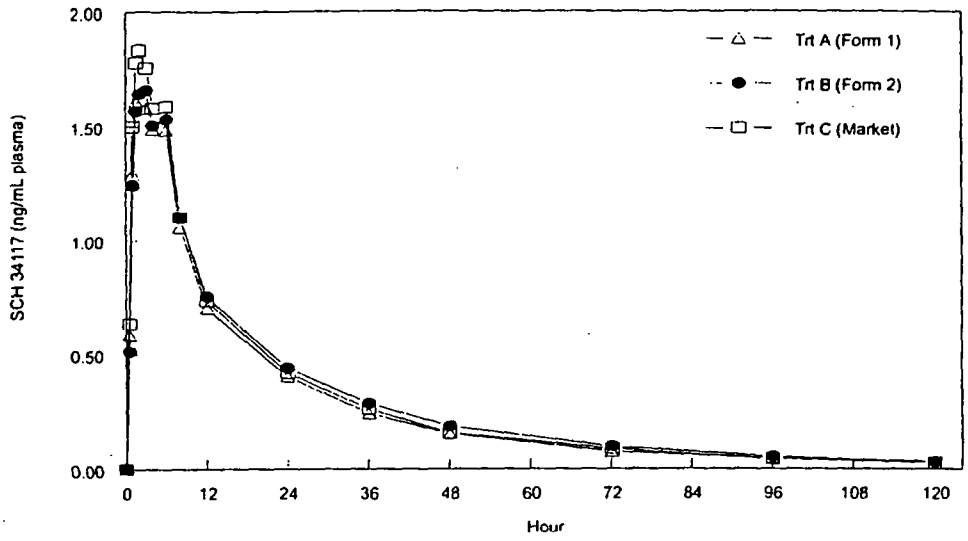
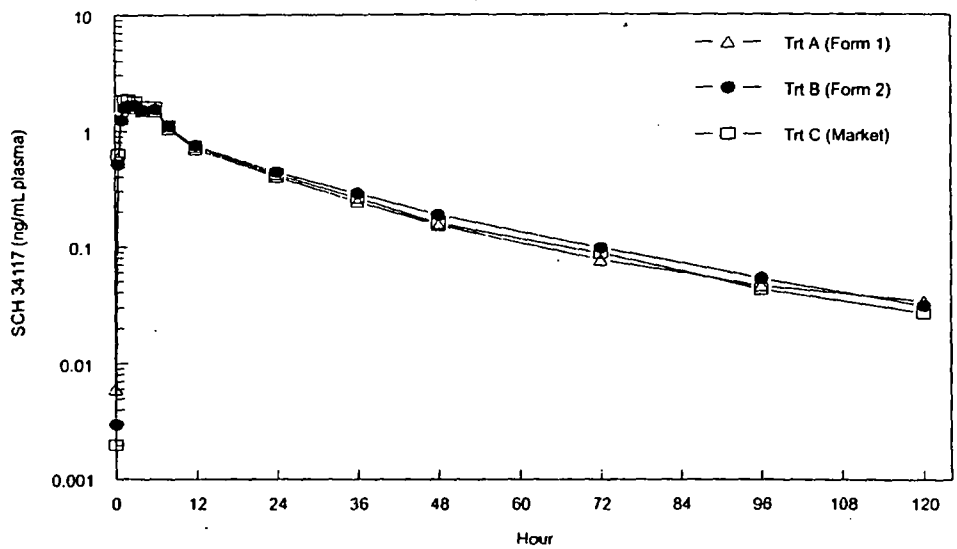
**Pharmacokinetics:** The mean (%CV) pharmacokinetic parameters for DL and 3-OH DL following single-dose administration of DL 5 mg tablet, DL 5 mg capsule (Form 1) and DL 5 mg capsule (Form 2) are summarized below:

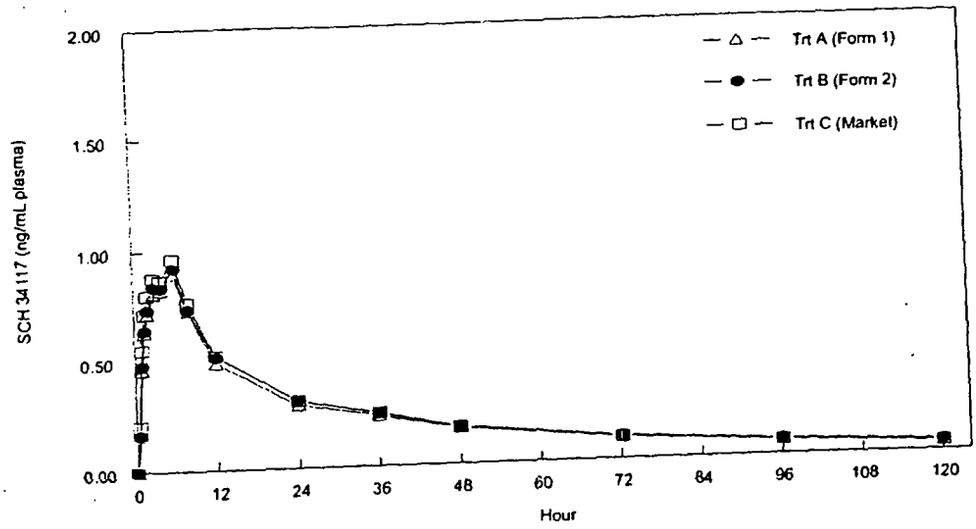
Linear:linear



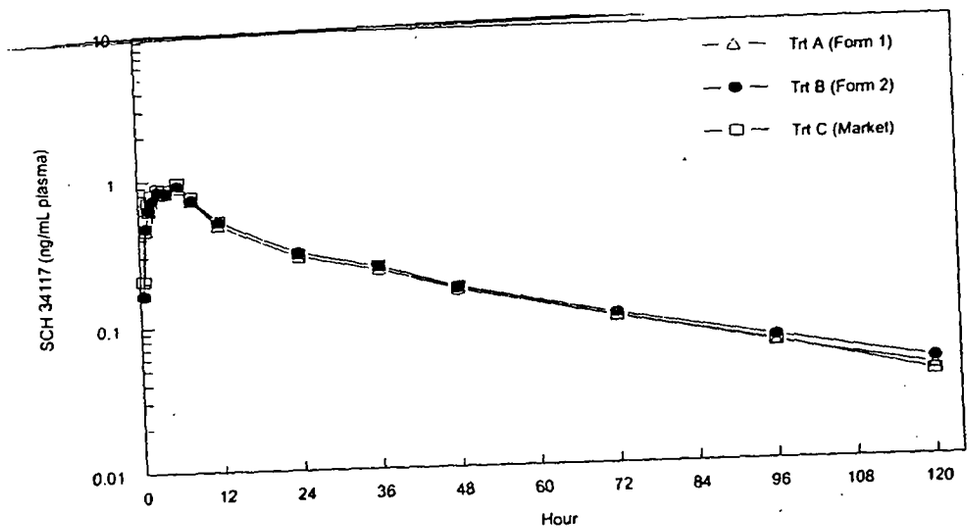

Log:linear



Linear:linear




Log:linear



| Parameter (Unit) | Form 1 (5 mg Capsule) (Treatment A) Arithmetic Mean (%CV) | Form 2 (5 mg Capsule) (Treatment B) Arithmetic Mean (%CV) | 5 mg Tablet (Treatment C) Arithmetic Mean (%CV) |
|---|---|---|---|
| DL | | | |
| Cmax (ng/mL) | 1.90 (39) | 1.90 (31) | 2.05 (36) |
| AUC(I) (ng·hr/mL) | 33.7 (36) | 36.7 (85) | 35.6 (34) |
| AUC(tf) (ng·hr/mL) | 32.1 (36) | 35.0 (78) | 34.2 (35) |
| Tmax (hr) | 3.14 (59) | 3.26 (55) | 2.65 (55) |
| t1/2 (hr) | 22.6 (38) | 21.6 (30) | 22.4 (37) |
| 3-OH DL | | | |
| Cmax (ng/mL) | 0.938 (25) | 0.973 (23) | 1.00 (27) |
| AUC(I) (ng·hr/mL) | 26.4 (25) | 27.9 (50) | 27.5 (26) |
| AUC(tf) (ng·hr/mL) | 24.4 (24) | 25.5 (42) | 25.7 (26) |
| Tmax (hr) | 4.68 (37) | 4.79 (41) | 5.08 (33) |
| t1/2 (hr) | 32.2 (24) | 31.3 (20) | 30.1 (13) |

Following single-dose administration of DL 5 mg tablet, DL 5 mg capsule (Form 1) and DL 5 mg capsule (Form 2) the mean pharmacokinetic parameters for DL and 3-OH DL were similar. The relative bioavailability and the 90% confidence intervals for log-transformed Cmax and AUC are presented below:

| Parameter | Treatment[a] | Relative Bioavailability | Confidence Interval |
|---|---|---|---|
| DL | | | |
| Cmax | A/C | 92 | 88-97 |
| | B/C | 94 | 90-99 |
| | A/B | 98 | 93-103 |
| AUC (tf) | A/C | 94 | 89-99 |
| | B/C | 96 | 91-101 |
| | A/B | 98 | 93-103 |
| AUC (I) | A/C | 94 | 89-100 |
| | B/C | 96 | 90-101 |
| | A/B | 99 | 93-104 |
| 3-OH DL | | | |
| Cmax | A/C | 94 | 90-97 |
| | B/C | 98 | 94-101 |
| | A/B | 96 | 93-100 |
| AUC (tf) | A/C | 95 | 91-99 |
| | B/C | 97 | 93-101 |
| | A/B | 98 | 94-102 |
| AUC (I) | A/C | 96 | 92-101 |
| | B/C | 98 | 94-103 |
| | A/B | 98 | 94-102 |

a: A = DL 5 mg Capsule (Form 1); B = DL 5 mg Capsule (Form 2); C = DL 5 mg Tablet
b: 90% confidence interval based on log-transformed data.

The 90% confidence intervals for log-transformed Cmax and AUC for DL and 3-OH DL for the capsule formulations relative to the tablet as well as between capsule formulations met bioequivalence criteria (80% -125%).

**Safety:** Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects. Overall, 43 of 63 (68%) subjects reported treatment-emergent adverse events. The most frequently reported adverse event was headache. All reported adverse events were mild to moderate in

severity. Eight subjects required additional therapy to treat adverse events. No subject discontinued participation in the study due to adverse events. No serious or unexpected adverse events were reported.

**Sponsor's Conclusions:**

- Single oral doses of DL 5 mg tablet, DL 5 mg capsule (Form 1) and DL 5 mg capsule (Form 2) were safe and well tolerated.
- DL 5 mg tablet and DL 5 mg capsule (mainly DL polymorph Form 1) were bioequivalent.
- DL 5 mg tablet and DL 5 mg capsule (mainly DL polymorph Form 2) were bioequivalent.
- DL 5 mg capsule (mainly DL polymorph Form 1) and DL 5 mg capsule (mainly DL polymorph Form 2) were bioequivalent.

This study was conducted to evaluate the bioequivalence of the to-be-marketed 5 mg tablet formulation of DL and DL 5 mg capsules formulated with mainly Form 1 and Form 2 as well as the bioequivalence of capsules formulated with mainly Form 1 or Form 2.
The results of the study show that 1) the DL 5 mg tablet and the DL 5 mg capsule (Form 1) were bioequivalent, 2) the DL 5 mg tablet and the DL 5 mg capsule (Form 2) were bioequivalent and, 3) the DL 5 mg capsule (Form 1) and DL 5 mg capsule (Form 2) were bioequivalent. These results confirm the lack of pharmacokinetic relevance of the 2 solid state polymorphic forms of DL.

**Reviewer's comments:**
The sponsor conducted the present study appropriately to achieve the objectives. The data are acceptable. This reviewer agrees with the sponsor's conclusion.



APPEARS THIS WAY
ON ORIGINAL

**Title of the Study:** SCH 34117: Rising Multiple-Dose Safety and Tolerance of SCH 34117 in Healthy Volunteers. (Protocol No. C98-013).

**Investigator(s):** Jerry M. Herron, M.D.

**Studied Period:** 14 April 1998 to 25 June 1998

**Clinical Phase:** I

**Objective(s):** The objectives of this study were (1) to evaluate the safety and tolerability of desloratadine when administered orally at multiple doses of 5, 7.5, 10 and 20 mg to healthy subjects; and (2) determine the multiple-dose pharmacokinetic profile of desloratadine in healthy subjects.

**Design/Procedure:** Randomized, double-blind (within dose group), parallel group, placebo-controlled, rising multiple-dose study. Subjects were divided into four dose groups. Within each dose group, 12 subjects were randomized to receive either desloratadine or matching placebo in 5:1 ratio according to a computer generated random code supplied by SPRI. Following an overnight fast each group of subjects received one dose of desloratadine or placebo followed 72 hours later by the same dose for 14 days. Dose escalation did not occur until the safety and tolerability of the previously administered dose had been evaluated. Blood was collected at pre-specified times for safety and pharmacokinetic evaluations. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.

**Assay:** All plasma samples were assayed for desloratadine concentration using [redacted] method with a [redacted] (LOQ= [redacted] ng/mL).

**Number of Subjects:** Forty-eight planned; 49 enrolled.

**Diagnosis and Criteria for Inclusion:** Adult male or female subjects between 18-45 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis) were empaneled for this study.

**Test Product, Dose, Mode of Administration, Batch No(s):** Desloratadine 2.5 mg tablets, oral, Batch No. 38833-075; desloratadine 5 mg tablets, oral, Batch No. 38833-077, desloratadine 10 mg tablets, oral, BatchNo. 38833-079.

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** Desloratadine placebo tablets, oral, Batch No. 38833-072.

**Duration of Treatment:** Single doses were administered in the morning (approximately 8 a.m.) for all four dose groups on Day 1 and Days 4-17. Subjects were followed for 168 hours following dosing on Day 17.

**Criteria for Evaluation:** Electrocardiograms and routine clinical laboratory tests were performed throughout the study and adverse events were recorded for safety evaluation. In addition, blood samples were collected for 72 hours following dosing on Day 1 and 168 hours following dosing on Day 17 for determination of pharmacokinetic parameters (Cmax, Tmax, AUC, clearance and half-life).

**Statistical Methods:** The pharmacokinetic parameters for each dose were summarized using means, standard deviations and coefficients of variation. In addition, an analysis of variance was done extracting effects due to treatment (dose). The analysis was done on log-transformed dose-adjusted as well as unadjusted AUC(tf) and Cmax values.

**RESULTS:**

**Subjects Disposition:** Forty-nine subjects were enrolled. Forty subjects (10/dose level) completed active treatments while 8 received placebo. One subject discontinued for personal reasons.

**Demographic and Baseline Characteristics**: Subjects between the ages of 24 and 45 years (mean = 37.3 years) and weighing between 135 and 218 pounds (mean = 166.8 lb) were enrolled. Thirty-five subjects were Black, 13 were Caucasian and 1 was classified as other. Subjects of comparable age, weight and height were enrolled in each dose group.

**Safety:** Blood pressure, pulse, rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects. Twenty-six (19/41 desloratadine and 7/8 placebo) of the 48 subjects enrolled (54%) reported treatment emergent adverse events. The most common adverse event (regardless of association to the study drug or placebo) was headache.
All reported adverse events were mild to moderate in severity. Three subjects required concomitant treatment with acetaminophen for a headache and one subject required acetaminophen for back pain. There was no apparent increase in the overall incidence of adverse events as the dose of desloratadine was increased from 5mg to 20 mg. No subject discontinued participation in the study due to an adverse event.

**Pharmacokinetics:**

**Single-Dose Pharmacokinetics:** The associated arithmetic (%CV) and geometric mean derived pharmacokinetic
parameters for desloratadine following a single-dose are shown in following table.

**Table** . Arithmetic (%CV) and Geometric Mean Pharmacokinetic Parameters of Desloratadine (Day 1) After A Single Dose of 5, 7.5, 10 or 20 mg to Healthy Adult Male Volunteer (Protocol No. C98-013).

| Parameter[a] (Single Dose) | 5 mg | | 7.5 mg | | 10 mg | | 20 mg | |
|---|---|---|---|---|---|---|---|---|
| | Arithmetic Mean (%CV) | Geometric Mean | Arithmetic Mean (%CV) | Geometric Mean | Arithmetic Mean (%CV) | Geometric Mean | Arithmetic Mean (%CV) | Geometric Mean |
| Cmax | 1.83 (35) | 1.73 | 2.28 (31) | 2.19 | 4.08 (22) | 3.99 | 7.08 (39) | 6.67 |
| DN[b]-Cmax | 1.83 | -- | 1.52 | | 2.04 | | 1.77 | |
| AUC(0-24hr) | 29.4 (42) | 27.2 | 26.6 (29) | 25.5 | 55.0 (36) | 52.3 | 97.5 (39) | 91.5 |
| DN[b]- AUC(0-24hr) | 29.4 | -- | 17.8 | | 27.5 | | 24.4 | |
| AUC(I) | 32.5[c] (65) | 28.6 | 43.7 (37) | 40.7 | 71.1[d] (27) | 69.1 | 169 (46) | 153 |
| DN[b]-AUC(I) | 32.5[c] | -- | 29.2 | | 35.6[d] | | 42.3 | |
| Tmax | 6.00 (50) | 6.00[e] | 2.95 (41) | 3.00[e] | 2.95 (78) | 2.00[e] | 3.95 (59) | 5.00[e] |
| t1/2 | 33. 4 (85) | 16.8[f] | 19.0 (24) | 18.1[f] | 34.6 (81) | 23.2[f] | 19.2 (26) | 18.2[f] |
| CL/F | 126.0 (82) | -- | 200.9 (47) | -- | 114.4 (56) | -- | 144.8 (50) | -- |
| Vd/F | 2911(30) | -- | 5241 (39) | -- | 3689 (30) | -- | 3712 (36) | |

a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax; t1/2-hr.; CL/F - L/hr.; Vd/F – L.
b: Dose-normalized to 5 mg.
c: n=6 [Excluding Subjects 2, 4, 7 and 9; their extrapolated area (from time tf to infinity) was >25% of AUC(tf)].
d: n=7 [Excluding Subjects 32, 35 and 36; their extrapolated area (from time tf to infinity) was >25% of AUC(tf)].
e: Median Tmax.
f: Harmonic mean t1/2.

Peak desloratadine concentrations are observed between 3 and 6 hours. Cmax and AUC(0-24hr) values exhibited moderate intersubject variability. The dose normalized (to 5 mg) Cmax values were similar among dose groups. The relationship between Cmax and dose and between AUC(I) and dose showed that there was a dose related increase in desloratadine Cmax and AUC(I) between 5 mg and 20 mg.

**Multiple-Dose Pharmacokinetics:** Cmin values (0 hour) for Days 14 through 17 were analyzed at each dose level for attainment of steady state. The results indicate that steady state was

attained by Day 14 (10 doses) following once daily dosing. The arithmetic (%CV) and geometric mean derived pharmacokinetic parameters after multiple dosing (QD x 14 days) are provided in the following table.

**Table** . Arithmetic (%CV) and Geometric Mean Pharmacokinetic Parameters of Desloratadine After Once Daily Dosing for 14 Days (Day 17) At 5, 7.5, 10 or 20 mg to Healthy Adult Male Volunteers (Protocol C98-013).

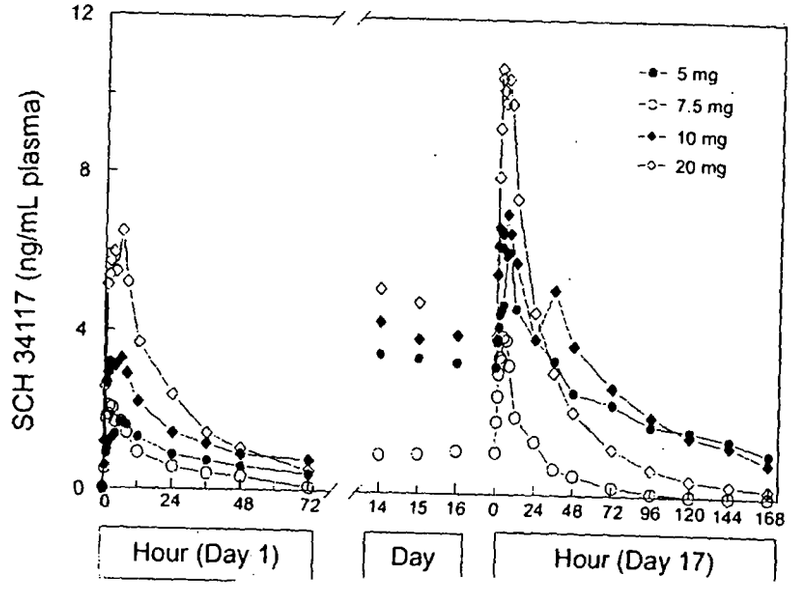
| Parameter[c] (Multiple Dose) | 5 mg[a] | | 7.5 mg[a] | | 10 mg[a] | | 20 mg[a] | |
|---|---|---|---|---|---|---|---|---|
| | Arithmetic Mean (%CV)[b] | Geometric Mean | Arithmetic Mean (%CV)[b] | Geometric Mean | Arithmetic Mean (%CV)[b] | Geometric Mean | Arithmetic Mean (%CV)[b] | Geometric Mean |
| Cmax | 6.33 (95) | 4.23 | 4.18 (19) | 4.11 | 7.81 (73) | 5.41 | 12.3 (39) | 11.6 |
| DN[d]-Cmax | 6.33 | | 2.79 | | 3.91 | | 3.08 | |
| AUC (0-24hr) | 113 (107) | 66.5 | 57.1 (28) | 55.1 | 135 (92) | 84.7 | 185 (35) | 177 |
| DN[d]-AUC (0-24hr) | 113 | | 38.1 | | 67.6 | | 46.4 | |
| Tmax | 6.40 (20) | 6.00[e] | 4.60 (29) | 4.00[e] | 9.50 (148) | 2.50[e] | 4.35 (71) | 4.00[e] |
| t1/2 | 40.4 (85) | 23.5[f] | 18.8 (18) | 18.3[f] | 37.4 (65) | 28.7[f] | 26.7 (26) | 24.9[f] |
| R | 1.64 (58) | | 1.39 (23) | | 1.11 (43) | | 1.23 (36) | |
| CLss/F | 111.2 (72) | | 141.2 (29) | | 311.5 (213) | | 118.2 (29) | |
| Vdss/F | 3527 (45) | | 3758 (27) | | 9643 (172) | | 4276 (18) | |

a:Dose
b n=10
c Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax ; t1/2-hr.; CLss/F – L/hr; Vdss/F-L.
d: Dose-normalized to 5 mg.
e: Median Tmax.
f: Harmonic mean t1/2.

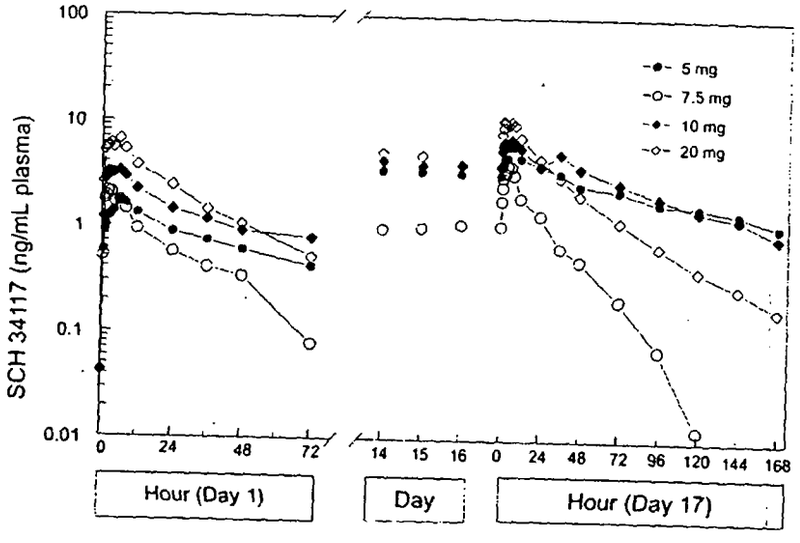
Plasma desloratadine concentrations exhibited high intersubject variability primarily in the 5 and 10 mg dose groups as evidenced by %CV for Cmax and AUC between 73-107%. The harmonic mean t1/2 and apparent total body clearance (arithmetic mean) values at steady state were similar to those following a single-dose, suggesting that the elimination kinetics of desloratadine were not altered following multiple dosing.

Mean plasma profiles are in the following figure.

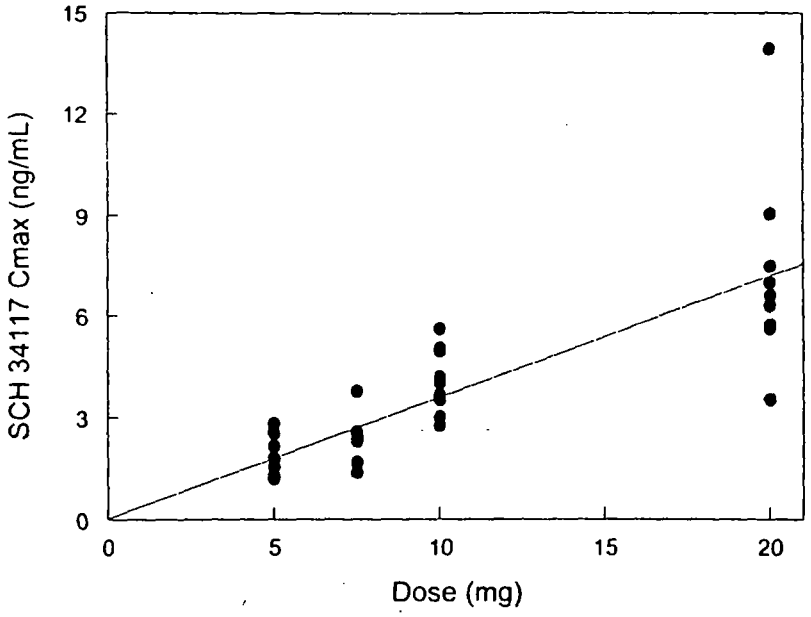
Linear:linear



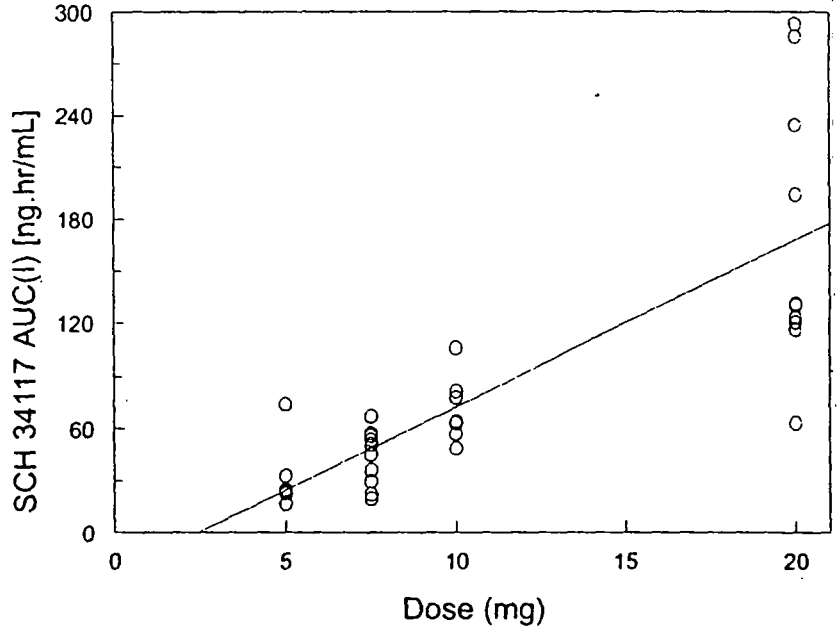

Log:linear



Cmax




~~AUC(I)~~




**SPONSOR'S Conclusions:**

- Multiple oral doses of desloratadine between 5 mg and 20 mg administered to healthy adult male volunteers was safe and well tolerated.
- There appears to be a dose-related increase in plasma desloratadine concentration over the dose range of 5mg to 20 mg.
- Steady state was attained by Day 14 (10 doses).

- Following once daily dosing to steady state, desloratadine did not accumulate to a clinically significant extent.
- There appears to be no clinically relevant difference between the single and multiple dose half-life (harmonic mean) and apparent total body clearance (arithmetic mean).

**REVIEWER'S COMMENTS:**

The sponsor's accumulation ratio estimation is not appropriate. The sponsor's method, i.e., AUC 0-24 at ss/AUC0-72, (1.22 – 1.64) underestimates accumulation ratio comparing to the value of AUC 0-24 at ss divided by AUC 0-24 after single dose. The sponsor does not state the R value in the labeling. (Refer to the labeling comment.)



APPEARS THIS WAY
ON ORIGINAL

**Title of the Study: SCH 34117: Evaluation of the Dose-Proportionality, Linearity and pharmacokinetics of Desloratadine Administered as an Oral Tablet to Healthy Adult Subjects**
**(Protocol C98-214).**

**Investigator(s):** Jerry M. Herron, M.D.

**Studied Period:** 01 June 1998 - 28 July 1998

Clinical Phase: I

**Objective(s):** The objective of this study was to evaluate the dose proportionality, linearity and pharmacokinetic (PK) profile of desloratadine after single oral doses of desloratadine at four dose levels (5 mg, 7.5 mg, 10 mg and 20 mg) following administration to healthy adult subjects.

**Design/Procedure:** Randomized open-label, single-dose, four-way cross-over study.
Healthy adult subjects received one of four treatments, one in each period. The order was determined by a computer-generated random code provided by SPRI. Blood samples were collected at pre-specified times for pharmacokinetic and safety evaluations (at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hour after dosing). ECG's and vital signs were obtained at pre-specified times for safety evaluation. Volunteers were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events.

**Assay:**
Plasma samples were assayed for desloratadine content using a validated ( ) assay (LOQ = ( ) ng/mL).

**Number of Subjects:** Twenty healthy subjects planned and enrolled.

**Diagnosis and Criteria for Inclusion:** Adult male or female subjects between 18-45 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis) and having a BMI between 19-27 were empaneled for this study.

**Test Product, Dose, Mode of Administration, Batch No(s):** Desloratadine: 5 mg tablets, Batch No. 38833-142; 7.5 mg tablets, Batch No. 38833-140; 10 mg tablets, Batch No. 38833-144. All treatments were administered orally after an overnight fast.

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** None

**Duration of Treatment:** Single doses were administered in the morning (approximately 8 a.m.) during each treatment period and subjects were followed for 168 hours postdose.

**Criteria for Evaluation:** Blood samples were collected over 168 hours for determination of PK parameters (AUC and Cmax) of desloratadine under fasted conditions.

**Statistical Methods:** The pharmacokinetic parameters for each dose were summarized using means, standard deviations and coefficients of variation. Linear regression analysis was used to determine the relationship of dose and AUC using log transformed data. The regression model was used to extract in sequential order, effects due to subject, dose (linearity), and deviation from linearity (lack-of-fit, LOF).
All of the derived PK parameters were statistically analyzed using a crossover analysis of variance (ANOVA) model. The effects due to subject, period and treatment (dose) were extracted. Dose-adjusted (to 1 mg) AUC and Cmax were analyzed in the log-scale. The power to detect a 20% difference between treatment means for an alpha level of 0.05 (two-tailed) was

computed using the pooled residual error and associated degrees of freedom from the ANOVA. The primary PK parameters were examined for extreme values.

**RESULTS:**

**Clinical Pharmacology:**

**Subject Disposition:** Twenty subjects were enrolled and completed the study. Each received single oral doses of 5 mg, 7.5 mg, 10 mg and 20 mg on four separate occasions.

**Demographic and Baseline Characteristics:** Subjects between the ages of 19 and 45 (mean 36.9 years) with body mass index between 19 and 27 (mean = 23.9) were enrolled into the study. Three subjects were Caucasian and 17 were Black.

**Safety:** Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects. Overall, 12 of 20 (60%) subjects reported treatment-emergent adverse events. The most frequently reported adverse event was headache. There appears to be no difference between the dose groups in the number of subjects reporting AEs. All reported adverse events were mild in severity except one episode of headache which was reported as moderate. No subject discontinued participation in the study due to adverse events.

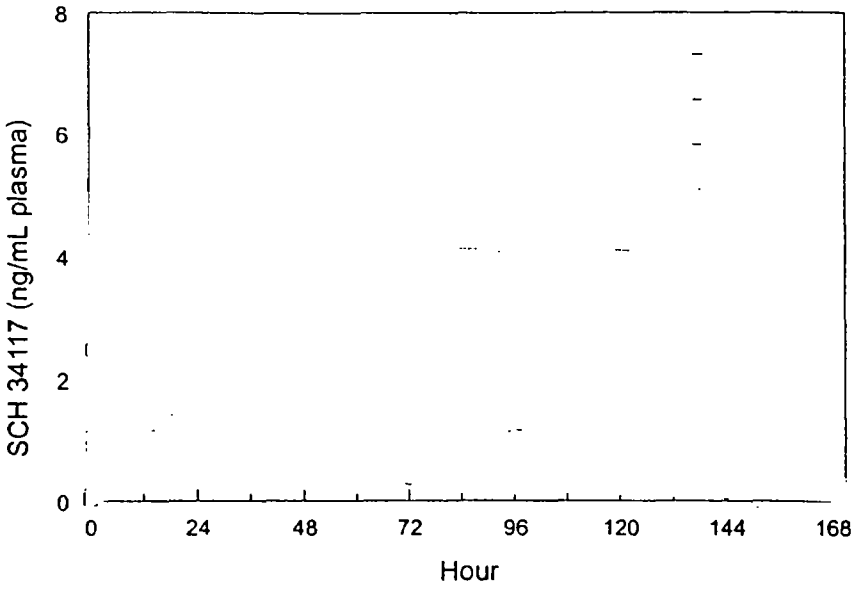
The arithmetic mean (%CV), geometric and harmonic mean PK parameters of desloratadine are provided in the table below.

| Parameter[b] | 5 mg[a] | | 7.5 mg[a] | | 10 mg[a] | | 20 mg[a] | |
|---|---|---|---|---|---|---|---|---|
| | Arithmetic Mean (%CV) | Geometric Mean | Arithmetic Mean (%CV) | Geometric Mean | Arithmetic Mean (%CV) | Geometric Mean | Arithmetic Mean (%CV) | Geometric Mean |
| Cmax | 2.18 (33) | 2.07 | 3.03 (31) | 2.88 | 3.80 (29) | 3.66 | 8.08 (26) | 7.83 |
| DN[c]-Cmax | 2.18 | 2.07 | 2.02 | 1.92 | 1.90 | 1.83 | 2.02 | 1.96 |
| AUC(tf) | 78.0 (127) | 53.3 | 104 (93) | 80.4 | 126 (98) | 95.1 | 290 (92) | 222 |
| DN[c]-AUC(tf) | 78.0 | 53.3 | 69.2 | 53.6 | 63.0 | 47.6 | 72.4 | 55.4 |
| T max | 4.55 (70) | 6.00[d] | 4.13 (72) | 3.00[d] | 4.45 (71) | 4.50[d] | 3.90 (71) | 3.00[d] |
| t1/2 | 29.4 (86) | 21.2[e] | 31.4 (80) | 23.8[e] | 31.7 (96) | 22.1[e] | 32.3 (76) | 24.1[e] |

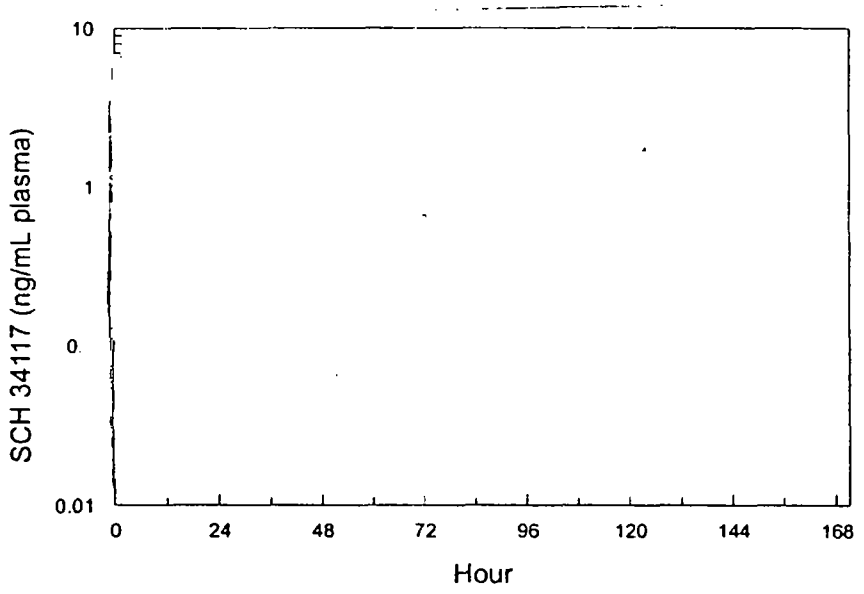
a: n=20b: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax and t1/2-hr.
c: Dose-normalized to 5 mg.
d: Median Tmax values.
e: Harmonic mean t1/2 values.

Peak plasma desloratadine concentrations (Cmax) were observed about 4 hours after dosing over the dose range 5 mg to 20 mg, suggesting no dose-related changes in the absorption rate of desloratadine. The intersubject variability (%CV) was less than 35% for Cmax, however, it was significantly higher (92-127%CV) at all dose levels for AUC.

Linear:linear




Log:linear




Linear regression analysis of dose and log transformed AUC(tf) and Cmax showed that none of the slopes were statistically significantly different from 1 and the power to detect a 20% difference in slope 92%. Dose proportionality was also supported by the results of an analysis of variance of log-transformed dose adjusted (to 1 mg) AUC value which showed no statistically significant differences over the dose range 5 mg to 20 mg. Cmax Value was marginally statististical significant deviation from linearity (p=0.049).

**REVIEWER'S COMMENTS:**
The sponsor conducted the study appropriately and the data are acceptable. This reviewer agrees with the sponsor's conclusion.



APPEARS THIS WAY
ON ORIGINAL

**Title of the Study:** SCH 34117: Rising Single-Dose Safety and Tolerance of SCH 34117 in Healthy Volunteers. (Protocol No. I97-248).

**Investigator(s):** Michael Seiberling, M.D.

**Studied Period:** 24 SEP 1997 to 11 NOV 1997

**Clinical Phase:** I

**Objective(s):** The objectives of this study were (1) to evaluate the safety and tolerability of SCH 34117 when administered orally at single doses of 2.5, 5, 10 and 20 mg to healthy subjects; and (2) determine the single-dose pharmacokinetic profile of SCH 34117 in healthy subjects.

**Design/Procedure:** Randomized, double-blind, parallel group, placebo-controlled rising single-dose study. Forty-eight subjects were divided into four dose groups. Within each dose group, 12 subjects were randomized to receive either SCH 34117 or matching placebo in 5:1 ratio according to a computer generated random code supplied by SPRI.

Following an overnight fast each group of subjects received one dose of SCH 34117 or placebo in a rising-dose manner. Dose escalation did not occur until the safety and tolerability of the previously administered dose had been evaluated. Blood and urine (Groups III and IV only) were collected at pre-specified times (at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hr) for safety and pharmacokinetic evaluations. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.

**ASSAY:** All plasma samples were assayed for SCH 34117 concentration using [redacted] method (LOQ= [redacted] ng/mL).

**Number of Subjects:** Forty-eight healthy subjects (Each dose group n=10 ; n=2 for placebo)

**Diagnosis and Criteria for Inclusion:** Adult male or female subjects between 18-45 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis) and having weights (+15%) in accordance with current actuarial tables were empaneled for this study.

**Test Product, Dose, Mode of Administration, Batch No(s):** SCH 34117 2.5 mg tablets, oral, Batch No. 51848-102; SCH 34117 10 mg tablets, oral, Batch No. 51848-104.

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** SCH 34117 placebo tablets, oral, Batch No. 38833-003.

**Duration of Treatment:** Single doses were administered in the morning (approximately 8 a.m.) for all four dose groups and subjects were followed for 168 hours postdose.

**Criteria for Evaluation:** Electrocardiograms and routine clinical laboratory tests were performed throughout the study and adverse events were recorded for safety evaluation. In addition, blood samples were collected over 168 hours for determination of pharmacokinetic parameters (Cmax, Tmax, AUC, CL/F, t1/2).

**Statistical Methods:** The pharmacokinetic parameters for each dose were summarized using means, standard deviations and coefficients of variation. In addition, an analysis of variance was done extracting effects due to treatment (dose). The analysis was done on log-transformed dose-adjusted as well as unadjusted AUC up to masureable plasma concentrion time (AUC(tf)) and Cmax values.

**RESULTS:**

**Clinical Pharmacology:** The mean (%CV) pharmacokinetic parameters and plasma profiles of SCH 34117 following oral, single-dose administration of 2.5 mg to 20 mg is presented below:

| Parameter (Unit) | N | 2.5 mg Dose Mean (%CV) | 5 mg Dose Mean (%CV) | 10 mg Dose Mean (%CV) | 20 mg Dose Mean (%CV) |
|---|---|---|---|---|---|
| Cmax (ng/mL) | 10 | 0.80 (51) | 1.67 (40) | 4.26 (73) | 8.36 (22) |
| AUC(tf)(ng·hr/mL) | 10 | 9.77 (93) | 20.7 (39) | 70.4 (75) | 158 (92) |
| DN[a]-Cmax(ng/mL) | 10 | 0.32 (51) | 0.33 (40) | 0.43 (73) | 0.42 (22) |
| DN[a]-AUC(tf) (ng·hr/mL) | 10 | 3.91 (93) | 4.14 (39) | 7.04 (75) | 7.90 (92) |
| Tmax (hr) | 10 | 3.55 (61) | 1.70 (25) | 2.15 (68) | 2.20 (66) |
| t1/2 (hr) | 10 | NE | NE | NE | 24.6 (70) |

a: Dose-normalized to 1 mg
NE-Not estimated

The peak plasma SCH 34117 concentrations (Cmax) were observed between 1.7 and 3.6 hr after dosing. The mean Cmax and AUC(tf) of SCH 34117 ranged from 0.8 to 8.36 ng/mL and 9.77 to 158 nγVhr/mL, respectively, for doses between 2.5 mg and 20 mg. Plasma concentrations of SCH 34117 increased with increasing doses.

**Safety:** Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects. Overall, 5 of 48 (10%) subjects reported treatment-emergent adverse events. All reported adverse events were mild in severity and considered by the investigator not to be related to study drug administration. No subject discontinued participation in the study due to adverse events and no intervention was required to treat any adverse event except for subject #14 who required topical iodine treatment for scrapes to his right ear and cheek after falling off his bicycle when he was "cut-off" by a car.

**SPONSOR'S CONCLUSIONS:**

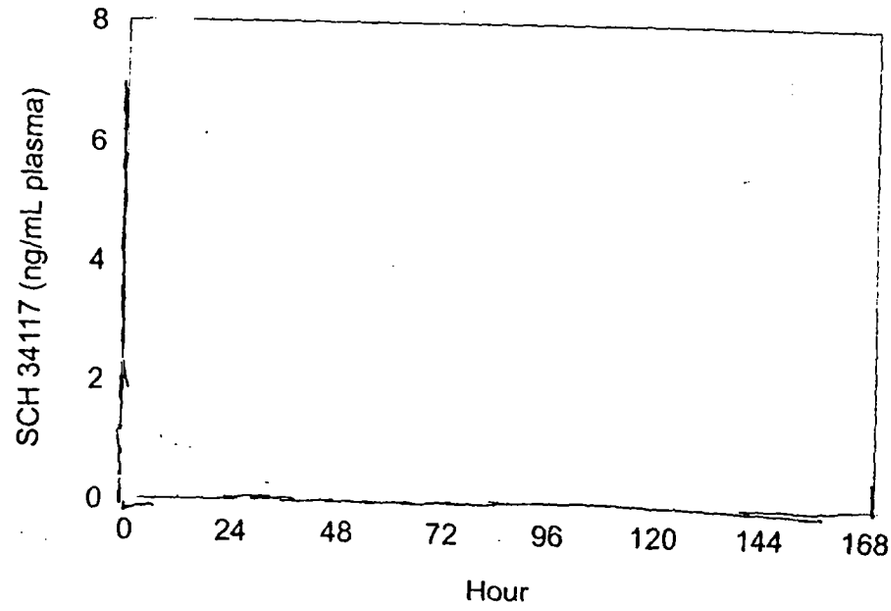
- Single oral doses of SCH 34117 2.5, 5, 10 and 20 mg were well tolerated when administered to healthy male subjects.
- Plasma concentrations of SCH 34117 increased with increasing doses.

**REVIEWER'S COMMENTS:**

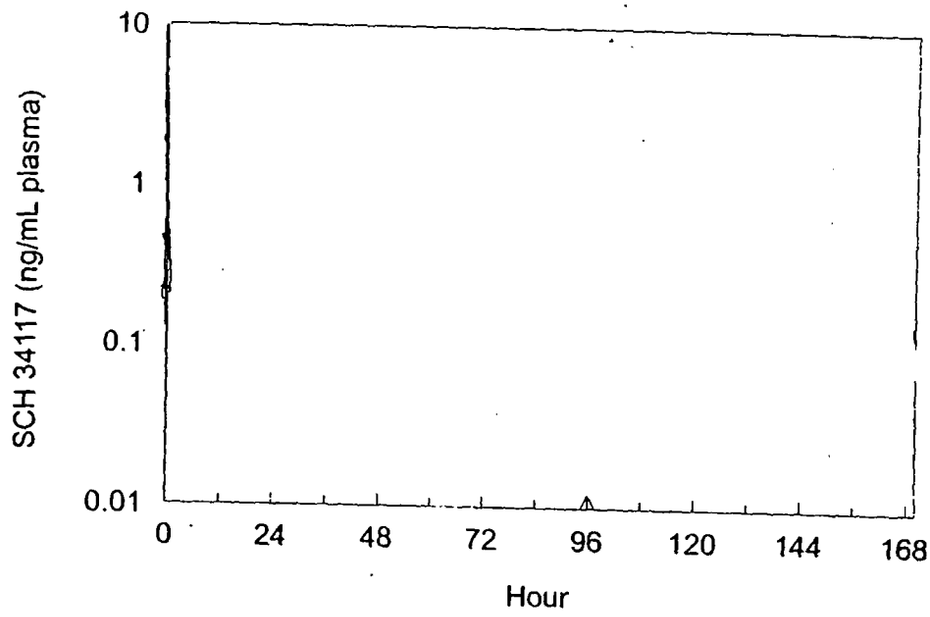
This was the first study in which SCH 34117 was administered to humans in the form of an immediate-release tablet. The objective of this rising, single-dose study was to evaluate the tolerability of SCH 34117 when administered orally at doses of 2.5, 5, 10 and 20 mg.
The inter-subject variability was generally high for both parameters [AUC(tf): 39-93% and Cmax: 22-73%]. The reason of the large inter-subject variability is not known.

There was a dose related increase in plasma SCH 34117 concentrations, however, this increase was not dose proportional in this dose range. This reviewer agrees with the sponsor's opinion that this may be due, in part, to the fact that the time for measurable plasma concentration values were earlier for those treated with 2.5 and 5 mg than those treated with 10 and 20 mg. It should be noted that the dose proportionality has been investigated more appropriately in Study C-98-014 within the dose range of 5-20 mg. (Please refer to the individual study review).

Linear:linear




Log:linear



**Title of the Study:** SCH 34117: Evaluation of the Electrocardiographic Pharmacodynamic Effects Following Administration of Multiple High-doses of SCH 34117 (Protocol C98-357).

**Investigator(s):** Jerry M. Herron, M.D.

**Studied Period:** 20 OCT 1998 – 04 DEC 1998

**Clinical Phase:** I

**OBJECTIVE(S):** The primary objective of this study was to evaluate the electrocardiographic (pharmacodynamic) effects of desloratadine in subjects treated with 45 mg desloratadine (nine times the anticipated dose of 5 mg.
The secondary objectives of this study were to determine the pharmacokinetic (PK) profile of desloratadine and its safety and tolerability.

**DESIGN AND PROCEDURE:** Randomized, two-way crossover, double-blind, multiple-dose, placebo controlled study.
Twenty-four (24) healthy subjects (12 males and 12 females) each received multiple-dose treatment during two separate treatment periods. Multiple ECGs were recorded on Day –1 (Baseline), daily and Day 10 (follow-up) and 2 hours post-dose daily during the study. The change from Baseline of the multiple ECGs obtained on both Day –1 (Baseline) and Day 10 were used for the ECG pharmacodynamic determinations. The order in whichsubjects received treatments was assigned according to a computer-generated random code provided by SPRI.

**Blood sampling:** Blood samples were collected at pre-specified times (at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 24 hr after dosing) for pharmacokinetic and safety evaluations. Blood was also collected for genotyping analysis. Vital signs were obtained at pre-specified times for safety evaluation.
Volunteers were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events.

**Assay:** Plasma samples were assayed for desloratadine (SCH 34117) and 3-OH desloratadine (SCH 45581) using [redacted] assay (LOQ [redacted] pg/mL) for both analytes.

**Number of Subjects:** Twenty-four healthy subjects (12 male and 12 female)

**Diagnosis and Criteria for Inclusion:** Adult male or female subjects (non-smokers) between 18-50 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram (QTc <420 ms) and routine laboratory tests (blood chemistry, hematology, and urinalysis) and having a body mas index (BMI) between 19-27 were empaneled for this study.

**Test Product, Dose, Mode of Administration, Batch No(s):** SCH 34117 7.5 mg tablets, Batch No. 38833-140 administered as 45 mg (6 tablets)/day. Treatments were administered orally on an empty stomach only on the PK testing day (Day 10).

**Table** Formulation for Desloratadine 7.5 mg and Placebo Tablets (Protocol C98-357)

| Tablet Strength | 7.5 mg | Placebo |
|---|---|---|
| Formula. No. | 3409 | 3391 |
| Batch No. | 38833-140 | 38833-072 |
| FMR No. | 98565D02 | 98500D02 |
| Manf. Date | 3/12/98 | 11/24/97 |
| Recertification Date | 9/98 | 11/98 |
| Batch Size | [redacted] tablets | [redacted] |
| Manf. Site | [redacted] | [redacted] |

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** Placebo tablets, Batch No. 38833-072 administered as 6 tablets/day.

**Duration of Treatment:** SCH 34117 45 mg (6 tablets of 7.5 mg tablet) or placebo administered once daily in the morning (9 a.m.). All treatments were administered for 10 days during each of the 2 treatment periods. Each treatment period was separated by at least a 14 day washout period.

**Criteria for Evaluation:** Blood samples were collected over 24 hours (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 24 hr after dosing) for determination of pharmacokinetic parameters (AUC and Cmax) on Day 10. ECGs were obtained over a 16 hour period on Days –1 and 10 for determination of pharmacodynamic parameters.

**Statistical Methods:** Summary statistics were calculated for the plasma SCH 34117 and SCH 45581 concentrations at each time point and for the derived pharmacokinetic parameters. In addition to the arithmetic means, the geometric means were calculated for Cmax and AUC and the median for Tmax. The primary pharmacodynamic parameter for this study was the difference between Baseline (Day –1) maximum ventricular rate, PR, QRS, QT, and QTc intervals and the Day 10 maximum ventricular rate, PR, QRS, QT and QTc intervals.
This difference was analyzed using a linear model extracting effects due to sequence, subject within sequence, period and treatment. Using the pooled variance from this model, 95% confidence interval for the mean difference was calculated. Descriptive statistics for maximum PR, QRS, QT and QTc intervals was provided for Baseline, Day 10 and Day 10 change from Baseline and percent change for the parameters.

**Pharmacokinetics:** The plasma concentration data for desloratadine (following administration of desloratadine 45 mg) was used to estimate the following pharmacokinetic parameters:
Cmax - maximum observed plasma concentration (Day 10)
Cmin - the observed minimum plasma concentration (pre-dose levels Days 7, 8, 9 and 10)
Tmax - time of observed maximum plasma concentration (Day 10)
AUC(0-24 hr) - area under the plasma concentration vs time curve from time 0 to 24 hours (Day 10)
Cl/F - apparent total body clearance (Day 10)

Model-independent methods were used to calculate the pharmacokinetic parameters. The maximum concentration (Cmax), time of maximum concentration(Tmax) and the final quantifiable sampling time (tf) were the observed values. The areaunder the plasma concentration-time curve from time zero to 24 hours post-dose,AUC(0-24hr), was calculated using the linear trapezoidal method. CL/F was estimated by following: CL/F=Daily dose/AUC(0-24hr).

**Pharmacodynamics:** The primary endpoint for this study was the effect of high-dose desloratadine (45 mg) on the difference between Baseline (Day-1) maximum ventricular rate PR, QRS, QT and QTc intervals and the corresponding Day 10 maximum ECG parameters.
Electrocardiograms ( and reporting ventricular rate and PR, QRS, QT and QTc intervals as well as and reporting rhythm lead were obtained at screening, on Day –1 at approximately 9 a.m., 10 a.m., 11 a.m., 12 p.m., 1 p.m., 2 p.m., 3 p.m., 5 p.m., 7 p.m., 9 p.m., 9 a.m. (pre-dose) on Day 1 and daily during each treatment phase (approximately 2 hours after the 9 a.m. morning dose). Additionally, ECGs were obtained prior to blood sample collections prior to (0-hour) and 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours after the 9 a.m. dose on Day 10 of each treatment period. ECGs were performed after at least 3 minutes in the supine position. QTc intervals were calculated automatically by the ECG system with use of the Bazett formula. ECG results were closely monitored throughout the study. Each Day-0 and Day -10 automated ECG was overread by the same board-certified internist to verify that the QT and RR intervals were accurately recorded by the computer.
ECG results were monitored throughout the study. If any QTc interval on any ECG increased by >25% compared to Baseline (the ECG obtained prior to dosing on Day 1), or if any ECG finding (in the investigator's opinion) precluded further treatment, the subject would not continue to receive any study treatments during that treatment phase. Normal study ECGs and monitoring continued until the end of the treatment phase. The Investigator was to have immediately notified the study monitor or his/her designee if study treatment was discontinued, or if, in the Investigator's opinion, an adverse ECG-related finding was observed. If such an event occurred during the first treatment phase, the subject would not return for the second treatment phase of the study.

**Pharmacogenetic Profiling:** Genotyping by cytochrome-based P450 allelic specific amplification can be useful in phenotypic metabolism of drugs. To determine the predicted CYP450 phenotype of subjects enrolled in this study, 10 mL of whole blood in was collected for genotype analysis via DNA purification, of CYP2D6 ("A", "B", "D", "E" and "T" alleles) and CYP2C19 ("m1", "m2", "m3" and "m4" alleles).

**RESULTS:**

**Demographic and Baseline Characteristics:** Overall, 24 subjects (12 males and 12 females) between the ages of 20 and 48 years inclusive (mean =35.6 years), with BMIs between 19.7 and 27.5 (mean =24.3) were enrolled in to the study. Ten subjects were Caucasian and 14 were Black.

**Pharmacokinetics:**

The mean pharmacokinetic parameters of SCH 34117 and SCH 45581 on Day 10 are summarized below:

**Table** Mean Pharmacokinetic Parameters of Desloratadine and 3-OH Desloratadine on Day 10 (Protocol C98-357)

| Parameter | Unit | SCH 34117 | %CV | SCH 45581 | %CV |
|---|---|---|---|---|---|
| Cmax | ng/mL | 63.8 | 85 | 12.2 | 56 |
| Cmax[a] | ng/mL | 57.3 | 79 | 12.6 | 52 |
| Cmax (geometric mean) | ng/mL | 50.1 | -- | 8.95 | -- |
| Tmax | hr | 4.54 | 58 | 4.04 | 47 |
| Tmax[a] | hr | 4.52 | 59 | 3.96 | 48 |
| Tmax (median) | hr | 5.0 | -- | 4.0 | -- |
| AUC(0-24hr) | ng·hr/mL | 1057 | 100 | 185 | 52 |
| AUC(0-24hr)[a] | ng·hr/mL | 944 | 97 | 192 | 49 |
| AUC(0-24hr) (geometric mean) | ng·hr/mL | 747 | -- | 141 | -- |

n=24
a: n=23, excluding Subject 22
%CV were not calculated for non-arithmetic means

SCH 34117 and SCH 45581 concentrations were detected in Period I plasma samples from Subject No. 22 who received placebo during that period. Inclusion or exclusion of this subject did not change the conclusions.

SCH 34117 was slowly absorbed (median Tmax 5.0 hours). Five subjects exhibited higher concentrations of SCH 34117 (Cmax >100 ng/mL; AUC >2300 n Vhr/mL) with the corresponding SCH 45581 (Cmax < 2.5 ng/mL; AUC <48 n Vhr/mL) concentrations lower than all other volunteers in the study.

**Table** Maximum and Maximum Change for the ECG Parameters on Day 10 Following Placebo or Desloratadine Administration (Protocol C98-357)

| Parameter | Maximum Day 10 | | Change (Maximum Day 10 - Maximum Day -1) | |
|---|---|---|---|---|
| | Placebo | Desloratadine | Placebo | Desloratadine |
| PR[a] | 196 (2) | 188 (3) | 28 (1) | -20 (1) |
| QRS[a] | 112 (2) | 108 (1) | 12 (1) | 12 (1) |
| QT[a] | 436 (1) | 420 (1) | 36 (1) | -56 (1) |
| QTc[a] | 429 (1) | 433 (1) | -18 (1) | 24 (1) |
| Ventricular Rate[b] | 112 (1) | 117 (1) | 30 (1) | 30 (2) |

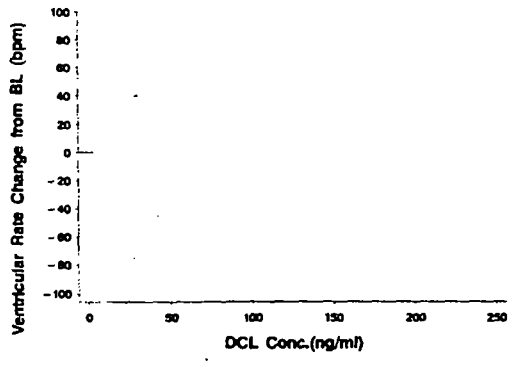
( ) – frequency
a:Units – msec
b:Units – beats/minute

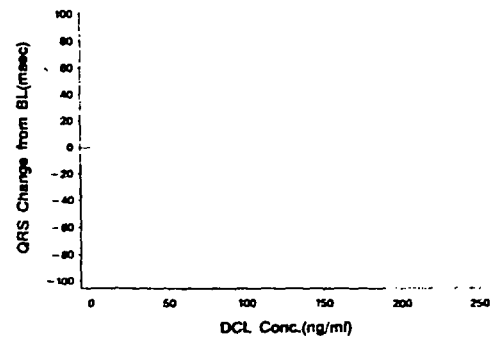
**Table** Mean Difference Between Maximum ECG Parameters on Day 10 and Baseline (Day -1) Following Placebo or Desloratadine Administration (Protocol C98-357)

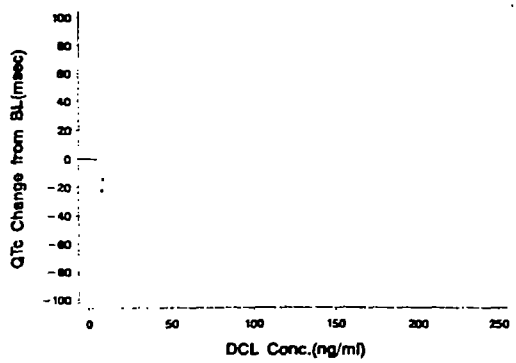
| Parameter | Mean ([Maximum Day 10]-[Maximum Day -1]) | | | 95% | 95% |
|---|---|---|---|---|---|
| | Placebo | DCL 45 mg | p-value | LCI[a] | UCI[b] |
| PR | 6.2 | 2.3 | 0.10 | -8.5 | 0.8 |
| QRS | 0.0 | -0.7 | 0.63 | -3.5 | 2.2 |
| QT | 3.8 | -17.8 | 0.00 | -32.3 | -11.0 |
| QTc | 0.3 | 4.3 | 0.09 | -0.6 | 8.7 |
| Ventricular Rate | 4.2 | 13.6 | 0.00 | 3.7 | 15.1 |

a:LCI - Lower confidence interval.
b:UCI - Upper confidence interval.

Subgroup analysis (by gender) showed a significant treatment effect for PR interval and ventricular rate (p-values=0.02) in female but not for males. For QT both males and females show significant treatment effects.
No statistically significant change was detected for QTc interval for either males or females. The estimated slopes resulting from regression analysis (mixed model) of the change from Baseline for QTc, QRS and ventricular rate and plasma desloratadine plasma concentration were 0.08, -0.002 and 0.06, respectively. These slopes are close to zero demonstrating the absence of a clinically relevant correlation between the ECG parameter and plasma desloratadine concentrations.






**Safety:** Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects.
Fourteen of twenty-four (58%) reported at least one adverse event during SCH 34117 treatment period and 12 of 24 (50%) subjects reported at least one adverse event during the placebo treatment period. The most common adverse event (regardless of association to treatment) was headache 13 (54%) SCH 34117 treatment group and 11 (46%) in the placebo treatment group. All reported adverse events were mild to moderate in severity. No subject discontinued participation in the study due to adverse events.

**SPONSOR'S CONCLUSIONS:**

- Desloratadine 45 mg (qd) for 10 consecutive days was safe and well tolerated.
- At 9-fold the anticipated clinical dose, desloratadine did not show any clinically relevant prolongation of the QTc interval. An increase in ventricular rate was observed.
- Somnolence/sedation was not reported by any subject.
- Desloratadine was slowly absorbed (median Tmax = 5 hours) and slowly eliminated.
- The geometric desloratadine mean values for all subjects were 50 ng/mL for Cmax and 747 n Vh r/mL for AUC(0-24hr).
- The desloratadine metabolism to 3-OH desloratadine was slow in 5 out of 24 subjects. Based on genotyping analysis, these subjects were predicted to be extensive metabolizers for CYP2D6 and CYP2C19 phenotypes.
- There appears to be no relationship between CYP2D6 and CYP 2C19 status and the metabolism of SCH 34117.
- The mean exposure to 3-OH desloratadine was 35.6% that of desloratadine in all subjects compared to only 1% in slow metabolizers.

**REVIEWER'S COMMENTS:**
The study has been done appropriately. In general, this reviewer agrees the sponsor's conclusion.
This data indicates wide therapeutic range of DCL.

**Title of the Study:** SCH 34117: The Absorption, Metabolism and Excretion of $^{14}$C-SCH 34117 in Healthy Male Volunteers (Protocol C98-097-01)

**Investigator(s):** Albert Cohen, M.D.

**Studied Period:** April 28, 1998 – May 16, 1998

**Clinical Phase:** I

**Objective(s):** To characterize the absorption, metabolism and excretion of $^{14}$C-desloratadine ( $^{14}$C-SCH 34117) following a single oral 10 mg dose to healthy male subjects.

**Design:** Open label single dose design

**Number of Subjects:** Six adult male volunteers (age 18-40 years) were enrolled in and completed this study.

**Diagnosis and Criteria for Inclusion:** Adult, non-smoking, male volunteers between the ages of 18 and 40 years, in good health based upon medical history, physical exam, electrocardiogram, urine screen for drugs and laboratory safety tests.

**Test Product, Dose, Mode of Administration, Batch No(s):** $^{14}$C-SCH 34117, 10 mg (100 µCi) capsule formulation, oral, 38101-134

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** N/A

**Treatment:**
This was an open-label, single-dose, absorption, metabolism and excretion study of 14 C-SCH 34117. Six healthy adult male subjects were empanelled and completed this study. Subjects met all study entry criteria and provided written informed consent before receiving a single capsule containing ~10 mg (~104 µCi) of 14 C-SCH 34117. Each dose was administered orally with 200 mL of room-temperature, non-carbonated water.
On Day –1, approximately 10 hr prior to dosing (Day 1), all subjects received a light snack (sandwich, fruit and non-caffeinated beverage), after which an absolute overnight fast was maintained. On Day 1, after completion of 0-hr vital signs, each subject received a dose of approximately 9.92 mg of 14 C-SCH 34117 (~104 µCi) administered orally as a capsule. The subjects continued to fast until the 4-hr study-related procedures had been completed, at which time a light lunch was served. Water intake was restricted to 240 mL ingested at lunch, 6, 10, 12 and 16 hr post-dose. Subjects remained ambulatory during the 4-hr period. All subjects were confined to the study site until the 240 hr study procedures were completed. No strenuous physical activity was permitted. All clinical data and adverse events were recorded on the case report form. Blood, urine and feces were collected over 10 days for pharmacokinetic evaluations. Blood samples (15 mL) were collected for pharmacokinetic evaluations into heparinized [redacted] tubes at 0 hr (predose) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hr after dose administration for determination of plasma SCH 34117 concentrations. At 3, 6, 12 and 24 hr after dose administration, an additional 20 mL of blood were collected for metabolite profiling. Three aliquots 0.5 mL each of whole blood were accurately and precisely transferred to individual combustion cones [redacted] with combustion pads [redacted] These combustion cones were placed into labeled scintillation vials and immediately frozen to at least –20°C. The remaining blood from each sample was centrifuged and the resultant plasma separated and stored frozen at -20°C or below pending analysis. Urine samples were collected at 0 hr (predose) and in block intervals at 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216 and 216-240 hr after dose administration. Total collection volume at each block interval was recorded. Samples were stored frozen at or below -20°C pending analysis. Fecal samples were collected at 0 hr (predose) and then all bowel movements were collected following drug administration up to 240 hr. Time of collection relative to drug administration was recorded for each collection. Samples were stored frozen at or below -20°C pending analysis.

**Pharmacogenetic Profiling**
After study completion, the protocol was amended to include genotyping of the subjects; only three subjects (Subjects 1, 3 and 4) returned for this sampling. An additional blood sample was collected retrospectively from these subjects. Blood samples were shipped to [redacted] for

genomic DNA isolation and molecular genotyping analysis of CYP2D6 ("A", "B", "D", "E", "G", and "T" alleles) and CYP2C19 ("m1", "m2", "m3" and "m4" alleles).
**Criteria for Evaluation:** Pharmacokinetic parameters [Cmax, Tmax, t½, AUC, Ae(day), Ae(total)], reported adverse events, chemistry panel, CBC, urinalysis, and ECG.

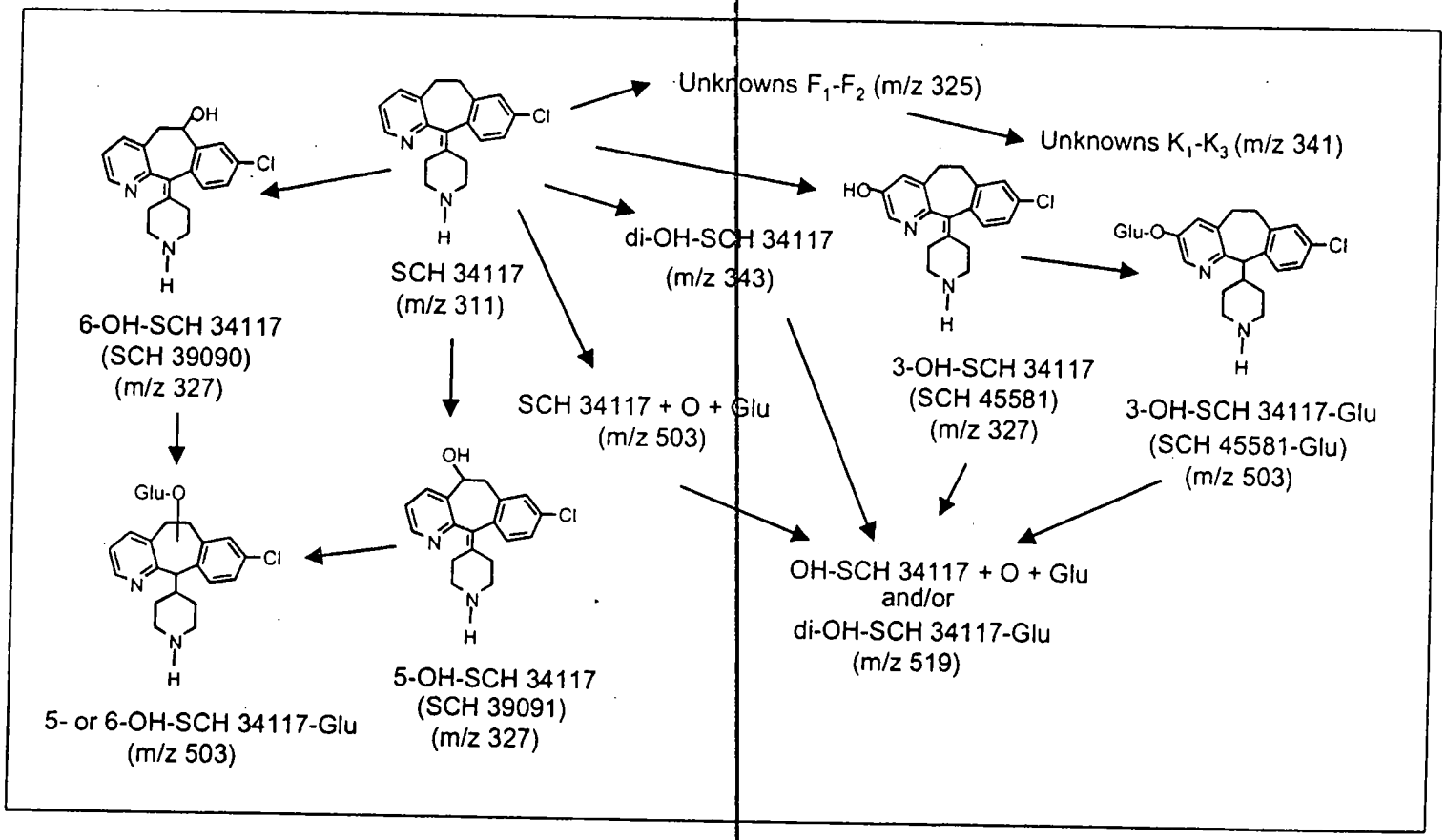
**Statistical Methods:** Descriptive statistics (mean, standard deviation and %coefficient of variation)

**RESULTS:**
**Clinical Pharmacology:** The mean (%CV) pharmacokinetic parameters for desloratadine (SCH 34117) in plasma and total radioactivity in plasma and blood following a single 10 mg oral dose of $^{14}$C-SCH 34117 were as follows (The SCH 34117 plasma concentration-time profile of Subject 5 was different from that of Subjects 1-4 and 6. In addition, the urinary and fecal metabolite profiling data showed that Subject 5 metabolized 14 C-SCH 34117 more slowly than the other subjects. Thus, the data for Subject 5 were not included in the calculation of the mean pharmacokinetic values and are discussed separately in this section):

| Parameter (units) | | SCH 34117 | | $^{14}$C-SCH 34117 | |
|---|---|---|---|---|---|
| | | [a] Mean | Subject 5 | [a] Mean | Subject 5 |
| Cmax | (ng/mL or ng equiv/g)[b] | 4.32 | 4.59 | 44.6 | ND |
| Tmax | (hr)[c] | 5.80 | 12 | 7.60 | ND |
| AUC(tf) | (ng·hr/mL or ng equiv·hr/g)[d] | 77.7 | 436 | 971 | ND |

ND = Not determined
a: Excluding Subject 5
b: Maximum observed plasma concentration
c: Time of maximum observed plasma concentration
d:Area under the plasma concentration-time curve from time zero to time of the final quantifiable sample

Mean cumulative excretion of radioactivity (0-240 hr) was 41% in urine and 47% in feces. Generally, metabolite profiles in plasma, urine and feces showed that SCH 34117 was metabolized to numerous metabolites; including a primary circulating plasma metabolite, SCH 45581-glucuronide (3-OH-SCH 34117-glucuronide). SCH 45581 and SCH 45581-glucuronide were also major fecal and urinary metabolites, respectively. However, one subject (characterized as a pharmacokinetic outlier; Subject 5) exhibited higher concentrations of SCH 34117 in plasma and excreta suggesting that he may be a poor metabolizer of SCH 34117. This subject also exhibited correspondingly lower amounts of SCH 45581 and SCH 45581-glucuronide in the feces and urine, respectively. All metabolites detected or identified by [redacted] following oral administration of $^{14}$C-SCH 34117 were similarly characterized after an oral dose of $^{14}$C-SCH 29851 (Loratadine). Following diagram summarizes a proposed biotransformation pathway.


Unknowns $F_1$-$F_2$ (m/z 325)
Unknowns $K_1$-$K_3$ (m/z 341)
SCH 34117
(m/z 311)
di-OH-SCH 34117
(m/z 343)
6-OH-SCH 34117
(SCH 39090)
(m/z 327)
3-OH-SCH 34117
(SCH 45581)
(m/z 327)
3-OH-SCH 34117-Glu
(SCH 45581-Glu)
(m/z 503)
SCH 34117 + O + Glu
(m/z 503)
OH-SCH 34117 + O + Glu
and/or
di-OH-SCH 34117-Glu
(m/z 519)
5-OH-SCH 34117
(SCH 39091)
(m/z 327)
5- or 6-OH-SCH 34117-Glu
(m/z 503)

**Pharamcogenetic profiling**: Results of the molecular genotyping of Subjects 1, 3 and 4 showed that these subjects were extensive metabolizers of both CYP2D6 and CYP2C19 isoforms. No additional blood samples were collected for Subjects 2, 5 and 6, therefore, no profiling was completed.

**Efficacy:** Not evaluated.

**Safety:** Desloratadine (10 mg) orally administered as a capsule, labeled with $^{14}C$ (100 µCi) was safe and well-tolerated.

**SPONSOR'S CONCLUSIONS:**

- A single dose of $^{14}$C-SCH 34117 capsule (~100 µCi) was safe and well-tolerated following oral administration.
- SCH 34117 was well absorbed and extensively metabolized following oral administration. Drug-derived radioactivity was excreted in the urine (41%) and feces (47%).
- With the exception of a single subject, SCH 34117 was extensively metabolized; the major pathway consisted of hydroxylation, mainly at the C-3 position, and subsequent glucuronidation as well as relatively minor quantities of other hydroxylated metabolites and their respective glucuronides.
- The metabolism of SCH 34117 in Subject #5 was slower than that of the other 5 subjects. As a result, the pharmacokinetics of SCH 34117 in this subject were characterized by a prolonged elimination.

**REVIEWER'S COMMENTS:**

The sponsor appropriately characterized the absorption, metabolism, and excretion of DCL following a single oral administration of $^{14}$C-SCH capsule 34117.

The sponsor's description of "well absorbed---" is not quite correct. The absolute bioavailability is not investigated in human.

The observed high inter-subject variability in the present study (e.g., Subject 5) is consistent with the other studies. The reason for the variability is not known. The pharmacogentic results are not sufficient to answer the inter-subject variability of this drug.

**Title of the Study: SCH 34117: Evaluation of the Pharmacokinetics and Electrocardiographic Pharmacodynamics of Desloratadine with Concomitant Administration of Ketoconazole (Protocol No. C98-352).**

**Investigator(s):** Jerry M. Herron, M.D.

**Studied Period:** 28 SEP 1998 – 07 NOV 1998

**Clinical Phase:** I

**Objective(s):** To evaluate the effects of co-administration of desloratadine and ketoconazole on the pharmacokinetic parameters and electrocardiographic pharmacodynamics of desloratadine. The secondary objective of this study was to observe the safety and tolerability of desloratadine in subjects concomitantly receiving ketoconazole.

**Methodology:** Randomized, two-way crossover, third-party blind, multiple-dose, placebo controlled study. Twenty-four (24) healthy subjects (12 males and 12 females) each received multiple-dose treatment during two separate treatment periods. ECGs were recorded on Day –1 (Baseline) daily and on Day 10 (follow-up). The change from Baseline of the multiple ECGs obtained on both Day –1 (Baseline) and Day 10 were used for the ECG pharmacodynamic determinations. The order in which subjects received treatments was ssigned according to a computer-generated random code provided by SPRI. Blood samples were collected at pre-specified times for pharmacokinetic and safety evaluations. Vital signs were obtained at pre-specified times for safety evaluation. Subjects were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events. Plasma samples were assayed for SCH 34117 and SCH 45581 using a validated ( assay (LOQ= ng/mL). Plasma ketoconazole concentrations were determined by ( with ( (LOQ= mg/mL).

**Number of Subjects:** Twenty-four healthy subjects (12 male and 12 female)

**Diagnosis and Criteria for Inclusion:** Adult male or female subjects (non smokers) between 18-50 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram (QTc <420 ms) and routine laboratory tests (blood chemistry, hematology, and urinalysis) and having a BMI between 19-27 were empaneled for this study.

**Test Product, Dose, Mode of Administration, Batch No(s):** SCH 34117 7.5 mg tablets, Batch No. 38833-140 and ketoconazole (Nizoral [ Janssen Pharmaceutical) 200 mg/tablets, Lot No. 98P0579E. Treatments were administered orally on an empty stomach only on the PK testing day (Day 10). One x 7.5 mg SCH 34117 tablet was administered qd and 1 x 200 mg ketoconazole tablet bid.

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** SCH 34117 7.5 mg tablets, Batch No. 38833 140 and placebo tablets, Batch No. 38833-072. Treatments were administered orally on an empty stomach. SCH 34117 tablets were administered qd and placebo tablets bid.

**Duration of Treatment:** SCH 34117 7.5 mg administered once daily in the morning (8 a.m.) with concurrent administration of placebo or ketoconazole 200 mg which were administered q12h (8 a.m. and 8 p.m.). All treatments were administered for 10 days during each of the 2 treatment periods. Each treatment period was separated by at least 7 days washout period.

**Criteria for Evaluation:** Blood samples were collected over 24 hours for determination of pharmacokinetic parameters (AUC and Cmax) on Day 10. ECGs were obtained over a 16 hour period on Day –1 and 10 for determination of PR, QR, QRS, QTc intervals and ventricular rate.

**Statistical Methods:** The bioavailability of desloratadine given with ketoconazole compared to desloratadine given alone were expressed as the ratio of the treatments. It was based on log-transformed AUC and Cmax. Confidence intervals for these estimates of bioavailability and the power to detect a 20% difference between treatment means for an alpha level of 0.05 (two-tailed) were also computed. Summary statistics for desloratadine and ketoconazole (e.g., means and standard deviations) were provided for the concentration data at each timepoint. The primary pharmacodynamic parameters for this study were the differences between Baseline (Day –1) maximum PR, QRS, QT and QTc intervals and the Day 10 maximum PR, QRS, QT and QTc intervals. These differences were analyzed using a linear model extracting effects due to sequence, subject within sequence, period and treatment. Using the pooled variance from these models, 95% confidence interval for the mean difference were calculated. Descriptive statistics for maximum

PR, QRS, QT and QTc intervals were provided for Baseline, Day 10 and Day 10 change from Baseline and percent change for the parameters.

**RESULTS:**
**Clinical Pharmacology:**
**Subject Disposition:** Twenty-four subjects were enrolled and completed treatment.

**Demographic and Baseline Characteristics:** Overall, 24 subjects (12 male and 12 female) between the ages of 19 and 50 years inclusive (mean = 36.9 years) with BMIs between 20 and 27 (mean=25.6) were enrolled into the study. Seven subjects were Caucasian and 17 were Black.

**Pharmacokinetics:**
The mean pharmacokinetic parameters of desloratadine and 3-OH desloratadine on Day 10 are summarized below:

| | Desloratadine | | | | | |
|---|---|---|---|---|---|---|
| | Treatment A Desloratadine with Placebo | | | Treatment B Desloratadine with Ketoconazole | | |
| Parameter | Arithmetic Mean | %CV | Geometric Mean | Arithmetic Mean | %CV | Geometric Mean |
| Cmax (ng/mL) | 12.4 | 61 | 10.1 | 15.8 | 63 | 13.1 |
| Tmax[a] (hr) | 6.10 | 65 | 5.5[a] | 5.94 | 59 | 5.0[a] |
| AUC(0-24hr) (ng·hr/mL) | 225 | 74 | 168 | 272 | 79 | 203 |
| | 3-OH Desloratadine | | | | | |
| Cmax (ng/mL) | 2.06 | 76 | 1.24 | 3.09 | 60 | 2.19 |
| Tmax[a] (hr) | 4.98 | 58 | 5.0[a] | 5.92 | 43 | 5.0[a] |
| AUC(0-24hr) (ng·hr/mL) | 29.0 | 71 | 19.0 | 55.0 | 59 | 39.9 |

a: Median Tmax.

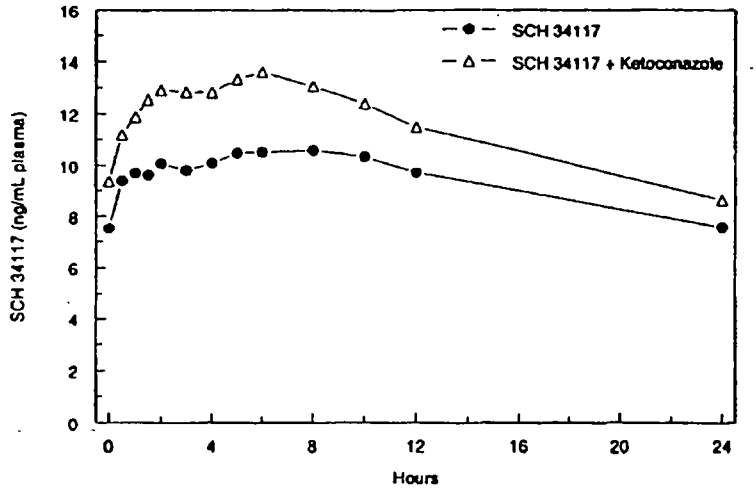
Desloratadine was slowly absorbed with a median Tmax value of 5 hours for both treatments. Steady-state geometric means for Cmax and AUC(0-24hr) of desloratadine and 3-OH desloratadine increased with concomitant administration of ketoconazole.

| Parameter | Treatment Comparison | Ratio (%) | Power[a] (%) | 90% Confidence Interval[b] | Pairwise p-Value |
|---|---|---|---|---|---|
| | | Desloratadine | | | |
| Cmax (ng/mL)[c] | B/A | 129 | 34 | 106-156 | 0.034 |
| Cmax (ng/mL)[d] | B/A | 145 | 59 | 127-167 | 0.001 |
| AUC(0-24hr) (ng·hr/mL)[c] | B/A | 121 | 38 | 101-145 | 0.086 |
| AUC(0-24hr) (ng·hr/mL)[d] | B/A | 139 | 100 | 134-145 | 0.001 |
| | | 3-OH Desloratadine | | | |
| Cmax (ng/mL)[c] | B/A | 177 | 14 | 127-247 | 0.008 |
| Cmax (ng/mL)[d] | B/A | 143 | 25 | 113-180 | 0.015 |
| AUC(0-24hr) (ng·hr/mL)[c] | B/A | 210 | 22 | 163-270 | 0.001 |
| AUC(0-24hr) (ng·hr/mL)[d] | B/A | 172 | 98 | 160-186 | 0.001 |

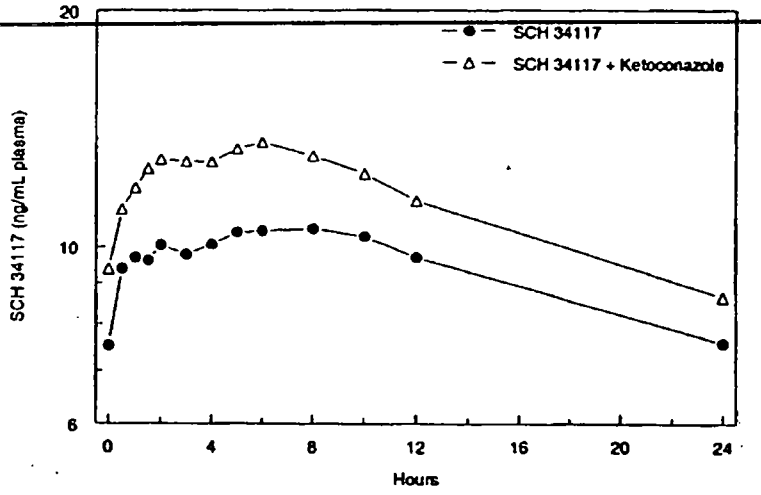
a: Power to detect a 20% difference between log-transformed treatment means at $\alpha$=0.05
b: 90% Confidence interval based on log-transformed data
c: n=24
d: n=22, excluding Subjects 10 and 11
Treatment A: SCH 34117 with Placebo
Treatment B:SCH 34117 with Ketoconazole

Co-administration of desloratadine and ketoconazole resulted in a 29-45% increase in the mean Cmax of desloratadine.

Linear:linear




Log:linear




Similarly an increase ranging between 21 to 39% was observed for mean AUC(0-24hr). The mean Cmax and AUC values for 3-OH desloratadine also increased in the presence of ketoconazole. The increase ranged from 43 - 77% for Cmax and 72-110% for AUC(0-24hr).

**Pharmacodynamics:** No QTc interval increased by >5.4% as compared to Baseline nor were there any ECG findings, in the opinion of the Investigator, that precluded further treatment. The maximum QTc values recorded after once daily administration for 10 days of either desloratadine/placebo or desloratadine/ketoconazole were 431 msec and 435 msec, respectively.
The p-value summaries for maximum change in ventricular rate, PR, QRS, QT and QTc are shown in the following table:

| Parameter | Mean ([Maximum Day 10]-[Maximum Day -1]) Desloratadine/ Placebo | Desloratadine/ Ketoconazole | p-value | 95% LCI[a] | 95% UCI[b] |
|---|---|---|---|---|---|
| PR | 0.0 | 5.4 | 0.14 | -12.6 | 1.9 |
| QRS | -1.3 | -0.3 | 0.56 | -4.5 | 2.5 |
| QT | -7.2 | -3.7 | 0.61 | -17.4 | 10.4 |
| QTc | 2.3 | 5.4 | 0.14 | -7.3 | 11 |
| Ventricular Rate | 12.2 | 5.6 | 0.05 | -0.1 | 13.3 |

a: LCI - Lower confidence interval.
b: UCI - Upper confidence interval.

The results of statistical evaluation show that there is no significant treatment effect (interaction of DCL and ketoconazole) on ECG variable except ventricular rate where the change was greater following desloratadine given alone than with ketoconazole. Subgroup analysis by gender shows a significant treatment effect for females ($p<0.04$) but not males for the PR interval. However, no PR intervals greater than 200 ms was observed during treatment for any females. Therefore, these differences were not considered to be clinically relevant.

**Safety:** Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects. Overall, 13 of 24 (54%) subjects reported treatment-emergent adverse events. The most frequently reported adverse event was headache 13 (54%). All reported adverse events were mild in severity except for four subjects (No. 4, 16, 23 and 24) each reporting moderate headaches. No subject discontinued participation in the study due to adverse events. There was no apparent difference between the treatment groups in the number of subjects reporting AEs.

**SPONSOR'S CONCLUSIONS:**

- ~~Doses of desloratadine 7.5 mg when co-administered with ketoconazole~~ (200 mg bid) were safe and well tolerated.
- No clinically important ECG changes were seen during co-administration by desloratadine and ketoconazole.
- Mean desloratadine Cmax and AUC(0-24hr) values were increased by 1.3- and 1.2-fold when esloratadine was co-administered with ketoconazole.
- Mean 3-OH desloratadine Cmax and AUC(0-24hr) values were increased by 1.8- and 2.1-fold when desloratadine was co-administered with ketoconazole.

**REVIEWER'S COMMENTS:**

This study was conducted to evaluate the effects of co-administration of desloratadine and ketoconazole, a potent inhibitor of cytochrome P450 3A4 enzymes, on the pharmacokinetic parameters and electrocardiographic pharmacodynamics of desloratadine.

The increase in plasma concentrations suggests that the metabolism of desloratadine and 3-OH desloratadine may be partially mediated by CYP3A4. This is consistent with the in vitro human metabolism study results.

The systemic exposure after 7.5 mg DCL with ketoconazole appeared to be less than the exposed in the study c98-357 (dose 45 mg QD). Provided the safety in C98-357, this reviewer is of the opinion that the dose adjustment is not warranted.

**Title of the Study: SCH 34117: Evaluation of the Pharmacokinetics and Electrocardiographic Pharmacodynamics of Desloratadine with Concomitant Administration of Erythromycin (Protocol C98-353).**

**Investigator(s)**: Thomas Hunt, M.D.

**Studied Period**: 04 SEP 1998 – 09 NOV 1998

**Clinical Phase: I**

**Objective(s)**: To evaluate the effects of co-administration of desloratadine and erythromycin on the harmacokinetic parameters and electrocardiographic pharmacodynamics of desloratadine te secondary objective of this study was to observe the safety and tolerability of desloratadine i subjects concomitantly receiving erythromycin.

**Methodology**: Randomized, two-way crossover, third-party blind, multiple-dose, placebo-controlled study. Twenty-four (24) healthy subjects (12 males and 12 females) each received multiple-dose in treatment during two separate treatment periods. The order in which subjects received treatments DL plus placebo or DL plus erythromycin was determined according to a computer-generated random code provided by SPRI. Blood samples were collected at pre-specified times for pharmacokinetic and safety evaluations. ECGs were recorded on Day –1 (Baseline), daily and on Day 10 (follow-up). Vital signs were obtained at pre-specified times for safety evaluation.

Subjects were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events.

**ASSAY:**

Plasma samples were assayed for SCH 34117 and SCH 45581 using [redacted] assay (LOQ=[redacted] ng/mL). Plasma erythromycin concentrations were determined by [redacted] LOQ=[redacted] ng/mL).

**Number of Subjects**: Twenty-four healthy subjects (12 male and 12 female)

**Diagnosis and Criteria for Inclusion**: Adult male or female subjects (non-smokers) between 18-50 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram (QTc <420 ms) and routine laboratory tests (blood chemistry, hematology, and urinalysis) and having a BMI between 19-27 were empaneled for this study.

**Test Product, Dose, Mode of Administration, Batch No(s)**: SCH 34117 7.5 mg tablets (1 x 7.5 mg tablet qd), Batch No. 38833-140 and erythromycin (Erythrocin ( Stearate Film Tab ( Abbott Laboratories) 250 mg tablets (2 x 250 mg tablets q8h), Lot No. 36773AF21. Both treatments were administered orally (and after an overnight fast on Day 10).

**Reference Therapy, Dose, Mode of Administration, Batch No(s)**: SCH 34117 7.5 mg tablets (1 x 7.5 mg tablet qd), Batch No. 38833-140 and placebo tablets (2 tablets q8h), Batch No. 38833-072. Both treatments were administered orally (and after an overnight fast on Day 10).

**Duration of Treatment**: SCH 34117 7.5 mg administered once daily in the morning (8 a.m.) with concurrent administration of placebo or erythromycin 500 mg which were administered q8h (8 a.m., 4 p.m. and 12 a.m.). All treatments were administered for 10 days during each of the 2 treatment periods. Each treatment period was separated by at least 7 days washout period.

**Criteria for Evaluation**: Blood samples were collected over 24 hours for determination of pharmacokinetic parameters (AUC and Cmax) on Day 10. ECGs were obtained over a 16 hour period on Days –1 and 10 for determination of PR, QRS, QT, QTc intervals and ventricular rate.

**Statistical Methods**: The bioavailability of desloratadine given with erythromycin compared to desloratadine given alone was expressed as the ratio of the treatments based on log-transformed AUC and Cmax data. Confidence intervals for these estimates of bioavailability and the power to detect a 20% difference between treatment means for an alpha level of 0.05 (two-tailed) were also computed. Summary statistics for desloratadine and erythromycin (e.g., means and standard deviations) are provided for the concentration data at each timepoint. The primary pharmacodynamic parameters for this study were the differences between Baseline (Day –1) maximum PR, QRS, QT and QTc intervals and the Day 10 maximum PR, QRS, QT and QTc intervals. These differences were analyzed using a linear model extracting effects due to sequence, subject within sequence, period and treatment. Using the pooled variance from this model, 95%

confidence intervals for the mean difference was calculated. Descriptive statistics for maximum PR, QRS, QT and QTc intervals were provided for Baseline, Day 10 and Day 10 change from Baseline.

**RESULTS**
**Clinical Pharmacology:**

**Subject Disposition:** Twenty-four subjects were enrolled and completed treatment.

**Demographic and Baseline Characteristics:** Overall, 24 subjects (12 male and 12 female) between the ages of 19 and 46 years inclusive (mean = 30.5 years) with BMIs between 18 and 27 (mean=22.9) were enrolled into the study. Eighteen subjects were Caucasian, 5 were Hispanic and 1 was Asian.

**Pharmacokinetics:**
The mean (%CV) pharmacokinetic parameters of desloratadine and 3-OH desloratadine on Day 10 are summarized below:

| | Desloratadine | | | |
|---|---|---|---|---|
| | Treatment A Desloratadine with Placebo | | Treatment B Desloratadine with Erythromycin | |
| Parameter | Arithmetic Mean | Geometric Mean | Arithmetic Mean | Geometric Mean |
| Cmax (ng/mL) | 6.51 (54) | 6.00 | 8.07 (52) | 7.41 |
| Tmax[a] (hr) | 2.88 (63) | 2.00[a] | 2.77 (81) | 2.00[a] |
| AUC(0-24hr) (ng·hr/mL) | 100 (78) | 86.4 | 114 (82) | 98.2 |
| | | 3-OH Desloratadine | | |
| Cmax (ng/mL) | 2.98 (27) | 2.85 | 4.30 (30) | 4.09 |
| Tmax[a] (hr) | 4.71 (30) | 5.00[a] | 4.31 (50) | 4.5[a] |
| AUC(0-24hr) (ng·hr/mL) | 51.3 (28) | 49 | 72.7 (33) | 68.6 |

a: Median Tmax.

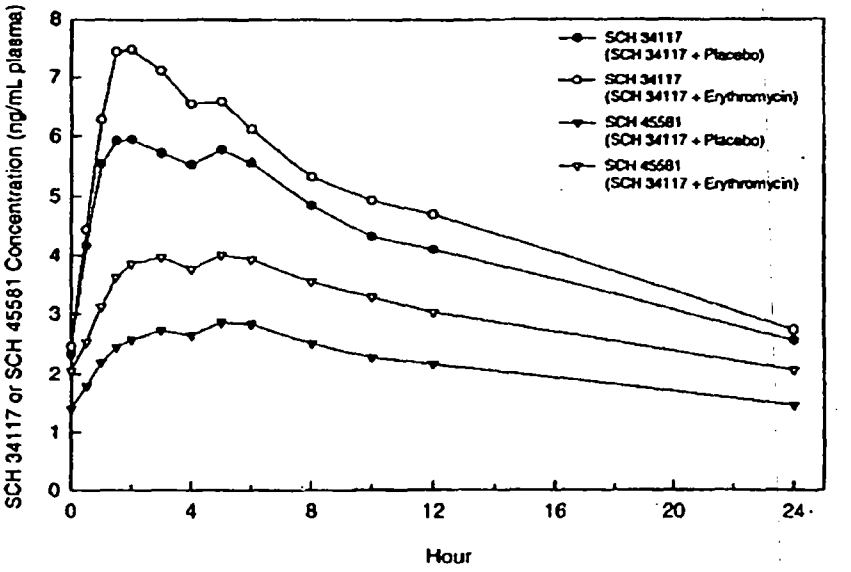
Desloratadine was slowly absorbed with a median Tmax value of 2 hours for both treatments. Steady-state geometric means for Cmax and AUC(0-24hr) of desloratadine and 3-OH desloratadine increased with concomitant administration of erythromycin.

| Parameter | Treatment Comparison | Ratio (%)[a] | Power[b] (%) | 90% Confidence Interval[c] |
|---|---|---|---|---|
| | | Desloratadine | | |
| Cmax (ng/mL) | B/A | 124 | 100 | 117-131 |
| AUC(0-24hr) (ng·hr/mL) | B/A | 114 | 100 | 108-119 |
| | | 3-OH Desloratadine | | |
| Cmax (ng/mL) | B/A | 143 | 100 | 139-148 |
| AUC(0-24hr) (ng·hr/mL) | B/A | 140 | 100 | 134-146 |

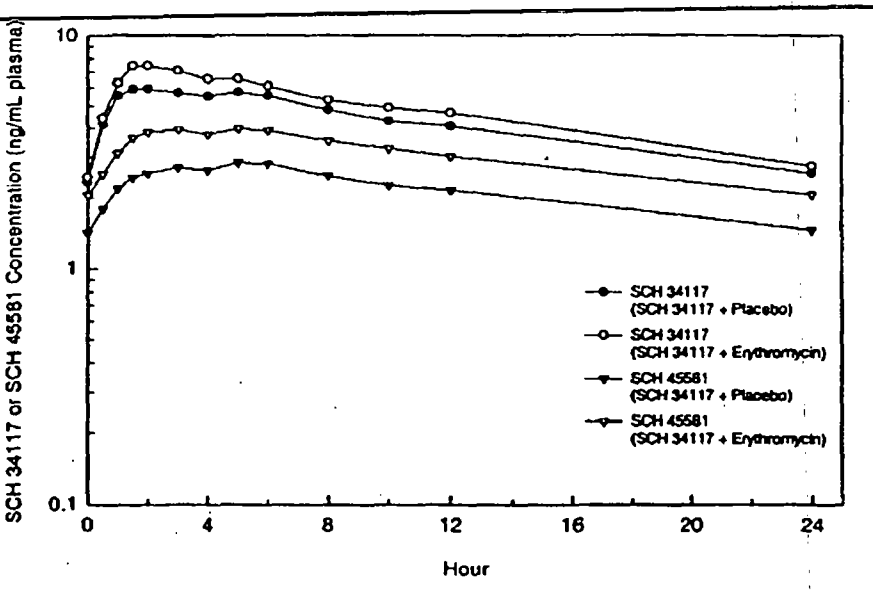
a: Treatment A: Desloratadine with Placebo
Treatment B: Desloratadine with Erythromycin
b: Power to detect a 20% difference between log-transformed treatment means at $\alpha$=0.05
c: 90% Confidence interval based on log-transformed data

Co-administration of desloratadine and erythromycin resulted in an increase in the mean Cmax and AUC of desloratadine by 24% and 14%, respectively. Similarly, the 3-OH desloratadine Cmax and AUC values were both increased by approximately 40% in the presence of erythromycin. (Refer to the following figures.)

Linear:linear




Log:linear



**Pharmacodynamics:** No QTc interval increased by >8% as compared to Baseline nor were there any ECG findings, in the opinion of the Investigator, that precluded further treatment. The maximum QTc value recorded after once daily administration for 10 days of either desloratadine/placebo or desloratadine /erythromycin was 445 msec.
The p-value summaries for maximum change in ventricular rate, PR, QRS, QT and QTc are shown in the following table:

| | Mean ([Maximum Day 10]-[Maximum Day -1]) | | | | |
|---|---|---|---|---|---|
| Parameter | Desloratadine/ Placebo | Desloratadine/ Erythromycin | p-value | 95% LCI[a] | 95% UCI[b] |
| PR | 4.2 | 2.3 | 0.45 | -3.2 | 7.1 |
| QRS | -1.3 | -0.8 | 0.54 | -2.0 | 1.1 |
| QT | -8.9 | -8.3 | 0.89 | -9.6 | 8.5 |
| QTc | 7.8 | 9.8 | 0.53 | -8.4 | 4.5 |
| Ventricular Rate | 9.5 | 11.5 | 0.31 | -5.7 | 1.9 |

a: LCI - Lower confidence interval.
b: UCI - Upper confidence interval.

The results of statistical evaluation show that there is no significant treatment effect (interaction of DCL and erythromycin) on any ECG variable.

**Safety:** Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluation showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects.
Overall, 10 of 24 (42%) subjects reported treatment-emergent adverse events. The most frequently reported adverse events were abdominal pain 9 (38%), headache 7 (29%), dizziness 7 (29%) and nausea 5 (21%). The majority of gastro-intestinal system disorders were reported during co-administration of desloratadine and erythromycin. This reflects the poor GI tolerability of erythromycin. In general, more subjects reported adverse events when desloratadine was administered with erythromycin than when administered alone. All reported adverse events were mild to moderate in severity. No subject discontinued participation in the study due to adverse events and no intervention was required to treat any adverse event.

**CONCLUSIONS:**

- Desloratadine 7.5 mg when co-administered with erythromycin (500 mg tid) were safe and well tolerated.
- No clinically important ECG changes were seen during co-administration of desloratadine and erythromycin.
- Mean desloratadine Cmax and AUC(0-24hr) values were increased by 24% and 14%, respectively, when desloratadine was co-administered with erythromycin.
- Mean 3-OH desloratadine Cmax and AUC(0-24hr) values were increased by 40% and 43%, respectively, when desloratadine was co-administered with erythromycin.

**REVIEWER'S COMMENTS:**
The increase in plasma concentrations suggests that the metabolism of desloratadine and 3-OH desloratadine may be partially mediated by CYP3A4. This is consistent with the in vitro human metabolism study results.
The systemic exposure after 7.5 mg DCL with erythromycin appeared to be less than the exposed in the study C98-357 (dose 45 mg QD). Provided the safety of DCL in Study C98-357, this reviewer is of the opinion that the dose adjustment is not warranted.

**Title of Study:** SCH 34117: Single-Dose Pharmacokinetics In Subjects With Various Degrees of Chronic Liver Disease (Protocol C98-354)

**Investigator(s):** Robert Noveck, M.D.

**Studied Period:** 14 AUGUST 1998 – 13 SEPTEMBER 1998

**Clinical Phase:** I

**Objective(s):** To compare the pharmacokinetics of desloratadine in subjects with normal liver function to subjects with various degrees of stable chronic liver disease. The secondary objective was to determine the safety and tolerability of single-dose administration of desloratadine in patients with chronic liver disease.
**Methodology:** Open-label, single-dose, parallel-group, single-center study in adult subjects (males or females) with either normal liver function (n=8) or with chronic liver disease (n=12) selected for this study; subjects with hepatic impairment were assigned to one of three liver function groups according to their score by Pugh's Modification of Child's Classification of Severity of Liver Disease. Following single-dose administration of desloratadine 7.5 mg, blood samples were collected at pre-specified times for pharmacokinetic and safety evaluations. Vital signs were obtained at pre-specified times for safety evaluation. Volunteers were continuously observed and questioned throughout the confinement period for the possible occurrence of adverse events. Plasma samples were assayed for desloratadine and 3-OH desloratadine using a validated [redacted] assay (LOQ= [redacted] pg/mL).

**Number of Subjects:** Twenty subjects (8 healthy and 12 with chronic liver disease)

**Diagnosis and Criteria for Inclusion:** Adult male or female subjects between 18-65 years of age inclusive with chronic liver impairment and healthy volunteers with no evidence of hepatic impairment who were in good health based on medical history, physical examination, electrocardiogram and routine laboratory tests (blood chemistry, hematology, and urinalysis) were empaneled for this study.

**Test Product, Dose, Mode of Administration, Batch No(s):** SCH 34117 7.5 mg tablets. Batch No. 38833-140. Treatment was administered on an empty stomach.

**Duration of Treatment:** Single-dose of desloratadine 7.5 mg administered following a 10 hour fast.

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** None.

**Criteria for Evaluation:** Blood samples were collected over 240 hours for determination of pharmacokinetic parameters (AUC, Cmax, Tmax, K, CL/F and t1/2).

**Statistical Methods:** Summary statistics were calculated for the concentration data at each sampling time and the derived pharmacokinetic parameters. Analyses of variance were used to extract the group effect (among 4 groups, as well as between combined hepatic dysfunction groups and normal subjects for the original scale and log-transformed AUC (tf) and Cmax values. Pairwise comparisons, without adjustments for multiple comparisons, were also performed. The harmonic mean of t1/2 was tabulated in addition to arithmetic mean, because the t1/2 of a few subjects were more than two standard deviations from the mean.

**RESULTS**
**Clinical Pharmacology:**
**Subject Disposition:** Twenty volunteers (8 healthy and 12 with hepatic dysfunction) were enrolled and completed this study.

**Demographic and Baseline Characteristics:** Twenty volunteers (8 healthy and 12 with hepatic dysfunction) between the ages of 42 and 65 years inclusive (mean = 50.5 years) weighing between 66.5 and 108 kg (mean = 82.1 kg) were enrolled in this study. Eleven subjects were Caucasian and 9 were Black, 4 were female and 16 were male.

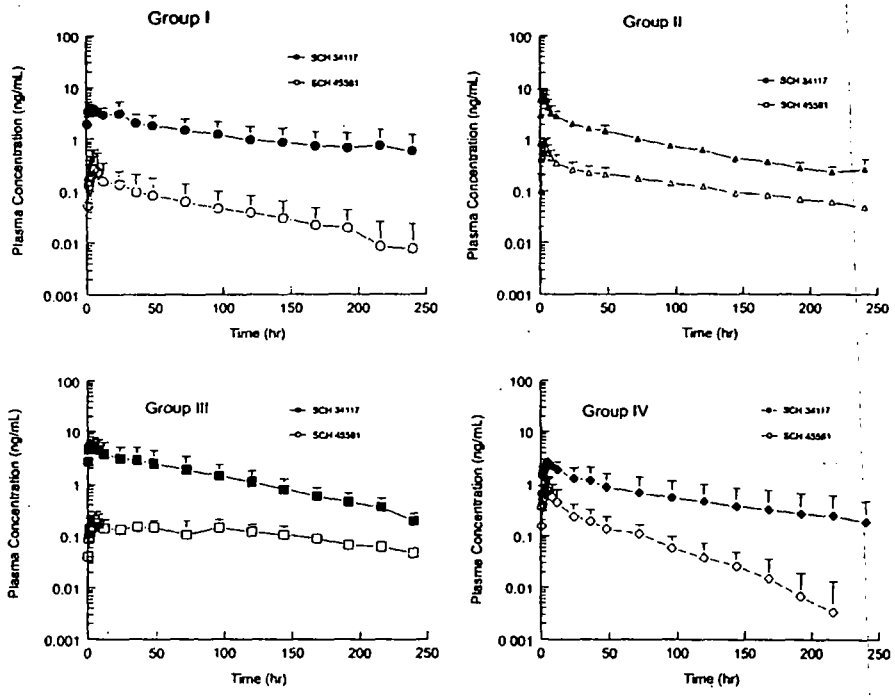
**Pharmacokinetics:** The mean pharmacokinetic parameters of desloratadine and 3-OH desloratadine are summarized below:

| Group | | Pharmacokinetic Parameters of SCH 34117 Cmax (ng/mL) | Tmax (hr) | AUC(tf) (ng· hr/mL) | AUC(I) (ng·hr/mL) | t½ (hr) | CL/F (L/hr) |
|---|---|---|---|---|---|---|---|
| Mild | Arithmetic Mean | 5.14 | 9.63 | 325 | 406 | 77.3 | 32.2 |
| (n=4) | %CV | 19 | 113 | 62 | 72 | 52 | 85 |
| | Geometric Mean | 5.07 | 6.75[a,c] | 269 | 312 | 60.6[b] | 24.0 |
| II/Moderate | Arithmetic Mean | 7.04 | 1.63 | 233 | 248 | 60.6 | 31.0 |
| (n=4) | %CV | 42 | 29 | 20 | 19 | 10 | 18 |
| | Geometric Mean | 6.48 | 1.75[a] | 230 | 245 | 60.3[b] | 30.6 |
| III/Severe | Arithmetic Mean | 6.24 | 2.38 | 355 | 384 | 64.0 | 23.8 |
| (n=4) | %CV | 38 | 76 | 61 | 57 | 28 | 44 |
| | Geometric Mean | 5.90 | 1.75[a] | 316 | 345 | 60.7[b] | 21.7 |
| IV/Normal | Arithmetic Mean | 2.95 | 5.50 | 152 | 181 | 54.3 | 86.2 |
| (n=8) | %CV | 21 | 22 | 83 | 95 | 74 | 70 |
| | Geometric Mean | 2.89 | 5.00[a] | 110 | 120 | 43.4[b] | 62.3 |

a Median
b: Harmonic mean
c: Tmax for 2 subjects was within the first 1.5 hr and at least 12 hr for the other 2 subjects.

| Group | | Pharmacokinetic Parameters of SCH 45581 Cmax (ng/mL) | Tmax (hr) | AUC(tf) (ng·hr/mL) | AUC(I) (ng·hr/mL) | AUC(I) SCH 45581 / AUC(I) SCH 34117 x 100% |
|---|---|---|---|---|---|---|
| I/Mild | Arithmetic Mean | 0.299 | 10.3 | 12.7 | 27.9 | 19.8 |
| (n=4) | %CV | 115 | 90 | 113 | [b] | [b] |
| | Geometric Mean | 0.158 | 6.00[a] | 1.54 | 27.9 | |
| II/Moderate | Arithmetic Mean | 0.677 | 4.50 | 35.6 | 41.8 | 17.2 |
| (n=4) | %CV | 57 | 13 | 24 | 17 | 20.7 |
| | Geometric Mean | 0.587 | 4.50[a] | 34.8 | 41.4 | |
| III/Severe | Arithmetic Mean | 0.216 | 28.0 | 25.9 | 36.0 | 11.3 |
| (n=4) | %CV | 45 | 162 | 33.8 | 16 | 45.6 |
| | Geometric Mean | 0.192 | 5.50[a] | 24.5 | 35.6 | |
| IV/Normal | Arithmetic Mean | 0.835 | 13.8 | 22.3 | 27.0[c] | 40.4 |
| (n=8) | %CV | 75 | 171 | 67 | 49 | 70.1 |
| | Geometric Mean | 0.507 | 5.00[a] | 13.5 | 21.3[c] | |

a: Median
b: %CV was not reported for n=2
c: n=7




Group I = Mild hepatic impairment
Group II = Moderate hepatic impairment
Group III = Severe hepatic impairment
Group IV = Normal

Subjects with hepatic dysfunction exhibited greater exposure to desloratadine than normal subjects. The eometric mean Cmax and AUC (tf) values for subjects with hepatic dysfunction (combined) were up to 2.3 and 2.4 times greater than normal subjects. When the groups with hepatic dysfunction were not combined, pairwise comparisons revealed that the geometric mean Cmax value for normal subjects was significantly lower than that for subjects with severe hepatic dysfunction. Pairwise comparisons between subjects with different degrees of hepatic dysfunction did not show any differences among the groups tested. harmacokinetic simulation studies to assess accumulation at steady state predicted that no subject had exposures greater than subjects dosed with 45 mg daily for 10 days. In addition, the normal volunteers with a long half-life were similar to those with hepatic dysfunction.

**Safety:** Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for the population. Overall, 10 of 20 (50%) subjects reported treatment-emergent adverse events. The most frequently reported adverse event were headache and abdominal pain. All reported adverse events were mild in severity except one (a headache) which was reported as moderate. Five subjects required additional therapy. No subject discontinued participation in the study due to adverse events.

**SPONSOR'S CONCLUSIONS:**

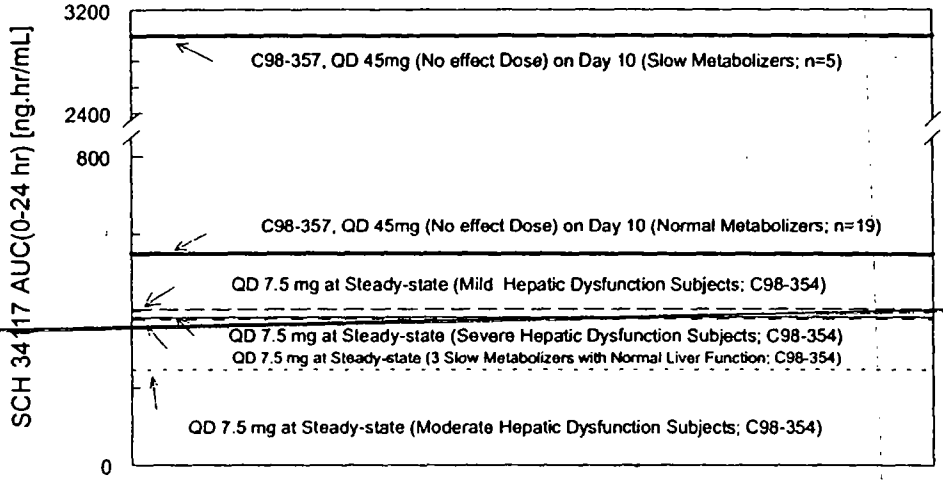
- No dosage adjustment of desloratadine is recommended in patients with hepatic dysfunction.
- A single dose of desloratadine 7.5 mg administered to subjects with various degrees of hepatic dysfunction was safe and well tolerated.
- Subjects with hepatic dysfunction had mean AUC and Cmax values that were up to 2.3 and 2.4 times greater,respectively, than healthy subjects, however, there was considerable overlap of the AUC values among all 4 groups.

**Reviewer's comments:**

The objective of this single-dose study was to evaluate the pharmacokinetics of desloratadine in subjects with normal liver function and subjects with various degrees of stable chronic liver disease. The following is the sponsor's justification of why no dose adjustment is warranted for hepatic patients:

Overall, subjects with hepatic dysfunction exhibited greater exposure to desloratadine than healthy volunteers. However, there was considerable overlap of the AUC values among all 4 groups. In addition, subjects with long half-lives, with and without hepatic dysfunction, had similar exposures (AUC). Pharmacokinetic simulation studies to assess accumulation at steady state were performed using subjects from this study who had long half-lives.

Following Figure describes AUC(0-24 hr) for QD 45 mg vs Predicted Steady-state AUC(0-24 hr) after QD 7.5 mg to 3 Slow Metabolizers with Normal Liver Function and Subjects with Hepatic Dysfunction (Mild, moderate and Severe) (Protocol C98-354)




The pharmacokinetic analysis was performed using a non linear regression program [redacted] The results of this analysis predicted that no subject had exposures greater than subjects dosed with 45 mg daily for 10 days.
In this study there was no evidence that elevated concentrations were associated with a change on the safety profile of desloratadine. Accordingly, the variation in plasma desloratadine and 3-OH desloratadine concentrations are not considered to be clinically relevant and do not compromise the safety of subjects with hepatic dysfunction administered the clinical dose (5 mg). Therefore, no dosage adjustment of desloratadine is recommended in patients with hepatic dysfunction.

This reviewer agrees with the above rationale, provided the safety of the 45 mg dose in Study C98-357.

**Title of the Study:** SCH 34117: Influence of Food on the Oral Bioavailability of SCH 34117 Tablets Administered to Healthy Subjects: A Two Way Crossover Study. (Protocol No. C98-215).

**Investigator(s):** Thomas Marbury, M.D.

**Studied Period:** 19 May 1998 - 26 June 1998

**Clinical Phase:** I

**Objective(s):** The objective of this study was to evaluate the effect of food on the bioavailability of SCH 34117.

**Design/Procedure:** Randomized, open-label, two-way crossover study. Eighteen subjects received each treatment on two separate occasions. The order in which subjects received treatments was assigned according to a computer-generated random code provided by SPRI. Blood samples were collected at pre-specified times for pharmacokinetic and safety evaluations. ECG's and vital signs were obtained at pre-specified times for safety evaluation. Volunteers were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events. Plasma samples were assayed for SCH 34117 using [redacted] assay (LOQ = [redacted] ng/mL).

**Number of Subjects:** Eighteen healthy subjects

**Diagnosis and Criteria for Inclusion:** Adult male or female subjects between 18-45 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis) and having a BMI between 19-27 were empaneled for this study.

**Test Product, Dose, Mode of Administration, Batch No(s):** SCH 34117 7.5 mg tablets, oral, Batch No. 38833-140 administered with a standardized high-fat breakfast.

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** SCH 34117 7.5 mg tablets, oral, Batch No. 38833-140, administered following an overnight fast.

**Duration of Treatment:** Single doses were administered in the morning (approximately 8 a.m.) during each treatment period and subjects were followed for 168 hours postdose.

**Criteria for Evaluation:** Blood samples were collected over 168 hours for determination of pharmacokinetic parameters (AUC and Cmax) under fed and fasted conditions.

**Statistical Methods:** The pharmacokinetic parameters for each dose were summarized using means, standard deviations and coefficients of variation. In addition, an analysis of variance was done extracting effects due to treatment (dose). The analysis was done on log-transformed as well as nontransformed AUC(tf) and Cmax values. The 90% confidence intervals for the difference in the least-square means of the two treatments and the power to detect a 20% difference between treatment means for an alpha level of 0.05 (two-tailed) were calculated from the pooled residual error and associated degrees of freedom from the analysis of variance.

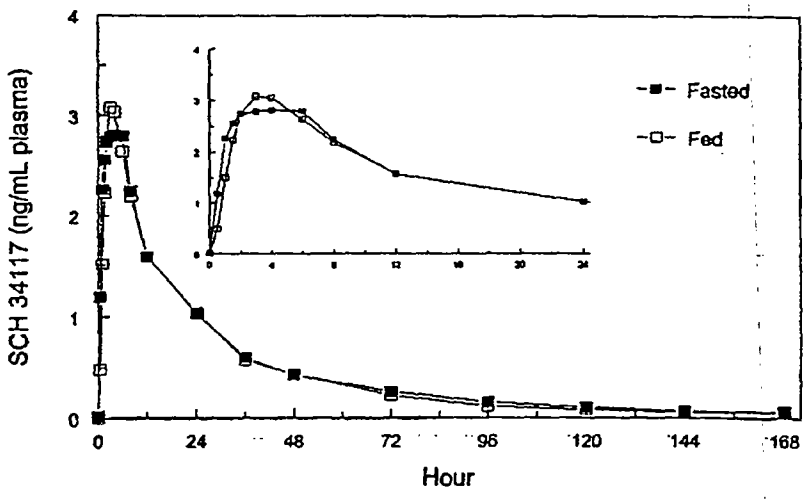
**RESULTS**

**Clinical Pharmacology:** The mean (%CV) pharmacokinetic parameters of SCH 34117 following oral, single-dose administration of 7.5 mg under fed and fasted conditions is presented below:

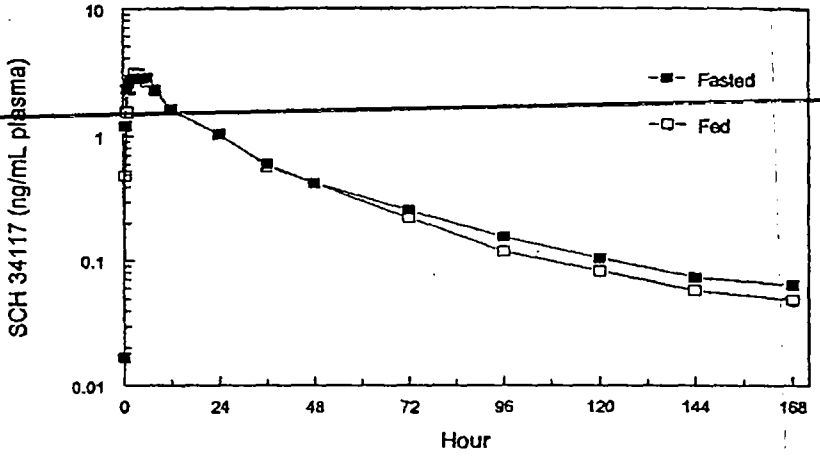
| | N | FED | FASTED |
|---|---|---|---|
| Parameter (Unit) | | Mean (% CV) | Mean (%CV) |
| Cmax (ng/mL) | 18 | 3.53 (33) | 3.30 (36) |
| AUC(tf)(ng·hr/mL) | 18 | 73.8 (81) | 77.5 (92) |
| AUC(I)(ng·hr/mL) | 17 | 62.5 (40) | 63.5 (45) |
| Tmax (hr) | 18 | 4.75 (108) | 3.36 (60) |
| t1/2 (hr) | 18 | 20.9 (86) | 22.0 (100) |
| tf (hr) | 18 | 75.3 (41) | 78.0 (39) |

The following figure describes the mean plasma profiles of DCL with/without food.

Linear:linear




Log:linear




The estimates of bioavailability (log-transformed) of SCH 34117 under fed condition relative to that after fasting is presented below:

| Parameter | Point Estimate (%)[c] | 90% Confidence Interval[d] |
|---|---|---|
| Cmax (ng/mL)[a] | 108 | 99-118 |
| AUC (tf) (ng·hr/mL)[a] | 100 | 93-107 |
| AUC (I) (ng·hr/mL)[b] | 101 | 93-108 |

a: n=18
b: n=17
c: Ratio of the mean value for fed vs fasted. $\alpha$=0.05 (two-tailed)
d: $\alpha$=0.05 (two-tailed)

**Safety:** Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects. Overall, 9 of 18 (50%) subjects reported treatment-emergent adverse events. The most frequently reported adverse event was headache. All reported adverse events were mild in severity except one which was reported as moderate. No subject discontinued participation in the study due to adverse events and no intervention was required to treat any adverse event.

**CONCLUSIONS:**

- Single oral doses of desloratadine 7.5 mg administered under fed and fasted conditions were safe and well tolerated.
- Food had no effect on the oral bioavailability of desloratadine.

**REVIEWER'S COMMENTS:**

The sponsor conducted the study appropriately. The data is acceptable.



APPEARS THIS WAY
ON ORIGINAL

Appendix 2. Proposed labeling

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

Appendix 3. Assay

**Analysis**

The analytical methods used in pharmacokinetic studies conducted in support of this application are summarized in the following table. Plasma concentrations for DL were analyzed [redacted] method with a lower limit of quantitation of [redacted] ng/mL (Studies 197-248, C98-013, C98-214 and C98-215). For the remaining studies plasma concentrations for DL and 3-OH DL were analyzed using [redacted] method with a lower limit of quantitation of [redacted] pg/mL.

**Reviewer's comment on the analysis:**
The analytical method employed in the present submission is appropriate and acceptable. For analytical performance in individual study, please refer to the individual study review. For pre-study validation, please refer to the following "summary of the pre-study validation".

Redacted 1

pages of trade secret and/or confidential commercial information

Appendix 4. Clinical Pharmacology and Biopharmaceutics Study Summary

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 1 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| C98-097-01 | Oral | Open-label, single-dose study<br><br>$^{14}$C-(Carbon labeled) DL capsule | 10 mg | 38101-134 (10 mg) Schering, NJ, USA 3/98 | 6 | | 4/28/98[a] | • DL is extensively metabolized since unchanged DL AUC is a 8% of plasma total radioactivity AUC.<br>• Drug-derived radioactivity was eliminated into the feces (47%) and urine (41%). Plasma, urine and fecal metabolite profiles (Subject Nos. 1-4 and 6) showed that DL was metabolized by hydroxylation and glucuronidation at the 3-position. Subject No. 5 appeared to metabolize DL more slowly and excreted a relatively high percentage of the dose as unchanged drug in urine and feces.<br>• Dihydroxy-DL glucuronides excreted in urine accounted for an additional 5.7% of the dose excreted.<br>• All DL metabolites detected or identified were similarly characterized in another study in male healthy volunteers who received an oral dose of $^{14}$C-loratadine. | |

a: Protocol amendment sent on 2/9/99.

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 2 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| C98-215-01 | Oral | Randomized, Open-label, two-way crossover study<br>DL Tablet | 7.5 mg | 38833-140 Schering, NJ, USA 3/98 | 18 | | 5/20/98 | • Food (high fat high caloric meal) had no effect on the oral bioavailability of DL.<br>• Single oral doses of DL 7.5 mg administered under fed and fasted conditions were safe and well tolerated. | |

a: Protocol amendment sent on 2/9/99.

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 3 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| I97-248-01 | | Randomized, double-blind, parallel group, placebo-controlled rising single-dose study. | | | 48[a] | | NA[c] | • The peak plasma DL concentrations (Cmax) were observed between 1.7 and 3.6 hours after dosing.<br>• The mean Cmax and AUC (tf) of DL ranged from 0.8 to 8.36 ng/mL and 9.77 to 158 ng·hr/mL, respectively, for doses between 2.5 and 20 mg.<br>• Plasma concentrations of DL increased with increasing doses.<br>• Single oral doses of DL 2.5, 5, 10 and 20 mg were well tolerated when administered to healthy male subjects. | |
| | Oral | DL Tablet | 2.5, 5, 10 and 20 mg | 51848-102 (2.5 mg) Schering, NJ USA 8/97<br>51848-104 (10 mg) Schering, NJ USA 8/97 | | | | | |
| | Oral | Placebo Tablet | 0 mg | 38833-003 (0 mg) Schering, NJ USA 8/97 | | | | | |

a: Twelve subjects at each dose level (2.5, 5, 10 and 20 mg) were randomized to receive DL or placebo in a 5:1 ratio.
b: This study was not amended to the IND. The final study report was sent for information to IND on 3/9/98.
c: NA-not applicable.

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 4 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| C98-013-01 | Oral | Randomized, double-blind (within dose group), placebo-controlled, parallel group, rising multiple-dose study<br>DL Tablet | 5, 7.5, 10 and 20 mg | 38833-075 (2.5 mg) Schering, NJ, USA 11/97<br>38833-077 (5 mg), Schering, NJ, USA 11/97<br>38833-079 (10 mg) Schering, NJ, USA 11/97<br>38833-072 (placebo), Schering, NJ, USA 11/97 | 49[a] | | 4/14/98 | • Following single-dose administration peak DL concentrations were observed between 3 and 6 hours.<br>• Cmax and AUC (0-24 hour) values exhibited moderate intrasubject variability.<br>• There was a dose related increase in DL Cmax and AUC (I) between 5 and 20 mg.<br>• Steady state was attained by Day 14 (10 doses) following once daily dosing with 5, 7.5 10 and 20 mg doses. Plasma DL concentrations exhibited high intersubject variability primarily in the 5 and 10 mg dose groups as evidenced by %CV for Cmax and AUC between 73-107%.<br>• The harmonic mean t1/2 and apparent total body clearance values at steady state were similar to those following a single-dose, suggesting that the elimination kinetics of DL were not altered following multiple dosing.<br>• Multiple oral doses of DL between 5 and 20 mg administered to healthy adult male volunteers were safe and well tolerated. | |

a: Forty nine subjects were enrolled and 48 subjects completed the study. One subject discontinued for personal reasons. Within each dose group 12 subject were randomized to receive desloratadine or placebo in a 5:1 ratio.

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 5 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| C98-214-01 | Oral | Randomized, Open-label, single-dose, four-way crossover study<br><br>DL Tablet | 5, 7.5, 10 and 20 mg | 38833-142 (5 mg) Las Piedras, PR 3/98<br><br>38833-140 (7.5 mg) Schering, NJ, USA 3/98<br><br>38833-144 (10 mg) Las Piedras, PR 3/98 | 20 | | 5/27/98 | • No dose-related changes in the absorption rate of DL based on the similarity of Tmax (4 hours) over the dose range 5 to 20 mg.<br>• The intersubject variability (%CV) was less than 35% for Cmax, however, it was significantly higher (92-127% CV) at all dose levels for AUC.<br>• Linear regression analysis of dose and log transformed AUC (tf) and Cmax showed that none of the slopes were statistically significantly different from 1 and the power to detect a 20% difference in slope was ≥92%. Dose proportionality was also supported by the results of an analysis of variance of log-transformed dose adjusted (to 1 mg) Cmax and AUC values which showed no statistically significant differences over the dose range 5 to 20 mg. | |

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 6 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| C98-352-01 | | Randomized, multiple dose, third-party blind, placebo-controlled, two-way crossover study | | | 24 | | NA | • The increases in Cmax[b] and AUC[b] (45% and 39%, respectively) of DL and 43% and 72% for 3-OH DL were considered not to be clinically relevant.<br>• The metabolism of DL and 3-OH DL may be partially mediated by CYP 3A4. | |
| | Oral | DL | 7.5 mg | 38833-140 Kenilworth, NJ, USA 3/98 | | | | | |
| | Oral | Placebo Tablet | 0 mg | 38833-072 Las Piedras, PR 11/97 98P0579E | | | | | |
| | Oral | Ketoconazole Tablet[a] | 200 mg | Janssen Pharmaceuticals, Inc. | | | | | |

a: Material purchased by Investigator from commercial source.
b: Excludes 2 subjects (Nos. 10 and 11) with anomalous pharmacokinetic behavior.

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 7 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| C98-353-01 | | Randomized, multiple dose, third-party blind, placebo controlled, two-way crossover study | | | 24 | | | • The increase in Cmax and AUC (24% and 14%, respectively) of DL and 43% and 40% for 3-OH DL were considered not to be clinically relevant.<br>• The metabolism of DL and 3-OH DL may be partially mediated by CYP 3A4. | |
| | Oral | DL Tablet | 7.5 mg | 38833-140 Kenilworth, NJ USA 3/98 | | | | | |
| | Oral | Placebo Tablet | 0 mg | 38833-072 Las Piedras, PR 11/97 | | | | | |
| | Oral | Erythromycin Tablet[a] | 250 mg | Abbott | | | | | |

a: Material purchased by Investigator from commercial source.

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 8 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| C98-354 | Oral | Open-label, single-dose, parallel group study<br>DL Tablet | 7.5 mg | 38833-140, Kenilworth, NJ USA 3/98 | 20 | | | • There were no significant differences in DL pharmacokinetics between subjects with varying degrees of hepatic dysfunction.<br>• Subject with hepatic dysfunction exhibited greater exposure (up to 2.4 fold) than normal subjects.<br>• From simulation studies it was concluded that no dosage adjustment is required because hepatic dysfunction subjects were indistinguishable from normal volunteers with long half-lives and the exposure was predicted not to exceed that achieved following multiple doses of DL 45 mg. | |

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 9 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| C98-356-01 | Oral | Open-label, parallel group, multiple-dose, study<br>DL Tablet | 7.5 mg | 38833-140<br>Kenilworth, NJ<br>USA<br>3/98 | 48 | | | • AUC and Cmax for DL were 3% and 10% respectively, higher in females than males. The 3-OH DL values were increased by 48% and 45%, respectively.<br>• AUC and Cmax for DL were 32% and 18%, respectively higher in Blacks compared with Caucasians, while for the 3-OH metabolite there were 10% lower.<br>• Based on these changes no dosage adjustment is required for gender or race. | |

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 10 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| C98-357-01 | | Randomized, double-blind, multiple-dose, placebo controlled, two-way crossover study | | | 24 | | | • DL was absorbed with a median Tmax of 5 hours and was slowly eliminated.<br>• There was no correlation between the slower metabolism of DL of 5 subjects and their predicted phenotype for CYP 2D6 and CYP 2C19. | |
| | Oral | DL Tablet | 7.5 mg | 38833-140, Kenilworth, NJ USA 3/98 | | | | | |
| | | Placebo Tablet | 0 mg | 38833-072 Las Piedras, PR 11/97 | | | | | |

Firm **Schering-Plough Corporation**
Drug **Desloratadine tablet**
NDA

**ATTACHMENT A**
(Table 11 of 13)

**BIOPHARMACEUTICS STUDY SUMMARY**

| Study Number | Route | Study Designs Dosage Form(s) | Dose (mg) | Batch No. Plant/Date Manufactured | No. of Subj. | IND No. | Sub-mission Date | Applicant Conclusion | Prev. Agency Resp. on Study or Protocol with Date of |
|---|---|---|---|---|---|---|---|---|---|
| P00117 | Oral | Randomized, open-label, multiple-dose, 3-way crossover study<br>DL Tablet | 5 mg | 38833-142 (5 mg), Las Piedras, PR 3/98 | 24 | | | • The bioavailability (AUC) of DL, 3-OH DL and 3-OH DL glucuronide were equivalent following oral administration of 5 mg DL and 10 mg loratadine; the relative bioavailability based on AUC was 95, 100 and 102%, respectively.<br>• The administration of DL 7.5 mg results in a higher bioavailability of DL compared with administration of 10 mg loratadine.<br>• DL, 3-OH DL and 3-OH DL glucuronide Cmax and AUC values appeared dose-proportional following administration of 5 and 7.5 mg DL.<br>• 3-OH DL was extensively glucuronidated; exposure to 3-OH DL glucuronide was approximately 22-fold higher than to 3-OH DL. | |
| | | | 7.5 mg | 38833-(7.5 mg) Kenilworth, NJ, USA 3/98 | | | | | |
| | | Loratadine[a] Tablet | 10 mg | | | | | | |

a: Commercial product purchased by the Investigator.