SIGNALS OF NEUROTOXICITY

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m²	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m²
Rat	OGT 918: 420, 1680 mg/kg/d, 4 weeks.	Brain: vacuolation of white matter – 5/15 (0), 5/15 (LD), 3/15 (HD)		LD: 2,520 HD: 10,080		14X 55X
	OGT 918: 180, 840, 4200 mg/kg /d, 4 weeks.	Brain: vacuolation of white matter – 14/30 (0), 26/30 (LD), 26/30 (MD), 12/30.		LD: 1,080 MD: 5,040 HD: 25,200		6X 27X 136X
Juvenile Rat	OGT 918: 20, 60, 180 mg/kg/d, PN Days 12 - 70.	Brain, sciatic/tibial nerves: vacuolation in female weanlings at ≥ 20 mg/kg/d. Both genders had head tilting to the left. Learning, locomotor, auditory startle, righting reflex and vision were unremarkable.				
Dog	OGT 918: 85, 165, 495, 825 mg/kg/d, 2 weeks	Ataxia, absent/diminished pupillary, palpebral or patellar reflexes ≥ 495 mg/kg/d.		9900		≥ 54x
	OGT 918: 35, 70, 105, 140 mg/kg/d 4 weeks	Tremor, absent corneal reflexes –105 mg/kg/d.		2100		11X
Monkey	OGT 924: 750, 2000, 52 weeks	Brain: vascular mineraliza -tion, mineralization (LD & HD) & necrosis (LD) of white matter-males. Spinal cord: vascular mineralization (HD)	LD: 34,600 HD: 57,800		4X 7X	

Dogs had clinical signs of neurotoxicity without histopathology findings. Rats and monkeys had no clinical signs suggestive of neurotoxicity but had histopathology findings of neurotoxicity

CARDIAC TOXICITY

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m²	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m²
Rat	OGT 918: 90, 180, 420, 840 mg/kg/d. 13 weeks	Degenerative cardiomyop –athy HD males.	HD: 194,170(M) 15,900		22X 2X	
	OGT 918: 180, 420, 840, 1680 mg/kg/d, 52 weeks.	Cardiomyopathy at all doses including control, not dose-dependent, lowe –r incidence at control.	LD: 36,485 M + F		4X	
Monkey	OGT 918: 165, 495, 1650 mg/kg /d, 4 weeks	Acute inflammation of heart in 2/10 (HD) and 1/10 (MD) monkeys found dead.		LD: 1,980 MD: 5,940 HD: 19,800		11X 32X 107X

RENAL TOXICITY

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m²	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m²
Rat	OGT 918: 90, 180, 420, 840 mg/kg/d. 13 weeks.	Chronic, progressive neph–ropathy.	HD: 194,170(M) 15,900		22X 2X	
	OGT 924: 300, 600, 1200 mg/kg/d. 26 weeks.	Chronic, progressive neph–ropathy all doses include–ing control, may not be drug related.	28,400 (LD)		3X	
	OGT 918: 180, 420, 840, 1680 mg/kg/d, 52 weeks.	Chronic, progressive neph–ropathy at all doses including control, not dose–dependent, lower inciden–ce at control.	LD: 36,485 M + F		4X	

CATARACTS

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m²	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m²
Rat	OGT 924: 300, 600, 1200 mg/kg/d. 26 weeks.	Cataract at 1200 mg/kg/d	HD: 68,000 (M)		8X	
	OGT 918: 180, 420, 840, 1680 mg/kg/d, 52 weeks.	Cataracts at LD-M (1/28), MD-M (1/29), HMD-M (18/27), HMD-F (9/23)	LD 36,485 M + F		4X	

BONE MARROW TOXICITY

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m²	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m²
Rat	OGT 918: 420, 1680 mg/kg/d, 4 weeks	Bone marrow hypocellula–rity with fat replacement at HD.		HD: 10,080		55X
Rat	OGT 924: 330, 1020, 3670 mg/kg/d, 4 weeks	Bone marrow hypocellula–rity with fat replacement at MD and HD.	LD: 30,000 MD: 92,000 HD: 263,000		3X 10X 30X	
Rat	OGT 918: 180, 840, 4200 mg/kg/d, 4 weeks	Bone marrow hypocellula–rity with fat replacement at MD and HD.		MD: 5,040 HD: 25,200		27X 136X
		Bone marrow hypocellula–rity with necrosis at HD.		HD: 25,200		136X
Monkey	OGT 924: 750, 2000 mg/kg/d, 52 weeks.	Bone marrow hypocellula–rity with fat replacement at HD.	HD-F: 79,900		9X	

LYMPHOID/LYMPHOCYTE TOXICITY (DEPLETION)

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m^2	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m^2
Rat	OGT 924: 330, 1020, 3670 mg/kg/d, 4 weeks	Lymphoid/lymphocyte depletion in spleen, thymu –s & mesenteric lymph node at MD and HD	LD: 30,000 MD: 92,000 HD: 263,000		3X 10X 30X	
Rat	OGT 918: 420, 1680, 4 weeks	Lymphoid/lymphocyte depletion in spleen, thymu –s, mesenteric & submaxi –llary lymph nodes at HD		HD: 10,080		55X
Rat	OGT 918: 180, 840, 4200, 4 weeks	Lymphoid/lymphocyte depletion in spleen, thymu –s, mesenteric & submaxi –llary lymph nodes at HD		HD: 25,200		136X
Rat	OGT 918: 180, 420, 840, 1680, 52 weeks	Lymphoid atrophy in spleen (≥ MD), thymus (≥ LD), & mesenteric lymph node (≥ MD).	LD: 36,485 MD: 66,445 HD: 92,135		4X 8X 10X	
Dog	OGT 918: 35, 70, 105, 140 mg/kg /d, 4 weeks	Thymic involution at (≥ LD),		LD: 700 MD: 1400 HMD: 2100 HD: 2800		4X 8X 11X 15X
Dog	OGT 918: 20, 40, 80 mg/kg/d, 2 weeks	Atrophy (lymphoid depleti –on) of Peyer's patches of ileum (HD), lymphoid depletion in mesenteric lymph node (≥ MD), ↓ thymocytes (HD).		LD: 400 MD: 800 HD: 1600		2X 4X 9X
Dog	OGT 918: 240 mg/kg/d OGT 924: 550 mg/kg/d, 2 weeks	Atrophy (lymphoid depleti –on) of Peyer's patches of ileum	918: 272,000 924: 36,000		31X 4X	
Dog	OGT 918: 120 mg/kg/d	Atrophy (lymphoid depleti –on) of Peyer's patches of ileum		918: 2,400		13X
Mouse	OGT 918: 124, 1200, 2400 mg/ kg/d, 2 weeks	Thymus – involution at ≥ MD		MD: 3600		20X

PANCREATIC TOXICITY

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m²	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m²
Rat	OGT 924: 330, 1020, 3670 mg/kg/d, 4 weeks.	Acinar cell vacuolation at HD.	HD: 263,000		30X	
	OGT 918: 90, 180, 420, 840 mg/kg/d, 13 wee -ks	Acinar cell vacuolation at MD & HD.	MD: 30,350 M HD: 194,170 M		3X 22X	
	OGT 924: 300, 600, 1200 mg/kg /d 26 weeks.	Acinar cell vacuolation at HD.	HD: 65,350 M+F		7X	
	OGT 918: 180, 420, 840, 1680 mg/kg/d, 52 wee -ks.	Cytoplasmic vacuolation at HMD.	HMD:84,650 M		10X	
Mouse	OGT 918: 124, 1200, 2400 mg/kg/d, 2 weeks	Vacuolation, apical cytopl -asm at ≥ 1200 mg/kg/d.		MD: 3600		20X
Monkey	OGT 918: 60, 300, 600 mg/kg/d 4 weeks	↓ zymogen granules in glandular acini at MD & HD.		MD: 6,000 HD: 12,000		32X 65X
	OGT 924: 750, 2000 mg/kg/d, 52 weeks	↓ zymogen granules in glandular acini at LD & HD.	LD: 43,700 M+F HD: 68,850 M+F		5X 8X	

HEPATOTOXICITY

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m²	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m²
Rat	OGT 918: 180, 420, 840, 1680 mg/kg/d, 52 wee -ks	Toxicity in animals found dead but not in animals that survived till terminal sacrifice. Hepatoc necrosis at LD & HMD Cytoplasmic vacuolation at HD Lymphocyte infiltration ≥ HMD	LD: 15,900 M+F MD: 45,670 M+F HMD:82,770 M+F HD:167,570 M+F		2X 5X 9X 19X	
Dog	OGT 918: 35, 70, 105, 140 mg/kg /d, 4 weeks	Centrilobular hepatic vacu -olation at HMD.		HMD: 2100		11X
Monkey	OGT 918: 165, 495, 1650 mg/kg /d, 4 weeks	Hepatic necrosis & inflammation (MD & HD). Hepatic vacuolation ≥ LD		LD: 1,980 MD: 5, 940 HD: 19,800		11X 32X 107X
	OGT 924: 750, 2000 mg/kg/d, 52 weeks	Hepatic vacuolation, pigm -ented macrophages	LD: 43,700 M+F HD: 68,850 M+F		5X 8X	

Mouse	OGT 918: 124, 1200, 2400 mg/kg/d, 2 weeks	Hepatocyte cytoplasmic vacuolation ≥ LD		LD: 720 MD: 3600 HD: 7200		4X 20X 39X

HEMATOLOGY

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m²	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m²
Rat	OGT 924: 330, 1020, 3670 mg/kg/d, 4 weeks	↓ RBC, HCT ≥ 1020 mg/kg/d.	92,000		≥ 10X	
	OGT 918: 90, 180, 420, 840 mg/kg/d, 13 weeks.	↓ RBC, HCT ≥ 90 mg/kg/d.	15,900		≥ 2X	
	OGT 924: 300, 600, 1200 mg/kg /d. 26 weeks.	↓ RBC, HGB, HCT ≥ 600 mg/kg/d.	48,050 M + F		≥ 5X	
	OGT 918: 180, 420, 840, 1680 mg/kg/d, 52 weeks.	↓ RBC, MCHC ≥ 180 mg/kg/d	36,485 M + F		≥ 4X	
Dog	OGT 918: 35, 70, 105, 140 mg/kg /d, 4 weeks dose escalation study	↓ RBC, HCT, HGB ≥ 70 mg/kg/d.		1400		8X
Monkey	OGT 918: 165, 495, 1650 mg/kg -/d, 4 weeks.	↓ RBC, HCT, HGB at 1650 mg/kg/d.		19,800		107X
	OGT 924: 750, 2000 mg/kg/d, 52 weeks	↓ RBC, HCT, HGB at 2000 mg/kg/d.	57,800 (M) 79,900 (F)		7X 9X	

SPERM

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m²	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m²
Rat	OGT 924: 300, 600, 1200 mg/kg /d. 26 weeks	↓ Sperm motility (54%-71%), concentration (27%-54%), and # of normal sperms (23%-44%), not dose-dependent.	LD 28,400 M + F		3X	
Monkey	OGT 924: 750, 2000, 52 weeks	↓ sperm concentration 48% (LD), 62% (HD) relative to control.	LD: 34,600 HD: 57,800		4X 7X	

TESTICULAR, EPIDIDYMAL & SEMINAL VESICLE TOXICITY

SPECIES	STUDY DESIGN	TOXICITY	AUC (ng.h/ml)	mg/m²	MULTIPLE OF THERAPEUTIC DOSE (100 mg TID)	
					AUC (ng.h/ml)	mg/m²
Dog	OGT 918: 240 mg/kg/d, 2 weeks.	Testicular degeneration	272,000		31x	
Rat	OGT 918: 180, 840, 4200 mg/kg /d, 4 weeks	Testes: ↓spermatogenesis ≥ MD Epididymis: Hypospermia ≥ LD Seminal vesicle: Atrophy ≥ MD		MD: 5,040 HD: 25,200 LD: 1,080 MD: 5,040 HD: 25,200		≥ 27X 136X ≥ 6X ≥ 27X 136X
Rat	OGT 918: 420, 1680 mg/kg/d, 4 weeks	Testes: ↓spermatogenesis HD Epididymis: Hypospermia ≥ LD Seminal vesicle: Atrophy HD		HD:10,080 LD: 2,520 HD:10,080		55X 14X 55X
Rat	OGT 924: 330, 1020, 3670 mg/ kg/d, 4 weeks	Testes: ↓spermatogenesis ≥ MD Epididymis: Hypospermia ≥ MD Seminal vesicle: Atrophy ≥ MD	MD: 92,000		10X	
Rat	OGT 918: 20, 60, 180 mg/kg/d, 13 weeks	OGT 918: 20, 60, 180 mg/kg/d, 13 weeks	LD: 2,700		≥ 0.3X	
Rat	OGT 918: 90, 180, 420, 840 mg/kg/d, 13 weeks	Testes: atrophy, degenera -tion, dystrophy ≥ MD	MD: 30,350		≥ 3X	
Rat	OGT 924: 300, 600, 1200 mg/kg /d. 26 weeks	Testes: atrophy, degenera -tion ≥ LD, no recovery	LD: 30,700		≥ 3X	
Rat	OGT 918: 180, 420, 840, 1680 mg/kg/d, 52 wee -ks	Testes: aspermatogenesis, multinucleated giant cells, interstitial edema, atrophy of seminiferous tubule, interstitial cell hyperplasia Testes: atrophy, degenera -tion, dystrophy ≥ LD Little/no recovery	LD: 40,210		5X	
Monkey	OGT 918: 750, 2000 mg/kg/d, 52 weeks	Seminal vesicle: Mineralization ≥ LD	LD: 34,600		4X	

Summary of General Toxicology

Human therapeutic dose = 100 mg TID = 300 mg/d = 5.0 mg/kg = 185 mg/m^2.
Human $AUC_{0\text{-}6\ hr}$ for 100 mg TID = 8911ng.h/ml

SPECIES	STUDY DESIGN	KEY FINDINGS	DOSE (mg/m^2)	MULTIPLE OF HUMAN EXPOSURE
Dog	OGT 918: 120 mg/kg 0GT 924: 275 mg/kg Oral (capsule), 11 days	Diarrhea with both, ↑AST, atrophy (lymphoid depletion) of Peyer's patches in ileum (OGT 918);	120 mg/kg = 2400 275 mg/kg = 5500	13X 28X
	OGT 918: 85, 165, 495, 825 mg/kg/d Oral (capsule) 2 weeks	Neurotoxicity signal: ataxia, absent/diminished pupillary, palpebral or patellar reflexes (HMD, HD); Mortality: ¼, 4/4, 4/4 for LD, MD & HD. ↑AST ≥ 85 mg/kg/d, ↑ALT @ MD, ↓ body wt., necrosis of crypts of epithelium with dilatation and plugging, necrosis of villous tips (≥ 85 mg/kg/d); and thymus (involution). No NOAEL.	85 mg/kg = 1700 165 mg/kg = 3300 495 mg/kg = 9900 825 mg/kg = 16,500	9X 18X 54X 89X
	OGT 918: 20, 40, 80 mg/kg/d Oral (capsule) 2 weeks	Diarrhea & vomiting at all doses. Bloody diarrhea at HD. ↓Body wt. at HD, ↑AST at MD & HD, lymphoid depletion of Peyer's patches, colon mucosal irritation, thymic involution at HD, lymphoid depletion at MD. NOAEL = 20 mg/kg/d.	20 mg/kg = 400 40 mg/kg = 800 80 mg/kg = 1600	2X 4X 9X
	OGT 918: 240 mg/kg 0GT 924: 550 mg/kg Oral (capsule) 2 weeks	OGT 918: 4/6 Diarrhea→bloody/mucoid →black tarry stool, ↓ food intake, ↓ body wt., AST ↑ 25x pre-study value, 1/6, testicular degeneration – mild, dilated mucosal crypts filled with mucopolysaccharides, ↑ALT, atrophy – ileal Peyer's patches OGT 924: diarrhea-2/6. No wt loss. AST ↑ 10x pre-study value, atrophy – ileal Peyer's patches	$AUC_{0\text{-}8hr}$ (ng.h/ml) $T_{1/2}$ = 4 hr OGT 918:240 mg/kg M+F = 272,000 OGT 924:550 mg/kg M+F = 36,000	$AUC_{0\text{-}6hr}$ (ng.h/ml) AUC = 8911 $T_{1/2}$ = 6hr 31X 4X
	OGT 918: 35, 70, 105, 140 mg/kg/d. Dose escalation study for 4 weeks.	Mortality: ½ HMD. This animal had black watery stool, pale gums, prostration, absent corneal reflexes, dilated pupils, noisy breathing and was cold to touch. Diarrhea & vomiting. Red mucoid stool and tremors (HMD). HCT, HGB and RBC ↓ ≥ MD, AST ↑ in MD, HMD and HD males by 9.7-fold, 8.6-fold and 13.3-fold respectively. ALT ↑ in HMD and HD males by 1.6-fold each. Target organs: GI tract – small & large intestine (congestion of mucosa, inflammation, necrosis of villous tips, mucosal erosion). No histopathology suggestive of neurotoxicity.	35 mg/kg = 700 70 mg/kg = 1400 105 mg/kg = 2100 140 mg/kg = 2800	4X 8X 11X 15X

Rat Toxicology Studies: Total doses were administered as three equally divided doses/day.

SPECIES	STUDY DESIGN DOSE (mg/kg/d)	KEY FINDINGS	DOSE (mg/m^2)	MULTIPLE OF HUMAN EXPOSURE
Rat	OGT 918: 1680 OGT 924: 1680 Oral, 5 days	Diarrhea 7/8 animals – OGT 918 0/8 animals – 0GT 924	1680 = 10,080	55X
Rat	OGT 918: 1200, 1680 OGT 924: 2740, 3830 Oral, 5 days	Diarrhea 9/10 animals (LD), 8/10 (HD) – OGT 918 1/10 animals (LD), 1/10 (HD) – OGT 924	1200 = 7,200 1680 = 10,080 2740 = 16,440 3830 = 22,980	39X 55X 89X 124X
Rat	OGT 918: 840, 1680, 3400 Oral, 8 days	Mortality: 1/10 (HD) Diarrhea 7/10 (LD); 10/10 (MD & HD)	840 = 5,040 1680 = 10,080 3400 = 20,400	27X 55X 110X

SPECIES	STUDY DESIGN DOSE (mg/kg/d)	KEY FINDINGS	DOSE (mg/m^2)	MULTIPLE OF HUMAN EXPOSURE
Rat	OGT 918: 180, 840, 4200 Oral, 4 weeks	Mortality: 30/30 (HD) – Days 7 – 15 Diarrhea: 30/30 (HD), 7/30 (MD) ↓ body wt, ↓ body wt. gain (HD) ↑ AST, ALT (MD), ↑ urinary Ca (LD, MD) Target organs: GI tract: ↑ mitotic figures - cecal epithelium, stomach - hemorrhage, depletion of goblet cells - entire intestines, villous atrophy - jejunum, ileum. Prostate - atrophy, spleen, thymus, lymph nodes - lymphocyte depletion, pituitary - atrophy of pars distalis, bone marrow - hypocellularity, testis -↓ spermatogenesis, epididymis - hypospermia, seminal vesicle - atrophy. Most lesions observed in MD and HD. No NOAEL.	180 = 1,080 840 = 5,040 4200 = 25,200	6X 27X 136X
Rat	OGT 918: 420, 1680 Oral, 4 weeks	Diarrhea & swollen abdomen – 30/30 (HD). ↓ body wt, ↓ body wt. gain (HD), ↑ AST, ALT (HD). Bone marrow - hypocellularity, pituitary - atrophy, brain – vacuolization of white matter, GI tract: ↑ mitotic figures - cecal epithelium, villous atrophy – small intestines, thymus, spleen, lymph nodes –lymphoid depletion, testis & epididymis - ↓ spermatogenesis, hypospermia seminal vesicle & prostate – atrophy. Most lesions observed in HD. No NOAEL.	420 = 2,520 1680 = 10,080	14X 55X
Rat	OGT 924: 330, 1020, 3670 Oral, 4 weeks	Diarrhea: 1/20 (LD), 1/20 (MD), 1/20 (HD). Red Stool 2/20 (HD). Red discharge from mouth. ↓ in # of zymogen granules, 37% ↓ HD females. Feed consumption 38% ↓ HD males, 28% ↓ HD females. AST 159% ↑ HD males, 246% ↑ HD females. ALT 145% ↑ HD males, ↑ 88% HD females. Target organs: 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). Most lesions in MD & HD. No NOAEL.	$AUC_{0\text{-}8hr}$ (ng.h/ml) $T_{1/2}$ = 4 hr 330 = 30,000 1020 = 92,000 3670 = 263,000	$AUC_{0\text{-}6\ hr}$ 8911 ng.h/ml $T_{1/2}$ = 6 hr 3X 10X 30X

SPECIES	STUDY DESIGN DOSE (mg/kg/d)	KEY FINDINGS	DOSE (mg/m^2)	MULTIPLE OF HUMAN EXPOSURE
Rat	OGT 918: 20, 60, 180 Oral, 13 Weeks	No diarrhea. Abdominal swelling – HD males. 12% ↓ body wt. gain – HD males. At end of recovery, % ↓ in body weight gain was 52% (LD & MD males) and 61% (HD) males. Values for females are 42% (LD) and 25% (MD). HD females rather had an increase in body weight gain relative to control. Target organs: 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). NOAEL = 20 mg/kg/day.	$AUC_{0\text{-}8hr}$ (ng.h/ml) $T_{1/2}$ = 4 hr 20 = 2700 60 = 6700 180 = 19,600	$AUC_{0\text{-}6\ hr}$ 8911 ng.h/ml $T_{1/2}$ = 6 hr 0.3X 0.8X 2X

Rat	0GT 918: 90, 180, 420, 840 Oral, 13 weeks	Diarrhea: 5/40 (LD), 8/40 (MD), 10/40 (HMD), 29/40 (HD). ↓ body wt. gain 11% (HMD males), 31% (HD males), 19% (HD females). Target organs: testes (atrophy/degeneration, dystrophy), kidney (dilatation-collecting tubule & pelvis, nephropathy), heart (degenerative cardiomyopathy), pancreas (acinar cell vacuol -ization), thymus (involution) and uterus (dilatation). NOAEL = 90 mg/kg/day.	AUC_{0-8hr} (ng.h/ml) $T_{1/2}$ = 4 hr 90 M =17,280 F = 14,520 M + F = 15,900 180 M = 30,350 F = 60,990 M + F = 45,670 420 M = 88,400 F = 77,150 M + F = 82,770 840 M = 194,170 F = 140,980 M + F = 167,570	$AUC_{0-6\ hr}$ 8911 ng.h/ml $T_{1/2}$ = 6 hr 2X 2X 2X 3X 7X 5X 10X 9X 9X 22X 16X 19X
Rat	OGT 924: 300, 600, 1200 Oral, 26 weeks	No diarrhea. Scaly tail – dose-related ↑; wart-like lesions on tail – dose-related ↑ in males. Body wt. ↓ - 12% (MD males), 23% (HD males). ↓ sperm motility, concentration and # of normal sperms (not dose-related). Target organs: GI tract – esophagus (serosal fibrosis), stomach (cytoplasmic vacuolation of chief cells), large intestine (mucosal necrosis), pancreas (acinal cell vacuolation), salivary gland (cytokaryomegaly – seromucu -s acinar cells), epididymides (hypospermia), testes (degeneration/atrophy), mesenteric lymph node (lymphoid depletion), skin of the tail (hyperkeratosis, acanthosis, pyogranulom - atous dermatitis), eye (posterior synechia, cataract) and kidney (chronic progressive nephropathy). No NOAEL.	AUC_{0-8hr} (ng.h/ml) $T_{1/2}$ = 4 hr 300 M =30,700 F = 26,100 M + F = 28,400 600 M = 55,900 F = 40,200 M + F = 48,050 1200 M = 68,000 F = 62,700 M + F = 65,350	$AUC_{0-6\ hr}$ 8911 ng.h/ml $T_{1/2}$ = 6 hr 3X 3X 3X 6X 5X 5X 8X 7X 7X
Rat	OGT 918: 180, 420, 840, 1680 Oral, 52 weeks	Mortality: 44/60 (HD), 15/60 HMD, 9/60 (MD), 8/60 (LD), 11/60 ([redacted] diet control group), 3/60 (purified diet control group). Cause of death/moribundity was not ascertained for most of these animals. Other causes identified included chronic renal disease, enteropathy, gavage error, pituitary tumor (2/30 MD females), leukemia. Mean body wt: MD-14%↓-females, 18%↓-males; HMD-32%↓-males, 26%↓-females. Diarrhea: 45/60 (HD), 26/60 (HMD) – weeks 1-4; 46/60 (HD), 0/60 (HMD) – weeks 5-8; subsided by weeks 13-16. Equatorial cataracts: 1/28 (LD-M), 1/29 (MD-M), 18/27 (HMD-M), 9/23 (HMD-F). Partial recovery. Target organs: epididymides (hypospermia), heart (cardiomyopathy), kidn -ey (nephropathy, lymphocyte infiltration, protein casts, hyperplasia and mineralization), testes (atrophy of seminiferous tubules, aspermatogenesis, edema, and hyperplasia of interstitial cells), mammary gland (galactocele, active secretion) and tail (suppu -rative inflammation). Toxicities occurred at all dose levels with very little/no recovery. No NOAEL.	AUC_{0-8hr} (ng.h/ml) $T_{1/2}$ = 4 hr 180 M = 40,210 F = 32,760 M + F = 36,485 420 M = 76,750 F = 56,140 M + F = 66,445 840 M = 84,650 F = 99,620 M + F = 92,135 1680 – no data	$AUC_{0-6\ hr}$ 8911 ng.h/ml $T_{1/2}$ = 6 hr 5X 4X 4X 9X 6X 8X 10X 11X 10X

Monkey Toxicology Studies

SPECIES	STUDY DESIGN DOSE (mg/kg/d)	KEY FINDINGS	DOSE (mg/m^2)	MULTIPLE OF HUMAN EXPOSURE
Monkey	OGT 918: 165, 495, 1650, Oral, 4 weeks	Mortality: 3/10 (MD), 5/10 (HD). SS ↑ AST MD & HD. Acute inflammation of heart noted in 2/10 (HD) and 1/10(MD) dead animals. Target organs: 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). No NOAEL.	165 = 1,980 495 = 5,940 1650 = 19,800	11x 32x 107x
Monkey	OGT 924: 750, 2,000, 4,000 Oral, 4 weeks	↓ in # of zymogen granules in glandular acini of the exocrine pancreas was noted in most animals of all treated groups as well as one moribund control animal. No NOAEL.	$AUC_{0\text{-}8hr}$ (ng.h/ml) 750 M = 57,000 F = 36,000 M + F = 47,000 2000 M = 90,000 F = 86,000 M + F = 88,000 4000 M = 87,000 F = 80,000 M + F = 83,000	$AUC_{0\text{-}8hr}$ 8911 ng.h/ml 6X 4X 5X 10X 10X 10X 10X 9X 9X
Monkey	OGT 918: 60, 300, 600 IV infusion, 4 weeks	Mortality: 1/4 HD male, 1/4 HD female, 1/4 LD female. Deaths due to septicemia from infusion procedure and catheter problems (inflammatory changes). ↓ bodt wt. gain in MD & HD, ↑ AST (HD), ↓ in # of zymogen granules in glandular acini of the exocrine pancreas (all doses), severe lymphocytic depletion in thymus (MD & HD). Target organs: thymus (lymphoid depletion), pancreas (↓ zymogen granules). NOAEL = 60 mg/kg/d	60 = 720 300 = 3,600 600 = 7,200	12X 58X 116X
Monkey	OGT 924: 750, 2000 Intra gastric via cathe -ter for 19 weeks, then by gavage till week 52.	Mortality: 5/24 – control; 1/12 – LD; 4/24 – HD. Most deaths due to sepsis following gastric catheterization. RBC,HGB, HCT SS ↓-HD-F, reticulocytes 50% ↓-HD-F, PT SS↓-HD-F, 136% ↑ platelets-HD-M at end of recovery. Sperm concentration: 48% ↓-LD, 62% ↓-HD. Target organs: GI tract – cecum, colon, stomach (pigmented macrophages, granulomatous inflammation), Liver (pigmented macrophages, vacuolation), Pancreas (↓ zymogen granule staining), adrenal gland (mineralization), thyroid gland (vacuolated macrophage), seminal vesicle (mineralization), lymph nodes – mesenteric & submandibular (granuloma, mineralized, pigmented macrophage), mammary gland (lymphocytic infiltrate), skin (acanthosis/hyperkeratosis), cervix (lymphocytic infiltrate), skeletal muscle (inflammation, necrosis/degeneration), brain (mineralization, necrosis), spinal cord (mineralization) and kidney (angiectasis-glomerulus). No NOAEL. Lesion in HD showed little/no recovery.	$AUC_{0\text{-}8hr}$ (ng.h/ml) $T_{1/2}$ ~ 2 hr 750 M = 34,600 F = 52,800 2000 M = 57,800 F = 79,900	$AUC_{0\text{-}8hr}$ 8911 ng.h/ml $T_{1/2}$ = 6 hr 4X 6X 7X 9X

Mouse Toxicology Studies

SPECIES	STUDY DESIGN DOSE (mg/kg/d)	KEY FINDINGS	DOSE (mg/m^2)	MULTIPLE OF HUMAN EXPOSURE
Mouse	OGT 918: 240, 1200, 2400 Oral, 2 weeks	Mortality: 4/15(0), 5/15(LD), 4/15(MD), 8/15(HD). Most deaths due to gavage error. 1 HD death was drug-related – diarrhea, dilatation of intestines 12% ↓ body wt (HD); ↑ AST all doses. Liver: cytoplasmic vacuolation, thymic involution (MH & HD). No NOAEL.	240 = 720 1200 = 3600 2400 = 7200	4X 20X 39X

Recommendations:

Pharmacology/Toxicology recommends approval of this drug for the proposed indication. The preclinical studies are adequate to support the safety of the 100 mg/day, TID.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

X. APPENDIX/ATTACHMENTS:

APPENDIX I

TELEPHONE CALL REPORT

Participants: Dr Steigerwald, CDER, FDA

Mr Robert Ibbotson, OGS (RMI)

Date: 4th August 1999

Time and Location: 15:00 EDT; Offices of NEBR, Northborough, MA USA

A call was placed with Dr Steigerwald of CDER, FDA following —— communication with Ms Julie Rhee – OGS' assigned CSO at FDA. —— have been chasing comments to the IND submission for several weeks now and Julie Rhee, in her recent communication, said that Dr Steigerwald would be available to discuss the pre-clinical issues presented in the IND and again raised in the fax communication sent to FDA on 7th July 1999.

Dr Steigerwald caused confusion initially by stating that he had clearly presented FDA's stance on these issues at the pre-IND meeting. This was contrary to RMI's understanding and also the recorded minutes of that meeting. —— asked Dr Steigerwald for clarification of his statement. Dr Steigerwald went on to comment that for an Orphan drug such as OGT 918 he considered that it would be difficult for him to insist that full carcinogenicity studies and additional chronic toxicology studies would be necessary to support the NDA submission. Dr Steigerwald apologised for not providing comments before now, but bearing in mind the wealth of data that we had provided in the IND and also his current workload, this was proving difficult. However, he would complete an NDA style review in due course. He went on to say that if carcinogenicity studies were required, it is likely that these would only be requested as a post-approval, or Phase IV, commitment.

RMI acknowledged that Dr Steigerwald was performing a full NDA type of review on the data and advised him that further data will be forthcoming later in the year with respect to ongoing reproductive toxicology work. Dr Steigerwald commented that it is typical with Orphan products that any issues of concern are covered on the label rather than delay the approval of essential drugs for orphan diseases.

—— asked Dr Steigerwald if he had any information regarding the question OGS posed to FDA on the clinical protocols. Dr Steigerwald said he did not and it would be best to continue to approach Julie Rhee for a response to these issues.

The teleconference was closed by ——and RMI thanking Dr Steigerwald for his time and input.

/S/

Robert Ibbotson
6th August 1999

APPENDIX II

SUMMARY OF ECAC DISCUSSION AND RECOMMENDATIONS

Executive CAC
Date of Meeting: December 18, 2001
Mouse and Rat Carcinogenicity Dose-Selection Evaluation
Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Tim McGovern, Ph.D., HFD-170 Alternate Member
Bob Osterberg, Ph.D., HFD-520, Alternate Member
Karen Davis-Bruno, Ph.D., HFD-510, Team Leader
John Colerangle, DVM, Ph.D., HFD-510, Presenting Reviewer

Author of Draft Minutes: John Colerangle

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

IND #: 60197
Drug Name: OGT 918 (Zavesca™).
Sponsor: Oxford GlycoSciences.

Background:
The initial IND was submitted to the division on April 21, 2000. On November 5, 2001, the sponsor submitted a 13-week and a 1-year oral toxicity study (Pharmacology/Toxicology amendment, Serial # N-008SX) of SC-48334 in rats to support the doses selected for the proposed 2-year carcinogenicity study.

Carcinogenicity Dose Selection:
Sponsor proposed the use of MTD as a basis of dose selection. In a 13-week oral toxicity study, doses of 0, 90, 180, 420, and 840 mg/kg/day were administered as three equally divided doses, to Sprague-Dawley rats (20/sex/dose). No test article related deaths were noted during the study. Decreased bodyweight gains of 11% and 31% respectively were seen in 420 and 840 mg/kg/d males and at 7% and 19% respectively at the same doses in female rats. While a decrease in food consumption may explain the weight loss in males, there was no such finding in females. The histopathology findings of the kidney, heart, stomach and testes (please see table on next page) observed at 840 mg/kg/d also indicate that an MTD was reached in this study.

BODY WEIGHT CHANGES IN MALES					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
Pre dose wt (g)	135 ± 6.91	134 ± 8.76	137 ± 7.57	136 ± 6.75	138 ± 7.17
Week 13 wt (g)	518 ± 41.98	509 ± 40.70	506 ± 38.84	478 ± 34.80*	404 ± 62.06*
Wt. gain	383	375	369	342	266
Decrement (g)	-	8	14	41	117
% Decrement	-	**2**	**4**	**11**	**31**

Week 17 wt. (g) (Recovery)	531 ± 60.31	517 ± 52.68	521 ± 49.82	519 ± 48.40	462 ± 57.80
BODY WEIGHT CHANGES IN FEMALES					
Pre dose wt (g)	116 ± 5.90	116 ± 4.81	117 ± 6.55	120 ± 5.44	118 ± 6.49
Week 13 wt (g)	268 ± 35.03	278 ± 23.75	290 ± 28.40*	261 ± 17.39	241 ± 17.51*
Wt. gain	152	162	173	141	123
Decrement (g)	-	-	-	11	29
% Decrement	-	-	-	7	19
Week 17 wt. (g) (Recovery)	279 ± 39.35	286 ± 33.91	307 ± 31.80	275 ± 9.96	252 ± 15.12

* $p < 0.05$

1-YEAR ORAL TOXICITY STUDY

Mortality: In the 1-year oral toxicity study, the following survival rates were observed.

Dose (mg/kg/d)	0	0	180	420	840	1680*
Accidental Death	10/60	2/60	4/60	7/60	10/60	
Drug-related mortality			4/60	2/60	5/60	44/60
Total mortality	10/60	2/60	8/60	9/60	15/60	44/60

*Terminated at week 20

Body weight: Based on the body weight changes observed in the 1-year study, body weight effects at 840 mg/kg/d may be significant in a two year bioassay, supporting 420 mg/kg/d as the HD which correlates with the 13-week study finding.

BODY WEIGHT CHANGES AT WEEK 52												
Dose (mg/kg/d)	0		0		180		420		840		1680*	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
% Decrease					9	8	18	14	32	26		

*Terminated at week 20

Histopathology: Selected histopathology from animals sacrificed at week 52.

HISTOPATHOLOGY - WEEK 52 DATA								
Dose (mg/kg/d)	0		180		420		840	
Sex	M	F	M	F	M	F	M	F
Heart: Cardiomyopathy	4/15	4/15	8/18	6/15	15/19	12/15	11/16	4/12
Kidney: Nephropathy	8/15	5/15	16/18	7/15	12/19	5/15	12/16	
Kidney: Mineralization		4/14	2/18	4/15	12/19	12/15	11/16	7/12
Kidney: Protein casts	1/15	5/15	8/18	12/15	5/19	5/15	7/16	7/12
Kidney: Hyperplasia, pelvic epithelium	1/15		2/18	3/15	4/19	7/15	2/16	7/12

Selected histopathology of early decedents suggests that heart (cardiomyopathy, atrial thrombosis, myocardial necrosis) and kidney (vacuolization of tubular epithelium, mineralization, nephropathy/nephrosis) are target organs. Incidence of significant cardiac and renal findings at ≥ 840 mg/kg/d in early decedents is consistent with lesions that might impair survival in a two-year bioassay.

EXECUTIVE CAC RECOMMENDATIONS AND CONCLUSIONS

Rat: The Committee did not concur with the sponsor's proposed oral gavage doses of 60, 180 and 420 mg/kg/day for the 2 year bioassay. The committee recommended doses of 30, 60 and 180 mg/kg/day based on MTD due to cardiomyopathy.

If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:
(a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups
(b) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group
(c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
(d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, HFD-510
/Kdavis-Bruno, HFD-510
/JColerangle, HFD-510
/SWu, HFD-510
/ASeifried, HFD-024

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Colerangle
5/6/02 11:44:47 AM
PHARMACOLOGIST

Karen Davis-Bruno
5/6/02 11:48:13 AM
PHARMACOLOGIST

Carcinogenicity Assessment Committee (CAC/CAC-EC) Cover Sheet
Review of Carcinogenicity Study Design/Dose Selection Protocols

Application (IND/NDA) number: 60,197.
Division: Metabolic and Endocrine Drug Products.
CAS#: N/A.
Drug name: OGT 918 (Zavesca™).
Pharmacological Classification: Glucosyltransferase inhibitor.
Sponsor/Applicant: Oxford GlycoSciences, The Forum, 86 Milton Park, Abingdon Oxon OX14 4RY, UK.
Sponsor/Applicant contact name: Bruce Manning.
Sponsor/Applicant telephone and fax number: 508-393-3100 (T); 508-393-3780 (F).
Date submitted (stamp date): January 13, 2003.
45-day date (from submission stamp date): March 1, 2003.
P/T Reviewer(s): John Colerangle.
Date Review Completed: February 13, 2003.
Date of Exec CAC review: February 25, 2003.
CAC members: Joe Contrera, Abby Jacobs, Karen Davis Bruno, Jeri El Hage, Frank Sistare, Roswitha Kelly.

BACKGROUND

The initial IND was submitted to the division on April 21, 2000. On August 16, 2001, the sponsor submitted an NDA (# 21-348) to the Division. On January 13, 2003, the sponsor submitted a 13-week oral toxicity study (Pharmacology/Toxicology amendment, Serial # N-013SX) of OGT 918 in mice to support the doses selected for the proposed 2-year carcinogenicity study.

A. Summary of Sponsor's Proposal for Review:
Species/strain: Mouse/Crl: CD-1™(ICR)BR
Number/sex/dose: 50/sex/group.
Route: Oral (gavage).

	Male	Female
Doses proposed:	0, 0, 100, 420, 630 mg/kg/d	0, 0, 100, 420, 1020 mg/kg/d

Basis of dose selection: Sponsor proposed the use of MTD as a basis of dose selection. In the 13-week study, mice were dosed with OGT 918 at 100, 420 and 840 mg/kg/d (total dose) administered TID 6 hours apart. There were no drug-related deaths. The sponsor proposed a HD of 630 mg/kg/d for males in the 2-year carcinogenicity study. This was based on 31% decrease in body weight gain in males dosed 840 mg/kg/d for 13 weeks. Since there was no decrement in body weight gain in females dosed 840 mg/kg/d for 13 weeks, the sponsor proposed a HD of 1020 mg/kg/d for females in the 2-year carcinogenicity study. This dose was selected to be a dose between the 1200 mg/kg/d (caused 4% decrease in actual body weight) used in the 2-week study and the 840 mg/kg/d used in the 13-week study.

13-week - Body weights: (g)

MALES	Week 1	Week 13	Wt. Gain	Decrement	% Decrement in B. Wt. Gain	Decrease in Actual B. Wt. (%)
0	35.1	39.0	3.9	0	0%	0%
100	35.1	39.9	4.8	+ 0.9	+ 23%	0%
420	34.1	38.8	4.7	+ 0.8	+ 21%	0%
840	34.7	37.4	2.7	- 1.2	- 31%	4%
FEMALES	**Week 1**	**Week 13**	**Wt. Gain**	**Decrement**	**% Decrement in B. Wt. Gain**	**% Decrease in Actual B. Wt.**
0	26.6	30.4	3.8	0	0%	0%
100	27.3	31.3	4.0	+ 0.2	+ 5%	0%
420	26.5	30.5	4.0	+ 0.2	+ 5%	0%
840	28.1	32.3	4.2	+0.4	+ 11%	0%

B. Summary of Reviewer's Recommendations to CAC:

	Male	Female
Doses recommended by reviewer:	0, 0, 100, 420, 630 mg/kg/d	0, 0, 100, 420, 840 mg/kg/d

C. Basis for Recommendation (experimental details from sponsor's submission):
The reviewer concurs with the HD (630 mg/kg/d) selected for males but recommends a HD of 840 mg/kg/d for females in the mouse carcinogenicity study based on the following reasons:

- In the 13-week study, there were no drug-related deaths. Body weight gain was decreased by 31% in males dosed 840 mg/kg/d for 13 weeks. Hence, the 840 mg/kg/d dose may be too high for males in the 2-year study. Since there was no decrement in body weight gain in females dosed 840 mg/kg/d for 13 weeks, the reviewer recommends a HD of 840 mg/kg/d for females in the 2-year carcinogenicity study.

- There was no severe tissue histopathology in the 840 mg/kg/d mice following 13 weeks exposure to OGT 918. 4/10 males dosed 840 mg/kg/d had vacuolation in the brain that was minimal to mild in severity.

- Reviewer recommends 840 mg/kg/d as the MTD based on the 13-week study and the HD for females in the 2-year carcinogenicity study.

Questions for Executive CAC

- Does ECAC concur that the 840 mg/kg/d seems to be a reasonable HD for females and 630 for males in the proposed 2-year carcinogenicity study?

CAC Recommendations

- The Committee recommended the following doses for males and females: 210, 420 and 840 mg/kg/d. The recommendation for the high dose is based on an extrapolation from the 2-week study to 1/3 the lethal dose of 2400 mg/kg/d and on body weight effects. ECAC suggested increasing the proposed low dose to 210 mg/kg/d because 100 mg/kg/d produces drug exposures in mice less than clinical exposure.

- Committee did express some concern about the consequences of gavaging the animals three times daily.

Carcinogenicity Assessment Committee (CAC/CAC-EC) Cover Sheet
Review of Carcinogenicity Study Design/Dose Selection Protocols

Application (IND/NDA) number: IND 60, 197.
Division: Metabolic and Endocrine drug Products.
CAS#: N/A.
Drug name: OGT 918 (Zavesca™).
Pharmacological Classification: Glucosyltransferase inhibitor.
Sponsor/Applicant: Oxford GlycoSciences, The Forum, 86 Milton Park, Abingdon Oxon OX14 4RY, UK.
Sponsor/Applicant contact name: Bruce Manning.
Sponsor/Applicant telephone and fax number: 508-393-3100 (T); 508-393-3780 (F).
Date submitted (stamp date): November 7, 2001.
45-day date (from submission stamp date): December 22, 2001.
P/T Reviewer(s): John Colerangle.
Date Review Completed: December 10, 2001.
Date of Exec CAC review: December 18, 2001.
CAC members: Joseph DeGeorge, Joe Contrera, Tim McGovern, Frank Sistare, Bob Osterberg.

BACKGROUND

The initial IND was submitted to the division on April 21, 2000. On November 5, 2001, the sponsor submitted a 13-week and a 1-year oral toxicity study (Pharmacology/Toxicology amendment, Serial # N-008SX) of SC-48334 in rats to support the doses selected for the proposed 2-year carcinogenicity study.

A. Summary of Sponsor's Proposal for Review:

Species/*strain*: Rat/IGS (Crl: CD®(SD) IGS BR)
Number/sex/dose: 50/sex/group.
Route: Oral (gavage).

	male	female
Doses proposed:	0, 0, 60, 180, 420 mg/kg/d	0, 0, 60, 180, 420 mg/kg/d

Doses will be administered as 3 equal doses 6 hr apart.

Basis of dose selection: MTD

Sponsor proposed the use of MTD as a basis of dose selection. In a 13-week oral toxicity study, doses of 0, 90, 180, 420, and 840 mg/kg/day were administered as three equally divided doses, to Sprague-Dawley rats (20/sex/dose). No test article related deaths were noted during the study. Decreased bodyweight gains of 11% and 31% respectively were seen in 420 and 840 mg/kg/d males and of 7% and 19% respectively at the same doses in female rats. While a decrease in food consumption may explain the weight loss in males, there was no such finding in females. The histopathology findings of the kidney, heart, stomach and testes (please see table on next page) observed at 840 mg/kg/d also indicate that an MTD was reached in this study.

BODY WEIGHT CHANGES IN MALES					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
Pre dose wt (g)	135 ± 6.91	134 ± 8.76	137 ± 7.57	136 ± 6.75	138 ± 7.17
Week 13 wt (g)	518 ± 41.98	509 ± 40.70	506 ± 38.84	478 ± 34.80*	404 ± 62.06*
Wt. gain	383	375	369	342	266
Decrement (g)	-	8	14	41	117
% Decrement	-	**2**	**4**	**11**	**31**
Week 17 wt. (g) (Recovery)	531 ± 60.31	517 ± 52.68	521 ± 49.82	519 ± 48.40	462 ± 57.80

BODY WEIGHT CHANGES IN FEMALES					
Pre dose wt (g)	116 ± 5.90	116 ± 4.81	117 ± 6.55	120 ± 5.44	118 ± 6.49
Week 13 wt (g)	268 ± 35.03	278 ± 23.75	290 ± 28.40*	261 ± 17.39	241 ± 17.51*
Wt. gain	152	162	173	141	123
Decrement (g)	-	-	-	11	29
% Decrement	-	-	-	**7**	**19**
Week 17 wt. (g) (Recovery)	279 ± 39.35	286 ± 33.91	307 ± 31.80	275 ± 9.96	252 ± 15.12

*** $p < 0.05$**

Histopathology:

INCIDENCE AND SEVERITY OF HISTOPATHOLOGY IN MALES – WEEK 14					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
Heart Degenerative cardiomyopathy					4/15 2/15(1) 2/15(2)
Stomach Submucosal edema					1/15(3)
Stomach Ulceration/erosion					2/15(2)
Testes Atrophy/degeneration		1/15(2)	3/15 2/15(2) 1/15(4)		13/15 1/15(3) 9/15(4) 3/15(5)
Testes Dystrophy					4/15 1/15(2) 3/15(3)
Kidney Nephropathy, chronic progressive					1/15 (4)
Kidney Dilation, collecting tubule		1/15(2)	2/15(2)	2/15(2)	8/15 1/15(1) 4/10(2) 2/15(3) 1/15(4)

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

1-YEAR ORAL TOXICITY STUDY

Mortality: In the 1-year oral toxicity study, the following survival rates were observed.

Dose (mg/kg/d)	**0**	**0**	**180**	**420**	**840**	**1680***
Accidental Death	10/60	2/60	4/60	7/60	10/60	
Drug-related mortality			4/60	2/60	5/60	44/60
Total mortality	**10/60**	**2/60**	**8/60**	**9/60**	**15/60**	**44/60**

***Terminated at week 20**

Body weight: Body weight (g) changes during this period are indicated in the table below. Based on the body weight changes observed in the 1-year study, body weight effects at 840 mg/kg/d may be significant in a two year bioassay, supporting 420 mg/kg/d as the HD which correlates with the 13-week study finding.

BODY WEIGHT CHANGES AT WEEK 52												
Dose (mg/kg/d)	**0**		**0**		**180**		**420**		**840**		**1680***	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
% Decrease					9	8	18	14	32	26		

***Terminated at week 20**

Histopathology: Selected histopathology from animals sacrificed at week 52.

HISTOPATHOLOGY - WEEK 52 DATA								
Dose (mg/kg/d)	0		180		420		840	
Sex	M	F	M	F	M	F	M	F
Heart: Cardiomyopathy	4/15	4/15	8/18	6/15	15/19	12/15	11/16	4/12
Kidney: Nephropathy	8/15	5/15	16/18	7/15	12/19	5/15	12/16	
Kidney: Mineralization		4/14	2/18	4/15	12/19	12/15	11/16	7/12
Kidney: Protein casts	1/15	5/15	8/18	12/15	5/19	5/15	7/16	7/12
Kidney: Hyperplasia, pelvic epithelium	1/15		2/18	3/15	4/19	7/15	2/16	7/12

Selected histopathology of early decedents suggests that heart (cardiomyopathy, atrial thrombosis, myocardial necrosis) and kidney (vacuolization of tubular epithelium, mineralization, nephropathy/nephrosis) are target organs. Incidence of significant cardiac and renal findings at ≥ 840 mg/kg/d in early decedents is consistent with lesions that might impair survival in a two-year bioassay.

Kinetics submitted:	rodent	human
pharmacokinetics	13 weeks	4 weeks
metabolism	In vitro & in vivo	In vitro
protein binding	0%	0%

B. Summary of Reviewer's Recommendations to CAC:

	male	female
Doses recommended by reviewer:	0, 0, 60, 180, 420 mg/kg/d	0, 0, 60, 180, 420 mg/kg/d

C. Basis for Recommendation (experimental details from sponsor's submission):
The reviewer concurs with the doses selected for the rat carcinogenicity study based on the following reasons:

- In a 13-week oral toxicity study at doses of 0, 90, 180, 420, and 840 mg/kg/d, no test article related deaths were noted.

- Decreased bodyweight gains of 11% and 31% respectively were seen in 420 and 840 mg/kg/d males and 7% and 19% respectively at the same doses in female rats. While a decrease in food consumption may explain the weight loss in males, there was no such finding in females.
- Based on the body weight gain decrements, 420 mg/kg/d seems to be a reasonable MTD for the proposed 2-year carcinogenicity study.

Questions for Executive CAC

- Does ECAC concur that the doses evaluated and the study evaluation provides an adequate evaluation of the carcinogenic potential in the rat?

- Does ECAC concur that 420 mg/kg/d seems to be a reasonable HD for the proposed 2 year carcinogenicity study?

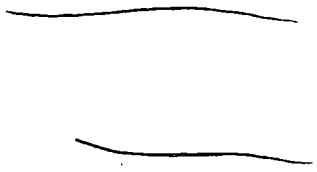
CAC Recommendations: The committee did not concur with the sponsor's proposed oral gavage doses of ——————mg/kg/day for the 2 year bioassay. The committee recommended doses of 30, 60 and 180 mg/kg/day based on MTD due to cardiomyopathy.

PHARMACOLOGY/TOXICOLOGY COVER SHEET

IND number: 60197.
Review number: 2.
Sequence number/date/type of submission: # 008SX; November 5, 2001; Dose Selection Study and Carcinogenicity study protocol.
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Oxford GlycoSciences, The Forum, 86 Milton Park, Abingdon Oxon OX14 4RY, UK.
Manufacturer for drug substance: G. D. Searle and Company, 4901 Searle Parkway, Skokie, IL 6007.

Reviewer name: John Colerangle
Division name: Metabolic & Endocrine Drug Products.
HFD #: 510.
Review completion date: December 10, 2001

Drug:
Trade name: Zavesca™.
Generic name (list alphabetically): Miglustat.
Code name: OGT 918, SC-48334.
Chemical name: 1,5 (Butlyimino)-1,5-dideoxy-D-glucitol
CAS registry number: 72599-27-0
Mole file number: N/A.
Molecular formula/molecular weight: $C_{10}H_{21}NO_4$; 219.28
Structure:



Relevant INDs/NDAs/DMFs: [redacted] Oxford GlycoSciences.

Drug class: Glycoslytransferase inhibitor (An imino sugar)
Indication: Gaucher Disease (Lysosomal glycolipid storage disease)
Clinical formulation:

Ingredient	Content
OGT 918	50/100 mg
Sodium starch glycollate	[redacted]
Povidone (K30)	
Magnesium sterate	
[redacted]	[redacted]

Route of administration: Oral.

Proposed clinical protocol: OGT 918-004: A Phase II Randomized study of open-label OGT 918 and cerezyme given as monotherapy or combination therapy in adult patients with type 1

Gaucher disease. Up to 36 adult patients with Gaucher disease who have received enzyme replacement therapy for a minimum of two years will be randomized into one of three arms;

- OGT 918 and Cerezyme combination therapy
- OGT 918 alone
- Cerezyme alone

Patients randomized to an OGT 918 arm will receive a dose of 100 mg TID OGT 918 for six months.

Previous clinical experience: Previously studied under IND ——— as a treatment for HIV.
Phase I: Over 130 patients received doses up to 1000 mg t.i.d. and up to 6 months of dosing.
Phase II:

a. 60 patients received 3000 mg/day t.i.d. for 24 weeks. Symptoms reported were: G.I. symptoms (diarrhea, flatulence, nausea and abdominal pain), fatigue headache and, less frequently, granulocytopenia, paraesthesia and dizziness.
b. 67 HIV-infected subjects were randomized to receive one of 8 possible combinations of OGT918 (0, 1500 or 3000 mg/day) as monotherapy or in combination with zidovudine (0, 300 or 600 mg/day) for 12 weeks. 18 continued treatment for 24 weeks. Symptoms reported were: diarrhea and flatulence were the most commonly reported. There were no deaths in either study.

An adverse event was reported on January 18, 1999 in study OGT918-001 for Gaucher disease. This is an ongoing study in Europe and occurred during the 30 day safety sign-off period for this IND. The event was increasing abdominal pain, nausea, anorexia, subfebrile temperature and constipation. The patient was started on drug on Dec. 15th. The patient was admitted to the hospital on December 18th. Evaluation indicted an "enormously enlarged liver", with evidence of a probable local portal vein thrombosis in the right posterior segment. It was not clear if this was present prior to dose initiation. The report considers that this could be related to the Gaucher disease, but the timing makes it difficult to rule out drug effect. After a follow-up visit, the investigator suggests that it is unlikely that it was due to OGT 918 therapy. Patient was discontinued from drug.

OGT 918-001: A Phase I/II Study of Open-Label OGT 918 in adult patients with Gaucher Disease. The objective is to evaluate the tolerability and PK of OGT 918 AT 100 mg TID. Minimum dosing period of 12 months is proposed. 28 patients were enrolled in the study and 22 completed the 12 month protocol. Six patients were withdrawn. Of the 22 patients who completed, 18 continued into an optional extended use protocol. Fourteen patients currently continue in the extended use protocol with two patients having now received 30 months treatment as part of the extension phase of the protocol.

The majority of patients received a dose of 100 mg TID throughout the 12 month study. OGT 918 has been well tolerated, with the main adverse event being diarrhoea which has been noted in 89% of patients on at least one occasion. Most cases were mild and either resolved spontaneously or responded to anti-motility agents.

Prevalence of Most Common Adverse Events (>10%)

	0-1 mth	1-3 mths	3-6 mths	6-9 mths	9-12 mths	Overall
Number of patients at beginning of time interval	28	26	24	23	22	28
Diarrhoea	22 (79%)	19 (73%)	12 (50%)	12 (52%)	5 (23%)	25 (89%)
Weight decrease	0	4 (15%)	5 (25%)	6 (26%)	3 (14%)	11 (39%)
Headache	5 (18%)	5 (19%)	3 (13%)	2 (9%)	0	8 (29%)
Flatulence	4 (14%)	5 (19%)	5 (21%)	1 (4%)	1 (5%)	8 (29%)
Abdominal Pain	4 (14%)	3 (12%)	2 (8%)	3 (13%)	3 (14%)	7 (25%)
Rhinitis	1 (4%)	1 (4%)	2 (8%)	1 (4%)	1 (5%)	5 (18%)
Tremor	0	1 (4%)	1 (4%)	2 (9%)	4 (18%)	4 (14%)
Nausea	2 (7%)	1 (4%)	1 (4%)	0	0	4 (14%)
Purpura	0	0	0	2 (9%)	3 (14%)	4 (14%)
Myalgia	0	0	1 (4%)	1 (4%)	1 (5%)	3 (11%)
Paraesthesia	1 (4%)	1 (4%)	2 (8%)	1 (4%)	2 (9%)	3 (11%)
Anorexia	1 (4%)	2 (8%)	2 (8%)	0	0	3 (11%)
Dyspepsia	1 (4%)	2 (8%)	2 (8%)	1 (4%)	0	3 (11%)
Upper resp tract infection	0	0	3 (13%)	0	0	3 (11%)
Influenza-like symptoms	2 (7%)	1 (4%)	2 (8%)	1 (4%)	1 (5%)	3 (11%)

Notes: All percentages are based on the number of patients in the safety population at the beginning of the time interval. A patient may appear in more than one category.

OGT 918-003: A Phase I/II Study of Open-Label OGT 918 in adult patients with type 1 Gaucher Disease. Patients were to receive a dose of 50 mg TID for 6 months. 12 patients will be recruited. This study has recently completed recruitment and 18 patients have been enrolled in South Africa and Israel. Several patients experienced gastrointestinal problems (diarrhea, vomiting, gastritis) during the first month of treatment which have since resolved. The majority of cases were mild, and the two patients who experienced the most severe symptoms were temporarily dose reduced. These patients have since returned to the protocol dose of 50 mg TID with no further problems. The majority of patients in the South African center have experienced mild to moderate weight loss, although this has not been the case in the Israeli center. Two patients have experienced tremors on the trial to date. One patient has a medical history which is considered to attribute to this finding, and the second patient has undergone a full neurological assessment which has suggested that this event is not OGT 918 related.

These clinical studies in Gaucher Disease are currently ongoing in Europe, Israel and South Africa.

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Introduction and drug history: OGT 918 was originally developed by G.D. Searle as an anti-HIV drug. The compound was generated from synthetic analogues of D-Glucose by replacing the oxygen molecule with nitrogen. These analogues were found to be potent inhibitors of α-glucosidase I and to inhibit HIV replication in vitro. Clinical studies in HIV positive patients were carried out with both OGT 918 (then known as sC-48334), and it's prodrug SC-49483, a perbutylated derivative of the parent compound. Trials of both compounds were subsequently terminated during the Phase II stage of development due to the difficulty in achieving the high

plasma concentrations required to inhibit HIV replication. The tolerability profile of OGT 918 showed gastrointestinal disorders to be the primary toxicity.

In the present IND, OGT 918 is indicated for the treatment of Gaucher Disease. Gaucher disease is an inherited functional deficiency of glucocerebrosidase (β-glucosidase) which leads to glycolipid accumulation in variuos tissues. OGT 918 has been shown to inhibit glucosyltransferase, which is the enzyme responsible for the generation of glycosphingolipids. The sponsor's approach to treating Fabry's and Gauchers 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.

OGT 918 has been extensively tested both pre-clinically and clinically by G.D. Searle, and the majority of data presented in this IND comes from their previous testing of the compound. Oxford Glycosciences proposes additional preclinical studies to cover gaps in available information. The sponsor indicates that this agent has Orphan Product Status.

Studies reviewed within this submission:

- 13-Week oral toxicity study of SC-48334 in rats with a 4-week recovery period.
- 1 year oral toxicity study of SC-48334 in rats with a 4-week recovery period.

Studies <u>not</u> reviewed within this submission: None.

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

I. GENERAL TOXICOLOGY

STUDY TITLE: 13-WEEK ORAL TOXICITY STUDY WITH SC-48334 IN RATS WITH A 4-WEEK RECOVERY PERIOD.

Key study findings:

- 1/20 males in the 90 mg/kg/day was found dead (week 4). Cause of death was not apparent. 1/20 males (90 mg/kg/d) and 1/20 females (180 mg/kg/d) died an accidental death during weeks 10 and 8 respectively. 1/20 males (420 mg/kg/d) died 5 minutes post dose during week 9. Sponsor attributed cause of death to gavage error.
- In the MHD and HD groups, body weight gain was decreased by 11% and 31% respectively (M) and by 7% and 19% respectively for (F). While a decrease in food consumption may explain the weight loss in males, there was no such finding in females.
- Anterior synechia, chronic uveitis and pthisis were observed in 1/20 and 2/20 females and 1/20 males respectively. Dacroadenitis was observed in 1/20 LD males, 2/20 MD males and 1/20 MHD males. At the end of the recovery period, 1/20 MD females had chronic uveitis. Pthisis bulbi was observed in 1/20 LD females, 1/20 MHD females and 1/20 HD males.
- Hematology parameters (RBC, HGB, HCT, PLT) were slightly but statistically significantly decreased in HD males relative to control. These effects were reversed during the recovery period, however MCH became statistically significantly increased in HD males. HGB were also slightly but statistically significantly decreased in HD females relative to control. HCT decreased dose-dependently in females achieving statistical significance at both the MHD and HD levels. WBC increased dose-dependently in females achieving statistical significance in all treated groups. This increament was due to neutrophilia and lymphocytosis.
- BUN, AST, ALT and Ca were statistically significantly increased in HD males. The increased BUN may be due to the observed nephropathy and other histopathology changes in the kidney. Increases in AST and ALT have no histopathology correlates. Albumin and alkaline phosphatase were statistically significantly decreased in all treated males. Total protein was statistically significantly decreased in HD males and females. Globulin decreased in treated females achieving statistical significance at MD and above. Cholesterol and Ca levels were slightly but statistically significantly increased in HD, MHD and HD females. Mg level was also statistically significantly decreased in MHD and HD females. At the end of the recovery period, these changes were reversed in females. HD males had slight but statistically significantly decreased globulin level and statistically significantly increased A/G ratio relative to control.
- Urine pH was statistically significantly increased in MHD and HD males relative to control. Urine Ca was statistically significantly increased in both males and females in the MD, MHD and HD groups. Urine Na, K and Cl were statistically significantly decreased in all treated females. Specific gravity was also statistically significantly decreased in females MD, MHD and HD groups. Urine volume increased statistically significantly in all treated females. Urine phosphorus was statistically significantly decreased only in MD and MHD females. These changes were reversed at the end of the recovery period.
- Absolute weight of the spleen was statistically significantly decreased in HD males and females. Absolute and relative weights of the liver (F) and the relative weight of same organ (M) were statistically significantly increased in all treated groups. There is no correlative liver histopathology to explain the increased relative weights. Absolute weight of the kidney was statistically significantly decreased in HD males. Relative weight of the kidney was statistically significantly increased in both HD males and females. Absolute and relative weights of the ovaries were statistically significantly decreased in females in the MD group

and above. Absolute and relative weights of the pituitary gland were statistically significantly increased in all treated females. Relative weights of the brain (M & F) and adrenal gland (F) were statistically significantly increased at the HD level. Absolute weight of the heart was statistically significantly decreased in HD (M) but statistically significantly increased in MD (F). Absolute weight of the testes was statistically significantly decreased in LD and HD males. Relative weight of the testes was increased in MHD group but decreased in the HD group. The decreased relative weight of the testes correlates with the atrophy/degenerative and dystrophic changes observed. Absolute weight of the epididymides was statistically significantly decreased in the LD and HD males. Relative weight of the epididymides was also statistically significantly decreased in HD males. The decreased weight of the epididymides may also explain the decreased weight of the testes. At the end of the recovery period, the weights of the testes and epididymides were still statistically significantly decreased in HD males while the absolute weight of the pituitary was statistically significantly increased only in MD females.

- The target organs of toxicity were the kidneys (nephropathy, mineralization, eosinophilic/proteinaceous casts, dilatation of pelvis and collecting ducts), heart (degenerative cardiomyopathy), eye (pthisis bulbi), pancreas (vacuolization), thymus (involution), testes (atrophy/degeneration, dystrophy) and the stomach (erosion/ulceration).
- The atrophy/degeneration of the testes, mineralization and proteinaceous casts of the kidney were partially reversed. Eosinophilia of the pancreas was observed in males in the MD, MHD and HD groups at the end of the recovery period.
- Based on the histopathology, NOAEL could not be established.

Study no: PSA-90C-3476
Volume #, and page #: Vol. 1, pg. 42.
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 #s 88K040-301I, 88K042-302G. No information on purity.
Formulation/vehicle: A solution of SC-48334 in deionized water.

Methods (unique aspects):
Dosing: Animals were dosed three times daily at approximately 8 hr apart for 13 weeks. Doses used were 90, 180, 420 and 840 mg/kg/day.
Species/strain:
#/sex/group or time point (main study): 20/sex/group.
Satellite groups used for toxicokinetics or recovery: Another 20/sex/group were allocated for TK studies.
Age: ~ 5 weeks.
Weight: 116-118 g (F); 135-135 g (M).
Doses in administered units: 90, 180, 420 and 840 mg/kg/day.
Route, form, volume, and infusion rate: Oral (gavage), 10 ml/kg)

Observations and times:
Clinical signs: Daily.
Body weights: Weekly.
Food consumption: Weekly.
Ophthalmoscopy: Before study initiation and during weeks 12 and recovery week 17.

EKG: Not evaluated.
Hematology: Blood samples were collected from 5/sex/group fasted overnight during week 6, from all surviving animals during week 14, and for recovery animals during week 18 for routine hematology evaluation.
Clinical chemistry: Blood samples were collected from 5/sex/group fasted overnight during week 6, from all surviving animals during week 14, and for recovery animals during week 18 for routine clinical chemistry evaluation.
Urinalysis: Urine samples were collected from 5/sex/group during week 6, from all surviving animals during week 14, and for recovery animals during week 18 for routine urinalysis evaluation.
Gross pathology: Organs/tissues collected for gross pathology examination is indicated in the list of addendum.
Histopathology: Organs/tissues collected for histopathology examination is indicated in the list of addendum.
Organs weighed: Organs/tissues weighed is indicated in the list of addendum.
Toxicokinetics: Animals were bled after the first daily dose, and during week 13 after dosing. The sampling times were 0.5, 1, 2, 4 and 8 hours post dose.

Results:
Mortality and Clinical signs:

INCIDENCE OF MORTALITY AND CLINICAL SIGNS										
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
Rough hair coat			1/20			1/20	2/20		5/20	
Desquamation, Tail		1/20		3/20	1/20	2/20	4/20	12/20	14/20	17/20
Enlarged abdomen						5/20	15/20	18/20	20/20	20/20
Necrotic tail									1/20	
Bloody feces									1/20	
Blood stained urine						1/20			2/20	
Found dead			1/20							
Moribund sacrifice			1/20							
Accidental death						1/20	1/20			

- Animal # 30977 = M (90 mg/kg/d) was found dead (week 4). Grossly there was red nasal discharge . Histopathology revealed moderate multifocal congestion of the lungs. Cause of death was not determined.
- Animal # 30961 = M (90 mg/kg/d) was sacrificed moribund (week 10). Necropsy showed ulcer/erosion of the oral cavity and a fracture between the second and third ridge of the upper palate. Subcutaneous tissues surrounding these areas were diffusely red. Sponsor suggested accidental death. Histopathology revealed chronic multifocal inflammation of the parathyroid gland.
- Animal # 31037 = F (180 mg/kg/d) died an accidental death during week 8. Sponsor stated that the cage closed on animal neck. Necropsy revealed hemorrhage on ventral surface of skull with dark red surrounding tissue.
- Animal # 31059 = M (420 mg/kg/d) died 5 minutes post dose during week 9. Dark red fluid was observed in the thoracic cavity. Lungs showed moderate, multifocal areas of congestion.

Body weights:

BODY WEIGHT CHANGES IN MALES					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
Pre dose wt (g)	135 ± 6.91	134 ± 8.76	137 ± 7.57	136 ± 6.75	138 ± 7.17
Week 13 wt (g)	518 ± 41.98	509 ± 40.70	506 ± 38.84	478 ± 34.80*	404 ± 62.06*
Wt. gain	383	375	369	342	266
Decrement (g)	-	8	14	41	117
% Decrement	-	**2**	**4**	**11**	**31**
Week 17 wt. (g) (Recovery)	531 ± 60.31	517 ± 52.68	521 ± 49.82	519 ± 48.40	462 ± 57.80
BODY WEIGHT CHANGES IN FEMALES					
Pre dose wt (g)	116 ± 5.90	116 ± 4.81	117 ± 6.55	120 ± 5.44	118 ± 6.49
Week 13 wt (g)	268 ± 35.03	278 ± 23.75	290 ± 28.40*	261 ± 17.39	241 ± 17.51*
Wt. gain	152	162	173	141	123
Decrement (g)	-	-	-	11	29
% Decrement	-	-	-	**7**	**19**
Week 17 wt. (g) (Recovery)	279 ± 39.35	286 ± 33.91	307 ± 31.80	275 ± 9.96	252 ± 15.12

*** p < 0.05**

Food consumption: (g/week)

FOOD CONSUMPTION CHANGES IN MALES					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
Week 1	157 ± 9.84	158 ± 8.29	156 ± 8.86	146 ± 8.37*	130 ± 11.89*
Week 13	186 ± 16.00	194 ± 20.89	190 ± 13.68	192 ± 19.26	164 ± 21.82*
Decrement (g/week)	-	-	-	-	22
% Decrement	-	-	-	-	**12**
Week 17 (Recovery)	185 ± 16.91	188 ± 17.11	185 ± 13.60	185 ± 17.17	186 ± 17.08
FOOD CONSUMPTION CHANGES IN FEMALES					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
Week 1	125 ± 6.29	127 ± 8.57	126 ± 8.89	126 ± 8.57	111 ± 13.75*
Week 13	127 ± 20.24	131± 14.83	143 ± 20.67	129 ± 9.80	129 ± 20.93
Decrement (g/week)	-	-	-	-	-
% Decrement	-	-	-	-	-
Week 17 (Recovery)	126 ± 7.96	132 ± 9.24	145 ± 15.63	131 ± 10.91	130 ± 22.48

*** p < 0.05**

Ophthalmoscopy:

INCIDENCE OF OPHTHALMIC FINDINGS (WEEK12)										
Dose (mg/kg/d)	**0**		**90**		**180**		**420**		**840**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Anterior synechia (OD)										1/20
Choroidal (OS)					1/20					
Chronic uveitis (OD)										2/20
Dacroadenitis (OU)			1/20							
Dacroadenitis (OS)			1/20		2/20		1/20			
Pthisis (OD)		1/20							1/20	
INCIDENCE OF OPHTHALMIC FINDINGS (WEEK17 - RECOVERY)										
Chronic uveitis (OD)						1/20				
Pthisis bulbi (OD)		1/20						1/20	1/20	

OD = right eye; OS = left eye; OU = both eyes.

Electrocardiography: No data.

Hematology:

HEMATOLOGY CHANGES IN MALES – WEEK 14					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
RBC (10^6/UL)	9.37 ± 0.57	8.79 ± 0.50*	8.93 ± 0.84	9.09 ± 0.55	8.64 ± 0.70*
HGB (g/dl)	15.7 ± 0.95	14.7 ± 1.09*	15.0 ± 1.18	15.3 ± 0.82	14.8 ± 1.20*
HCT (%)	53.1 ± 2.63	51.1 ± 3.29	50.6 ± 3.55	52.3 ± 2.43	50.1 ± 3.68*
PLT (10^3/UL)	939 ± 73.9	909 ± 381.3	917 ± 258.2	821 ± 185.6	630 ± 332.7*
MALES – RECOVERY WEEK 18					
MCH (pg)	15.7 ± 0.50	15.8 ± 1.41	16.9 ± 1.05	16.2 ± 0.51	17.2 ± 0.23*

HEMATOLOGY CHANGES IN FEMALES – WEEK 14					
HGB (g/dl)	14.9 ± 0.89	14.8 ± 0.81	14.7 ± 1.09	14.2 ± 1.07	13.9 ± 1.31*
HCT (%)	51.0 ± 2.70	50.8 ± 2.17	49.8 ± 2.81	48.5 ± 3.18*	48.1 ± 3.80*
WBC (10^3/UL)	4.0 ± 1.82	5.8 ± 1.43*	5.9 ± 2.39*	6.0 ± 1.92*	6.8 ± 2.32*
Neutrophils–seg (10^3/UL)	0.5 ± 0.54	0.5 ± 0.25	0.7 ± 0.73	0.6 ± 0.39	1.2 ± 1.46*
Lymphocytes (10^3/UL)	3.5 ± 1.44	5.2 ± 1.34*	5.1 ± 2.08*	5.3 ± 1.99*	5.4 ± 1.94*
FEMALES – RECOVERY WEEK 18					
MCH (pg)	17.2 ± 0.39	16.9 ± 0.18	17.2 ± 0.26	17.1 ± 0.48	17.7 ± 0.22*

*** p < 0.05**

Clinical chemistry:

CLINICAL CHEMISTRY CHANGES IN MALES – WEEK 14					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
BUN (mg/dl)	12.0 ± 1.3	13.0 ± 1.8	13.0 ± 1.4	12.0 ± 2.0	15.0 ± 5.5*
T PRO (g/dl)	6.6 ± 0.38	6.3 ± 0.18	6.3 ± 0.24	6.3 ± 0.22	6.0 ± 0.40*
ALB (g/dl)	4.3 ± 0.27	4.0 ± 0.26*	4.0 ± 0.18*	4.1 ± 0.23	4.0 ± 0.39*
GLOB (g/dl)	2.3 ± 0.31	2.4 ± 0.23	2.2 ± 0.20	2.2 ± 0.16	2.0 ± 0.26*
AST (IU/L)	175 ± 62.7	165 ± 42.9	154 ± 30.2	181 ± 41.4	335 ± 267.4*
ALT (IU/L)	42.0 ± 10.9	38.0 ± 7.2	38.0 ± 7.0	42.0 ± 12.5	81.0 ± 60.1*
ALKP (IU/L)	99.0 ± 13.3	73.0 ± 16.3*	70.0 ± 13.7*	78.0 ± 18.7*	80.0 ± 22.8*
Ca (mg/dl)	9.8 ± 0.35	9.7 ± 0.34	9.8 ± 0.32	10.1 ± 0.43	10.1 ± 0.49*
MALES – RECOVERY WEEK 18					
GLOB (g/dl)	2.9 ± 0.62	3.0 ± 0.28	2.4 ± 0.22	3.0 ± 0.08	2.2 ± 0.11*
A/G RATIO	1.57 ± 0.27	1.3 ± 0.14	1.7 ± 0.15	1.3 ± 0.08	2.0 ± 0.17*
CLINICAL CHEMISTRY CHANGES IN FEMALES – WEEK 14					
CREAT (mg/dl)	0.7 ± 0.07	0.6 ± 0.06*	0.7 ± 0.06	0.6 ± 0.08*	0.6 ± 0.06*
T PRO (g/dl)	6.6 ± 0.23	6.5 ± 0.29	6.8 ± 0.49	6.5 ± 0.33	6.2 ± 0.35*
GLOB (g/dl)	2.0 ± 0.16	1.9 ± 0.20	1.8 ± 0.18*	1.8 ± 0.25*	1.8 ± 0.20*
CHOL (mg/dl)	79 ± 23.3	93 ± 19.3	100 ± 23.9*	111 ± 23.9*	99 ± 17.0*
Ca (mg/dl)	9.7 ± 0.33	9.8 ± 0.29	10.2 ± 0.38*	10.2 ± 0.37*	10.1 ± 0.40*
Mg (mEq/l)	2.6 ± 0.24	2.6 ± 0.25	2.5 ± 0.16	2.4 ± 0.17*	2.2 ± 0.16*
FEMALES – RECOVERY WEEK 18					
All parameters had returned to normal limits.					

*** p < 0.05**

Urinalysis:

CLINICAL CHEMISTRY CHANGES IN MALES – WEEK 14					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
pH	6.8 ± 0.33	6.9 ± 0.39	7.2 ± 0.37	7.3 ± 0.42*	7.2 ± 0.55*
Urine Ca (mg/dl)	4.2 ± 2.78	6.0 ± 3.20	7.4 ± 4.54*	16.7 ± 9.15*	25.8 ± 11.87*
MALES – RECOVERY WEEK 18					
All parameters had returned to normal limits.					
CLINICAL CHEMISTRY CHANGES IN FEMALES – WEEK 14					
Urine Ca (mg/dl)	9.2 ± 4.90	11.7 ± 4.94	18.2 ± 10.47*	19.5 ± 7.45*	29.7 ± 12.99*
Urine PHOS (mg/dl)	146 ± 118.7	89 ± 48.3	73 ± 36.3*	73 ± 40.2*	104 ± 97.3
Urine Na (mMol/l)	48 ± 23.5	29 ± 17.4*	26 ± 9.2*	22 ± 12.8*	29 ± 17.3*
Urine K (mMol/l)	84 ± 42.6	54 ± 24.6*	49 ± 20.6*	47 ± 22.4*	59 ± 28.2*
Urine Cl (mMol/l)	52 ± 29.5	30 ± 16.8*	27 ± 12.3*	24 ± 12.7*	29 ± 14.6*
Urine vol. (ml)	9.0 ± 5.36	19.2 ± 9.17*	27.7 ± 13.40*	24.8 ± 11.21*	24.2 ± 13.45*
SP GR	1.022 ± 0.008	1.016 ± 0.006	1.014 ± 0.006*	1.014 ± 0.005*	1.016 ± 0.007*
FEMALES – RECOVERY WEEK 18					
All parameters had returned to normal limits.					

*** p < 0.05**

Organ weights:

ORGAN WT. CHANGES IN MALES – WEEK 14					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
Adrenal gland rel. wt. (%)	0.0109 ±0.002	0.0116 ± 0.002	0.0118 ± 0.002	0.0121 ± 0.001	0.0154± 0.003*
Heart abs. wt. (g)	1.44 ± 0.13	1.56 ± 0.25	1.61 ± 0.29	1.41 ± 0.22	1.20 ± 0.27*
Spleen abs. wt. (g)	0.64 ± 0.10	0.76 ± 0.17*	0.68 ± 0.09	0.62 ± 0.12	0.51 ± 0.13*
Kidney abs. wt. (g)	3.14 ± 0.36	3.42 ± 0.48	3.39 ± 0.27	3.22 ± 0.30	2.75 ± 0.39*
Kidney rel. wt. (%)	0.66 ± 0.07	0.73 ± 0.06	0.72 ± 0.04	0.74 ± 0.04	0.77 ± 0.17*
Liver rel. wt. (%)	2.64 ± 0.29	3.03 ± 0.29*	3.13 ± 0.41*	3.11 ± 0.44*	3.15 ± 0.31*
Testes abs. wt. (g)	3.13 ± 0.21	3.27 ± 0.26	3.14 ± 0.51	3.34 ± 0.14	1.77 ± 0.66*
Testes rel. wt. (%)	0.66 ± 0.070	0.70 ± 0.074	0.674 ± 0.111	0.775 ± 0.081*	0.483 ± 0.141*
Epididymides abs. wt. (g)	1.37 ± 0.14	1.21 ± 0.11*	1.26 ± 0.15	1.29 ± 0.11	0.95 ± 0.18*
Epididymides rel. wt. (%)	0.288 ± 0.041	0.258 ± 0.020	0.271 ± 0.041	0.302 ± 0.037	0.264 ± 0.044*
Brain rel. wt. (%)	0.445 ± 0.037	0.452 ± 0.035	0.463 ± 0.037	0.485 ± 0.048*	0.578 ± 0.083*
MALES – RECOVERY WEEK 18					
Testes abs. wt. (g)	3.47 ± 0.37	3.17 ± 0.28	3.44 ± 0.35	3.25 ± 0.21	1.84 ± 0.75*
Testes rel. wt. (%)	0.689 ± 0.033	0.648 ± 0.008	0.701 ± 0.122	0.672 ± 0.088	0.417 ± 0.124*
Epididymides abs. wt. (g)	1.42 ± 0.10	1.34 ± 0.13	1.34 ± 0.19	1.23 ± 0.15	0.94 ± 0.16*
Epididymides rel. wt. (%)	0.284 ± 0.024	0.274 ± 0.001	0.273 ± 0.047	0.242 ± 0.027	0.216 ± 0.021*
ORGAN WT. CHANGES IN FEMALES – WEEK 14					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
Heart abs. wt. (g)	0.88 ± 0.08	0.94 ± 0.07	0.96 ± 0.09*	0.91 ± 0.08	0.81 ± 0.08
Spleen abs. wt. (g)	0.42 ± 0.09	0.47 ± 0.08	0.39 ± 0.05	0.40 ± 0.05	0.34 ± 0.05*
Kidney rel. wt. (%)	0.75 ± 0.07	0.76 ± 0.04	0.72 ± 0.07	0.79 ± 0.04	0.85 ± 0.07*
Liver abs. wt. (g)	6.56 ± 0.59	7.57 ± 0.68*	8.52 ± 1.18*	7.72 ± 0.73*	7.28 ± 0.75
Liver rel. wt. (%)	2.73 ± 0.18	3.01 ± 0.23*	3.29 ± 0.36*	3.33 ± 0.23*	3.48 ± 0.26*
Ovaries abs. wt. (g)	0.12 ± 0.02	0.11 ± 0.02	0.09 ± 0.02*	0.08 ± 0.01*	0.08 ± 0.01*
Ovaries rel. wt. (%)	0.048 ± 0.009	0.042 ± 0.008	0.035 ± 0.008*	0.036 ± 0.007*	0.040 ± 0.008*
Pituitary abs. wt. (g)	0.016 ± 0.003	0.021 ± 0.007*	0.023 ± 0.007*	0.021 ± 0.004*	0.017 ± 0.004
Pituitary rel. wt. (%)	0.006 ± 0.001	0.008± 0.002*	0.009 ± 0.002*	0.009 ± 0.002*	0.008 ± 0.002*
Brain rel. wt. (%)	0.812 ± 0.073	0.777 ± 0.075	0.750 ± 0.075	0.842 ± 0.065	0.929 ± 0.054*
FEMALES – RECOVERY WEEK 18					
Pituitary abs. wt. (g)	0.02 ± 0.003	0.02 ± 0.002	0.03 ± 0.003*	0.02 ± 0.001	0.02 ± 0.002

Relative weight (% b.wt) = % body weight

Gross pathology:

WEEK 14										
Dose (mg/kg/d)	**0**		**90**		**180**		**420**		**840**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Kidney Enlarged pelvis (es)	2/15	1/15	1/15	2/15			1/15	2/15	1/15	5/15
Eye White intraocular material										1/15
Thymus Red foci		2/15		1/15	4/15	3/15	3/15	2/15	3/15	1/15
Submaxillary LN Diffusely red	1/15		1/15	1/15	4/15	1/15	1/15			1/15
Uterus Fluid filled lumen		1/15		1/15		1/15		1/15		4/15
RECOVERY SACRIFICE										
Uterus Fluid filled lumen										1/15

Histopathology:

INCIDENCE AND SEVERITY OF HISTOPATHOLOGY IN MALES – WEEK 14					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
Kidney Nephropathy, chronic progressive					1/15 (4)
Kidney Dilation, collecting tubule		1/15(2)	2/15(2)	2/15(2)	8/15 1/15(1) 4/10(2) 2/15(3) 1/15(4)
Kidney Mineralization					1/15(1)
Kidney Eosinophilic/proteinaceous casts		10/15 4/15(1) 3/15(2) 3/15(3)	12/15 4/15(1) 7/15(2) 2/15(3)	10/15 5/15(1) 2/15(2) 3/15(3)	4/15(2)
Kidney Dilatation, pelvis		1/15(x)		1/15(x)	1/15(x)
Kidney Regenerative epithelium		8/15 3/15(1) 3/15(2) 2/15(3)	5/15 1/15(1) 3/15(2) 1/15(3)	5/15 1/15(1) 3/15(2) 1/15(3)	2/15(2)
Heart Degenerative cardiomyopathy					4/15 2/15(1) 2/15(2)
Eye Pthisis bulbi					1/15(x)
Pancreas Vacuolization, acinar cells			1/15(1)		2/15 1/15(3) 1/15(4)
Stomach Submucosal edema					1/15(3)
Stomach Ulceration/erosion					2/15(2)
Thymus Involution					1/15(3)
Thymus Congestion					4/15 3/15(2) 1/15(3)
Testes Atrophy/degeneration		1/15(2)	3/15 2/15(2) 1/15(4)		13/15 1/15(3) 9/15(4) 3/15(5)
Testes Dystrophy					4/15 1/15(2) 3/15(3)
Tail Erosion/ulceration					1/15(3)
Tail Acanthosis/hyperkeratosis					6/15(3)
Tail Abscess					2/15(x)
RECOVERY SACRIFICE					
Kidney Eosinophilic/proteinaceous casts	1/5(2)	1/5(2)	5/5 2/5(1) 2/5(2) 1/5(3)		
Kidney Regenerative epithelium			2/5 1/5(1) 1/5(3)	1/4(1)	

Pancreas Eosinophilia			1/5(3)	1/4(3)	
Testes Atrophy/degeneration					5/5 1/5(2) 4/5(4)
INCIDENCE AND SEVERITY OF HISTOPATHOLOGY IN FEMALES – WEEK 14					
Dose (mg/kg/d)	**0**	**90**	**180**	**420**	**840**
Kidney Eosinophilic/proteinaceous casts		2/15(1)	2/15 1/15(2) 1/15(3)	1/15(2)	
Kidney Dilatation, pelvic	1/15(x)	3/15(x)		3/15(x)	5/15(x)
Pancreas Vacuolization, acinar cells					2/15(1)
Tail Acanthosis/hyperkeratosis					5/15 1/15(2) 4/15(3)
Tail Abscess					1/15(x)
RECOVERY SACROFICE					
Kidney Mineralization	1/5(2)	1/5(2)	2/5 1/5(1) 1/5(2)		

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

Toxicokinetics:

		Day 1		Day 86	
		AUC[a] (mcg/ml)-(HR)	AUC[a]/Dose	AUC[a] (mcg/ml)-(HR)	AUC[a]/Dose
		8 HR	8 HR	8 HR	8 HR
Dose (mg/kg)	SEX				
90	Female	8.002	0.089	17.283	0.192
	Male	12.035	0.134	14.521	0.161
	M + F	10.018	0.111	15.902	0.177
180	Female	16.812	0.093	30.354	0.169
	Male	22.717	0.126	60.986	0.339
	M + F	19.765	0.110	45.670	0.254
420	Female	33.040	0.079	88.395	0.210
	Male	44.879	0.107	77.152	0.184
	M + F	38.959	0.093	82.773	0.197
840	Female	73.059	0.087	194.171	0.231
	Male	67.894	0.081	140.975	0.168
	M + F	70.477	0.084	167.573	0.199

[a] AUC values are significant to three figures.

Summary of individual study findings:

Toxicology summary:

OGT 918 was administered by oral gavage at doses of 0, 90, 180, 420, and 840 mg/kg/day, as three equally divided doses TID, to Sprague-Dawley rats (20/sex/dose). At the end of 13 weeks, 15 animals/sex/group were sacrificed and the remainder was sacrificed after a 4-week treatment-free period. No test article related deaths were noted during the study. Clinical observations considered related to treatment were enlarged abdomens in 180, 420, and 840

mg/kg/day animals, desquamated and scabby tails In 420 and 840 mg/kg/day animals, and diarrhea or soft stools in 840 mg/kg/day animals. Decreased bodyweight gains of 11% and 31% respectively were seen in 420 and 840 mg/kg/day males and at 7% and 19% respectively at the same doses in female rats. While a decrease in food consumption may explain the weight loss in males, there was no such finding in females.

Statistically significant changes in clinical chemistry parameters included increases in ALT, AST, and urea nitrogen for 840 mg/kg/day males, and increases in serum calcium for 180 mg/kg/day females and 420 and 840 mg/kg/day animals. Statistically significant decreases were seen in ALP levels for all treated males, and globulin values for 180 and 420 mg/kg/day females and 840 mg/kg/day animals. Statistically significant changes in hematology parameters included increases in WBC and lymphocyte count for all treated females, and decreases in RBC count, hemoglobin, and hematocrit for 840 mg/kg/day animals. Statistically significant increases in urinalysis parameters included urinary calcium for 180, 420, and 840 mg/kg/day animals, and urinary pH for 420 and 840 mg/kg/day animals. Decreases were seen in urinary specific gravity, inorganic phosphorus, sodium, potassium, and chloride for all treated females.

Organ weights were changed for several organs and included heart (higher for females at 180 mg/kg/day, lower for males at 840 mg/kg/d), liver (higher for females at 90, 180 and 420 mg/kg/day and for all treated males), and spleen (lower for females at 840 mg/kg/d, higher for males at 90 mg/kg/d); ovaries (lower at 180, 420 and 840 mg/kg/day) and pituitary (higher at all doses) for females; and epididymides (lower at 90 and 840 mg/kg/d), salivary glands (lower at 840 mg/kg/d), and testes (higher at 420, lower at 840 mg/kg/d) for males. Treatment-related macroscopic changes noted at the 840 mg/kg/d dose were enlarged lumens of the gastrointestinal tract, small testes, and crusted tails.

Microscopically, treatment-related changes in males were observed in the heart (degenerative cardiomyopathy), kidney (renal collecting tubular dilation and proteinaceous casts) and testes (testicular dystrophy and atrophy/degeneration). These changes were present at all doses, with the testicular changes occurring in a dose-related manner. A low incidence of vacuolation of pancreatic acinar cells was found in both sexes at 840 mg/kg/d. Renal tubular mineralization was found in females given 840 mg/kg/d. Recovery was partly complete after 4 weeks of recovery. A NOAEL could not be established in this study.

Toxicology conclusions:
The highest dose of 840 mg/kg/day was tolerated for the duration of the study but with clinical evidence of diarrhea and effects on bodyweight. Decreased bodyweight gains of 31% and 19% were seen at 840 mg/kg/day in males and females respectively. The histopathology findings of the kidney, heart, stomach and testes observed at 840 mg/kg/d also indicate that an MTD was reached in this study. Thus a dose of 840mg/kg/d would not be appropriate for a 2-year study.

Histopathology Inventory for IND #

Study	# PSA-90C-3476
Species	Rat
Adrenals	X*
Aorta	X
Bone Marrow smear	
Bone (femur)	X
Brain	X*
Cecum	X
Cervix	X
Colon	X
Duodenum	X
Epididymis	X*
Esophagus	X
Eye	X
Fallopian tube	
Gall bladder	
Gross lesions	X
Harderian gland	X
Heart	X*
Ileum	X
Injection site	X
Jejunum	X
Kidneys	X
Lachrymal gland	X*
Larynx	
Liver	X*
Lungs	X*
Lymph nodes, cervical	X*
Lymph nodes, mandibular	
Lymph nodes, mesenteric	X
Mammary Gland	X
Nasal cavity	X
Optic nerves	X
Ovaries	X*
Pancreas	X*
Parathyroid	X
Peripheral nerve	
Pharynx	
Pituitary	X*
Prostate	X*
Rectum	X
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X
Skeletal muscle	X
Skin	X
Spinal cord	X
Spleen	X
Sternum	X*
Stomach	X
Testes	X
Thymus	X*
Thyroid	X*
Tongue	X*
Trachea	X
Urinary bladder	X
Uterus	X
Vagina	
Zymbal gland	X

X, histopathology performed
*, organ weight obtained

II. GENETIC TOXICOLOGY

Study title: An Evaluation of the Mutagenic Potential of SC-48334 in the Ames Salmonella/Microsome Assay.

Key findings: Valid, Negative

Study title: An Evaluation of the Mutagenic potential of SC-48334 (NBDG Route) in the Ames Salmonella/Microsome assay.

Key findings: Valid, Negative

Study title: Bacterial Reverse Mutation Test

Key findings: Valid, Negative

Study title: An Evaluation of the Mutagenic Potential of SC-48334 in the CHO/HGPRT Mutation Assay.

Key findings: Valid, Negative

Study title: In Vitro Mammalian Cell Cytogenetic Test: Human Lymphocytes

Key findings: Valid, Negative

Study title: An Evaluation Of The Potential Of SC-48334 To Induce Micronucleated Polychromatic Erythrocytes In The Bone Marrow Cells Of Mice.

Key findings: Valid, Negative

Reviewer's Signature:

/S/

.....

John Colerangle, DVM, Ph.D. Date

Team Leader's Signature:

/S/

.....

Karen Davis-Bruno, Ph.D. Date

cc: IND Arch
HFD 510
HFS 510/Colerangle/Davis-Bruno/Wu
Review Code: ND
File Name: ECAC60197.doc

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/s/

John Colerangle
12/21/01 09:10:14 AM
PHARMACOLOGIST
P/T 2 = ECAC

Karen Davis-Bruno
12/21/01 09:14:25 AM
PHARMACOLOGIST

SUPERVISORY PHARMACOLOGIST REVIEW

Pharmacology/Toxicology Memo
May 10, 2002
Re: Approvability of NDA 21-348 based on clinical neurotoxicity concerns
Sponsor: Oxford GlycoSciences
Product: Zavesca, OGT 918

Evaluation: Clinical signs of neurotoxicity (tremor, paresthesia, numbness, abnormal electro-diagnostic testing indicative of peripheral neuropathy, memory loss) have been observed in clinical trials with OGT 918 treatment. Nonclinical histopathology and clinical signs indicative of neurotoxicity were observed in the dog, rat and monkey.

Ataxia, diminished/absent pupillary, palpebral or patellar reflexes were observed in dogs at exposures ≥50X the therapeutic dose based on surface area. Tremor and absent corneal reflexes were observed at exposures ≥10X therapeutic based on surface area. Histopathologic correlates were not observed in the dog. Monkey brain (vascular mineralization, mineralization and necrosis of white matter) and spine (vascular mineralization) histopathology was observed at exposures ≥4X therapeutic exposure based on AUC. Clinical signs were not observed. Monkeys did not exhibit signs of recovery. Vacuolation of the white matter was observed in rats at exposures ≥6X therapeutic based on surface area. A Segment III reprotoxicity study in which pregnant rats were dosed 20, 60, 180 mg/kg/day from gestation day 6 through lactation until post-partum day 20 revealed F1 generation males with Rotarod test latency of 38% compared to controls in litters exposed to 180 mg/kg/day. A similar trend was observed in females (28%) although it was not statistically significant. This is suggestive of impaired locomotor coordination. A juvenile rat study in weanlings dosed post-natal days 12-70 given ≥20 mg/kg/day had marked vacuolation of the brain and sciatic/tibial nerves. Both genders exhibited head tilting. Development of learning, locomotor, auditory function, righting reflex and vision were unremarkable. Balanopreputial separation was delayed in males given 180 mg/kg/day and delayed vaginal perforation occurred in females given ≥20 mg/kg/day.

The observed nonclinical neurotoxicity is limited by the minimal scope of neurologic evaluation performed in standard toxicity studies. Typically standard staining is not specific to detect neurologic lesions and sectioning is very limited (1-3 sections). This may explain the sporadic nature of the findings observed.

The toxicity of OGT 918 appears related to its mechanism of action. OGT 918 inhibits glucosylceramide synthase, which transfers glucose to ceramide to form glucosylceramide, the building block of glucosphingolipids. Earlier analogues of deoxynorjirimycin were associated with cytotoxicity due to ceramide accumulation in tissues. Ceramide is associated with inducing apoptosis. Ceramide accumulation was not examined in animals but might explain the neurotoxicity observed. Alternatively alternations in glucosylceramides (therapeutic mechanism of action) may create toxic effects when it occurs in tissues where this effect is undesirable (i.e. tissues where the beneficial drug effect may not be needed).

The mechanism of action combined with limited neurologic assessments in conjunction with clinical signs indicative of neurotoxicity is concerning. Therefore

Pharmacology/Toxicology recommends the following evaluations to address the clinical concerns.

Recommendations to the Sponsor:

1. Neurologic histopathologic assessments in standard toxicity studies are limited. A thorough re-evaluation of brain, spine and nerve histopathology in the chronic monkey study (SA 4078) are suggested. Special staining for neurologic tissue, neuroanatomical sectioning and ultrastructural assessments are recommended. Determination of ceramide and glucosylceramide levels in these monkeys would be useful, if possible.

2. Based on the clinical concerns for neurotoxicity in conjunction with findings in animals, further neurologic evaluation in rodents is suggested. This dedicated neurologic study should consider evaluation of ceramide and glucosylceramide levels, specific staining for various neurologic tissue (e.g. brain, spine, nerve), extended neuroanatomical sectioning and ultrastructural assessments in conjunction with a rigorous assessment of learning/memory (e.g. Morris maze).

/S/

Karen Davis-Bruno; Ph.D.
Supervisory Pharmacologist; HFD-510