

Reproduction parameters . . . . . Copulated females sacrificed on day 14 of gestation; assessment for number of corpora lutea, implantation sites, live/dead fetuses, and resorptions, distribution of fetuses in the uterus, fertility indices, precoital interval, male and female mating index, dead embryos, sex of fetus, weight of fetus/placenta  
 Statistics . . . . . Deemed unnecessary.

## Results:

*Mortality:* No deaths were reported.

*Clinical Observations:* Fecal changes were observed at all dose levels and included enlarged fecal pellets and reduced number of fecal pellets. Observations increased with increasing dose. Small sized stool was noted at the mid- and high-doses and no stool observed at the high-dose. Soft stool was also noted in 1-2 animals/sex at each dose level.

*Body Weight:* Mean body weights in females were reduced compared to dosing day 1 in all groups after 3 days dosing (Day 17) with mid- and high-dose groups demonstrating greater losses (7 and 11.5 g, respectively) than control animals (Table 25). By the seventh day of dosing (Day 21), all groups had recovered except for high dose animals (reduced by 0.8 g). By dosing day 14 (Day 28), all groups were comparable. Body weight gain from day 0-6 of gestation was reduced by 28% and 40% in mid- and high-dose dams, respectively. Over the entire dosing period, body weight gain was reduced by 35% in high-dose dams. Absolute body weight was reduced by 8% over the same time period. Body weight gain in males was not affected throughout the study.

**Table 25:** Summary of effects on body weight in females.

Dose (mg/kg)	0	6	12	24
Premating BW gain (g)				
Day 17	-3.7	-2.2	-7	-11.5
Day 21	no change	2.6	0.6	-0.8
Day 28	9.5	7.6	10.2	8.3
Gestation BW gain				
Day 0-6 - % $\Delta$ from control		-6	-28	-40
Day 0-14 - % $\Delta$ from control		-6	-13	-22
BW gain over entire dosing period: (Day 14 Premating – Day 6 Gestation) % $\Delta$ from control		-19	-14	-35

*Food Intake:* Food consumption was reduced by 19% in high-dose dams after the first week of dosing but recovered in the second week. Mean food consumption was again reduced by 17% after gestation day 7 but recovered thereafter. No significant findings were noted in males.

*Estrus cycle:* No drug-related effects were observed.

*Necropsy:* No drug-related effects on organ weights (testis or epididymis) or macroscopic findings were noted. However, histologic examination of the reproductive organs revealed an

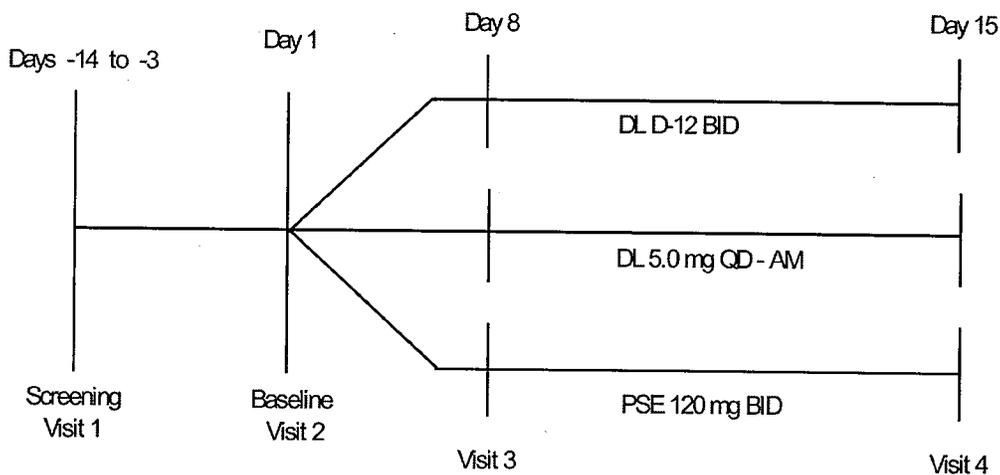
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- Astemizole 3 months
- MAO Inhibitors 14 days
- Nasal, oral, or ocular decongestants 3 days
- Topical anti-inflammatory drugs (other than corticosteroids) 3 days
- Nasal atropine or ipratropium bromide 1 week
- Systemic antibiotics (unless on a stable dose for prophylactic therapy) 2 weeks
- Nasal saline 12 hours
- Ocular saline 12 hours
- Ocular levocabastine 3 days

#### (j) Conduct

The diagram below illustrates the conduct of the study:



Follow-up visits on Days 8 and 15 (Visits 3 and 4).

During the 3-14 day “diary run-in period” (between Screening and Baseline) subjects completed diary cards addressing SAR symptoms, adverse events, and the use of concomitant medications. Both instantaneous and reflective (previous 12 hours) signs and symptoms were recorded in the diary. Symptom severity was scored using a 0-3 scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, and 3=severe symptoms). Diary cards were completed upon arising (before dosing) and approximately 12 hours later. Subjects who qualified at Screening and Baseline were randomized and treated with study medication for two weeks.

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In order to qualify at Screening the subject must have had reflective scores as follows:

- Nasal rhinorrhea score of at least 2 (moderate)
- Nasal congestion score of at least 2 (moderate)
- Total nasal symptom score of at least 6
- Total non-nasal symptom score of at least 5

In order to qualify at Baseline the subject must have had a minimum of three complete days of diary entries (AM and PM). On the morning of Baseline, the seven bi-daily reflective scores (three calendar days prior to Baseline and AM of the day of Baseline) must have shown:

- Total nasal rhinorrhea score of at least 14
- Total nasal congestion score of at least 14
- Total nasal symptom score of at least 42
- Total non-nasal symptom score of at least 35

Follow-up visits were scheduled on Day 8 and Day 15. During the treatment period patients continued to record the severity of their signs and symptoms, both reflective and instantaneous, twice daily. Other information recorded in patient diaries included the daily number of hours the subject was exposed to outside air, any adverse events, additional medication taken, and whether the study medication was taken as directed.

At each visit the "overall condition of SAR" for the entire time period since the last visit was jointly graded by the Investigator and the subject, using a 0-3 scale. At Visits 3 and 4, after the diaries had been reviewed, the subject and Investigator jointly graded the response to test drug treatment, based on the entire time period since the last visit. For this parameter a 1-5 scale was used, ranging from "complete relief" (1) to "treatment failure" (5) [S8/P00355/917-918].

The table below outlines the various study procedures. Electrocardiograms were performed at baseline and at Visit 4 (1-3 hours post dose).

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Study Flow Chart (Study P00355)		[S8/P00355/898]			
	Screening	Baseline			
	Visit 1	Visit 2	Visit 3	Visit 4	
Study Days	Days -3 to -14	Day 1	Day 8	Day 15	
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Physical Exam/Medical Disease History	X				
Concomitant Medications Review	X	X	X		X
Vital Signs (blood pressure, pulse, respiration rate)	X	X	X		X
Body Height and Weight	X				
Skin Test <sup>a</sup>	X				
12-Lead Electrocardiogram	X				X
Pregnancy Test	X				X
Complete blood count, blood chemistry, urinalysis	X				X
Rhinitis Signs and Symptoms (Joint)	X				
Rhinitis Signs and Symptoms and Severity from Diary		X			
Overall Condition of Seasonal Allergic Rhinitis	X	X	X		X
Evaluation of Therapeutic Response			X		X
Dispense Diaries	X	X	X		
Provide Instruction on Symptom Diary	X	X	X		
Collect/Review Symptom Diary		X	X		X
Dispense Study Medication		X	X		
Collect/Count Study Medication			X		X
Adverse Events Evaluation		X	X		X

a: If not done within previous 12 months.

Each study site recorded daily pollen counts and rain days for the time period from first patient screened to last patient completed.

(k) Data Analysis

*Sample Size/Power*

The primary statistical comparison of the antihistamine efficacy of DL D-12 was based on the comparison of DL D-12 to PSE in the change from baseline in the total symptom score minus congestion as rated by the patient in the diary. For this comparison, a sample size of 200 evaluable patients per treatment group was chosen in order to allow 90% power to detect a difference of 1.6 points between treatment groups, assuming a pooled standard deviation of 4.25 points and two-tailed alpha level of 0.05. The primary statistical comparison for the decongestant efficacy of DL D-12 was based on the comparison of DL D-12 to DL5 in the change from baseline in the nasal congestion score. With a sample size of 200 evaluable patients per arm and a two-tailed alpha level of 0.05, and a pooled standard deviation of 0.6 points, the study had a power or 90% to detect a difference of 0.2 points or more between groups. [S8/P00355/925]

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#### *Efficacy Variables*

The severity of signs and symptoms of allergic rhinitis were scored twice daily (AM and PM) as “reflective” and “instantaneous” by the patient. The baseline values were considered to be the average of the last 3 days of diary data prior to Baseline (Day 1) and the AM evaluation on the Baseline day. Change from baseline scores were calculated for each of the first four days of treatment, the average over each Week, and the average over the two weeks of treatment, for the following efficacy variables: total symptom score, minus congestion (sum of 7 individual symptom scores), total symptom score (sum of the 8 individual symptom scores<sup>2</sup>), nasal symptom score (sum of the 4 individual nasal symptom scores), non-nasal symptom score (sum of the 4 individual non-nasal symptom scores), and each of the 8 individual symptom scores. Separate analyses were performed on the AM, PM and mean AM+PM scores, both for reflective and instantaneous evaluations.

The primary efficacy variable for the antihistamine component was the average AM+PM reflective total symptom score, excluding congestion, expressed as a change from baseline, over the two weeks of treatment. The comparison for this variable was DL D-12 versus PSE. The primary efficacy variable for the decongestant component was the average AM+PM reflective nasal congestion score, expressed as a change from baseline, over the two weeks of treatment. The comparison for this variable was DL D-12 versus DL5. Pairwise comparisons were made using linear contrasts of the treatment means, obtained from a two-way analysis of variance model that extracts sources of variation due to treatment and center. All other efficacy variables discussed above were considered secondary efficacy variables and were analyzed at each time point using the same two-way model.

#### *Missing Data*

The primary time point for efficacy was the average over Days 1-15 of treatment. Any data that a subject had during this time were included in the average, and no data were imputed in calculating the average. As discussed below, a total of 37 subjects discontinued the study early. Five subjects ( 1 in DL D-12, 1 in DL, and 3 in PSE) did not have any post-baseline data and were not included in the efficacy analysis.

Whenever any 1 of the individual symptom scores was missing, the total was considered missing. For all of the derived variables (e.g. Days 1-8, Days 9-15, Days 1-15), the corresponding values were averaged over all non-missing days in the interval. For variables using a mean function, averages could be computed even if there were missing

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<sup>2</sup> The 8 symptom scores are: rhinorrhea, nasal congestion, nasal itching, sneezing, itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate. The first four are considered the nasal symptoms, and the latter four are considered the non-nasal

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data. For example, if the AM data were missing, an overall Day 1-8 mean AM+PM mean could still be computed using the remaining PM values [S8/p00355/52].

*Analysis Population*

The protocol dictated that all analyses and summaries of efficacy and safety data would be based on all randomized subjects who received at least one dose of study medication (termed the “intent-to-treat” population by the Applicant) [S8/P00355/924]. The protocol stated that a second population, termed the “evaluable subject subset” was to be defined as randomized subjects who meet “key eligibility and evaluability criteria.” [S8/P00355/924] “Confirmatory” efficacy analyses were to be based on this subset. The specific “key eligibility and evaluability criteria” were not defined.

(2) Patient Disposition

A total of 598 subjects were randomized to treatment at 20 centers in the US. All randomized subjects received at least one dose of study drug [S8/p00355/56]. A total of 37 subjects discontinued study drug treatment prior to study completion (11 on DL D-12, 7 on DL5, and 19 on PSE). The table below provides the outcomes of the study subjects, by treatment group. The overall rate of discontinuation was slightly higher in the PSE group. The rate of discontinuation due to adverse event and the rate of discontinuation for treatment failure were highest in the PSE group.

Disposition of Study Subjects (Study P00355)		[S8/p00355/57]		
	DL D-12	DL5	PSE	
Number Randomized	200	198	200	
Number (%) Completed	189 (94.5)	191 (96.5)	181 (90.5)	
Number (%) Discontinued	11 (5.5)	7 (3.5)	19 (9.5)	
Reason for Discontinuation				
Adverse Event	7 (3.5)	4 (2.0)	9 (4.5)	
Treatment Failure	1 (<1)	0	4 (2.0)	
Lost to Follow-up	2 (1.0)	0	0	
Non-Compliance	0	2 (1.0)	2 (1.0)	
Did Not Meet Protocol Eligibility	1 (<1)	0	1 (<1)	
Did Not Wish to Continue	0	1 (<1)	3 (1.5)	

(3) Efficacy Review

The Applicant provided analyses of both the ITT and an “efficacy-evaluable” population. [S8/p00355/58]. This review will consider only the ITT analyses. **Reviewer’s Note: The definitions of the ITT population was slightly different in the protocol and study report. In the protocol the ITT population was defined as all randomized subjects who received at least one dose of study medication [S8/p00355/924]. In the study report the ITT population was defined as all randomized subjects who had baseline plus some post-baseline efficacy data [S8/p00355/58]. As mentioned below,**

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there were five patients who were not included in the efficacy analysis because they did not have any post-baseline diary data. It is unlikely that the exclusion of this small number of patients would affect the outcome of the study. It is also unclear how patients with no post-baseline data could be included in the analysis, except by carrying forward the baseline data in place of the missing post-baseline data.

(a) Baseline and Demographic Features

The demographic and baseline features of the study subjects were similar across groups. [S8/p00355/59] The majority of subjects in all three groups were female, and approximately 80% were Caucasian. The mean age was approximately 35 years and the mean duration of SAR ranged from 17.9 to 19.6 years. Very few patients at either end of the age spectrum (<18 and ≥65 years) were studied. The table below summarizes this baseline and demographic data.

Demographic and Baseline Characteristics (Study P00355, ITT population)		[S8/p00355/60]		
Demographic Characteristics	DL D-12 (N = 200)	DL (N = 198)	PSE (N = 200)	
Age (years)				
Mean	34.9	36.4	34.5	
Median	34	37	35	
Range (Min-Max)	12-74	12-76	12-68	
Age Subgroup, n (%)				
12 to < 18 years	18 (9)	23 (12)	25 (13)	
18 to < 65 years	177 (89)	173 (87)	172 (86)	
≥ 65 years	5 (3)	2 (1)	3 (2)	
Sex, n (%)				
Male	79 (40)	69 (35)	76 (38)	
Female	121 (61)	129 (65)	124 (62)	
Race, n (%)				
Caucasian	161 (81)	152 (77)	163 (82)	
Black	24 (12)	26 (13)	19 (10)	
Asian	4 (2)	4 (2)	6 (3)	
Hispanic	8 (4)	13 (7)	7 (4)	
American Indian	0	0	1 (1)	
Other	3 (2)	3 (2)	4 (2)	
Weight (lbs)				
Mean	168.4	163.2	167.0	
Median	165	155	160	
Range (Min-Max)	75-303	58-340	68-312	
Height (in)				
Mean	66.3	65.9	66.3	
Median	66	66	66	
Range (Min-Max)	52-78	54-75	54-77	
Duration of SAR (years)				
Mean	19.6	17.9	18.0	
Median	17	14	15	
Range (Min-Max)	2-69	2-56	2-54	

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Compliance was assessed by asking the subject (and/or parent or guardian) if they had taken study drug as instructed and by examining the subject's drug supply [S8/p00355/32]. According to this assessment, the majority of subjects were  $\geq 90\%$  compliant with the dosing regimen [S8/p00355/61].

### (b) Primary Endpoints

The primary efficacy variables defined in the protocol were the change from Baseline in average AM+PM reflective total symptom score excluding nasal congestion for the antihistamine component, and the change from Baseline in average AM+PM reflective nasal congestion score (from the diary) for the decongestant component. The primary time point for both variables was the average over the 15-day treatment period. The primary comparison for the antihistamine component was DL D-12 versus PSE. The primary comparison for the decongestant component was DL D-12 versus DL.

The table below shows the treatment comparisons for the antihistamine component (reflective AM+PM total symptom score, excluding nasal congestion, change from baseline to treatment period). The cells displaying the relevant comparison on this variable, DL D-12 vs. PSE, are shaded. DL D-12 was significantly more effective than PSE on this variable. The DL D-12 group demonstrated a 46% decline in symptoms and the PSE group demonstrated a 36% decline in symptoms. **However, the relative improvement seen with DL D-12 compared to the improvement seen with a presumably inactive drug (PSE), appears small. Further, the study was powered with the intention of showing a difference between groups of 1.6. The difference demonstrated (1.47) did not reach this amount.** This power calculation assumed a pooled standard deviation of 4.25. The actual pooled standard deviation was 4.18 [S8/p00355/63].

Also of note, the DL5 treatment did not appear to be effective on this variable, although this variable is intended to demonstrate antihistamine efficacy. On this variable DL5 was virtually identical to PSE, a drug which is not considered to have antihistamine properties. Also, DL D-12 was significantly superior to DL5. Finally, it is important to recognize that, although the trial was designed with the intention of demonstrating both the antihistamine and decongestant activity of DL D-12 (versus PSE and DL5, respectively), the only comparison necessary for approval is the antihistamine comparison. The rationale for this is discussed further in the Introduction and Background section of this review.

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Antihistamine Comparison (Study P00355):										[S8/p00355/63]
Total Symptom Score, Excluding Nasal Congestion (Reflective, AM+PM)										
	DL D-12			DL5			PSE			
	N	mean	%change	N	mean	%change	N	mean	%change	
Baseline	199	14.18		197	14.82		197	14.06		
Change from Baseline to Days 1-15	199	-6.54	-46.0%	197	-5.09	-33.5%	197	-5.07	-35.9%	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
	<0.001*			<0.001*			0.953			

\*= p<0.05

Shaded= Relevant treatments for antihistamine comparison

The table below shows the treatment comparisons for the decongestant component (reflective AM+PM nasal congestion score, change from baseline to treatment period). The cells displaying the relevant treatments for comparison on this variable, DL D-12 and DL5, are shaded. DL D-12 was statistically significantly superior to DL5 in reducing the reflective nasal congestion score. However the relative improvement seen with DL D-12 was small, considering the improvement seen with a presumably inactive drug (DL5) (-37.4% versus -26.7%).

Another interesting observation is the fact that DL D-12 appears to have greater decongestant activity than PSE. This raises the possibility that, in the setting of improvement in the non-congestion symptoms, patients may have difficulty distinguishing nasal congestion from the overall improvement. However, DL5 was not shown to be superior to PSE in regard to antihistamine activity.

Decongestant Comparison (Study P00355):										[S8/p00355/65]
Nasal Congestion Score (Reflective, AM+PM)										
	DL D-12			DL5			PSE			
	N	mean	%change	N	mean	%change	N	mean	%change	
Baseline	199	2.47		197	2.50		197	2.46		
Change from Baseline to Days 1-15	199	-0.93	-37.4	197	-0.66	-26.7	197	-0.75	-31.2	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
	0.006*			<0.001*			0.166			

\*= p<0.05

Shaded= Relevant treatments for decongestant comparison

(c) Secondary Endpoints

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*Reflective Scores*

The table below summarizes the data for the reflective antihistamine comparisons (total symptom score, excluding nasal congestion, AM+PM) for the various intervals studied. The cells representing the most relevant comparison on this endpoint, DL D-12 vs. PSE, are shaded. DL D-12 was statistically superior to PSE on this variable at all intervals except Day 1. As seen with the primary endpoint, DL5 did not appear to be effective. It was inferior to DL D-12 at all intervals, and was not significantly different than PSE. In fact, for the Day 1, Day 2, Day 4, and Days 9-15, PSE was numerically superior to DL5.

Antihistamine Comparison (Study P00355):										[S8/p00355/63]
Total Symptom Score, Excluding Nasal Congestion (Reflective, AM+PM)										
	N	DL D-12 mean	% change	N	DL5 mean	% change	N	PSE mean	% change	
Baseline	199	14.18		197	14.82		197	14.06		
Change from Baseline to:										
Day 1	196	-3.62	-23.3	191	-2.57	-15.1	195	-3.01	-18.8	
Day 2	199	-5.47	-37.8	195	-3.90	-25.2	197	-4.01	-27.9	
Day 3	197	-6.14	-43.6	197	-4.20	-28.0	197	-4.15	-29.5	
Day 4	197	-6.28	-44.7	196	-4.44	-29.5	194	-4.55	-32.8	
Days 1-8	199	-6.09	-42.8	197	-4.48	-29.5	197	-4.41	-31.4	
Days 9-15	193	-7.13	-50.4	191	-5.84	-38.6	185	-6.03	-42.5	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
Day 1	0.187			0.024*			0.340			
Day 2	0.001*			<0.001*			0.796			
Day 3	<0.001*			<0.001*			0.904			
Day 4	<0.001*			<0.001*			0.824			
Days 1-8	<0.001*			<0.001*			0.873			
Days 9-15	0.021*			0.006*			0.682			

\*= p<0.05

Shaded: Relevant treatments for antihistamine comparison

The table below summarizes the data for the reflective decongestant comparisons (nasal congestion score, AM+PM) for the various intervals studied. The cells representing the most relevant comparison on this endpoint, DL D-12 vs. DL5, are shaded. DL D-12 was statistically superior to DL5 on this variable at all intervals except Day 1. As seen with the primary endpoint, DL D-12 was unexpectedly superior to PSE on nasal congestion during several intervals (Day 2, Day 3, Day 4, and Days 1-8).

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Decongestant Comparison (Study P00355):									[S8/p00355/65]
Nasal Congestion Score (Reflective, AM+PM)									
	N	DL D-12 mean	% change	N	DL5 mean	% change	N	PSE mean	% change
Baseline	199	2.47		197	2.50		197	2.46	
Change from Baseline to:									
Day 1	198	-0.60	-22.0	195	-0.45	-16.1	195	-0.57	-21.0
Day 2	199	-0.84	-34.3	196	-0.50	-20.8	197	-0.67	-28.1
Day 3	197	-0.89	-36.3	197	-0.56	-23.0	197	-0.69	-29.0
Day 4	197	-0.92	-37.5	195	-0.58	-23.6	195	-0.71	-30.1
Days 1-8	199	-0.88	-35.7	197	-0.58	-23.5	197	-0.68	-28.5
Days 9-15	193	-0.99	-39.8	192	-0.77	-31.1	185	-0.84	-34.8
Pairwise Comparison p-values									
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE		
Day 1	0.663			0.069			0.169		
Day 2	0.015*			<0.001*			0.019*		
Day 3	0.009*			<0.001*			0.084		
Day 4	0.009*			<0.001*			0.094		
Days 1-8	0.002*			<0.001*			0.126		
Days 9-15	0.058			0.005*			0.359		

\*=p<0.05

Shaded cells: relevant treatments for antihistamine comparison

Finally, the table below summarizes the data on the reflective, AM+PM, total symptom scores (*including nasal congestion*) for the Day 1-15 comparison. This table shows that DL D-12 was slightly, but statistically significantly superior to both DL5 and PSE on this endpoint. Thus, when compared on the same endpoint, DL D-12 was shown to be statistically superior to each of its component drugs. **Reviewer's Comment: One caveat is that the desloratadine component was not dosed in the same manner alone and in the combination product. In the combination product the desloratadine was dosed as 2.5mg BID, while the desloratadine in the comparator was dosed as 5mg QD. This was presumably done because desloratadine 2.5mg BID is not a currently approved regimen.**

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Total Symptom Score (including nasal congestion), Reflective, AM+PM (Study P00355, ITT population):										
		DL D-12			DL5			PSE		
	N	mean	%change	N	mean	%change	N	mean	%change	
Baseline	199	16.66		197	17.33		197	16.52		
Change from Baseline to Day 1-15	199	-7.48	-44.8%	197	-5.75	-32.6%	197	-5.82	-35.2%	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
	<0.001*			<0.001*			0.891			

\*p<0.05

*End Of Dosing Interval*

The instantaneous scores are intended to assess the end of dosing interval efficacy. The Applicant proposes that the AM+PM instantaneous score is most appropriate for the antihistamine comparison because both of the treatments being compared (DL D-12 and PSE) are dosed twice-daily. However, the Applicant proposes that the AM instantaneous score is most appropriate for the decongestant comparison because one of the treatments being compared (DL5) is dosed once-daily. **Reviewer's Comment: This approach to the analysis of the end of dosing interval decongestant activity will exclude the PM instantaneous scores. The daytime (PM) end of dosing interval efficacy is an important aspect of the overall assessment of efficacy of DL D-12. Because this is a double-dummy study, with DL5 intended as a "placebo" in regard to decongestant activity, it is not necessary to exclude the PM scores. Therefore, the AM+PM instantaneous nasal congestion scores will also be discussed.**

The table below provides the end of dosing interval data for the antihistamine comparison, over the 2-week treatment period (Days 1-15). For this interval, as well as all of the other intervals and time points, the DL D-12 group was superior to the PSE group in regard to instantaneous mean total symptom scores, excluding nasal congestion. The relative improvement seen with DL D-12 for Days 1-15, while statistically significant, was small, considering the improvement seen with PSE, which is not felt to have antihistamine activity (-45.1% vs. -35.6%). As suggested by the reflective scores, DL5 did not appear to have significant antihistamine activity. The relative reduction in instantaneous symptoms with DL5 was similar to PSE and inferior to DL D-12.

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End of Dosing Interval, Antihistamine Comparison (Study P00355):										[S8/p00355/69]
Total Symptom Score, Excluding Nasal Congestion (Instantaneous, AM+PM)										
	DL D-12			DL5			PSE			
	N	mean	%change	N	mean	%change	N	mean	%change	
Baseline	199	13.87		197	14.75		197	13.82		
Change from Baseline to Days 1-15	199	-6.27	-45.1	197	-5.19	-35.2	197	-4.92	-35.6	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
	0.001*			0.011*			0.513			

\*= p<0.05

Shaded cells= relevant treatments for antihistamine comparison

The table below provides the end of dosing interval data for the decongestant comparison, for the entire 2-week treatment period (Days 1-15). As discussed above, this analysis uses only the AM data. For this interval, as well as all of the other intervals and time points, the DL D-12 group was superior to the DL5 group in regard to instantaneous nasal congestion score improvement. The relative improvement seen with DL D-12 for Days 1-15, while statistically significant, was small, considering the improvement seen with DL5, which is not felt to have decongestant activity (-33% vs. -22.8%). Finally, as seen with the reflective scores, DL D-12 was statistically superior to PSE on the instantaneous nasal congestion score.

End of Dosing Interval, Decongestant Comparison (Study P00355):										[S8/p00355/71]
Nasal Congestion Score (Instantaneous, AM)										
	DL D-12			DL5			PSE			
	N	mean	%change	N	mean	%change	N	mean	%change	
Baseline	199	2.42		197	2.50		197	2.45		
Change from Baseline to Days 1-15	199	-0.81	-33%	197	-0.60	-22.8%	197	-0.66	-27.7%	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
	0.032*			0.002*			0.359			

\*= p<0.05

Shaded cells= relevant treatments for antihistamine comparison

As discussed above, the Applicant has chosen to present the AM instantaneous nasal congestion scores as the most appropriate comparison to illustrate end of dosing interval efficacy. This reviewer believes that the AM+PM comparison would be more appropriate. However, using AM+PM instantaneous nasal congestion scores does not alter the conclusions drawn from the AM instantaneous comparison. The improvement in instantaneous nasal symptoms scores (Day 1-15) seen with DL D-12 (-34.2%) was

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superior to the improvement seen with DL5 (-24.5%), with a p-value of 0.003 [S8/p00355/74].

*Other Secondary Endpoints*

Additional secondary endpoints included:

- Other subject-evaluated reflective and instantaneous total symptom scores, excluding nasal congestion (AM and PM)
- Other subject-evaluated reflective and instantaneous nasal congestion scores (AM and PM)
- Subject-evaluated total symptom score (reflective and instantaneous, AM, PM and AM+PM)
- Individual symptom scores, reflective and instantaneous (AM and PM)
- Joint subject-investigator evaluation of overall condition of SAR
- Joint subject-investigator evaluation of therapeutic response

Each of the subject-evaluated scores were analyzed at Days 1, 2, 3, 4, and Week 1 (Days 1-8), Week 2 (Days 9-15), and for the average over the 2-week treatment period (Days 1-15).

The following tables summarize the Day 1-15 comparisons for total symptom scores, excluding nasal congestion, and nasal congestion scores, both reflective and instantaneous. The results of these comparisons do not alter the conclusions drawn based upon the comparisons considered above (AM+PM scores, and end of dosing interval scores). The results support the conclusion that DL D-12 provides a small, but statistically significant benefit over DL5 for the decongestant effect (nasal congestion score), and over PSE for the antihistamine effect (total symptom scores, excluding nasal congestion). As seen in the prior analyses, DL5 did not seem to have an antihistamine effect (the effect was indistinguishable from PSE and inferior to the effect seen with DL D-12).

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**Total Symptom Scores, Excluding Nasal Congestion:** [S8/p00355/73]

Time Point	DL D-12			DL			PSE						
	N	Mean	Mean % Change	N	Mean	Mean % Change (DL D-12 vs. DL)	N	Mean	Mean % Change	N	Mean	Mean % Change (DL D-12 vs. PSE)	
AM Reflective Baseline	199	13.90		197	14.56	0.032	197	13.80		197	13.80	0.743	
Days 1-15	199	-6.33	(-45.2)	197	-4.91	(-32.8)	0.001	197	-4.93	(-35.1)	197	-4.93	0.001
AM Instant. Baseline	199	13.76		197	14.86	<.001	197	13.85		197	13.85	0.792	
Days 1-15	199	-6.06	(-43.5)	197	-5.11	(-34.2)	0.029	197	-4.86	(-34.8)	197	-4.86	0.005
PM Reflective Baseline	199	14.46		196	15.07	0.046	197	14.33		197	14.33	0.670	
Days 1-15	199	-6.75	(-46.2)	196	-5.26	(-33.7)	<.001	197	-5.20	(-36.2)	197	-5.20	<.001
PM Instant. Baseline	198	13.97		196	14.63	0.054	197	13.79		197	13.79	0.599	
Days 1-15	198	-6.45	(-45.9)	196	-5.26	(-35.7)	0.006	197	-4.98	(-36.1)	197	-4.98	<.001

**Nasal Congestion Scores:** [S8/p00355/74]

Time Point	DL D-12			DL			PSE						
	N	Mean	Mean % Change	N	Mean	Mean % Change (DL D12 vs. DL)	N	Mean	Mean % Change	N	Mean	Mean % Change (DL D12 vs. PSE)	
AM/PM NOW Baseline	199	2.41		197	2.49	0.066	197	2.44		197	2.44	0.473	
Days 1-15	199	-0.84	(-34.2)	197	-0.64	(-24.5)	0.003	197	-0.71	(-29.6)	197	-0.71	0.050
AM PRIOR Baseline	199	2.47		197	2.52	0.253	197	2.45		197	2.45	0.603	
Days 1-15	199	-0.90	(-36.1)	197	-0.66	(-26.3)	<.001	197	-0.71	(-29.0)	197	-0.71	0.007
PM PRIOR Baseline	199	2.47		196	2.49	0.715	197	2.47		197	2.47	0.898	
Days 1-15	199	-0.97	(-38.0)	196	-0.66	(-26.1)	<.001	197	-0.80	(-32.8)	197	-0.80	0.014
PM NOW Baseline	199	2.39		196	2.48	0.106	197	2.43		197	2.43	0.462	
Days 1-15	199	-0.86	(-33.7)	196	-0.68	(-24.9)	0.010	197	-0.75	(-30.5)	197	-0.75	0.118

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Analysis of the Day 1-15 reflective individual antihistamine symptom scores (rhinorrhea, nasal itching, sneezing, itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate) revealed results which were similar to those seen with the total symptom scores (excluding nasal congestion). DL D-12 was statistically superior to both PSE and DL5 for each of the individual symptoms in this analysis [S8/p00355/75-76].

The overall condition of SAR was evaluated jointly by the subject and investigator, and recorded on a scale of 0-3. For Day 1-15, DL D-12 was numerically slightly superior to both DL5 and PSE. This difference did not reach statistical significance, as shown in the table below.

Overall Condition of SAR, determined by subject and investigator jointly (Study P00355, ITT population):										
	DL D-12			DL5			PSE			[S8/p00355/79]
	N	mean	%change	N	mean	%change	N	mean	%change	
Baseline	199	2.56		196	2.59		195	2.53		
Change from Baseline to Day 1-15	199	-1.06	-40.0%	196	-0.95	-33.8%	195	-0.91	-33.6	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
	0.062			0.161			0.641			

An evaluation of the therapeutic response was performed by the subject and investigator jointly. The response was recorded on a scale of 1 (complete relief) to 5 (treatment failure). For Day 1-15, DL D-12 was numerically slightly superior to both DL5 and PSE (2.94 vs. 3.14 and 3.07). This difference did not reach statistical significance ( $p=0.054$  for the comparison with DL5, and  $p=0.217$  for the comparison with PSE) [S8/p00355/80].

*Statistical/Analytical Issues*

The applicant reports that there was a Baseline imbalance between the DL group and the DL D-12 and PSE groups in AM+PM reflective total symptom score, excluding congestion as well as for the AM reflective, AM instantaneous, PM reflective, and PM instantaneous scores. The Applicant states that an analysis of covariance, which included Baseline score as a covariate, did not result in inferences that were different than those drawn from the protocol-specified ANOVA, discussed above [S8/p00355/81].

In calculating the average over Days 1-15, no data were imputed for subjects who discontinued early. A total of 37 subjects discontinued early (11 in the DL D-12 group, 7 in the DL group, and 19 in the PSE group). Five subjects were not included in the efficacy analysis because they did not have any post-baseline diary data (1 in DL D-12, 1 in DL, and 3 in PSE).

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The Applicant states that the test for treatment-by-center effect was not significant ( $p > 0.63$ ) for either of the primary efficacy variables.

(4) Reviewer's Comments on Efficacy

This randomized, double-blind, double-dummy study was designed to demonstrate that DL D-12 has superior antihistamine effects as compared with PSE, and that DL D-12 has superior decongestant effects, as compared with DL5. The assumption that has traditionally been made by the Division is that the symptoms related to antihistamine effects (e.g. total symptom score, excluding nasal congestion) are distinguishable from those related to decongestant effects (e.g. nasal congestion).

The pre-specified primary endpoint in regard to the antihistamine effect was the change from baseline in the reflective AM+PM total symptoms score, excluding nasal congestion. The primary comparison on this variable was DL D-12 versus PSE. The results of the study demonstrated that DL D-12 was statistically superior to PSE on this variable. While the Applicant did not pre-specify the effect size that would be considered to be clinically significant, the study was powered to demonstrate a difference between groups of 1.6. The actual difference between groups was demonstrated to be 1.47. Thus, the conclusion can be that DL D-12 is slightly, but statistically significantly, superior to PSE on this measure of antihistamine activity.

The pre-specified primary endpoint in regard to the decongestant effect was the change from baseline in the reflective AM+PM nasal congestion score. The primary comparison on this variable was DL D-12 versus DL5. The results of the study demonstrated that DL D-12 was statistically superior to DL5 on this variable. The difference between groups was small, but statistically significant.

The various secondary analyses of symptom scores supported the conclusions drawn from the primary endpoints. Instantaneous symptom scores demonstrated that the efficacy of DL D-12 is maintained at the end of the dosing interval. Assessments of the overall condition of SAR and of the therapeutic response, which were performed jointly by the subject and investigator, favored DL D-12 but failed to reach statistical significance.

Two observations complicate the interpretation of this study: 1) the DL5 treatment did not appear to demonstrate antihistamine activity that could be distinguished from the effects of PSE; 2) the DL D-12 treatment had significantly greater decongestant activity than did the PSE treatment. These two observations raise the possibility that patients with SAR have difficulty distinguishing the decongestant and antihistamine effects of these drugs.

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(5) Safety Review

Studies P00355 and P00362 were performed under identical protocols. Safety data from the two studies will be considered collectively. The review of this data can be found in the Overview of Safety section of this Review.

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Appendix: Study P00362

**B. Individual Study Review: STUDY #P00362: “Efficacy and safety of desloratadine (sch 34117) + pseudoephedrine, bid, versus its components in the treatment of subjects with seasonal allergic rhinitis”**

(1) Study Description

This parallel group study compared three treatment groups: desloratadine 5mg QD (DL5), pseudoephedrine 120mg BID (PSE), and desloratadine D-12 BID (DL D-12). This was a two-week study in subjects with seasonal allergic rhinitis (SAR) performed during the Fall season, 1999 [S8/p00362/1-1334]. The protocol for this study was identical to the protocol for Study 00355. For details of the study design the reader is referred to the review of Study 00355.

(2) Patient Disposition

A total of 650 subjects were randomized to treatment at 20 centers in the US. All randomized subjects received at least one dose of study drug [S8/p00362/56]. A total of 46 (7.1%) subjects discontinued study drug treatment prior to study completion (14 on DL D-12, 14 on DL5, and 18 on PSE). The table below provides the outcomes of the study subjects, by treatment group. The overall rate of discontinuation was slightly higher in the PSE group. The rate of discontinuation due to adverse event was highest in the PSE group and the rate of discontinuation for treatment failure was lowest in the DL D-12 group.

<b>Disposition of Study Subjects (Study P00362)</b>		<b>[S8/p00362/57]</b>		
	DL D-12	DL5	PSE	
Number Randomized	214	214	222	
Number (%) Completed	200 (93.5)	200 (93.5)	204 (91.9)	
Number (%) Discontinued	14 (6.5)	14 (6.5)	18 (8.1)	
Reason for Discontinuation				
Adverse Event	7 (3.3)	5 (2.3)	12 (5.4)	
Treatment Failure	2 (1)	5 (2.3)	5 (2.3)	
Did Not Wish to Continue	1 (<1)	0	0	
Lost to Follow-up	1 (<1)	2 (1)	0	
Non-Compliance	3 (1.4)	2 (1)	1 (<1)	

(3) Efficacy Review

The Applicant provided analyses of both the ITT population (all randomized subjects who had baseline plus some post-baseline efficacy data) and an “efficacy-evaluable” population. [S8/p00362/58]. This review will consider only the ITT analyses. The reader

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is referred to comments in the review of Study 00355 regarding slight differences in the definition of the ITT population between the protocol and study report.

(a) Baseline and Demographic Features

The demographic and baseline features of the study subjects were similar across groups. [S8/p00362/60] The majority of subjects in all three groups were female, and approximately 85% were Caucasian. The mean age was approximately 36 years and the mean duration of SAR ranged from 18.1 to 19.4 years. Very few patients at either end of the age spectrum (<18 and ≥65 years) were studied. The table below summarizes this baseline and demographic data.

<b>Demographic and Baseline Characteristics (Study P00362, ITT population)</b>		<b>[S8/p00362/60]</b>		
Demographic Characteristics	DL D-12 (N = 214)	DL (N = 214)	PSE (N = 222)	
Age (years)				
Mean	35.8	36.8	36.4	
Median	36	37	36	
Range (Min-Max)	12-76	12-78	12-78	
Age Subgroup, n (%)				
12 to < 18 years	17 (8)	25 (12)	13 (6)	
18 to < 65 years	192 (90)	182 (85)	206 (93)	
≥ 65 years	5 (2)	7 (3)	3 (1)	
Sex, n (%)				
Male	77 (36)	69 (35)	76 (38)	
Female	137 (64)	148 (69)	144 (65)	
Race, n (%)				
Caucasian	177 (83)	178 (83)	191 (86)	
Black	19 (9)	12 (6)	14 (6)	
Asian	2 (1)	2 (1)	0	
Hispanic	13 (6)	19 (9)	17 (8)	
American Indian	0	1 (<1)	0	
Other	3 (1)	2 (1)	0	
Weight (lbs)				
Mean	170.2	163.2	167.0	
Median	165	155	160	
Range (Min-Max)	100-367	58-340	68-312	
Missing	1	0	1	
Height (in)				
Mean	66.2	65.9	66.0	
Median	66	66	66	
Range (Min-Max)	56-76	57-80	56-78	
Duration of SAR (years)				
Mean	18.1	19.4	19.2	
Median	15	17	17	
Range (Min-Max)	2-65	2-59	2-59	

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Compliance was assessed by asking the subject (and/or parent or guardian) if they had taken study drug as instructed and by examining the subject's drug supply. According to this assessment, the majority of subjects were  $\geq 90\%$  compliant with the dosing regimen [S8/p00362/61].

#### (b) Primary Endpoints

The primary efficacy variables defined in the protocol were the change from Baseline in average AM+PM reflective total symptom score excluding nasal congestion for the antihistamine component, and the change from Baseline in average AM+PM reflective nasal congestion score (from the diary) for the decongestant component. The primary time point for both variables was the average over the 15-day treatment period. The primary comparison for the antihistamine component was DL D-12 versus PSE. The primary comparison for the decongestant component was DL D-12 versus DL.

The table below shows the treatment comparisons for the antihistamine component (reflective AM+PM total symptom score, excluding nasal congestion, change from baseline to treatment period). The cells displaying the relevant comparison on this variable, DL D-12 vs. PSE, are shaded. DL D-12 was significantly more effective than PSE on this variable. The DL D-12 group demonstrated a 43% decline in symptoms and the PSE group demonstrated a 35.4% decline in symptoms. **However, the relative improvement seen with DL D-12 compared to the improvement seen with a presumably inactive drug (PSE), appears small. Further, the study was powered with the intention of showing a difference between groups of 1.6. The difference demonstrated (1.37) did not reach this amount.** This power calculation assumed a pooled standard deviation of 4.25. The actual pooled standard deviation was 4.07 [S8/p00362/63].

Also of note, the DL5 treatment did not appear to be effective on this variable, although this variable is intended to demonstrate antihistamine efficacy. On this variable DL5 was virtually identical to PSE, a drug which is not considered to have antihistamine properties. Also, DL D-12 was significantly superior to DL5.

Antihistamine Comparison (Study P00362):										[S8/p00362/63]
Total Symptom Score, Excluding Nasal Congestion (Reflective, AM+PM)										
	DL D-12			DL5			PSE			
	N	mean	%change	N	mean	%change	N	mean	%change	
Baseline	213	15.19		212	14.66		221	14.86		
Change from Baseline to Days 1-15	213	-6.65	-43.0%	212	-5.35	-36.1%	221	-5.28	-35.4%	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
	<0.001*			0.001*			0.862			

\*= p<0.05

Shaded: Relevant treatments for antihistamine comparison

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The table below shows the treatment comparisons for the decongestant component (reflective AM+PM nasal congestion score, change from baseline to treatment period). The cells displaying the relevant treatments for comparison on this variable, DL D-12 and DL5, are shaded. DL D-12 was statistically significantly superior to DL5 in reducing the reflective nasal congestion score. However the relative improvement seen with DL D-12 was small, considering the improvement seen with a presumably inactive drug (DL5) (-36% versus -28.9%).

In Study P00355, DL D-12 appeared to have greater decongestant activity than PSE, raising the possibility that desloratadine may have decongestant properties. In the current study, DL D-12 was numerically, but not statistically, superior to PSE on the nasal congestion endpoint. As was discussed in the review of Study P00355, it is also possible that, in the setting of improvement in the non-congestion symptoms, patients may have difficulty distinguishing nasal congestion from their overall improvement.

Decongestant Comparison (Study P00362):										[S8/p00362/65]
Nasal Congestion Score (Reflective, AM+PM)										
	DL D-12			DL5			PSE			
	N	mean	%change	N	mean	%change	N	mean	%change	
Baseline	214	2.55		213	2.56		221	2.56		
Change from Baseline to Days 1-15	214	-0.92	-36.0	213	-0.73	-28.9	221	-0.83	-31.8	
Pairwise Comparison p-values										
	DL D-12 vs. PSE			DL D-12 vs. DL5			DL5 vs. PSE			
	0.006*			0.005*			0.150			

\*= p<0.05

Shaded: Relevant treatments for decongestant comparison

**(c) Secondary Endpoints**

*Reflective Scores*

The table below summarizes the data for the reflective antihistamine comparisons (total symptom score, excluding nasal congestion, AM+PM) for the various intervals studied. The cells representing the most relevant comparison on this endpoint, DL D-12 vs. PSE, are shaded. DL D-12 was statistically superior to PSE on this variable at all intervals. As seen with the primary endpoint, DL5 did not appear to be effective. It was inferior to DL D-12 at all intervals, and was not significantly different than PSE.

increased incidence of mild spermatic cellular debris at the high dose (10 of 25 males vs 5 of 25 control animals).

*Reproductive parameters:* Fertility indices were not affected. However, pre-implantation loss was increased in a dose-dependent manner compared to control animals and the number of implantation sites and fetuses were reduced at the high dose (Table 26). The increased pre-implantation loss at the mid-dose was within historical control values. These findings indicate an embryocidal effect of SCH 34117.

**Table 26:** Summary of effects on reproductive parameters.

Dose (mg/kg)	0	6	12	24
Pre-implantation loss %/animal	1.3	2.2	9.6	17.2
Implantation sites #/animal	15.1	13.9	13.9	11.2
Fetuses #/animal	14.1	13	12.9	10.5

**Key study observations:** The NOAEL for fertility effects was > 24 mg/kg; a NOAEL of 12 mg/kg in females and males was identified for “general toxicity findings”. Effects at the high dose included increased pre-implantation loss, decreased numbers of implantation sites and fetuses, and an increased incidence of mild spermatic cellular debris.

**Oral (gavage) fertility study of SCH 34117 in male rats**

*Study No.:* ——— *Volume:* 1.29

*Study Dates:* Starting date 12/16/1998; report issued 8/4/1999

*Testing Lab:* \_\_\_\_\_

*Test Article:* SCH 34117 (Batch# 97-34117-X-03-RA; purity = 100%) in 0.4% aqueous methylcellulose

*Concentration:* 0.6-8 mg SCH 34117/ml

*Dose Volume:* 5 ml/kg/day

*GLP:* The study was accompanied by a signed GLP statement.

*QA report:* Yes.

The protocol for this study was not reviewed by the Division.

**Methods:** CrL:CD(SD)IGS Br rats (males: 11 weeks old; 301-412 g; females: 12 weeks old; 202-348g) were assigned to the following treatment groups:

Dose (mg/kg/day)	0	3	12	40
No. of male rats/group – main	25	25	25	25
No. of male rats/group – 18 week recovery	15	0	0	15

Male rats were orally administered vehicle or SCH 34117 for 70 days prior to mating and throughout the mating period until euthanasia (total dosing period 106-108 days). Doses were selected based upon results of a pilot study (P-6821, see Original IND 55,364 review) and the fertility study reviewed above. Female rats (25/dose group) were not dosed during this study. The report stated that recovery data would be submitted as an addendum to final report. This data was submitted to IND 55,364 Serial # 159 (dated June 23, 2000) and is reviewed currently. During the mating period, each female was placed in cohabitation with a male for a maximum of 14 days. The following observations were made:

Clinical observation . . . Males: at least 1 time daily. Females: once weekly.  
Body weight . . . . . Males: twice/week. Females: weekly until confirmed mating, then on days 0, 7, and 14 of gestation.  
Food consumption . . . . twice/week in males; not measured in females.  
Necropsy . . . . . Males euthanized ~ 25 days after confirmed mating, females euthanized on day 14 of gestation. Gross external and visceral examination; males: brain, pituitary gland, prostate gland, testes and epididymal weights recorded. Females: uteri and ovaries exposed to collect reproduction data  
Histopathology . . . . . males: coagulating gland, prostate gland, seminal vesicles, testis and epididymis from all males  
Reproduction parameters . . . . . Copulated females sacrificed on day 14 of gestation; assessment for number of corpora lutea, implantation sites, live/dead embryos, and resorptions (early/late), distribution of implantation sites, resorptions, and embryos in the uterus. Male mating and fertility indices, and precoital interval were calculated.  
Sperm analysis . . . . . sperm collected from all rats to assess motility. Left testis used to determine spermatid count and sperm count determined from left epididymis.  
Statistics . . . . . Two-tailed tests with analysis of variance, Dunnett's test, Kruskal-Wallis test and Mann-Whitney U-test.

## Results:

*Mortality:* No drug related effects were noted in males. One low-dose male was euthanized in extremis on study day 65 due to malaligned upper incisors and 36% body weight loss. One non-mated female each from the mid-dose and high-dose groups were euthanized on days 93 and 14, respectively.

*Clinical Observations:* No drug-related effects were noted.

*Body Weight:* Body weight gain in high-dose males was reduced from study day 21 onward. Following the pre-mating period, body weight gain was reduced by 29%; body weight gain was reduced by 35% following the last day of dosing (Table 27). At the end of the recovery period, no significant difference in body weight gain or absolute body weight was observed between the control and high-dose groups.

**Table 27:** Summary of effects on body weight gain.

Dose (mg/kg)	3	12	40
Body weight gain			
Premating period - %Δ from control	-3	-9	-29
End of dosing - %Δ from control	-8	-11	-35
End of recovery - %Δ from control			3

*Food Intake:* Food consumption was consistently reduced in high-dose males up to 19%. No differences between the control and high-dose groups were noted during the recovery period.

*Necropsy:* Reductions in absolute organ weights were noted in the prostate, testes, epididymis, and cauda epididymis, primarily at the high dose (Table 28). Similar findings were observed in relative organ to body weight in the prostate, and testes though not in the other organs listed. These findings were not recoverable. Gross examination revealed bilateral small and soft testes at the mid- and high-doses, and pale pituitary and small prostate at the high dose. Findings in the testes were not reversible. There was no histopathologic correlate for the prostatic findings.

**Table 28:** Summary of findings at necropsy in male rats.

	Dose (mg/kg)				
	0	3	12	40	40- Recov
absolute organ weight changes					
Prostate: % Δ from control		14	-13	-33	-17
Right testis: % Δ from control		-1	-11	-38	-36
Left testis: % Δ from control		-3	-15	-42	-45
Right epididymis: % Δ from control		-3	-10	-19	-24
Left epididymis: % Δ from control		-1	-14	-21	-29
Right cauda epididymis: % Δ from control		-2	-16	-23	-25
Left cauda epididymis: % Δ from control		1	-21	-27	-31
grossscopic observations					
N =	25	25	25	25	15
Right testis					
Small	0	0	4	14	8
Soft	0	0	5	14	7
Left testis					
Small	0	1	6	16	10
Soft	0	1	7	17	10
Left epididymis					
Enlarged	0	0	0	1	0
Pituitary					
Pale	0	0	0	1	0
Prostate					
Small	0	0	0	2	0
Urinary bladder					
Thickened	0	0	0	1	0
Adipose tissue					
Necrotic	0	0	0	1	0

**Histopathology:** Histologic examination of the reproductive organs revealed dose-related degeneration of the seminiferous tubules, spermatid giant cells, epithelial spermatogenic droplets, spermatid retention and seminiferous tubule atrophy in the testes (Table 29). Additional findings in the epididymis included vacuolation, spermatid cellular debris, oligospermia and hyperplasia. With the exception of spermatid cellular debris, these findings were not observed in the previously reviewed fertility study at doses up to 24 mg/kg, possibly due to the shorter duration of dosing. Following the recover period, most findings were only minimally reversible.

**Table 29: Summary of histopathologic findings in male rats.**

Dose (mg/kg)	0	3	12	40	40-Recovery
Gross observations					
N =	25	24	25	25	15
Right testis					
Degeneration, seminiferous tubules					
Minimal	0	1	8	2	1
Mild	0	1	1	3	1
Moderate	0	0	0	2	1
Severe	0	0	4	14	7
Spermatid giant cells					
Minimal	0	0	1	0	0
Mild	0	1	1	4	0
Moderate	0	0	0	1	0
Droplets, spermatogenic, epithelium					
Minimal	0	1	0	2	0
Mild	0	0	0	2	0
Retention, spermatid					
Minimal	0	2	9	4	1
Atrophy, seminiferous tubule, focal					
Minimal	0	0	1	0	1
Mild	0	1	1	4	1
Moderate	0	0	0	0	1
Atrophy, seminiferous tubule, diffuse					
Moderate	0	0	0	1	0
Severe	0	0	4	14	7
Alteration, spermatogenic epithelium					
Minimal	0	0	0	2	1
Mild	0	0	1	3	1
Moderate	0	0	0	2	0
Right Epididymis					
Vacuolation, cytoplasmic, epithelial					
Minimal	0	0	0	13	5
Mild	0	0	0	2	0
Moderate	0	0	0	1	0
Cellular debris, spermatid					
Minimal	0	1	7	0	2
Mild	0	1	1	1	2
Moderate	0	0	1	19	1
Severe	0	0	4	0	0
Oligospermia					
Mild	0	0	1	0	2
Moderate	0	0	0	4	1
Severe	0	0	4	15	6
Hyperplasia					

Minimal	0	0	0	7	3
Mild	0	0	0	0	4
Pituitary gland Vacuolation – cytoplasmic, Rathke's Pouch, macrophage					
Minimal	2			11	3

*Sperm analysis:* Mean sperm numbers in the testis and epididymis and mean sperm production in the testis were reduced at the mid- and high-doses while reductions were also observed in 2 animals of the low-dose group (Table 30). Likewise, the percentage of motile sperm was also dose-dependently reduced in SCH 34117-treated animals with mid- and high-dose groups showing a 25.5% and 58.6% reduction compared to control animals. Following the recovery period, sperm numbers remained reduced at a level comparable to those at the end of the main study period while sperm motility appeared to almost fully recover.

**Table 30:** Summary of spermatogenic endpoints.

Dose (mg/kg)	0	3	12	40	0-Rec	40-Rec
Sperm numbers (# of sperm in millions/gram of tissue)						
Left testis – mean values	77.6	78.4	60.8	20.3	93	31.3
% change from control		1	-22	-74		-74
Left epididymis - mean values	446.3	462.4	271	134.7	354.5	155.4
% change from control		4	-39	-70		-56
<b>Sperm motility (%)</b>						
Motile sperm	84	75.8	58.5	25.4	84.3	75.6

*Reproductive parameters:* Male mating indices were comparable among all treatment groups (96-100%; Table 31). However, male fertility indices were reduced at the mid and high doses (76 and 37.5%, respectively compared to 100% and 95.8% in control and low-dose animals) and were associated with reduced sperm numbers and motility at these doses. Fertility indices were unaffected in a previous study up to 24 mg/kg but with a shorter dosing duration. Mean pre-coital intervals were comparable between groups. Following the recovery period, mating index in treated males was reduced but was similar to the mean historical control value (89.3%). The fertility index was only minimally improved following the recovery period.

**Table 31:** Summary of effects on reproductive parameters in males.

Parameter	Dose (mg/kg)					
	0	3	12	40	0-Rec	40-Rec
Male mating index (%)	100	100	96	96	100	87-93
Male fertility index (%)	100	95.8	76	37.5	93-100	54-57

One female in the mid- and high-dose groups showed no evidence of mating. Mean numbers of implantation sites, and viable embryos were reduced at the mid- and high-doses compared to control values, and the incidence of pre-implantation loss was increased at the high dose (Table

32). The litter proportion of early resorptions at the high dose (27.9%) was increased relative to control (6.7%) but may be due to the low numbers of females showing implantations due to adverse effects on sperm in males. No significant differences were observed in reproductive parameters between the two recovery groups.

**Table 32:** Summary of effects on reproductive parameters in females.

Parameter	Dose (mg/kg)			
	0	3	12	40
Viable embryos	15.4	13.9	12.4	7.9
Implantation sites	16.2	14.4	13.4	9.1
Pre-implantation loss	1.8	3.9	3.7	7.2

Shaded area indicates statistically significant difference from control value.

**Key study observations:** The NOAEL for fertility effects was 3 mg/kg; a NOAEL was not identified in males for general toxicity findings due to histological findings at all doses tested in the reproductive organs. Most findings were not reversible following an 18 week recovery period.

**Oral (gavage) embryo-fetal developmental toxicity and toxicokinetic study of SCH 34117  
in rats**

*Report No.:* P-6922      *Study No.:* 97114      *Volume:* 1.31

*Study Dates:* Starting date 9/12/1997; report issued 5/9/1999  
*Testing Lab:* Safety Evaluation Center, Schering Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 34117 (Batch# 97-34117-X-02RA; purity = 99%) in 0.4% aqueous methylcellulose  
*Concentration:* 1.2-9.6 mg SCH 34117/ml  
*Dose Volume:* 5 ml/kg/day  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

The protocol for this study was not reviewed by the Division.

**Methods:** Crl:CD(SD) BR VAF/Plus female rats (11 weeks old; 227-307 g) were assigned to the following treatment groups:

Dose (mg/kg/day)	0	6	24	48
No. of teratology females	25	25	25	25
No. of toxicokinetic females	0	9	9	9

Each female rat was cohabitated with a breeder male on a one-to-one basis until positive evidence of mating was observed. Female rats in which copulation was confirmed received a daily oral dose of vehicle or test drug once daily on days 6 through 15 of gestation in order to assess its effects on dams, fetuses and offspring. The following observations were made:

**Dams:**

Clinical observation . . . daily examination of mated females  
Body weight . . . . . Days 0, 6, 9, 12, 15, 18 and 21 of gestation  
Food consumption . . . . Days 0 to 6, 6 to 10, 10 to 15 and 15 to 21 of gestation  
Blood collection . . . . . bled at 4, 8, and 24 hours post dose on gestation day 15  
Necropsy . . . . . mated females sacrificed on gestation day 21; uteri and contents removed and weighed, dams examined for external and visceral changes  
Reproduction parameters . . . . . determination of number of implantation sites, corpora lutea, fetuses (live/dead), and resorptions, distribution of fetuses in the uterus.

**Fetuses (F<sub>1</sub>):**

External exam . . . . . abnormal conditions, sexed, body weights  
Skeletal/Soft tissue exam . . . . . 50% of fetuses from each litter fixed and examined for soft tissue defects, kidneys graded for hydronephrosis. Remaining fetuses examined for gross visceral changes and skeletal examination.  
Dead fetuses and resorptions . . . examined grossly for external defects and for visceral and skeletal defects.

Statistical analysis: Continuous data analyzed by ANOVA; categorical data analyzed Chi-square test

**Results:****Dams:**

*Mortality:* One mid-dose dam died due to a dosing accident.

*Clinical Observations:* Drug-related clinical observations included reduced numbers of fecal pellets, large fecal pellets or no stool in mid- and high-dose animals.

*Body Weight:* Maternal body weight gain was dose-dependently reduced compared to control animals during the dosing period by 12%, 56%, and 92% at the low, mid and high doses, respectively (significant at the mid and high doses).

*Food Intake:* Food consumption was reduced during gestation days 6 to 10 in mid- and high-dose dams by 33% and 53%, respectively, compared to control animals. The reduction was 14% and 27%, respectively, from days 10 to 15 and values were comparable to controls once dosing ended.

*Necropsy:* No drug-related effects were noted.

*Reproduction Parameters:* No drug-related effects on reproduction parameters were noted. However, fetal body weight was reduced at mid- and high-doses by 8% and 10%, respectively, and may be related to the observed maternal toxicity at these doses.

*Toxicokinetics:* Systemic exposure to SCH 34117 under the dosing conditions of this study are summarized in Table 33. Exposure increased sub-proportionally with increasing dose and T<sub>max</sub>

was achieved within 24 hours. Mean plasma concentrations at 24 hours were 28-69% of the respective C<sub>max</sub> values indicating slow elimination of SCH 34117.

**Table 33:** Systemic exposure to SCH 34117 following oral administration.

Parameter	Dose (mg/kg)		
	6	24	48
C <sub>max</sub> (ng/ml)	487	1569	2468
T <sub>max</sub> (hr)	8	4	8
AUC(0-24 hr) (ng.hr/ml)	7875	31606	49238

**Fetuses (F1):**

*Skeletal and visceral examination:* No drug-related findings were noted following examination for gross or skeletal malformations. Skeletal variations were observed at the mid- and high-doses and consisted of unossified/reduced bone ossification in cervical vertebral centra, sternebra, and proximal phalanges of the paws (Table 34) and may be related to the observed maternal toxicity and reduced fetal growth *in utero* as indicated by reduced fetal weight in these dose groups.

**Table 34:** Summary of effects on skeletal variations in fetuses: total (%)

Observation	Dose (mg/kg)			
	0	6	24	48
Cervical vertebral centra unossified				
-fetal incidence	39 (22.8)	41 (23)	56 (35.2)	80 (46)
-litter incidence	16 (66.7)	15 (62.5)	15 (68.2)	21 (84)
Sternebra unossified				
-fetal incidence	2 (1.2)	1 (0.6)	19 (11.9)	18 (10.3)
-litter incidence	2 (8.3)	1 (4.2)	8 (36.4)	10 (40)
Sternebra reduced ossification				
-fetal incidence	12 (7)	16 (9)	30 (18.9)	35 (20.1)
-litter incidence	7 (29.2)	10 (41.7)	16 (72.7)	18 (72)
Shortened ribs				
-fetal incidence	0	0	1 (0.6)	5 (2.9)
-litter incidence	0	0	1(4.5)	2 (8)
Unossified proximal phalanges, hind paws				
-fetal incidence	69 (40.4)	63 (35.4)	75 (47.2)	124 (71.3)
-litter incidence	18 (75)	19 (79.2)	18 (81.8)	24 (96)
Total skeletal				
-fetal incidence	108 (63.2)	102 (57.3)	117 (73.6)	147 (84.5)
-litter incidence	23 (95.8)	22 (91.7)	22 (100)	24 (96)

Shaded area indicates statistically significant difference from control value.

**Key study observations:** A NOAEL of 48 mg/kg was identified for teratologic effects while 6 mg/kg was identified for developmental toxicity based upon reduced fetal weights and skeletal variations at the mid and high doses. The NOAEL for maternal toxicity was 6 mg/kg and was based upon reduced body weight gain and food consumption at the two highest doses. The decreased fetal weight and delayed ossification may be secondary to the maternal toxicity.

**Oral embryo-fetal development study of SCH 34117 in rabbits***Report No.:* P-6802      *Study No.:* 97116      *Volume:* 1.32

*Study Dates:* Starting date 9/29/1997; report issued 5/17/1998  
*Testing Lab:* Safety Evaluation Center, Schering-Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 34117 (Batch# 97-34117-X-02RA; purity = 99%; Batch# 97-11001-139; purity = 100%) in 0.4% aqueous methylcellulose  
*Concentration:* 7.5-30 mg SCH 34117/ml  
*Dose Volume:* 2 ml/kg/day  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

The protocol for this study was not reviewed by the Division.

**Methods:** New Zealand white rabbits (5-6 months old; 2.91 – 3.99 kg) were assigned to the following treatment groups:

Nominal Dose (mg/kg/day)	0	15	30	60
No. of copulated females – main study	20	20	20	20
No. of copulated females – plasma analysis	0	3	3	3

Females were mated with males with day of mating designated as Day 0 of pregnancy. Females in which copulation was confirmed received a daily dose of vehicle or test drug by gastric intubation (gavage) once daily on days 7 through 19 of gestation. The following observations were made:

**Dams:**

Clinical observation . . . daily  
 Body weight . . . . . Days 0, 7, 10, 13, 16, 19, 22, 25, 28, and 30 after mating.  
 Food consumption . . . visual estimate recorded daily gestation days 0-30  
 Blood collection . . . . . bled at 1, 3, 12 and 24 hours post dose on gestation day 19  
 Necropsy . . . . . mated females sacrificed on gestation day 30; uteri and contents removed, dams examined for external and visceral changes  
 Reproduction parameters . . . . . determination of number of implantation sites, corpora lutea, fetuses (live/dead), and resorptions, distribution of fetuses in the uterus.

**Fetuses (F<sub>1</sub>):**

External exam . . . . . abnormal conditions, body weights assessed at necropsy  
 Morphologic exam . . . fetuses internally sexed, assessed for gross visceral changes, and skeletal examinations.  
 Dead fetuses and resorptions . . examined grossly for external defects and for visceral and skeletal defects.  
 Statistical analysis . . . . . Continuous data analyzed by ANOVA; categorical data analyzed Chi-square test

**Results:****Dams:**

*General signs:* Drug-related clinical observations included soft stool, reduced numbers of fecal pellets, large fecal pellets or no stool in all SCH 34117-treated groups with increasing incidence occurring at increasing doses.

*Body weight:* High-dose animals lost weight (0.0007 kg) during dosing period (days 7-19) while control animals gained 0.1731 kg. This finding was most apparent during days 10-16 when high-dose animals lost 0.0393 kg.

*Food consumption:* Food consumption was reduced in high-dose animals from gestation day 7 onward.

*Necropsy:* No drug-related findings were observed.

*Reproduction Parameters:* High-dose animals demonstrated an increased incidence of resorptions compared to control animals (Table 35). In addition, the mean number of fetuses in the high-dose group (7.5) was slightly lower than controls (8.75), although this effect was not statistically significant. These findings may be related to the maternal toxicity observed at the high dose.

**Table 35:** Effects of SCH 34117 on reproductive parameters following oral administration.

Parameter	Dose (mg/kg)			
	0	15	30	60
Resorptions				
Mean	0.25	0.19	0.33	1
% resorptions	2.8	2.2	3.9	11.8
% animals with resorptions	18.8	11.8	27.8	37.5

Shaded area indicates statistically significant difference from control value.

*Toxicokinetics:* Systemic exposure to SCH 34117 under the dosing conditions of this study are summarized in Table 36. Exposure increased supra-proportionally with increasing dose and T<sub>max</sub> was achieved within 3-12 hours.

**Table 36:** Systemic exposure to SCH 34117 following oral administration.

Parameter	Dose (mg/kg)		
	15	30	60
C <sub>max</sub> (ng/ml)	230	456	1166
T <sub>max</sub> (hr)	1	1	3
AUC(0-24 hr) (ng.hr/ml)	1660	4087	12987

**Fetuses:**

*Fetal Gross/Skeletal observations:* There were no drug-related fetal gross or visceral malformations or variations except for a slight but statistically insignificant increase in bipartite

sternebra in the high dose group (fetal incidence of 4 and litter incidence of 2 vs 1 and 1, respectively, in controls).

**Key study observations:** SCH 34117 did not induce any teratogenic effects at the doses up to 60 mg/kg. A NOAEL of 30 mg/kg was identified for maternal and *in utero* effects due to reduced maternal body weight gain and increased incidence of resorption at the high dose. The increased resorption may be a secondary effect due to the severe maternal toxicity observed at the high dose.

### Oral peri- and post-natal development study of SCH 34117 in rats

*Study No.:* 97117 *Volume:* 1.33

*Study Dates:* Starting date 1/9/1998; report issued 5/23/1999  
*Testing Lab:* Safety Evaluation Center, Schering Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 34117 (Batch# 97-34117-X-02 RA; purity = 99%) in 0.4% aqueous methylcellulose  
*Concentration:* 0.6-3.6 mg SCH 34117/ml  
*Dose Volume:* 5 ml/kg/day  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

The protocol for this study was not reviewed by the Division.

**Methods:** Mated female \_\_\_\_\_ rats (12 weeks old; 231-322 g) were assigned to the following treatment groups:

Dose (mg/kg/day)	0	3	9	18
No. of copulated females	25	25	25	25

Female rats (F<sub>0</sub>) were placed with males (1:1) for mating until positive evidence of mating was found. The day of mating was designated as Day 0. Mated females received a daily dose of vehicle or test drug by esophageal intubation once a day during the peri-natal (day 6 of gestation) and lactation periods (day 21 postpartum). On day 4 postpartum, the number of offspring per litter was adjusted by randomly selecting 4 male and 4 female offspring, keeping 8 offspring alive when 4 of each sex were not available. No adjustment was made when the number of offspring per litter was less than 8. On day 21 postpartum, one male and female were randomly selected from each litter for postweaning behavioral and developmental measurements, and for later breeding to produce a F<sub>2</sub> generation. The following observations were made:

#### Dams:

Clinical observation . . . daily from gestation day 0 until lactation day 21  
 Body weight . . . . . Days 0, 6, 9, 12, 15, 18 and 21 of gestation and on lactation days 1, 4, 7, 14, and 21.  
 Food consumption . . . Gestation days 0-6, 6-12, 12-15, and 15-21, and lactation days 1-4, 4-7, 7-10 and 10-14.

- F<sub>0</sub> parturition . . . . . Assessment for abnormal labor, nursing, or nesting behavior, length of gestation.
- Necropsy . . . . . Lactation day 21, examined for external and visceral changes and implantation sites.

**Offspring (F<sub>1</sub>):**

- Litter size . . . . . number of live and dead offspring recorded daily until lactation Day 21. Survival rate calculated for lactation Days 0, 1-4 and 5-21.
- Sex determination . . . . . pups sexed externally on lactation days 0, 4, and 21
- Clinical observation . . . . . daily from lactation days 0-21
- Body weight . . . . . Days 0, 4, 7, 14, and 21 postpartum; weaned F<sub>1</sub> rats weighed weekly until mating, after mating F<sub>1</sub> females weighed on pregnancy Days 0, 6, 9, 12, 15, 18 and 21, and on lactation days 1 and 4.
- Maturational and Behavioral Evaluations
- Surface righting test: lactation day 5 through 12
  - Auditory startle test: lactation day 10 through 15
  - Eye opening: lactation day 12 through 16
  - Incisor eruption: lactation day 9 through 14
  - Negative geotaxis test: lactation day 6 through 10
  - Open field test: lactation days 15, 16 and 17
- Gross visceral exam . . . . . animals not selected for post-weaning measurements and breeding sacrificed on day 21 of lactation and subjected to gross visceral examination
- F<sub>1</sub> post-weaning measurements . . . . . one male and female from each litter: body weights measured weekly, observed daily from post-partum day 22 through sacrifice, F<sub>1</sub> females checked for vaginal opening from Day 29 through Day 35 postpartum, F<sub>1</sub> males checked for preputial separation from postpartum day 39 through day 50.
- F<sub>1</sub> estrus cycle determination . . . . . evaluated from 1 week prior to mating and during mating period by vaginal cytology
- F<sub>1</sub> mating . . . . . at 11-12 weeks of age, one male from each litter was placed with a female from a different litter within the same dose group for up to 2 weeks. Female was separated once mating occurred. Unmated females paired for up to one more week with a proven male from same dose group.

**Offspring (F<sub>2</sub>):**

- Clinical observation . . . . . litter size (number born alive and dead), sex, weight and observations, survival calculated until day 4, sacrifice on Day 4, gross external examination.

Statistical analysis: Continuous data analyzed by ANOVA; categorical data analyzed Chi-square test

**Results:****Dams:**

*Mortality:* There were no SCH 34117-related deaths. Two non-pregnant high-dose females were sacrificed on gestation day 24 when they failed to produce litters.

*Clinical Observations:* Drug-related clinical findings included soft stool (mid- and high-dose), reduced fecal pellets (high-dose) and large fecal pellets (all doses). In addition, one high dose female had total litter loss and had been eating poorly while another did not appear to be caring for or nursing the pups which were not lively (4 died by day 4).

*Body Weight:* High-dose dams had a mean weight loss of 4 g during gestation days 6-9 (Table 36). Weight gain was dose-dependently reduced at the two lower doses but findings were not significant. Body weight gain over the entire course of the dosing period, however, was comparable among groups.

*Food Intake:* Food consumption was reduced by 10-14% in high-dose dams on gestation days 6-12 and lactation days 1-4 (Table 37). Consumption was comparable among all groups at other time points.

**Table 37:** Summary of effects on clinical findings.

Parameter	Dose (mg/kg)			
	0	3	9	18
Body weight gain (g) - gestation	14	10	5	-4
Food consumption – gestation days 6-12 % change from control values		6	-6	-14
Food consumption (g/animal/d) – lactation days 1-4 % change from control values		-8	-6	-10

Shaded area indicates statistically significant difference from control value.

*Parturition:* No abnormalities in the length of gestation, number of implantation sites or number of pups per litter were noted in the control group or drug-treated groups.

*Necropsy:* No remarkable observations were noted following gross and visceral observations.

#### **Offspring (F<sub>1</sub>):**

*Pup survival:* The survival rate was at least 99% in all groups on the day of birth but was reduced at the high-dose (92.9%) on days 1-4 (Table 38). Of the 22 that died in the high-dose group, 12 were from one litter and eighteen of the total twenty-eight pup deaths were due to cannibalization. Survival rates were comparable thereafter and no effects on survival were noted during the post-weaning period.

**Table 38:** Effect of SCH 34117 on pup survival.

Parameter	Dose (mg/kg)			
	0	3	9	18
Survival (%) – days 1 to 4	99.7	98.2	97.7	92.9

*Sex determination:* Male/female ratios in the treated groups were not affected by treatment of maternal animals.

*Clinical observations:* No SCH 34117-related findings were observed during the pre-weaning, pre-mating, gestation, and lactation periods.

**Body weight:** Body weight gain from birth to day 7 or day 21 postpartum was slightly reduced (8-12%) in mid- and high-dose offspring (Table 39). During the pre-mating and F1 gestation periods, no significant effects on body weight gain were noted although body weights of high-dose animals tended to remain below those of control animals.

**Table 39:** Summary of effects on F<sub>1</sub> clinical findings.

Parameter	Dose (mg/kg)			
	0	3	9	18
Body weight gain: % change from control				
days 0-7 postpartum		-7	-11	-12
days 0-21 postpartum		-5	-8	-9

Shaded area indicates statistically significant difference from control value.

**Neurobehavioral/Developmental tests:** A dose-related effect on righting reflex was observed as the percentage of pups in each group that was able to right themselves in two seconds was reduced on day 5 at the mid-dose (18%) and up to day 9 at the high-dose (30.3% on day 5, 3.4% by day 9). This effect may be due to the delayed growth of the pups. No effects were noted in tests of auditory startle, eye opening, incisor eruption, vaginal opening, preputial separation, passive avoidance or open field tests.

**Estrus cycles:** Sponsor states that there were no drug-related findings noted although no data was provided.

**Parturition and fertility:** All rats in all groups mated. Although the conception rate was reduced at the mid- and high-doses (84 and 86%, respectively vs 100% in control animals), these values fell within the historical range of the laboratory from 1989-1998 (80 to 100%).

**Necropsy:** No SCH 34117-related gross external and visceral findings were observed in culled and dead F<sub>1</sub> pups or F<sub>1</sub> adults.

#### **Offspring (F2):**

No significant differences were noted in body weight on days 0 or 4. Pup survival was reduced at the high-dose (92.9% vs 97.5% in controls) although the finding was not significant. There were no SCH 34117-related gross external or visceral observations.

**Key study observations:** The NOAEL for developmental toxicity of the F<sub>1</sub> pups was 3 mg/kg due to reduced body weight gain and fetal development effects. A NOAEL of > 18 mg/kg was selected for reproductive indices of the first generation offspring and development of the second generation offspring. A NOAEL of 9 mg/kg was observed for the F<sub>0</sub> dams due to reduced body weight gain and food consumption at the high dose.

**Summary of Reproductive Toxicology Studies:** Oral fertility studies with SCH 34117 in rats, embryo-fetal developmental toxicity studies in rats and rabbits, and a peri- and post-natal development study in rats were submitted to this NDA by the sponsor. Doses were selected based upon pilot studies which were submitted to the IND. In the initial fertility study (6, 12, and 24 mg/kg), treatment-related effects were noted and included clinical signs at all doses (enlarged and reduced numbers of fecal pellets, small, soft or no stool), reduced body weight gain at the mid and high doses (14-35%), reduced food consumption in high-dose dams (17-19%) and microscopic observations in high-dose males (mild spermatid cellular debris). No effects on fertility were observed although preimplantation loss was increased and numbers of implantation sites and fetuses were decreased at the high dose. The NOAEL for fertility effects was > 24 mg/kg; a NOAEL of 12 mg/kg was identified for general toxicity findings. A second fertility study was performed in which males only were dosed (3, 12 and 40 mg/kg) for 106-108 days. General findings included reduced body weight gain and food consumption at the high-dose (35% and 19%, respectively), reduced organ weights at the high-dose (prostate, testis, epididymis; 19-42%), small and soft testes at all doses, microscopic findings at all doses including atrophy and degeneration of the seminiferous tubules, spermatid giant cells, spermatid cellular debris and oligospermia, and reduced sperm numbers (22-74%), production and motility (25-59%) at the mid- and high-doses. While mating indices were comparable at all doses, fertility indices were reduced at the mid- and high-doses by 24 and 63.5%, respectively. The number of implantation sites and viable embryos were also reduced in females mated with mid- and high-dose males and the incidence of preimplantation loss was increased. The NOAEL for fertility effects in males in this study was 3 mg/kg while a NOAEL of < 3 mg/kg was identified for general toxicity findings.

An embryo-fetal development study in rats (6, 24 and 48 mg/kg) produced similar clinical signs in dams as in the fertility study as well as reduced body weight gain (56-92%) and food intake (up to 53%) at the mid- and high-doses. No drug-related effects were observed on reproduction parameters although fetal body weight was reduced 8-10% at the mid- and high-doses. There were no skeletal or visceral malformations although skeletal variations were observed at the mid- and high-doses (unossified/reduced ossification of vertebra, sternebra and proximal phalanges). These effects, however, could be due to the observed maternal toxicity. Thus, a NOAEL of > 48 mg/kg was selected for teratologic effects; a NOAEL of 6 mg/kg was identified for general toxicity findings in dams. In rabbits (15, 30, 60 mg/kg), findings included clinical signs in all groups, and body weight loss (0.0007 kg), reduced food consumption, and increased resorptions at the high dose. No drug-related gross or visceral malformations or variations were observed. Thus, a NOAEL of > 60 mg/kg was selected for teratologic effects; a NOAEL of 30 mg/kg was identified for general toxicity findings in dams.

In the peri- and post-natal study (3, 9, 18 mg/kg), similar clinical signs were noted in high-dose dams of the parent generation as well as reduced food consumption at the high-dose. Survival rate of offspring of high-dose dams was reduced by 7% although 65% of deaths were due to cannibalization. Body weight gain was reduced (8-12%) and a dose-related effect on righting reflex was observed in mid- and high-dose offspring. No significant drug-related effects were observed in the F<sub>2</sub> generation fetuses. Thus, a NOAEL of 3 mg/kg was selected for developmental toxicity in F<sub>1</sub> pups; a NOAEL of > 18 mg/kg was selected for F<sub>1</sub> reproductive

indices and F<sub>2</sub> development; a NOAEL of 9 mg/kg was identified for general toxicity findings in parental dams.

Based upon the results of these studies, the Pregnancy Category for the labeling should be "C" due to adverse fetal effects. This conclusion is in contrast to the sponsor's proposal of a category "B".

#### **Review of Sponsor's Response to Toxicology Concerns (N-000, B-2; 3/20/2000):**

Following submission of the Original NDA submission, the sponsor was asked to address an outstanding issue which was outstanding from the previous IND reviews. The sponsor was asked to clarify the term "mineralization" as related to findings in the ovaries of monkeys (i.e., type of minerals) in the 3 month toxicity study (P-6976). A review of the sponsor's response to this issue follows.

The sponsor performed an assay to further characterize the ovarian mineralization in the three month monkey study. Alizarin red stain which reacts with cations and von Kossa stain which reacts with anions were applied to sections of ovary from one monkey in the control group and three monkeys in the high-dose group (72 mg/kg). Material considered to be mineralization by light microscopic examination was positive using the two special stains in high-dose animals while the control animal was positive only with the alizarin red stain. Positive staining of material considered to be mineralization with both alizarin red stain and von Kossa stain suggests that both anions and cations are present. The blue appearance of the material on hematoxylin and eosin-stained sections and the positivity with both special stains, the mineral is most likely composed of calcium phosphate and/or calcium carbonate. In contrast, calcium pyrophosphate and calcium oxalate do not stain with alizarin red. The sponsor further presented background data from control monkeys of numerous previous studies which showed that up to 25-100% of control monkeys displayed minimal to mild ovarian mineralization. Thus, the finding should be considered a normal background change and not a SCH 34117-related effect. The sponsor's response to this issue is acceptable.

#### **OVERALL SUMMARY AND EVALUATION:**

SCH 34117 is an active metabolite of loratadine (Claritin) and is an antihistamine acting with greatest potency at the H<sub>1</sub> receptor. Currently, the NDA application 21-165 propose to market SCH 34117 (5 mg oral tablet) for the indication of seasonal allergic rhinitis for patients 12 year or older. In support of the current application the Sponsor has submitted preclinical studies to this NDA and to IND 55,364 including: in vitro and in vivo pharmacology, safety pharmacology, ADME studies in rats, mice, monkeys and rabbits, acute single dose oral and intraperitoneal studies in rats, mice, and monkeys, subacute oral toxicity studies up to 3 months duration in rats and monkeys, reproductive toxicology studies in rats and rabbits, and genetic toxicity studies.

*Pharmacodynamics:* SCH 34117 demonstrated a high selectivity for H<sub>1</sub>-receptors over H<sub>2</sub> or H<sub>3</sub>-receptors and displayed a 14-fold greater affinity for the H<sub>1</sub>-receptor than loratadine in cloned H<sub>1</sub> human receptor subtypes (IC<sub>50</sub> = 51 and 721 nM, respectively). This finding was confirmed in isolated guinea pig lung tissue (IC<sub>50</sub> = 840 and 3030 nM for SCH 34117 and loratadine, respectively). SCH 34117 was also ~ 18-fold more potent than loratadine in rat brain H<sub>1</sub>-receptor activity (SCH 34117 K<sub>i</sub> = 4.8-7 nM) and was comparable in potency to its primary unconjugated metabolites. In an *in vitro* assessment of antihistaminic activity using guinea pig isolated ileum, SCH 34117 was up to 20-fold more potent than loratadine and was 4 to 8.5-fold more potent in inhibiting histamine-induced bronchospasm *in vivo* (SCH 34117 ED<sub>50</sub> = 0.11-0.27 mg/kg, IV). *In vivo* studies performed for the loratadine program demonstrated that SCH 34117 was 2.5-4 times more potent than loratadine following oral administration in mice and guinea pigs. SCH 34117 also expressed a high affinity for cloned human M<sub>1</sub> and M<sub>3</sub> receptor subtypes (IC<sub>50</sub> = 48 and 125 nM). In a separate study, SCH 34117 showed greatest activity at central H<sub>1</sub> receptors (IC<sub>50</sub> = 17 nM) while activity at peripheral H<sub>1</sub> receptors was similar to that at M<sub>2</sub> muscarinic receptors (IC<sub>50</sub> = 131-168 nM). Other receptor sites tested showed significantly reduced activity. Thus, the results in the Clinical Pharmacology of the labeling submitted by the sponsor concerning the increased relative potency of SCH 34117 compared to loratadine are acceptable.

Anti-allergic and anti-inflammatory effects of SCH 34117 were demonstrated in numerous *in vitro* and *in vivo* tests. SCH 34117 exhibited 2-3-fold greater oral potency over loratadine in histamine-induced wheal and flare reactions. SCH 34117 inhibited superoxide anion production by PMN, histamine induced activation of endothelial cells, P-selectin expression, release of IL-4 and IL-13, and IL-6 and IL-8, release of histamine, tryptase, LTC<sub>4</sub> and PGD<sub>2</sub>, release of RANTES, and attenuated eosinophil chemotaxis and adhesion. Weak inhibitory activity of TNF- $\alpha$  was also observed. *In vivo* functional assays demonstrated that SCH 34117 was more potent than loratadine in inhibiting the guinea pig nasal response to histamine challenge (ED<sub>50</sub> = 0.9  $\mu$ g) and in inhibiting cough in ovalbumin sensitized guinea pigs (0.3-1 mg/kg, po). In monkeys, SCH 34117 (5-6.5 mg/kg, po) reduced the bronchospasm and associated increase in airway resistance and decrease in compliance induced by allergen challenge and histamine-induced bronchospasm. Comparable findings in response to histamine challenge were observed with 8 mg/kg loratadine. No effect on decongestion was noted in cats (3 mg/kg, IV). Comments in the proposed label concerning the \_\_\_\_\_ effects of SCH 34117 should be removed since a definitive connection between these properties and the indication of \_\_\_\_\_'s has not been demonstrated.

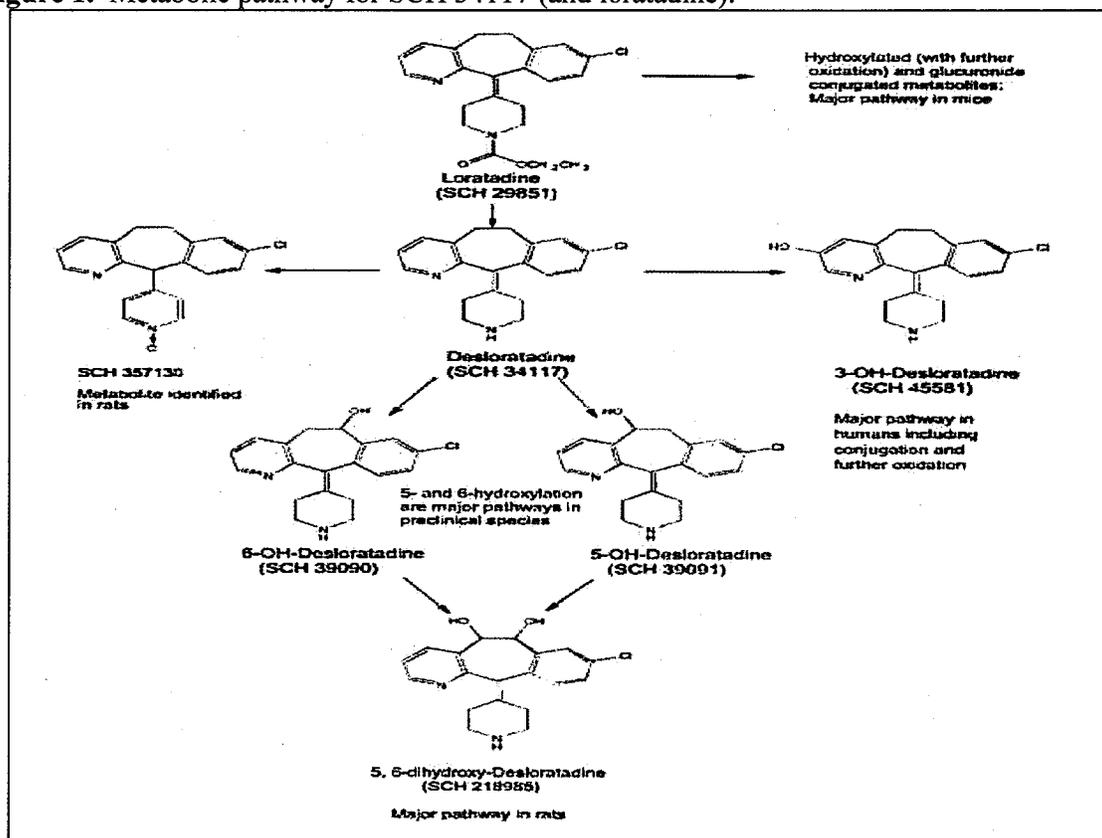
The results of these studies suggest that SCH 34117 may have value as an antihistamine in the treatment of seasonal allergic rhinitis.

*Safety Pharmacology:* In vivo assessments of SCH 34117-related effects on cardiovascular function demonstrated that no significant in vivo cardiovascular effects were observed in rats or monkeys (doses up to 12 mg/kg, oral, or 10 mg/kg, intraperitoneal) or in guinea pigs (25 mg/kg SCH 34117, IV). In a study cited by the sponsor<sup>2</sup>, loratadine (30 and 100 mg/kg, IV) did not alter cardiovascular parameters in the guinea pig (plasma levels = 27.8-61 µg/ml), in contrast to terfenadine, quinidine and diphenhydramine which induced significant cardiovascular and ECG effects. Resulting SCH 34117 concentrations (1.46 µg/ml) were 370-fold greater than its C<sub>max</sub> in man after a single oral dose of 10 mg loratadine. In vitro studies showed that SCH 34117 and loratadine were significantly less potent than terfenadine in inhibiting rat ventricular myocyte and guinea pig cardiac K<sup>+</sup> channels. SCH 34117 did exert effects on various cardiac parameters in vitro at concentrations ranging from 5-100 µM. SCH 34117 blocked hKv1.5 channels cloned from human ventricle and expressed in a mouse cell line (Ltk-), in a concentration-, voltage-, and time-dependent manner. SCH 34117 (1 to 100 µM) also inhibited a cloned human hKv1.5 current with an K<sub>D</sub> of 12.5 µM, but was less potent than loratadine or terfenadine (K<sub>D</sub>=1.0 and 0.8 µM, respectively). Thus, the relative potency is terfenadine > loratadine > SCH 34117. SCH 34117 was ~ 7-fold less potent than loratadine in blocking KV1.5 channel in HEK 293 cells and loratadine (10 µM) failed to significantly alter HERG currents. Both drugs (up to 10 µM) had minimal effects on I<sub>HERG</sub> current (15-20%) compared to terfenadine and quinidine (IC<sub>50</sub> = 82 and 168 nM, respectively). 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 enhanced a quinidine-induced increase. Loratadine had no effects on QT, QRS or JT intervals at up to 50 µM. SCH 34117 also decreased V<sub>max</sub> 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<sup>+</sup> current more effectively than 100 µM loratadine; loratadine showed preferential binding to channel in inactivated state. Other effects included reduced delayed rectifier current (iK<sub>r</sub>) current to ~ ½ control value at 6 x 10<sup>-6</sup> M as the concentration at which ½ current is blocked (k<sub>0.5</sub>) was 5 x 10<sup>-6</sup> M (k<sub>0.5</sub> for loratadine was 8.7 x 10<sup>-6</sup>). SCH 34117 had no effect at 10<sup>-5</sup> M on inward rectifier current (iK<sub>1</sub>) although the curve was flatter at 3 x 10<sup>-5</sup> M; loratadine had more pronounced effect than SCH 34117. Since SCH 34117 has been shown to have less or equal potency compared to loratadine in inhibiting rat and guinea pig cardiac K<sup>+</sup> 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, and loratadine-induced cardiac effects have not been observed in humans, SCH 34117 is considered to be reasonably safe in this regard. In terms of general safety pharmacology studies, SCH 34117 induced no effect on the rat gastrointestinal, renal or central nervous systems at oral doses up to 12 mg/kg.

<sup>2</sup> Hey, JA, Del Prado, M, Cuss, FM, Egan, RW, Sherwood, J, Lin, CC, and Kreutner, W. (1995). Antihistamine activity, central nervous system and cardiovascular profiles of histamine H1 antagonists: comparative studies with loratadine, terfenadine and sedating antihistamines in guinea-pigs. *Clinical and Experimental Allergy*, 25: 974-984.

In studies performed under NDA 19-658, loratadine was 10-fold less potent than diphenhydramine in inducing neurological, behavioral, and autonomic effects in mice, dogs, monkeys and in inducing a sedative effect in cats.

*Pharmacokinetics:* SCH 34117 was generally well absorbed with an oral bioavailability of 45-94% observed in rats and 47-57% in monkeys. Plasma concentrations of SCH 34117 increased supra-proportionally with dose in rats and drug accumulation was evident. Systemic exposure was greater in females than in males. In monkeys, plasma SCH 34117 levels increased proportionally to supra-portionally. Following loratadine administration, systemic exposure to SCH 34117 was greater in all species tested except for rabbits. T<sub>max</sub> was achieved within 4 hours in rabbits, mice and monkeys and 1.5-12 hours in rats; elimination half-life 2-5 hours in mice and rats and 8-11.3 hours in monkeys. Drug accumulation was evident and no gender differences were observed. In rats, SCH 34117 was widely distributed with highest levels detected in the pituitary, adrenal gland, lung, liver, spleen, thyroid, and mesenteric lymph nodes. Distribution of <sup>14</sup>C-loratadine in pregnant rats demonstrated that radioactivity crossed the placental barrier equally at the post-embryonic period and near-term. Tissue distribution was similar in maternal and fetal tissues with lower levels found in the fetus. Plasma protein binding of SCH 34117 was variable across species as the mouse, rat, monkey and humans demonstrated 94.4%, 90.5%, 85.8% and 85.0% binding, respectively. The comparative species metabolism of SCH 34117 is summarized in Figure 1. SCH 34117 was extensively metabolized in rats, mice and monkeys and the metabolites are excreted either unchanged, as glucuronides or as further oxidized and conjugated products. Metabolism of SCH 34117 occurred through hydroxylation (primarily at the 5- and 6-positions and the 3-position to a lesser degree) and glucuronidation in the species tested. Hydroxylation at the 3-position was more extensive in humans. Male rats achieved relatively high circulating levels of SCH 357130 while N-oxidation was observed in monkeys. In vitro studies confirmed the results of the in vivo studies and demonstrated that the hydroxylated metabolites are formed in humans although unchanged SCH 34117 was the primary compound detected. The metabolism profile of SCH 34117 is generally similar to that of loratadine with no SCH 34117-specific metabolites formed. Excretion of SCH 34117-related radioactivity was primarily through the feces with a large portion contributed through the bile. Approximately 20-40% was excreted through the urine.

**Figure 1.** Metabolic pathway for SCH 34117 (and loratadine).

**Acute Toxicity:** Acute, oral and intraperitoneal studies in mice and rats, as well as an oral study in monkeys were submitted to IND 55,364. 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.

**Subchronic Toxicity:** Studies were conducted in rats and monkeys for up to 3 months duration with both SCH 34117 and loratadine in order to support a bridging strategy to the loratadine chronic toxicology program. The primary toxicity findings in both species, similar to loratadine, was systemic phospholipidosis in organ systems throughout the body. The kidney and epididymides were target organs in rats.

In rats, treatment-related mortality occurred at a dose of 240 mg/kg SCH 34117 in one of two 2-week studies and at a dose of 120 mg/kg in males and 30 mg/kg or greater in females in a three month study. Systemic phospholipidosis was the primary toxicity finding in tissues throughout the body. In addition, kidney necrosis and luminal cellular debris of the epididymides were

observed following 3-month administration. The toxicity profile of SCH 34117 was similar to that of the active control (loratadine) group. However, loratadine showed greater induction potential of cytochrome P450 and PROD than SCH 34117. The NOAEL in the 3-month toxicity study was 3 mg/kg in females and 30 mg/kg in males. These doses resulted in mean systemic exposures ( $AUC_{0-24 \text{ hr}}$ ) of 1890 ng.hr/ml and 9490 ng.hr/ml in females and males, respectively.

In monkeys, no treatment-related mortality was observed at doses up to 18 mg/kg for 3 months. Systemic phospholipidosis was again the primary toxicity finding in organs/tissues throughout the body. The toxicity profiles observed in SCH 34117-treated groups were comparable to the active (loratadine) control group at similar SCH 34117 systemic exposure levels. The NOAEL in the 3-month toxicity study was 12 mg/kg which resulted in mean systemic exposures ( $AUC_{0-24 \text{ hr}}$ ) of 21613 ng.hr/ml.

*Chronic Toxicity:* The similar toxicological findings following SCH 34117 and loratadine administration in the 3 month rat and monkey studies at similar exposure levels of SCH 34117 support bridging to the chronic loratadine toxicology program. Therefore, the Sponsor was not required to perform chronic toxicity studies with SCH 34117.

*Reproduction:* Effects of SCH 34117 on fertility were studied in both sexes. In females, oral doses up to 24 mg/kg (~ 560 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) did not influence fertility although preimplantation loss was increased and numbers of implantation sites and fetuses were decreased at this dose. In males, oral doses of 12 mg/kg (~ 180 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) or greater reduced fertility (24-64%). A dose of 3 mg/kg (~ 30 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) had no effect on fertility. General findings in males included reduced organ weights at the high-dose (prostate, testis, epididymis; 19-42%), small and soft testes at all doses, and microscopic findings at all doses (atrophy and degeneration of the seminiferous tubules, spermatid giant cells, spermatic cellular debris and oligospermia, reduced sperm numbers, production and motility at the mid- and high-doses). The number of implantation sites and viable embryos were reduced in females mated with mid- and high-dose males and the incidence of preimplantation loss was increased. The findings in males were generally non-reversible.

Embryo-fetal development studies were performed in rats and rabbits. Oral administration at doses up to 48 mg/kg/day (~ 870 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) in rats and 60 mg/kg/day (~ 230 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) in rabbits during the period of organogenesis produced no evidence of teratogenicity. Skeletal variations in rat fetuses (unossified/reduced ossification of vertebra, sternebra and proximal phalanges) and reduced fetal body weight observed at a dose of 24 mg/kg (~ 560 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) or greater were attributable to maternal toxicity (reduced body weight gain; 56-92% and food intake; up to 53%). No evidence of toxicity was observed at the

next lowest dose tested, 6 mg/kg (~ 140 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose).

An oral peri- and post-natal study was performed in rats. A dose of 3 mg/kg SCH 34117 (~ 30 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) had no toxicologically significant effects on F<sub>1</sub> pup survival, pre-weaning growth or F<sub>1</sub> development. A dose of 9 mg/kg (~ 190 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) or greater led to reduced fetal weight (8-12%) and a dose-related effect on righting reflex. No significant effects were observed in the F<sub>2</sub> generation at doses up to 24 mg/kg (~ 520 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose).

Based upon the results of these studies, the Pregnancy Category for the labeling should be "C" due to adverse fetal effects. This conclusion is in contrast to the sponsor's proposal of "B".

*Genotoxicity:* Genetic toxicology studies assessing SCH 34117 were submitted to IND 55,364 and included a bacterial reverse mutation assay (Ames test), an *in vitro* chromosome aberration assay using human lymphocytes and an *in vivo* mouse bone marrow erythrocyte micronucleus assay. SCH 34117 was negative under the conditions tested in each of the assays. The sponsor also submitted two assays (a bacterial reverse mutation assay and an *in vitro* chromosome aberration assay using human lymphocytes) to the NDA as part of their effort to qualify the presence of two synthesis impurities. These studies also produced negative results.

*Carcinogenicity:* Carcinogenicity studies have not been performed with SCH 34117. A two-year study in rats and an eighteen-month study in mice performed with loratadine induced hepatic carcinogenicity in male mice and male and female rats. In addition, the mouse study was not considered to have achieved the maximum tolerated dose (MTD). The sponsor requested a waiver from performing carcinogenicity studies with SCH 34117 based upon SCH 34117 exposure ratios achieved during carcinogenicity studies performed with loratadine. CDER's Pharmacology/Toxicology Senior Policy Team considered the waiver request and concluded that the rat carcinogenicity study performed with loratadine sufficiently assesses the carcinogenic liability of SCH 34117 since the study resulted in an unbound DCL-derived rodent to human exposure multiple exceeding a factor of 25. However, the waiver for the mouse carcinogenicity study was not acceptable since appropriate SCH 34117 exposure multiples were not achieved in the carcinogenicity study with loratadine and the mouse study was not considered to have achieved an appropriate high dose. Thus, the sponsor was informed that a two-year mouse carcinogenicity study would be required. The Senior Policy Team felt that the study could be performed as a Phase 4 commitment since loratadine is an approved drug product and a significant portion of the population is already exposed to its metabolite SCH 34117, the genotoxicity studies for SCH 34117 resulted in negative findings and the carcinogenic potential has at least been partially assessed in the studies performed in rats and mice with loratadine. A study protocol was submitted by the sponsor for CAC concurrence and the Executive CAC

provided concurrence with changes in the proposed dose selection (see Exec CAC minutes dated August 3, 2000). The sponsor should submit the final study report within three years of the NDA approval or study initiation, whichever occurs first.

*Special Toxicity:* There were no Special Toxicity studies performed in support of IND 55,354 or NDA 21-165. However, two studies were performed in support of loratadine (NDA 19-658) to assess phospholipidosis in rats and dermal sensitization in guinea pigs. Vacuolated peripheral lymphocytes were observed in all rats administered loratadine (240 mg/kg, po, 2 weeks) with no differences noted between Wistar and CD rats. The dermal sensitization test was negative.

*Excipients, Degradants and Impurities:* As part of the qualification for the drug substance impurities ~~\_\_\_\_\_~~ the sponsor performed two genotoxicity assays with SCH 34117 with added levels of ~~\_\_\_\_\_~~ which produced negative findings at impurity levels exceeding those proposed by the sponsor. In a letter dated June 26, 2000, the Sponsor was requested to limit levels of ~~\_\_\_\_\_~~ impurities to not more than ~~\_\_\_\_\_~~ in the drug substance, or provide further qualification for the drug substance impurities (3 month toxicity study using appropriate levels of impurities ~~\_\_\_\_\_~~). The Sponsor submitted information for qualification and their proposed levels (NMT ~~\_\_\_\_\_~~; for ~~\_\_\_\_\_~~ and NMT ~~\_\_\_\_\_~~ for ~~\_\_\_\_\_~~ were found to be acceptable (see Addendum to Chemistry Consult, dated August 14, 2000).

In conclusion, the pharmacology, pharmacokinetics and toxic potential of SCH 34117 has been evaluated extensively in multiple *in vitro* and *in vivo* studies with SCH 34117 and also with loratadine. Treatment-related disturbances related to systemic phospholipidosis were observed in rats and monkeys following repeat oral dosing in subchronic studies. However, NOAELs observed in all repeat dose studies demonstrated wide safety margins relative to the proposed therapeutic oral dose (5 mg/day; AUC = 56.9 ng.hr/ml) all observed toxicity based on systemic exposures to SCH 34117.

SCH 34117 showed no potential for mutagenic/clastogenic activity in a series of *in vitro* assays and an *in vivo* assay. Loratadine induced hepatic carcinogenicity in male mice and male and female rats. Although the rat study was considered to have adequately assessed the carcinogenic potential of SCH 34117, based upon exposure criterion, the mouse study did not since it did not achieve an appropriate high dose. Thus, the sponsor was informed that a two-year mouse carcinogenicity study with SCH 34117 would be required as a Phase 4 commitment. A study protocol was submitted and a modified dose selection scheme was recommended by the Executive CAC.

The potential of SCH 34117 for reproductive toxicity was characterized in rats and/or rabbits, at high multiples over the proposed clinical dose. Results of these studies revealed effects on male fertility but no teratogenic effects in either species. However, effects on fetal development were evident. Thus, the pregnancy category should be C.



2 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

[REDACTED]

**RECOMMENDATIONS**

1. The NDA for descarboethoxyloratadine is approvable from a preclinical standpoint pending incorporation of the suggested revisions for the labeling sections entitled: Clinical Pharmacology, Carcinogenesis, Mutagenesis, and Impairment of Fertility, Pregnancy Category, and OVERDOSAGE as indicated above.
2. The sponsor should submit the final study report for the Phase 4 mouse carcinogenicity study within three years of the NDA approval or study initiation, whichever occurs first.

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Timothy J. McGovern, Ph.D., Pharmacologist

**Comment for letter to Sponsor:**

The final study report for the Phase 4 mouse carcinogenicity study should be submitted within three years of the NDA approval or study initiation, whichever occurs first.

CC: Original NDA 21-165  
HFD-570/Division File  
HFD-570/C.J. Sun  
HFD-570/D. Nicklas  
HFD-570/G. Trout  
HFD-570/V. Borders  
HFD-570/T.J. McGovern  
HFD-540/B. Hill  
HFD-590/K. Hastings

Attachments: Exposure ratio calculation table  
For NDA Division file only:  
IND 55,364 Original Review  
IND 55,364, Review #2  
IND 55,364, Review #3  
IND 55,364, Review #4  
Minutes of Senior Pharmacology/Toxicology Policy Team  
IND 55,364, Review #5  
IND 55,364, Review #6

Studies	DCL AUC	DCL+ DCL metabolites AUC	Animal:human ratio	PB correction	derivation of animal AUC
Human - 5 mg	56.9	711.25			
<b>rat: fertility</b>					
3 mg/kg	1950	8863.64	12	8	3 mos tox study, males
12mg/kg	10440	47454.55	67	44	40% of 30 mg/kg dose in 3 m
24 mg/kg	31606	143663.64	202	134	Embryo-fetal rat study
<b>rat: embryo fetal</b>					
6 mg/kg	7875	35795.45	50	33	Embryo-fetal rat study
24 mg/kg	31606	143663.64	202	134	Embryo-fetal rat study
48 mg/kg	49238	223809.09	315	208	Embryo-fetal rat study
<b>rat: Seg III</b>					
3 mg/kg	1619	7359.09	10	7	1 month rat tox study
9	10999	49995.45	70	47	30% of 30 mg/kg dose in 1 m
24	29331	133322.73	187	124	80% of 30 mg/kg dose in 1 m
<b>rabbit: embryo-fetal</b>					
60 mg/kg	12987	NA	230		Embryo-fetal rabbit study
<b>Overdosage</b>					
rat-125 mg/kg	21944.5	99747.73	140	93	1-week Pk study at 120 mg/kg
rat-250 mg/kg	27441	124731.82	175	116	1-week Pk study at 240 mg/kg
Mouse-250 mg/kg	7115	19229.73	27	10	single oral dose of 6.5 mg/kg;
Mouse-353 mg/kg	10046	27151.35	38	15	
Monkey 250 mg/kg	21422	NA	380		3-month monkey tox study; 11
<b>Carcinogenicity</b>					
Mouse - 40 mg/kg	1861	5029.73	7	3	28-day dietary study w/ortadi
Rat - 25 mg/kg	7017	31895.45	45	30	28-day dietary study w/ortadi
Rat - 10 mg/kg	1619	7359.09	10	7	28-day dietary study w/ortadi
<b>Species</b>	<b>DCL/14C ratio</b>	<b>Protein binding (%)</b>			
Mouse	0.37	94.4			
Rat	0.22	90.5			
Human	0.08	85.6			
Monkey	NA	85.8			

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

IND No. 55,364

Serial No. 000

Submission Date: 09 MAR 98

Reviewer: Timothy J. McGovern, Ph.D.

Review Completed: 22 MAY 98

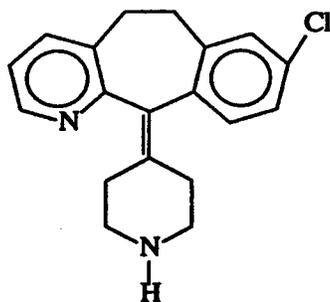
Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: Schering-Plough Corporation

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

Chemical Name: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinylidene)

Structure:



Molecular Weight: 310.82

Formula: C<sub>18</sub>H<sub>31</sub>N<sub>4</sub>O<sub>3</sub>

Related INDs/NDAs/DMFs: NDA 19-658, IND —, IND — NDA 20-704

Class: Anti-histamine

Indication: Allergic rhinitis/chronic idiopathic urticaria

Clinical Formulation: <u>Components</u>	<u>Amount/tablet type (mg)</u>		
	<u>2.5 mg</u>	<u>5 mg</u>	<u>10 mg</u>
SCH 37114	2.5	5	10
Dibasic calcium phosphate dihydrate USP	-----	-----	-----
Cellulose microcrystalline NF	-----	-----	-----
Corn starch NF	-----	-----	-----
Blue	-----	-----	-----
Clear	-----	-----	-----
Carnauba Wax NF	-----	-----	-----
White Wax NF	-----	-----	-----
<b>Total tablet wt.</b>	<b>106.61</b>	<b>106.61</b>	<b>106.61</b>

**Route of Administration:** Oral (tablet)

**Proposed Clinical Protocol:**

*Objective:* Phase II, dose-finding study to examine clinical efficacy and safety of SCH 34117

*Dose:* 2.5, 5, 7.5, 10, and 20 mg

*Frequency:* Once per day

*Duration of clinical study:* 2 weeks

*Patient population:* Patients with seasonal allergic rhinitis

**Previous Clinical Experience:** Phase I, rising single-dose study (2.5 - 20 mg) in healthy male volunteers. The follow-up physical examination and vital signs for all patients were normal and no clinically relevant changes were reported.

**Previous Review(s), Date(s) and Reviewer(s):** None

A Pre-IND meeting was held with the sponsor on 1/12/98 to discuss the potential for bridging to the development program of the SCH 34117 parent compound loratadine (SCH 29851). See the Meeting Minutes for a review of this discussion.

The following table summarizes the studies submitted in the original IND package:

APPEARS THIS WAY ON ORIGINAL

**Preclinical Studies Submitted and Reviewed in this IND:**

Study	Report #	Volume
<b>Pharmacology:</b>		
Comparative antihistaminic activity	Abstract	1.3
Onset of antihistamine activity	D-26677	1.3
Antihistamine activity in monkeys	D-28097	1.3
Anticholinergic actions in guinea pig right atria	P-5950	1.3
Associated muscarinic side-effects	Cited Ref.	1.3
Comparative antihistaminic activity	Cited Ref.	1.3
Comparative effects on cardiac K <sup>+</sup> channels	Cited Ref.	1.3
Effects on human cardiac potassium channel Kv1.5	Cited Ref.	1.3
<b>Safety Pharmacology:</b>		
Comparative CNS and cardiovascular profiles	Cited Ref.	1.3
<b>Pharmacokinetics:</b>		
Metabolic profiling in rat, mouse and monkey	D-28407	1.9
Rising single-dose study in healthy human volunteer	I97-248-01	1.17
<b>Acute Toxicology:</b>		
Single-dose oral administration, mice	P-6771	1.15
Single-dose intraperitoneal administration, mice	P-6772	1.15
Single-dose oral administration, rats	P-6769	1.15
Single-dose intraperitoneal administration, rats	P-6770	1.15
Single-dose oral administration, monkeys	P-6808	1.15
<b>Multiple Dose Toxicology:</b>		
14-day oral safety profile, rats	D-18289	1.15
14-day, oral toxicology, rats	P-6526	1.4
14-day, oral toxicology, monkeys	P-6527	1.7
<b>Reproductive Toxicology:</b>		
Pilot Segment I, rats	P-6821	1.16
Pilot Segment II, rats	P-6718	1.16
Pilot Segment II, rabbits	P-6719	1.16
Segment II, rabbits (incomplete submission)	P-6802	1.9
<b>Genetic Toxicology:</b>		
Bacterial reverse mutation assay (Ames test)	P-6609	1.16
Chromosome aberration in human lymphocytes	P-6692	1.16

**Studies Not Reviewed in this IND:** Four validation studies for the determination of loratadine and SCH 34117 in mouse (Study \_\_\_\_\_ Vol. 1.10), rat (\_\_\_\_\_ Vol. 1.11), cynomolgus monkey (\_\_\_\_\_ Vol. 1.13) and human plasma (\_\_\_\_\_ Vol. 1.14) by \_\_\_\_\_ The assay for Studies \_\_\_\_\_ and \_\_\_\_\_ was validated over the range of \_\_\_\_\_ ng/ml using a \_\_\_\_\_ ml sample. The assay for Study \_\_\_\_\_ was validated over the range of (\_\_\_\_\_ ng/ml using a \_\_\_\_\_ ml sample. The assay for Study \_\_\_\_\_ was validated over the range \_\_\_\_\_ ng/ml using a \_\_\_\_\_ ml sample.

**Studies Previously Reviewed:** None

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

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## PHARMACOLOGY

**Antihistaminic activity:** SCH 34117 displayed greater H<sub>1</sub>-receptor affinity than the parent drug loratadine, as the two drugs displaced radioligand binding to a cloned H<sub>1</sub> human receptor subtype with IC<sub>50</sub> values of 51 and 721 nM, respectively<sup>3</sup>. Both compounds were highly selective and showed little affinity for H<sub>2</sub> or H<sub>3</sub>. In isolated guinea pig lung tissue, representative of peripheral H<sub>1</sub> receptors, SCH 34117 again showed greater affinity as IC<sub>50</sub>s of 840 and 3030 nM for SCH 34117 and loratadine, respectively, were reported.

SCH 34117 displayed greater antihistaminic potency than loratadine in various animal models. In guinea pigs, antihistaminic activity of SCH 34117, measured by the inhibition of histamine-induced bronchospasm, showed 4- to 8.5-fold greater potency compared to loratadine (Table 1). Onset of activity was rapid (within 2 minutes) and the peak activity for both compounds was between 30 and 60 minutes. SCH 34117 also displayed a 20-fold greater potency than loratadine (concentrations not provided) in antagonizing histamine-induced contractions of isolated strips of guinea pig ileum<sup>1</sup>. *In vivo*, SCH 34117 also exhibited 2-3 fold greater oral potency over loratadine (doses not provided) in histamine-induced weal and flare reactions<sup>1</sup>. In monkeys, both loratadine (8 mg/kg) and SCH 34117 (6.5 mg/kg), administered by gastric intubation, almost completely inhibited the effects of histamine on airway resistance and compliance. Differences between placebo and treatment groups were significant (p<0.01), but treatment groups were not significantly different from each other.

**Table 1.** Comparative antihistaminic activity of SCH 34117 and loratadine.

Measured Endpoint	SCH 34117	Loratadine
ED <sub>50</sub> -G. Pig; inhibition of histamine-induced bronchospasm (iv, 2 min)	0.27 mg/kg	2.3 mg/kg
ED <sub>50</sub> -G. Pig, inhibition of histamine-induced bronchospasm (iv, 60 min)	0.11 mg/kg	0.41 mg/kg

**Anticholinergic activity:** In studies with cloned human M<sub>1</sub>-M<sub>3</sub> receptor subtypes, SCH 34117 expressed a high affinity for the M<sub>1</sub> and M<sub>3</sub> receptor subtypes (IC<sub>50</sub> of 48 and 125 nM, respectively)<sup>1</sup>. Conversely, a weak affinity for the M<sub>2</sub> receptor (IC<sub>50</sub> 250-1000 nM) indicated selective anticholinergic activity. Loratadine did not possess any binding activity with muscarinic receptors.

Anticholinergic effects were assessed *in vitro* by decreases in spontaneous right atrial rate induced by acetylcholine before and after loratadine, SCH 34117, astemizole or terfenadine dosing (all at 10 μM; corresponding to a concentration of 3820 ng/ml for loratadine, roughly 1000-fold that existed in the therapeutic setting) using right atria from male guinea pigs. The potency of SCH 34117 was comparable to diphenhydramine (Table 2), but significantly less than atropine, as slight anticholinergic activity was noted at 0.1 μM SCH 34117, with significant inhibition noted at 1 and 10 μM (occurring at a concentration 21-fold higher than reported human drug plasma levels). Neither loratadine nor astemizole inhibited responses to acetylcholine.

<sup>3</sup> Handley, DA, McCullough, JR, Fang, Y, Wright, SE, and Smith, ER. (1997). Descarboethoxyloratadine, a metabolite of loratadine, is a superior antihistamine (Abstract P164). *Annals of Allergy, Asthma and Immunology*. 78: 143.

**Table 2.** In vitro anticholinergic activities in guinea pig right atria.

Substance	pA <sub>2</sub>	K <sub>i</sub> nM	Relative Potency
Astemizole	NA	NA	NA
Atropine	9.03	1.83	1.000
Diphenhydramine	6.73	298	0.006
Loratadine	NA	NA	NA
SCH 34117	6.81	206	0.009
Terfenadine	NA	NA	NA

NA - Anticholinergic activity not manifested at 10  $\mu$ M and value could not be determined.

pA<sub>2</sub> - the value represented by the logarithm of 1/[the molar concentration of inhibitor requiring that twice as much agonist be used to elicit the same response as when no inhibitor was present).

K<sub>i</sub> - apparent dissociation constant of inhibitor-receptor complex

The muscarinic side-effects of SCH 34117 on pilocarpine-induced salivary secretion (1 mg/kg sc), a functional model for M<sub>3</sub> receptors, topical-induced mydriasis, and oxotremorine hypothermia (measures of M<sub>2</sub> and M<sub>3</sub> receptor response) and OXO-induced tremor (M<sub>3</sub>-mediated) were assessed along with fexofenadine, carebastine, terfenadine, loratadine and ebastine in mice<sup>4</sup>. Only SCH 34117 inhibited pilocarpine-induced salivation in mice (IC<sub>50</sub> = 10.8 mg/kg po and 3.2 mg/kg sc). Loratadine significantly inhibited salivation (24%) only at highest dose (30 mg/kg po). SCH 34117 (10 mg/kg) and atropine (1 mg/kg) also partially inhibited pilocarpine-induced acinar cell degranulation in the submandibular gland, while fexofenadine and carebastine were virtually inactive. SCH 34117 also produced a potent and long lasting (>120 min) mydriasis after topical administration (ED<sub>50</sub> = 2.7 mg/kg). None of the compounds tested affected oxotremorine hypothermia and OXO-induced tremor.

**Cardiac Potassium Channels:** The effects of SCH 34117, loratadine and terfenadine on a variety of cardiac K<sup>+</sup> channels were investigated in ventricular myocytes and in *Xenopus* oocytes expressing the *HERG* delayed rectifier<sup>5</sup>. Terfenadine suppressed all of the channels tested (inward rectifier of the rat and guinea pig, I<sub>K1</sub>; transient outward K<sup>+</sup> current of rat, I<sub>to</sub>; maintained K<sup>+</sup> current of rat, I<sub>ped</sub>; and delayed rectifier K<sup>+</sup> channels of guinea pig myocytes, I<sub>Ks</sub> and I<sub>Kr</sub>) with greater potency than loratadine and SCH 34117, which were of generally comparable potency (Table 3). Loratadine had little or no suppressive effect on rat ventricular myocyte I<sub>K1</sub> at doses up to 10  $\mu$ M; similar results were observed in guinea pig cardiomyocytes. The suppression at 10  $\mu$ M (15%) was irreversible upon washout. SCH 34117 had similar effects at doses up to 2.5  $\mu$ M (5% suppression) and irreversibly and non-specifically suppressed I<sub>K1</sub> at 10  $\mu$ M. In contrast, the I<sub>K1</sub> was suppressed by 40% at 1  $\mu$ M terfenadine. Loratadine had no significant effect on the delayed rectifier channel (I<sub>Ks</sub>) until doses > 1  $\mu$ M were tested; 25  $\mu$ M induced a 60% suppression (considered non-specific as this dose also suppressed I<sub>Ca</sub> and I<sub>Na</sub>). SCH 34117 was slightly less potent than loratadine and terfenadine was again more potent in suppressing I<sub>Ks</sub>, inducing a 21% suppression at 0.25  $\mu$ M. Terfenadine, but not loratadine, almost completely abolished (90%) the time dependent component of tail current from I<sub>Kr</sub> at 1  $\mu$ M in native guinea pig myocytes.

<sup>4</sup> Cardelus, I, Puig, J, Bou, J, Jauregui, J, Fernandez, AG and Palacios, JM. (1997). Xerostomia and mydriasis: Two possible muscarinic peripheral side effects associated with descarboethoxyloratadine, the main metabolite of loratadine. Proc. British Pharmacological Soc.: P149.

<sup>5</sup> Ducic, I, Ko, CM, Shuba, Y, and Morad, M. (1998). Comparative effects of loratadine, and terfenadine on cardiac K<sup>+</sup> channels. J. Cardiovascular Pharmacol. In press.

Similar results were obtained with terfenadine (60% suppression) and loratadine (5% suppression) at 1  $\mu\text{M}$  in  $I_{K_r}$  expressed in *Xenopus* oocytes. The outward transient current ( $I_{to}$ ) was also more potently regulated by terfenadine (40% suppression) than by loratadine (5% or less suppression) at 2.5  $\mu\text{M}$ . SCH 34117 was either ineffective or had a significantly smaller effect in suppressing  $I_{to}$  than terfenadine at 1  $\mu\text{M}$  and induced only an 8% suppression at 2.5  $\mu\text{M}$ . The maintained component of  $I_{to}$  ( $I_{ped}$ ) was also more potently suppressed by terfenadine (28% and 40-50% at 1 and 2.5  $\mu\text{M}$ , respectively) than by loratadine (22% at 2.5  $\mu\text{M}$ ) or SCH 34117 (15 and 22% at 1 and 2.5  $\mu\text{M}$ , respectively).

**Table 3.** Relative potency in  $K^+$  channel inhibition.

<b>K<sup>+</sup> channel</b>	<b>Relative potency</b>
$I_{K1}$	terfenadine > loratadine = SCH 34117
$I_{Ks}$	terfenadine > loratadine > SCH 34117
$I_{K_r}$	terfenadine > loratadine
$I_{to}$	terfenadine > loratadine = SCH 34117
$I_{ped}$	terfenadine > loratadine = SCH 34117

In a second study cited by the sponsor, the effects of SCH 34117 on cardiac  $K^+$  channel (hKv1.5) cloned from human ventricle and stably expressed in a mouse cell line (Ltk-) were assessed<sup>6</sup>. SCH 34117 blocked hKv1.5 channels, which generate the ultra-rapid delayed outward  $K^+$  current in human atria, in a concentration-, voltage-, and time-dependent manner. SCH 34117 (1 to 100  $\mu\text{M}$ ) inhibited hKv1.5 current with an apparent affinity constant ( $K_D$ ) of 12.5  $\mu\text{M}$ , but was less potent than loratadine or terfenadine ( $K_D = 1.0$  and 0.8  $\mu\text{M}$ , respectively). Thus, the relative potency is terfenadine > loratadine > SCH 34117. The blockade by SCH 34117 increased over the voltage range, indicating that SCH 34117 binds preferentially to the open state of the channel. In addition, a concentration of 20  $\mu\text{M}$  increased the time constant of deactivation of tail currents, thus inducing a "crossover" phenomenon.

### Summary of Pharmacology

SCH 34117 displayed a 14-fold greater affinity for the  $H_1$ -receptor than loratadine and was up to 20-fold more potent than loratadine in antihistaminic activity in guinea pigs. Antihistaminic potency on airway effects was comparable in monkeys. SCH 34117 also showed an affinity for  $M_1$ - and  $M_3$ -receptors, but not for  $M_2$ -receptors. In contrast, loratadine displayed no affinity for muscarinic receptors. SCH 34117 dose-dependently expressed anticholinergic activity by decreasing the spontaneous right atrial rate in male guinea pigs (0.1 to 10  $\mu\text{M}$ ) 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 also 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

<sup>6</sup> Caballero, R, Delpon, E, Valenzuela, C, Longobardo, M, Franqueza, L, and Tamargo, J. (1997). Effect of descarboethoxyloratadine, the major metabolite of loratadine, on the human cardiac potassium channel Kv1.5. *Br. J. Pharmacol.*, 122, 796-798.

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 were significantly less potent than terfenadine in inhibiting rat and guinea pig cardiac  $K^+$  channels. SCH 34117 (1 to 100  $\mu$ M) also inhibited a cloned human hKv1.5 current with an  $K_D$  of 12.5  $\mu$ M, but was less potent than loratadine or terfenadine ( $K_D=1.0$  and 0.8  $\mu$ M, respectively).

## SAFETY PHARMACOLOGY

**Cardiovascular effects:** Loratadine (30 and 100 mg/kg, iv) did not alter BP, HR, QTc interval, PR interval, QRS interval or the normal ECG wave form in the guinea pig at plasma levels (27.8 - 61  $\mu$ g/ml) at least 5500X greater than plasma levels in man<sup>7</sup>. Although SCH 34117 was not administered directly, the resulting SCH 34117 concentrations (1.46  $\mu$ g/ml) were 370X greater than the SCH 34117  $C_{max}$  in man after a single oral dose of 10 mg loratadine. Promethazine (5 mg/kg, iv) was also devoid of adverse cardiovascular and ECG effects. In contrast, terfenadine (10 mg/kg, iv) induced hypotension, bradycardia and prolongation in the QTc interval up to 500 ms and produced a torsades de pointes-like syndrome. Similarly, quinidine (50 mg/kg, iv) produced hypotension, bradycardia and QTc prolongation. Diphenhydramine (20 mg/kg, iv) also produced significant cardiovascular and ECG effects (bradycardia, hypotension, and increased the PR and QRS interval), but did not prolong the QTc interval or torsades-like arrhythmias.

## PHARMACOKINETICS AND TOXICOKINETICS

### Single/Multiple Dose Pharmacokinetics:

The toxicokinetics of two 14-day oral toxicity studies were submitted and are summarized briefly in Figures 1 (rat) and 2 (monkey), and in greater detail in the Toxicology section of this review. Exposures to SCH 34117 increased supra-proportionally with dose in the rat following oral administration (1-8 mg/kg/day) on Day 1 (Figure 1) and were generally greater on Day 10 compared to Day 1 at doses > 1 mg/kg/d, indicating the potential for drug accumulation. In addition, exposure levels in females were consistently greater (1.6- to 4.9-fold) than in males at comparable doses and exposure durations. Maximum plasma concentrations also increased supra-proportionally, but not to the extent of AUC. In contrast, SCH 34117 exposure in male monkeys increased sub-proportionally with dose following oral administration on Day 1 (Figure 2). In female monkeys, although exposures increased proportionally at the mid-dose and supra-proportionally at the high-dose, exposure levels in females at the two lower doses, were 2- to 5-fold less than those in males at comparable doses and exposure durations. Exposures were not significantly different between Days 1 and 14 at the two lower SCH 34117 doses, although indications of drug accumulation were present at the high dose as exposures increased 1.4- to 1.8-fold. Maximum plasma concentrations also increased sub-proportionally compared to dose.

<sup>7</sup> Hey, JA, Del Prado, M, Cuss, FM, Egan, RW, Sherwood, J, Lin, CC, and Kreutner, W. (1995). Antihistamine activity, central nervous system and cardiovascular profiles of histamine H1 antagonists: comparative studies with loratadine, terfenadine and sedating antihistamines in guinea-pigs. *Clinical and Experimental Allergy*, 25: 974-984.

Exposures increased proportionally in human male volunteers administered single doses of SCH 34117 (Table 4) and, similar to rats and monkeys, drug accumulation (of SCH 34117) was observed following multiple doses of loratadine (Table 5). Mean  $T_{max}$  was achieved between 2.5-12 hours in the rat following SCH 34117 administration on Day 1, increasing with increasing dose, and at 2.5 hours at Day 10. A similar mean  $T_{max}$  was achieved in the monkey (2.5-8 hours) following SCH 34117 administration and in humans administered single doses (2.5-20 mg; 1.7-3.6 hours). The terminal phase half-life of SCH 34117 in the rat, monkey and human was approximately 2-4 hours, 7-12 hours and 24.6 hours (single 20 mg dose), respectively.

Administration of 10 mg/kg loratadine (equimolar to 8 mg/kg/d SCH 34117) in the rat resulted in greater exposures to SCH 34117 than to the parent compound (2.3- to 14.7-fold). These exposures were, however, less than those observed following administration of high-dose SCH 34117 with the exception of males at Day 1. SCH 34117 exposure was again greater in female rats and greater on Day 10 than on Day 1. Administration of 8 mg/kg/d loratadine (equimolar to 6.5 mg/kg/d SCH 34117) in the monkey also resulted in greater exposures to SCH 34117 than to the parent compound (6.7- and 7.4-fold in females and males, respectively) on Day 1, and increased to 13- and 36-fold, respectively by Day 14. Exposures were less than those observed following administration of high-dose SCH 34117 (65-80%). Similar to administration of SCH 34117, SCH 34117 exposure was greater in males (~1.6-fold) and was greater on Day 14 than on Day 1 (1.3-fold).

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Figure 1. SCH 34117 exposure in rats during 14-day oral toxicity study.

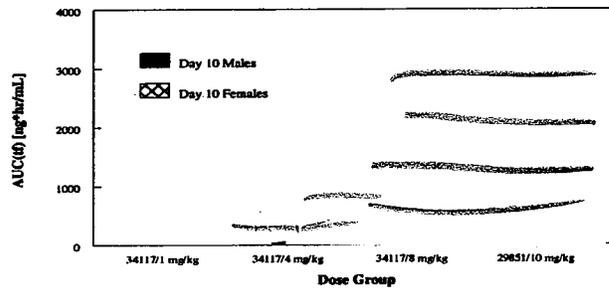
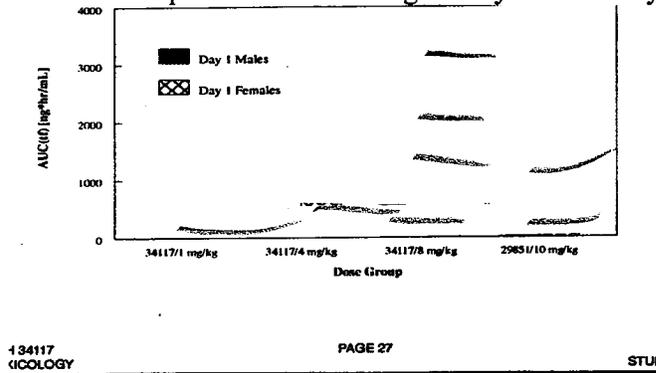
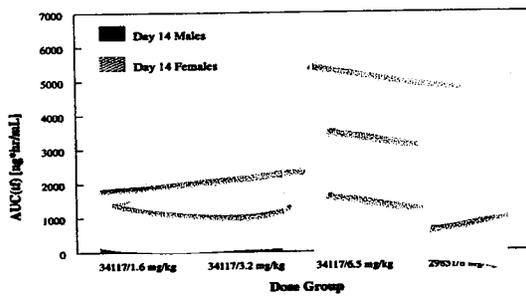
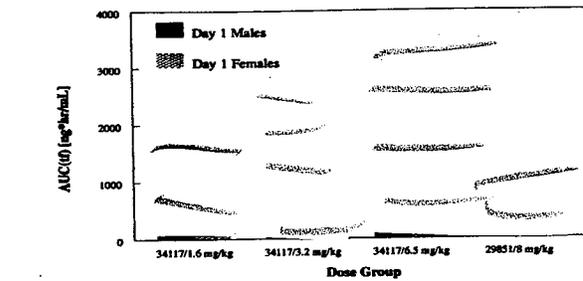


Figure 2. SCH 34117 exposure in monkeys during 14-day oral toxicity study.



**Table 4.** Single dose toxicokinetics of SCH 34117 in humans.

SCH 34117 (mg)	t <sub>1/2</sub> (hr)	T <sub>max</sub> (hr)	C <sub>max</sub> (ng/ml)	AUC(0-t hr) <sup>a</sup> (ng.h/ml)
2.5		3.55	0.80	9.77
5		1.7	1.67	20.7
10		2.15	4.26	70.4
20	24.6	2.20	8.36	158

<sup>a</sup> AUC(0-t hr) values calculated using the mean concentration data. t = 78 hr.

**Table 5.** Plasma SCH 34117 concentrations in humans following single and multiple dose administrations of loratadine.

Loratadine (mg)	t <sub>1/2</sub> (hr)	T <sub>max</sub> (hr)	AUC(0-t hr) <sup>a</sup> (ng.h/ml)
<b>Single dose</b>			
10	15.6	1.7	29.1
	24.9	2.0	50.9
<b>Multiple dose</b>			
10		4.6	73.4
		2.7	48.4
		3.0	97
		3.0	112
		2.9	93.5

<sup>a</sup> AUC(0-t hr) values calculated using the mean concentration data. t = 24-84 hr.

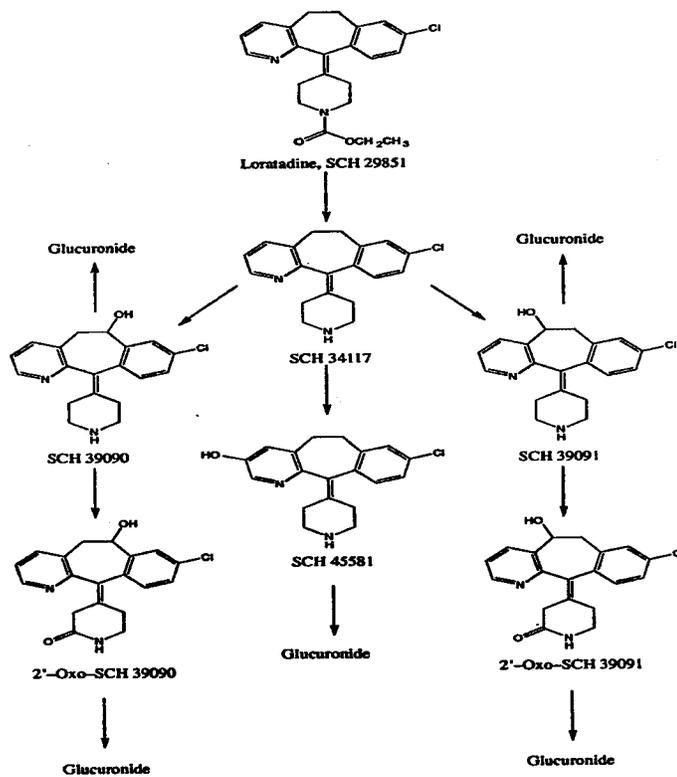
**Absorption:** The blood and plasma concentration of administered radioactivity in rats and mice and plasma and bile concentrations in a monkey following single oral doses of SCH 34117 or loratadine were measured by liquid scintillation spectrometry. Radioactivity was equally distributed between blood and plasma regardless of the administered compound (2-9 mg/kg SCH 34117: 0.30-0.66 µg.eq/g; 8-9 mg/kg loratadine: 0.43-1.17 µg.eq/g) in rats and mice. In monkeys, the administered doses were well absorbed as concentrations of radioactivity were greater in the bile (13.7-150 µg.eq/g) than in plasma (0.26-7.28 µg.eq/g).

**Plasma Protein Binding:** Plasma protein binding of SCH 34117 was comparable between rats, monkeys and humans (70-76%; See NDA 19-658 original Summary, dated 10/30/87). Binding of loratadine was significantly greater (97-99%)

**Metabolism:** The metabolism of loratadine and SCH 34117 is summarized in Figure 3. Loratadine is primarily metabolized to SCH 34117 through the 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. In a pilot study to obtain comparative metabolism data on radiolabeled SCH 34117 and loratadine (both compounds at least 98% radiochemically pure) using male rats, mice and a monkey received single doses of <sup>14</sup>C-loratadine, <sup>14</sup>C-SCH 34117 or SCH 34117 (target doses of 8 mg loratadine/kg and 6.5 mg SCH 34117/kg). Table 6 shows that the results are comparable to the original metabolic profile reported for loratadine and that no metabolites are specific to SCH

34117 administration. However, metabolites specific to loratadine were detected in the pooled plasma and bile of male mice (monohydroxy loratadine glucuronide, monoketo-monohydroxy loratadine, monohydroxy loratadine glucuronide). In addition, previously unreported metabolites were observed in rat urine and plasma following dosing with SCH 34117 and loratadine (unknown metabolite RM1: m/z 323; 5,6-dihydroxy-SCH 34117, and three unknown metabolites RM3: m/z 339). Also, a significant portion of loratadine was hydroxylated directly without first being metabolized to SCH 34117 in the mouse.

**Figure 3:** Proposed metabolic pathway of Loratadine/SCH 34117.



**Table 6.** Relative abundance of metabolites following oral, single dose administrations.

Matrix	Metabolite	Administered Compound						
		SCH 34117			//	SCH 29851		
		Rat	Mouse	Monkey	Rat	Mouse	Monkey	
Plasma	SCH 34117	+++	+++	+++	+++	+	+	
	loratadine						+	
	RM1 (m/z 323; unknown)	+++			+++			
	5-OH SCH 34117	+	+	+	++	++	++	
	6-OH SCH 34117	+	+	++	++	++	+	
	monohydroxy SCH 29851 glucuronide					+++		
	monoketo-monohydroxy SCH 29851					+		
	MM5 (m/z 339; unknown)		++			+		
	3-OH SCH 34117-glucuronide			+			++	
	5-OH SCH 34117-glucuronide			++			+++	
	6-OH SCH 34117-glucuronide			+			+	
	monohydroxy SCH 34117 glucuronide			+			+	
Urine	SCH 34117	+	++	+	+	+	+	
	RM3 (m/z 339; 3 unknowns)	++			++		+	
	5-OH SCH 34117	+++	+++	++	+++	+++	+	
	6-OH SCH 34117	+++	++	++	+++	++		
	5,6-dihydroxy-SCH 34117	+++			++			
	monoketo-SCH 29851				+			
	3-OH SCH 34117-glucuronide			+			+	
	5-OH SCH 34117-glucuronide			+++			+++	
	6-OH SCH 34117-glucuronide			+			+	
	monohydroxy SCH 34117 glucuronide			+			+	
	Bile	SCH 34117	+	+++		+	+	
		5-OH SCH 34117	+++	++	++	+++	+	++
6-OH SCH 34117		+++	+	++	+++	+	++	
3-OH SCH 34117-glucuronide (rat)		++			+++			
monohydroxy SCH 29851 glucuronide						+		
3-OH SCH 34117-glucuronide (mouse)			+			+		
dihydroxy-SCH 29851 monogluc.						+++		
5-OH SCH 34117-glucuronide				+			+	
6-OH SCH 34117-glucuronide				+			+	

**Excretion:** Following single oral doses of SCH 34117 or loratadine, radioactivity was excreted primarily in the feces of rats (71-79%) and mice (39-54%), although a significant portion was excreted in the urine (25-36% in rats; 20-41% in mice). In monkeys, radioactivity was detected primarily in the bile (46-58%) and urine (40-48%), with a small portion excreted in the feces (8-9%) after 48 hours. Previous studies in the development of loratadine are in agreement with these results as excretion in rats, mice, rabbits and monkeys was primarily through the feces, although a significant portion was also excreted in the urine (See Original NDA 19-658 Review, dated 10/30/1987).

### Summary of Pharmacokinetics and Toxicokinetics

The comparative pharmacokinetics of SCH 34117 are summarized in Table 7. 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.

**Table 7.** Comparative pharmacokinetics of SCH 34117.

	Rat	Mouse	Monkey	Human
<b>Single dose</b>				
<b>AUC (ng.h/ml)</b>				
-8 mg/kg	2027			
-6.5 mg/kg			3172	
-20 mg				158
<b><math>T_{1/2}</math> (hr)</b>				
-8 mg/kg	3.3-3.7			
-6.5 mg/kg			7.8	
-20 mg				24.6
<b><math>T_{max}</math> (hr)</b>				
-8 mg/kg	12			
-6.5 mg/kg			2.5	
-20 mg				2.2
<b>Protein binding (%)</b>	70		71	77
<b>Excretion (oral dose)</b>				
-Urine (0-48 hr)	35.6	40.8	39.8	
-Feces (0-48 hr)	78.9	37.8	8.24	
-Bile (48 hr)			58.4	

**TOXICOLOGY****ACUTE TOXICITY:**

The following single-dose studies in mice, rats and monkeys are summarized in Table 8, page 16.

**Mouse, Acute Oral Toxicity**

*Study No.:* P-6771      *Report No.:* 97238      *Volume:* 1.15

*Study Dates:* Starting date 10/22/97; report issued 2/13/98  
*Testing Lab:* Schering-Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 34117 (Batch 97-11001-139)  
*Concentration:* 10-20 mg SCH 34117/ml  
*Dose Volume:* 5-25 ml/kg  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

**Mouse, Acute Intraperitoneal Toxicity**

*Study No.:* P-6772      *Report No.:* 97239      *Volume:* 1.15

*Study Dates:* Starting date 10/22/97; report issued 2/13/98  
*Testing Lab:* Schering-Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 34117 (Batch 97-11001-139) in 0.4% (w/v) aqueous methylcellulose  
*Concentration:* 10-20 mg/ml  
*Dose Volume:* 2.5-25 ml/kg  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

**Rat, Acute Oral Toxicity**

*Study No.:* P-6769      *Report No.:* 97236      *Volume:* 1.15

*Study Dates:* Starting date 10/20/97; report issued 2/13/98  
*Testing Lab:* Schering-Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 34117 (Batch 97-11001-139) in 0.4% (w/v) aqueous methylcellulose  
*Concentration:* 50-200 mg/ml  
*Dose Volume:* 1-10 ml/kg  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

**Rat, Acute Intraperitoneal Toxicity**

*Study No.:* P-6770      *Report No.:* 97237      *Volume:* 1.15

*Study Dates:* Starting date 10/20/97; report issued 2/13/98  
*Testing Lab:* Schering-Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 34117 (Batch 97-11001-139) in 0.4% (w/v) aqueous methylcellulose  
*Concentration:* 50 mg/ml  
*Dose Volume:* 0.5-10 ml/kg  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

**Monkey, Acute Rising Dose Oral Toxicity**

*Study No.:* P-6808      *Report No.:* 97240      *Volume:* 1.15

*Study Dates:* Starting date 11/5/97; report issued 2/12/98  
*Testing Lab:* Schering-Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 34117 (Batch 97-34117-X-02 RA) in 0.4% (w/v) aqueous methylcellulose  
*Concentration:* 2.35-50 mg/ml  
*Dose Volume:* 3.75-5 ml/kg  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

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**Table 8.** Acute toxicity of administered SCH 34117 in mice, rats and monkeys.

Species/ Route	Study # and Dose (mg/kg)	n	Mortality	Occurrence	LD <sub>50</sub> (mg/kg)	Other findings	
<b>Mice</b>  Oral    IP	<b>P-6771</b> 50 125 250 500	10			M: 353 F: 353	ataxia, convulsions, gasping, hypoactivity, tremors, cool to touch, no feces, pallor, prostration, urogenital staining (M), salivation (1 F); (500 mg/kg)	
		10					
		10					
		10	10	w/in 1 hr			
	<b>P-6772</b> 25 50 125 250 500	10			M: 49 F: 46	hypoactivity ( $\geq 50$ ), ataxia, convulsions, tremors, prostration, dehydration ( $\geq 125$ ), gasping ( $\geq 250$ ), cool to touch (1 each; 50, 250, 500), pallor (1 M; 125), urogenital staining (M; 50 and 125), inguinal swelling (1M; 50)	
		10	3M, 4F	Day 2 to 4			
		10	10	2 min to 5 d w/in 24 h			
		10	10	w/in 24 h			
<b>Rats</b>  Oral    IP	<b>P-6769</b> 50 125 250 500 2000	10			M: 616 F: 549	cool to touch, hypoactivity, dehydration and urogenital staining ( $\geq 250$ ), vocalizations, convulsions, tremors, salivation and chromodacryorrhea (2000), scant feces (250 & 500), no feces (250 & 2000), chromorhinorhea ( $\geq 500$ ), gasping & abdominal distension (1M; 250) <b>BW:</b> Males: $\downarrow$ Day 8; $\uparrow$ Day 15 (50-500) Females: $\downarrow$ Day 8 and 15 (50-500)	
		10					
		10	1M	Day 5			
		10	1M, 1F	24 hr to 2 d			
		10	10	w/in 15 min			
	<b>P-6770</b> 25 50 125 250 500	10			M: 178 F: 68	inguinal swelling ( $\geq 25$ ), ataxia, cool to touch and hypoactivity ( $\geq 50$ ), abdominal distension, no/scant feces and urogenital staining (50, 125 & 500), dehydration (50, 250 & 500), convulsions (125-500), tremors & ocular discharge (125 & 250), gasping (125 & 500), prostration (250 & 500), chromodacryorrhea & hyperactivity (500), $\uparrow$ respiration & scabs (250), chromorhinorhea (50 & 500) <b>BW:</b> $\downarrow$ Day 8; $\uparrow$ Day 15 (M:50-250; F:50)	
		10	3F	5, 9, or 14 d			
		10	3M; 4F	w/in 24 h			
		10	3M; 4F	w/in 24 h			
		10	4M; 5F	15 min - 7 d			
<b>Monkey</b>  Oral	<b>P-6808</b> 11.75 23.5 46.9 93.75 125 250	2	None			emesis in males ( $\geq 23.5$ ) and females ( $\geq 93.75$ ), diarrhea (1M: 93.75; 1F: 250), <b>Food consumption:</b> $\downarrow$ Day 2 (M: 46.9 & 93.75)	
		2					
		2					
		2					
		2					
		2					

In mice, the maximum non-lethal doses were 250 mg/kg (oral) and 25 mg/kg (ip). The minimum lethal doses were 500 mg/kg (oral) and 50 mg/kg (ip). In rats, the maximum non-lethal doses

were 125 mg/kg (oral) and 25 mg/kg (ip). The minimum lethal doses were 250 mg/kg (oral) and 50 mg/kg (ip). In monkeys, the maximum oral dose of 250 mg/kg did not induce lethality. However, emesis, diarrhea and reduced food consumption were observed in some animals administered  $\geq 23.5$ , 93.75 and 46.9 mg/kg, respectively.

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**Results:** Results are summarized in tables 9-12.

**Mortality:** The deaths of one low-dose male and one high-dose female, found dead on Days 9 and 8, respectively, following blood sample collection, were attributed to extravascular blood loss. In addition, six plasma analysis subgroup rats (2 males and 3 females from the loratadine group and 1 male from the mid-dose SCH 34117 group) were found dead after bleeding samples were obtained on Days 1 and 10. These deaths were also attributed to extravascular blood loss and/or trauma of jugular bleeding.

**Clinical Observations:** No treatment-related effects.

**Body Weight:** No toxicologically significant treatment-related effects due to SCH 34117. However, mean body weight gains for the loratadine-treated animals were slightly reduced (14-16%) compared to vehicle controls (Table 9).

**Food Intake:** Food consumption (reported as g/kg/day) was significantly increased (13.2%) only in high-dose males during Week 2 (Table 9).

**Ophthalmoscopy:** No toxicologically significant treatment-related effects.

**Hematology:** No toxicologically significant treatment-related effects.

**Clinical Chemistry:** SCH 34117 induced a slight, but dose-dependent, increase in AP (6-27%) in treated males, in addition to a 20% increase in ALT in high-dose males (Table 9). Loratadine also increased levels of ALT (26%), AST (64%), AP (9%) and total bilirubin (48%).

**Table 9.** Clinical observations and chemistry findings in rats.

Dose (mg/kg/d)	Males					Females				
	0	1	4	8	Lorat.	0	1	4	8	Lorat.
<b>Body Weight Gain</b>										
%Δ vs control group		↓4	↓4	no Δ	↓14	↓5.8	↓11	↓6.7	↓15.6	
<b>Food Consump. (g/day)</b>										
%Δ vs control group		no Δ	no Δ	↑7	↑14	↓2	↑4	↑2	↑2	
<b>Clinical Chemistry</b>										
AP										
%Δ vs control group		↑6	↑9	↑27	↑9	↑1	↑7	↑3	↓5	
ALT										
%Δ vs control group		↑6	↑4	↑20	↑26	↑2	↑9	↑2	↓3	
AST										
%Δ vs control group		↑6	↓1	↑8	↑64	↑4	↓3	↓10	↓13	
Total bilirubin										
%Δ vs control group		↑22	↑9	↑6	↑48	↑2	↑13	↓5	↓4	

**Urinalysis:** No toxicologically significant treatment-related effects.

**Organ Weights:** No toxicologically significant treatment-related effects.

**Enzyme Induction:** Administration of mid- or high-dose SCH 34117 did not significantly increase drug metabolizing enzyme activity due to high inter-animal variability, although “a trend suggestive of slight induction” was noted (Table 10; PROD activity was increased by 113 and 183% in males and 31 and 46% in females, at the mid- and high-dose, respectively). Administration of loratadine significantly increased PROD (131 and 519%, females and males, respectively) and EROD (49%; males only) activities. Neither compound altered absolute or relative liver weight, microsomal protein or cytochrome P-450 content.

**Table 10.** Enzyme induction in rats.

Dose (mg/kg/d)	Males					Females				
	0	1	4	8	Lorat.	0	1	4	8	Lorat.
<b>Enzyme Induction</b>										
PROD (pmol/min/mg mic. prot.)	47		100	133	291	13		17	19	30
EROD (pmol/min/g liver)	1791		2509	2357	2670	1673		1691	1874	1866

Shaded areas indicate a significant difference from vehicle controls.

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

**Histopathology:** No toxicologically significant treatment-related effects were observed. However, various findings with unclear toxicological significance and generally low severity were reported (Table 11). The sponsor did not assess these findings in the lower-dose groups.

**Table 11.** Histopathological changes following 14-day SCH 34117 administration in rats.

Dose (mg/kg/d)	Males					Females				
	0	4	8	Lorat.	0	1	4	8	Lorat.	
<b>Histology*</b> n=	10	2	10	10	10	1	1	9	10	
Eye - retinal folds	2(1.5)		3(1)	1(1)	1(1)			2(1)	0	
Brain										
-pineal cytopl. vacuolat.	0		1(3)	0	0			0	0	
Thymus - thrombosis	0		1(NR)	0	0			0	0	
Liver - focal necrosis	1		0	0	0		1(2)	1(1)	2(1)	
Kidneys - hydronephrosis	0	1(3)	1(3)	0	0	1(4)		0	0	
Mandib. Lymph Nodes										
- lymphoid hyperplasia	0		1(1)	0	0			0	0	
Epididymes - mono. cell infil.	2(1)		3(1)	5(1)						
Uterus - eosino. infil.					4(1)			5(1)	2(1)	

\* Incidence(severity). Severity based upon 0-4 scale in which 0, 1, 2, 3, 4 indicate none, minimal, mild, moderate or severe, respectively. NR - not reported.

**Toxicokinetics:** Table 12 summarizes the results of the toxicokinetic analysis in which plasma levels were measured using \_\_\_\_\_ Exposures to SCH 34117 increased supra-proportionally with dose following oral administration on Day 1 as 4- and 8-fold increases in dose resulted in 5.4- to 9.9-fold and 22.8- to 34.7-fold increases, respectively, in exposure. Exposures were generally greater at Day 10 compared to Day 1 at doses > 1 mg/kg/d, indicating the potential for drug accumulation, and 4- and 8-fold increases in dose resulted in 23- to 35-fold and 50- to 61-fold increases, respectively, in exposure. In addition, exposure levels in females

were consistently greater (1.6- to 4.9-fold) than in males. Maximum plasma concentrations also increased supra-proportionally compared to dose, but not to the extent of AUC. Mean  $T_{max}$  was achieved between 2.5-12 hours on Day 1, increasing with increasing dose, and at 2.5 hours on Day 10. The terminal phase half-life was approximately 2-4 hours following administration.

Administration of 10 mg/kg/d loratadine (equimolar to 8 mg/kg/d SCH 34117) resulted in greater exposures to SCH 34117 than to the parent compound (2.3- to 14.7-fold). Exposures were generally less than those observed following administration of high-dose SCH 34117 (10-57%) with the exception of males at Day 1 (increased by 17%). Similar to administration of SCH 34117, SCH 34117 exposure was greater in females (1.8- to 2.1-fold) and was greater on Day 10 than on Day 1 (1.6- to 1.8-fold).

**Table 12.** 14-day toxicokinetics of SCH 34117 and loratadine in the rat.

Dose (mg/kg/d)	Analyte	Day	$t_{1/2}$ (hr)	$T_{max}$ (hr)	$C_{max}$ (ng/ml)	AUC(tf) <sup>a</sup> (ng.h/ml)		
						Males	Females	Avg.
1 (SCH 34117)	SCH 34117	1	3.5	2.5	4.5	30.7	78.7	58.3
		10	NA	2.5	6.8	30.1	60.4	54.3
4 (SCH 34117)	SCH 34117	1	2.6	8	39.1	166	781	474
		10	3.5	2.5	58.9	359	1056	708
8 (SCH 34117)	SCH 34117	1	3.3 (M)	12	138	700	3425	2027
		10	3.7 (M)	2.5	154	1882	2976	2421
10 (Loratadine)	SCH 34117	1	4.6	1	103	820	1497	1158
		10	4.3	2.5	174	1296	2686	1789
	Loratadine	1	2.5	0.7	92.8	351	252	301
		10	2.3	1	89.2	285	183	245

<sup>a</sup> AUC(tf) values calculated using the mean concentration data (generally 3 males and 3 females at each timepoint).  
M: data available for males only.

The high-dose of 8 mg SCH 34117/kg/day was selected as the NOAEL for this study. Target organs of toxicity could not be identified at the doses selected for this study.

#### Rat, 14-day Oral Toxicity

Report No.: D18289 Study No.: SN 83111 Volume: 1.15

**Study Dates:** Starting date not provided; report issued 6/29/84  
**Testing Lab:** Schering-Plough Research Institute, Lafayette, NJ  
**Test Article:** SCH 34117 (Batch# 16378-106-1; purity not provided) in 0.4% (w/v) aqueous methylcellulose  
**Concentration:** mg SCH 34117/ml  
**Dose Volume:** 5 ml/kg/day  
**GLP:** The study was unaudited.  
**QA report:** No.

**Methods:** ~~Male~~ rats were assigned to the following treatment groups:

Dose (mg/kg/day)	0	15	60	240
No./sex toxicity study	13	13	13	13
No./sex plasma analysis, Day 1	4	4	4	4
No./sex plasma analysis, Day 13	4	4	4	4

Each rat received a daily dose of vehicle or test drug by gastric intubation for 14 days. The following observations were made:

Clinical observation . . . daily  
 Body weight . . . . . weekly  
 Food consumption . . . weekly  
 Water consumption . . . not assessed  
 Ophthalmoscopy . . . . . predose and week 2  
 Hematology . . . . . Days 7 and 14; control, low- and mid-dose animals (high-dose animals not tested due to high mortality). Endpoints included hematocrit, hemoglobin, erythrocyte count, mean corpuscular hemoglobin concentration, total and differential leukocyte counts, and platelet counts.  
 Clinical chemistry . . . . . Days 7 and 14; control, low- and mid-dose animals (high-dose animals not tested due to high mortality). Endpoints included glucose, urea nitrogen, glutamic-pyruvic transaminase (GPT), glutamic oxaloacetate transaminase (GOT), and alkaline phosphatase.  
 Urinalysis . . . . . not performed  
 Enzyme induction . . . . . not performed  
 Organ weights . . . . . at sacrifice; limited to kidneys, livers and lungs  
 Gross pathology . . . . . at sacrifice  
 Histopathology . . . . . at sacrifice; limited to kidneys, livers, lungs and pancreas, in addition to organs with gross lesions  
 Toxicokinetics . . . . . Day 1 from 4 rats/sex/ treatment group at 1, 3 and 6 hours; Day 13 from 4 rats/sex/group in the low- and mid-dose groups at 1, 3 and 6 hours

**Results:** Results are summarized in tables 13-16.

*Mortality:* All high-dose rats were either found dead or sacrificed in anticipation of death on Days 2 through 6.

*Clinical Observations:* No treatment-related effects were observed in controls, low- or mid-dose animals. High-dose animals exhibited chromorhinorrhea, slow righting-reflex, chromodacryorrhea, and distended abdomen and salivation (females only) between Days 2 through 6.

*Body Weight:* A reduction in body weight gain (13-26%) was observed in all but one high-dose animal by Day 6. Mid-dose males and females also exhibited a ~12 and 14% reduction in body weight, respectively, compared to controls after 2 weeks. Low-dose females displayed a ~6% reduction in body weight compared to controls.

**Food Intake:** Mean food consumption was reduced (~65%) in high-dose animals by Day 6. Food consumption was also significantly lower for mid-dose males at week 1 (13%), and mid-dose females at week 1 and 2 (21 and 20%, respectively).

**Ophthalmoscopy:** The sponsor reported that no toxicologically significant treatment-related effects were observed, however, no data was included to support conclusion.

**Hematology:** Reduced leukocyte counts were observed in high dose rats sacrificed on day 5 and 6 (Table 13). The incidence of lymphocytic cytoplasmic vacuoles was reported in all animals, with greater incidence and severity observed in mid- and high-dose animals.

**Clinical Chemistry:** Markedly higher transaminase values (GPT and/or GOT; 324-1460%) were limited to all high-dose rats sacrificed on Day 6 (Table 14). In addition, BUN levels were moderately increased (23-46%) in the same group.

**Table 13.** Clinical findings in rats dosed for 14 days (6 days for high-dose animals).

Dose (mg/kg/d)	Males			Females		
	15	60	240*	15	60	240*
<b>Hematology</b>						
Leukocyte count						
%Δ vs control group	↓13	↓4	↓68	↓16	↑11	↓53
Lymphocytes w/ cytoplasmic vacuoles						
%Δ vs control group	↓20	↑3900	↑1030	↑40	↑6920	↑2000
<b>Clinical Chemistry</b>						
GPT						
%Δ vs control group	↓5	↓12	↑324	↓2	↓26	↑1260
GOT						
%Δ vs control group	↓20	↓29	↑1460	↑8	↑1	↑1444
BUN						
%Δ vs control group	↑9	↑2	↑23	↑2	↓2	↑46

\* Data for high-dose group derived from Day 6 due to high mortality. Compared with Day 7 control groups.

**Organ Weights:** Organ weight assessment was limited to the liver, kidney and lung. Relative liver weights were increased in mid-dose males and high-dose animals (29-30%) and relative kidney weights were increased at the high-dose (34-38%; Table 14). Relative lung weight was also increased in mid- and high-dose females (62 and 31%, respectively).

**Gross Pathology:** Treatment-related gross tissue/organ changes were observed only in the high-dose groups (Table 14). Changes included discoloration and accentuated lobular markings in the liver, pink/red areas, pale areas in the spleen and white discoloration in the duodenum and/or jejunum. In addition, gaseous distention was noted in various areas of the GI tract (10 of 18) and dry fecal matter was noted in 2 rats. Twelve animals exhibited dried blood or bloody exudate on their faces and four displayed chromodacryorrhea.

**Table 14.** Gross tissue/organ changes following 14-day SCH 34117 administration in rats.

Dose (mg/kg/d)	Males				Females			
	0	15	60	240*	0	15	60	240*
<b>Relative organ weights (% of body weight)</b>								
Liver								
%Δ vs control group		↓2	↑29	↑29	↑1	↑3	↑30	
Kidney								
%Δ vs control group		↑2	↑5	↑34	↑2	↑4	↑38	
Lung								
%Δ vs control group		↑5	↑13	↑8	↑4	↑62	↑31	
<b>Gross pathology n=</b>	<b>5</b>	<b>5</b>	<b>5</b>	<b>9</b>	<b>5</b>	<b>5</b>	<b>5</b>	<b>9</b>
Liver - discoloration	0	0	0	7	0	0	0	6
- markings	0	0	0	3	0	0	0	1
Lungs - pink/red	0	0	1	5	1	0	1	5
Spleen - pale	0	0	0	1	0	0	0	1
Duodenum/jejunum								
-white discoloration	0	0	0	3	0	0	0	1
Colon - dry fecal matter	0	0	0	1	0	0	0	1
Face - dry blood/ - bloody exudate	0	0	0	1	0	0	0	2
- bloody exudate	0	0	0	5	0	0	0	4
Chromodacryorrhea	0	0	0	3	0	0	0	1

\* Data for high-dose group derived from Day 6 due to high mortality. Compared with Day 7 control groups.

**Histopathology:** The histopathology assessment was limited to the kidneys, livers, lungs and pancreas, in addition to organs with gross lesions. Hepatocyte vacuolation was observed in rats from all groups; vacuolation was diffuse in controls but of greater severity and zonal in treated animals (Table 15). Periportal vacuolation was observed in low- and mid-dose animals; vacuolation was centrilobular in high-dose animals. The hepatocytes in the centrilobular region were minimally enlarged in 1/10 low-, 7/10 mid- and 2/18 high-dose animals and mildly enlarged in 4/18 high-dose animals. In addition, the cytoplasm of the hepatocytes in the centrilobular region was basophilic (minimal) in 8/10 low- and 6/10 mid-dose animals. Single cell hepatocyte necrosis was also observed in a mid-dose and high-dose animals.

In the lung, treatment-related histologic observations included the presence of foam cells in pulmonary alveoli in animals from all treatment groups, as well as congestion, edema and mild acute pneumonia in high-dose rats. Vacuolation of the cortical tubular epithelium of the kidney was also noted in mid- and high-dose animals, as well as necrosis of the cortical and medullary tubular epithelium in high-dose animals. In addition, vacuolation of acinar cells in pancreas was present in all high-dose rats, as well as in the jejunum epithelium of one high-dose animal. Hyperactive goblet cells and the presence of cellular debris were present in the jejunum of another high-dose animal and hypoactive germinal centers in the mesenteric lymph node of one high-dose animal and in spleens of two high-dose animals were also reported.

**Table 15.** Histopathological changes following 14-day SCH 34117 administration in the rat.

Dose (mg/kg/d)	Males				Females			
	0	15	60	240*	0	15	60	240*
<b>Liver</b>								
-hepatocyte vacuolation	5	5	5	9	5	5	5	9
-single cell necrosis	0	0	1	5	0	0	0	3
-congestion	0	0	0	2	0	0	0	4
<b>Lung</b>								
-foam cells (alveoli)	0	0	4	9	0	4	5	9
-congestion	0	0	0	6	0	0	0	5
-edema	0	0	0	1	0	0	0	3
-mild pneumonia	0	0	0	0	0	0	0	1
<b>Kidney</b>								
-CTE vacuolation	0	0	0	8	0	0	3	5
-necrosis	0	0	0	6	0	0	0	4
-congestion	0	0	0	2	0	0	0	2
Pancreas - acinar cell vac.	0	0	0	9	0	0	0	9

\* Data for high-dose group derived from Day 6 due to high mortality.

CTE: cortical tubular epithelium

*Toxicokinetics:* Table 16 summarizes the results of the toxicokinetic analysis. Plasma levels were similar in both males and females and increased sub-proportionally with increasing dose. Plasma levels in mid-dose animals on Day 13 were approximately — those reported on Day 1, indicating that drug accumulation may occur with increasing doses. Less than 7.5% of the drug was recovered as SCH 34117 in the 24-hour urine samples throughout the study.

**Table 16.** Plasma levels of SCH 34117 in the rat.

Dose (mg/kg/d)	Day	3-hr plasma concentration (ng/ml)		Day	24-hr urinary recovery (%)	
		Males	Females		Males	Females
15	1	—	—	1	2.35	4.80
	13	—	—	12	2.45	3.43
60	1	—	—	1	2.90	3.63
	13	—	—	12	2.23	7.1
240	1	—	—	1	1.15	1.45
	13	*	*	12	*	*

\* High dose rats died or were sacrificed prior to Day 12.

A NOAEL could not be selected for this study due to adverse findings at the lowest dose and an incomplete histologic assessment. The target organs of toxicity identified in this study were the liver, lung, kidneys and pancreas, although other target organs may not have been identified due to the incomplete assessment.



**Results:** Results are summarized in tables 17-20.

*Mortality:* None.

*Clinical Observations:* No treatment-related effects were observed. The presence of soft-feces in one mid-dose female once during Week 1 was considered to be an incidental finding.

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

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

*Physical examination:* No toxicologically significant treatment-related effects on body temperature, respiratory rate, heart rate, blood pressure and ECG.

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

*Veterinary examination:* No toxicologically significant treatment-related effects were observed. Incidental findings included alopecia of legs, desquamation of nasal skin, menses and sores/wounds.

*Hematology:* No toxicologically significant treatment-related effects.

*Clinical Chemistry:* No toxicologically significant treatment-related effects were observed other than a dose-dependent increase in triglyceride levels (25-126%) in SCH 34117-treated males (Table 17). Levels in high-dose males were increased by 62% prior to dosing, indicating a net increase of 64% after dosing. In addition, males administered loratadine showed a 44% increase in triglyceride levels compared to controls. However, prior to dosing, levels were increased by 56%, resulting in a net decrease of 12%.

*Urinalysis:* No toxicologically significant treatment-related effects other than a dose-related increase (60-121%) in the urine osmolarity of SCH 34117-administered males (Table 17).

**Table 17.** Clinical findings in monkeys administered SCH 34117.

Dose (mg/kg/d)	Males					Females				
	0	1.6	3.2	6.5	Lorat.	0	1.6	3.2	6.5	Lorat.
<b>Clin. Chemistry</b>										
Triglycerides										
%Δ vs control group		↑25	↑56	↑126	↑44		↑28	↑113	↓14	↑34
<b>Urinalysis</b>										
Osmolarity										
%Δ vs control group		↑60	↑85	↑121	↑30		↑2	↓8	↓24	↑8

*Organ Weights:* No toxicologically significant treatment-related effects.

*Enzyme Induction:* Administration of high-dose SCH 34117 produced a slight induction of liver microsomal cytochrome P-450 enzymes that was comparable to that of loratadine (Table 18; PROD activity was increased by 73% in males and 80% in females, respectively). However, neither compound altered absolute or relative liver weight, cytochrome P-450 content or benzphetamine N-demethylase or 7-ethoxycoumarin. Microsomal protein content (mg/g) was also unaltered except for a slight, but significant, increase (13%) in high-dose females.

**Table 18.** Enzyme induction in monkeys administered SCH 34117.

Dose (mg/kg/d)	Males					Females				
	0	1.6	3.2	6.5	Lorat.	0	1.6	3.2	6.5	Lorat.
<b>Microsomal prot. (mg/g liver)</b>	22.6	20.8	22.5	21.2	24.0	21.8	21.4	22.6	24.7	24.1
<b>Enzyme Induction</b>										
PROD (pmol/min/mg mic. prot.)	1.1	0.9	1.3	1.9	2.0	2.5	3.2	3.4	4.5	4.1
EROD (pmol/min/mg mic. prot.)	469	569	540	905	1038	304	433	602	1220	926

Shaded areas indicate a significant difference from vehicle controls.

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

*Histopathology:* No definitive toxicologically significant treatment-related effects were observed. However, numerous findings with unclear dose-responses and low severity were noted (Table 19). A true assessment of these findings was not possible since animal numbers were small and the sponsor failed to examine low- and mid-dose tissue in cases in which the high-dose incidence was greater than that of control groups. However, the observed findings are not considered to be of great concern, especially due to the low severity and similarity to findings observed with the active loratadine control group.

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**Table 19.** Histopathological changes after 14-day administration in monkey.

<i>Dose (mg/kg/d)</i>	Males				Females			
	0	3.2	6.5	Lorat.	0	3.2	6.5	Lorat.
<b>Histology*</b> n=	<b>3</b>	<b>1</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>1</b>	<b>3</b>	<b>3</b>
Eye - mci	0		1(1)	0	0		1(1)	2(1)
Brain - mci	2(1)		3(1)	1(1)	2(1)		2(1)	2(1)
- mineralization	0		2(1)	2(1)	1(1)		0	2(1)
Sciatic nerve - inflamm	0		0	0	0		1(1)	0
Sal gland: mandib								
- mci	1(1)	1(1)	2(1)	2(1)	2(1)		3(1)	3(1)
- sialolith	0		0	0	0		1(1)	0
Mandib Lymph node								
- hemorrhage	0		0	1(1)	0		1(1)	1(1)
- sinusoidal eos.	0		1(2)	0	1(1)		0	1(1)
Trachea - pigment	0		0	0	0		1(1)	0
Thyroid gland								
- follicular cyst	0		1(2)	2(1.5)	0		0	1(1)
Esophagus - mci	0		1(1)	1(1)	0		0	1(1)
Thymus - hemorrhage	0		1(1)	0	0		0	1(1)
Tongue - glossitis	0		2(1.5)	0	0		0	1(1)
Heart - mci	1(1)		3(1.3)	2(1)	3(1)		1(1)	2(1)
- fibrosis	0		1(1)	0	0		0	0
- vacuolation	0		1(1)	0	0		0	0
- eos. Infiltr.	1(1)		2(1)	1(2)	0		0	1(1)
Aorta - intimal prolifer	0		1(2)	0	0		0	0
Stomach - mci	0		2(1)	1(1)	1(1)		0	0
- inflammation	1(1)		1(2)	1(1)	0		0	0
- gland. ectasia	0		0	0	0		1(1)	0
Duodenum - pigment	0		1(1)	1(1)	0		0	1(2)
Liver - Kup cell pigment	0		0	0	0		1(1)	1(1)
Spleen - lymph hyperpl	1(1)		2(1.5)	1(1)	1(1)		0	2(2)
- pigment	0		0	0	0		1(1)	1(1)
Pancreas - mci	1(1)		0	0	0		2(1)	0
- congestion	0		0	0	0		1(1)	0
Kidneys-nephritis(tubule)	1(2)		2(1)	1(1)	0		1(1)	2(1.5)
- mci	3(1)		3(1)	2(1)	2(1)		3(1)	3(1)
-mac pigment	0		0	0	0		1(1)	0
-med. Int. basophilia	0		0	0	1(1)		2(1)	1(1)
Adrenal cortex								
- hypertrophy/focal	0		0	0	0		1(1)	0
Urinary bladder(inflamm)	0		1(1)	0	0		0	0
Skeletal muscle-inflamm	0		0	0	1(2)		2(2)	0
Bone marrow - lym fol	0		1(1)	0	0		0	1(1)
Lung - foamy alv mac	0		2(1)	2(1)	1(1)		1(1)	0
- mineralization	0		1(2)	0	0		0	0
- vasculitis	0		1(1)	0	0		0	0
- bronchitis	0		1(1)	0	0		0	0
Prostate - mci	0		2(1)	2(1)	0		0	0
Skin - mci	0		0	0	1(1)		2(1)	0
- inflammation	0		0	0	0		1(1)	0
Mammary gland - cyst	2(1.5)		1(2)	2(1)	1(1)		2(1.5)	1(2)
Ovaries - mineralization					1(1)		2(1.5)	2(1)
Uterus - adenomyosis					0		1(1)	0

\* Incidence(severity). Severity based upon 0-4 scale in which 0, 1, 2, 3, 4 indicate none, minimal, mild, moderate or severe, respectively. **mci**: monocellular infiltration.

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