificed and necropsied. On day 15, the LD animals were necropsied (7 day recovery). Body weight losses ranging from 3% to 26% occurred over approximately one week. Dose dependent ↓ food consumption was noted at all doses. OGT 918 caused ↓ platelet count, reticulocyte count, absolute lymphocyte count and ↑ AST at all dose levels; ↑ partial thromboplastin time and ALT at 165 mg/kg/day or more; and ↑ white blood cell count, absolute neutrophil count and ↓ Na, K, and Cl at 495 mg/kg/day or more. Treatment-related changes were found in the spleen, thymus and lymph nodes of animals that died on test or were sacrificed in a moribund condition. Changes found in the GI tract included necrosis of the crypt epithelium with dilation and plugging, necrosis of the villus tips, and presence (greater than normal) of bacteria in the deep crypts. At least partial evidence of recovery was noted in the 165 mg/kg/day group (which was the only group in which recovery was assessed). During the recovery period, food consumption, bodyweights and clinical chemistry effects tended to move back toward control levels. Because of the changes in food consumption, bodyweight, clinical pathology variables or microscopic pathology which occurred at 85 mg/kg/day, a NOAEL could not be established. The most sensitive organ system appeared to be the GI tract. No histopathology suggestive of neurotoxicity. 495 mg/kg = 160x clinical dose based on mg/m^2. 825 mg/kg = 266x clinical dose.
PSA-89C-3467. Two wee –k oral range-finding toxicity study of OGT 918 in the dog.	OGT 918: 20, 40, 80 Doses were administered orally (capsule) to 2/sex/ group in three divided doses/day for 2 weeks.	No deaths. Loose stools, diarrhea and vomiting were observed at all doses. ½ HD females displayed more severe signs of toxicity, including bloody diarrhea, dehydration and lethargy. Body weight loss in both sexes and decreases in food consumption in females was observed at HD. No OGT 918 related hematological effects were identified. ↑ in AST occurred in both sexes at MD and HD; otherwise there were no OGT 918 related clinical chemistry changes of toxicological importance. Microscopically, there was evidence of lymphoid depletion of Peyer's patches and colonic mucosal irritation in the same HD female that displayed the more severe clinical signs. Evidence of mild lymphoid

		depletion occurred at MD and of thymic involution at HD. NOAEL = 20 mg/kg/d based on histopathology.
PSA-90S-3533: Four week escalating dosage oral toxicity study of SC-48334 in the dog	OGT 918: 35, 70, 105, 140 mg/kg/d total dose. Dog: 2/sex/group. Two different escalating regimens were used: one with continuous dosing and one with a two day rest period between dose escalations. Dogs in Groups 1 (control, empty capsules) and 3 were dosed daily throughout the study. Group 2 was dosed Thursday through Monday during Weeks 1, 2 and 3 and then weekly during Week 4. Total doses for Groups 2 and 3 were 35, 70, 105 and 140 mg/kg/day for Weeks 1, 2, 3, and 4, respectively. Group 4 was dosed at 140 mg/kg/day during Week 4 only. Animals were dosed three times daily with equally divided doses separated by approximately 8 hours.	One male animal in the 105 mg/kg/day dose group died on day 28. This animal had black watery stool, pale gums, prostration, absent corneal reflexes, dilated pupils, noisy breathing and was cold to touch. Vomitus and soft/watery/mucoid stools were commonly observed in the treated animals with no obvious differences between the different dose groups. During the last two days of dosing, at least two animals (105 mg/kg) had eye discharge, red mucoid stool and tremors. Hematocrit, hemoglobin and RBC count were generally ↓ in the MD, HMD and HD groups. In general, AST was significantly ↑ in Groups MD, HMD and HD males by 9.7-fold, 8.6-fold and 13.3-fold respectively. ALT was slightly but significantly ↑ in HMD and HD males by 1.6-fold each. While the mean serum ALT level for the female HD group was not statistically significant, it was increased 2.8-fold relative to control because on day 29, one out of two females in the HD group had a markedly increased ALT level (85.7 µ/l relative to 27.7 and 25.4 µ/l for controls). Alkaline phosphatase was slightly ↑ in some HMD animals. Albumin was ↓ in the MD and HMD females. The most prominent gross pathology changes were hyperemia of the small and large intestines, and melena or bloody contents in the bowel. The melena was commonly found in the lower small intestine, cecum, and/or colon. The target organ of toxicity is the GI tract specifically the small and large intestine (congestion of mucosa, inflammation, necrosis of villi tips, mucosal erosion). No histopathology suggestive of neurotoxicity.105 mg/kg = 34x clinical dose based on mg/m^2.

Subacute Toxicity Studies (GLP Studies)

STUDY NUMBER/TITLE	DOSES (mg/kg) /DURATION	KEY TREATMENT-RELATED TOXICOLOGIC FINDINGS
PSA-93C-3971: Six day repeated dose oral range finding study of SC-48334 in Rhesus monkeys.	OGT 924: 500, 2500 Doses were administered by gavage to 3/F/group in three divided doses for 6 days.	No deaths. There were no apparent test article-related clinical observations noted. SC-48334 was systemically available in the cynomolgus monkey after oral administration of the prodrug SC-49483 as a suspension. The peak plasma concentrations of SC-48334 were 6.46 ± 0.53 and 15.0 ± 1.4 µg/ml for the low and high doses, respectively. The times to reach the C_{max} (T_{max}) were 1.0 and 0.5 hours for the low and high doses, respectively. Sponsor stated that these concentrations are in a similar range to those thought to be necessary for efficacy in the clinic (10 – 20 µg/ml)
PSA-88S-3319: Two week oral range-finding toxicity study of SC-48334 in the mouse.	OGT 918: 60, 300, 600 Doses were administered by gavage to 10M and 5 F/group four times/day to give total daily doses of 240, 1200 and 2400 mg/kg/day.	4/15 (0), 5/15 (LD), 4/15 (MD) and 8/15 (HD) animals were found dead or sacrificed in extremis. Most deaths appeared due to trauma (perforated esophagus, granular material in thoracic cavity, pleuritis, pyothorax, pericarditis, myocarditis and pneomonitis), but reviewer suggests some HD deaths might be drug related. One HD male died due to drug (findings of dilation of intestines has been observed with alcohol sugars). G.I. toxicity evidenced by watery stool, swollen or red anal tissues. Only stomach was examined (not rest of g.i. tract). Decreased body wt. in MD and HD animals of both sexes. Males: 7 and 12% lower than controls for MD, HD respectively. Females: 4 and 12% for MD, HD respectively. Not statistically significant. Increased AST and ALP (1.4-4.6X) all dose groups; AP decreased in MD females and all HD animals. Cytoplasmic vacuolation of hepatocytes was noted along with an increase in relative liver wts in MD females and HD both sexes. Hematology data incomplete (no data for HD group). Absolute kidney wt. decreased in HD males correlated with cortical tubular epithelium degeneration. Thymic involution in MD females, all HD. Decreased absolute and relative weights of testes in HD males. No histopathology correlate. Absolute wt. of heart was decreased in MD and HD females. Histopathology does not explain the decreased heart wts. NOAEL was not established since some animals were not examined histopathologically. Serum chemistry battery is incomplete.
PSA-92S-3905: Oral capsule comparative study of SC-48334 and SC-49483 in the dog.	OGT 918: 240 OGT 924: 550. Dogs (3/sex/test article) were dosed with capsules in three evenly divided oral	No deaths. The OGT 918 dogs showed signs of reduced activity, anorexia, bloody stools and dehydration during the second week. In contrast, the OGT 924 dogs remained alert and active throughout the study. Abnormal stools and vomitus were observed in both test article groups. 3/6 dogs given OGT 918 had soft or watery stools during the

	doses per day, for 14 days	first week of the study. During the second week of the study, 4/6 dogs had red watery or mucoid stools that progressed to black tarry stools in 3/6 dogs. In contrast, all the OGT 924 dogs had soft or watery stools during the first week and only two showed this change in the second week. None of the OGT 924 dogs developed the black tarry stools. Food consumption was greatly reduced in the OGT 918 dogs in the first week of the study and almost ceased in the second week. This resulted in bodyweight losses of 1.8 to 2.3 kg per dog over the duration of the study. Bodyweight losses in the OGT 924 dogs were negligible. Neither compound had a definite effect on the testis or serum testosterone concentration, although one OGT 918 dog had mild testicular degeneration considered secondary to debilitation. AST was significantly ↑ for both OGT 918 (about 25 times pre-study values) and OGT 924 (about 10 times pre-study values) groups. ALT was ↑ in 1/6 dogs given OGT 918. The dogs given OGT 918 had a greater output of mucus into the lumen of the large intestine which was evident histologically by the presence of dilated mucosal crypts filled with mucopolysaccharides as identified by histochemical staining. In contrast, the GI tracts of dogs given OGT 924 were morphologically normal. Atrophy of the ileal Peyer's patches was evident with both test articles. The effect was greater in the OGT 918 dogs. OGT 918 was absorbed and systemically available after administration of OGT 918 and after administration of its prodrug, OGT 924. Mean peak plasma concentrations (Cmax) of OGT 918 were 66.68 µg/Ml at 1.33 hours for the dogs dosed with OGT 918 and 6.26 µg/ml at 2.42 hours for the dogs dosed with OGT 924. The AUC for OGT 918 was about eight-fold higher after administration of OGT 918 itself than after administration of the prodrug, OGT 924.
PSA-88S-3341: 4-Week oral toxicity study in rats.	OGT 918: 180, 840, 4200 mg/kg/d Rats 15/sex/group were dosed (divided into 3 doses/day) for 4 weeks by gavage.	All HD rats died prior to sacrifice due to severe diarrhea (day 5 –17). Watery stool was observed in all HD animals and in 7/15 MD animals. Ventral staining and swollen abdomen were observed in HD males and females and in 1/15 MD female. Swollen limbs were seen in HD males and females on Day 1 only. Bodyweight, bodyweight gain and food consumption were severely ↓ in the HD group. These parameters were also ↓ in the MD group, however, ↓ in bodyweight gains in the MD females were sporadic. In the animals that survived until the scheduled necropsy the following clinical chemistry parameters were affected: serum AST and ALT activities and glucose concentrations were significantly ↑ in the MD group; Ca concentration was significantly ↑ in the MD females; cereatinine and total protein were ↓ in the MD group; total globulin concentration and more specifically the α_1 fraction, were ↓ in the MD males; and albumin was significantly ↓ in MD females only. The toxicological significance of these findings is uncertain. Urinary Ca was ↑ in the LD and MD groups. Platelet values were significantly lower in the LD females and MD males and females. In the HD animals killed in extremis, changes observed in the neutrophils were indicative of a toxic state. Thymus weights (abs. & rel) were ↓ in the MD group and spleen weights were ↓ in the MD males only. The ovary and uterus weights were ↓ in the MD females. The target organs of toxicity include the GI tract (↑ in the mitotic figures in cecal epithelium, hemorrhage of stomach, depletion of goblet cells throughout the intestine, villous atrophy in the jejunum and ileum), prostate (atrophy), and lymphocyte depletion in the spleen, thymus and lymph nodes, pituitary (atrophy of the pars distalis), bone marrow (hypocellularity), testis (↓ spermatogenesis), epididymis (hypospermia), seminal vesicles (atrophy). Most of the target organs were observed in the HD and MD groups. In addition, hypospermia in the epididymis was observed in the 180 mg/kg/day male. Based on these findings a NOAEL could not be determined.

PSA-88S-3378: 4-Week oral toxicity study in rats.	OGT 918: 420, 1680 mg/kg/d Rats 15/sex/group were dosed (divided into 3 doses/day) for 4 weeks by gavage.	There were no treatement-related deaths. Clinical signs considered treatment related in HD animals consisted of watery stool, red stool, swollen anus, swollen abdomen, swollen limbs, ↓ fecal quantity, ventral staining, and generalized paleness. Ventral staining and ↓ fecal quantity were also observed in the LD animals. Body weight, bodyweight gain and food consumption were ↓ in the males and females of the HD group. Serum AST and ALT activity, glucose and urea concentrations were significantly ↑ in the HD animals of both sexes. Serum Ca was significantly ↑ in the HD males and slightly ↑ in the females. Serum Cl levels were ↓ in HD males only. Inorganic P was ↓ in HD male and females. Creatinine concentration was ↓ at all doses and in both sexes. HD males and females exhibited significant ↓ in total protein and globulin. Specifically, the γ and α_1 fractions were ↓ in both sexes and the β and α_2 fractions in males only. Albumin was significantly ↓ in females only. Urinary Ca was ↑ in the HD males and females and in the LD females. Urinary Cl concentration was ↑ in the HD males only. Platelet values were significantly ↓ at all dose levels and in both sexes. Absolute neutrophils ↑ and lymphocytes ↓ in the HD group. Neutrophils were ↑ in the LD males also. Weights (abs. & rel.) of the uterus were significantly ↓ in HD females. Weights of the thymus were significantly ↓ in both sexes and at all dose levels. Absolute weights of the brain (LD & HD females – vacuolation of white matter), heart, kidney, liver, pituitary and spleen significantly ↓ in both sexes mostly at HD unless otherwise stated. Relative weights of the kidney, liver and thyroid were significantly ↑ in both sexes and at all dose levels. The increased rel. wts. correlate with the ↓ in body weight. The ↓ weights of the ovary and uterus had no correlative histopathology. The ↓ abs. wts. of the testis, prostate (LD & HD) and epididymis were significantly ↓ at the HD. The ↓ in rel. wt. of the prostate correlate with ↓ secretory cells/depletion of secretion. Even though rel. wts. of the testis and epididymis were ↑ (due to ↓ in body wt.) hypospermia and ↓ in cell layers lining the seminiferous tubules were observed. The target organs of toxicity included the bone marrow (hypocellularity), pituitary (atrophy), brain (vacuolization of white matter), GI tract (↑ mitotic figures in cecal epithelium, villous atrophy of small intestine), lymphoid depletion in the spleen, thymus and lymph nodes, testis and epididymis (↓ spermatogenesis, hypospermia at LD & HD) and prostate and seminal vesicle (atrophy). Most of the toxicities occurred at the HD. NOAEL could not be established.
PSA-89C-3506: Four week oral dose escalation toxicity study with SC-48334 in rats.	OGT 918: 420, 840, 1680, 2400 mg/kg/d 10 males/group; dose escalation study.	The purpose of this exploratory study in male rats was to determine whether the diarrhea and GI lesions observed in previous studies at doses of 1680 mg/kg/day and above could be decreased or avoided by exposing the animals to a low dose of OGT 918 for 1 week and then increasing the dose weekly. There were 4 groups of animals in the study. A control group (Group 1) was treated throughout the study with dionized water. An escalating dose group (Group 2) received 420, 840, 1680 and 2400 mg/kg/day OGT 918 during Weeks 1, 2, 3 and 4, respectively. Group 3 was not dosed during Weeks 1 and 2, but received 1680 mg/kg/day during Weeks 3 and 4. Group 4 was not dosed during Weeks 1 through 3, but received 2400 mg/kg/day during Week 4. The escalating dose group had similar mean bodyweights, bodyweight gains and food consumptions compared to those of the control group after 1 week of treatment at 420 mg/kg/day. Bodyweights, bodyweight gains and food consumptions were lower than those of the controls after the dose was increased to 840 mg/kg/day. Animals lost 2% and 15% of the mean bodyweight during Weeks 3 and 4 when the dose was escalated to 1680 and 2400 mg/kg/day, respectively. During the first week of treatment with 1680 (Group 3, Week 3) and 2400 mg/kg/day (Group 4, Week 4), mean bodyweights decreased approximately 11% for each group. At a dose of 420 mg/kg/day (Week 1), 1/10 animals had soft feces.

		After increasing the dose to 840 mg/kg/day (Week 2), 3/10 animals had soft feces, 3/10 had enlarged abdomens, and 1/10 had blood-like diarrhea. Generally at dose levels of 1680 and 2400 mg/kg/day, the escalating group had an incidence of GI signs of toxicity lower than the non-escalating dose groups at the corresponding dose level, but much greater than that of controls. There were 2/10 animals in the escalating dose group that died before the end of Week 4; no mortality occurred in the non-escalating groups. Macroscopic examination of the GI tract organs in the escalating and non-escalating dose groups revealed signs commonly found in animals with history of chronic diarrhea but were not specific for any one cause or pathologic process producing the response. There were no differences between the escalating dose group and the 1680 or 2400 mg/kg/day dose groups. Based on results from this study, an escalating dose schedule of OGT 918 (420, 840, 1680 and 2400 mg/kg/day for Weeks 1, 2, 3 and 4, respectively) was only marginally effective in reducing incidences of GI signs of toxicity when compared with a dose level of 1680 mg/kg/day administered for 2 weeks. No protective effect was apparent when the dose level was escalated to 2400 mg/kg/day, and there was no evidence to indicate that the incidence or severity of the microscopic GI lesions were reduced by the escalating dose schedule.
PSA-93S-3951: Four week gavage toxicity study of SC-49483.	OGT 924: 330, 1020, 3670 mg/kg/d. Rats 15/sex/group were dosed (divided into 3 doses/day) for 4 weeks by gavage.	No deaths. Watery/soft stool was noted at a low incidence in all treated animals Red stool was observed in 2/15 HD animals. Other clinical observations included swollen abdomen seen in 1/15 and 3/15 animals in the MD and HD groups respectively. Red discharge around the mouth was observed in 1/15 animals of the HD group. Mean body weights were significantly ↓ in the HD males by 44% and by 37% in females relative to controls. Feed consumption was significantly ↓ by 38% in males and by 28% in females only at HD relative to control. Changes in hematology parameters included: ↓ hemoglobins, hematocrits, and platelet counts, mainly at MD and HD; absolute neutrophil counts were ↑ in MD females and HD males and females; and absolute lymphocyte counts were ↓ in HD males. Enlarged platelets were observed in blood smears of 0/15, 1/18, 1/14, and 11/14 animals from the control, LD, MD, and HD groups examined at week 5. AST was significantly ↑ by 159% and 246% in HD males in females relative to control. ALT was significantly ↑ by 145% and 88% in HD males and females relative to control; creatinine was slightly but significantly ↓ in both HD males and females by 18% and 14% respectively relative to control; total protein and globulin were ↓ at week 5 in MD females and HD males and females; Cholesterol values were slightly but significantly ↑ in MD and HD groups relative to controls. Triglyceride levels were also ↑ by 40% at all dose levels in females. Ca was ↑ in male animals of the HD group by 6% while inorganic phosphorus was significantly ↓ in male animals of the HD group by 17% relative to control. Urinary creatinine concentration was significantly ↓ in MD and HD animals. Ca concentration was significantly ↑ and inorganic phosphorus was ↓ in all treated female groups and MD and HD males. Thymus, spleen, and prostate weights were ↓ at the HD. The target organs of toxicity include the pancreas (acinar cell vacuolation), salivary gland acinar cells (mucous cell atrophy/serous cell hypertrophy, prominent apoptosis), stomach (chief cell vacuolation), thyroid (follicular cell vacuolation), pituitary (intracytoplasmic eosinophilic droplets), spleen-thymus-mesenteric lymph node (lymphocyte depletion), uterus-prostate-seminal vesicle (atrophy), testes-epididymis (degeneration of germinal epithelium, hypospermia). A NOAEL could not be determined. At the lowest dosage level, changes were observed in urinary calcium and inorganic phosphorus excretion, and in serum cholesterol and triglyceride concentrations in females, and in body weight gain, hemoglobin concentration, and the submandibular salivary gland and epididymis morphology in males.
PSA-89C-3346: 28 day oral study in Rhesus	165, 495, 1650 mg/kg/d (divided 3x/day).	3/5 females, 2/5 males (HD) and 3/5 females (MD) died between days 7 and 21. Dosing was suspended on day 18 in HD group due to high

monkeys.	5/sex/group	mortality/toxicity. Evidence of GI. Tox in all treated animals. Emesis noted after dosing indicates that portion of the dose was lost (PK from this study are likely to be inaccurate). Suppression of body weight gain in all treatment group accompanied by decreased appetite in some animals. (Partially reversed in HD animals after the 10 days off drug). Gross lesions observed in dead animals/animals sacrificed moribund had discoloration or hemorrhage of the GI tract and loss of stomach rugae. Epithelial erosions, ulcerations, necrosis, hemorrhage and inflammation. WBC counts ↑ in MD & HD (number and % of banded neutrophils were ↑). Some recovery noted in HD after 10 days off drug. Absolute and relative thymus wts were ↑ in MD and HD. Relative spleen wts were decreased in HD. Lymphoid alterations (congestion) were noted at MD and HD. The alterations in neutrophils may be related to GI toxicity. Likewise, thymic, spleen and lymph nodes may also be related to GI tox, but a direct effect cannot be ruled out. Platelets ↑ in HD on day 28. Hb and Hct ↓ and fibrinogen ↑. APT was ↑ on day 7 in HD animals. Acute inflammation of the heart was noted in 2 HD and 1 MD dead animals. AST ↑ in all dose groups, not statistically significant in LD group. ALT ↑ in MD and HD days 7-14, but returned to control levels by end of study. BUN/creatinine ratio ↑ over controls but not baseline on days 14 and 28. Relative liver weights ↑ in HD animals; enlarged liver noted in all dose groups with histopath correlations of acute inflammation and hepatocellular necrosis at MD and HD. Hepatic vacuolation was observed in all animals and concluded by the pathologist to ↑ in severity and incidence with dose. Non statistically significant ↑ in absolute and relative adrenal weights and relative wts of kidneys and ↓ testes and prostate in HD monkeys. The target organs of toxicity include the GI tract (ulcer, inflammation, necrosis, hemorrhage – colon, cecum), mesenteric lymph node (lymphoid hyperplasia), liver (vacuolar change, necrosis, inflammation), kidney (infarct, hyaline casts) and adrenal (congestion). NOAEL could not be established because of histopathology observed at the LD.
PSA-93C-3965: Twenty-eight day repeated dose oral toxicity study of SC-49483 administered to Cynomolgus monkeys.	OGT 924 was administere –d to Cynomolgus monkeys (4/sex/group) for 4 weeks. Doses of 250, 667 and 1333 mg/kg were given TID at 8 hour intervals for total doses of 750, 2000 and 4000 mg/kg/day, respectively.	No test article-related deaths occurred. 2/4 HD males died; one on Day 1 and one on Day 6. Their deaths were associated with acute pneumonitis resulting from the aspiration of the dosing suspension. ¼ control females died of acute peritonitis and intestinal bloat. Clinical signs revealed an increased incidence of yellow and/or white colored feces and yellow discharge from the anus of the MD and HD animals. This material appeared to be test article excreted through the GI tract. Soft feces were observed in all males groups, including controls, and in HD females. No test article-related changes were observed in bodyweights, feed consumption, or ophthalmic findings. Hemoglobin, hematocrit and erythrocyte values were slightly, but statistically significantly ↓ in HD males. No test article-related changes were observed in other hematology parameters or in clinical chemistry, radioimmunoassay, or in urinalysis parameters. There were no apparent test article-related organ weight changes and no test article-related gross changes noted at necropsy. A ↓ in the number of zymogen granules in the glandular acini of the exocrine pancreas was noted in most animals of all treated groups as well as one moribund control animal. Sponsor stated that the ↓ in zymogen granules was not associated with correlative functional changes and does not appear to be clinically significant. No other test article-related histologic changes were observed. NOAEL could not be established since at the LD a ↓ in the number of zymogen granules in the glandular acini of the exocrine pancreas was noted.
P30S4144: 4 week i.v. infusion toxicity study with SC-48334 in Cynomolgus monkeys.	OGT 918: 60, 300, 600 mg/kg/d as 5 minutes infusion divided into 3 equal doses administered TID. 4/sex/group.	No treatment-related deaths. Three animals were sacrificed prior to the end of the study due to septicemia from the infusion procedure (inflammatory changes associated with the indwelling catheter). ¼ HD males, ¼ LD females and ¼ HD females had severe suppurative inflammation, evidence of acute meningitis, subcutaneous hemorrhage, inflammation in the inguinal region as well as hemorrhage and inflammation in the lungs. These changes were indicative of catheter problems. In addition to inflammatory changes in the sections

		catheter problems. In addition to inflammatory changes in the sections of the catheter sites, the HD female had adhesions, fibrosis, and suppurative inflammation in the lungs. Sponsor stated that the inflammatory changes associated with the catheter as well as the inflammatory changes observed in the lungs and brain are suggestive of septicemia. Clinical signs of hypoactivity (1/4 HD males, ¼ LD females) and mucoid feces (1/4 MD males) were observed. At week 4, cumulative body weight gain was statistically significantly ↓ in MD and HD males. T4 was significantly ↓ in HD males and T3 was also ↓, but not significantly. T3 ↓ in HD females (T4 was also ↓, but not significantly). There were no clear changes in TSH or testosterone. Moderately ↓ total protein and globulin and mildly ↑ AST were noted. HD females had elevated AST as early as day 2 (3X baseline). By the end of the study, AST was significantly ↑ in the HD group. In males, there was a slight trend for ↑ serum Ca (11.2 controls, 12.6 HD) and a statistically significant ↓ in Cl in MD and HD males. In females, there was a similar trend for Ca, but not Cl. Lower absolute and relative thymus weights in MD and HD animals. Significant ↑ in relative kidney weights in females (28%). No histopathologic correlates were noted associated with the ↑ AST levels. Severe lymphocytic depeletion was evident in the thymus at MD and HD. This correlates with the ↓ thymic weights. One LD female also had this finding, but it was not possible to differentiate this change from normal thymic involution. Also, zymogen granule depletion of the acinar cells of the exocrine pancreas was noted in HD groups. This also occurred in all MD males, ¼ LD males, ¼ LD and ¼ MD females. The changes in total protein and globulin may be related to changes in the thymus as lymphocyte depletion may result in ↓ immunoglobulin production. The target organ of toxicity is the thymus. NOAEL = 60 mg/kg/d LYMPHOCYTE SUBSET ANALYSIS: Since this test agent was being studied for treatment of HIV, samples were examined for potential effects on lymphocyte subsets. There was a decrease in CD8+HLA-DR+ T cells in HD females that was attributed to thymic depletion and not attributed to a cytotoxic effect of the test agent. The sponsor suggested that the effects on T3, T4, body weight gain, lymphocytic depeletion and clinical chemistry changes were related to stress of infusion of high doses.

Study Title: 13-Week Oral (Gavage) Toxicity Study in the Rat with a 4-Week Interim Kill and 4-Week treatment-free period.

KEY STUDY FINDINGS:

- At 180 mg/kg/day, transient abdominal swelling was seen, predominantly in males.
- Body weight gain was reduced in HD males by 12% over the whole treatment period. At the end of the recovery period, a decrement in body weight gain was observed in all treated animals except in HD females who had an increase in body weight gain relative to control.
- AST was statistically significantly increased in HD males. Na was slightly but statistically significantly increased in LD and HD males and creatinine was statistically significantly increased in all treated males. These changes were reversed at the end of the recovery period.
- Specific gravity of the urine of treated males were slightly but statistically significantly decreased.
- Absolute weights of the ovaries, kidney and adrenal gland were slightly but statistically significantly decreased in HD females due to increased body weight. Relative weight of the adrenal gland was also slightly but statistically significantly decreased in MD and HD females without any correlative histopathology. Relative weight of the kidney was statistically significantly decreased in all treated females. The kidney histopathology does

not seem to explain the decreased relative weight. At the end of the recovery period, relative weights of the brain (no correlative histopathology), liver and testes were statistically significantly increased in HD males. The liver and testes histopathology does not explain the decreased relative weights. This may be due to the decreased body weight in HD males. Relative weight of the brain was also statistically significantly increased in MD males.

- The target organs of toxicity include the epididymides (desquamated germ cells, ↓ or no spermatozoa), kidney (pelvic dilatation, tubular basophilia, cortical tubular dilatation, corticomedullary dilatation), liver (hepatocyte necrosis), submandibular lymph node (lymphoid hyperplasia) and testes (desquamated germ cells, seminiferous tubular atrophy).
- At the end of the recovery period, the testicular and epididymal changes were still present but at lower incidence suggesting partial recovery. The kidney changes were partially reversed. Histopathologic changes that were not present at the end of the 13 week treatment period but noted at the end of the recovery period included spleen (extramedullary hematopoiesis, hemosiderosis), submandibular lymph node (plasmacytosis) and uterus (luminal dilatation).
- NOAEL = 20 mg/kg/day based on the histopathology.

Study No: WVC/001
Volume # 14, and page # 1.
Conducting laboratory and location:

Date of study initiation: June 12, 1997.
GLP compliance: Yes (U.S.A., and United Kingdom).
QA- Report Yes (x) No ()

METHODS:
Dosing: The test article was administered orally by gavage 3 times daily up to total daily doses of 20, 60 and 180 mg/kg/day for 4 or 13 weeks. Groups 1 to 4 (25 animals /sex/group) were designated main study groups. The first 10 animals/sex/group were dosed three times daily, 7 days a week for 4 weeks up to the day of necropsy. The remaining 15 animals/sex/group were dosed three times daily, 7 days a week for at least 13 weeks upto necropsy. At the end of the 13 week experimental phase, 5 animals/sex/group were allocated to the treatment-free period and maintained, undosed, for a further 4 weeks until necropsy.

Species/strain: Rat: Crl:CD(SD)BR/
#/sex/group or time point: Groups 1-4 (25 animals /sex/group).
Age: 3-4 weeks old.
Weight: 134-195 g (males); 113-165 g.
satellite groups used for TK: Group 5 (9 animals/sex/group); Groups 6-8 (15 animals /sex/group). Groups 5-8 were used for toxicokinetic studies. 3 males and 3 females with the highest animal numbers from each group (6 to 8) were dosed three times daily, 7 days a week until sacrifice during week 6. The remaining animals were dosed three times daily, 7 days a week until completion of the toxicokinetic sampling regime during week 13.
Doses in administered units: 20, 60 and 180 mg/kg/day.
Route, form, volume, and infusion rate: Oral, solution, and 10 ml/kg.
Drug, lot#, radiolabel, and % purity: Lot 89K034-401J; 99.5% pure.
Formulation/vehicle: sodium starch glycollate, povidone (k30), magnesium sterate and ethanol in UPH water (vehicle).

OBSERVATIONS AND TIMES:
Clinical signs: All visible signs of reaction to treatment were recorded daily.

Mortality: All animals were examined twice daily for mortality and morbidity.
Body weights: All animals were weighed at the start of the study and then weekly thereafter up to the day of necropsy.
Food consumption: Recorded weekly throughout the treatment and treatment-free period.
Ophthalmoscopy: Animals in groups 1-4 were examined before the start of treatment. Subsequently, the first 10 animals/sex from each of the control and high dose groups were examined in week 4 and the remaining 10 animals/sex from each of the control and high dose groups were examined in week 13.
EKG: Not evaluated.
Hematology: Blood samples were obtained from the first 10 animals/sex/group during week 4 and from the remaining 10 animals/sex/group during week 12 of treatment. With the exception of the week 4 coagulation tests, which were taken without an overnight fast, blood samples were taken by tail venipuncture after overnight food deprivation. Routine hematological evaluation was conducted.
Clinical chemistry: Routine clinical chemistry evaluation was conducted. Blood collection is the same as for hematology.
Urinalysis: Urine samples were obtained from the first 10 animals/sex/group during week 3 and from the remaining 10 animals/sex/group during week 12 of treatment under food and water deprivation.
Gross pathology: After exanguination the cranial thoracic and abdominal cavities were opened and examined macroscopically. All abnormalities were recorded with details of the location, color, shape and size.
Organ weights: Organs weighed are indicated in the list of addendum.
Histopathology: With the exception of the eyes, optic nerves and testes, tissues evaluated are indicated in the list of addendum.
Toxicokinetics: TK was assessed on day 1 and in weeks 4 and 13. Blood samples were obtained from 2 animals/sex/satellite group at 0, 0.5, 1, 3, 6 and 24 hours after the first dose of the day.

RESULTS
Clinical signs: Transient abdominal swelling was observed predominantly in HD males.
Mortalities: There were no treatment-related mortalities during this study. 2/10 LD males, animal #s 36 and 43, were found dead prematurely on days 42 and 23 of treatment respectively. At necropsy animal # 36 had fluid in the trachea and thoracic cavity suggesting a dosing error. Animal # 43 convulsed prior to being dosed and died shortly after. Necropsy revealed abnormal contents in the trachea and thoracic cavity however no contributing factors to death could be found. Both deaths were not considered to be attributable to toxicity of OGT 918.

Body weights: (g)

WEEK 4 DATA

Dose (mg/kg/d)	0		20		60		180	
Sex	M	F	M	F	M	F	M	F
Day 1	172	133	168	133	169	134	170	132
Week 4	351	228	347	240	348	235	339	231
Wt. gain	179	95	179	107*	179	101*	169	99*
Decrement	0	0	0	↑	0	↑	10	↑
% Decrement							6%	

• $p< 0.05$

WEEK 13 DATA

Dose (mg/kg/d)	0		20		60		180	
Sex	M	F	M	F	M	F	M	F
Day 1	172	133	168	133	169	134	170	132

Week 13	522	298	527	310	501	303	478	298
Wt. gain	350	165	359	177	332	169	308*	166
Decrement	0	0	↑	↑	18	↑	42	↑
% Decrement					5%		12%	
RECOVERY DATA (WEEK 17)								
Week 13	522	298	527	310	501	303	478	298
Week 17	604	310	566	317	540	312	510	315
Wt gain	82	12	39	7	39	9	32	17
Decrement	0	0	43	5	43	3	50	↑
% Decrement	0	0	52	42	52	25	61	-

• **p< 0.05**

Food consumption: No treatment-related effects.

Ophthalmoscopy: There was no treatment related ocular abnormalities noted.

Electrocardiography: No data provided.

Hematology:

WEEK 13 DATA

EFFECT OF OGT 918 ON HEMATOLOGY PARAMETERS								
Dose (mg/kg/d)	0		20		60		180	
	M	F	M	F	M	F	M	F
MCV (fl)		56±1.3		56.1±1.7		57.0±1.4		57.6±2*
MCHC(g/dl)	33.8±0.3	34±0.4	34±0.4	33.7±0.7	33.4±0.6*	34.1±0.4	33.3±0.6*	33.2±0.6*
WBC		8.75 ± 2		9.78 ± 1		8.6 ± 2.5		11.9 ± 2**
Abs. Lymph. (10^{-3}/µl)		7.33 ± 1.9		8.2 ± 1.1		7.2 ± 2.1		10 ± 1.9**
PT (sec)	15.7 ± 0.6		16.7 ± 0.7 **		16.4 ± 0.9 **		17.2 ± 0.6***	

• **P<0.05, ** P<0.01, *** P<0.001**

RECOVERY DATA

EFFECT OF OGT 918 ON HEMATOLOGY PARAMETERS								
Dose (mg/kg/d)	0		20		60		180	
	M	F	M	F	M	F	M	F
Neutrophil (%)		13.5±3.9						21.2±5.0*
Basophil (10^3/ul)		0.01±0.01						0.00±0.01*
PT (sec)	14.3±0.3		14.2±0.5		14.7±0.8		15.4±1.0*	

Clinical chemistry:

WEEK 13 DATA

EFFECT OF OGT 918 ON CLINICAL CHEMISTRY PARAMETERS								
Dose (mg/kg/d)	0		20		60		180	
	M	F	M	F	M	F	M	F
ALP (U/L)	271 ± 35	216 ± 39	291 ± 40	202 ± 47	265 ± 47	185 ± 34	224 ± 34 **	172 ± 55 *
AST (U/L)	73 ± 5		71 ± 10		76 ± 8		82 ± 6 *	
CREAT (mg/dl)	0.7±0.0		0.8±0.1**		0.8±0.1**		0.7±0.1**	
GLOB (g/dl)	3.5±0.1		3.6±0.2		3.4±0.2		3.3±0.2*	
T. PRO (g/dl)	7.1±0.2		7.3±0.2		7.0±0.2		6.9±0.2*	
PHOS (mg/dl)		5.9±0.3		5.6±0.6		5.0±1.0**		5.1±0.7*
Na (mmol/l)	145±1		147±1**		145±1		146±1**	

*** P<0.05, ** P<0.01, *** P<0.001**

At the end of the treatment-free period, these parameters were comparable to control levels suggesting reversibility.

Urinalysis: WEEK 13 DATA

EFFECT OF OGT 918 ON URINALYSIS PARAMETERS								
Dose (mg/kg/d)	0		20		60		180	
	M	F	M	F	M	F	M	F
SG	1.026		1.020**		1.020**		1.022**	

* P<0.05, ** P<0.01

Organ Weights:

WEEK 13 DATA

EFFECT OF OGT 918 ON ORGAN WEIGHTS								
Dose (mg/kg/d)	0		20		60		180	
	M	F	M	F	M	F	M	F
Ovaries (g) M SD		0.081 0.01		0.083 0.009		0.078 0.014		0.070* 0.005
Adrenals (g)		0.070 0.008		0.073 0.008		0.064 0.007		0.060 0.008
Adrenals %		0.024 0.003		0.024 0.003		0.022 0.002*		0.022* 0.003
Kidney (g)		2.12 0.25		2.03 0.18		2.09 0.13		1.93 0.18*
Kidney %		0.74 0.05		0.67* 0.07		0.72* 0.04		0.69* 0.04
EFFECT OF OGT 918 ON ORGAN WEIGHTS AT THE END OF RECOVERY PERIOD								
Brain %	0.37 0.05		0.41 0.02		0.42* 0.05		0.44* 0.03	
Liver %	3.32 0.27		3.27 0.19		3.42 0.39		3.83* 0.30	
Testes %	0.53 0.19		0.61 0.08		0.67 0.14		0.75* 0.07	

* P<0.05, ** P<0.01, % = relative to body wt.

Gross pathology:

WEEK 13 DATA

EFFECT OF OGT 918 ON GROSS PATHOLOGY								
Dose (mg/kg/d)	0		20		60		180	
	M	F	M	F	M	F	M	F
Ovaries Abnormal size								1/10
Cecum Abnormal color								1/10
Ileum Abnormal color								1/10
Jejunum Abnormal color								1/10

Histopathology:

WEEK 13 DATA

EFFECT OF OGT 918 ON HISTOPATHOLOGY								
Dose (mg/kg/d)	0		20		60		180	
	M	F	M	F	M	F	M	F
Epididymides ↓ spermatozoa							2/10	
Epididymides No spermatozoa					1/10			
Epididymides Desquamated germ cells	1/10(1)		2/10(1)		2/10(1)		6/10 3/10(1) 3/10(2)	

Kidney Pelvic dilatation			1/10(1)		1/10(1)		1/10(1)	
Kidney Tubular basophilia					1/10(3)			
Kidney Cortical tubular dilatation							1/10(1)	
Kidney Corticomedullary mineralization		1/10(2)						5/10(2)
Liver Hepatocyte necrosis							1/10(1)	
Submandibular l. node Lymphoid hyperplasia							1/10(3)	
Testes Desquamated germ cells					6/10 4/10(1) 2/10(2)		1/10(1)	
Testes Seminiferous tubular atrophy					2/10 1/10(2) 1/10(4)			

1 = minimal; 2 – slight; 3 = moderate; 4 = marked

RECOVERY DATA

EFFECT OF OGT 918 ON HISTOPATHOLOGY								
Dose (mg/kg/d)	**0**		**20**		**60**		**180**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Kidney Corticomedullary mineralization								1/10(2)
Kidney: interstitial Inflammatory cell infiltration					1/10(1)			
Kidney Pelvic dilatation					2/10			
Kidney Tubular basophilia			1/10(2)		1/10(2)			
Kidney Corticotubular dilatation					1/10(1)			
Spleen Extramedullary hematopoiesis								1/10(1)
Spleen Hemosiderosis								1/10(1)
Submandibular l. node Plasmacytosis								1/10(1)
Uterus Luminal dilatation							1/10(1)	1/10(1)
Testes Desquamated germ cells	1/10(1)		1/10(1)		2/10(1)		1/10(1)	
Testes Seminiferous tubular atrophy	1/10(4)		1/10(3)		3/10 1/10(1) 2/10(2)			
Epididymides Desquamated germ cells			1/10(2)		1/10(3)		1/10(1)	

1 = minimal; 2 – slight; 3 = moderate; 4 = marked

Toxicokinetics: AUC_{0-6} (µg.h/ml).

Dose level (mg/kg/day)	Week 1 : AUC0-6h		Week 4 : AUC0-6h		Week 13 . AUC0-6h	
	Males	Females	Males	Females	Males	Females
20	3.3925	2.8150	2.9275	2 4120	4.3950	4.4225
60	8.5675	7.1363	7.1963	6.1825	10.1338	9.6775
180	18 2425	19.3275	17.6813	21.4463	20 4550	26.6963

Summary of Study Findings:
In a 13-week study in rats, OGT 918 was administered by oral gavage at doses of 20, 60 and 180 mg/kg/d. Groups of rats were sacrificed after either 4 or 13 weeks and a further group was sacrificed after a 4-week recovery period following 13 weeks of treatment. Body weight gain was reduced by 12% in HD (2x the maximum clinical dose of 100 mg TID based on AUC) males over the whole treatment period. Decrements in body weight continued into the recovery period. HD females rather had an increase in body weight gain relative to control. The target organs of toxicity include the epididymides (desquamated germ cells, ↓ or no spermatozoa), kidney (pelvic dilatation, tubular basophilia, cortical tubular dilatation, corticomedullary dilatation), liver (hepatocyte necrosis), submandibular lymph node (lymphoid hyperplasia) and testes (desquamated germ cells, seminiferous tubular atrophy). At the end of the recovery period, the testicular and epididymal changes were still present but at a lower incidence suggesting partial recovery. The kidney changes were partially reversed. Histopathologic changes that were not present at the end of the 13 week treatment period but noted at the end of the recovery period included spleen (extramedullary hematopoiesis, hemosiderosis), submandibular lymph node (plasmacytosis) and uterus (luminal dilatation). NOAEL = 20 mg/kg/day (0.3x the maximum clinical dose of 100 mg TID based on AUC) based on the histopathology. The NOAEL provides a < 1x multiple of the 100 mg clinical dose.

Study title: Re-evaluation of Lymphoid Tissues from a 13-Week Oral (Gavage) Toxicity Study in Rats with a 4-Week Treatment-Free Period.
Study no: K00/024
Rationale: To re-evaluate the effect of SC-48334 on Rat lymphoid tissues. Sections of lymphoid tissues were previously examined by the reviewing pathologist under study number WVC/001.
Dosing: Animals were dosed for 13 weeks with 20, 60 and 180 mg/kg/d of SC-48334 followed by a 4-week recovery period. These total doses were administered as three equally divided doses/day. Tissues sections were evaluated by light microscopy.
Results: There was no evidence of a generalized effect of treatment on lymphoid tissues and an effect was only detected in the mesenteric lymph node of males dosed at 180 mg/kg/day. There was also no detectable effect of treatment on the cellularity of cells in the T-cell or B-cell compartments of any of the tissues examined. A generalized effect of treatment was not detected, in the thymus, spleen and lymph nodes. Gut associated lymphoid tissue (GALT) was only encountered fortuitously in the sections evaluated. There was no indication of an effect of treatment on the presence, or proportion, of GALT.

Study title: 13-week oral toxicity study with SC-48334 in rats with 4 weeks recovery.

Key study findings:
- A dose-dependent increase in incidence of soft feces/diarrhea (all doses), urine stained tail and abdominal enlargement at doses ≥ 180mg/kg/day was noted. The diarrhea subsided upon termination of treatment.
- Body weight gain was decreased by 11% and 31% in HMD and HD males respectively and by 19% in HD females at the end of the treatment period. At the end of the recovery period, body weight gain was still decreased by 18% in HD males and females.
- Food consumption was decreased by 12% in HD males at the end of the treatment period. At the end of the recovery period, food consumption in HD males was comparable to that of control.
- 1/20 and 2/20 HD females were observed with anterior synechiae and chronic uveitis respectively during treatment. Dacryoadenitis was observed in all treated males (not dose-dependent) relative to control. 1/20 HD males was observed with phthisis of the right eye. At

the end of the recovery period, chronic uveitis was observed in 1/20 MD female. Phthisis bulbi was also observed in 1/20HD males, 1/20 control females and 1/20 HMD female.

- MCH was statistically significantly increased HD females. RBC count was slightly but statistically significantly decreased in LD and HD males. HGB was slightly but statistically significantly decreased in LD males and in HD males and females. HCT was also slightly but statistically significantly decreased in the HD group and in HMD females. Platelets were statistically significantly decreased in HD males by about 33% relative to control. WBC and lymphocytes were statistically significantly increased in all treated females. Non segmented neutrophils were also statistically significantly increased in HD females. Most of these parameters returned to normal limits at the end of the recovery period, except for statistically significantly decreased RBC in HD females and an increase in HD males.
- BUN was slightly but statistically significantly increased in HD males. This increment was due to one HD male (# C31082) whose BUN (36 mg/dl) was 3-fold that of control. The increased BUN level correlate with the marked chronic, progressive nephropathy observed in this same animal. Total protein and creatinine were slightly but statistically significantly decreased in the HD group and in HMD and HD females respectively. Globulin was slightly but statistically significantly decreased in the HD group and in the MD and HMD females. Alkaline phosphatase was statistically significantly decreased in all treated males and in MD females. Ca was slightly but statistically significantly increased in the HD group and in the MD and HMD females. Mg was slightly but statistically significantly increased in LD males but decreased in the HMD and HD females. A/G ratio (MD, & HMD females) and cholesterol (MD, HMD & HD females) were slightly but statistically significantly increased relative to control. At the end of the recovery period, globulin was slightly but statistically significantly decreased in HD males whereas A/G ratio was significantly increased in HD males.
- Urine volume was statistically significantly increased in all treated females. Urine pH was slightly but statistically significantly increased in HMD and HD males. Ca was statistically significantly increased in animals at doses ≥ MD. Specific gravity of urine was slightly but statistically significantly decreased in all treated females. Phosphorus was significantly decreased in MD and HMD females. Na, K and Cl were statistically significantly decreased in all treated females. All urinalysis parameters returned to normal limits at the end of the recovery period.
- Relative liver weights were also statistically significantly increased in all treated groups but was only dose-dependent in females. In the absence of correlative histopathology, the only reasonable explanation for the increase in relative liver weights may be the slight decreases in body weight (HD females). In HD males, the 2X increase in liver enzymes may explain the increased relative liver weight. The weights (absolute & relative) of the testes were statistically significantly decreased in HD males whereas the relative weight was significantly increased in HMD males. The decreased relative weight of the testes correlate with the atrophy/degeneration observed microscopically. The decreased relative weight of the liver did not return to control value at the end of the recovery period. Absolute weight of the epididymides was slightly but statistically significantly decreased in HD males. The decrement was still present at the end of the recovery period. The weights of the ovaries were statistically significantly decreased at doses ≥ MD relative to control. While the absolute weight of the pituitary was statistically significantly increased in all treated females except HD females, the relative weight was significantly decreased in all treated females. These increments were very much reversed upon termination of treatment except for MD females whose relative weight was still significantly increased. Absolute weight of the kidney was statistically significantly decreased in HD males. Relative kidney weight was significantly increased in the HD group and in HMD males. While there is no correlative histopathology in females to explain the increased relative weight, HMD and HD males had nephropathy and dilatation of collecting tubule and pelvis. Relative weight of the adrenal

gland was also statistically significantly increased in HD males with no correlative histopathology. Absolute weight of the spleen was significantly increased in LD males but decreased in the HD group. Similarly, absolute weight of the heart was significantly increased in MD females but decreased in HD males.

- The target organs of toxicity include the testes (atrophy/degeneration, dystrophy), kidney (dilatation-collecting tubule & pelvis, nephropathy), heart (degenerative cardiomyopathy), pancreas (acinar cell vacuolization), Thymus (involution) and uterus (dilatation).
- NOAEL = 90 mg/kg/day based on histopathology.

Study no: PSA-90C-3476
Volume #, and page #: Vol. 13, pg. 118.
Conducting laboratory and location:

Date of study initiation: February 16, 1989.
GLP compliance: Yes (USA)
QA report: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: Lot # 88K040-3011 and 88KO42-302G, 99.5% pure.
Formulation/vehicle: OGT 918 dissolved in deionized water.

Methods (unique aspects):
Dosing:
Species/strain:Rat/Crl: CD®BR
#/sex/group or time point (main study): 20/sex/group.
Satellite groups used for toxicokinetics or recovery: 20/sex/group for TK.
Age: 5 weeks at study initiation.
Weight: 135 g (M); 116 G (F).
Doses in administered units: 90, 180, 420 and 840 mg/kg/d total dose. These doses were divided into three equal doses administered at 8 hr intervals for 13 weeks.
Route, form, volume, and infusion rate: Oral (gavage), solution, 10ml/kg.

Observations and times:
Clinical signs: Twice daily.
Body weights: Weekly.
Food consumption: Weekly.
Ophthalmoscopy: Conducted prior to initiation of treatment and during weeks 12 and 17 on main study animals.
EKG: Not conducted.
Hematology: Blood was collected from 5/sex/group during week 6, from all surviving animals during week 14 and from recovery animals during week 18. Animals were fasted overnight before blood collection.
Clinical chemistry: Blood was collected from 5/sex/group during week 6, from all surviving animals during week 14 and from recovery animals during week 18. Animals were fasted overnight before blood collection.
Urinalysis: Urine samples were collected from 5/sex/group during week 6, from all surviving animals during week 14 and from recovery animals during week 18.
Gross pathology: Organs/Tissues collected for gross pathology examination is indicated in the list of addendum.
Organs weighed: Organs weighed are indicated in the list of addendum.
Histopathology: Tissues collected for histopathology examination is indicated in the list of addendum.

Toxicokinetics: All animals were bled on the first day of dosing and during week 13. On day 1, 4/sex/group were bled at 0.5, 1, 2, 4 and 8 hr post dose. During week 13, 3/sex/group were bled at the same time points.

Results:

Mortality: There were no treatment related deaths.

Clinical signs: Incidence of clinical signs (empty cells indicated zero incidence).

Dose (mg/kg/d)	0		90		180		420		840	
Sex	M	F	M	F	M	F	M	F	M	F
Soft feces			2/20	3/20	4/20	4/20	4/20	6/20	18/20	11/20
Rhinorrhea			1/20							3/20
Urine stained abdomen							1/20	2/20	6/20	8/20
Urine stained tail							5/20	1/20	5/20	2/20
Enlarged abdomen						5/20	15/20	18/20	20/20	20/20
Dehydrated						2/20	2/20		6/20	
Blood-like feces									1/20	
Blood-like urine						1/20			2/20	

Diarrhea/soft feces subsided upon termination of treatment.

Body weights: (g)

Dose (mg/kg/d)	0		90		180		420		840	
Sex	M	F	M	F	M	F	M	F	M	F
Day 0	135	116	134	116	137	117	136	120	138	118
Week 13	518	268	509	278	506	290*	478*	261	404*	241*
Gain	383	152	375	162	369	173	342	141	266	123
Decrement	0	0	8	-	14	-	41	11	117	29
% decrement	0	0	2	-	4	-	11	7	31	19
Recovery (Wk. 17)	531	279	517	286	521	308	519	275	462	252
Gain	396	163	383	170	384	191	383	155	324	134
Decrement	0	0	13	-	12	-	13	8	72	29
% decrement	0	0	3	-	3	-	3	5	18	18

* p <0.05

Food consumption: (g/week).

Dose (mg/kg/d)	0		90		180		420		840	
Sex	M	F	M	F	M	F	M	F	M	F
Week 1	157	125	158	127	156	126	146*(7%↓)	126	130*(17%↓)	113*(10%↓)
Week 13	186	127	194	131	190	143	192	129	164*(12%↓)	129
Recovery (week 17)	185	126	188	132	185	145	185	131	186	130

* p <0.05

Ophthalmoscopy:

SC-48334 (mg/kg/day)

Observation	Males 0	90	180	420	840	Females 0	90	180	420	840
Week 12										
Antisynechiae, OD	0	0	0	0	0	0	0	0	0	1
Choroidal, OS	0	0	1	0	0	0	0	0	0	0
Chronic Uveitis, OD	0	0	0	0	0	0	0	0	0	2
Dacryoadenitis										
OU	0	1	0	0	0	0	0	0	0	0
OS	0	1	2	1	0	0	0	0	0	0
Phthisis, OD	0	0	0	0	1	0	0	0	0	0
Phthisical, OD	0	0	0	0	0	1	0	0	1	0
Retinal atrophy, OU	0	0	0	0	0	0	0	0	0	1*
Week 17										
Chronic Uveitis, OD	0	0	0	0	0	0	0	1	0	0
Phthisis Bulbi, OD	0	0	0	0	1	1	0	0	1	0

OD Right eye.
OU Both eye.
OS Left eye.

* This animal had the observation at the pre-study examination and was inadvertently placed on test.

Electrocardiography: No data.
Hematology:

WEEK 14 DATA

Dose (mg/kg/d)		0		90		180		420		840	
Sex		M	F	M	F	M	F	M	F	M	F
RBC(E6/UL)	M	9.37		8.79*		8.93		9.09		8.64*	
	SD	0.57		0.50		0.84		0.55		0.70	
HGB (g/dl)	M	15.7	14.9	14.7*	14.8	15.0	14.7	15.3	14.2	14.8*	13.9*
	SD	0.95	0.89	1.09	0.81	1.18	1.09	0.82	1.07	1.20	1.31
HCT (%)	M	53.1	51.0	51.5	50.8	50.6	49.8	52.3	48.5*	50.1*	48.1*
	SD	2.63	2.70	3.29	2.17	3.55	2.81	2.43	3.18	3.68	3.80
MCHC (%)	M	29.5		28.7*		29.7		29.2		29.6	
	SD	0.83		0.65		1.02		0.67		1.02	
PLT (E3/UL)	M	939		909		917		821		630*	
	SD	74		381		258		186		333	
PT (sec)	M	21.3		12.3*		17.5		17.6		19.8	
	SD	9.05		1.41		7.20		7.34		8.37	
WBC (E3/UL)	M		4.0		5.8*		5.9*		6.0*		6.8*
	SD		1.82		1.44		2.39		1.92		2.32
N-SEG (E3/UL)			0.5		0.5		0.7		0.6		1.2*
			0.54		0.25		0.73		0.39		1.46
LYMP(E3/UL)	M		3.5		5.2*		5.1*		5.3*		5.4*
	SD		1.44		1.34		2.08		1.99		1.94

* p <0.05

WEEK 18 DATA (RECOVERY)

Dose (mg/kg/d)		0		90		180		420		840	
Sex		M	F	M	F	M	F	M	F	M	F
RBC(E6/UL)	M	15.7	8.99	15.8	8.85	16.9	8.77	16.2	9.00	17.2*	8.28*
	SD	0.5	0.18	1.41	0.50	1.05	0.35	0.51	0.28	0.23	0.16
MCH (pg)	M		17.2		16.9		17.2		17.1		17.7*
	SD		0.39		0.18		0.26		0.48		0.22
PLT (E3/UL)	M	1054		1340*		1146		1156		1003	
	SD	109		111		157		96		124	

* p <0.05

Clinical chemistry:

WEEK 14 DATA

Dose (mg/kg/d)		0		90		180		420		840	
Sex		M	F	M	F	M	F	M	F	M	F
BUN (mg/dl)	M	12		13		13		12		15*	
	SD	1.3		1.8		1.4		2.0		5.5	
TPRO (g/dl)	M	6.6	6.6	6.3	6.5	6.3	6.8	6.3	6.5	6.0*	6.2*
	SD	0.38	0.23	0.18	0.29	0.24	0.49	0.22	0.33	0.40	0.35
ALB (g/dl)	M	4.3	4.6	4.0*	4.6	4.0*	5.0*	4.1	4.8	4.0*	4.4
	SD	0.27	0.29	0.26	0.28	0.18	0.50	0.23	0.31	0.39	0.34
GLOB (g/dl)	M	2.3	2.0	2.4	1.9	2.2	1.8*	2.2	1.8*	2.0*	1.8*
	SD	0.31	0.16	0.23	0.20	0.20	0.18	0.16	0.25	0.26	0.20
AST (IU/L)	M	175		165		154		181		335*	
	SD	62.7		42.9		30.2		41.4		267.4	
ALT (IU/L)	M	42		38		38		42		81*	
	SD	10.9		7.2		7.0		12.5		60.1	
ALKP (IU/L)	M	99	62	73*	52	70*	46*	78*	56	80*	63
	SD	13.3	18.6	16.3	17.2	13.7	12.9	18.7	18.8	22.6	19.9
Ca (mg/dl)	M	9.8	9.7	9.7	9.8	9.8	10.2*	10.1	10.2*	10.1*	10.1*
	SD	0.35	0.33	0.34	0.29	0.32	0.38	0.43	0.37	0.49	0.40
Mg (mEq/L)	M	2.3	2.6	2.5*	2.6	2.4	2.5	2.2	2.4*	2.3	2.2*
	SD	0.17	0.24	0.24	0.25	0.20	0.16	0.18	0.17	0.23	0.16
CREAT (mg/dl)	M		0.7		0.6		0.7		0.6*		0.6*

	SD		0.07		0.06		0.06		0.05		0.06
A/G RATIO	M		2.3		2.4		2.8*		2.8*		2.5
	SD		0.30		0.34		0.46		0.47		0.37
CHOL (mg/dl)	M		79		93		100*		111*		99*
	SD		23.3		19.3		23.9		23.9		17.0

* p <0.05

WEEK 18 DATA (RECOVERY)

Dose (mg/kg/d)		0		90		180		420		840	
Sex		M	F	M	F	M	F	M	F	M	F
GLOB (g/dl)	M	2.9		3.0		2.4		3.0		2.2*	
	SD	0.62		0.28		0.22		0.08		0.11	
A/G RATIO	M	1.5		1.3		1.7		1.3		2.0*	
	SD	0.27		0.14		0.15		0.08		0.17	

* p <0.05

Urinalysis:

WEEK 14 DATA

Dose (mg/kg/d)		0		90		180		420		840	
Sex		M	F	M	F	M	F	M	F	M	F
Vol (ml)	M	23.7	9.0	29.7	19.2*	29.8	27.7*	36.2*	24.8*	25.8	24.2*
	SD	9.22	5.36	11.84	9.17	12.12	13.4	8.81	11.21	12.51	13.45
pH	M	6.8		6.9		7.2		7.3*		7.2*	
	SD	0.33		0.39		0.37		0.42		0.55	
Ca (mg/dl)	M	4.2	9.2	6.0	11.7	7.4*	18.2*	16.7*	19.5*	25.8*	29.7*
	SD	2.78	4.90	3.20	4.94	4.54	10.47	9.15	7.45	11.87	12.99
SP GR	M		1.022		1.016*		1.014*		1.014*		1.016*
	SD		0.008		0.006		0.006		0.005		0.007
PHOS (mg/dl)	M		146		89		73*		73*		104
	SD		118.7		48.3		36.3		40.2		97.3
Na (mmol/L)	M		48		29*		26*		22*		29*
	SD		25.3		17.4		9.2		12.8		17.3
K (mmol/L)	M		84		54*		49*		47*		59*
	SD		42.6		24.6		20.6		22.4		28.2
Cl (mmol/L)	M		52		30*		27*		24*		29*
	SD		29.5		16.8		12.3		12.7		14.6

* p <0.05

WEEK 18 DATA (RECOVERY): At the end of the recovery period, all urinalysis parameters had returned to normal limits.

Organ weights: (g)

WEEK 14 DATA (ABSOLUTE WEIGHTS)

Dose (mg/kg/d)		0		90		180		420		840	
Sex		M	F	M	F	M	F	M	F	M	F
Heart (g)	M	1.44	0.88	1.56	0.94	1.61	0.96*	1.41	0.91	1.20*	0.81
	SD	0.13	0.075	0.25	0.068	0.29	0.088	0.22	0.076	0.27	0.083
Spleen (g)	M	0.64	0.42	0.76*	0.47	0.68	0.39	0.62	0.40	0.51*	0.34*
	SD	0.096	0.094	0.175	0.076	0.087	0.048	0.115	0.054	0.133	0.052
Kidney (g)	M	3.14		3.42		3.39		3.22		2.75*	
	SD	0.36		0.48		0.27		0.30		0.39	
Liver (g)	M		6.56		7.57*		8.51*		7.72*		7.28
	SD		0.59		0.68		1.17		0.73		0.75
Testes (g)	M	3.13		3.27		3.14		3.34		1.77*	
	SD	0.21		0.26		0.51		0.14		0.66	
Epididymides (g)		1.37		1.21		1.26		1.29		0.95*	
	SD	0.14		0.11		0.15		0.11		0.18	
Ovaries (g)	M		0.12		0.11		0.09*		0.08*		0.08*

	SD		0.022		0.022		0.019		0.013		0.013
Pituitary (g)	M		0.016		0.021*		0.023*		0.021*		0.017
	SD		0.004		0.004		0.007		0.004		0.004

* p <0.05

WEEK 14 DATA (RELATIVE WEIGHTS)

Dose (mg/kg/d)		0		90		180		420		840	
Sex		M	F	M	F	M	F	M	F	M	F
Adrenal (%)	M	0.011		0.012		0.012		0.012		0.015*	
	SD	0.002		0.002		0.002		0.001		0.003	
Kidney (%)	M	0.66	0.75	0.73	0.76	0.73	0.72	0.74*	0.79	0.77*	0.85*
	SD	0.07	0.07	0.06	0.04	0.04	0.07	0.04	0.04	0.17	0.07
Liver (%)	M	2.64	2.73	3.03*	3.01*	3.13*	3.29*	3.11*	3.33*	3.15*	3.48*
	SD	0.29	0.18	0.29	0.23	0.41	0.36	0.44	0.23	0.31	0.26
Brain (%)	M	0.44	0.81	0.45	0.78	0.46	0.75	0.49	0.84	0.58*	0.93*
	SD	0.037	0.073	0.035	0.075	0.037	0.075	0.048	0.065	0.084	0.054
Testes (%)	M	0.66		0.70		0.67		0.78*		0.48*	
	SD	0.07		0.07		0.11		0.08		0.14	
Ovaries (%)	M		0.048		0.042		0.035*		0.036*		0.040*
	SD		0.009		0.008		0.008		0.007		0.008
Pituitary (%)	M		0.006		0.008*		0.009*		0.009*		0.008*
	SD		0.001		0.002		0.002		0.002		0.002

Relative to body wt; * p <0.05

Week 18 data (recovery) for absolute weights showed no significant changes relative to control.

WEEK 18 DATA (RECOVERY) – RELATIVE WEIGHTS

Dose (mg/kg/d)		0		90		180		420		840	
Sex		M	F	M	F	M	F	M	F	M	F
Testes (%)	M	0.69		0.65		0.70		0.67		0.42*	
	SD	0.03		0.01		0.12		0.09		0.12	
Epididymides (g)		0.28		0.27		0.27		0.24		0.21*	
	SD	0.02		0.00		0.05		0.03		0.02	
Pituitary (g)	M		0.021		0.021		0.025*		0.023		0.020
	SD		0.003		0.002		0.003		0.001		0.002

* p <0.05

Gross pathology:

WEEK 14 DATA (EMPTY CELLS INDICATE ZERO INCIDENCE)

Dose (mg/kg/d)	0		90		180		420		840	
Sex	M	F	M	F	M	F	M	F	M	F
Kidney: Large pelvis(es)	2/15	1/15	1/15	2/15			1/15	2/15	1/15	5/15
Kidney: Rough surface									1/15	
Kidney: Small									1/15	
Stomach: Dark foci	1/15	4/15	2/15	1/15	5/15	4/15	2/15	2/15	4/15	1/15
Mesenteric L. node Diffusely dark									1/15	
Seminal vesicle Small									1/15	
Testes: Small							1/15		12/15	
Uterus Lumen filled with fluid		1/15		1/15		1/15		1/15		4/15
WEEK 18 DATA (RECOVERY)										
Testes: Small									4/15	

Histopathology:

WEEK 14 DATA (EMPTY CELLS INDICATE ZERO INCIDENCE)

Dose (mg/kg/d)	0		90		180		420		840	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Kidney, Nephropathy Chronic, progressive									1/15(4)	
Kidney Dilatation, collecting tubule			1/15(2)		2/15(2)		2/15(2)		8/15 1/15(1) 4/15(2) 2/15(3) 1/15(4)	
Kidney Dilatation, pelvis		1/15(x)	1/15(x)	3/15(x)			1/15(x)	3/15(x)	1/15(x)	5/15(x)
Heart, Degenerative cardiomyopathy									4/15 2/15(1) 2/15(2)	
Pancreas, acinar cell vacuolization					1/15(1)				2/15 1/15(3) 1/15(4)	
Stomach Submucosal edema									1/15(3)	
Thymus Involution									1/15(3)	
Testes Atrophy/degeneration					1/15(4)				13/15 1/15(3) 9/15(4) 3/15(5)	
Testes Dystrophy									4/15 1/15(2) 3/15(3)	
Uterus Dilatation										3/15(x)
WEEK 18 DATA (RECOVERY)										
Testes Atrophy/degeneration									5/5 1/5(2) 4/5(4)	

X = present; 1 = minimal; 2 = slight; 3 = moderate; 4 = marked; 5 = severe

Toxicokinetics:

Dose (mg/kg/d)		T_{max} (hr)		C_{max} (µg/ml)		$AUC_{0\text{-}8\ hr}$ (µg.hr/ml)	
		DAY 1	**DAY 86**	**DAY 1**	**DAY 86**	**DAY 1**	**DAY 86**
90	MALE	0.5	0.5	3.41	8.65	8.00	17.28
	FEMALE	1.0	0.5	3.59	6.71	12.04	14.52
	M + F	0.5	0.5	3.20	7.68	10.02	15.90
180	MALE	0.5	1.0	4.99	12.57	16.81	30.35
	FEMALE	1.0	1.0	5.64	16.00	22.72	60.99
	M + F	1.0	1.0	5.09	14.28	19.77	45.67
420	MALE	0.5	0.5	9.24	31.90	33.04	88.40
	FEMALE	1.0	1.0	9.40	19.60	44.88	77.15
	M + F	1.0	0.5	9.16	25.27	38.96	82.77
840	MALE	1.0	0.5	22.78	69.07	73.06	194.17
	FEMALE	1.0	1.0	14.40	44.33	67.89	140.98
	M + F	1.0	1.0	18.59	55.23	70.48	167.57

Summary of Study Findings:

In a 13-week study, rats were dosed orally by gavage with OGT 918 at doses of 90, 180, 420 and 840 mg/kg/d. The doses were divided into three equal doses administered at 8 hr intervals for 13 weeks. Dose-dependent increases in incidence of diarrhea/soft feces and enlarged abdomen (≥ MD) was observed. The diarrhea subsided upon termination of treatment. Body weight gain was decreased by 11% and 31% in HMD males (10x the maximum clinical dose of 100 mg TID based on $AUC_{0\text{-}6hr}$) and HD males (22x the maximum clinical dose of 100 mg TID based on $AUC_{0\text{-}6hr}$) and by 19% in HD females (16x the maximum clinical dose of 100 mg TID based on $AUC_{0\text{-}6hr}$) at the end of the treatment period. At the end of the recovery period, body

weight gain was still decreased by 18% in HD males and females. Food consumption was decreased by 12% in HD males at the end of the treatment period but increased to control level at the end of the recovery period. Degenerative cardiomyopathy and nephropathy were observed in HD males. Dilatation of the collecting tubule of the kidney was observed in all treated males whereas dilatation of the pelvis was observed in the LD, HMD and HD groups. The target organs of toxicity include the testes (atrophy/degeneration, dystrophy), kidney (dilatation-collecting tubule & pelvis, nephropathy), heart (degenerative cardiomyopathy), pancreas (acinar cell vacuolization), Thymus (involution) and uterus (dilatation). NOAEL = 90 mg/kg/day (2x the maximum clinical dose of 100 mg TID based on $AUC_{0\text{-}6hr}$) based on histopathology.

Study title: 26-Week oral gavage toxicity study with SC-49483 In rats with 4 weeks recovery.

Key study findings:

- There were no treatment-related deaths. Dose-related increase in scaly tail was observed in both sexes. Wart-like lesions on the tail also showed a dose-dependent increase in treated males. In treated females, the incidence were not dose-related.
- Mean body weight was decreased by 12% in MD males and by 23% and 9% in HD males and females respectively at the end of the treatment period. After the 4-week recovery period, mean body weight was still decreased by 10% in MD males and by 17% and 8% in HD males and females respectively. Animals in the pair-fed control group also had decreased mean body weight (8%-10%) which was partially reversed to 6% at the end of the recovery period.
- Mean food consumption was decreased by 8% and 13% in MD and HD males and by 15% and 7% in the pair-fed control males and females respectively. At the end of the recovery period, mean food consumption was decreased by only 2% and 3% in HD males and females respectively and by 5% and 9% in pair-fed control males and females respectively.
- RBC, hemoglobin and platelets were slightly but statistically significantly decreased in MD and HD females relative to control. Hemoglobin concentration was slightly but statistically significantly decreased in MD males whereas platelets were significantly decreased in HD males. Hematocrit was only significantly decreased in HD females. These decreases are suggestive of slight anemia. WBC was statistically significantly increased in MD and HD females in a dose related manner. Lymphocytosis was noted in HD females. Segmented neutrophils were significantly increased in MD and HD males but not in a dose-related manner. These changes were reversed at the end of the recovery period.
- Albumin and alkaline phosphatase were slightly but statistically significantly decreased in all treated males relative to control. The low alkaline phosphatase activity may be associated with reduced osteoblast activity. Cholesterol and bile acids (3-fold) were significantly increased in HD males. Statistically significantly increases in AST (2-fold) in HD males and ALT (2 to 3-fold in MD and HD males respectively) were noted. Electrophoresis revealed that albumin and γ-globulin concentrations were slightly but statistically significantly decreased in all treated males. α-1 globulin concentration was only significantly increased in MD males. Following recovery, albumin concentration was slightly but statistically significantly decreased in MD and HD males whereas globulin concentration was slightly but significantly decreased in HD males.
- Ca excretion was statistically significantly increased in all treated females while urine Ca concentration was only significantly increased in MD and HD females. Cl excretion was statistically significantly increased MD and HD males. These changes were reversed at the end of the recovery period.

- Relative weight of the small intestine was slightly but statistically significantly increased (dose-dependently) in all treated males and in HD females. Though the relative weights of the small intestine were slightly reduced in MD and HD males at the end of the recovery period, they were still significantly increased relative to control. Relative weights of the large intestine and cecum were slightly but statistically significantly increased in MD males and in HD males and females. At the end of the recovery period, relative weight of the large intestine was still significantly increased only HD males. Relative weight of the kidney was slightly but statistically significantly increased in MD males. While this was reversed at the end of the recovery period, relative weight of the kidney in HD males was slightly but statistically significantly increased relative to control. Relative weight of the brain was slightly but statistically significantly increased in MD and HD males. At the end of the recovery period, even though the relative weight of the brain was slightly decreased in HD males, it was still significantly different from control. Also relative weights of the liver and pituitary were increased.
- Sperm motility, sperm concentration and the number of normal sperms were decreased in all treated males relative to control. Amorphous sperms and sperms with decapitated heads were increased in all treated males relative to control. At the end of the treatment-free period, partial recovery of the altered sperm parameters was observed. It is likely full recovery will occur with time.
- Thyroxine level was slightly but statistically significantly decreased in all treated males but slightly and significantly increased in HD females. Triiodothyronine was slightly but statistically significantly decreased in HD males and pair fed control males relative to control males. These changes were reversed at the end of the recovery period.
- Dry bone weight was slightly but statistically significantly decreased (dose-dependently) only in treated males. None of the bone minerals (Ca, P) analyzed were significantly different from control. Serum 1, 25-dihydroxyvitamin D was statistically significantly decreased only in MD females.
- Fecal protein (expressed as % nitrogen) was slightly but statistically significantly increased in MD and HD males and in the pair fed control group. Fecal fat content was also slightly but statistically significantly increased in HD and pair-fed control males only. The concurrent increase in % nitrogen and fat in pair fed controls suggest that these changes are due to levels of food consumption rather than due to test article exposure.
- Of the lymphocyte subsets in rat peripheral blood, only $CD3^+CD4^+$ and $CD45RA^+$ were statistically significantly increased in HD females and males respectively relative to controls. Lymphocyte subsets from spleen of treated rats were not significantly different from those of control. However, all lymphocyte subsets of the pair-fed control female rats were significantly lower relative to those of non pair-fed control. Lymphocyte subsets from rat thymus did not show any significant change in numbers with treatment.
- The target organs of toxicity include the GI tract – esophagus (serosal fibrosis), stomach (cytoplasmic vacuolation of chief cells), large intestine (mucosal necrosis), pancreas (acinal cell vacuolation), salivary gland (cytokaryomegaly – seromucus acinar cells), epididymides (hypospermia), testes (degeneration/atrophy), mesenteric lymph node (lymphoid depletion), skin of the tail (hyperkeratosis, acanthosis, pyogranulomatous dermatitis), eye (posterior synechia, cataract) and kidney (chronic progressive nephropathy).
- The incidence of testicular lesions was decreased at the end of the recovery period but the severity appear to have increased. The incidence of kidney lesions was decreased at the end of the recovery period.
- NOAEL could not be established because of the nephropathy and testicular lesions at the LD.

Study no: SA 4085

Volume #, and page #: Vol. 16, pg. 1.
Conducting laboratory and location: [redacted]

Date of study initiation: July 23, 1993.
GLP compliance: Yes (U. S. A. and Japan).
QA report: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: Lot # 93-K003-B2A; [^{14}C]SC-49483; 100% pure.
Formulation/vehicle: A suspension of SC-49483 in a vehicle of 0.5% methylcellulose (w/v), and 0.1% Polysorbate 80 (v/v) in reverse osmosis water.

Methods (unique aspects):
Dosing: 100, 200 and 400 mg/kg was administered three times/day at 8 hours intervals. Total dosage/day was 0, 300, 600 and 1200 mg/kg/day.
Species/strain: Rats/Crl: CD (SD) BR
#/sex/group or time point (main study): 30 /sex/group in groups 1 and 7; 48/sex/group in groups 2, 3 and 6; and 15/sex/group in groups 4 and 5.
Satellite groups used for toxicokinetics or recovery: Please see study design below.

Group	Dosage Level (mg/kg/day)[a]	Dose (mg/kg/dose)	Number of Animals[b] Male	Female
1 (Control)	0	0	30[c]	30[c]
2	300	100	48[c,d]	48[c,d]
3	600	200	48[c,d]	48[c,d]
4	300	100	15[d,e]	15[d,e]
5	1200	400	15[d,e]	15[d,e]
6	1200	400	48[c,d,f]	48[c,d,f]
7 (Pair-fed control)	0	0	30[e,f]	30[e,f]

The dose volume will be 10 mL/kg/dose. The control group will receive the carrier only. The daily dosage will be divided into three doses/day, separated by approximately 8 hours (at approximately 6:00, 14:00 and 22:00).

a. **Extra animals will be used as replacement animals at the discretion of the study director.**
b. **Five animals/sex in Groups 1 through 3, 6, and 7 (designated as interim sacrifice animals) will be necropsied after 13 weeks of treatment. Fifteen animals/sex in Groups 1 through 3, 6, and 7 (designated as terminal sacrifice animals) will be necropsied after 26 weeks of treatment. Ten animals/sex in Groups 1 through 3, 6, and 7 (designated as recovery animals) will continue without treatment for 4 weeks after 26 weeks of treatment and then necropsied.**
c. **The last 18 animals in Groups 2, 3, and 6, and all animals in Groups 4 and 5 will be designated for pharmacokinetic analyses.**
d. **Animals in Groups 4 and 5 will receive [14C] SC-49483 once on Day 1 and once during Weeks 13 and 26. Unlabelled SC-49483 will be used for all other doses of these animals.**
e. **Animals in Group 7 will be pair-fed with the high-dose (Group 6) animals. Animals in Group 7 will not be dosed.**

Age: 5 weeks old.
Weight: Males (133.0-188.4 g); Female (119.1-180.3 g).
Doses in administered units: 300, 600 and 1200 mg/kg/day.
Route, form, volume, and infusion rate: Oral (gavage); 10 ml/kg/dose.

Observations and times:
Clinical signs: Twice daily.
Body weights: Recorded on the first day of treatment, twice weekly for the first four weeks and weekly thereafter.
Food consumption: Weekly.
Ophthalmoscopy: All animals were examined before initiation of treatment and during weeks 8, 16, 26 and 30 (all animals except those designated for the repeat mass balance and for pharmacokinetic analysis).

EKG: No conducted.
Hematology: Blood samples were collected from 10/sex/group in Groups 1 through 3, 6, and 7 during Weeks 4 and 14 and from all animals in Groups 1 through 3, 6, and 7 (except animals designated for pharmacokinetic analysis) during Weeks 27 and 31/32 (recovery animals) for routine hematology evaluation.
Clinical chemistry: Blood samples were collected as specified for hematology. Routine clinical chemistry evaluation was conducted. At weeks 28 and 32, blood was also collected for vitamin D analysis. Blood samples were also collected from each animal in Groups 1 through 3, 6, and 7 (except animals designated for pharmacokinetic analysis) at scheduled sacrifices for hormone (Thyroid stimulating hormone, thryoxine, triiodothyronine, testosterone, luteinizing hormone and parathyroid hormone) analysis.
Urinalysis: Urine samples were collected from 10/sex/group in Groups 1 through 3, 6, and 7 during Weeks 4 and 14 and from all animals in Groups 1 through 3, 6, and 7 (except animals designated for pharmacokinetic analysis) during Weeks 27 and 31/32 (recovery animals). Animals were fasted overnight, and urine was collected over approximately 24 hours before blood sampling; water was provided ad libitum. Routine urinalysis evaluation was conducted.
Gross pathology: Organs/Tissues isolated for gross pathology examination is indicated in the list of addendum.
Organs weighed: Organs weighed are indicated in the list of addendum.
Histopathology: Tissues isolated for histopathology examination is indicated in the list of addendum.
Toxicokinetics: All animals in groups 4 and 5 (300 and 1200 mg/kg/day) were administered [^{14}C]SC-49483 at the morning dose on Day 1 and once during weeks 13 and 26. Additional animals were dosed with [^{14}C]SC-49483 to repeat the mass balance portion of the study for Day 1. All other doses for these animals were with unradiolabeled SC-49483. The specific radioactivity of [^{14}C]SC-49483 was ~1.8 µCi/mg for group 4 animals and ~ 0.6 µCi/mg for group 5 animals.
Blood collection (SC-49483): Up to 18 animals /sex/group/interval in groups 2, 3 and 6 were bled for PK analysis on day 1 and once during weeks 13 and 26. The first set of animals were bled at ~ 0.25 and 2 hr after the first dose, the second set was bled 0.5 and 4 hr after the first dose and the last set was bled at 1 and 8 hr after the first dose on day 1and once during weeks 13 and 26.
Blood collection ([^{14}C]SC-49483): On day 1 and once during weeks 13 and 26, 6 animals/sex/group/interval in groups 4 and 5 dosed with [^{14}C]SC-49483 were bled for PK analysis at ~ 1 or 4 hr after the morning dose.
Urine and feces collections ([^{14}C]SC-49483): 3 animals/sex/group on day 1 and during weeks 13 and 26 and one animal/sex/group during week 30 in groups 4 and 5 dosed with ([^{14}C]SC-49483) were placed in individual metabolism cages, and urine and feces were collected for 168 hours at 24 hr intervals.
Other:
Bone mineral analysis: The entire right femur from each animal at the terminal and recovery sacrifices was collected. The dry weight of the bone and fat-free dry weight of ash, Ca and P contents were determined for the femur of each animal at the terminal sacrifice. In addition, the fifth lumbar vertebrae, the right fifth rib, and the right lower incisor from each animal was collected at the terminal and recovery sacrifices.
Sperm Evaluation: At scheduled sacrifices (Weeks 14, 27, and 32), sperm were collected from the left epididymis from each male in Groups 1 through 3, 6, and 7 (except those designated for pharmacokinetic analysis) and evaluated for concentration, motility, and morphology. The left epididymis was weighed before sperm collection. At Weeks 27 and 32, the sperm evaluation was done in a blinded fashion.