

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

Summary of Toxicology

Acute, oral and intraperitoneal studies were performed in mice and rats, as well as an oral study in monkeys. Maximum nonlethal doses, oral and intraperitoneal, of 250 and 25 mg/kg, respectively, and minimum lethal doses of 500 and 50 mg/kg, respectively, were observed in mice. In the rat, maximum nonlethal doses, oral and intraperitoneal, were 125 and 25 mg/kg, respectively, and the minimal lethal doses were 250 and 50 mg/kg, respectively. No mortalities were observed in the acute monkey study at doses up to 250 mg/kg. Targets of acute toxicity appeared to be the CNS (hypoactivity, ataxia, convulsions, tremors, prostration) and respiratory system (gasping, increased respiratory rate) in mice and rats, and the gastrointestinal system (emesis, diarrhea) in monkeys.

Subacute, oral studies were performed for 14 days in rats (low-dose study: 1, 4 and 8 mg/kg SCH 34117 and 10 mg/kg loratadine; high-dose study: 15, 60 and 240 mg/kg SCH 34117) and monkeys (1.6, 3.2 and 6.5 mg/kg SCH 34117 and 8 mg/kg loratadine). In the low-dose rat study, no target organs of toxicity were observed and the NOAEL was identified as 8 mg/kg. In the high-dose study, however, the identified target organs of toxicity were the liver, lung, kidneys and pancreas, although not all target organs may have been identified due to the limited histological examination included in this study. Observed toxicities included increased liver, lung and kidney relative weights associated with histologic findings (vacuolation, necrosis, congestion and foam cells). Other findings included 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). Since adverse findings were observed at all doses tested, a NOAEL was not identified for this study. In the monkey, no target organs of toxicity were clearly identified, although a number of histologic findings were of slightly increased incidence at the high-dose compared to controls. Since the sponsor did not evaluate tissues from animals administered lower doses and since small numbers of animals were used, it was not possible to clearly discern the significance of the findings. Other findings in the monkey included increased triglyceride levels and urine osmolarity, as well as increased levels of EROD and PROD. The high dose of 6.5 mg/kg was selected as the NOAEL for this study.

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Addendum: Histopathology inventory for IND 55,364.

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

* Organ weight obtained

REPRODUCTIVE TOXICOLOGY

Rat (oral) Pilot Segment I Reproductive Toxicity Study

Report No.: P-6821 Study No.: 97111 Volume: 1.16

Study Dates: Starting date 9/12/97; report issued 2/10/98
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch 97-11001-139; purity = 99.8%) in 0.4% (w/v) aqueous methylcellulose
Concentration: 1.2-9.6 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 rats were assigned to the following treatment groups:

Dose (mg /kg/day):	0	6	24	48
No./sex	8	8	8	8

All rats were dosed once daily by esophageal intubation. Males were dosed for 21 days prior to mating and throughout the mating period. Females were dosed for 14 days prior to and throughout mating until Gestation Day 7. After the pre-mating dosing period, each female was placed with a male from the same dose group for seven days. Each morning, females were checked for evidence of mating, at which time mated females were housed individually. In the absence of mating after seven days, females were placed with a proven male from the same dose group for up to seven additional days.

Results: Results are summarized in Table 21.

Mortality: One high-dose female was found dead on the first day of mating (15 days of dosing). Death was associated with large fecal pellets for five days followed by a period of reduced fecal pellets and a 7.4% body weight loss during the first week of dosing which was not regained.

Clinical signs: Reduced stool and large fecal pellets were noted in mid- and high-dose animals, primarily during the pre-mating dosing period. No stool was observed in one high-dose animal.

Body weight: Pre-mating body weight gain of high-dose males and females was reduced (59 and 116%, respectively). The high-dose treatment effect was still present in females during the gestation period as body weight gain was reduced by 54% compared to control animals on Gestation Day 6. By Gestation Day 14, body weight gain was reduced by 18%. May be related to reduced food consumption since this was observed at a similar dose in an embryo-fetal development study in rats.

Necropsy: No abnormal findings were observed.

Mating and fertility indices: Reduced male and female mating indices (43 and 29%, respectively) were noted at the high-dose. However, there were no clear effects on fertility. Also, an increased time to identify positive evidence of mating (143 to 325%) was noted at the mid- and high-dose.

Vaginal cytology: No abnormalities were observed.

Uterine/ovarian exam: Effects were limited to the high-dose group (data was available for 4 females) and included reduced corpora lutea/animal, fewer implantation sites and fetuses and an increased number of early resorptions/animal. Reduced implantation sites and fetuses/animal in the mid-dose group were due to decreases in one animal and are not considered drug-related.

Table 21. Results of Pilot Segment I reproductive study in rats.

Dose (mg/kg)	Males				Females			
	0	6	24	48	0	6	24	48
Body wt gain, pre mating								
% Δ vs control		↓18	↓11	↓59	↑28	↑34	↓116	
Body wt gain, gestation Day 6								
% Δ vs control					↓18	↓8	↓54	
Clinical observations								
<u>Premating period:</u>								
-reduced stool	0	0	0	5	0	0	2	7
-large fecal pellets	0	0	4	5	0	0	8	5
-chromorrhinorrhea	0	1	0	2	0	0	0	0
<u>Gestation period:</u>								
-reduced stool					0	0	0	1
-large fecal pellets					0	0	2	0
Precoital Interval								
% Δ vs control					↑17	↑143	↑325	
Mating Index (%)								
% Δ vs control		no Δ	no Δ	↓43	no Δ	no Δ	↓29	
Fertility Index (%)								
% Δ vs control		no Δ	↓13	↓13	no Δ	↓13	↓20	
Corpora lutea (#/animal)								
% Δ vs control					↓2	↓6	↓21	
Implantation sites (#/animal)								
% Δ vs control					↓3	↓26	↓23	
Fetuses (#/animal)								
% Δ vs control					↓1	↓28	↓38	
Resorption (#/animal)								
% Δ vs control					↓33	↑11	↑233	
Preimplantation loss								
% Δ vs control					↑39	↑789	↑39	
Postimplantation loss								
% Δ vs control					↓33	↑11	↑233	

A NOAEL of 24 mg/kg was identified in this study, while the lethal dose was 48 mg/kg. Thus, the oral high-dose in the definitive rat fertility study should be less than 48 mg/kg, in concurrence with the sponsor's conclusion. It should be noted that ICH Guidelines for Detection of Toxicity to Reproduction (ICH S5A and S5B) recommend pre mating administration for males

to be at 4-weeks in duration assuming that a toxicity study of at least 1-month duration demonstrates no effects on spermatogenesis (pre-mating administration of 9-10 weeks in the case of positive findings); the present dose-ranging study included a 3-week pre-mating administration for males. The sponsor should consult the ICH Guidelines when performing the definitive Segment I study.

Rat (oral) Pilot Segment II Reproductive Toxicity Study

Report No.: P-6718 Study No.: 97113 Volume: 1.16

Study Dates: Starting date not provided; report issued 12/22/97
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch 97-11001-139; purity = 99.8%) in 0.4% (w/v) aqueous methylcellulose
Concentration: 0.6-9.6 mg SCH 34117/ml
Dose Volume: 5 ml/kg/day
GLP: This report was unaudited.
QA report: No.

Methods: Crl:CD(SD)BR VAF/Plus female rats (~12 weeks old) were assigned to the following treatment groups:

Dose (mg /kg/day):	0	3	12	24	48
No./dose group	6	6	6	6	6

All rats were dosed once daily by esophageal intubation from Days 6-15 after mating.

Results: Results are summarized in Table 22.

Mortality: None.

Clinical signs: None

Body weight: Maternal body weight gain was dose-dependently reduced during the dosing period (significant in upper-middle and high-dose animals, 52 and 72%, respectively; $p < 0.01$).

Necropsy: No abnormal findings were observed.

Uterine/ovarian exam: All rats were pregnant and the numbers of corpora lutea, implantations, resorptions and fetuses in SCH 34117-treated groups were comparable to the control group.

Fetal body weight: The mean fetal body weights in the high-dose group were significantly lower ($p < 0.01$) than the controls (12.5%).

Fetal examination: Other than the presence of an omphalocele in one upper-middle dose fetus, no abnormal changes were observed. This malformation is considered to be a common finding in rats and not a drug-related effect.

Table 22. Results of Pilot Segment II reproductive study in rats.

<i>Dose (mg/kg)</i>	<i>Females</i>				
	<i>0</i>	<i>3</i>	<i>12</i>	<i>24</i>	<i>48</i>
Maternal body wt gain -dosing period					
% Δ vs control		↓5	↓28	↓52	↓72
Fetal body wt					
% Δ vs control		↓4	↓4	↓9	↓12

Drug treatment did not induce adverse clinical effects and was not teratogenic in the offspring. A NOAEL of 12 mg/kg was identified in this study based upon the significant reduction in maternal body weight gain observed in upper-mid and high-dose animals. The high-dose in the definitive embryo-fetal development rat study should not exceed 48 mg/kg due to the combined reduction in maternal and fetal body weights observed in the high-dose group.

Rabbit (oral) Dose Range-finding Segment II Reproductive Toxicity Study

Report No.: P-6719 *Study No.:* 97115 *Volume:* 1.16

Study Dates: Starting date 7/18/97; report issued 2/4/98
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch 97-11001-139; purity = 99.8%) in 0.4% (w/v) aqueous methylcellulose
Concentration: 12.5-150 mg SCH 34117/ml
Dose Volume: 2 ml/kg/day
GLP: This report was unaudited.
QA report: No.

Methods: Hra (NZW) SPF rabbits (females; ~ 6 months of age; unmated in Phase I and mated in Phase II) were assigned to the following treatment groups:

<i>Dose (mg /kg/day):</i>	<i>0</i>	<i>25</i>	<i>50</i>	<i>100</i>	<i>150</i>	<i>225</i>	<i>300</i>
No./dose group - Phase I	1		1	1	1	1	1
No./dose group - Phase II	4	4	4	4			

All rats were dosed once daily by gastric intubation. In Phase I, rabbits were given 2 to 7 doses depending upon when signs of toxicity occurred. In Phase II, mated female rabbits were dosed from Day 7 through Day 19 after mating.

Results:

Phase I: Deaths occurred at doses \geq 150 mg/kg/day (7 doses at 150 mg/kg, 3 doses at 225 mg/kg and 2 doses at 300 mg/kg). At 150 and 225 mg/kg, reduced stool was observed prior to death. Animals given 100 or 50 mg/kg were dosed for 5 or 3 days, respectively, and observed for 7 days. No unusual clinical signs or necropsy findings were observed. Food consumption was reduced in rabbits dosed with \geq 100 mg/kg (graded as "ate poorly") and body weights were suppressed in all rabbits during the dosing period (3-13%). Food consumption in the rabbit given 100 mg/kg returned to normal within a day after dosing was stopped.

Phase II: Based upon the results of Phase I, in which animals dosed with ≥ 150 mg/kg/day died, animals in Phase II were administered 0, 25, 50 or 100 mg/kg/day.

Mortality: Three high-dose females were found dead on Gestation Days 13, 17 and 23, respectively. A fourth had blood in the litter pan on Day 27, aborted on Day 28 and was subsequently sacrificed.

Clinical signs: Clinical signs observed in high-dose rabbits prior to death included lack of stool, soft stool, small fecal pellets and a reduced number of fecal pellets. In the mid-dose group findings included reduced numbers of fecal pellets, abnormally shaped pellets, and soft stool. No unusual clinical signs were noted in the low-dose group except for one female which had a slight amount of blood in the litter pan on Days 26-29 and red vaginal discharge on Day 26.

Body weight: Reduced in 4 high-dose animals that died.

Food Consumption: Reduced in 4 animals that died. Slightly decreased in mid-dose group.

Necropsy: One of the high-dose animals which died had pale tissues, lungs and kidneys, which is not considered an unusual finding in rabbits.

Uterine/ovarian exam and fetal body weight: Drug-related effects on reproduction parameters and fetal body weight were not evident in the low- and mid-dose groups. Data was unavailable for the high-dose group due to maternal mortality.

Fetal gross examination: No SCH 34117-related findings were observed. One control animal exhibited omphalocele.

A NOAEL of 50 mg/kg was identified in this study based upon the observed maternal deaths at the high-dose. Thus, the high-dose in a definitive embryo-fetal development study in rabbits should be between 50 and 100 mg/kg/day, in concurrence with the sponsor's conclusion.

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Rabbit (oral) Segment II Reproductive Toxicity Study
Report No.: P-6802 *Study No.:* 97116 *Volume:* 1.9

The sponsor submitted only preliminary data tables of body weights, necropsy observations, reproduction data, fetal gross observations and skeletal observations. The following review is based upon the summary provided in the Integrated Toxicology Summary (Volume 1.3).

Study Dates: Starting date 9/12/97; report issued 2/10/98
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch 97-11001-139 and 97-34117-X-02RA; purity = NA) in 0.4% (w/v) aqueous methylcellulose
Concentration: 7.5-30 mg SCH 34117/ml
Dose Volume: 2 ml/kg/day
GLP: The study was an unaudited report.
QA report: No.

Methods: Hra (NZW) SPF rabbits (females; ~ 5 to 6 months of age) were assigned to the following treatment groups:

Dose (mg /kg/day):	0	15	30	60
No. teratology study	20	20	20	20
No. plasma analysis	3	3	3	3

All rabbits were dosed once daily from Day 7 through Day 19 after mating by gastric intubation. The following observations were made:

Clinical observation: . . . daily
 Body weight: Days 0, 7, 10, 13, 16, 19, 22, 25, 28 and 30
 Food consumption: . . . gestation days 0-30
 Plasma Analysis Days 19/20 (1, 3, 12 and 24 hours)
 Necropsy/C-section: . . . Day 30
 Uterine/ovarian exam: . number of implantation sites, corpora lutea, fetuses and resorptions
 Fetal body weights Day 30
 Fetal gross/skeletal exam . at sacrifice

Results:

Mortality: None.

Clinical signs: A change in formed stool was observed in most mid- and high-dose rabbits and some low-dose rabbits.

Body weight: Mean body weight gain in high-dose rabbits was significantly reduced compared to controls over gestation days 10-16 (125%).

Food Consumption: A slight decrease in food consumption was noted in high-dose animals on scattered days throughout the study.

Necropsy: No treatment-related effects.

Uterine/ovarian exam: The mean number of resorptions was increased in the high-dose group.

Plasma analysis: Exposure to SCH 34117 increased dose-proportionally between 15 and 30 mg/kg and supra-proportionally between 30 and 60 mg/kg (mean AUCs of 1660, 4087 and 12987 ng.hr/ml at doses of 15, 30 and 60 mg/kg, respectively). Plasma concentrations peaked within 3 hours.

Fetal body weight: No treatment-related effects were observed.

Fetal gross/skeletal examination: No SCH 34117-related findings were observed.

A NOAEL was not identified in this study due to the preliminary and incomplete nature of the submission. The sponsor, however, concluded in this summary that the NOAEL for both maternal and *in utero* effects was 30 mg/kg based upon the higher incidence of resorptions in the high-dose group and that the drug provided no evidence of teratogenic potential under the conditions of this study. The sponsor should submit a complete report of this study.

Summary of Reproductive Toxicology Studies

Pilot Segment I and II studies in rats and a pilot Segment II study in rabbits were submitted by the sponsor. In addition, preliminary data tables for the definitive Segment II study in rabbits were submitted. In the Segment I study, most treatment-related effects in rats orally administered SCH 34117 (6-48 mg/kg), were observed at the high-dose and included one death (female), reduced stool, large fecal pellets, reduced pre-mating body weight gain of males and females and reduced male and female mating indices, although no clear effects on fertility were observed. An increased time to identify positive evidence of mating (143 to 325%) was also noted at the mid- and high-dose. Reproductive effects were limited to the high-dose group and included reduced corpora lutea/animal, fewer implantation sites and fetuses and an increased number of early resorptions/animal. A NOAEL of 24 mg/kg and a lethal dose of 48 mg/kg were identified for this study. The sponsor should consult ICH guidelines for reproductive toxicology studies when initiating the definitive Segment I study since males were dosed for only 21 days prior to mating in this pilot study. In the pilot Segment II study, female rats were dosed (3-48 mg/kg) once daily by esophageal intubation. Significant findings included a dose-dependent reduction in maternal body weight gain during the dosing period (upper-middle and high-dose animals, 52 and 72%, respectively) and reduced fetal body weights at the high-dose (12.5%). A NOAEL of 12 mg/kg was identified in this study. The oral high-dose in the definitive rat Segment I study should be less than 48 mg/kg and the high-dose in the definitive Segment II study should not exceed 48 mg/kg.

In the pilot Segment II study in rabbits (dosed 25 to 100 mg/kg), three high-dose females were found dead and one was aborted during gestation. Clinical signs included lack of stool, soft stool, small fecal pellets, reduced number of fecal pellets and reduced body weight and food consumption. Effects on reproduction parameters were unavailable for the high-dose group due to maternal mortality and were not evident in the low- and mid-dose groups. In addition, no SCH 34117-related findings were observed during the fetal examination. A NOAEL of 50 mg/kg was identified in this study and the high-dose in a definitive embryo-fetal development study in rabbits should be between 50 and 100 mg/kg/day. Preliminary findings from the definitive Segment II study (15-60 mg/kg) included a change in formed stool in most mid- and high-dose rabbits and some low-dose rabbits and a reduced mean body weight gain in high-dose rabbits (125%). Although an increased number of resorptions occurred in the high-dose group, no changes in fetal body weight or gross/skeletal examinations were observed. Exposure increased dose-proportionally between 15 and 30 mg/kg and supra-proportionally between 30 and 60 mg/kg and plasma concentrations peaked within 3 hours. The NOAEL for both maternal and *in utero* effects was 30 mg/kg. The sponsor should submit a complete report of this study when it becomes available.

GENETIC TOXICOLOGY

In vitro Reverse Mutation Assay (Ames Assay)

Report No.: P-6609 Study No.: 97027 Volume: 1.16

Study endpoint: Mutagenicity
Study Dates: Starting date 2/20/97; report issued 9/17/97
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch 97-11001-139) diluted in 50% ethanol
GLP: The study was accompanied by a signed GLP statement.
QA report: Yes.

Methods: SCH 34117 was assayed in 5 Salmonella tester strains and 1 E. coli strains ± metabolic activation by Aroclor 1254-induced rat liver S9 fraction. The following strains and positive controls were used in 2 plate incorporation tests:

Strain	Positive Controls Without S9 (µg/plate)	Positive Controls With S9 (µg/plate)
TA 1535	sodium azide (5)	2-aminoanthracene (2.5)
TA 97a	9-aminoacridine (75)	2-aminoanthracene (2.5)
TA 98	2-Nitrofluorene (5)	2-aminoanthracene (2.5)
TA 100	sodium azide (5)	2-aminoanthracene (2.5)
TA 102	Cumene hydroperoxide (50)	2-aminoanthracene (5)
WP2 uvrA	N-Ethyl-N'-nitro-N-nitrosoguanidine (2)	2-aminoanthracene (20)

SCH 34117 and positive controls were dissolved in 50% ethanol. A dose-ranging assay was performed to determine cytotoxicity (a reduction in revertant colony counts by ~ 30%, inhibition of background bacterial lawn growth and "additional factors based on scientific judgment") after

a 72 hr incubation at 8 half-log concentrations (1.6-5000 µg/plate). Based upon the results of the dose-ranging study, the two mutagenicity assays were conducted at the following concentrations:

Bacterial strain	Phase	EXP 1 Doses (µg/plate)	EXP 2 Doses (µg/plate)
TA 1535	nonactivation	31.3, 62.5, 125, 250, 500	62.5, 125, 250, 500, 1000
TA 97A	nonactivation	3.91, 7.81, 15.6, 31.3, 62.5	3.91, 7.81, 15.6, 31.3, 62.5
TA 98	nonactivation	62.5, 125, 250, 500, 1000	31.3, 62.5, 125, 250, 500
TA 100	nonactivation	15.6, 31.3, 62.5, 125, 250	15.6, 31.3, 62.5, 125, 250
TA 102	nonactivation	15.6, 31.3, 62.5, 125, 250	7.81, 15.6, 31.3, 62.5, 125
WP2uvrA	nonactivation	94, 188, 375, 750, 1500	188, 375, 750, 1000, 1500
TA 1535, WP2uvrA	activation	94, 188, 375, 750, 1500	94, 188, 375, 750, 1500
TA 97A	activation	7.81, 15.6, 31.3, 62.5, 125	3.91, 7.81, 15.6, 31.3, 62.5
TA 98	activation	31.3, 62.5, 125, 250, 500	31.3, 62.5, 125, 250, 500
TA 100, TA 102	activation	31.3, 62.5, 125, 250, 500	15.6, 31.3, 62.5, 125, 250

The experiments were performed using triplicate plates at each concentration incubated for 48 hours ± S9. Tests were valid if overnight bacterial cultures reached a density of 5×10^8 cells/ml, the mean number of revertant colonies/plate was within the range of the historical solvent control values of the same strain and the mean number of revertants/plate in the positive controls was at least three-fold greater than the mean of its concurrent solvent control for TA 1535, and at least two-fold greater than the mean of their respective concurrent controls for *E. coli* and other *Salmonella* strains. Tests were positive that produced increases in revertant counts, as compared to solvent controls, with or without metabolic activation, in one of the six tester strains. The magnitude of increase was at least two-fold above the solvent control for strains TA 97A, TA 98, TA 100, TA 102 and WP2uvrA, and three-fold above the solvent control for strain TA 1535. In addition, a dose-response increase of revertant counts in treated plates above that of the solvent control was observed in at least two dose levels, and the increases were reproducible in independent trials.

Results: In the dose-ranging study, significant cytotoxicity was observed without S9 activation at concentrations of ≥ 500 µg/plate for TA 1535, TA 98, TA 100 and WP2uvrA. In strains TA 97A and TA 102, cytotoxicity was observed at concentrations ≥ 50 and 158 µg/plate, respectively. Complete cytotoxicity was observed in all *Salmonella* strains at ≥ 1581 µg/plate and 5000 µg/plate WP2uvrA, respectively. Background lawn growth and microcolonies were markedly reduced in all *Salmonella* strains at 500 µg/plate, and in the WP2uvrA strain at 1581 µg/plate. In the activation phase, cytotoxicity was observed in the TA 97A strain at ≥ 158 µg/plate, ≥ 500 µg/plate for strains TA 100, TA 98 and TA 102, and ≥ 1581 µg/plate for TA 1535 and WP2uvrA. Marked cytotoxicity was observed in TA 102 at 500 µg/plate, and in all strains at 1581 µg/plate. Complete cytotoxicity was observed at 5000 µg/plate in all strains.

In the first mutagenicity trial, SCH 34117 did not increase revertant colony counts, ± S9 activation. Positive controls significantly increased the number of revertant colonies. In the nonactivation phase, cytotoxicity to revertant colonies was observed at 62.5 µg/plate for TA 97a, 125 µg/plate and above for TA 102, 250 µg/plate for TA 100, 500 µg/plate and above for TA 98 and at 1500 µg/plate for WP2uvrA. Slight cytotoxicity to the background lawn was observed at 250 µg/plate for TA 102, and marked cytotoxicity to background lawn and microcolonies were

response, or if the test article induced statistically significant increases in the number of cells with chromosome aberrations in at least two consecutive concentrations in two donors.

Results: Osmolality of the test sample was comparable to that of the solvent control. The pH of the test sample was 8.5 versus 8.0 for the solvent control. In all assays a precipitate was formed at doses of 500 to 1500 $\mu\text{g/ml}$. Lysis was also observed after dosing with 1000 and 1500 $\mu\text{g/ml}$; and at the time of washing the cell cultures at 125-1500 $\mu\text{g/ml}$.

Under the conditions tested in this assay, SCH 34117 did not induce chromosomal aberrations, polyploidy or endoreduplication in cell cultures with or without metabolic activation at doses up to 15 $\mu\text{g/ml}$ and 10 $\mu\text{g/ml}$ (male and female donor, respectively: 24 hour treatment/27 hour harvest without metabolic activation), 25 and 10 $\mu\text{g/ml}$ (male and female donor, respectively: 48 hour treatment/51 hour harvest without metabolic activation), 125 and 100 $\mu\text{g/ml}$ (male and female donor, respectively: 3 hour treatment/24 hour harvest with metabolic activation), 125 and 130 $\mu\text{g/ml}$ (male and female donor, respectively: 3 hour treatment/48 hour harvest with metabolic activation) and 90 and 50 $\mu\text{g/ml}$ (male and female donor, respectively: 3 hour treatment/24 hour harvest without metabolic activation). Doses above those cited above induced levels of cytotoxicity which lead to mitotic indices $< 40\%$ and these cultures were not assessed for chromosomal aberrations. Increased incidences of chromosome aberrations were observed in cultures dose with the positive control agents, cyclophosphamide and mitomycin C. Negative and solvent controls were within historical ranges.

SCH 34117 is considered negative for inducing chromosome aberrations in cultured whole blood human lymphocytes from a male and female donor in the presence or absence of an exogenous metabolic activation system at doses up to 125 $\mu\text{g/ml}$ in the male donor and 130 $\mu\text{g/ml}$ in the female donor.

OVERALL SUMMARY AND EVALUATION

Pharmacology: SCH 34117 displayed a 14-fold greater affinity for the H_1 -receptor than loratadine and was more up to 20-fold more potent than loratadine in its antihistaminic activity in guinea pigs. The potency of the two compounds was comparable in inhibiting histamine-induced airway effects in monkeys. SCH 34117 also showed a similar affinity for M_1 and M_3 -receptors, but not for M_2 -receptors. In comparison, loratadine displayed no affinity for muscarinic receptors. SCH 34117 dose-dependently expressed anticholinergic activity by decreasing the spontaneous right atrial rate in male guinea pigs (0.1 to 10 μM) and showed similar potency to diphenhydramine, but was significantly less potent than atropine. In addition, SCH 34117 was more potent than loratadine in inhibiting pilocarpine-induced salivation in mice ($IC_{50} = 10.8$ mg/kg po and 3.2 mg/kg sc; loratadine significantly inhibited salivation (24%) only at highest dose of 30 mg/kg po). SCH 34117 was more potent than fexofenadine and carebastine, but less potent than atropine in inhibiting pilocarpine-induced acinar cell degranulation in the submandibular gland. SCH 34117 also produced a potent and long lasting (>120 min) mydriasis after topical administration ($ED_{50} = 2.7$ mg/kg), but did not affect oxotremorine hypothermia and

OXO-induced tremor. Both SCH 34117 and loratadine displayed limited potency in inhibiting rat and guinea pig cardiac K^+ channels. SCH 34117 (1 to 100 μM) also inhibited a cloned human hKv1.5 current with an K_D of 12.5 μM , but was less potent than loratadine or terfenadine ($K_D = 1.0$ and 0.8 μM , respectively).

Safety Pharmacology: In a study cited by the sponsor and included in the IND package, loratadine (30 and 100 mg/kg, iv) did not alter cardiovascular parameters in the guinea pig (plasma levels = 27.8-61 $\mu\text{g/ml}$). Resulting SCH 34117 concentrations (1.46 $\mu\text{g/ml}$) were 370X greater than its C_{max} in man after a single oral dose of 10 mg loratadine. However, terfenadine, quinidine and diphenhydramine induced significant cardiovascular and ECG effects. This study, in combination with in vitro assessments of rat and guinea pig cardiac K^+ channels and the 14-day oral toxicity study in monkeys, suggests that SCH 34117 does not possess significant cardiovascular activity. The acting Medical Officer, Dr. Peter Honig, was consulted and agreed that no further preclinical assessment of cardiovascular effects is necessary.

Pharmacokinetics: Following multiple-dose oral administration (14 day, 1-8 mg/kg in rats, 1.6-6.5 mg/kg in monkeys), plasma levels and systemic exposures to SCH 34117 increased supra-proportionally with dose in rats and female monkeys, and proportionally in male monkeys. Exposures were generally greater in female rats than in males, and greater in male monkeys than in females. Drug accumulation was evident in both species. At similar doses, exposures were greater in monkeys. Maximum plasma concentrations in rats were achieved within 2.5-12 hours on Day 1, increasing with increasing dose, and within 2.5 hours on Day 10. In the monkey, mean T_{max} was achieved within 2.5-8 hours. The terminal phase half-life of SCH 34117 was ~ 2-4 hours in the rat, increasing to ~ 7.5-12 hours in monkeys and 24.6 hours in humans. Administration of 10 or 8 mg/kg/d loratadine in the rat and monkey, respectively, resulted in greater exposures to SCH 34117 than to the parent compound. Whether administered as SCH 34117 or loratadine, radioactivity was equally distributed between blood and plasma in rats and mice, and plasma protein binding is comparable among rats, monkeys and humans (70-76%). The metabolism of SCH 34117 is comparable to its parent, loratadine, which is primarily metabolized to SCH 34117 via removal of the carboethoxy group. This compound is further metabolized and the metabolites are excreted unchanged, as glucuronides or as further oxidized and conjugated products. However, metabolites specific to loratadine were detected in the pooled plasma and bile of male mice (monohydroxy SCH 29851 glucuronide, monoketo-monohydroxy SCH 29851, monohydroxy SCH 29851 glucuronide). In addition, previously unreported metabolites were detected in rat urine and plasma following dosing with SCH 34117 and loratadine. Also, a significant portion of loratadine was hydroxylated directly without first being metabolized to SCH 34117 in mice. Fecal excretion is the primary route of elimination, although a significant portion is also excreted in the urine following oral administration.

Acute Toxicity: Acute, oral and intraperitoneal studies were performed in mice and rats, as well as an oral study in monkeys. Maximum nonlethal doses, oral and intraperitoneal, of 250 and 25 mg/kg, respectively, and minimum lethal doses of 500 and 50 mg/kg, respectively, were observed in mice. In the rat, maximum nonlethal doses, oral and intraperitoneal, were 125 and 25 mg/kg, respectively, and the minimal lethal doses were 250 and 50 mg/kg, respectively. No

mortalities were observed in the acute monkey study at doses up to 250 mg/kg. Targets of acute toxicity appeared to be the CNS and respiratory system in rats and mice and the gastrointestinal system in monkeys.

Subacute Toxicity: Subacute, oral studies were performed for 14 days in rats (low-dose study: 1, 4 and 8 mg/kg SCH 34117 and 10 mg/kg loratadine; high-dose study: 15, 60 and 240 mg/kg SCH 34117) and monkeys (1.6, 3.2 and 6.5 mg/kg SCH 34117 and 8 mg/kg loratadine). In the low-dose rat study, no target organs of toxicity were observed and the NOAEL was identified as 8 mg/kg. In the high-dose study, however, the identified target organs of toxicity were the liver, lung, kidneys and pancreas, although a 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). Other findings included 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. A NOAEL was not identified for this study. In the monkey, no target organs of toxicity were clearly identified, although a number of histologic findings were of slightly increased incidence at the high-dose compared to controls. The significance of the findings could not be determined since the sponsor did not evaluate tissues from animals administered lower doses and since small numbers of animals were used. Other findings included increased triglyceride levels and urine osmolarity, as well as increased levels of EROD and PROD. The high dose of 6.5 mg/kg was selected as the NOAEL for this study.

Reproductive Toxicology: In a Segment I study in rats (6-48 mg/kg SCH 34117, oral) most treatment-related effects were observed at the high-dose and included one death (female), reduced stool, large fecal pellets, reduced pre-mating body weight gain and male and female mating indices, although no clear effects on fertility were observed. Time to identify positive evidence of mating was also increased (143 to 325%) at the mid- and high-dose. Reproductive effects included reduced corpora lutea/animal, fewer implantation sites and fetuses and an increased number of early resorptions/animal at the high-dose. A NOAEL of 24 mg/kg and a lethal dose of 48 mg/kg were identified for this study. The sponsor should consult ICH guidelines for reproductive toxicology studies when initiating the definitive Segment I study, as males were dosed for only 21 days prior to mating in this pilot study. In a pilot Segment II study (3-48 mg/kg), significant findings in female rats included reduced maternal body weight gain during the dosing period (upper-middle and high-dose animals) and fetal body weights at the high-dose. A NOAEL of 12 mg/kg was identified in this study. The high-dose in the definitive rat Segment I and Segment II studies should be less than 48 mg/kg and should not exceed 48 mg/kg, respectively.

In the pilot Segment II study in rabbits (25 to 100 mg/kg), clinical signs included deaths, lack of stool, soft stool, small fecal pellets, reduced number of fecal pellets and reduced body weight and food consumption. Effects on reproduction parameters, unavailable for the high-dose group due to maternal mortality, were not evident in the low- and mid-dose groups and no findings were observed during the fetal examination. A NOAEL of 50 mg/kg was identified in this study and the high-dose in a definitive embryo-fetal development study should be between 50 and 100 mg/kg/day. Preliminary findings from the definitive Segment II study (15-60 mg/kg) included a

change in formed stool at the mid- and high-dose and in some low-dose rabbits, as well as reduced mean body weight gain at the high-dose. Although an increased number of resorptions occurred in the high-dose group, no changes in fetal body weight or gross/skeletal examinations were observed. Exposure increased dose-proportionally between 15 and 30 mg/kg and supra-proportionally between 30 and 60 mg/kg and plasma concentrations peaked within 3 hours. A preliminary NOAEL of 30 mg/kg was identified and the sponsor should submit a complete report of this study.

Genotoxicity: SCH 34117 was negative in the bacterial mutation test (Ames assay) using the plate incorporation method at concentrations up to 1500 µg/plate. SCH 34117 was also negative in a chromosome aberration assay in cultured whole blood human lymphocytes in the presence or absence of an exogenous metabolic activation system at doses up to 125 µg/ml in the male donor and 130 µg/ml in the female donor. Significant cytotoxicity occurred at doses higher than the maximum reported.

The sponsor has proposed a Phase II, multiple-dose study to examine the clinical efficacy and safety of SCH 34117 (2.5-20 mg/day) for 2 weeks in patients with seasonal allergic rhinitis. The preclinical 14-day studies in rats and monkeys resulted in NOAELs of 8 and 6.5 mg/kg/day, respectively, although both studies resulted in numerous histological findings of slightly greater incidence at the high dose compared to control groups. A definitive assessment of these findings could not be determined since the sponsor did not evaluate the tissues of the low- and intermediate-dose groups. However, these findings are not of great concern since they were of generally low severity and did not fit within the general toxicity profile of SCH 34117 and its parent compound loratadine. Furthermore, the expected exposure levels in clinical trials at the proposed maximum dose of 20 mg/day should be considerably less than those reported in the preclinical studies. A previously completed Phase I single-dose study (2.5-20 mg) in healthy male volunteers resulted in a mean AUC of 158 ng.h/ml at the high-dose. This exposure level could reasonably be expected to rise to 300 ng.h/ml in a 14-day study, assuming drug accumulation observed in clinical trials with loratadine. An exposure of this level is still considerably below those observed in rats and monkeys at the doses in which the questionable histological findings were observed. Thus, the proposed clinical trial is considered to be reasonably safe to proceed.

RECOMMENDATIONS

1. The clinical trial may proceed as proposed (up to 20 mg SCH 34117/day for 14 days).
2. In the future, the sponsor should evaluate tissue histopathology from low- and intermediate-dose groups when high-dose groups show a higher incidence than control groups.
3. The sponsor should complete a full histological examination of all tissues and organs in future toxicity studies.

4. The submitted pilot Segment I reproduction toxicity study in rats consisted of a 3-week pre-mating administration interval in males. It should be noted that ICH Guidelines for Detection of Toxicity to Reproduction (ICH S5A and S5B) recommend pre-mating administration for males to be 4-weeks in duration, assuming that a toxicity study of at least 1-month duration demonstrates no effects on spermatogenesis (pre-mating administration of 9-10 weeks in the case of positive findings). The sponsor should consult the ICH Guidelines when performing the definitive Segment I and other reproductive toxicology studies.
5. The sponsor should submit a complete report of the Segment II reproduction toxicology study in rabbits (Study No. P-6802) when it becomes available.

Timothy J. McGovern, Ph.D., Pharmacologist

Draft Comments for Letter to Sponsor:

1. In the future, tissue histopathology from low- and intermediate-dose groups should be evaluated when high-dose groups show an increased incidence or severity compared to control groups.
2. A full histological survey of tissues/organs should be performed in future toxicity studies.
3. The ICH Guidelines for Reproduction Toxicology (S5A and S5B) should be consulted when performing the definitive Segment I and other reproductive toxicology studies.
4. Please submit a complete report of the Segment II reproduction toxicology study in rabbits (Study No. P-6802) when it becomes available.

Original IND 55,364

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HFD-570/T.J. McGovern

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

IND No. 55,364	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):**

<u>Review Type</u>	<u>Date of Submission(s)</u>	<u>Reviewer</u>	<u>Date of Review</u>
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

_____ No.: _____ Study No.: SN 98088 Volume: 1

Study Dates: Starting date 4/6/98; report issued 7/29/98
Testing Lab: _____
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

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.

Dose (mg/kg/d)	Males						Females					
	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	↓18	↓34	↓19		↑3	↓20	↓15	↓31**	↓32
Food Consump. (g/day)												
%Δ vs control group		no Δ	↑6	↓4	↓34	↓1		↓2	↓6	↓9	↓39	↓20

* 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.

Dose (mg/kg/d)	Males					Females				
	3	30	60	120	Lorat.	3	30	60	120	Lorat.
Hematology										
WBC										
%Δ vs control group	↑37	↑16	↑24	↑26	↑4	↓14	↓11	↓31	↓66	↓30
Lymphocytes										
%Δ vs control group	↑40	↑14	↑19	↓4	↑7	↑2	↑9	↓31	↓87	↓22
Eosinophils										
%Δ vs control group	↑33	↑7	↓33	↓53	↓27	↓7	no Δ	↓33	↓87	↓60
Erythrocyte										
%Δ vs control group	↑1	↑12	↑9	↑4	↑9	↓2	↑6	↑21	↑21	↑26
Hemoglobin										
%Δ vs control group	↑2	↑13	↑11	↑3	↑10	↑1	↑5	↑18	↑17	↑21
Hematocrit										
%Δ vs control group	↑1	↑12	↑11	↑3	↑9	no Δ	↑5	↑18	↑18	↑23
Platelets										
%Δ vs control group	↑9	↓2	↑2	↑25	↑4	↓1	↓1	↓2	↑16	↓10
Clinical Chemistry										
AP										
%Δ vs control group	↑13	↑36	↑25	↑64	↑32	↓16	↓22	↓38	↓15	↓19
ALT										
%Δ vs control group	no Δ	↓18	↑13	↑21	↑24	↑38	↓9	no Δ	↑128	↑9
AST										
%Δ vs control group	↑4	↑7	↑6	↑93	↓9	↑11	↓11	↑54	↑355	↑20
Urea nitrogen										
%Δ vs control group	↑8	↑15	no Δ	↑46	↑8	↓7	no Δ	↑7	↑187	↑33
Cholesterol										
%Δ vs control group	no Δ	↑25	↓4	↑29	↓2	↓5	↓5	↑57	↑92	↑100
Total protein										
%Δ vs control group	no Δ	↑14	↑6	↑3	↑13	↑4	↑9	↑12	↓10	↑4
Globulin										
%Δ vs control group	no Δ	↑21	↑16	↑21	↑21	↓5	no Δ	↑24	↓10	↑5
A/G ratio										
%Δ vs control group	↑1	↓7	↓10	↓20	↓9	↑12	↑8	↓15	↓4	↓4
Glucose										
%Δ vs control group	↑6	no Δ	↑4	↑33	↓6	↓3	↑6	↓6	↓10	↓14
Urinalysis										
Osmolarity										

%Δ vs control group	↓5	↑10	↓32	↑6	↓2	↓14	↓44	↓53	↓14	↓44
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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.

Dose (mg/kg/d)	Males					Females				
	3	30	60	120	Lorat.	3	30	60	120	Lorat.
Abs. Organ weight										
Adrenal gland										
%Δ vs control group	↓8	↓11	↓17	↓4	↓22	↓10	↓11	↓2	↓1	↓5
Brain										
%Δ vs control group	↓2	↓1	no Δ	↓6	↓3	↓3	↓1	↓5	↓11	↓3
Heart										
%Δ vs control group	↓2	↓4	↓7	↓18	↓11	↑1	↓7	↓2	↓20	↓11
Kidney										
%Δ vs control group	↓3	no Δ	↑2	↑4	↓7	no Δ	no Δ	↑9	↑21	↑2
Liver										
%Δ vs control group	↓3	↑21	↑26	↑56	↑28	↓8	↓5	↑12	no Δ	↑31
Lung										
%Δ vs control group	↑4	↑25	↑38	↑34	↑36	↑16	↑29	↑72	↑17	↑70
Spleen										
%Δ vs control group	↓2	↓12	↓21	↓15	↓26	↓23	↓28	↓34	↓59	↓26
Thymus										
%Δ vs control group	↑4	↓14	↓17	↓29	↓16	↑7	↓4	↓4	↓60	↓5
Prostate										
%Δ vs control group	↓1	↓9	↓7	↓19	↓5					
Ovary										
%Δ vs control group						↓7	↑9	↑5	↓40	↑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.

Dose (mg/kg/d)	Males						Females					
	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.

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Table 5. Histopathological changes following final sacrifice of rats.

Dose (mg/kg/d)	Males						Females					
	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 denervation	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 T_{max} increased with increasing dose from 1-4 hours to 24 hours. Generally C_{max} 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 T_{max} 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 _(0-24 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 included the liver, kidneys, lung, spleen, thymus and female reproductive organs.

Monkey, 28-day Oral (Gavage) Toxicity

Study No.: _____ Study No.: 98089 Volume: 1

Study Dates: Starting date 3/26/98; report issued 7/29/98
Testing Lab: _____
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 gas chromatography (GC).

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.

Dose (mg/kg/d)	Males				Females			
	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.

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

Dose (mg/kg/d)	Males					Females				
	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 T_{max} was 1.5 to 2.5 hours, increasing to 4 hours at the high dose. C_{max} 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. T_{max} 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 1 at 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.

Dose (mg/kg/d)	Analyte	Day 1			Day 14		
		T _{max} (hr)	C _{max} (ng/ml)	AUC _(0-24 hr) (ng.h/ml)	T _{max} (hr)	C _{max} (ng/ml)	AUC _(0-24 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.

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Addendum: Histopathology inventory for IND 55,364.

Study No.	P-652	D1828	SN 9808	P-6527	SN 9808
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).

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 55,364

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

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:			
Draft clinical/gross necropsy tables from 3-mos monkey toxicology study	032	SN 98212	1
Reproductive Toxicology:			
Pilot perinatal and post-natal development study in rats	031	SN 97512	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.

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
C _{max} (ng/ml)	277	454	604	1355	290	341	594	1028	663	692
T _{max} (hr)	4	3.3	4	4	11.3	6.7	11.3	19.3	23.3	24
AUC _(0-36 hrs) (ng.hr/ml)	4778	8018	11258	22818	7137	7760	14003	29293	18007	19892
Mean loratadine parameters after loratadine administration										
C _{max} (ng/ml)					178	382	726	694	739	522
T _{max} (hr)					2.3	2	3.3	4	4	2
AUC _(0-36 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 T_{max} 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 T_{max} 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)

Study No.: _____ Study No.: 98212 Volume: 1

Study Dates: Starting date; not provided; report issued: not applicable
 Testing Lab: _____
 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 (F₀): 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 through 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	↓48%	↓6	↓9%	↑7%

Shaded areas indicate statistically significant difference from control.

F₀ parturition: No SCH 34117-related effects on pregnancy or labor.

Necropsy (F₀ generation): No treatment-related findings were observed. One low-dose rat had a thickened uterine wall.

F₁ survival: No treatment-related effects were observed. The percentages of dying pups were similar between control and drug treatment groups.

Body weight (F₁): 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 (F₁ 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.

Timothy J. McGovern, Ph.D., Pharmacologist

Original IND 55,364

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 #4

IND No. 55,364	Serial No. 048	Submission Date: 01 APR 1999
	075	13 AUG 1999
	084	17 SEP 1999
	088	05 OCT 1999

Reviewer: Timothy J. McGovern, Ph.D.**Review Completed:** 31 JAN 2000**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):**

<u>Review Type</u>	<u>Date of Submission(s)</u>	<u>Reviewer</u>	<u>Date of Review</u>
Original Review	March 9, 1998	McGovern	May 22, 1998
Review #2	July 8-October 19, 1998	McGovern	October 27, 1998
Review #3	November 23, 1998	McGovern	December 15, 1998

Background: The submission of Serial No 048 contains summary reports of 3-month oral (gavage) toxicity studies in rats and monkeys (Study # P-6973 and P-6976, respectively). The sponsor previously submitted draft tables of clinical observations and gross findings from a 3-month monkey study (Serial No 032) in order to gain Agency concurrence on the Sponsor's plan not to perform an additional 3-month study in monkeys to fulfill bridging requirements to the chronic studies performed in the development program for loratadine. The sponsor was informed that a final decision on this issue must await submission of the histopathology and PK/TK data

from the 3-month monkey study (see Review #3). The sponsor's intent with the current submissions is to submit supporting toxicology information for planned chronic idiopathic urticaria trials which will be six weeks in duration and are planned to start in late April, 1999, to support bridging to the chronic toxicology program performed with loratadine and to obtain a waiver for carcinogenicity studies assessing SCH 34117. Currently, trials up to 4 weeks in duration have been performed based upon summary reports of 4-week toxicology studies in rats and monkeys. A Pre-NDA meeting was held May 11, 1999 to discuss, among other issues, the use of the 3-month studies to bridge to the chronic loratadine development program. Submission 075 contains the sponsor's request for a waiver from performing carcinogenicity studies in support of the desloratadine bridging strategy and includes the in vivo mouse micronucleus assay. Submission 088 includes additional information in support of the carcinogenicity waiver request. Submission 084 includes the final 3-month toxicology study reports including toxicokinetic data.

The issue regarding the carcinogenicity waiver request was addressed by the Senior Pharmacology/Toxicology Policy Group on September 14, 1999. The background packages provided to the Policy Group and the minutes of the Policy Group meeting are included as Attachments 1, 2 and 3 at the end of this review. See the minutes of the Policy Group meeting for the final recommendations regarding the sponsor's waiver request.

The following table summarizes the studies submitted in these submissions:

Preclinical Studies Submitted and Reviewed in this IND:

Study	Report #	Serial #	Volume
Multiple Dose Toxicology:			
Summary report of 3-mos oral (gavage) rat toxicology study	P-6973	048	12.1
Summary report of 3-mos oral (gavage) monkey toxicology study	P-6976	048	12.2
Final report of 3-mos oral (gavage) rat toxicology study	P-6973	084	23.1
Final report of 3-mos oral (gavage) monkey toxicology study	P-6976	084	23.4
Genetic Toxicology:			
Mouse bone marrow erythrocyte micronucleus study of SCH 34117	P6912	075	21.7

Studies Not Reviewed in this IND: None.

Studies Previously Reviewed: None

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

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TOXICOLOGY
 MULTIPLE-DOSE TOXICITY:

Rat, 3-Month Oral (Gavage) Toxicity

Doc. No.: P-6973 Study No.: Sponsor Study No.: 97016 Vol.: 23.1

Study Dates: Starting date: 3/9/1998; summary report issued: 7/1999
Testing Lab: _____
Test Article: SCH 34117 (Batch 97-34117-X-03-RA; purity not reported) in 0.4% methylcellulose; SCH 29851 (Batch MI-A-00851; purity not reported)
Concentration: 0.6-24 mg/ml.
Dose Volume: 5 ml/kg.
GLP: This report included a signed GLP report.
QA report: Yes.

Methods: Sprague-Dawley rats (5-7 weeks old, 169-291 g) were assigned to the following treatment groups:

Dose (mg SCH 34117/kg/day):	Veh. Control	3	30	60	120	120 mg loratadine/kg/day
No./sex	10	10	10	10	10	10

Each rat received a daily dose of vehicle, test drug or comparative dose of loratadine by oral (gavage) administration for 3 months. The following observations were made:

Clinical observation . . . assessed daily
 Body weight weekly
 Food consumption . . . weekly
 Water consumption . . . not assessed
 Health exam not assessed
 Ophthalmoscopy pre-test and Week 12; left eye only
 ECG not assessed
 Hematology Weeks 4 and 13
 Clinical chemistry . . . Weeks 4 and 13
 Urinalysis Weeks 4 and 13
 Enzyme induction . . . Liver samples assayed for protein content, cytochrome P450 content, 7-pentoxoresorufin O-dealkylase (PROD) activity and 7-ethoxyresorufin O-dealkylase (EROD)
 Organ weights at sacrifice (for specific tissues/organs see Addendum, page 32)
 Gross pathology at sacrifice
 Histopathology at sacrifice, all tissues were examined in the control (vehicle and comparative) high-mid-dose and high-dose rats (for specific tissues/organs see Addendum, page 32). Target organs were evaluated to the no-effect level in the low- and low-mid-dose groups.

Toxicokinetics blood samples obtained from 2 rats/sex/group/time point from the dosed rats at approximate times of 1, 2.5, 4, 8, 12 and 24 hours after dosing on Days 1 and during week 9.

Results:

Mortality: Mortality was noted following blood collection on Day 1 in all groups except for the low-dose group; vehicle control animals were not bled. The animals that died were replaced. Treatment-related mortality was noted in high-dose males (9 of 10, Days 19-63), in females at doses \geq 30 mg/kg DCL (lower-middle-dose: 2 of 10, days 41 and 68; upper-middle-dose: 6 of 10, days 9-63; high-dose: 10 of 10, days 19-36) and in comparative controls (6 of 10, days 23-87).

Table 1: Total incidence of mortality.

Dose (mg SCH 34117/kg/day):	0	3	30	60	120	120 mg loratadine/kg/day
Males	0	0	0	0	9	0
Females	0	0	2	6	10	6

Clinical Observations: Anti-cholinergic effects were the primary drug-related clinical observations in this study (Table 2). These included enlarged, few or no feces in animals administered doses of \geq 30 mg/kg SCH 34117 and loratadine-treated animals. Increases in the incidence of hypothermia, lethargy, paleness, rough coat, extended abdomen, thin appearance, ataxia, labored respiration/respiratory sounds, wet urogenital region and hunched posture were also noted in these groups. The incidence in the loratadine-control group showed greater similarity to the 60 mg/kg SCH 34117 group than the 120 mg/kg SCH 34117 group, likely due to differences in systemic exposure to SCH 34117.

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Table 2. Clinical observations in rats following 3-month administration.

Observation	Females						Males					
	0	3	30	60	120	120 - Lor	0	3	30	60	120	120 - Lor
Feces - few	0	0	8	10	10	10	0	1	1	10	10	7
Feces - none	0	0	0	1	0	3	0	0	0		1	1
Feces - enlarged	0	0	10	9	10	10	0	0	10	10	10	10
Hunched posture	0	0	0	6	10	10	0	1	0	1	10	1
Hypothermic	0	0	0	0	6	0	0	0	0	1	5	0
Lethargic	0	0	0	3	9	2	0	0	0	1	4	3
Pale	0	0	1	7	10	7	0	0	0	1	7	1
Rough coat	0	0	3	9	10	9	0	1	0	1	9	1
Thin appearance	0	1	5	10	10	10	0	1	0	1	8	2
Ataxic	0	0	0	0	1	0	0	0	0	1	2	1
Convulsive	0	0	0	1	0	0	0	0	0	0	1	0
Labored respiration	0	0	2	5	9	5	0	0	1	2	6	0
Nasal discharge - red	0	0	0	0	0	5	0	1	0	2	6	0
Respiratory sounds - rales	0	0	2	3	3	0	0	1	1	0	4	1
Swollen abdomen	0	0	0	0	0	2	0	0	0	0	2	0
Urogenital region - wet	0	0	1	1	7	2	0	0	0	0	1	0

Body Weight: Body weight gain was significantly reduced in upper-mid and high-dose males and females administered ≥ 30 mg/kg (Table 3). In males, significant reductions in the upper-mid and high-dose groups were observed from Days 29 and 8, respectively. In females, significant reductions in the lower-mid, upper-mid and high-dose groups were observed from Days 43, 22 and 36, respectively. The active control groups were also reduced (from Days 22 in males and 29 in females) and were comparable to the upper-mid-dose DCL groups.

Table 3: Change in body weight gain following 3-months treatment.

Dose (mg SCH 34117/kg/day):	3	30	60	120	120 mg Lor/kg/day
Males					
% Δ from control	↓1	↓12	↓33	↓99*	↓30
Females					
% Δ from control	↓7	↓33	↓73	↓139**	↓62

*: Day 54.

** : Day 36.

Food consumption: Food consumption was reduced in male rats administered 60 or 120 mg/kg SCH 34117 beginning on Day 8. The statistically significant reduction in the high dose group (36-54%) was continuous, while that in the 60 mg/kg group was intermittent, ranging from 22% at Day 8 to 9-12% on Days 78-91. Significant reductions in active control males were noted only on Days 8 and 57 (16 and 19%, respectively). Females were more significantly affected as reductions were consistently reported in the same three groups from Day 8 onward. Reductions ranged from 24-32% in the 60 mg/kg group, 36-75% in the 120 mg SCH 34117/kg group, and 13-36% in the loratadine treatment group.

Ophthalmoscopy: No treatment-related findings were reported.

Hematology: The high-dose SCH 34117 groups could be assessed only at Day 23 due to high mortality. Significant, but small, increases in erythrocyte, hemoglobin and hematocrit levels were noted (Table 4). In addition, total leukocyte counts were reduced and platelet counts were increased. WBC differentiation demonstrated reduced lymphocytes and eosinophils. At day 92, findings included a slight reduction in mean corpuscular hemoglobin concentration in active male controls, increased erythrocyte hemoglobin, and increased hematocrit in the two mid-dose female groups and the female active control group. Monocyte reductions were also noted in upper-mid dose and active control males, while prothrombin and activated partial prothrombin time were reduced in males, but increased in females.

Table 4. Hematologic findings in rats following 3-month administration.

	Males						Females					
	Dose (mg/kg)						Dose (mg/kg)					
Hematology	0	3	30	60	120*	120 - L	0	3	30	60	120*	120 - L
Leukocyte % Δ from control		↑4	↓4	↑5	↓32	↓7		↑14	0	↑17	↓25	↓13
Erythrocyte % Δ from control		↑4	↑2	0	↑16	↑1		↑2	↑10	↑12	↑10	↑13
Hemoglobin % Δ from control		↑1	↑2	↓1	↑12	↓3		↑2	↑10	↑11	↑7	↑7
Hematocrit % % Δ from control		↑2	↑2	↑1	↑12	0		↑2	↑10	↑12	↑6	↑11
Platelets % Δ from control		0	↓14	↑7	↑32	↓1		↓2	↓12	↑8	↑51	↑15
Lymphocytes % Δ from control		↑2	0	↑4	↓49	↑6		↑10	↑1	↓5	↓67	↓27
Monocytes % Δ from control		↑7	↓64	↓66	↑147	↓70		↑48	↓71	↑176	↑8	↓33
Eosinophils % Δ from control		0	↓15	↓20	↓69	↓40		↑38	↓15	↓54	↓79	↓46
Neutrophils % Δ from control		↑9	↓4	↑36	↑50	↑50		↑48	↑16	↑170	↑377	↑115
Prothrombin time (seconds)	13	13	12	12	13	11.5	1 1	11	10. 9	11		11.5
APTT (seconds)	12	11	9.7	9.6	9.9	9.4	1 0	10	9.8	11		11

Shaded areas indicate statistically significant difference from control group ($p < 0.05$).

* Day 23.

Clinical Chemistry: The high-dose SCH 34117 groups were only assessed on Day 23 due to high mortality. Drug-related findings are summarized in Table 5 and include slight alterations in albumin, increases in cholesterol, globulin, and total protein. Aspartate aminotransferase, alanine aminotransferase and BUN were also increased 2.5 to 5-fold, 1 to 2-fold, and 1.5 to 2-fold, respectively, in males and females, while A/G ratio, glucose, and triglycerides were slightly to moderately reduced.

Table 5. Clinical chemistry findings in rats following 3-month administration.

Clinical chemistry	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	3	30	60	120*	120-L	3	30	60	120*	120-L
Albumin % Δ from control	↑5	↑11	↑11	↓12	↑16	↑6	↑4	↓14	↓17	↓12
Cholesterol % Δ from control	↑12	↑26	↑46	↑69	↑12	↑11	↑21	↑66	↑24	↑124
Globulin % Δ from control	no Δ	↑9	↑23	↑15	↑27	↑10	↑15	↑15	↓12	↑35
Total protein % Δ from control	↑5	↑12	↑17	↓3	↑22	↑7	↑7	↓7	↓15	↑1
Aspartate aminotrans % Δ from control	↑2	↓11	↓14	↑489	↓14	↑2	↑22	↑60	↑250	↑32
Alanine aminotrans % Δ from control	↑8	↑11	↑14	↑231	↑25	↑37	↑39	↑16	↑103	↓20
AG ratio % Δ from control	↑2	↓1	↓15	↓21	↓13	↓5	↓8	↓24	↓1	↓37
Glucose % Δ from control	↓6	↓6	↓10	↓51	no Δ	↓5	↓10	↓16	10	↓12
Triglycerides % Δ from control	↑17	↓22	↓72	↓65	↓74	↑10	↑21	↑74	↓51	↓50
BUN % Δ from control	↓7	no Δ	no Δ	↑159	↑14	no Δ	↓6	↑81	↑207	↑88

Shaded areas indicate statistically significant difference from control group ($p < 0.05$).

120-L: 120 mg/kg loratadine active control group.

* Day 23.

Enzyme Induction: Liver weight, liver to body weight ratio and microsomal protein content were all increased in male rats administered 30 and 60 mg/kg SCH 34117 and 120 mg/kg loratadine (Table 6). The high-dose SCH 34117 groups were not assessed due to the high incidence of mortality. These findings were consistent only in the female active control group. In addition, cytochrome P450 induction was greater in females while induction of PROD was greater in males. Responses tended to be greater in the active control animals compared to the animals administered 60 mg/kg SCH 34117.

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Table 6. Enzyme induction in rats following 3-month drug administration.

Dose (mg/kg/d)	Males					Females				
	0	3	30	60	120-L	0	3	30	60	120-L
Liver weight										
% Δ from control		↓1	↑40	↑39	↑79	↓1	↓9	↑1		↑62
Liver/Body wt ratio										
% Δ from control		no Δ	↑41	↑67	↑111	↑7	↑7	↑41		↑115
Microsomal protein (mg/tot liver)										
% Δ from control		↑21	↑98	↑71	↑102	↓4	↑15	↑36		↑172
cytochrome P450										
% Δ from control										
Nmol/mg microsomal protein		↓6	↑7	↑9	↑13	no Δ	↑15	↑47		↑94
Nmol/g liver		↑13	↑52	↑38	↑29	↓8	↑41	↑88		↑215
Nmol/total liver		↑11	↑110	↑86	↑129	↓8	↑31	↑89		↑403
Enzyme Induction										
% Δ from control										
PROD										
pmol/min/mg micros. protein		↓5	↑688	↑140	↑233	↑6	↑232	↑97		↑15
pmol/min/g liver		↑17	↑1053	↑210	↑287	no Δ	↑310	↑110		↑86
pmol/min/total liver		↑19	↑1568	↑332	↑615	↓1	↑275	↑107		↑198
EROD										
pmol/min/mg micros. protein		↓37	↓16	↓51	↓49	↓12	↑32	↑14		↑11
pmol/min/g liver		↓28	↑2	↓41	↓45	↓19	↑57	↑44		↑76
pmol/min/total liver		↓28	↑47	↓20	↓3	↓21	↑44	↑41		↑176

Shaded areas indicate a significant difference from vehicle controls.

Urinalysis: Urine volumes were increased in loratadine-treated animals and in males administered the mid-doses after 3 months treatment (Table 7). In addition, urine osmolarity was reduced in the same groups. Results in the high-dose DCL group were not consistent and may be due to the earlier sampling time for this group.

Table 7. Urinalysis results in rats following 3-month administration.

Urinalysis	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	3	30	60	120*	120-L	3	30	60	120*	120-L
4-hour volume										
% Δ from control	28	35	11	-39	44	-10	20	66	3	39
24-hour volume										
% Δ from control	13	87	53	-19	62	-2	21	20	20	99
Osmolarity										
% Δ from control	-17	-51	-43	6	-55	8	-17	-56	-18	-43

Shaded areas indicate statistically significant difference from control group (p < 0.05).

120-L: 120 mg/kg loratadine active control group.

* Day 22/23.

Organ Weight: The high-dose female desloratadine group was not assessed due to high mortality and only one high-dose male was assessed. Findings from the other dose groups demonstrated increases in liver, lung, adrenal, heart and kidney weights, and decreases in spleen, thymus and

uterus weights (Table 8). The active control group was generally comparable to the mid-dose groups.

Table 8. Organ weight changes in rats following 3-month administration.

Organ weight	Males					Females				
Dose group (mg/kg)	3	30	60	120	120-L	3	30	60	120	120-L
n =	10	10	10	1	10	10	8	4	0	4
Liver										
AOW-% Δ from control	3	27	48	10	69	4	4	10		76
RTB	4	34	78	127	101	5	16	44		121
RTBr	6	31	53	15	73	1	5	15		87
Lungs										
AOW-% Δ from control	-11	20	44	40	22	10	68	130		105
RTB	-10	27	73	187	46	11	88	197		156
RTBr	-9	24	49	46	25	7	70	138		119
Spleen										
AOW-% Δ from control	-2	-24	-24	-52	-17	-4	-18	-30		-15
RTB	-1	-19	-8	-2	-1	-3	-9	-10		7
RTBr	1	-21	-21	-50	-15	-7	-17	-27		-10
Thymus										
AOW-% Δ from control	11	-4	-23	-43	-3	19	-11	-31		-36
RTB	10	3	-7	18	15	20	no Δ	-11		-20
RTBr	14	-1	-20	-40	-1	15	-11	-28		-32
Uterus										
AOW-% Δ from control						32	22	-47		-51
RTB						33	35	-33		-38
RTBr						28	24	-45		-48
Adrenals										
AOW-% Δ from control	-3	-10	-11	41	-4	2	-6	11		13
RTB	-3	-6	7	188	14	2	5	45		44
RTBr	1	-7	-7	48	-1	-2	-5	15		20
Brain										
AOW-% Δ from control	-3	-3	-4	-4	-3	3	-1	-4		-6
RTB	-3	3	15	96	16	4	11	25		19
Heart										
AOW-% Δ from control	-3	-7	-11	-18	-9	4	-4	-7		-1
RTB	-3	-2	7	67	7	5	8	22		25
RTBr	no Δ	-4	-8	-15	-7	1	-3	-3		6
Kidneys										
AOW-% Δ from control	1	-4	-3	33	-1	2	1	22		48
RTB	1	2	16	173	18	3	13	59		90
RTBr	4	no Δ	no Δ	38	2	-1	3	27		57

Shaded areas indicate statistically significant difference from control group ($p < 0.05$).

120-L: 120 mg/kg loratadine (active control group).

AOW: Absolute organ weight RTB: Relative to body weight RTBr: Relative to brain weight

Gross Pathology: The primary gross findings following the final sacrifice were likely due to the pharmacological effects of the drug and included dilatation in the gastrointestinal tract, the kidney, uterus and urinary bladder at a slightly higher incidence in drug-treated animals than in

controls (Table 9). Kidney discoloration and heart foci were also noted. In animals dying early, these findings, as well as stomach discoloration and reduced spleen and thymus size, were reported.

Table 9. Gross observations in rats following 3-month oral administration.

Observation	Males						Females					
Final sacrifice												
Dose (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
n =	10	10	10	10	1	10	10	10	8	4	0	4
Colon - dilatation	0	0	0	0	0	1	0	0	0	0	0	0
Heart - focus	0	0	0	0	0	1	0	0	0	0	0	0
Lg Intest. - dilatation	0	0	0	0	1	0	0	0	0	0	0	0
Kidney - discoloration	0	0	0	0	1	1	0	0	0	1	0	1
- dilatation	1	0	0	2	0	1	0	0	0	0	0	1
Testis - small	1	0	0	1	0	4						
Urinary bladder - dilatation	0	0	0	0	0	1	0	0	0	0	0	0
Uterus - dilatation							0	2	1	0	0	0
-small							0	0	0	1	0	1
scheduled deaths												
n =	0	0	0	0	9	0	0	0	2	6	10	6
Stomach - dilatation	0	0	0	0	1	0	0	0	0	1	0	3
Colon - dilatation	0	0	0	0	0	0	0	0	0	1	1	4
- dilated/impacted	0	0	0	0	0	0	0	0	0	0	1	0
Duodenum - dilatation	0	0	0	0	0	0	0	0	0	1	0	0
Ileum - dilatation	0	0	0	0	1	0	0	0	0	1	0	0
Lg Intest. - dilatation	0	0	0	0	1	0	0	0	0	0	2	0
- impaction	0	0	0	0	0	0	0	0	0	0	3	0
- stricture	0	0	0	0	0	0	0	0	0	0	1	0
Jejunum - dilatation	0	0	0	0	1	0	0	0	0	1	0	0
Kidney - discoloration	0	0	0	0	1	0	0	0	0	0	0	0
- dilatation	0	0	0	0	0	0	0	0	0	0	0	1
Liver - discoloration	0	0	0	0	0	0	0	0	0	0	1	0
- focus	0	0	0	0	0	0	0	0	0	0	0	1
Spleen - focus	0	0	0	0	1	0	0	0	0	0	0	0
-small	0	0	0	0	3	0	0	0	0	0	5	1
Stomach - dilatation	0	0	0	0	0	0	0	0	0	1	1	0
-discoloration	0	0	0	0	1	0	0	0	0	0	0	0
-enlarged	0	0	0	0	1	0	0	0	0	0	0	0
Thymus - small	0	0	0	0	0	0	0	0	0	0	1	0
Uterus - dilatation	0	0	0	0	0	0	0	0	1	0	0	0

Histopathology: Histological findings are summarized in Table 10. The primary findings were ubiquitous indicators 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 was comparable to those at 120 mg/kg loratadine.

Table 10. Histological changes in rats following 3-month administration.

Histopathology	Males						Females						
	0	3	30	60	120	120-L	0	3	30	60	120	120-L	
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L	
Adrenals – vacuolation	10	0	0	10	10	10	10	0	0	0	10	10	10
Minimal	0			0	7	0	0			2	1	4	
Mild	0			0	0	0	0			0	9	2	
Brain – vacuolation of choroid plexus	10	0	0	10	10	10	10	0	0	0	10	10	10
Minimal	0			0	2	0	0			2	2	5	
Mild	0			0	8	0	0			6	5	1	
Moderate	0			0	0	0	0			1	3	3	
Bone – cell infiltr, mononuc cell, myofiber	10	0	10	10	10	10	10	0	10	10	10	10	10
Minimal	0		0	0	5	0	0		0	6	1	5	
Mild	0		0	0	5	0	0		0	0	1	7	4
Moderate	0		0	0	0	0	0		0	0	0	2	0
Vacuolation – myofiber													
Minimal	0		0	0	6	0	0		0	0	7	0	6
Mild	0		0	0	3	0	0		0	0	2	10	3
Moderate	0		0	0	1	0	0		0	0	0	0	0
Fibrosis, myofiber													
Minimal	0		0	0	6	0	0		0	0	2	2	5
Mild	0		0	0	0	0	0		0	0	2	7	4
Degeneration, myofiber													
Minimal	0		0	0	9	0	0		0	0	5	6	8
Mild	0		0	0	0	0	0		0	0	2	0	0
Moderate	0		0	0	0	0	0		0	0	1	0	0
Bone marrow –	10	0	10	10	10	10	10	0	10	10	10	10	10
Hypercellularity – min	0		0	0	0	2	0		0	0	2	0	0
Hypocellularity – min	0		0	0	1	0	0		0	0	0	4	2
- mild	0		0	0	2	0	0		0	0	0	0	1
Mastocytosis – min	0		0	0	1	0	0		0	0	0	0	0
- mild	0		0	0	1	0	0		0	0	0	0	0
Vacuolation – scattered													
minimal	0		0	0	5	0	0		0	0	2	2	5
mild	0		0	0	3	0	0		0	0	1	5	1
moderate	0		0	0	1	0	0		0	0	0	3	1
Atrophy, fat													
Mild	0		0	0	1	0	0		0	0	0	0	0
Moderate	0		0	0	6	0	0		0	0	0	8	3
Epididymides	10	10	10	10	10	10							
Cellular debris, luminal													
Minimal	1	0	2	3	7	0							
Mild	0	0	3	6	2	8							
Moderate	0	0	0	0	0	1							
Vacuolation, epithel													
Minimal	1	0	6	1	0	2							
Mild	0	0	0	4	2	4							
Moderate	0	0	0	5	8	4							
Oligospermia													

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Minimal	0	0	0	0	2	0						
Mild	0	0	1	0	1	2						
Moderate	1	0	0	1	0	2						
Severe	0	0	0	0	0	1						
Eyes – vacuolation of	10	0	10									
Ciliary body, m-phage												
Minimal	0		0	0	6	0	0	0	0	1	8	0
Vacuolation, myofiber												
Minimal	0		0	6	5	5	0		1	10	7	10
Mild	0		0	0	5	0	0		0	0	3	0
Vacuolation, retinal, epithelium												
minimal	0		0	0	5	0	0	0	0	5	5	3
Gliosis – minimal	0		0	0	1	0	0	0	0	0	0	0
Heart	10	0	10									
Cell. Infiltration mononuclear cel												
Minimal	0		0	0	5	2	0	0	0	1	4	7
Mild	0		0	0	1	0	0	0	0	1	3	2
Vacuolation, myofiber, base												
Minimal	0		0	1	6	4	2	2	6	6	3	3
Mild	0		0	0	0	0	0	0	0	2	0	6
Vacuolation, myfiber, Interstitial												
Minimal	0		0	0	8	0	0	0	0	3	2	1
Mild	0		0	0	0	0	0	0	0	0	8	5
Degeneration, myofiber minimal	1		0	0	3	0	1	1	1	0	0	0
Kidneys	10	0	10									
Vacuolation, epithel												
Minimal	0		0	9	1	7	0	0	3	3	3	0
Mild	0		0	1	4	2	0	0	0	4	5	5
Moderate	0		0	0	5	0	0	0	0	3	2	5
Necrosis												
Minimal	2		0	6	9	5	0	0	1	6	6	7
Hyperplasia, epith, pelv												
Mild	0		0	0	0	1	0	0	0	0	0	0
Erosion, pelvis												
Moderate	0		0	0	0	1	0	0	0	0	0	0
Dilatation, tubular												
Minimal	1		0	0	2	1	0	0	0	1	2	0
Mild	0		0	0	0	0	0	0	0	1	0	2
Moderate	0		0	0	1	0	0	0	0	0	0	0
Lymph nodes	10	1	10	10	10	10						
Vacuolation, m-phage												
Minimal	0	0	1	5	0	2	0	0	0	3	0	1
Mild	0	0	0	0	4	0	0	0	0	7	3	6

Histopathology	Males						Females					
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Moderate Atrophy, lymphoid	0	0	0	0	6	0	0	0	0	0	7	3
Minimal	0	0	0	0	3	0	0	0	0	2	2	3
Mild	0	0	0	0	0	0	0	0	0	1	5	2
Moderate	0	0	0	0	6	0	0	0	0	0	3	2
Liver	10											
Cell. Infiltr., mononuc. cell, decreased	0	0	0	1	10	2	0	0	0	4	8	7
Vacuolation, kupfer cell												
Minimal	0	0	0	0	4	0	0	0	0	1	4	8
Mild	0	0	0	0	5	0	0	0	0	0	5	1
Moderate	0	0	0	0	1	0	0	0	0	0	0	0
Vacuolation, centrilob., hepatocellular												
Minimal	0	0	0	5	1	1	0	0	0	8	1	4
Mild	0	0	0	1	7	1	0	0	0	1	9	6
Moderate	0	0	0	0	2	0	0	0	0	0	0	0
Vacuolation, biliary, epithelium												
Minimal	0	0	0	6	0	4	0	0	2	1	0	0
Mild	0	0	0	1	1	2	0	0	1	2	0	2
Moderate	0	0	0	0	6	0	0	0	0	4	1	5
Severe	0	0	0	0	3	0	0	0	0	3	9	3
Hypertrophy, centrilob												
Minimal	0	0	0	0	1	0	0	0	5	5	1	2
Mild	0	0	4	2	8	0	0	0	3	2	9	4
Moderate	0	0	6	8	0	10	0	0	0	1	0	4
Lungs	10	0	10									
Vacuolation, epithel	0		0	7	6	3	0	0	4	4	2	6
Minimal	0		0	0	2	1	0	0	0	3	8	4
Mild												
Vacuolation, alv mac	0		0	1	1	4	0	0	5	0	8	3
Minimal	0		0	0	1	0	0	0	0	4	0	2
Mild												
Moderate												
Material, proteinacious, alveolar	0		0	3	6	0	0	0	0	4	9	1
Minimal	0		0	0	3	0	0	0	0	1	1	0
Mild	0		0	0	1	0	0	0	0	3	0	9
Moderate												
Esophagus	10	0	10									
Cell infiltr, mononuc cell												
minimal	0		0	0	6	1	0	0	0	5	5	6

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
mild	0		0	0	0	0	0	0	0	0	0	1
Vacuolation, myofiber												
minimal	0		0	3	2	1	0	0	1	3	1	0
mild	0		0	0	5	0	0	0	0	6	9	10
Degeneration, myofiber												
minimal	0		0	1	2	0	0	0	1	1	1	2
Ovaries							10	10	10	10	10	10
Vacuolation, sex cord												
Minimal							0	0	0	9	10	10
Mild							0	0	0	1	0	0
Vacuolation, corp lutea												
Minimal							0	0	0	1	2	0
Mild							0	0	0	4	7	4
Moderate							0	0	0	4	1	5
Severe							0	0	0	0	0	1
Vacuolation, rete ducts												
Minimal							0	0	0	2	0	0
Mild							0	0	1	0	1	1
Moderate							0	0	0	0	2	1
Severe							0	0	0	0	1	0
Necrosis, granulosa cell												
Minimal							0	0	0	0	6	3
Mild							0	0	0	0	1	1
Atrophy, follicular												
Minimal							0	0	0	0	1	1
Pancreas	10											
Single cell necrosis												
Minimal	0	0	0	0	1	0	0	0	0	0	0	0
Vacuolation, ductular												
Minimal	0	0	0	6	0	0	0	0	1	1	0	0
Mild	0	0	0	0	2	0	0	0	0	3	1	6
Moderate	0	0	0	0	6	0	0	0	0	0	4	2
Severe	0	0	0	0	2	0	0	0	0	1	5	1
Vacuolation, acinar cell												
Minimal	1	1	2	0	0	2	0	0	0	1	4	2
Mild	0	0	0	0	8	0	0	0	0	2	3	3
Moderate	0	0	0	0	0	0	0	0	0	0	2	0
Parathyroid glands	5	0	0	7	9	8	7	0	9	7	7	9
Vacuolation, chief cell												
Minimal	0			0	9	0	0		0	4	7	8
Mild	0			0	0	0	0		0	2	0	1
Pituitary gland	10	0	10	10	10	10	10	0	10	10	10	10
Vacuolation, par anterior												
Minimal	0		0	1	9	2	0		0	10	10	10
Prostate	10	0	10	10	10	10						
Vacuolation, epithel												

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Minimal	0		0	1	2	0						
Mild	0		0	0	6	1						
Moderate	0		0	0	1	0						
Immaturity												
Minimal	0		0	0	7	0						
Salivary gland	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, sublingual, ductular												
Minimal	0			0	1	0	0	0	1	0	0	
Mild	0			0	1	0	0	0	0	3	0	
Moderate	0			0	7	0	0	0	8	7	10	
Severe	0			0	1	0	0	0	0	0	0	
Vacuolation, sublingual, acinar cell												
Minimal	0			0	5	0	0	0	8	7	8	
Mild	0			0	4	0	0	0	0	3	2	
Vacuolation, parotid, ductular												
Minimal	0			0	5	0	0	0	4	6	5	
Mild	0			0	3	0	0	0	2	4	5	
Moderate	0			0	2	0	0	0	1	0	0	
Vacuolation, parotid, acinar cell												
Minimal	9			7	0	3	6	8	4	0	1	
Mild	0			0	4	0	0	0	2	6	7	
Moderate	0			0	5	0	0	0	0	4	0	
Vacuolation, submandib, ductular												
Minimal	0			0	2	0	0	0	4	0	2	
Mild	0			0	4	0	0	0	5	6	5	
Moderate	0			0	3	0	0	0	0	4	3	
Severe	0			0	1	0	0	0	0	0	0	
Vacuolation, submandib, acinar cell												
Minimal	0			0	3	0	0	0	5	3	1	
Mild	0			0	0	0	0	0	0	1	0	
Moderate	0			0	0	0	0	0	0	3	0	
Necrosis, parotid												
Minimal	0			0	2	0	0	1	1	0	0	
Necrosis, submandib												
Minimal	0			0	2	0	0	0	0	2	0	
Atrophy, sublingual												
Minimal	0			0	8	0	0	0	5	4	8	
Mild	0			0	0	0	0	0	0	6	2	
Atrophy, parotid												
Minimal	0			0	3	0	0	0	0	1	2	
Mild	0			0	3	0	0	0	0	3	0	
Moderate	0			0	2	0	0	0	1	2	1	
Severe	0			0	2	0	0	0	0	4	2	

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Atrophy, submandib												
Minimal	0			0	4	0	0	0	7	2	2	2
Mild	0			0	2	0	0	0	1	3	2	2
Moderate	0			0	0	0	0	0	0	2	1	1
Seminal vesicles	10	0	10	10	10	10						
Vacuolation, epithel												
Minimal	1		0	6	0	3						
Mild	0		0	1	0	2						
Moderate	0		0	0	7	0						
Severe	0		0	0	3	0						
Immaturity												
Minimal	0		0	0	2	0						
Skeletal muscle	10	0	10	10	10	10	10	10	10	10	10	10
Cell. Infiltr., mononuc cell,												
Minimal	0		0	0	5	0	0	0	0	5	2	3
Mild	0		0	0	4	0	0	0	0	0	6	0
Moderate	0		0	0	0	0	0	0	0	0	2	1
Vacuolation												
Minimal	0		0	1	5	0	0	0	0	3	1	3
Mild	0		0	0	5	0	0	0	0	2	8	2
Moderate	0		0	0	0	0	0	0	0	0	1	0
Fibrosis, interstitial												
Mild	0		0	0	0	0	0	0	0	0	4	1
Degeneration, myofiber												
Minimal	0		0	0	4	0	0	1	1	3	6	1
Mild	0		0	0	3	0	0	0	0	0	2	1
Severe	0		0	0	0	0	0	0	0	0	0	1
Skin	10	0	10	10	10	10	10	0	10	10	10	10
Cell. Infiltr., mononuc cell,												
myofiber	0		0	0	3	0	0		0	1	7	4
Minimal												
Vacuolation, epith	0		0	1	2	0	0		0	4	1	2
Minimal	0		0	0	5	0	0		0	4	4	4
Mild	0		0	0	3	0	0		0	0	5	0
Moderate												
Vacuolation, myofiber	0		0	2	2	0	0		0	5	0	1
Minimal	0		0	0	3	0	0		0	4	4	4
Mild	0		0	0	5	0	0		0	0	6	4
Moderate												
Necrosis, epithelial	0		0	0	1	0	0		0	1	1	0
Minimal	0		0	0	1	0	0		0	0	0	0
Mild												
Atrophy, fat	0		0	0	2	0	0		0	0	0	2
Minimal	0		0	0	1	0	0		0	0	0	0
Mild	0		0	0	1	0	0		0	0	4	2
Moderate	0		0	0	6	0	0		0	0	6	3
Severe												
Harderian glands	10	0	0	10	10	10	10	10	10	10	10	10

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Single cell necrosis												
Minimal	0			0	0	0	0	0	0	3	5	3
Mild	0			0	0	0	0	0	0	0	1	2
Vacuolation, epithel												
Minimal	0			0	4	0	0	0	0	1	4	2
Mild	0			0	0	0	0	0	0	0	0	1
Pigment accum, lumina												
Minimal	0			0	6	0	0	0	0	0	1	2
Atrophy												
Minimal	1			0	5	0	0	0	1	3	5	7
Mild	0			0	0	0	0	0	0	0	1	0
Stomach	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, epith												
Minimal	0			0	4	0	0		0	0	2	0
Vacuolation, myofiber												
Minimal	0			0	2	0	0		0	2	1	2
Mild	0			0	7	0	0		0	4	9	5
Necrosis, mucosal												
Minimal	0			0	1	0	0		0	0	0	0
Congestion, mucosal												
Minimal	0			0	1	0	0		0	0	0	0
Large intestine	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, lymphoid nodule, macrophage												
Minimal	0			0	1	0	0		0	0	1	0
Mild	0			0	1	0	0		0	0	0	0
Vacuolation, myofiber												
Minimal	0			0	8	0	0		0	0	3	0
Mild	0			0	0	0	0		0	2	5	2
Dilatation, luminal												
Minimal	0			0	0	0	0		0	0	0	0
Mild	0			0	1	0	0		0	0	0	0
Severe	0			0	0	0	0		0	0	1	3
Small intestine	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, lymphoid nodule, macrophage												
Minimal	0			0	3	0	0		0	1	0	0
Vacuolation, duodenal gland												
Minimal	0			0	7	0	0		0	5	7	5
Vacuolation, lamina propria,												
Minimal	0			0	6	0	0		0	2	5	3

Histopathology	Males						Females					
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
macrophage	0			0	6	0	0		0	0	5	0
Minimal												
Mild	0			0	3	0	0		0	3	6	4
Vacuolation,	0			0	0	0	0		0	1	1	0
myofiber												
Minimal												
Mild												
Spleen	10	0	10	10	10	10	10	1	10	10	10	10
Vacuolation, m-phage												
Minimal	0		0	0	0	1	0	0	0	1	0	0
Mild	0		0	0	2	0	0	0	0	9	0	6
Moderate	0		0	0	3	0	0	0	0	0	3	4
Severe	0		0	0	5	0	0	0	0	0	7	0
Fibrosis, capsular												
Minimal	0		0	0	1	0	0	0	0	0	0	0
Atrophy, lymphoid												
Minimal	0		0	0	1	0	0	0	0	3	1	4
Mild	0		0	0	2	0	0	0	0	1	1	2
Moderate	0		0	0	2	0	0	0	0	0	6	0
Sever	0		0	0	5	0	0	0	0	0	2	3
Testes	10	10	10	10	10	10						
Cellular debris, luminal												
Minimal	1	0	1	6	1	3						
Mild	0	0	0	1	0	6						
Vacuolation, sertoli cell												
Minimal	7	6	5	5	1	3						
Mild	0	0	0	1	0	2						
Moderate	1	0	0	0	0	5						
Hypospermatogenesis												
Minimal	1	4	2	3	1	1						
Mild	0	0	0	0	0	1						
Moderate	1	0	0	1	0	2						
Severe	0	0	0	1	0	3						
Thyroid	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation												
Minimal	0			0	3	0	0	0	4	7	6	
Mild	0			0	4	0	0	0	3	0	0	
Moderate	0			0	3	0	0	0	0	1	3	
Thymus	10	10	10	10	10	10	10	10	10	10	10	10
Cell infiltr, neutrophil												
Minimal	0	0	0	0	1	0	0	0	0	0	0	0
Vacuolation, m-phage												
Minimal	0	0	2	3	2	0	0	0	2	7	0	2
Mild	0	0	0	0	8	0	0	0	0	2	2	5
Moderate	0	0	0	0	0	0	0	0	0	0	8	1
Necrosis, scattere lymphoid												

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Minimal	0	0	0	0	2	0	0	0	1	1	2	0
Mild	0	0	0	0	1	0	0	0	0	0	2	0
Moderate	0	0	0	0	0	0	0	0	0	0	1	0
Hemorrhage												
Minimal	0	0	0	0	1	0	0	0	0	0	0	0
Mild	0	0	0	0	1	0	0	0	0	0	1	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	1
Atrophy, lymphoid												
Minimal	0	0	0	0	1	0	0	0	0	1	1	0
Moderate	0	0	0	0	1	0	0	0	0	1	4	3
Severe	0	0	0	0	5	0	0	0	0	0	5	1
Tongue	10	0	0	10	10	10	10	0	10	10	10	10
Cell. infiltr., mononuc cell,												
Minimal	0			0	8	0	0	0	1	5	2	
Mild	0			0	1	0	0	0	0	3	0	
Moderate	0			0	0	0	0	0	0	1	0	
Vacuolation												
Minimal	0			0	9	0	0	0	7	1	8	
Mild	0			0	1	0	0	0	2	9	1	
Fibrosis, interstitial												
Minimal	0			0	0	0	0	0	0	3	0	
Trachea	10	0	10	10	10	10	10	10	10	10	10	10
Vacuolation, m-phage												
Minimal	0		0	0	1	0	0	0	0	2	3	
Mild	0		0	0	0	0	0	0	2	6	0	
Moderate	0		0	0	0	0	0	0	0	0	1	
Vacuolation, epithel												
Minimal	0		0	3	1	5	0	0	3	0	0	
Mild	0		0	5	5	0	0	0	3	7	9	
Moderate	0		0	0	4	0	0	0	4	3	1	
Necrosis, epithelial												
Severe	0		0	0	0	0	0	0	0	1	1	0
Uterus							10	10	10	10	10	10
Immaturity												
Minimal							0	0	0	2	1	0
Mild							0	0	0	1	2	0
Moderate							0	0	0	1	3	8
Severe							0	0	0	0	3	0
Vacuolation, myometr												
Minimal							0	0	0	4	5	1
Mild							0	0	0	1	5	5
Vacuolation, endometrium, m-phage												
Minimal							0	0	2	4	1	2
Mild							0	0	0	5	8	6
Moderate							0	0	0	0	1	1
Vacuolation, epithel												
Minimal							0	0	2	5	0	1
Mild							0	0	0	3	1	3

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Moderate							0	0	0	2	9	6
Urinary bladder	10	0	0	10	10	10	10	10	10	10	10	10
Vacuolation, epithel												
Minimal	0			0	3	2	0	0	0	2	1	2
Mild	0			0	5	0	0	0	0	2	6	3
Moderate	0			0	2	0	0	0	0	1	2	3
Vacuolation, myofiber												
Minimal	0			0	6	0	0	0	2	4	5	4
Mild	0			0	4	0	0	0	0	0	4	1
Vagina							10	0	10	10	10	10
Cell infiltr, mononuc												
cell, myofiber							0		0	1	2	4
Minimal												
Vacuolation, m-phage							0		0	3	0	0
Minimal							0		0	1	7	6
Mild							0		0	0	3	2
Moderate												
Vacuolation, myofiber							0		0	3	3	5
Minimal							0		0	2	5	5
Mild												
Vacuolation, urethral							0		0	0	1	0
Minimal												
Vacuolation, epithel							0		0	1	6	3
Minimal							0		0	1	3	5
Mild												
Mammary glands	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation												
Minimal	0			0	0	0	0		0	5	1	4
Mild	0			0	0	0	0		0	4	9	5
Atrophy												
Minimal	0			0	2	0	0		0	0	0	0
Mild	0			0	2	0	0		0	0	0	0
moderate	0			0	2	0	0		0	0	0	0

120-L: 120 mg/kg loratadine active control group.

Toxicokinetics: Plasma concentrations increased supra-proportionally in a dose-dependent manner and were gender-dependent with exposure greater by up to 3.3-fold in females than in

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males following administration of SCH 34117 and loratadine (Table 11). SCH 34117 was slowly absorbed. The SCH 34117 exposure resulting from loratadine administration was similar to that observed at 60 mg/kg SCH 34117. Drug accumulation was observed with multiple dose administration, especially at the lowest dose. Loratadine exposure following loratadine administration was approximately 7 to 10-fold less than corresponding SCH 34117 exposure indicating extensive metabolism of loratadine.

Table 11. Toxicokinetics of SCH 34117 and loratadine.

Parameter	Dose (mg SCH 34117/kg)								Dose (mg SCH 29851/kg)		
	3		30		60		120		120		
	Day 1	Wk 9	Day 1	Wk 9	Day 1	Wk 9	Day 1	Wk 9	Day 1	Wk 9	
SCH 34117											
C _{max} (ng/ml)	Males	23.7	252	611	1150	1590	1650	2010	*	1250	2990
	Females	77	200	1000	2140	2140	4770	2320	*	1950	3370
T _{max} (hr)	Males	2.5	8	4	12	8	12	12	*	2.5	4
	Females	1	2.5	8	12	8	2.5	4	*	8	12
AUC (0-24 hr) (ng.hr/ml)	Males	169	1950	9490	26100	29000	34500	39000	*	23900	37800
	Females	556	1890	17700	42600	39800	69200	46300	*	39000	64200
R	Males		11.5		2.8		1.2		*		1.6
	Females		3.4		2.4		1.7		*		1.6
SCH 29851											
C _{max} (ng/ml)	Males									858	560
	Females									1260	779
T _{max} (hr)	Males									1	2.5
	Females									1	1
AUC (0-24 hr) (ng.hr/ml)	Males									4070	3940
	Females									5480	5990
R	Males										--
	Females										1.09

R = AUC (0-24 hr) week 9 / AUC (0-24 hr) day 1

NA: not applicable

* not assessed due to high mortality

A NOAEL of 3 mg/kg and 30 mg/kg was identified in females and males, respectively, due to kidney necrosis and reduced body weight gain. Systemic phospholipidosis (primarily vacuolation, atrophy and necrosis) was the main toxicity and was noted in organ systems throughout the body. Toxicity was more prominent in SCH 34117-treated animals based on a mg/kg basis. However, the toxicity profile was similar between the loratadine-treated group and the 60 mg/kg SCH 34117 as indicated by the pharmacokinetic similarities between the two groups.

Monkey, 3-Month Oral (Gavage) Toxicity

Study #: Schering Study #: 98212 Report #: P-6976 Volume: 23.4

Study Dates: Starting date: 7/1/1998; report issued: 6/1999
Testing Lab: Battelle, Columbus, OH
Test Article: SCH 34117 (Batch 97-34117-X-03-RA; purity not provided); SCH 29851 (Batch MI-A-00851; purity not provided)
Concentration: 1.2 to 14.4 mg/ml
Dose Volume: 5 ml/kg
GLP: This report was submitted with a signed GLP statement.
QA report: Yes.

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

Dose	0	6	12	18/24*	22/72*
(mg SCH 34117/kg/day):					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. The following observations were made:

Clinical observation . . . daily
 Body weight weekly
 Food consumption daily
 Water consumption . . . not assessed
 Health exam twice pre-study, Days 28 and 79; included body temperature, heart rate, and respiration rate
 Ophthalmoscopy Pre-test and week 12
 ECG Days -2, -5, 28 and 79; assessment included body temperature, heart rate, respiration, systolic blood pressure, diastolic blood pressure
 Hematology Days -12 and -5, and Days 23 and 92
 Clinical chemistry Weeks -2, and Days 12 and 24
 Urinalysis Days -12/13 and -5/6, and Days 22/23 and 91/92
 Enzyme induction Liver samples assayed for protein content, cytochrome P450 content, and 7-ethoxyresorufin O-deethylase. Results to be reported separately by sponsor.
 Organ weights at sacrifice (for specific tissues/organs see Addendum, page 32)
 Gross pathology at sacrifice
 Histopathology at sacrifice; organs/tissues collected from the control (vehicle and active), high-dose monkeys, monkeys sacrificed moribund and all gross lesions (for specific tissues/organs see Addendum, page 32).

Toxicokinetics 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.

Dose (mg/kg)	Males				Females			
	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 transferase % 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
Spleen - deformity	0	0	0	1	0	0	0	0	0	0

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	2
Mild	0	0	0	0	0	0			0	1
Atrophy, fat										
Severe	0	0	0	1	1	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. Infiltration, 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.

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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.

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.

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Addendum: Histopathology inventory for IND 55,364.

* 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

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.

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.

Timothy J. McGovern, Ph.D., Pharmacologist

Attachment I.
Attachment II.
Attachment III.

Original IND 55,364

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).

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22 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process