7 days. No unusual clinical signs or necropsy findings were observed. Food consumption was reduced in rabbits dosed with ≥ 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.

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 premating 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-Nitroflourene	(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 x 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

noted at 500 µg/plate for TA 1535, 500 µg/plate and above for TA 98 and at 1500 µg/plate for WP2uvrA. In the activation 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 and above for TA 100, 500 µg/plate for TA 98, 750 µg/plate and above for WP2uvrA and 1500 µg/plate for TA 1535. Slight cytotoxicity to the background lawn was observed at 250 µg/plate for TA 102, and at 1500 µg/plate for WP2uvrA. Marked cytotoxicity to background lawn and microcolonies were noted at 500 µg/plate for TA 100 and 102, and at 1500 µg/plate for TA 1535. Similar results were observed in the second mutation trial.

Thus, SCH 34117, up to 1500 µg/plate, was negative in the bacterial mutation test (Ames assay) using plate incorporation, in concurrence with the sponsor's conclusion.

Chromosome Aberration Study in Human Peripheral Lymphocytes

Report No.: P-6692 Study No.: *Volume:* 1.16

Study endpoint:	Clastogenicity
Study Dates:	Starting date 2/26/97; report issued 9/18/97
Testing Lab:	[redacted]
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: A series of chromosome aberration assays were performed ± metabolic activation (S9 fraction from Aroclor 1254-treated rats) using whole blood from two healthy donors, one male and one female. Duplicate cultures were exposed to either negative controls, solvent control, doses of SCH 34117 (adjusted in duplicate assays for toxicity) or doses of positive control. Assays were conducted with 24 and 48 hour treatment times without metabolic activation (male: 6.25-1500 µg/ml; female: 6.25-125 µg/ml) followed by 27 and 51 hour harvests, respectively. In addition, assays with a 3 hour treatment time ± metabolic activation (male: 6.25-1500 µg/ml; female: 12.5-200 µg/ml) followed by ~ 24 and 48 hour harvests were performed. The test drug was dissolved in 50% ethanol, while the positive controls, mitomycin C (for the nonactivation assays) and cyclophosphamide (for the activation assays) were dissolved in sterile deionized water. The mitotic index was assessed by analyzing the number of mitotic cells in 1000 cells/ culture. Cultures with a mitotic index < 40% of the solvent control were not scored for chromosome aberrations. One hundred cells, if possible, were analyzed from each duplicate culture for chromosome aberrations at the four highest dose levels of SCH 34117 (3 in the assay with metabolic activation, ~ 3 hr treatment and 24 hr harvest, donor 1), the negative control, solvent control and at one dose level of the positive control. At least 25 cells were analyzed from those cultures with greater than 25% of cells with one or more aberrations. In addition, the percentages of polyploidy and endoreduplication from at least one hundred cells from each duplicate culture were analyzed. A response was considered positive if the test article induced statistically significant increases in the number of cells with aberrations over those of the solvent controls at one or more concentrations in two donors and the increases showed a positive dose-

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 µg/ml. Lysis was also observed after dosing with 1000 and 1500 µg/ml; and at the time of washing the cell cultures at 125-1500 µg/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 µg/ml and 10 µg/ml (male and female donor, respectively: 24 hour treatment/27 hour harvest without metabolic activation), 25 and 10 µg/ml (male and female donor, respectively: 48 hour treatment/51 hour harvest without metabolic activation), 125 and 100 µg/ml (male and female donor, respectively: 3 hour treatment/24 hour harvest with metabolic activation), 125 and 130 µg/ml (male and female donor, respectively: 3 hour treatment/48 hour harvest with metabolic activation) and 90 and 50 µg/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 µg/ml in the male donor and 130 µg/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-recptors. 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 [redacted] 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 μg/ml). Resulting SCH 34117 concentrations (1.46 μg/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 premating 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 premating administration interval in males. It should be noted that ICH Guidelines for Detection of Toxicity to Reproduction (ICH S5A and S5B) recommend premating 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 (premating 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.

/S/

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 [redacted]
CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/P. Honig
HFD-570/G. Trout
HFD-570/T.J. McGovern

HFD-570 : DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review #6

IND No. —— **Serial No.** 159 **Submission Date:** 23 JUN 2000

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 28 JUL 2000

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

Sponsor: Schering Corporation, Kenilworth, NJ

Drug Names: Descarboethoxyloratadine (DCL) *Code Name:* SCH 34117
Class: Anti-histamine

Indication: Seasonal allergic rhinitis
Route of Administration: Oral (tablet)

Related INDs/NDAs: NDA 21-165

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

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

Review Type	Date of Submission(s)	Reviewer	Date of Review
Original Review	March 9, 1998	McGovern	May 22, 1998
Review #2	July 8-October 19, 1998	McGovern	October 27, 1998
Review #3	November 23, 1998	McGovern	December 15, 1998
Review #4	April 1 – October 5, 1999	McGovern	January 31, 2000
Review #5	April 26-November 1, 1999	McGovern	June 7, 2000

The following table summarizes the studies submitted and reviewed in this document:

Preclinical Studies Submitted and Reviewed in this IND:

Study	Report #	Volume
Sub-chronic Toxicology:		
Three-month dose-range finding study of SCH 34117 in mice	SN 97253	44.6
Genetic Toxicology:		
Bacterial mutagenicity study of SCH 45581	SN 99298	44.11
Mouse bone marrow erythrocyte micronucleus study of SCH 45581	SN 99539	44.11

Studies Submitted to the IND but not Reviewed: An addendum to the fertility study in male rats (—— submitted to NDA 21-165) was submitted to IND —— The review of the addendum which contains recovery data is incorporated with the main study review and can be

found in the Original Review for NDA 21-165. In addition, Study [redacted]

[redacted] or [redacted] was not reviewed.

Studies Previously Reviewed: None

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

Sub-Chronic Toxicity:

Mouse, 3-Month Oral (Diet) Dose-Ranging Toxicity Study
Sponsor Study No.: 97523 *Vol.*: 44.6

Study Dates:	Starting date: 5/17/1999; summary report issued: 5/22/2000
Testing Lab:	Schering Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch IRQ-98-13M1; purity not reported)
GLP:	This report included a signed GLP report.
QA report:	Yes.

This study was performed to determine doses for an 2 year carcinogenicity study of SCH 34117 in mice.

Methods: Mice (Crl/CD-1 BR VAF/Plus; 6 weeks old, 18.9-31 g) were assigned to the following treatment groups:

Dose (mg SCH 34117/kg/day):	Veh. Control	24	48	96	192
No./sex	10	10	10	10	10

SCH 34117 was given orally to mice as a dietary admixture *ad libitum* for 90 to 92 days. The following observations were made:

Clinical observation . . . assessed daily
Body weight . . . . . weekly
Food consumption . . . . weekly
Test article intake . . . . . weekly
Water consumption . . . not assessed
Health exam . . . . . not assessed
Ophthalmoscopy . . . . . pre-test and Weeks 4 and 12
ECG . . . . . not assessed
Hematology . . . . . Week 14
Clinical chemistry . . . . Week 14
Urinalysis . . . . . not assessed
Enzyme induction . . . . Liver samples assayed for protein content, cytochrome P450 content, 7-pentoxyresorufin O-dealkylase (PROD) activity and 7-ethoxy-resorufin O-dealkylase (EROD)

Organ weights . . . . . at sacrifice (organs included brain, epididymides, heart, kidneys, liver, lungs, ovaries, salivary glands, spleen, testes, thymus, uterus)
Sperm analysis . . . . . assessed in control and mid-high dose males
Gross pathology . . . . . at sacrifice
Histopathology . . . . . at sacrifice, all tissues were examined in the control (vehicle) and high-dose mice (for specific tissues/organs see Addendum, page 18). Target organs were evaluated to the no-effect level and all tissues from mice that died.
Toxicokinetics . . . . . not assessed; sponsor submitted data to NDA 21-165 (6/19/2000) from a 1 month TK study at doses used in current study.

Results:

Mortality: One high-dose male died on day 61 while another high-dose male and one mid-dose female were sacrificed in moribund condition on day 55 and 62, respectively (Table 1). However, the cause of death in the female was not explained and is not clearly related to the administered drug.

Table 1: Total incidence of mortality.

Dose (mg SCH 34117/kg/day):	0	24	48	96	192
Males	0	0	0	0	2
Females	0	0	0	1	0

Clinical Observations: Clinical observations were noted in the three highest dose groups and included abnormal stool (large fecal pellets), dehydration, hypoactivity and hunched appearance (Table 2).

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

Observation	Females					Males				
Dose (mg/kg)	0	24	48	96	192	0	24	48	96	192
Feces - enlarged	0	0	10	10	10	0	0	10	10	10
Hunched posture	0	0	0	0	3	0	0	0	0	1
Dehydration	0	0	0	0	2	0	0	0	0	1
Hypoactivity	0	0	0	1	1	0	0	0	0	1

Body Weight: Mean body weight gain were reduced by greater than 10% in the three highest dose-groups in males and in high-dose females (Table 3). Surviving high-dose males exhibited mean body weight loss of 1.2 g following the 13-week dosing period.

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

Dose (mg SCH 34117/kg/day):	0	24	48	96	192
Males					
Body weight – start dosing	28.8	28.5	28.3	28.9	28.5
Body weight – end dosing	35.8	36.2	34.4	34	27.3
% Δ in BW gain from control		↑10	↓13	↓27	↓ 1.2 g
Females					
Body weight – start dosing	21.9	21.6	21.9	21.9	21.5
Body weight – end dosing	28	28.5	29.4	29.6	23.8
% Δ in BW gain from control		↑13	↑23	↑26	↓63

Food consumption: Food consumption (g/animal/day) was reduced up to 22% and 27% in high dose males and females, respectively, compared to control animals throughout the study period.

Test article intake: Mean test article intake values were within 1.1% of the intended intake.

Ophthalmoscopy: No treatment-related findings were reported.

Hematology: Animal numbers in many groups were low (3). Lymphocyte and WBC numbers were reduced in SCH 34117-treated males and a slight decrease in lymphocytes was noted in high-dose females (Table 4).

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

	Males				Females			
	Dose (mg/kg)				Dose (mg/kg)			
Hematology	24	48	96	192	24	48	96	192
Lymphocytes % Δ from control	↓21	↓73	↓50	↓76	↑6	↑5	↑9	↓28
WBCs % Δ from control	↓12	↓65	↓40	↓55	↓19	↓20	↑8	↓5

Clinical Chemistry: The liver enzymes ALT, AST and AP were increased dose-dependently up to 6-fold of control values (Table 5). In addition, triglyceride levels were moderately decreased in males and females while glucose and cholesterol levels were decreased in high-dose males. Cholesterol levels were also reduced in upper-mid and high-dose females while BUN was increased in both high-dose males and females.

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

	Males				Females			
	Dose (mg/kg)				Dose (mg/kg)			
Parameter	24	48	96	192	24	48	96	192
Glucose % Δ from control	↓10	↓2	↓25	↓33	↓12	↑3	↑16	↑10
BUN % Δ from control	↓2	↑11	↑1	↑40	↓1	↑13	↑30	↑51
ALT % Δ from control	↓10	↑15	↑141	↑636	↓2	↑10	↑99	↑338
AST % Δ from control	↓10	↑6	↑58	↑353	↑2	↑15	↑58	↑162
AP % Δ from control	↑71	↑50	↑278	↑279	↑9	↑40	↑29	↑75
Cholesterol % Δ from control	↓13	↓6	↓1	↓55	↓17	↓3	↓40	↓53
Triglycerides % Δ from control	↓24	↓38	↓57	↓77	↓12	↓1	↓39	↓48

Enzyme Induction: Absolute liver weight, liver to body weight ratio and microsomal content were increased at the upper-mid and high doses (Table 6). Relative liver weight was increased at the three highest doses in males. EROD was increased at all doses (significant at the high-dose, 10 to 18-fold) and PROD levels were significantly increased (2.7 to 4.4-fold) at all doses but the highest in males. A similar pattern was noted in females although the levels of increase were not as great (EROD: 1.6 to 7-fold; PROD: 1.7 to 3.8-fold).

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

	Males					Females				
	Dose (mg/kg)					Dose (mg/kg)				
	0	24	48	96	192	0	24	48	96	192
Liver weight										
% Δ from control		↑6	↑7	↑17	↑30		↑6	↑9	↑35	↑36
Liver/Body wt ratio										
% Δ from control		↑4	↑12	↑26	↑69		↑6	↑8	↑93	↑64
Microsomal protein (mg/tot liver)										
% Δ from control		↑4	↑11	↑61	↑69		↑19	↑34	↑60	↑111
Cytochrome P450										
% Δ from control										
Nmol/mg microsomal protein		no Δ	no Δ	no Δ	↓30		↑26	↑32	↑37	↑21
Nmol/g liver		↓5	↑3	↑35	↓12		↑45	↑68	↑88	↑95
Nmol/total liver		↑4	↑10	↑59	↑19		↑53	↑84	↑138	↑163
Enzyme Induction										
% Δ from control										
PROD										
pmol/min/mg micros. protein		↑214	↑263	↑175	↓11		↑106	↑280	↑76	↓33
pmol/min/g liver		↑98	↑168	↑266	↑13		↑134	↑240	↑161	↑7
pmol/min/total liver		↑244	↑298	↑437	↑49		↑238	↑372	↑484	↑43
EROD										
pmol/min/mg micros. protein		↑180	↑150	↑312	↑992		↑58	↑90	↑160	↑233
pmol/min/g liver		↑160	↑151	↑439	↑1298		↑81	↑134	↑242	↑626
pmol/min/total liver		↑181	↑173	↑542	↑1543		↑90	↑154	↑526	↑603

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

Western blot analysis demonstrated a dose-related induction of CYP2B1/2 and CYP1A2 and that Cytochrome P-450 4A was increased at the two highest doses in males. Only protein levels of CYP2B1/2 were increased at all doses in females. The reduced activity of PROD at the higher doses suggests that CYP2B1/2may be inhibited at very high doses of SCH 34117.

Sperm Analysis: Mean sperm counts and concentrations of testicular spermatids or epididymides caudal sperm were not influenced by administration of the mid-high dose of SCH 34117.

Organ Weight: A dose-related increase in absolute and relative liver weight was observed at the upper-mid and high-doses (Table 7). Relative lung weight was also increased at the high dose. In addition, absolute and relative thymus weights were decreased at the high dose while uterine weight was decreased at the upper-mid and high-doses.

Table 7. Organ weight changes in mice following 3-month administration.

Organ weight	Males				Females			
Dose group (mg/kg)	24	48	96	192	24	48	96	192
Liver								
AOW-% Δ from control	5	6	15	29	7	13	36	40
RTB-% Δ from control	5	12	26	71	6	11	34	69
Lungs								
AOW-% Δ from control	5	-5	5	10	no Δ	6	11	11
RTB-% Δ from control	5	no Δ	14	46	1	1	8	36
Thymus								
AOW-% Δ from control	-7	-7	-17	-41	-29	3	-19	-47
RTB-% Δ from control	-7	-2	-10	-22	-30	1	-21	-36
Uterus								
AOW-% Δ from control					-14	-18	-33	-48
RTB-% Δ from control					-14	-20	-38	-39

AOW: Absolute organ weight RTB: Relative to body weight

Gross Pathology: Gross findings included distention in the gastrointestinal tract, discoloration of the kidney, and reduced size of the uterus primarily at the highest dose (Table 8). Kidney discoloration was the only finding with a histological correlate (necrosis) other than systemic phopsholipidosis.

Table 8. Gross observations in mice following 3-month oral administration.

Observation	Males					Females				
Dose (mg/kg)	0	24	48	96	192	0	24	48	96	192
n =	10	10	10	10	10	10	10	10	10	10
Stomach – altered content, black	0	0	0	0	1	0	0	0	0	0
Lg Intest. - distension	0	0	0	0	3	0	0	0	1	3
Kidney – discoloration, pale and/or tan	0	0	0	1	3	0	0	0	0	4
Uterus - small						0	0	0	0	3

Histopathology: Histological findings are summarized in Table 9. The primary findings were ubiquitous indicators of systemic phospholipidosis and included vacuolation, atrophy, necrosis and inflammatory cell infiltration. Findings were generally of greatest incidence and severity at the highest SCH 34117 dose.

Table 9. Histological changes in mice following 3-month administration.

Histopathology	**Males**					**Females**				
Dose group (mg/kg)	0	24	48	96	192	0	24	48	96	192
Brain – vacuolation of choroid plexus	**10**	**0**	**10**	**10**	**10**	**10**	**0**	**0**	**10**	**10**
Minimal	0		0	0	5	0			0	6
Mild	0		0	0	4	0			0	4
Moderate	0		0	0	1	0			0	0
Bone marrow –	**10**	**0**	**0**	**10**	**10**	**10**	**0**	**0**	**10**	**10**
Vacuolation– macrophage										
minimal	0			0	2	0			0	3
mild	0			0	6	0			0	5
moderate	0			0	1	0			0	1
Atrophy, fat										
Minimal	0			0	0	0			0	1
Epididymides	**10**	**0**	**10**	**10**	**10**					
Cellular debris, increased										
Minimal	0		0	0	4					
Mild	0		0	0	1					
Single cell necrosis , epithel.										
Minimal	0		0	0	3					
Mild	0		0	0	1					
Granuloma, sperm										
Mild	0		0	0	1					
Vacuolation, epithelium										
Minimal	0		0	7	0					
Mild	0		0	1	4					
Moderate	0		0	0	6					
Oligospermia										
Mild	0		0	0	1					
Eyes –	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Vacuolation, retinal, epithelium										
minimal	0	0	2	8	1	0	0	3	7	1
mild	0	0	0	1	3	0	0	0	3	6
moderate	0	0	0	1	3	0	0	0	0	1
Gall bladder–	**10**	**9**	**9**	**9**	**9**	**10**	**10**	**10**	**10**	**10**
Vacuolation, epithelium										
minimal	0	0	0	0	1	0	0	0	0	3
mild	0	0	0	0	1	0	0	0	0	0
Heart	**10**	**0**	**10**	**10**	**10**	**10**	**0**	**10**	**10**	**10**
Vacuolation, myofiber,										
Minimal	0		0	6	4	0		0	5	3
Mild	0		0	0	6	0		0	0	7
Necrosis, myofiber										
Minimal	0		0	0	2	0		0	0	1
Kidneys	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Vacuolation, epithelium										
Minimal	0	0	5	4	2	0	3	3	3	0
Mild	0	0	0	5	3	0	0	4	5	5
Moderate	0	0	0	1	5	0	0	3	2	5
Necrosis, epithelium										

Histopathology	Males					Females				
Dose group (mg/kg)	0	24	48	96	192	0	24	48	96	192
Minimal	0	0	0	2	3	0	0	0	0	4
Mild	0	0	0	0	3	0	0	0	0	0
Lymph nodes	**10**	**0**	**10**	**10**	**10**	**10**	**0**	**0**	**10**	**10**
Vacuolation, macrophage mandibular										
Minimal	0		0	0	0	0			0	3
Vacuolation, macrophage mesenteric										
Minimal	0		0	6	0	0			6	1
Mild	0		0	0	8	0			0	7
Moderate	0		0	0	2	0			0	2
Necrosis, lymphoid, mandibular										
Mild	0		0	0	0	0			0	1
Liver	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Vacuolation, kupfer cell										
Minimal	0	0	0	0	4	0	0	0	0	6
Mild	0	0	0	0	4	0	0	0	0	2
Moderate	0	0	0	0	1	0	0	0	0	0
Vacuolation, centrilob., hepatocellular										
Minimal	0	0	6	7	7	0	0	0	0	6
Mild	0	0	0	2	0	0	0	0	0	4
Moderate	0	0	0	0	3	0	0	0	0	0
Hypertrophy, centrilob										
Minimal	0	0	5	4	7	0	0	0	0	6
Mild	0	0	1	5	0	0	0	0	0	4
Moderate	0	0	0	0	3	0	0	0	0	0
Lungs	**10**	**0**	**10**	**10**	**10**	**10**	**0**	**10**	**10**	**10**
Accumulation, alv macrophage										
Minimal	0		0	0	3	0		0	1	2
Mild	0		0	0	6	0		0	0	6
Moderate	0		0	0	1	0		0	0	2
Vacuolation, alv macroph										
Minimal	0		0	0	6	0		0	0	2
Mild	0		0	0	3	0		0	0	8
Moderate	0		0	0	1	0		0	0	0
Vacuolation, epithelium										
Minimal	0		0	10	8	0		0	9	1
Mild	0		0	0	2	0		0	0	9
Crystal, eosinophilic										
Minimal	0		0	0	4	0		0	0	6
Mild	0		0	0	1	0		0	0	1
Moderate	0		0	0	0	0		0	0	1
Esophagus	**10**	**0**	**10**	**10**	**10**	**10**	**0**	**10**	**10**	**10**
Vacuolation, myofiber										
minimal	0		0	4	5	0		0	1	2
mild	0		0	0	5	0		0	0	7
moderate	0		0	0	0	0		0	0	1
Ovaries						**10**	**0**	**2**	**10**	**10**
Vacuolation, sex cord										

Histopathology	Males					Females				
Dose group (mg/kg)	0	24	48	96	192	0	24	48	96	192
Mild						0	0	0	0	5
Moderate						0	0	0	0	5
Vacuolation, corp lutea										
Minimal						0	0	0	0	1
Mild						0	0	0	0	2
Moderate						0	0	0	0	6
Necrosis, granulosa cell										
Minimal						0	0	0	0	4
Mild						0	0	0	0	3
Moderate						0	0	0	0	2
Pancreas	**10**	**0**	**0**	**10**	**10**	**10**	**0**	**0**	**10**	**10**
Vacuolation, epithelium exocrine										
Minimal	0			0	2	0			0	2
Mild	0			0	8	0			0	8
Parathyroid glands	**10**	**0**	**7**	**7**	**10**	**10**	**0**	**9**	**10**	**10**
Vacuolation, chief cell										
Minimal	0		0	0	2	0		0	0	0
Pituitary gland	**10**	**0**	**10**	**9**	**10**	**10**	**0**	**9**	**10**	**10**
Vacuolation, pars anterior										
Minimal	0		0	6	7	0		0	7	4
Mild	0		0	0	3	0		0	0	5
Moderate	0		0	0	0	0		0	0	1
Salivary gland	**10**	**0**	**0**	**10**	**10**	**10**	**0**	**0**	**10**	**10**
Vacuolation, ductular										
Minimal	0			0	5	0			0	5
Mild	0			0	1	0			0	1
Vacuolation, acinar										
Minimal	0			0	0	0			0	0
Atrophy, sublingual										
Mild	0			0	0	0			0	0
Cellular infiltration, mononuclear cell										
Minimal	0			0	0	0			0	0
Seminal vesicles	**10**	**1**	**0**	**10**	**10**					
Vacuolation, epithelium										
Mild	0	0		0	10					
Skeletal muscle	**10**	**0**	**0**	**10**	**10**	**10**	**0**	**0**	**10**	**10**
Vacuolation, myofiber										
Minimal	0			0	7	0			0	2
Mild	0			0	3	0			0	6
Moderate	0			0	0	0			0	2
Necrosis, myofiber										
Minimal	0			0	1	0			0	2
Skin	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Vacuolation, epithelium										
Minimal	0	0	0	4	2	0	0	0	4	1
Mild	0	0	0	0	5	0	0	0	0	6
Moderate	0	0	0	0	0	0	0	0	0	3
Panniculitis,										

Histopathology	Males					Females				
Dose group (mg/kg)	0	24	48	96	192	0	24	48	96	192
granulomatous										
mild	0	0	0	0	1	0	0	0	0	0
Harderian glands	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Pigment accumulation										
Minimal	0	0	0	3	0	0	0	3	0	0
Mild	0	0	2	5	5	0	0	2	9	5
Moderate	0	0	0	0	2	0	0	0	0	5
Cellular infiltration, macrophage										
Minimal	0	0	0	0	0	0	0	0	0	1
Stomach	**10**	**0**	**0**	**10**	**10**	**10**	**0**	**10**	**10**	**10**
Vacuolation, epithelium										
Minimal	0			0	4	0		0	3	3
Mild	0			0	3	0		0	0	4
Cellular infiltration, granulomatous										
Minimal	0			0	0	0		0	0	1
Single cell necrosis, epithelium										
Minimal	0			0	1	0		0	0	1
Small intestine	**10**	**0**	**10**	**10**	**10**	**10**	**0**	**10**	**10**	**10**
Vacuolation, lymphoid nodule, macrophage										
Minimal	0		0	0	0	0		0	0	1
Vacuolation, lamina propria, macrophage										
Minimal	0		0	2	6	0		0	0	4
Mild	0		0	0	3	0		0	0	5
Vacuolation, epithelium										
Minimal	0		0	3	6	0		0	6	9
Spleen	**10**	**0**	**10**	**10**	**10**	**10**	**0**	**10**	**10**	**10**
Vacuolation, m-phage										
Minimal	0		0	0	5	0		0	0	8
Mild	0		0	0	3	0		0	0	1
Necrosis, lymphoid										
Minimal	0		0	0	2	0		0	0	5
Mild	0		0	0	0	0		0	0	2
Depletion, lymphoid										
Minimal	0		0	3	4	0		0	0	6
Mild	0		0	0	4	0		0	0	2
Moderate	0		0	0	2	0		0	0	0
Testes	**10**	**0**	**0**	**10**	**7**					
Cellular debris, spermatic										
Minimal	2			0	4					
Thyroid	**10**	**0**	**10**	**10**	**10**	**10**	**0**	**10**	**10**	**10**
Vacuolation										
Minimal	0		0	1	3	0		0	0	5
Mild	0		0	0	1	0		0	0	4
Moderate	0		0	0	2	0		0	0	0
Thymus	**10**	**0**	**10**	**9**	**10**	**10**	**0**	**0**	**10**	**10**
Vacuolation, m-phage										
Minimal	0		0	0	4	0			0	3

Histopathology	Males					Females				
Dose group (mg/kg)	0	24	48	96	192	0	24	48	96	192
Mild	0		0	0	2	0			0	2
Necrosis, lymphoid										
Minimal	0		0	1	2	0			0	3
Mild	0		0	0	4	0			0	2
Moderate	0		0	0	0	0			0	1
Depletion, lymphoid										
Minimal	0		0	0	2	0			0	2
Mild	0		0	0	1	0			0	0
Moderate	0		0	0	2	0			1	1
Tongue	**10**	**0**	**0**	**10**	**10**	**10**	**0**	**0**	**10**	**10**
Vacuolation, myofiber										
Minimal	0			0	3	0			0	4
Mild	0			0	7	0			0	5
Moderate	0			0	0	0			0	1
Trachea	**10**	**0**	**10**	**10**	**10**	**10**	**0**	**10**	**10**	**10**
Vacuolation, epithelium										
Minimal	0		0	9	1	0		0	7	0
Mild	0		0	0	7	0		0	0	7
Moderate	0		0	0	2	0		0	0	3
Uterus						**10**	**10**	**10**	**10**	**10**
Vacuolation, epithelium, endometrium										
Minimal						0	0	0	0	9
Mild						0	0	0	0	1
Vacuolation, endometriu m-phage										
Minimal						0	0	0	0	4
Mild						0	0	0	0	4
Moderate						0	0	0	0	1
Atrophy										
Minimal						0	0	0	0	4
Mild						0	0	0	0	1
Urinary bladder	**10**	**0**	**10**	**10**	**10**	**10**	**0**	**0**	**9**	**10**
Vacuolation, epithelium										
Minimal	0		0	6	1	0		0	0	4
Mild	0		0	0	9	0		0	0	6
Vagina						**10**	**0**	**0**	**10**	**10**
Vacuolation, epithelium, cervix										
Mild						0			0	10
Ectasia, gland, clitoris										
mild						0			0	1
Mammary glands						**10**	**0**	**0**	**10**	**10**
Vacuolation										
Minimal						0			0	1
Mild						0			0	2
Moderate						0			0	1

This study was performed in order to determine doses in a 2 year Phase 4 mouse carcinogenicity study. An MTD of 48 mg/kg was selected in males due to systemic phospholipidosis at this dose and a significant reduction of body weight gain as well as kidney necrosis associated with systemic phospholipidosis at the next highest dose of 96 mg/kg. The MTD for females appears to be 96 mg/kg due to systemic phospholipidosis at this dose and findings of necrosis associated with systemic phospholipidosis and a significant reduction in body weight gain at the next highest dose of 192 mg/kg.

GENETIC TOXICOLOGY:

Bacterial Mutagenicity Study of SCH 45581

Report No.: P-6609 Study No.: 99298 *Volume:* 44.11

Study endpoint: Mutagenicity
Study Dates: Starting date 2/17/2000; report issued 5/23/2000
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 45581 (Batch 76214-141-4) diluted in DMSO
GLP: The study was accompanied by a signed GLP statement.
QA report: Yes.

Methods: SCH 45581 (3-hydroxy-desloratadine), a metabolite of 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-Nitroflourene	(5)	2-aminoanthracene	(2.5)
TA 100	sodium azide	(5)	2-aminoanthracene	(2.5)
TA 102	Cumene hydroperoxide	(200)	2-aminoanthracene	(5)
WP2 uvrA	N-Ethyl-N'-nitro-N-nitrosoguanidine	(2)	2-aminoanthracene	(20)

SCH 45581 and positive controls were dissolved in DMSO. Doses for Trial 1 were selected based upon results of a previous bacterial mutagenicity study with SCH 34117 and the two mutagenicity assays were conducted at the following concentrations:

Bacterial strain	Phase	Trial 1 Doses (µg/plate)	Trial 2 Doses (µg/plate)	Trial 3 Doses (µg/plate)
TA 1535	nonactivation	94, 188, 375, 750, 1500	63,125,250, 500, 1000	16, 31, 63,125,250, 500
TA 97A	nonactivation	12, 23, 47, 94, 188	4, 8, 16, 31, 63	4, 8, 16, 31, 63, 125
TA 98	nonactivation	47, 94, 188, 375, 750	31, 63, 125, 250, 500	
TA 100	nonactivation	23, 47, 94, 188, 375	16, 31, 63, 125, 250	
TA 102	nonactivation	23, 47, 94, 188, 375	16, 31, 63, 125, 250	4, 8, 16, 31, 63, 125
WP2uvrA	nonactivation	94, 188, 375, 750, 1500	125, 250, 500, 1000, 2000	
TA 1535	activation	94, 188, 375, 750, 1500	63,125,250, 500, 1000	
TA 97A	activation	12, 23, 47, 94, 188	8, 16, 31, 63, 125	
TA 98	activation	47, 94, 188, 375, 750	31, 63, 125, 250, 500	
TA 100, TA 102	activation	23, 47, 94, 188, 375	31, 63, 125, 250, 500	
WP2uvrA	activation	94, 188, 375, 750, 1500	125, 250, 500, 1000, 2000	

The experiments were performed using triplicate plates at each concentration incubated for 48 hours ± S9. Cytotoxicity was evaluated based on a reduction in revertant colony counts by ~ 30%, inhibition of background bacterial lawn growth and "additional factors based on scientific judgment". Tests were valid if overnight bacterial cultures reached a density of at least 5 x 10^8 cells/ml for *Salmonella typhimurium* strain, and approximately 15 x 10^8 cells/ml for *E. coli*, the mean number of spontaneous revertant colonies/plate was within the range of the historical solvent control values of the same strain, the mean number of induced 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, and at least three doses with revertants are required for data evaluation for each trial. Tests were positive that produced increases in revertant counts, as compared to solvent controls, with or without metabolic activation, in at least 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 first mutagenicity trial, SCH 45581 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 23 µg/plate and above for TA 97a, 94 and 375 µg/plate for TA 102, and at 750 µg/plate and above for TA 1535. Microcolonies were observed at 188 µg/plate for TA 102, at 375 µg/plate for TA 1535 and TA 100, at 188, 375 and 750 µg/plate for TA 98, and at 1500 µg/plate for WP2uvrA. Cytotoxicity to background lawn was observed at 375 µg/plate and above for TA 1535, at 188 µg/plate for TA97a and TA 98, at 188 µg/plate and above for TA 100, at 94 µg/plate and above for TA 102 and at 1500 µg/plate for WP2uvrA. In the activation phase, cytotoxicity to revertant colonies was observed at 23 µg/plate and above for TA 97a, 188 µg/plate and above for TA 102, 375 µg/plate for TA 100, 750 µg/plate and above for TA 1535, and at 1500 µg/plate and above for WP2uvrA. Microcolonies were observed at 750 µg/plate for TA 98 and cytotoxicity to background lawn was observed at 375 µg/plate for both TA 100 and TA 102, at 750 µg/plate and above for TA 1535, and at 750 µg/plate for TA 98.

SCH 45581 did not increase revertant colony counts, ± S9 activation, in the second trial. However, the revertant counts in strain TA 97a were below historical control levels and were repeated in Trial 3. In the nonactivation phase, cytotoxicity to revertant colonies was observed at 16 µg/plate and above for TA 97a, 63 µg/plate for TA 100, 125 µg/plate for TA 98, and at 500 µg/plate and above for TA 1535 and WP2uvrA. Microcolonies were observed at 63 and 125 µg/plate for TA 102, at 125 and 250 µg/plate for TA 1535, at 250 µg/plate and above for TA 98, and at 125 µg/plate and above for TA 100. Cytotoxicity to background lawn was observed at 16 µg/plate and above for TA 98, at 63 µg/plate and above for TA 1535, at 125 µg/plate and above for TA 100, at 250 µg/plate and above for TA 98 and at 2000 µg/plate for WP2uvrA. Strains TA 1535 and 102 were repeated in Trail 3 due to cytotoxicity at all doses tested. In the activation phase, cytotoxicity to revertant colonies was observed at 31 µg/plate and above for TA 97a, 250 µg/plate and above for TA 100 and 102, 500 µg/plate for TA 98, and at 1000 µg/plate and above for WP2uvrA. Microcolonies were observed at 500 µg/plate for TA 98 and at 1000 µg/plate for TA 1535. Cytotoxicity to background lawn was observed at 500 µg/plate for both TA 100 and TA 98, at 1000 µg/plate for TA 1535, and at 2000 µg/plate for WP2uvrA.

In the third trial, SCH 45581 did not increase revertant colony counts without activation in strains TA 97a, TA 102 and TA 1535. Cytotoxicity to revertant colonies was observed at 31 µg/plate and above for TA 97a, and at 125 µg/plate for TA 102. Microcolonies were observed at 500 µg/plate for TA 1535. Cytotoxicity to background lawn was observed at 125 µg/plate for both TA 97a and 102, and at 250 µg/plate and above for TA 1535.

Thus, SCH 45581, up to 1000 µg/plate in *Salmonella* strains and up to 2000 µg/plate in *E. coli*, was negative in the bacterial mutation test (Ames assay) using plate incorporation, in concurrence with the sponsor's conclusion.

Mouse bone marrow erythrocyte micronucleus study of SCH 45581

Schering Study No.: 99539 *Volume*: 44.11

Study endpoint:	Clastogenicity
Study Dates:	Starting date 12/13/1999; report issued 5/22/2000
Testing Lab:	Schering Plough Research Institute, Lafayette, NJ
Test Article:	SCH 45581 (Batch No. 75669-17) in 0.4% methylcellulose
GLP:	The study was accompanied by a signed GLP compliance statement.
QA report:	Yes.

Methods: SCH 45581 was evaluated for its potential to induce micronuclei in the bone marrow of male and female Crl:CD-1 ˙ 'BR VAF/Plus mice (6 weeks old; 19.6-31.9 g; 6/sex/dose/sacrifice time) following two consecutive daily IP doses of 10, 20 or 40 mg/kg (dose volume: 10 ml/kg; concentrations: mg/ml). Dose selection was based upon dose-ranging studies. In the first study excessive mortality was observed following a single IP doses of 125-2000 mg/kg (10 ml/kg). In the second study, mice were administered two consecutive daily IP doses of 6.25, 12.5, 25, 50 and 100 mg/kg. Mortality was observed at doses of 50 and 100 mg/kg in males and at the high dose in females. The PCE/NCE ratio was reduced by 19 and 61% at doses

of 25 and 50 mg/kg, respectively, in males and 18 and 53%, respectively, in females. Adverse clinical signs included rough hair coat and hypoactivity at doses of 50 mg/kg and greater.

Two definitive micronucleus trials were performed and mice were sacrificed at 24 hours after the 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 two bone marrow smears were prepared for each mouse. A total of 2000 polychromatic erythrocytes (PCE) for each mouse 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 the total number was estimated based upon PCE/NCE ratio. Bone marrow toxicity was evaluated by the PCE/NCE ratio which was determined by the number of NCE enumerated during scoring approximately the first 200 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 were 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: There was no significant increase in micronucleus frequency at any dose in males or females. Clinical signs were observed in high-dose animals (rough hair coat). In trial one, dose-related bone marrow toxicity was observed (9, 12 and 33% decrease in PCE/NCE ratios in males and 11, 14 and 24% in females at the low-, mid- and high-doses, respectively). At 48 hours, bone marrow toxicity was noted in mid- and high-dose males and females (11-12% and 23-36% reduction in PCE/NCE ratio, respectively). Cyclophosphamide induced a 16-fold and 6-fold increase of micronucleus frequency over the vehicle controls in trials one and two, respectively. The results indicate that SCH 45581 was negative under the conditions of this micronucleus assay, in concurrence with the sponsor's conclusion. However, the high-dose of 40 mg/kg appears to be low, especially in females, since no significant toxicity was observed in the definitive trials and since mortality in females was observed only at doses of 100 mg/kg or greater in the dose-ranging trials.

OVERALL SUMMARY AND EVALUATION:

Multiple Dose Toxicology: A 3 month oral (dietary admixture) dose-ranging study in mice (24, 48, 96 and 192 mg/kg) was performed for the purpose of dose selection for a Phase 4, 2 year mouse carcinogenicity study. Drug-related mortality was observed in two high-dose males. Mean body weight gain was reduced by greater than 10% in the three highest dose-groups in males (high-dose males lost weight) and in high-dose females. The primary histological findings were

indicative of systemic phospholipidosis (vacuolation, atrophy, necrosis, cellular inflammation) and were found in organs and tissues throughout the body including the brain, epididymides, heart, kidneys, liver, lungs, ovaries, seminal vesicles, stomach, spleen, thyroid, thymus, uterus, urinary bladder, and vagina. Histologic findings in the liver, lung, thymus and uterus were associated with significant changes in absolute or relative organ weight. Other significant findings included increased levels of BUN, AST, ALT and AP which were associated with histologic changes. In addition, induction of cytochrome P-450 in females and the enzymes EROD (2 highest doses) and PROD (3 lowest doses) as well as Cyp 2B1/2 (males and females) and Cyp 1A2 and P450 A (males only) were noted. An MTD of 48 mg/kg was identified in males and 96 mg/kg was selected in females. The toxicity profile is comparable to that observed previously in rats and monkeys.

Genetic Toxicology: An *in vivo* mouse bone marrow micronucleus assay and an Ames assay were performed with SCH 45581 (the 3-hydroxy metabolite of SCH 34117). Both assays were negative although high dose selection in the former study could likely have been increased. The results are consistent with the genotoxicity battery performed with SCH 34117.

RECOMMENDATIONS

1. High doses of 48 mg/kg in males and 96 mg/kg in females in the 2 year mouse carcinogenicity study are recommended due to significant reductions in body weight gain and systemic findings of vacuolation and necrosis at the next higher doses in the 3 month dose-ranging study in mice.

2. The low and mid-doses in males should be lowered to 4 and 16 mg/kg, respectively, to provide an adequate dose response for the high dose. Similarly, the low and mid-doses in females should be increased to 10 and 32 mg/kg, respectively.

3. The above recommendations are pending the CAC's concurrence. /S/

Timothy J. McGovern, Ph.D., Pharmacologist

Addendum 1: Histopathology inventory for SCH 34117.

IND [redacted]
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

Addendum 1: Histopathology inventory for IND [redacted] * Organ weight obtained

Study No.	P-6526	D18289	SN 98088	P-6973	P-6527	SN 98089	P-6976	SN 97253
Duration	14-day	14-day	28-day	3-month	14-day	28-day	3-month	3-month
Species	rat	rat	rat	Rat	monkey	monkey	monkey	mouse
Adrenals	X*		X*	X*	X*	X*	X*	X
Aorta	X		X	X	X	X	X	X
Bone marrow smear	X		X	X	X		X	X
Bone (femur)	X		X	X	X	X	X	X
Bone (rib)					X	X		
Bone (strenum)	X		X		X	X		
Brain:	X*		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*	X*
Esophagus	X		X	X	X	X	X	X
Eye	X		X	X	X	X	X	X
Fallopian tube								
Fat								
Gall bladder					X	X	X	X
Gross lesions	X	X			X	X	X	X
Harderian gland	X		X	X				X
Heart	X*		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*	X*
Lacrimal gland					X	X	X	
Larynx								
Liver	X*	X*	X*	X*	X*	X*	X*	X*
Lungs	X*	X*	X*	X*	X*	X*	X*	X*
Lymph nodes, cervical								X
Lymph nodes (LALN)				X			X	
Lymph nodes, mandibular	X		X		X	X		X
Lymph nodes, mediastinalis								
Lymph nodes, mesenteric	X		X		X	X		X
Mammary gland	X		X	X	X	X		X
Nasal cavity								
Optic nerves			X					
Ovaries	X*		X*	X*	X*	X*	X*	X*
Oviduct								
Pancreas	X	X	X	X	X	X	X	X
Parathyroid	X		X	X	X	X	X	X
Peripheral nerve				X				X
Pharynx								
Pituitary	X*		X*	X*	X*	X*	X*	X
Prostate	X*		X*	X*	X*	X*	X*	X
Rectum								
Salivary gland	X*		X*	X*	X*	X*	X*	X*
Sciatic nerve	X		X		X	X		
Seminal vesicles	X		X	X	X	X	X	X
Skeletal muscle	X		X	X	X	X	X	X
Skin	X		X	X	X	X	X	X
Spinal cord	X		X	X	X	X	X	X
Spleen	X*		X*	X*	X*	X*	X*	X*
Stomach	X		X	X	X	X	X	X
Testes	X*		X*	X*	X*	X*	X*	X*
Thoracic Limb	X							
Thymus	X*		X*	X*	X*	X*	X*	X*
Thyroid	X*		X*	X*	X*	X*	X*	X
Tongue	X		X	X	X	X	X	X
Trachea	X		X	X	X	X	X	X
Urinary bladder	X		X	X	X	X	X	X
Uterus	X*		X*	X*	X*	X*	X*	X*
Uterine horn								
Vagina	X		X	X	X	X	X	X

17 pages redacted from this section of the approval package consisted of draft labeling

HFD-570 : DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review #5

IND No. [redacted] **Serial No.** 051 **Submission Date:** 26 APR 1999
094 01 NOV 1999

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 07 JUN 2000
2000

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

Sponsor: Schering Corporation, Kenilworth, NJ

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

Class: Anti-histamine

Indication: Seasonal allergic rhinitis

Route of Administration: Oral (tablet)

Proposed Clinical Protocols: None with these submissions.

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

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

Review Type	Date of Submission(s)	Reviewer	Date of Review
Original Review	March 9, 1998	McGovern	May 22, 1998
Review #2	July 8-October 19, 1998	McGovern	October 27, 1998
Review #3	November 23, 1998	McGovern	December 15, 1998
Review #4	April 1 – October 5, 1999	McGovern	January 31, 2000

The following table summarizes the studies submitted and reviewed in this document:

Preclinical Studies Submitted and Reviewed in this IND:

Study	Report #	Serial #
Safety Pharmacology:		
Effect of loratadine and its metabolite, descarboethoxyloratadine, on the QT interval in the isolated perfused rabbit heart model (Langendorff)	30523	051
Effect of IN-0133 on electrophysiological and mechanical properties of guinea pig ventricular muscle	30416	051
Effects of IN 0132 on the Na+ current in rabbit ventricular myocytes	30417	051
Report on the effect of IN-0132, IN-0133, 0049 and IN-0057 on two K currents, iKr and iKl in rabbit ventricular myocytes	30148	051
Pharmacokinetics:		
SCH 34117: A study of the tissue distribution of radioactivity in male and female sprague dawley rats and ⁀ rats following a single oral dose of ^{14}C-SCH 34117	P-6741	094

Studies Not Reviewed in this IND:

Studies Previously Reviewed: None

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

SAFETY PHARMACOLOGY: The sponsor submitted four reports which assessed the comparative potential to induce adverse cardiac events of SCH 34117 and loratadine; results of these studies are summarized in Table 1. SCH 34117 increased QT interval (up to 41% at 10 μM) in a dose- and time-dependent manner in isolated rabbit hearts, primarily due to increasing the QRS complex (up to 5-6-fold at 10 μM). SCH 34117 alone did not affect JT interval but enhanced a quinidine-induced increase. Loratadine had no effects on QT, QRS or JT intervals at concentrations up to 50 μM. In isolated perfused guinea pig left ventricular papillary muscle, SCH 34117 decreased Vmax and velocity of impulse conduction and increased excitation threshold (≥ 30 μM) while producing a negative inotropic effect (10 μM). No effect was noted on resting potential or action potential duration up to 100 μM. In isolated rabbit ventricular myocytes, SCH 34117 (100 μM) reduced Na+ current more effectively than 100 μM loratadine; loratadine showed preferential binding to channel in inactivated state. Other effects included reduced delayed rectifier current (iKr) to ~ ½ control value at 6 x 10^{-6} M as the concentration at

which ½ current is blocked (k0.5) was 5 x 10^{-6} M (k0.5 for loratadine was 8.7 x 10^{-6}). SCH 34117 had no effect at 10^{-5} M on inward rectifier current (iK1) although the curve was flatter at 3 x 10^{-5} M; loratadine had more pronounced effect than SCH 34117. Thus, SCH 34117 exerted effects on various cardiac parameters at concentrations ranging from 5-100 µM.

Table 1. Safety pharmacology studies demonstrating cardiac effects of SCH 34117.

Parameter/Model	**Activity**
Isolated, perfused rabbit hearts	SCH 34117: increased QT interval (15% and 41% at 5 µM and 10 µM, respectively, after 30 minutes); experiments prematurely terminated after 50 µM due to sustained ventricular fibrillation; NOEL = 1 µM. QT increase at 10 µM increased through first 100 minutes; could not be measured after 2 hours due to flattening of T wave; QRS interval increased 5 to 6-fold at 10 µM 2 hours after dosing; increased up to 34% at 0.5 µM after 3 hours; NOEL = 0.2 µM. No effect of SCH 34117 alone on JT interval. Produced nearly two-fold increase in JT interval at 0.5 µM in combination with quinidine compared to quinidine alone (15%). Loratadine (up to 50 µM) had no effect on QT, QRS or JT intervals
Perfused guinea pig left ventricular papillary muscle	**Remark: Drug listed in report as IN-0133, assumed to be SCH 34117.** No effect on resting potential or action potential duration at drug concentration of 10, 30 or 100 µM. SCH 34117 decreased Vmax at ≥ 30 µM with pacing at 1 Hz; decrease of 57% at 100 µM. Associated with decrease in velocity of impulse conduction and increase in excitation threshold. Decrease in Vmax enhanced at higher pacing frequencies. Full reversibility not obtained up to 2 hrs. Negative inotropic effect in 4 of 5 preparations at 10 µM (decreased isometric force to 70% of pre-drug level at 1 Hz).
Isolated rabbit ventricular myocytes	**Remark: Drug listed in report as IN-0133, assumed to be SCH 34117.** **Drug listed in report as IN 0132, assumed to be Loratadine.** Effects on Na+ current: SCH 34117 (100 µM; 5-10 min) reduced Na+ current at holding potentials of -100 to -80 mV more effectively than 100 µM loratadine. Loratadine showed preferential binding to channel in inactivated state. Effects on delayed rectifier current (iKr): SCH 34117 (6 x 10^{-6} M) reduced iKr current to ~ ½ control value at 10 mV. Only small remnant of iKr current visible at 3 x 10^{-5} M. Concentration at which ½ current is blocked (k0.5) = 5 x 10^{-6} M. k0.5 for loratadine = 8.7 x 10^{-6} M Effect on inward rectifier current (iK1): no effect at 10^{-5} M; IV curve flatter at 3 x 10^{-5} M. Loratadine had more pronounced effect than SCH 34117 and was more slowly reversible.

PHARMACOKINETICS AND TOXICOKINETICS:

Pharmacokinetic parameters in rats following oral (gavage) administration are summarized in Table 2. The Cmax and AUC for total radioactivity were 1.5-1.8 times higher in males. Plasma concentrations of unchanged drug at 3 hours were 2.6 times higher in females than in males. The plasma concentrations < LOQ — ng/ml) by 24 hours in males and 72 hours in females. The AUC for SCH 34117 was not calculated since the concentration fell below the LOQ before adequate elimination phase could be described.

Table 2. PK values following single oral dose of SCH 34117 (6.5 mg/kg) in SD rats.

Parameter	Males	Females
	Drug-derived radioactivity	
Cmax (µg equiv/g)	0.648	0.426
Tmax (hr)	6	3
AUC(tf) (µg equiv.hr/g)	13.9	7.65
	SCH 34117	
Cmax (µg/ml)	0.0995	0.259
Tmax (hr)	3	3
AUC(tf) (µg equiv.hr/g)	Not calculated	Not calculated

Previously submitted 14-day and 3-month studies in rats have demonstrated similar findings at comparable doses including increased SCH 34117 exposure in females.

Distribution: Table 3 summarizes the tissue distribution of a single oral (gavage) dose of ^{14}C-SCH 34117 (6.5 mg/kg) in Sprague Dawley rats. In males, tissues (excluding GI tract) with the highest concentrations of radioactivity (6 hours) were the pituitary, adrenal gland, lung, liver, and mesenteric lymph nodes. At 168 hr post-dose the concentration of radioactivity in most tissues was about 1- to 12-fold greater than those in plasma and the tissue to plasma ratios were generally higher than those at 6 hours. At 672 hours post-dose 0.071% of administered dose was in collected tissues and only thyroid had notable concentrations (consistent with loratadine studies). Females were similar to males in terms of tissue distribution and brown fat, peritoneal fat kidneys and thyroid concentrations were higher than plasma at 168 hours and only 0.002% of administered dose was noted in collected tissues. The tissues with lowest concentrations were the plasma, brain, blood, eyes, spinal cord, and testes. The results suggest a greater penetration of drug-derived radioactivity into tissues in female rats compared to males as mean plasma concentrations were 2- to 4-fold higher from 1 to 6 hours and radioactivity concentrations in many tissues in females at 1, 3 and 6 hours post-dose were approximately 1.5- to 2.5-fold greater in comparison to males.

Table 3. Tissue distribution of ^{14}C-SCH 34117 in rats after single oral gavage administration.

Tissue	Males (6 hrs)		Females (3 hrs)	
	Total radioactivity (µg equiv/g)	Tissue:Plasma ratio	Total radioactivity (µg equiv/g)	Radioactivity in peptide fraction
Plasma	0.648	1	0.426	1
Adrenal gland	17.7	27.2	30.2	70.9
Harderian gland	10.2	15.7	11.7	27.5
Kidney	7.90	12.2	13.3	31.2
Liver	15.4	23.8	20	46.9
Lungs	15.5	23.9	28.4	66.7
Mes. Lymph nodes	12	18.5	11.9	27.9
Pituitary	30.4	46.9	31.8	74.6
Spleen	8.17	12.6	14.7	34.5
Thyroid	8.44	13	14.3	33.6

In male Long Evans rat there was no difference in binding of radioactivity to pigmented or non-pigmented skin following a single oral gavage dose (6.5 mg/kg; Table 4). The eye had concentrations ranging from to µg equiv/g which declined slowly and were still detectable at 672 hours. The highest concentrations were detected in the liver and kidneys.

Table 4. Tissue distribution in male Long Evans rats after single oral gavage administration.

Tissue	Males (3 hrs)	
	Total radioactivity (µg equiv/g)	Tissue:Plasma ratio
Plasma	0.795	
Blood	0.875	1.1
Eyes (pigmented)	3.57	4.49
Kidney	9.27	11.7
Liver	26	32.7
Skin (non-pigmented)	1.58	1.99
Skin (pigmented)	1.72	2.16

Excretion: Following a single oral dose of ^{14}C-SCH 34117 to Sprague Dawley rats, 98 and 95% of administered radioactivity was recovered by 168 hours from males and females, respectively. 69-70% of the dose was recovered in feces while 25-27% was eliminated in urine. Negligible amounts were recovered in cage wash and as CO_2 (0.06-0.36%).

OVERALL SUMMARY AND EVALUATION

Safety Pharmacology: SCH 34117 dose- and time-dependently increased QT interval (up to 41% at 10 μM) in isolated rabbit hearts, due primarily to increasing the QRS complex up to 5-6-fold. SCH 34117 did not increase JT interval alone but did enhance a quinidine-induced increase. Loratadine had no effects on QT, QRS or JT intervals at up to 50 μM. SCH 34117 also decreased Vmax and velocity of impulse conduction and increased excitation threshold (≥ 30 μM) while producing a negative inotropic effect (10 μM) in isolated perfused guinea pig left ventricular papillary muscle. No effect was noted on resting potential or action potential duration up to 100 μM. In isolated rabbit ventricular myocytes, SCH 34117 (100 μM) reduced Na+ current more effectively than 100 μM loratadine; loratadine showed preferential binding to channel in inactivated state. Other effects included reduced delayed rectifier current (iKr) current to ~ ½ control value at 6×10^{-6} M as the concentration at which ½ current is blocked (k0.5) was 5×10^{-6} M (k0.5 for loratadine was 8.7×10^{-6}). SCH 34117 had no effect at 10^{-5} M on inward rectifier current (iK1) although the curve was flatter at 3×10^{-5} M; loratadine had more pronounced effect than SCH 34117. Thus, SCH 34117 exerted effects on various cardiac parameters in vitro at concentrations ranging from [redacted] μM. SCH 34117 was previously shown to have less or equal potency compared to loratadine in inhibiting rat and guinea pig cardiac K+ channels as well as a cloned human hKv1.5. All findings were observed during in vitro assessments while in vivo studies in monkeys for up to 3 months produced no drug-related effects on cardiac parameters. In addition, the absence of loratadine-induced adverse cardiac effects in humans suggests that SCH 34117 is reasonably safe in this regard. A previous consult with Dr. Peter Honig, acting Medical Officer, concluded that no further preclinical assessment of cardiovascular effects is necessary.

Pharmacokinetics: The Cmax and AUC for total radioactivity following oral gavage administration were 1.5-1.8 times higher in males compared to females. However, plasma concentrations of unchanged drug was 2.6 times greater in females at 3 hours after dosing. Plasma concentrations were less than the LOQ by 24 hours in male and 72 hours in female. Tissue distribution of a single oral (gavage) dose of ^{14}C-SCH 34117 in Sprague Dawley rats was observed primarily in the pituitary, adrenal gland, lung, liver, spleen and mesenteric lymph nodes. At 168 hr post-dose the concentration of radioactivity in most tissues was about 1- to 12-fold greater than those in plasma and the tissue to plasma ratios were generally higher than those at 6 hours. At 672 hours post-dose 0.071% of administered dose was in collected tissues and only thyroid had notable concentrations (consistent with loratadine studies). The results suggest a greater penetration of drug-derived radioactivity into tissues in female rats compared to males as mean plasma concentrations were 2- to 4-fold higher from 1 to 6 hours and radioactivity concentrations in many tissues in females at 1, 3 and 6 hours post-dose were approximately 1.5- to 2.5-fold greater in comparison to males. Tissue distribution if SCH 34117 is comparable to that observed during the loratadine development program. No difference in tissue distribution to pigmented or non-pigmented skin was noted in male Long Evans rats although radioactivity was detected in the eye. A single oral gavage dose of ^{14}C-SCH 34117 was excreted primarily in feces.

RECOMMENDATION

None at this time.

/S/

Timothy J. McGovern, Ph.D., Pharmacologist

Original IND [redacted]
CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/R. Nicklas
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. [redacted]	**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):

Review Type	Date of Submission(s)	Reviewer	Date of Review
Original Review	March 9, 1998	McGovern	May 22, 1998
Review #2	July 8-October 19, 1998	McGovern	October 27, 1998
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.

TOXICOLOGY
MULTIPLE-DOSE TOXICITY:

Rat, 3-Month Oral (Gavage) Toxicity

Doc. No.: P-6973 *Study No.:* [redacted] *Sponsor Study No.:* 97016 *Vol.:* 23.1

Study Dates: Starting date: 3/9/1998; summary report issued: 7/1999
Testing Lab: [redacted]
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-pentoxyresorufin 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.

..... 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 ≥ 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 ≥ 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.

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

Observation	Females						Males					
Dose (mg/kg)	**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	[redacted]	[redacted]	[redacted]
Females					
% Δ from control	↓7	[redacted]	[redacted]	[redacted]	[redacted]

*: 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	↓13	↓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	↓62	↓27
Monocytes % Δ from control		↑7	↓64	↓86	↑147	↓70		↑48	↓71	↑176	↑8	↓33
Eosinophils % Δ from control		0	↓15	↓20	↓59	↓80		↑38	↓15	↓78	↓79	↓46
Neutrophils % Δ from control		↑9	↓4	↑36	↑50	↑50		↑48	↑16	↑170	↑377	↑175
Prothrombin time (seconds)	13	13	12	12	13	11.5	11	11	10.9	11		11
APTT (seconds)	12	11	11	11	9.9	11	10	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				↓16	↑6	↑4	↓14		↓12
Cholesterol % Δ from control	↑12	↑26			↑12	↑11	↑21		↑24	
Globulin % Δ from control	no Δ	↑9		↑15		↑10	↑15	↑15	↓12	
Total protein % Δ from control	↑5			↓3		↑7	↑7	↓7	↓15	↑1
Aspartate aminotrans % Δ from control	↑2	↓11	↓14		↓14	↑2	↑22			↑32
Alanine aminotrans % Δ from control	↑8	↑11	↑14	↑231	↑25	↑37	↑39	↑16	↑103	↓20
AG ratio % Δ from control	↑2	↓1	↓15		↓13	↓5	↓8		↓1	
Glucose % Δ from control	↓6	↓6	↓10		no Δ	↓5			10	
Triglycerides % Δ from control	↑17	↓22				↑10	↑21	↑74		
BUN % Δ from control	↓7	no Δ	no Δ	↑159	↑14	no Δ	↓6			

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.

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

	Males					Females				
Dose (mg/kg/d)	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	[illegible]
Microsom protein (mg/tot liver)										
% Δ from control		↑21	↑98	↑71	↑102		↓4	↑15	↑36	[illegible]
Cytochrome P450										
% Δ from control										
Nmol/mg microsomal protein		↓6	↑7	↑9	↑13		no Δ	↑15	↑47	[illegible]
Nmol/g liver		↑13	↑52	↑138	↑29		↓8	↑41	↑88	[illegible]
Nmol/total liver		↑11	↑110	↑186	↑129		↓8	↑31	↑89	[illegible]
Enzyme Induction										
% Δ from control										
PROD										
pmol/min/mg micros. protein		↓5	↑688	↑140	[illegible]		↑6	[illegible]	↑97	↑15
pmol/min/g liver		↑17	↑1053	↑210	[illegible]		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	[illegible]	44	-10	20	66	3	39
24-hour volume % Δ from control	13	[illegible]	[illegible]	-19	[illegible]	-2	21	20	20	[illegible]
Osmolarity % Δ from control	-17	[illegible]	-43	6	[illegible]	8	-17	[illegible]	-18	[illegible]

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		48	10	69	4	4			76
RTB	4		78	127	10	5	16	44		124
RTBr	6		53	15	71	1	5	35		87
Lungs										
AOW-% Δ from control	-11	20	44	40	22	10	68	130		105
RTB	-10	27	73	187	46	11	88	209		156
RTBr	-9	24	49	46	25	7	70	138		119
Spleen										
AOW-% Δ from control	-2	24	-24	-52	-11	-4	-18	-30		-15
RTB	-1	19	-8	-2	-1	-3	-9	-10		7
RTBr	1	-21	-21	-50	-15	-7	-17	-29		-10
Thymus										
AOW-% Δ from control	11	-4	-23	-43	-3	19	-11	-37		-26
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	35		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	7	4	11	35		19
Heart										
AOW-% Δ from control	-3	-7	-11	-18	-9	4	-4	-7		-1
RTB	-3	-2	7	67	7	5	8	28		25
RTBr	no Δ	-4	-8	-15	-7	1	-3	-3		6
Kidneys										
AOW-% Δ from control	1	-4	-3	33	-1	2	1			48
RTB	1	2	14	173	12	3	13			
RTBr	4	no Δ	no Δ	38	2	-1	3			

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
Unscheduled deaths												
n =	0	0	0	0	9	0	0	0	2	6	10	6
Cecum - 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					
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**	**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**	**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**
Minimal	0		0	0	5	0	0		0	6	1	5
Mild	0		0	0	5	0	0		0	1	7	4
Moderate	0		0	0	0	0	0		0	0	2	0
Vacuolation – myofiber												
Minimal	0		0	0	6	0	0		0	7	0	6
Mild	0		0	0	3	0	0		0	2	10	3
Moderate	0		0	0	1	0	0		0	0	0	0
Fibrosis, myofiber												
Minimal	0		0	0	6	0	0		0	2	2	5
Mild	0		0	0	0	0	0		0	2	7	4
Degeneration, myofiber												
Minimal	0		0	0	9	0	0		0	5	6	8
Mild	0		0	0	0	0	0		0	2	0	0
Moderate	0		0	0	0	0	0		0	1	0	0
Bone marrow –	**10**	**0**	**10**	**10**	**10**	**10**	**10**	**0**	**10**	**10**	**10**	**10**
Hypercellularity – min	0		0	0	0	2	0		0	2	0	0
Hypocellularity – min	0		0	0	1	0	0		0	0	4	2
- mild	0		0	0	2	0	0		0	0	0	1
Mastocytosis – min	0		0	0	1	0	0		0	0	0	0
- mild	0		0	0	1	0	0		0	0	0	0
Vacuolation – scattered												
minimal	0		0	0	5	0	0		0	2	2	5
mild	0		0	0	3	0	0		0	1	5	1
moderate	0		0	0	1	0	0		0	0	3	1
Atrophy, fat												
Mild	0		0	0	1	0	0		0	0	0	0
Moderate	0		0	0	6	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												
Minimal	0	0	0	0	2	0						

Histopathology	Males						Females					
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
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**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**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**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**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**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**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**	**10**	**10**	**10**	**10**	**10**	**10**	**1**	**10**	**10**	**10**	**10**
Vacuolation, mphage												
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