ıetics . . . . . samples taken from 2 animals/sex/group/time point at 1, 2, 4, 8, 12 and 24 hours after dosing on Days 1 and during week 9.

Results:

Mortality: One female treated with loratadine died on day 57. The sponsor did not provide a cause of death.

Clinical Observations: Anti-cholinergic effects, mainly in the high-dose group, were the primary drug-related clinical observations in this study (Table 11). These included few or no feces at the mid- and high-dose of SCH 34117 and loratadine-treated animals. A slight increase in the incidence of extended abdomen and hunched posture were also noted in these groups. Emesis (non-severe) occurred in only a few animals and on only 1-2 occasions per animal. Other findings unique to the loratadine-treated animals were also reported.

Table 11. Clinical observations in monkeys following 3-month administration of SCH 34117.

Observation	Males					Females				
	Dose (mg/kg)					Dose (mg/kg)				
	0	6	12	18/24	22/72 - loratadine	0	6	12	18/24	22/72 - loratadine
Abrasion - foot	0	0	0	0	1	0	0	0	0	0
- head	0	0	0	0	1	0	0	0	0	0
Alopecia - leg	0	0	0	0	2	0	0	1	0	0
Emesis	0	0	1	2	0	1	0	1	1	0
Feces - few	0	0	0	4	1	0	0	0	2	3
Feces - none	0	0	0	4	2	0	0	1	3	2
Feces - mucoid	0	0	0	0	0	0	0	0	0	1
Discoloration - body	0	0	0	1	0	0	0	0	0	0
Extended abdomen	0	0	0	1	1	0	0	0	0	2
Hunched posture	0	0	0	1	1	0	0	0	0	1
Lethargic	0	0	0	0	1	0	0	0	0	1
Swelling - foot	0	0	0	0	0	0	0	0	1	0
- leg	0	0	0	0	0	0	0	0	1	0

Few feces: first observed days 71-80 (F) and 66-71(M). F: lasted for 1 d at HD 34117, 11 d at 22 L. M: 14 d at HD 34117, 26 d at 22 L.
No feces: first observed days 72-83 (F) and 78-84 (M). F: lasted for 1 d at MD 34117, 5 d at HD 34117, and 1 d at 22 L. M: 3 d at HD 34117, 8 d at 22 L.

Body Weight: A dose-dependent decrease in body weight gain was noted in males following 3 months treatment with 6, 12 or 18/24 mg/kg SCH 34117 (Table 12). In females, however, body weight gain was increased in SCH 34117-treated animals. High data variability was present. Loratadine-treated animals demonstrated a 33-53% decrease in body weight gain.

Table 12: Alterations in body weight gain at Day 92.

	Males				Females			
Dose (mg/kg)	6	12	18/24	22/72-L	6	12	18/24	22/72-L
Body weight gain % Δ from control	↓44	↓58	↓93	↓53	↑250	↑167	↑150	↓33

Food consumption: No consistent changes in food consumption were noted in treated animals compared to control animals.

Ophthalmoscopy: No treatment-related effects were noted.

Health Exam: No drug-related effects on body temperature, heart rate or respiration were reported following 3-month drug administration.

ECG: All ECGs were within normal limits and no changes appeared to be drug related. QT and QTc intervals were not significantly affected by drug treatment.

Hematology: No treatment-related effects were noted following the three month administration.

Clinical Chemistry: In males treated with SCH 34117, reduced levels of cholesterol, AP and GGT and increased levels of AST and ALT were noted primarily at the high dose (Table 13). Loratadine-treated males showed similar effects to the high dose males. Increased levels of AST and decreased levels of AP were also noted in high-dose females. These findings, in addition to decreased cholesterol, were also noted in the loratadine-treated females.

Table 13: Clinical chemistry findings following 3-month drug administration.

Clinical chemistry	**Males**				**Females**			
	Dose group (mg/kg)				Dose group (mg/kg)			
	6	12	18/24*	22/72-L	6	12	18/24*	22/72-L
Alkaline phosphatase % Δ from control	↓15	↓25	↓61	↓53	↑16	↑9	↓24	↓14
Aspartate aminotransferase % Δ from control	↑6	↑12	↑47	↑47	↑15	↑30	↑52	↑78
Alanine aminotransferase % Δ from control	↓13	↑22	↑50	↑102	↓23	↓9	↑4	↑81
Gamma glutamyl transfe % Δ from control	↓18	↓23	↓47	↓46	↑9	↑7	↓12	↑1
Cholesterol % Δ from control	↑15	↑3	↓22	↓25	--	↑1	↑9	↓21

* Groups dosed with 18 mg/kg SCH 34117 or 22 mg/kg loratadine were increased to 24 and 72 mg/kg, respectively, during Study week 6.

Urinalysis: No significant treatment-related effects were noted although a large degree of variability was apparent in the data set.

Organ Weight: No statistically significant changes in absolute organ weight or organ weight changes relative to body or brain weight were observed. However, mean absolute organ weight values did suggest slight to moderate reductions in heart, spleen, testes, prostate, epididymes, and thymus in males and the uterus, ovaries and thymus in females (Table 14). Data variability was high. In addition, increased liver weight was noted in loratadine-treated animals.

Table 14: Organ weight changes following 92-day drug administration

Absolute organ weight	Males				Females			
	Dose group (mg/kg)				Dose group (mg/kg)			
	6	12	18/24*	22/72-L	6	12	18/24*	22/72-L
Liver % Δ from control	↓7	↓1	↑8	↑20	↓7	↓4	↑12	↑35
Heart % Δ from control	↓13	↓13	↓25	↓5	↓3	↑8	↑12	--
Spleen % Δ from control	↓23	↓16	↓36	↓27	↓19	↓16	↑1	↓7
Testes % Δ from control	↓24	↓52	↓62	↓78				
Prostate % Δ from control	↓30	↓48	↓51	↓58				
Epididymes % Δ from control	↓29	↓38	↓55	↓59				
Thymus % Δ from control	↓21	↓11	↓64	↓52	↓19	↓17	↓37	↓40
Uterus % Δ from control					↑11	↓8	↓17	↓40
Ovaries % Δ from control					↑7	↓21	↓31	↓21

*: Groups dosed with 18 mg/kg SCH 34117 or 22 mg/kg loratadine were increased to 24 and 72 mg/kg, respectively, during Study week 6.

Gross Pathology: The primary gross findings included dilatation of the cecum and colon which are likely related to the decreased fecal excretion noted above (Table 15). Findings of splenic adhesion and deformity in a high dose male and dilatation of other organs of the digestive system in 1 loratadine-treated female were also observed.

Table 15. Gross observations in monkeys (4/group) following 3-month oral administration.

Gross observations		Males					Females				
		Dose (mg/kg)					Dose (mg/kg)				
		0	6	12	18/24	22/72 – L	0	6	12	18/24	22/72 - L
Cecum	- dilatation	0	0	0	2	2	0	1	0	1	2
Colon	- dilatation	0	0	0	2	2	0	1	0	1	2
Duodenum	- dilatation	0	0	0	0	0	0	0	0	0	1
Ileum	- dilatation	0	0	0	0	0	0	0	0	0	1
Jejunum	- dilatation	0	0	0	0	0	0	0	0	0	1
Stomach	- dilatation	0	0	0	0	0	0	0	0	0	1
Heart	- focus	0	0	0	0	0	0	0	0	1	0
Spleen	- adhesion	0	0	0	1	0	0	0	0	0	0
	- deformity	0	0	0	1	0	0	0	0	0	0

BLANK PAGE

Histopathology: The primary microscopic findings in this study were indicative of systemic phospholipidosis such as vacuolation which occurred in multiple organs (Table 16). Other findings included atrophy, cellular infiltration and pigment accumulation. Findings at the high dose of SCH 34117 were comparable to those observed following administration of loratadine. In addition, ovarian mineralization was noted in high dose-SCH 34117 females and loratadine treated females. This finding was not addressed by the sponsor and was also noted in the 14-day and 6-week monkey studies.

Table 16: Histological findings following 3-month drug administration.

Histopathology	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	0	6	12	18/24	22/72	0	6	12	18/24	22/72
Adrenals n =	4	0	0	4	4	4	0	0	4	4
Eosinophilia										
Minimal	1			0	1	1			0	0
Mild	0			1	0	0			1	0
Moderate	0			0	1	0			0	1
Vacuolation, cortex, MF										
Mild	0			1	0	0			0	0
Brain	4	0	0	4	4	4	0	0	4	4
Corpora amylacea - Minimal	2			4	4	2			2	4
Bone	4	4	4	4	4	4	4	4	4	4
Vacuolation – myofiber										
Minimal	0	0	0	1	1	0	0	0	0	1
Mild	0	0	0	0	0	0	0	0	0	1
Bone marrow	4	4	4	4	4	4	4	4	4	4
Vacuolation – macrophage										
minimal	0	0	0	1	1	0	0	0	1	1
Atrophy, fat										
Mild	0	0	0	1	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	1
Eyes	4	0	0	4	4	4	0	0	4	4
Cellular infiltration, mononuc cell										
Minimal	0			1	0	0			1	0
Metaplasia, focal, corneal										
Minimal	0			1	0	0			0	0
Kidneys	4	0	0	4	4	4	0	0	4	4
Tubular basophilia - Minimal	0			0	0	0			1	0
Mineralization - Minimal	1			2	2	1			0	1
Fibrosis - Minimal	0			0	1	0			0	0
Cast(s) – minimal	0			1	0	0			1	0
Atrophy, tubular - minimal	0			0	1	0			1	0
Lymph nodes	4	4	4	4	4	4	0	0	4	4
Cellular infiltration, leukocyte										
Minimal	0	0	0	0	0	0			1	0
Apoptosis – minimal	0	0	0	0	0	0			1	0
Vacuolation – minimal	0	0	0	1	2	0			0	1
Hematopoiesis, extramedullary										
Minimal	0	0	0	0	0	0			1	0
Mild	0	0	0	1	0	0			0	3
Atrophy, lymphoid										
Minimal	0	0	0	0	1	1			0	0

Histopathology	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	0	6	12	18/24	22/72	0	6	12	18/24	22/72
Mild	0	0	0	1	0	0			0	1
Moderate	0	0	0	1	0	0			0	0
Liver	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Vacuolation, sinusoidal										
Minimal	0	0	0	0	1	0	0	0	0	0
Vacuolation, hepatocell, scattered										
Minimal	0	0	0	1	2	1	0	0	1	0
Vacuolation, hepatocell, periportal										
Mild	0	0	0	0	0	0	0	0	0	1
Vacuolation, biliary, epithelium										
Mild	0	0	0	1	1	0	0	0	1	1
Pigment accumulation										
Minimal	0	0	0	1	0	0	0	0	0	0
Fibrosis, capsular										
Minimal	0	0	0	1	0	0	0	0	0	0
Lungs	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Vacuolation, alveolar macrophage										
Minimal	0	0	0	2	2	1	0	0	3	1
Mild	0	0	0	2	1					
Vacuolation, bronchial, epithelium										
Minimal	0	0	1	2	1	0	0	1	3	2
Mild	0	0	0	1	1	0	0	0	0	2
moderate	0	0	0	1	0	0	0	0	0	0
Esophagus	**4**	**0**	**0**	**4**	**4**	**4**	**0**	**0**	**4**	**4**
Cellular infiltration, mononuc cell										
Minimal	1	0	0	2	1	1	0	0	1	1
Ovaries						**4**	**0**	**0**	**4**	**4**
Mineralization										
Minimal						1			0	2
Mild						0			3	1
Pancreas	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Vacuolation, ductular										
Minimal	0	0	0	0	0	0	0	0	0	1
Mild	0	0	0	0	1	0	0	0	1	0
Vacuolation, acinar										
Minimal	0	0	0	0	1	0	0	0	0	1
Parathyroid glands	**4**	**4**	**3**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Cellular infiltration, mononuc cell										
Minimal	0	0	0	0	1	0	0	0	0	0
Pituitary gland	**4**	**0**	**0**	**4**	**4**	**4**	**0**	**0**	**4**	**4**
Cellular infiltration, mononuc cell										
Minimal	0	0	0	0	0	0	0	0	1	0
Vacuolation, scattered, coarse										
Minimal	0	0	0	1	0	1	0	0	0	2
Salivary glands	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Vacuolation, ductular, submandib										
Minimal	0	0	0	1	3	0	0	2	0	2
Mild	0	0	0	2	0	0	0	0	2	1

Histopathology	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	0	6	12	18/24	22/72	0	6	12	18/24	22/72
Moderate	0	0	0	1	1	0	0	0	2	1
Skeletal muscle	4	4	4	4	4	4	0	0	4	4
Vacuolation										
Minimal	0	0	0	1	1	0			0	1
Mild	0	0	0	0	0	0			0	1
Hemorrhage										
Mild	0	1	0	0	0	0			0	0
Moderate	0	0	0	1	0	0			0	1
Skin	4	4	4	4	4	4	0	1	4	4
Vacuolation, myofiber										
Minimal	0	0	0	0	1	0		0	0	2
Mild	0	0	0	0	0	0		0	0	1
Atrophy, fat										
Severe	0	0	0	1	1	0		0	0	1
Stomach	4	4	4	4	4	4	4	4	4	4
Vacuolation, parietal cell										
Minimal	0	0	0	0	0	0	0	0	1	0
Vacuolation, myofiber										
Minimal	0	0	0	1	1	0	0	0	3	1
Dilatation, glandular										
Minimal	0	0	0	0	0	0	0	0	1	0
Large Intestine	4	4	4	4	4	4	4	4	4	4
Cell. Infitration, neutrophilic										
Minimal	0	0	0	0	0	0	0	0	1	0
Protozoa - minimal	0	0	0	0	0	0	0	0	1	0
Vacuolation, myofiber										
Minimal	0	0	0	1	0	0	0	0	1	0
Necrosis, epithelial, focal										
Minimal	0	0	0	1	0	0	0	0	0	0
Small intestine	4	4	4	4	4	4	4	4	4	4
Vacuolation, macrophage, lamina propria										
Minimal	0	0	0	1	0	0	0	0	0	0
Spleen	4	4	4	4	4	4	0	0	4	4
Parasite ova – minimal	0	0	0	0	0	0	0	0	1	1
Vacuolation, macrophage										
Minimal	0	0	0	1	0	0	0	0	0	2
Pigment accumulation										
Minimal	0	0	0	0	0	0	0	0	1	0
Atrophy, lymphoid										
Minimal	0	1	0	1	1	1	0	0	0	0
Mild	0	0	0	1	1	0	0	0	0	2
Thyroid	4	4	4	4	4	4	0	0	4	4
Cell infiltration, mononuclear cell										
Minimal	0	0	0	2	1	1	0	0	0	0
Thymus	4	4	4	4	4	4	0	0	4	4
Atrophy, lymphoid										
Minimal	1	0	0	0	0	0	0	0	1	2

Histopathology	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	0	6	12	18/24	22/72	0	6	12	18/24	22/72
Mild	0	0	0	1	0	0	0	0	0	0
Moderate	0	0	0	1	1	0	0	0	1	2
Trachea	4	4	4	4	4	4	4	4	4	4
Vacuolation, epithelial										
Minimal	0	0	0	0	1	0	0	0	0	1
Mild	0	0	0	2	0	0	0	0	1	2
Mammary glands	4	0	0	4	4	4	0	0	4	4
Cell infiltration, mononuc cell										
Minimal	0	0	0	0	3	0	0	0	4	3
Pigment accumulation										
Minimal	0	0	0	3	0	0	0	0	0	1
Mild	2	0	0	0	1	1	0	0	0	0

Toxicokinetics: SCH 34117 plasma concentrations increased in a dose-dependent manner and were gender independent following SCH 34117 administration. SCH 34117 was slowly absorbed, accumulating in plasma following multiple SCH 34117 dose administration. From the low to mid- SCH 34117 dose, exposure increased proportionally, while at the high-dose the increase was supra-proportional at Day 1 and Week 9 (Table 16). At day 1, 22 mg/kg loratadine resulted in SCH 34117 levels which were similar to those observed following 6 mg/kg SCH 34117. At week 9, the high-dose of 24 mg/kg SCH 34117 resulted in slightly lower systemic exposure (17%) to SCH 34117 than that observed following 72 mg/kg loratadine. Loratadine plasma concentrations were also gender independent. Although the loratadine dose was increased 3.3-fold, the systemic exposure to loratadine was reduced by 33% during week 9 compared to Day 1. SCH 34117 exposure following loratadine administration were ~ 5-times and 87-times greater than exposure to loratadine on Day 1 and Week 9, respectively. Comparatively, a single administration of 18 mg/kg SCH 34117 produced an ~ 4-fold greater exposure to SCH 34117 than did an equimolar (22 mg/kg) dose of loratadine.

Table 16. Toxicokinetics of SCH 34117 and loratadine.

Parameter	Dose (mg SCH 34117/kg)						Dose (mg SCH 29851/kg)	
	6		12		18	24	22	72
	Day 1	Wk 9	Day 1	Week 9	Day 1	Week 9	Day 1	Week 9
	SCH 34117							
Cmax (ng/ml)	500	770	769	1424	1209	2696	311	2894
Tmax (hr)	2	4	4	4	8	8	4	12
AUC (0-24 hr) (ng.hr/ml)	4937	11623	9821	21613	21422	54346	5494	65379
R	NA	2.35	NA	2.20	NA	NA	NA	NA
	SCH 29851							
Cmax (ng/ml)							348	104
Tmax (hr)							1	1
AUC (0-24 hr) (ng.hr/ml)							1121	753

R = AUC (0-24 hr) week 9 / AUC (0-24 hr) day 1 NA: not applicable

A NOAEL dose of 12 mg/kg SCH 34117 was identified due to the induction of phospholipidosis (vacuolation, atrophy, necrosis) in organ systems throughout the body. The toxicity profiles observed in the high-dose SCH 34117 and loratadine-treated groups were similar at comparable SCH 34117 exposure levels.

D.

E.

Summary of Toxicology Studies

Two 3-month oral gavage toxicity studies were performed with SCH 34117 in rats (3, 30, 60, and 120 mg/kg SCH 34117 and an active control of 120 mg/kg loratadine) and monkeys (6, 12, and 18/24 mg/kg SCH 34117 and an active control of 22/72 mg/kg loratadine) in order to support clinical studies and bridging to the chronic toxicology program performed for loratadine. In rats, high mortality was observed in rats administered 120 mg/kg SCH 34117. The primary histological findings were indicative of systemic phospholipidosis and included vacuolation, atrophy, necrosis, fibrosis and inflammatory cell infiltration. Findings were generally of greatest incidence and severity at the high SCH 34117 dose, while findings at the dose of 60 mg/kg were comparable to those at 120 mg/kg loratadine. In addition, ovarian mineralization was noted in high-dose females. Organ weight changes were noted at 60 mg/kg SCH 34117 and with the active control and included increases in liver, lung, adrenal, heart and kidney weights, and decreases in spleen, thymus and uterus weights. Body weight gain was significantly reduced at doses of 30 mg/kg or greater in females and 60 mg/kg or greater in males. Reduced eosinophils and lymphocytes (49-79%) were noted at the high-dose and aspartate aminotransferase was significantly increased (250-489%) at the HD SCH 34117. Loratadine showed greater induction potential of cytochrome P450 and PROD than SCH 34117. Plasma concentrations increased supra-proportionally and were greater in females. Drug accumulation was observed with multiple dose administration. The SCH 34117 exposure resulting from loratadine administration was similar to that observed at 60 mg/kg SCH 34117. NOAELs of 3 mg/kg and 30 mg/kg were identified for females and males, respectively. In monkeys, histopathological findings included indicators of systemic phospholipidosis (vacuolation,

fibrosis, atrophy) in organ systems throughout the body. Primary gross findings included dilatation of the organs of the digestive

system. Anti-cholinergic effects were noted clinically and body weight gain was dose-dependently reduced in males (44-93%) but increased (non-dose-dependently) in females (150-250%). Overall, findings at the high-dose of SCH 34117 were comparable to those observed following loratadine administration and mean systemic exposure to SCH 34117 between the two groups was within 17%. In addition, drug accumulation was observed at the two lower SCH 34117 doses and gender difference were not observed. A NOAEL of 12 mg/kg was identified in this study.

Addendum: Histopathology inventory for IND ——

* Organ weight obtained

Study No.	P-6526	D18289	SN 98088	P-6973	P-6527	SN 98089	P-6976
Duration	14-day	14-day	28-day	3-month	14-day	28-day	3-month
Species	rat	rat	rat	Rat	monkey	monkey	monkey
Adrenals	X*		X*	X*	X*	X*	X*
Aorta	X		X	X	X	X	X
Bone marrow smear	X		X	X	X		X
Bone (femur)	X		X	X	X	X	X
Bone (rib)					X	X	
Bone (strenum)	X		X		X	X	
Brain:	X*		X*	X*	X*	X*	X*
Cecum	X		X		X	X	
Cervix			X				
Colon	X		X		X	X	
Duodenum	X		X	X	X	X	X
Epididymis	X*		X*	X*	X*	X	X*
Esophagus	X		X	X	X	X	X
Eye	X		X	X	X	X	X
Fallopian tube							
Fat							
Gall bladder					X	X	X
Gross lesions	X	X			X	X	X
Harderian gland	X		X	X			
Heart	X*		X*	X*	X*	X*	X*
Hyphophysis							
Ileum	X		X	X	X	X	X
Injection site	NA	NA	NA		NA	NA	
Jejunum	X		X	X	X	X	X
Kidneys	X*	X*	X*	X*	X*	X*	X*
Lacrimal gland					X	X	X
Larynx							
Liver	X*	X*	X*	X*	X*	X*	X*
Lungs	X*	X*	X*	X*	X*	X*	X*
Lymph nodes, cervical							
Lymph nodes (LALN)				X			X
Lymph nodes, mandibular	X		X		X	X	
Lymph nodes, mediastinalis							
Lymph nodes, mesenteric	X		X		X	X	
Mammary gland	X		X	X	X	X	
Nasal cavity							
Optic nerves			X				
Ovaries	X*		X*	X*	X*	X*	X*
Oviduct							
Pancreas	X	X	X	X	X	X	X
Parathyroid	X		X	X	X	X	X
Peripheral nerve				X			
Pharynx							
Pituitary	X*		X*	X*	X*	X*	X*
Prostate	X*		X*	X*	X*	X*	X*
Rectum							
Salivary gland	X*		X*	X*	X*	X*	X*
Sciatic nerve	X		X		X	X	
Seminal vesicles	X		X	X	X	X	X
Skeletal muscle	X		X	X	X	X	X
Skin	X		X	X	X	X	X
Spinal cord	X		X	X	X	X	X
Spleen	X*		X*	X*	X*	X*	X*
Stomach	X		X	X	X	X	X
Testes	X*		X*	X*	X*	X*	X*
Thoracic Limb	X						
Thymus	X*		X*	X*	X*	X*	X*
Thyroid	X*		X*	X*	X*	X*	X*
Tongue	X		X	X	X	X	X
Trachea	X		X	X	X	X	X
Urinary bladder	X		X	X	X	X	X
Uterus	X*		X*	X*	X*	X*	X*
Uterine horn							
Vagina	X		X	X	X	X	X

GENETIC TOXICOLOGY

Mouse bone marrow erythrocyte micronucleus study of SCH 34117
Schering Study No.: 97118 *Report No.*: P-6912 *Volume*: 21.7

Study Dates:	Starting date 10/31/1997; report issued 11/19/1998
Testing Lab:	Schering Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Lot No. 97-34117-X-02RA; purity = %) in 0.4% methylcellulose
GLP:	The study was accompanied by a signed GLP compliance statement.
QA report:	Yes.
Parameter:	Clastogenicity

Methods: SCH 34117 was evaluated for its potential to induce micronuclei in the bone marrow of male and female CD-1 mice (6-8 weeks old; 20.1-32.1 g; 6/sex/dose/sacrifice time) following two consecutive daily intraperitoneal doses of 12.5, 25 or 50 mg/kg (dose volume: 5-20 ml/kg; concentrations: 2.5 mg/ml). Dose selection was based upon a dose-ranging study in which mice, administered two consecutive daily intraperitoneal doses of 2.5-40 mg/kg, exhibited reduced PCE/NCE ratio (10% compared to vehicle control animals) 72 hours following dosing and rough hair coat in males and one high-dose female was sacrificed on Day 4 due to severe clinical signs (rough hair coat, chromorhinorrhea and hunched posture) and the PCE/NCE ratio was reduced by 29% compared to controls. Two trials were performed and mice were sacrificed at 24 hours after final dose in the first trial and 48 hours after final dose administration in the second trial; animals treated with positive control were sacrificed at 24 and 48 hours after dosing in trials 1 and 2, respectively. Bone marrow erythrocytes were removed from the femur of five mice from each dose group/sex and three bone marrow smears were prepared for each mouse. With two of those smears, a total of 2000 polychromatic erythrocytes (PCE) were screened for micronuclei. The micronucleus frequency of each dose for each sex was calculated from the total number of micronucleated PCE in 10000 PCE pooled from five mice and compared with that of the vehicle control. Micronucleated NCE were evaluated during the screening of micronuclei in 2000 PCE for each mouse and compared with vehicle controls. Bone marrow toxicity was evaluated by the PCE/NCE ratio from approximately 20 PCE in each mouse. A trial was considered to be valid if the micronucleus frequency in vehicle controls was in the normal range (0.08 to 0.5%); a significant increase of micronucleus frequency in the positive control group above the vehicle control group; and data was available from at least three mice from the vehicle and positive control groups and from each test article dose group. The test article was considered to have caused a positive response if the test article induces a statistically significant increase of micronucleus frequencies in PCE at two consecutive doses. Cyclophosphamide (50 and 30 mg/kg for Trial 1 and 2, respectively) was used as a positive control.

Results: In trial one and two, two high dose males mouse died on Days 3 and 4. Clinical signs were observed in mid-dose males and high-dose males and females (rough hair coat at 25 mg/kg; urogenital staining, hypoactivity, scant feces, salivation at 50 mg/kg). Bone marrow toxicity was noted in males at all doses at 24 hours as PCE/NCE ratios varied from 1.23 in vehicle controls to

0.88, 0.79 and 0.65 at the low- mid- and high-doses corresponding to decreases of 28.5, 35.8, and 47.2%. In females, bone marrow toxicity was noted only at the highest dose (37.6% reduction in PCE/NCE ratio). At 48 hours, bone marrow toxicity was noted in high-dose males and females (39.3% and 33.6% reduction in PCE/NCE ratio, respectively). There was no significant increase in micronucleus frequency at any dose in males or females. Cyclophosphamide induced a 19.8 to 19.9-fold and 10.6 to 15.7-fold increase of micronucleus frequency over the vehicle controls in trials one and two, respectively. The results indicate that SCH 34117 was negative under the conditions of this micronucleus assay, in concurrence with the sponsor's conclusion.

OVERALL SUMMARY AND EVALUATION

Multiple Dose Toxicology: Two 3-month oral gavage toxicity studies were performed with SCH 34117 in rats (3, 30, 60, and 120 mg/kg SCH 34117 and an active control of 120 mg/kg loratadine) and monkeys (6, 12, and 18/24 mg/kg SCH 34117 and an active control of 22/72 mg/kg loratadine) in order to support clinical studies and bridging to the chronic toxicology program performed for loratadine. The primary histological findings were indicative of systemic phospholipidosis and were found in organs and tissues throughout the body including the adrenals, brain, bone and bone marrow, epididymides, eyes, heart, kidneys, lymph nodes, liver, lungs, esophagus, ovaries, pancreas, parathyroid and pituitary glands, prostate, salivary glands, seminal vesicles, skeletal muscle, stomach, intestines, spleen, testes, thyroid, thymus, tongue, trachea, uterus, urinary bladder, and vagina. Findings were most severe at the high SCH 34117 dose, while findings at 60 mg/kg were comparable to those at 120 mg/kg loratadine. Loratadine showed greater induction potential of cytochrome P450 and PROD than SCH 34117. Plasma concentrations increased supra-proportionally and were greater in females than in males. Drug accumulation was also observed with multiple dose administration. NOAELs of 3 mg/kg and 30 mg/kg were identified for females and males, respectively. The observed toxicity profile is consistent with that observed in previous studies with SCH 34117 or loratadine. In monkeys, histopathological findings also included indicators of systemic phospholipidosis in organ systems throughout the body including lymph nodes, liver, lungs, pancreas, salivary glands, stomach, thymus and trachea. Anti-cholinergic effects were noted clinically. Previous studies in monkeys with SCH 34117 (2-weeks at doses up to 6.5 mg/kg, see Original IND Review, and 4-weeks at doses up to 12 mg/kg, see Review #2) did not demonstrate definitive target organs of toxicity, although thyroid hyperplasia in high-dose males and ovarian mineralization in high-dose females were observed in the 4-week study. Thyroid hyperplasia was not observed in the 3-month study. However, ovarian mineralization was noted in high-dose females as well as the active loratadine group. The sponsor has previously been asked submit histopathology data for this finding in low and mid-dose groups in the 28-day monkey study for determination of NOAELs and to clarify the term "mineralization" (see Review # 2), but has not done so. Overall, the toxicity profile at the high-dose of SCH 34117 was comparable to that observed following loratadine administration and mean systemic SCH 34117 exposure in the two groups was comparable. A NOAEL of 12 mg/kg was identified in this study.

Genetic Toxicology: An in vivo mouse bone marrow micronucleus assay with SCH 34117 was concluded to be negative. These findings are consistent with the results of an Ames assay and an in vitro chromosome aberration assay reported previously.

Carcinogenicity Assessment Waiver Request: The sponsor submitted a carcinogenicity waiver request which was presented before the Senior Pharmacology/Toxicology Policy Group. The sponsor's proposal for the waiver from performing carcinogenicity studies for SCH 34117 was based primarily on rat and mouse SCH 34117 exposures achieving at least a 25-fold rodent to human exposure multiple in previous carcinogenicity studies with loratadine. The Senior Policy Group concluded that SCH 34117 was adequately assessed for carcinogenicity in rats since the carcinogenicity study performed for loratadine resulted in an unbound SCH 34117-derived rodent to human exposure multiple which exceeded 25. However, the Policy Group concluded that a 2 year mouse carcinogenicity study with SCH 34117 should be performed as a Phase 4 commitment since neither appropriate SCH 34117 exposure multiples nor a maximum tolerated dose were achieved in the mouse carcinogenicity study performed with loratadine. See Attachments 1, 2, and 3 for more detailed information on the sponsor's proposal and the Policy Group's recommendations.

RECOMMENDATIONS

3. The similar toxicological findings following SCH 34117 and loratadine administration in rats and monkeys at similar exposure levels of SCH 34117 in the 3-month toxicology studies support bridging to the chronic loratadine toxicology program. Therefore, the sponsor will not be required to perform additional chronic toxicity studies with SCH 34117.

4. The sponsor is requested to provide clarification of the term mineralization (i.e., type of minerals) as related to the findings in the ovaries of monkeys (Study P-6976). A previous request for low-dose and mid-dose histopathology data for this finding in the 28-day monkey study (Study SN 980089) is no longer considered necessary as the finding was not instrumental in determining a NOAEL in the 3-month study.

/S/

Timothy J. McGovern, Ph.D., Pharmacologist

Attachment I.
Attachment II.
Attachment III.

Original IND . ———
CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/R. Nicklas
HFD-570/G. Trout
HFD-570/T.J. McGovern
HFD-540/B. Hill

Draft Comments for Letter to Sponsor:

Please clarify the term "mineralization" as related to findings in the ovaries of monkeys (i.e., type of minerals) in the 3 month toxicity study (Study P-6976).

Redacted 11

pages of trade

secret and/or

confidential

commercial

information

HFD-570 : DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review #3

IND No. ——— **Serial No.** 031 **Submission Date:** 23 NOV 98
032 23 NOV 98

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 15 DEC 98

Information to be Conveyed to Sponsor: Yes ( ), No (✔)

Sponsor: Schering-Plough Corporation

Drug Names: Descarboethoxyloratadine (DCL) *Code Name:* SCH 34117

Class: Anti-histamine

Indication: Allergic rhinitis/chronic idiopathic urticaria

Route of Administration: Oral (tablet)

Proposed Clinical Protocols: None with these submissions.

Previous Clinical Experience: Phase I and Phase II studies in both healthy volunteers and patients with seasonal allergic rhinitis.

Previous Review(s), Date(s) and Reviewer(s):

Review Type	Date of Submission(s)	Reviewer	Date of Review
Original Review	March 9, 1998	McGovern	May 22, 1998
REVIEW #2	JULY 8-OCTOBER, 19, 1998		MCGOVERN
OCTOBER 27, 1998			

The submission of Serial No 032 contains draft tables of clinical observations and gross findings from a 3-month monkey study submitted to the Agency following a teleconference with the sponsor (11/18/98). The sponsor's intent with this submission is to gain Agency concurrence on the Sponsor's plan not to perform an additional 3-month study in monkeys in order to fulfill bridging requirements to the chronic studies performed in the development program for loratadine. The sponsor states that they will assume that no additional study is required until they are informed otherwise by the Agency.

The following table summarizes the studies submitted in these submissions:

Preclinical Studies Submitted and Reviewed in this IND:

Study	Serial No.	Report #	Volume
Pharmacokinetics and Toxicokinetics:			
TK of single oral doses of SCH 34117 or 29851 in cynomolgous monkeys	031	SN 97525	2
Multiple Dose Toxicology:	032	SN 98212	1
Draft clinical/gross necropsy tables from 3-mos monkey toxicology study	031	SN 97512	1
Reproductive Toxicology:			
Pilot perinatal and post-natal development study in rats			

Studies Not Reviewed in this IND: None.

Studies Previously Reviewed: None

Note: Portions of this review were excerpted directly from the sponsor's submission.

PHARMACOKINETICS and TOXICOKINETICS

Cynomolgus monkeys were administered a single dose of SCH 34117 (11.75 or 23.5 mg/kg) or loratadine (24, 160 or 320 mg/kg) by oral gavage (5 ml/kg, 2.35-64 mg/ml). Blood samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24 and 36 hours after dosing. All monkeys survived the dosing and observation period with no test-article or study-related clinical signs reported. Following administration of SCH 34117, exposure parameters increased in a proportional manner (Table 1) and Tmax was achieved at approximately 4 hours. The AUC was approximately twice as great in females than in males. Following loratadine administration, the Tmax for SCH 34117 was 1.5 to 6-fold greater than that reported for direct administration of SCH 34117 and tended to increase with dose. Exposure to SCH 34117 increased sub-proportionally from the low to mid-dose and then plateaued, possibly due to saturation. A dose of 24 mg/kg loratadine resulted in a SCH 34117 Cmax which was ~ 52% and 75% less in males and females, respectively, than that observed in animals administered a similar dose of SCH 34117. Systemic exposure was also reduced by ~ 27% and 66%. Exposures to SCH 34117 were roughly similar in groups administered 11.75 mg/kg SCH 34117 and 24 mg/kg loratadine, and groups administered 23.5 mg/kg SCH 34117, 160 mg/kg loratadine and 320 mg/kg loratadine. Females continued to demonstrate greater exposure levels, though not as dramatically as when SCH 34117 was administered directly. Exposure to loratadine following loratadine administration was significantly less than exposure to SCH 34117 (~33-90%) and also increased sub-proportionally from the low to mid-dose and before plateauing from the mid- to high-dose. Tmax was between 2 and 4 hours.

Table 1. Pharmacokinetics of SCH 34117 and loratadine following single oral gavage dosing.

Mean SCH 34117 parameters after SCH 34117 or loratadine administration										
Parameter	11.75 mg/kg SCH 34117		23.5 mg/kg SCH 34117		24 mg/kg loratadine		160 mg/kg loratadine		320 mg/kg loratadine	
	Male n=3	Female n=3	Male n=3	Female n=3	Male n=3	Female n=3	Male n=3	Female n=3	Male n=3	Female n=2
Cmax (ng/ml)	277	454	604	1355	290	341	594	1028	663	692
Tmax (hr)	4	3.3	4	4	11.3	6.7	11.3	19.3	23.3	24
$AUC_{(0\text{-}36\ hrs)}$ (ng.hr/ml)	4778	8018	11258	22818	7137	7760	14003	29293	18007	19892
Mean loratadine parameters after loratadine administration										
Cmax (ng/ml)					178	382	726	694	739	522
Tmax (hr)					2.3	2	3.3	4	4	2
$AUC_{(0\text{-}36\ hrs)}$ (ng.hr/ml)					708	1644	3808	6994	6802	4529

A previously submitted 14-day study in monkeys, which were administered lower doses of SCH 34117 (1.6-6.5 mg/kg) and loratadine (8 mg/kg), demonstrated significantly increased exposure levels in males at doses of 1.6 and 3.2 mg/kg compared to females, and similar exposure levels in both sexes at the high dose of 6.5 mg/kg, on Days 1 and 14. Reported AUCs increased sub-proportionally in males and proportionally (low to mid-dose) and supra-proportionally (mid to high-dose) in females; the Tmax on Day 1 (2.5-4 hours) was similar to that observed presently. In addition, the SCH 34117 AUC increased proportionally on Day 1 and sub-proportionally on Day 14 of a 28-day study in monkeys which were administered SCH 34117 (3-12 mg/kg) and loratadine (12 mg/kg); SCH 34117 Tmax was reported as 1.5 to 4 hours. An overall comparison of the resultant Day 1 AUCs from the three studies submitted to date demonstrate a dose-proportional increase from 1.6-12 mg/kg, although some variability is present.

TOXICOLOGY

MULTIPLE-DOSE TOXICITY:

Monkey, 3-Month Oral (Gavage) Toxicity (Draft Tables)

[redacted] *Study No.* [redacted] *Study No.*: 98212 *Volume*: 1

Study Dates: Starting date; not provided; report issued: not applicable
Testing Lab: [redacted]
Test Article: SCH 34117 (Batch & purity not reported)
Concentration: Not reported.
Dose Volume: Not reported.
GLP: This report was unaudited.
QA report: No.

Methods: Cynomolgus monkeys were assigned to the following treatment groups:

Dose (mg SCH 34117 /kg/day):	0	6	12	18/24*	**22/72* mg loratadine/kg/day**
No./sex	4	4	4	4	4

*: Groups dosed with 18 mg/kg SCH 34117 or 22 mg/kg loratadine were increased to 24 and 72 mg/kg, respectively, during Study week 6.

Each monkey received a daily dose of vehicle, test drug or comparative dose of loratadine by oral (gavage) administration for 3 months.

Results: Results are summarized in tables 2-3.

Mortality: None reported.

Clinical Observations: Anti-cholinergic effects were the primary drug-related clinical observations in this study (Table 2). These included few or no feces at the mid- and high-dose of SCH 34117 and loratadine-treated animals. A slight increase in the incidence of extended abdomen and hunched posture were also noted in these groups. Various findings unique to the loratadine-treated animals were also reported.

Table 2. Clinical observations in monkeys following 3-month administration of SCH 34117.

Observation	Males					Females				
	Dose (mg/kg)					Dose (mg/kg)				
	0	6	12	18/24	22/72 - loratadine	0	6	12	18/24	22/72 - loratadine
Abrasion - foot					1					
- head					1					
- mouth								1		
Alopecia - arm					1			2		
- body					1		1	1		
- head					1	1	1	1		
- leg					2			1		
- shoulder					1		1			
Emesis			1	2		1		1	1	
Feces - few				4	1				2	3
Feces - none				4	2			1	3	2
Feces - mucoid										1
Discoloration - body				1						
Extended abdomen				1	1					2
Hunched posture				1	1					1
Lethargic					1					1
Swelling - foot									1	
- leg									1	

Few feces: first observed days 71-80 (F) and 66-71(M). F: lasted for 1 d at HD 34117, 11 d at 22 L. M: 14 d at HD 34117, 26 d at 22 L.

No feces: first observed days 72-83 (F) and 78-84 (M). F: lasted for 1 d at MD 34117, 5 d at HD 34117, and 1 d at 22 L. M: 3 d at HD 34117, 8 d at 22 L.

Gross Pathology: The primary gross findings included dilatation of the cecum and colon which are likely related to the decreased fecal excretion noted above (Table 3). There was also a slight increase in dilatation of other organs of the digestive system in 1 loratadine-treated female.

Table 3. Gross observations in monkeys following 3-month oral administration.

Observation	Males					Females				
	Dose (mg/kg)					Dose (mg/kg)				
	0	6	12	18/24	22/72 - loratadine	0	6	12	18	22/72 - loratadine
Cecum - dilatation				2	2		1		1	2
Colon - dilatation				2	2		1		1	2
Duodenum - dilatation										1
Ileum - dilatation										1
Jejunum - dilatation										1
Stomach - dilatation										1
Heart - focus									1	
Spleen - adhesion - deformity					1 1					

A NOAEL could not be identified in this study since only draft tables for clinical observations and gross pathology were submitted. The sponsor was informed via telephone that a final decision as to whether this study would support the sponsor's bridging strategy for this development program must await submission and review of the histopathology and toxicokinetic data.

REPRODUCTIVE TOXICOLOGY

Rat (oral) Pilot Perinatal and Postnatal Development Study

Report No.: P-6817 *Study No.*: 97512 *Volume*: 9.1

Study Dates: Starting date 11/25/97; report issued 7/10/98
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch 97-34117-X-02RA; purity not reported) in 0.4% (w/v) aqueous methylcellulose
Concentration: 0.6-3.6 mg SCH 34117/ml
Dose Volume: 5 ml/kg/day
GLP: The study was an unaudited report.
QA report: No.

Methods: Crl:CD(SD)BR VAF/Plus female rats were assigned to the following treatment groups:

Dose (mg /kg/day):	0	3	9	18
No./dose group	5	5	5	5

Each female was placed with a male rat from the same strain and supplier. Cohabitation continued until positive evidence of mating was observed. Females were then dosed once daily by esophageal intubation (gavage) from pregnancy Day 6 through lactation Day 7. The following observations were made:

Clinical observation .. Dams examined daily
Body weight ..... Dams weighed on pregnancy days 0, 6, 9, 12, 15, 18, and 21, and on lactation days 1, 4, and 7.
F_0 parturition ..... Observed beginning day 21 of pregnancy for abnormal labor, nursing, or nesting behavior.
Necropsy ..... Lactation Day 7, examined for external and visceral changes, and implantation site.
Litter size ..... total numbers of live and dead offspring recorded daily for each litter until lactation Day 7. Pup survival calculated on lactation Days 0, 1-4, and 5-7.
Sex determination .... Offspring sexed externally on lactation Days 0 and 7
External examination/ . Offspring examined daily from lactation Day 0 through 7.
Appearance & behavior
Body weight ..... Offspring weighed on lactation days 0, 4, and 7.
Necropsy ..... Offspring sacrificed on lactation Day 7, examined for external and visceral changes

Results:

Mortality: All dams survived until scheduled sacrifice.

Clinical signs: Large fecal pellets, likely related to the anti-cholinergic effects of the drug, were observed in the SCH 34117-treated groups. The large pellets were observed in 3 of 5 low-dose, 5 of 5 mid-dose, and 3 of 5 high-dose animals and occurred primarily between gestation days 8 and 21.

Body weight (F_0): Overall mean maternal body weight was not significantly affected in any treatment group. However, mean body weight gain for high-dose dams was statistically lower (48%) than control animals during gestation days 6 though 12 (Table 4). Body weight gain in the low- and mid-dose groups was also reduced (not statistically significant) by 8 and 28%, respectively. This finding is considered to be treatment-related since similar findings were observed in an embryo-fetal developmental toxicity study in rats (Report # 6718; reviewed in Original IND Review) at doses of 24 and 48 mg/kg (52 and 72% reduction, respectively). On Day 21 of gestation, body weight gain compared to controls was reduced by 9% in the high-dose group, similar to the other treatment groups. By Day 7 of the lactation period, however, body weight gain in the high dose group was increased by 7%, while body weight gain continued to be reduced in the low and mid-dose groups by 33 and 47%, respectively.

Table 4. Body weight gain (% change vs control) in animals administered SCH 34117.

Dose group (mg/kg)	Day of treatment			
	Gestation Days 6-12	Gestation Day 12	Gestation Day 21	Lactation Day 7
3	↓8%	↓10	↓15%	↓33%
9	↓28%	↓24	↓16%	↓47%
18	[redacted]	↓6	↓9%	↑7%

Shaded areas indicate statistically significant difference from control.

F_0 parturition: No SCH 34117-related effects on pregnancy or labor.

Necropsy (F_0 generation): No treatment-related findings were observed. One low-dose rat had a thickened uterine wall.

F_1 survival: No treatment-related effects were observed. The percentages of dying pups were similar between control and drug treatment groups.

Body weight (F_1): Although mean pup weights in SCH 34117-dosed groups were not statistically different from control values, high-dose pup weights were consistently lower than control values (7-11%). Reduced pup weights (9%) were also observed in an embryo-fetal developmental toxicity study in rats at doses of 24 mg/kg or greater.

Necropsy (F_1 generation): All pups were grossly normal.

A dose of 18 mg/kg induced a significant decrease in maternal body weight gain in the present study. Based on available pharmacokinetic data and assuming dose-proportional increases in systemic exposure, this dose provides an estimated 80-fold exposure ratio compared to the proposed clinical dose of 7.5 mg SCH 34117. A previous embryo-fetal developmental study also demonstrated similar effects with shorter dosing duration at doses of 24-48 mg/kg. Thus, the oral high-dose in the definitive perinatal and postnatal study in rats should be 18 mg/kg, in concurrence with the Sponsor's conclusion.

OVERALL SUMMARY AND EVALUATION

The Sponsor submitted a single oral (gavage) dose toxicokinetic study and draft tables of clinical and gross histopathology data from a 3-month study in monkeys, and a pilot Segment II study in rats. The Sponsor had requested Division feedback as to whether the submitted data from the 3-month monkey study was sufficient to preclude the Sponsor from performing an additional 3-month study in monkeys in order to adequately describe the toxicity profile of SCH 34117 for the purpose of the Sponsor's bridging strategy to the development program for loratadine. However, clinical signs are not an adequate indicator of toxicity profile without other parameters such as histopathology. Thus, the limited nature of this submission preclude the Division from reaching a conclusion on this issue at this time. The Sponsor has been contacted by the Project Manager (see notes of teleconference of 12/10/98) and informed that a final decision on this issue must await submission of the histopathology and PK/TK data. In addition, the Sponsor's proposed oral high dose of 18 mg/kg for the definitive perinatal and postnatal developmental study in rats is acceptable.

RECOMMENDATIONS

1. A final decision as to whether the Sponsor needs to perform an additional 3-month study to support their bridging strategy to the loratadine drug development program must await submission of the histopathology and PK/TK data from the current 3-month study under review. This information was conveyed to the Sponsor by the Project Manager on 12/10/98.

2. The proposed oral high dose of 18 mg/kg for the definitive perinatal and postnatal developmental study in rats is acceptable.

/S/

Timothy J. McGovern, Ph.D., Pharmacologist

Original IND —
CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/A. Trontell
HFD-570/G. Trout
HFD-570/T.J. McGovern

HFD-570 : DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review #2

IND No. [ ]	**Serial No.**	007	**Submission Date:** 08 JUL 98
		009	29 JUL 98
		010	30 JUL 98
		019	18 SEP 98
		023	19 OCT 98

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 27 OCT 98

Information to be Conveyed to Sponsor: Yes (✔), No ( )

Sponsor: Schering-Plough Corporation

Drug Names: Descarboethoxyloratadine (DCL) *Code Name:* SCH 34117

Class: Anti-histamine

Indication: Allergic rhinitis/chronic idiopathic urticaria

Route of Administration: Oral (tablet)

Proposed Clinical Protocols:
Objective: Phase III, examining clinical efficacy and safety of SCH 34117
Dose: 5 and 7.5 mg in each proposed study
Frequency: Once per day
Duration of clinical studies: Two 2-week studies and one 4-week study
Patient population: Patients with seasonal allergic rhinitis

Previous Clinical Experience: Phase I, rising single-dose study (2.5-20 mg) in healthy male volunteers. Phase II, dose finding study (2.5-20 mg; two weeks) in patients with seasonal allergic rhinitis.

Previous Review(s), Date(s) and Reviewer(s):

Review Type	Date of Submission(s)	Reviewer	Date of Review
Original Review	March 9, 1998	McGovern	May 22, 1998

The submission of Serial No. 023 states that the Briefing Document (Serial No. 007) for a meeting with the sponsor (8/7/98) serves as a summary for the 28-day studies in rats and monkeys submitted as Serial No. 009, since submission No. 009 did not include a summary of results and conclusions. The preclinical studies are in support of the proposed 28-day clinical study included in the submission labeled Serial No. 010. Submission 019 states that toxicology

data submitted on July 2 and 16, 1998 (Serial Nos. 007 and 008, respectively) are considered adequate to support initiation of Clinical Study C98-225, the 28-day study in seasonal allergic rhinitis patients. These serial numbers did not correspond to those received by this reviewer and it is assumed that the sponsor is referring to Serial Nos. 007 and 009 submitted on July 8 and 29, 1998, respectively. Submission 023 adequately addressed the Division's concerns.

The following table summarizes the studies submitted in these submissions:

Preclinical Studies Submitted and Reviewed in this IND:

Study	Serial No.	Report #	Volume
Multiple Dose Toxicology:			
FDA Briefing Document	007		
4-week, oral (gavage) toxicity, rats	009	SN 98088	1
4-week, oral (gavage) toxicity, monkeys	009	SN 98089	1

Studies Not Reviewed in this IND: None.

Studies Previously Reviewed: None

Note: Portions of this review were excerpted directly from the sponsor's submission.

MULTIPLE-DOSE TOXICITY:

Rat, 28-day Oral Toxicity

Study No.: [redacted] *Study No.*: SN 98088 *Volume*: 1

Study Dates: Starting date 4/6/98; report issued 7/29/98
Testing Lab: [redacted]
Test Article: SCH 34117 (Batch 97-37114-X-03-RA; purity=100%) in 0.4% methyl-cellulose; Loratadine (Batch MI-A-00851; purity=100.5%)
Concentration: 0.6-24 mg SCH 34117/ml; 24 mg loratadine/ml
Dose Volume: 5 ml/kg/day
GLP: The study was an unaudited report.
QA report: No.

Methods: CRL:CD® (SD) BR VAF/Plus® rats (5-7 weeks old; males: 100-325 g; females: 80-300 g) were assigned to the following treatment groups:

Dose (mg/kg/day):	0	3	30	60	120	**120 mg loratadine/kg/day**
No./sex toxicity study	10	10	10	10	10	10

Rats received daily oral doses of vehicle, test drug or comparative dose of loratadine (equal to the high dose of SCH 34117 on a mg/kg basis) for 28 days. The following observations were made:

Clinical observation . . . twice daily
Body weight . . . . . weekly beginning Week -1
Food consumption . . . . weekly

Water consumption . . . not assessed
Ophthalmoscopy . . . . . prestudy and during Week 4
EKG . . . . . not performed
Hematology . . . . . Day 29
Clinical chemistry . . . . Day 29
Urinalysis . . . . . Day 29
Enzyme induction . . . . not assessed
Organ weights . . . . . at sacrifice; (for specific organs see Addendum, page 14)
Gross pathology . . . . . at sacrifice
Histopathology . . . . . at sacrifice; organs/tissues from vehicle control, comparative control and high-dose SCH 34117, rats dying prior to scheduled necropsy and all gross lesions. Organs identified as target organs in the high-dose group also processed and evaluated in all other groups (for specific tissues/organs see Addendum, page 14).
Toxicokinetics . . . . . Day 1 and during Week 3; samples collected 2 rats/sex/group (test and comparative article groups only)

Results: Results are summarized in tables 1-6.

Mortality: Mortality was not directly addressed in the submitted summary report, although an included protocol change stated that PK sampling in high-dose females during Week 3 was canceled due to excessive mortality of high-dose females during the Day 1 blood collection. Summary data tables for unscheduled deaths included 3 high-dose males and 1 low-dose and lower mid-dose, 3 upper mid-dose, 8 high-dose and 4 loratadine-treated females. In contrast, the submitted briefing document (Serial No. 007) contains a summary data table which provides different numbers (Table 1). The briefing document states that deaths/moribund sacrifices in the 3-60 mg/kg groups occurred on days on which rats were bled for plasma analyses and are not treatment-related. All male animals which died, with the exception of HD males, did so on Day 1 following bleeding. Similarly, all females which died, with the exception of HD females, did so on Day 15 following bleeding. Control animals were not bled and, thus, were not subjected to similar stress. Thus, it is arguable that deaths in the low to upper-mid-dose groups are related to bleeding procedures rather than drug treatment, especially since no mortality was observed in a previous 14-day study at doses up to 60 mg/kg/day. Deaths at 120 mg SCH 34117/kg in the current study, however, appear to be directly related to drug administration since the incidence was increased and deaths did not occur on days of bleeding.

Clinical Observations: Clinical signs with potential treatment-relatedness include enlarged feces, few feces, no feces, salivation, hunched posture, thin appearance, labored and rapid respiration, respiratory distress/respiratory sounds-rales, paleness, and wetness in urogenital region (Table 1). These findings were observed primarily at doses greater than or equal to 30 mg/kg and are thought to be associated with the anticholinergic properties of the test drug.

Body Weight: At Day 29, body weight gain of SCH 34117-treated males was reduced 18 and 34% at the upper-mid and high dose, respectively, and loratadine-treated males were reduced 19% (Table 1). High-dose males first showed significant reduction at Day 8. Similarly, body

weight loss (31g) compared to controls (increase of 55g) was first noted on Day 8 in high-dose females. Loratadine-treated females displayed a 32% reduction in body weight gain.

Food Intake: Reduced food consumption at Day 29 was observed in HD animals (Table 1). A decrease was first reported at Day 8 with the greatest reduction observed at Day 15 in females (25-34% in males; 39-74% in females). Consumption was also reduced in loratadine-treated females beginning at Day 8 (15-29%), although males showed significant reductions only at Days 8 and 22 (9 and 7%, respectively).

Table 1. Clinical observations in rats administered SCH 34117 or loratadine.

	Males						Females					
Dose (mg /kg/d)	0	3	30	60	120	Lorat.	0	3	30	60	120	Lorat.
Mortality*	0	2	2	2	5	2	0	1	1	3	8	4
Clin. Observations												
Enlarged feces			10	10	10	10			10	10	8	9
Few feces					10	1	1		1	10	10	9
No feces					1					1	2	
Alopecia					1							
Salivation			1		4					1	1	
Hunched posture					10						1	
Pale					3		1				9	
Rough coat					1						4	
Thin					8		1			1	10	1
Labored respiration			1		2				1		3	2
Rapid respiration		2	1	2	1						1	
Resp. distress/sounds					4						1	1
Eyes/ears discharge											2	
Nasal discharge											1	1
Urogenital region - wet											6	
Body Weight Gain %Δ vs control group		↓6	↓4					↑3	↓20	↓15		↓32
Food Consump. (g/day) %Δ vs control group		no Δ	↑6	↓4		↓1		↓2	↓6	↓9		

*** Control animals not bled for plasma analysis. Males: n = 12; females: n = 10.**
**** Body weight loss in grams.**
Shaded areas indicate a significant difference from vehicle controls.

Ophthalmoscopy: No treatment-related observations were reported.

Hematology: Slight increases in white blood cell and erythrocyte counts, hemoglobin and hematocrit and platelets (high-dose) were observed in treated males (Table 2). Similar changes were noted in females, however, white blood cell counts were reduced considerably in high-dose females. Reduced eosinophil levels in high-dose males and females (53 and 87%, respectively) and lymphocyte numbers in high-dose females (87%) were noted. Loratadine-treated animals were comparable to mid-dose SCH 34117 animals, demonstrating slight increases in erythrocyte counts, hemoglobin and hematocrit. Besides the changes in lymphocyte and eosinophil populations, the biological significance of these findings is questionable since the changes were generally not great in magnitude with limited evidence of a dose-response relationship.

Clinical Chemistry: Levels of AP (males only), AST and ALT were increased primarily at the high dose (Table 2). Additional changes included increased BUN and cholesterol at doses greater than or equal to 60 mg/kg. Total protein and globulin levels showed slight increases associated with a slight decrease in A/G ratio, especially in males. Also, glucose levels were slightly increased in high-dose males. Loratadine-treated animals also showed slight changes in some of the aforementioned parameters (usually comparable to animals administered 60 mg/kg SCH 34117) with a 2-fold increase in cholesterol (females) being the most significant change.

Urinalysis: Urine osmolarity was decreased in treated females but not in males (Table 2).

Table 2. Hematology and clinical chemistry findings in rats.

	Males					Females				
Dose (mg /kg/d)	3	30	60	120	Lorat.	3	30	60	120	Lorat.
Hematology										
WBC										
%Δ vs control group		↑16		↑26	↑4	↓14	↓11	↓31		↓30
Lymphocytes										
%Δ vs control group		↑14	↑19	↓4	↑7	↑2	↑9	↓31		↓22
Eosinophils										
%Δ vs control group	↑33	↑7	↓33		↓27	↓7	no Δ	↓33		↓60
Erythrocyte										
%Δ vs control group	↑1			↑4		↓2	↑6			
Hemoglobin										
%Δ vs control group	↑2			↑3		↑1	↑5			
Hematocrit										
%Δ vs control group	↑1			↑3		no Δ	↑5			
Platelets										
%Δ vs control group	↑9	↓2	↑2		↑4	↓1	↓1	↓2	↑16	↓10
Clinical Chemistry										
AP										
%Δ vs control group	↑13					↓16	↓22		↓15	↓19
ALT										
%Δ vs control group	no Δ	↓18	↑13		↑24	↑38	↓9	no Δ		↑9
AST										
%Δ vs control group	↑4	↑7	↑6		↓9	↑11	↓11	↑54		↑20
Urea nitrogen										
%Δ vs control group	↑8		no Δ		↑8	↓7	no Δ	↑7		
Cholesterol										
%Δ vs control group	no Δ		↓4		↓2	↓5	↓5			
Total protein										
%Δ vs control group	no Δ		↑6	↑3		↑4			↓10	↑4
Globulin										
%Δ vs control group	no Δ		↑16			↓5	no Δ	↑24	↓10	↑5
A/G ratio										
%Δ vs control group	↑1	↓7	↓10		↓9	↑12	↑8	↓15	↓4	↓4
Glucose										
%Δ vs control group	↑6	no Δ	↑4		↓6	↓3	↑6	↓6	↓10	↓14
Urinalysis										
Osmolarity										
%Δ vs control group	↓5	↑10	↓32	↑6	↓2	↓14			↓14	

Shaded areas indicate a significant difference from vehicle controls.

Organ Weights: SCH 34117-treated males exhibited decreases in heart, thymus and prostate weight (Table 3). In addition, lung and liver weights were increased. Females showed similar changes in heart and thymus weights, and also demonstrated slight increases in kidney and decreases in spleen and ovary weights. Brain weight was slightly decreased (6-11%) in high-dose animals. Loratadine-treated animals also exhibited significant alterations (usually comparable to animals administered 60 mg/kg SCH 34117) in adrenal gland and spleen weights (males only), heart (females only), and liver and lung weights. Generally, similar changes were observed in "relative to body weight" and "relative to brain weight" organ weights.

Table 3. Absolute organ weight changes following SCH 34117 administration in rats.

	Males					Females				
Dose (mg/kg/d)	3	30	60	120	Lorat.	3	30	60	120	Lorat.
Abs. Organ weight										
Adrenal gland										
%Δ vs control group	↓8	↓11	[redacted]	↓4	[redacted]	↓10	↓11	↓2	↓1	↓5
Brain										
%Δ vs control group	↓2	↓1	no Δ	[redacted]	↓3	↓3	↓1	↓5	[redacted]	↓3
Heart										
%Δ vs control group	↓2	↓4	↓7	[redacted]	↓11	↑1	↓7	↓2	[redacted]	
Kidney										
%Δ vs control group	↓3	no Δ	↑2	↑4	↓7	no Δ	no Δ	↑9	[redacted]	↑2
Liver										
%Δ vs control group	↓3	[redacted]				↓8	↓5	↑12	no Δ	[redacted]
Lung										
%Δ vs control group	↑4	↑25	[redacted]			↑16	[redacted]		↑17	[redacted]
Spleen										
%Δ vs control group	↓2	↓12	[redacted]	↓15	[redacted]	↓23	↓28	↓34	[redacted]	↓26
Thymus										
%Δ vs control group	↑4	↓14	↓17	[redacted]	↓16	↑7	↓4	↓4	[redacted]	↓5
Prostate										
%Δ vs control group	↓1	↓9	↓7	[redacted]	↓5					
Ovary										
%Δ vs control group						↓7	↑9	↑5	[redacted]	↑2

Gross Pathology: Following scheduled sacrifice, gross alterations included an impacted colon and deformed liver in a high-dose female, and an enlarged seminal vesicle in a high-dose male (Table 4). Following unscheduled deaths, dilatation was noted in numerous organs of a high-dose female and male. Additional observations at the high dose included lung discoloration and enlarged mandibular lymph nodes.

Table 4. Gross changes following SCH 34117 administration in rats.

	Males						Females					
Dose (mg/kg/d)	0	3	30	60	120	Lorat.	0	3	30	60	120	Lorat.
Gross alterations												
Scheduled Sacr. n =	**10**	**10**	**10**	**10**	**7**	**10**	**10**	**9**	**9**	**7**	**2**	**6**
Colon - impacted	0	0	0	0	0	0	0	0	0	0	1	0
Liver - deformity	0	0	0	0	0	0	0	0	0	0	1	0
Seminal ves. - enlarged	0	0	0	0	1	0						
Unscheduled Deaths n =	**0**	**0**	**0**	**0**	**3**	**0**	**0**	**1**	**1**	**3**	**8**	**4**
Cecum - dilatation	0	0	0	0	0	0	0	0	0	0	1	0
Duodenum - dilatation	0	0	0	0	0	0	0	0	0	0	1	0
Ileum - dilatation	0	0	0	0	0	0	0	0	0	0	1	0
Intestines - dilatation	0	0	0	0	1	0	0	0	0	0	0	0
Jejunum - dilatation	0	0	0	0	0	0	0	0	0	0	1	0
Lung - discoloration	0	0	0	0	0	0	0	0	0	0	2	0
LN-mandib - enlarged	0	0	0	0	1	0	0	0	0	0	2	0
Stomach - dilatation	0	0	0	0	1	0	0	0	0	0	0	0

Histopathology: Assessment of histopathological findings in animals following the final sacrifice demonstrated alterations, many indicative of systemic phospholipidosis, in numerous organs (Table 5). These findings were observed primarily at the upper-mid and high dose, although centrilobular hepatic hypertrophy and vacuolation were noted at 30 mg/kg SCH 34117 in males. Similar findings were observed in animals following unscheduled sacrifice. Additional observations in this group included villous atrophy of the ileum (1 of 8 HD females), mammary gland hyperplasia (1 of 8 HD females), inflammation of the esophageal muscularis (1 of 3 HD males, 2 of 8 HD females), cortical tubular necrosis in 1 of 3 HD males and 5 of 8 HD females), alveolar proteinosis in the lungs (1 of 3 UMD and 2 of 8 HD females), necrosis of pancreatic acini (1 of 8 HD females), and congestion (1 of 3 HD males) and lymphoid depletion (7 of 8 HD females) of the thymus. Findings in animals administered loratadine did not correlate with those of SCH 34117-administered animals in all cases and appeared to be less toxic than SCH 34117 at equivalent doses.

Table 5. Histopathological changes following final sacrifice of rats.

	Males						Females					
Dose (mg/kg/d)	0	3	30	60	120	Lorat.	0	3	30	60	120	Lorat.
Histology-final sacrifice												
Harderian gland n =	**10**	**0**	**0**	**0**	**7**	**10**	**10**	**0**	**0**	**0**	**2**	**6**
inflammation	0	0	0	0	1	0	0	0	0	0	0	1
Eye - retinal folds/cysts	0	0	0	0	1	0	0	0	0	0	1	0
Heart n =	**10**	**10**	**10**	**10**	**7**	**10**	**10**	**9**	**9**	**7**	**2**	**6**
cardiomyopathy	1	0	1	0	3	0	0	1	0	0	2	1
Kidney												
tub vacuolation (cortex)	1	0	0	2	7	5	0	0	0	0	2	2
hyperplasia, epith-pelvis	0	0	0	0	1	0	0	0	0	0	0	0
inflamm, chronic-pelvis	0	0	0	0	1	0	0	0	0	0	0	0
tub dilatation, (cortex)	0	0	0	0	1	0	0	0	0	0	2	0
Liver												
vacuolation-fine,centrilob	0	0	9	9	6	9	0	1	0	4	2	6
-coarse	0	0	0	1	0	1	0	2	0	0	0	0
centrilob hepat hypertr	0	0	10	10	6	10	0	0	0	4	2	6
kupfer cell hypert/vac	0	0	0	0	1	0	0	0	0	0	2	0
Lung												
alveolar histiocytosis	0	0	0	6	7	0	0	0	0	7	2	6
inflammation, chronic	0	0	0	0	1	0	0	0	0	0	0	0
Lymph node-mesenteric												
vacuolated histiocytes	0	0	0	0	4	0	0	0	0	3	2	1
lymphoid depletion	0	0	0	0	1	0	0	0	0	0	0	0
Lymph node - mandib												
vacuolated histiocytes	0	0	0	0	3	0	0	0	0	3	2	0
Ovary												
vacuolation							0	0	0	0	1	1
atrophy							0	0	0	0	1	0
Pancreas												
vacuolation, acinus	0	0	0	0	0	0	0	0	0	0	1	0
Prostate n =	**10**	**0**	**0**	**0**	**7**	**10**						
inflammation, chronic	0	0	0	0	1	0						
Skeletal Muscle n =	**10**	**10**	**10**	**10**	**7**	**10**						
myofiber deneration	0	0	0	0	4	0	0	0	0	0	2	0
Spleen												
lymphoid depletion	0	0	0	0	5	0	0	0	0	0	2	0
vacuolated histiocytes	0	0	0	0	7	0	0	0	0	6	2	0
hematopoiesis	0	0	0	0	1	0	0	0	0	0	0	0
Thymus												
vacuolated histiocytes	0	0	0	0	4	0	0	0	3	0	2	1
Urinary bladder n =	**10**	**0**	**0**	**0**	**7**	**10**	**10**	**0**	**0**	**0**	**2**	**6**
hyperplasia, epithelium	0	0	0	0	1	0	0	0	0	0	0	0
Uterus n =							**10**	**9**	**9**	**7**	**2**	**6**
↓ myo/endometrium							0	0	0	0	2	0
Vagina n =							**10**	**0**	**2**	**1**	**2**	**6**
epithelial mucification							0	0	0	0	2	1

Toxicokinetics: Plasma analysis information was not provided in the study report (Serial No 009), although a summary data table was provided in the briefing package (Serial No. 007). This information is summarized in Table 6. Following SCH 34117 administration Tmax increased

with increasing dose from 1-4 hours to 24 hours. Generally Cmax increased proportionally while AUC increased supra-proportionally. Systemic exposure was 2-3 fold greater in females than in males. Exposure to SCH 34117 following 120 mg/kg loratadine administration was similar to exposure following 60 mg/kg SCH 34117 administration, although the Tmax was reduced. The similarity in exposure may explain the greater comparability in toxicity of loratadine with 60 mg/kg SCH 34117 than with 120 mg/kg SCH 34117. The sponsor was requested to submit the full data set during a meeting on 8/7/98 (see meeting minutes).

Table 6. Toxicokinetics of SCH 34117 and loratadine in the rat.

Dose (mg/kg/d)	Analyte	Gender	T_{max} (hr)	C_{max} (ng/ml)	$AUC_{(0\text{-}24\ hr)}$ (ng.h/ml)
3 (SCH 34117)	SCH 34117	M	4	71.2	506
		F	1	134	1619
30 (SCH 34117)	SCH 34117	M	8	990	17088
		F	8	1780	36664
60 (SCH34117)	SCH 34117	M	8	1653	30447
		F	24	2869	57513
120 (SCH34117)	SCH 34117	M	24	3951	77579
		F	ND	ND	ND
120 (Loratadine)	SCH 34117	M	4	1774	37444
		F	1	2763	52232
	Loratadine	M	1	495	3395
		F	2.5	533	4483

M: males. F: females ND: not determined

The low-dose of 3 mg SCH 34117/kg/day in males and the lower mid-dose of 30 mg/kg/day in females were selected as the NOAELs for this study due to the histopathological findings in the liver and histiocytosis and the presence of vacuolated histiocytes in various organs. Target organs of toxicity were identified as the liver, kidneys, lung, spleen, thymus and the female reproductive organs.

Monkey, 28-day Oral (Gavage) Toxicity

[redacted] *Study No.:* [redacted] *Study No.:* 98089 *Volume:* 1

Study Dates: Starting date 3/26/98; report issued 7/29/98
Testing Lab: [redacted]
Test Article: SCH 34117 (Batch 97-34117-X-03-RA; purity not reported) in 0.4% (w/v) aqueous methylcellulose
Concentration: 0.6-2.4 mg SCH 34117/ml; 2.4 mg loratadine/ml
Dose Volume: 5 ml/kg/day
GLP: This report was unaudited.
QA report: No.

Methods: Cynomolgus monkeys (approximately 2 years of age; 2-4 kg) were assigned to the following treatment groups:

Dose (mg SCH 34117 /kg/day):	0	3	6	12	**12 mg loratadine/kg/day**
No./sex	4	4	4	4	4

Each monkey received a daily dose of vehicle, test drug or comparative dose of loratadine by oral (gavage) administration for 28 days. The following observations were made:

Clinical observation . . . twice daily
Body weight . . . . . weekly
Food consumption . . . . daily
Water consumption . . . not assessed
Ophthalmoscopy . . . . . once pretest and Week 4
Veterinary exam. . . . . twice pretest and Weeks 2 and 4; includes body temperature, respiratory rate, heart rate, blood pressure and ECG measured 4 hours after dosing to coincide approximately with Tmax.
Hematology . . . . . twice pretest and Day 29
Clinical chemistry . . . . twice pretest and Day 29
Urinalysis . . . . . twice pretest and Day 29
Enzyme induction . . . . not assessed
Organ weights . . . . . at sacrifice; (for specific organs see Addendum, page 14)
Gross pathology . . . . . at sacrifice
Histopathology . . . . . at sacrifice; organs/tissues from vehicle control, comparative control and high-dose SCH 34117, monkeys dying prior to scheduled necropsy and all gross lesions, organs in all groups identified as target organs from high-dose group (for specific tissues/organs see Addendum, page 14).
Toxicokinetics . . . . . Day 1 and during Week 3; samples collected at 1.5, 2.5, 4, 8, 12 and 24 hours post-dose; measured for SCH 34117 and loratadine (loratadine-dosed animals only) using [redacted].

Results: Results are summarized in tables 7-9.

Mortality: None.

Clinical Observations: No treatment-related effects were observed other than diarrhea in one high-dose male and female monkey.

Body Weight: No toxicologically significant treatment-related effects were observed.

Food Intake: No toxicologically significant treatment-related effects were observed.

Physical examination: No toxicologically significant treatment-related effects on body temperature, respiratory rate, heart rate.

Ophthalmoscopy: No toxicologically significant treatment-related effects were observed.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: No toxicologically significant treatment-related effects.

Urinalysis: No significant treatment-related effects were observed. However, the 4- and 24-hour urine volume in treated males tended to be reduced, although these findings were not statistically significant (Table 7).

Table 7. Clinical findings in monkeys administered SCH 34117.

	Males				Females			
Dose (mg /kg/d)	3	6	12	Lorat.	3	6	12	Lorat.
Urinalysis								
4-hr volume (Day 28)								
%Δ vs control group	↓42	↓36	↓48	↓42	↓39	↓18	↑32	↓30
24-hr volume (Day 29)								
%Δ vs control group	↓62	↓26	↓59	↓76	↓18	↓18	↑46	↓25

Organ Weights: No toxicologically significant treatment-related effects were observed.

Gross Pathology: No toxicologically significant treatment-related effects were observed.

Histopathology: The sponsor reported that preliminary evaluation of histopathology data indicate that there are no significant treatment-related findings. However, c-cell hyperplasia in the thyroid of one high-dose male and mineralization of the ovary in three high-dose females were noted (Table 8). Animals from the lower-dose groups were not examined except for one low-dose female which did not develop mineralization in the ovary. A previous 14-day study demonstrated ovarian mineralization in 2 of 3 rats administered 6.5 mg/kg; c-cell hyperplasia was not observed at 14 days. Thus, the uncertain treatment-relatedness of these findings suggest that the sponsor should examine the thyroid and ovary samples from the lower dose groups. Additionally, inflammation and infiltration of lymphoid cells were noted in various tissues, although the dose-dependency of these findings is unclear, especially when data from males and females are combined. Similar findings were observed at 14 days. Generally, findings in the loratadine-treated group were similar to those of the high-dose SCH 34117 group including the finding in the ovary but not the thyroid.

Table 8. Histopathological changes after 28-day administration in monkey.

	Males					Females				
Dose (mg/kg/d)	0	3	6	12	Lorat.	0	3	6	12	Lorat.
Kidney n =	4	0	0	4	4	4	0	0	4	4
-infiltrating cell,lymphoid	1	0	0	3	3	3	0	0	3	4
Salivary gland										
-infiltrating cell,lymphoid	0	0	0	2	2	4	0	0	4	4
Skeletal muscle										
- inflammation - chronic	1	0	0	2	1	0	0	0	0	2
Stomach										
-inflammation - chronic	0	0	0	0	0	0	0	0	1	0
Thyroid gland										
- hyperplasia, c-cell	0	0	0	1	0	0	0	0	0	0
Ovary n =						4	1	0	4	4
- mineralization						0	0	0	3	3

Toxicokinetics: Plasma analysis information was not provided in the study report (Serial No 009), although a summary data table was provided in the briefing package (Serial No. 007). This information is summarized in Table 9. Following SCH 34117 administration Tmax was 1.5 to 2.5 hours, increasing to 4 hours at the high dose. Cmax and AUC increased proportionally from the low to high dose on Day 1, although the mid-dose produced exposures that were lower than would be expected, and increased sub-proportionally on Day 14. Exposure to SCH 34117 following 12 mg loratadine/kg administration was similar to exposure following 6 mg SCH 34117/kg administration on Day 1 but slightly greater than on Day 14. Tmax was similar (2.5 hours) to that of administered SCH 34117. Drug accumulation was apparent regardless of administration form. Systemic exposure was 71-75% greater on Day 14 than on Day 1at the two lower doses of SCH 34117 and 19% greater at the high dose while exposure to SCH 34117 following loratadine administration was 2.8-fold greater on Day 14 than on Day 1. The sponsor was requested to submit the full data set during a meeting on 8/7/98 (see meeting minutes).

Table 9. Toxicokinetics of SCH 34117 and loratadine in the monkey.

		Day 1			Day 14		
Dose (mg/kg/d)	Analyte	T_{max} (hr)	C_{max} (ng/ml)	$AUC_{(0\text{-}24\ hr)}$ (ng.h/ml)	T_{max} (hr)	C_{max} (ng/ml)	$AUC_{(0\text{-}24\ hr)}$ (ng.h/ml)
3 (SCH 34117)	SCH 34117	2.5	189	1836	2.5	252	3153
6 (SCH 34117)	SCH 34117	2.5	232	2572	1.5	369	4506
12 (SCH 34117)	SCH 34117	4	870	8728	4	768	10388
12 (Loratadine)	SCH 34117	2.5	210	2218	2.5	458	6217

The NOAEL in males is at least 6 mg SCH 34117/kg/day due to thyroid hyperplasia. A NOAEL in females could not be determined due to the presence of mineralization in the ovaries of high-dose animals which was not assessed in low- or mid-dose animals. A final determination of the NOAELs is pending the submission of histopathology data for the thyroid and the ovary from the low- and mid-dose groups. Target organs of toxicity may include the thymus and the ovary.

Summary of Toxicology

Subacute, oral (gavage) studies were performed for 28 days in rats (3, 30, 60 and 120 mg/kg SCH 34117 and 120 mg/kg loratadine) and monkeys (3, 6 and 12 mg/kg SCH 34117 and 12 mg/kg loratadine). In rats, treatment-related mortality was observed in the high-dose groups. The primary target organs of toxicity were the liver, kidneys, lung, spleen, thymus and the female reproductive organs, although systemic phospholipidosis (vacuolation, histiocytosis) was observed in numerous organs, primarily at the upper-mid and high dose. Observed toxicities included increased lung, liver and kidney (female only) weights and decreased spleen, thymus and ovary weights, changes associated with centrilobular hepatic hypertrophy and vacuolation, cortical tubular necrosis, alveolar proteinosis (females), and congestion and lymphoid depletion of the thymus. Other histological findings included atrophy of the ileum, mammary gland hyperplasia, and pancreatic acini necrosis (one high-dose female). Other findings included clinical signs (enlarged, few or no feces, salivation, hunched posture, thin appearance, labored/rapid respiration, respiratory distress/respiratory sounds-rales, paleness, and wetness in the urogenital region, reduced body weight and food consumption), and gross changes (impacted colon, a deformed liver in a high-dose female, an enlarged seminal vesicle in a high-dose male, lung discoloration, enlarged mandibular lymph nodes and dilatation of numerous organs of one high-dose female and male). Findings in loratadine-treated animals were more comparable with animals administered 60 mg SCH 34117/kg than with 120 mg/kg SCH 34117, due likely to comparable systemic SCH 34117 exposures observed following administration. NOAELs of 3 mg/kg for males and 30 mg/kg for females were selected.

In the monkey, potential target organs of toxicity included the thymus in males and the ovaries. Hyperplasia of the c-cell was reported in one high-dose male and mineralization of the ovary in 3 of 4 high-dose females and active control animals were reported. These findings are currently of unclear significance since, although they were observed in the high-dose group, the low- and mid-dose groups were not assessed. Other findings included consistently reduced urine volume (not statistically significant) and diarrhea in one high-dose male and female. Loratadine-treated animals demonstrated similar toxicity profiles with animals given the high-dose SCH 34117, although the active control animals displayed similar, though slightly greater, exposure to SCH 34117 as the mid-dose SCH 34117 group. Thus, a NOAEL of at least 6 mg/kg was selected for males due to the thyroid finding. A NOAEL in females, however, could not be determined. A final selection of the NOAELs awaits submission of the histopathology data for the thyroid and ovaries from the low- and mid-dose groups.

Addendum: Histopathology inventory for IND [redacted]

Study No.	P-6526	D18289	SN 98088	P-6527	SN 98089
Duration	14-day	14-day	28-day	14-day	28-day
Species	rat	rat	rat	monkey	monkey
Adrenals	X*		X*	X*	X*
Aorta	X		X	X	X
Bone marrow smear	X		X	X	
Bone (femur)	X		X	X	X
Bone (rib)				X	X
Bone (strenum)	X		X	X	X
Brain:	X*		X*	X*	X*
Cecum	X		X	X	X
Cervix			X		
Colon	X		X	X	X
Duodenum	X		X	X	X
Epididymis	X*		X*	X*	X
Esophagus	X		X	X	X
Eye	X		X	X	X
Fallopian tube					
Fat					
Gall bladder				X	X
Gross lesions	X	X		X	X
Harderian gland	X		X		
Heart	X*		X*	X*	X*
Hyphophysis					
Ileum	X		X	X	X
Injection site	NA	NA	NA	NA	NA
Jejunum	X		X	X	X
Kidneys	X*	X*	X*	X*	X*
Lacrimal gland				X	X
Larynx					
Liver	X*	X*	X*	X*	X*
Lungs	X*	X*	X*	X*	X*
Lymph nodes, cervical					
Lymph nodes (LALN)					
Lymph nodes, mandibular	X		X	X	X
Lymph nodes, mediastinalis					
Lymph nodes, mesenteric	X		X	X	X
Mammary gland	X		X	X	X
Nasal cavity					
Optic nerves			X		
Ovaries	X*		X*	X*	X*
Oviduct					
Pancreas	X	X	X	X	X
Parathyroid	X		X	X	X
Peripheral nerve					
Pharynx					
Pituitary	X*		X*	X*	X*
Prostate	X*		X*	X*	X*
Rectum					
Salivary gland	X*		X*	X*	X*
Sciatic nerve	X		X	X	X
Seminal vesicles	X		X	X	X
Skeletal muscle	X		X	X	X
Skin	X		X	X	X
Spinal cord	X		X	X	X
Spleen	X*		X*	X*	X*
Stomach	X		X	X	X
Testes	X*		X*	X*	X*
Thoracic Limb	X				
Thymus	X*		X*	X*	X*
Thyroid	X*		X*	X*	X*
Tongue	X		X	X	X
Trachea	X		X	X	X
Urinary bladder	X		X	X	X
Uterus	X*		X*	X*	X*
Uterine horn					
Vagina	X		X	X	X

* Organ weight obtained

OVERALL SUMMARY AND EVALUATION

The identified target organs of toxicity in a 14-day oral (gavage) study in rats (15, 60 and 240 mg/kg SCH 34117) were the liver, lung, kidneys and pancreas, although the complete histologic assessment may have identified others. Observed toxicities included increased liver, lung and kidney relative weights associated with histologic findings (vacuolation, necrosis, congestion and foam cells) as well as clinical signs at the high dose (chromodacryorrhea, chromorhinorrhea, slow righting reflex, salivation), reduced body weights and food consumption, increased leukocyte counts, and increased levels of GPT, GOT and BUN. In the current 28-day oral (gavage) rat study (3, 30, 60 and 120 mg/kg SCH 34117 and 120 mg/kg loratadine), similar findings were observed as well as additional ones which may be the result of the extended dosing duration. Treatment-related mortality was observed in the high-dose groups. The primary target organs of toxicity were the liver, kidneys, lung, spleen, thymus and the female reproductive organs, although systemic phospholipidosis was observed in numerous organs. Pancreatic toxicity was not observed except for acinus vacuolation in one high-dose female. Observed toxicities included increased lung, liver and kidney (female) weights and decreased spleen, thymus and ovary weights; changes associated with centrilobular hepatic hypertrophy and vacuolation, cortical tubular necrosis, alveolar proteinosis (females), and congestion and lymphoid depletion of the thymus. Other findings included clinical signs, gross changes, and, for the most part, slight changes in hematologic and clinical chemistry parameters which demonstrated limited evidence of a dose-response relationship. The observed toxicities of loratadine-treated animals were comparable to animals administered 60 mg/kg SCH 34117 due, probably, to similar systemic exposures of SCH 34117, but generally less than the toxicity in animals administered 120 mg/kg SCH 34117. NOAELs of 3 mg/kg for males and 30 mg/kg for females were selected.

In the monkey, potential target organs of toxicity after 28-days administration (3, 6 and 12 mg/kg SCH 34117 and 12 mg/kg loratadine) included the thymus (hyperplasia of the c-cell) in males and the ovaries (mineralization). These findings are currently of unclear significance since the low- and mid-dose groups were not assessed. Also, neither finding had been reported in previous studies with loratadine. Other findings included reduced urine volume (not statistically significant) and diarrhea in one high-dose male and female. Increased triglyceride levels and urine osmolarity, observed in a 14-day study, were not noted at 28 days (enzyme levels not assessed in the 28 day study). Loratadine-treated animals demonstrated similar toxicity profiles with animals given the high-dose SCH 34117, although the active control animals displayed similar, though slightly greater, exposure to SCH 34117 as the mid-dose SCH 34117 group. Thus, a NOAEL of at least 6 mg/kg was selected for males due to the thyroid finding. A NOAEL in females, however, could not be determined. A final selection of the NOAELs awaits submission of the histopathology data for the thyroid and ovaries from the low- and mid-dose groups.

The sponsor proposed a multiple-dose study to examine the clinical efficacy and safety of SCH 34117 (5 or 7.5 mg/day) for 4 weeks in patients with seasonal allergic rhinitis in addition to two two-week studies at similar doses. The two-week studies are supported by the preclinical studies

submitted in the Original IND Review (dated 5/22/98). The submitted 28-day rat study supports the proposed clinical doses of 5 and 7.5 mg SCH 37114/day since it resulted in NOAELs of 3 and 30 mg/kg/day in males and females, respectively. Similarly, a NOAEL of at least 6 mg/kg in male monkeys was identified in the 28-day study and also supports the proposed clinical doses. However, a NOAEL, could not be determined in the 28-day monkey study due to histological findings at the high dose which were not assessed at the lower doses. The sponsor initiated the proposed clinical trials prior to formal review of the 28-day preclinical studies based upon a preliminary review and results of previous preclinical and clinical studies. However, the sponsor should evaluate and submit for review the pertinent histological data which may be used in determining appropriate doses in future clinical trials.

RECOMMENDATIONS

1. The sponsor should evaluate the thyroid glands and ovaries from low- and mid-dose animals of the 28-day monkey study (Study number 98089) due to the presence of c-cell hyperplasia in the thyroid gland and mineralization in the ovaries of high-dose animals. Also, a clarification of the term "mineralization" should be provided (i.e., type of minerals).

2. In the future, the sponsor should evaluate tissue histopathology from low- and intermediate-dose groups when high-dose groups show an increase in incidence and/or severity compared to control groups.

3. As requested in the meeting of 8/7/98, the sponsor should submit the line listings for the toxicokinetic data from the 28-day rat and monkey studies (Study numbers 98088 and 98089, respectively).

/S/

Timothy J. McGovern, Ph.D., Pharmacologist

Draft Comments for Letter to Sponsor:

1. Due to the presence of c-cell hyperplasia in the thyroid gland and mineralization in the ovaries of high-dose animals of the 28-day monkey study (Study number 98089), please evaluate these tissues from low- and mid-dose animals and submit the findings. Also, please clarify the term "mineralization" (i.e., type of minerals).

2. In future toxicity studies, tissues from other dose groups should be examined if there are any macroscopic findings in the low- or mid-dose groups or if an increase in the incidence of histological findings is observed in high-dose animals for a particular tissue.

3. As requested in the meeting of 8/7/98, please submit the line listings for the toxicokinetic data from the 28-day rat and monkey studies (Study numbers 98088 and 98089, respectively).

Original IND ——
CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/A. Trontell
HFD-570/L. Cobbs
HFD-570/T.J. McGovern