



(and norfluoxetine) administered with DL relative to Fluoxetine alone, were expressed as the ratio of two treatments for log-transformed C<sub>max</sub> and AUC values. Confidence intervals for this difference and the power to detect a 50% difference between treatment means for a  $\alpha$  level of 0.05 (two-tailed) were also computed. The primary pharmacokinetic parameters were examined for extreme values by reviewing the studentized residuals to see if the absolute value of any residual exceeded 3.

### **Pharmacodynamics**

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 35 maximum ventricular rate, PR, QRS, QT, and QTc intervals.

ECGs were obtained at Screening, on Day -1 at approximately 8 AM, 9 AM, 9:30 AM, 10 AM, 11 AM, 12 PM, 1 PM, 2 PM, 4 PM, 6 PM, 12 AM (midnight), and daily during the treatment phase (approximately two hours after the AM morning dose). Additionally, ECGs were obtained prior to blood sample collections at (zero hour) and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after the 8 AM dose on Day 35 of the treatment period.

### **Pharmacodynamic Analysis**

The primary pharmacodynamic parameter for this study is the difference between Day 35 maximum ventricular rate and PR, QRS, QT, and QTc intervals and baseline (Day -1) maximum ventricular rate and PR, QRS, QT, and QTc intervals.

This difference was analyzed using a linear model extracting source of variation due to treatment. The following pairwise comparisons were performed at the 0.05 level of significance using two-sided tests.

- DL plus Fluoxetine vs. DL,
- DL plus Fluoxetine vs. Fluoxetine.

Ninety-five percent CIs for the comparisons of pairs of treatments were computed. Descriptive statistics for maximum ventricular rate and PR, QRS, QT, and QTc intervals are provided for baseline, Day 35 and Day 35 change from baseline.

Additional pharmacodynamic endpoints include the following:

- Area under the QTc intervals versus time curve (AUC) at baseline and Day 35 of treatment.
  - AUC for QTc was calculated for each subject at baseline using values collected on Day -1 and values collected on Day 35 of treatment. Time 0-10 hours was the common time interval on Day -1 and Day 35.
  - Summary statistics were tabulated by treatment group for baseline AUC, Day 35 of treatment AUC and the changes of AUC (Day 35 AUC-baseline AUC). The change was analyzed using a linear model extracting source of variation due to treatment.
- Difference between the maximum QTc on Day 35 and minimum QTc at baseline.
  - Summary statistics were tabulated by treatment group for the minimum at baseline and the difference from the maximum on Day 35. The changes in QTc (Day 35 maximum - baseline minimum) were analyzed using a linear model extracting source of variation due to treatment

## RESULTS

### Analytical Method

#### In study Validation Results

**Table 2.** In-study validation information for DL, 3-OH DL, Fluoxetine and norfluoxetine

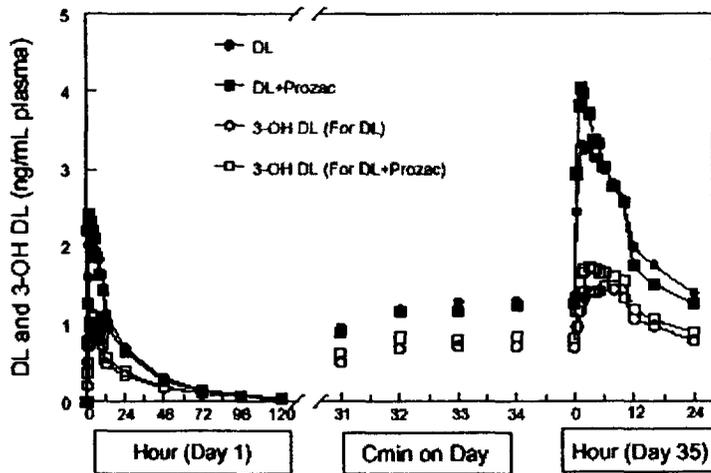
	<i>DL</i>	<i>3-OH DL</i>	<i>Fluoxetine</i>	<i>Norfluoxetine</i>
<b>Linearity</b>	Satisfactory: Standard	Satisfactory: Standard	Satisfactory:	Satisfactory:
<b>Accuracy</b>	Satisfactory:	Satisfactory:	Satisfactory:	Satisfactory:-
<b>Precision</b>	Satisfactory:	Satisfactory:	Satisfactory:	Satisfactory:
<b>Specificity</b>	Satisfactory: submitted	Satisfactory: submitted	Satisfactory: submitted	Satisfactory: submitted

### Pharmacokinetic Results

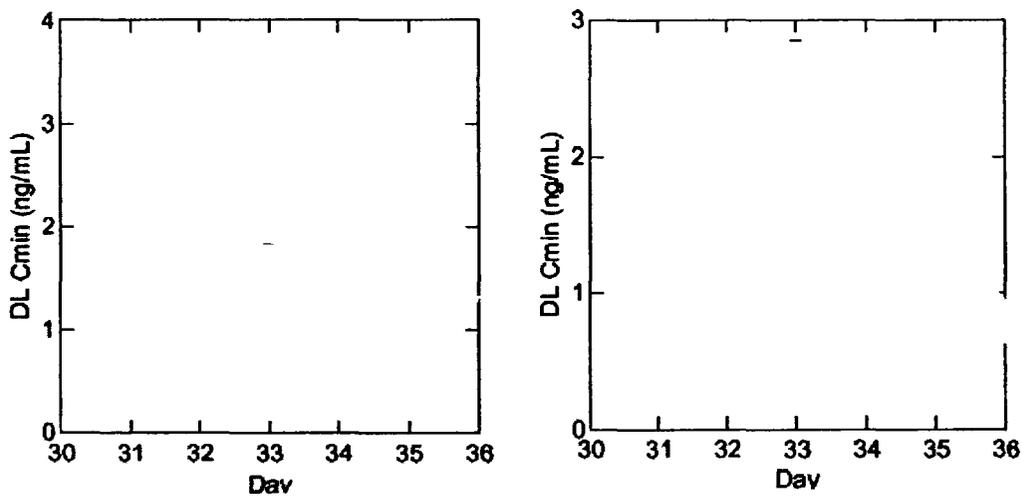
#### DL and 3-OH DL

All 54 subjects (39 males and 15 females) completed the study. None was identified as slow metabolizers of SCH 34117, based on their AUC ratio values (3-OH DL to DL ratio >10%). The mean plasma concentration-time profiles for DL and its metabolite administration of the treatments are shown in Figures 1. Plasma DL and 3-OH DL samples were collected on Days 31, 32, 33, 34 and 35 prior to dosing to determine if steady-state conditions were reached. The relationship between trough DL or 3-OH DL concentration (C<sub>min</sub>) and day was determined using a smoothing algorithm<sup>2</sup>. There was no trend of increasing concentrations between Days 33-35. This suggests that steady state for DL or 3-OH DL had been attained on Day 33 (5<sup>th</sup> dose of DL from Day 29) (Figure 2).

The mean pharmacokinetic parameters for DL and its metabolite are summarized in Table 3. The mean (arithmetic) C<sub>max</sub> value of DL increased by 18% with co-administration of Fluoxetine compared to DL alone however, Fluoxetine had no effect on AUC of DL (Figures 1,3,4 and Table 3),. The corresponding mean parameters of 3-OH DL increased by 14-18% with co-administration of Fluoxetine (Figures 3,4 and Table 3).



**Figure 1.** Mean DL and 3-OH DL plasma concentration-time profile following single and multiple administration of Clarinex 5 mg tablets with and without Prozac.

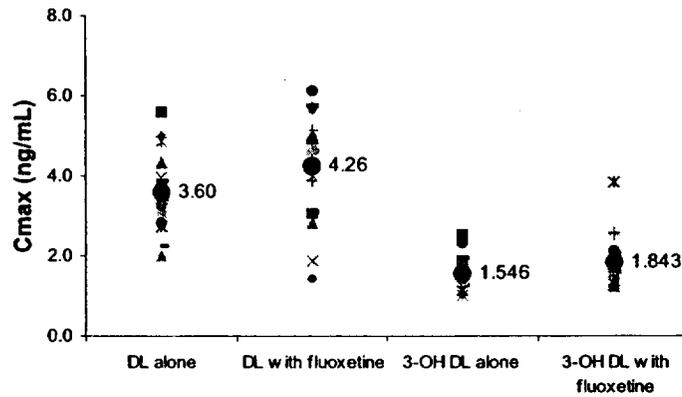


**Figure 2.** Relationship between individual DL Cmin and day following administration of Clarinex 5 mg without (left panel) and with (right panel) co-administration of Fluoxetine.

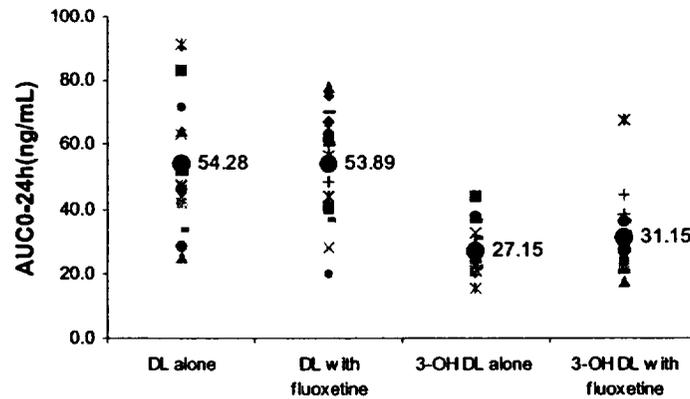
**Table 3.** Mean (CV%) pharmacokinetic parameters of DL and 3-OH on Day 35 following multiple administration of Clarinex 5mg with and without Fluoxetine

Parameter	Desloratadine				3-OH DL			
	DL with placebo		DL with Fluoxetine		DL with placebo		DL with Fluoxetine	
	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV
C <sub>max</sub> <sup>a</sup>	3.6	26	4.25	32	1.57	26	1.86	34
T <sub>max</sub> <sup>a</sup>	2.42	50	1.83	61	5.11	45	4.08	62
AUC(0-24h) <sup>a</sup>	54.3	36	53.9	30	27.2	26	31.1	36
AUC(0-24h)ratio <sup>a</sup>					56.8	43	32.7	58

a: Unit: C<sub>max</sub>-ng/mL; AUC-ng-hr/mL; T<sub>max</sub>-hr, AUC(tf) ratio (metabolite-to-parent)-%



**Figure 3.** Individual DL and 3-OH DL C<sub>max</sub> values on Day 35 following multiple administration of Clarinex 5mg tablets with and without Fluoxetine. Data level represent mean values.



**Figure 4.** Individual DL and 3-OH DL AUC<sub>0-24h</sub> values on Day 35 following multiple administration of Clarinex 5mg tablets with and without Fluoxetine. Data level represent mean values.

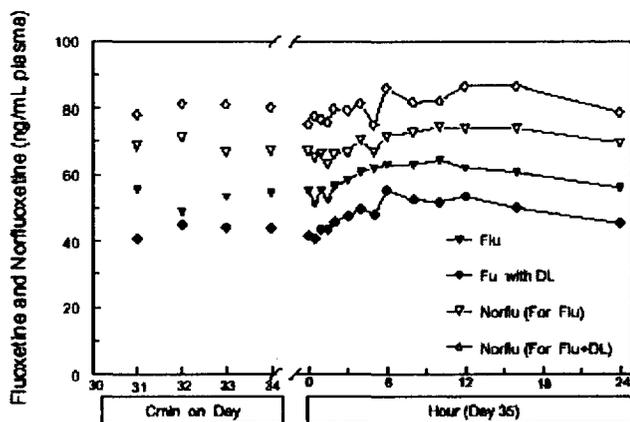
The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL, its metabolite with and without Fluoxetine are presented in Table 4. The point estimates (ratios) for AUC(I) and Cmax for DL and its metabolite indicate that co-administered of Fluoxetine with Clarinex 5 mg tablets caused increases in Cmax (15%) of DL and Cmax (17%) and AUC (13%) of 3-OH DL. According to the sponsor, these increments are clinically insignificant, suggesting that DL is not a substrate of CYP2D6. However, 90% CI applied to Cmax and AUCt were out of the 80-125% bioequivalence guideline.

**Table 4.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL, 3-OH DL with and without Fluoxetine

Parameter	(DL with flu) / (DL with PL)		(DL with flu) / (DL with PL)	
	Ratio	90% CI	Ratio*	90% CI
	DL		3-OH DL	
Cmax	115	95-139	117	100-136
AUC(0-24h)	100	82-123	113	96-132

### Fluoxetine and norfluoxetine

The relationship between trough Fluoxetine or norfluoxetine concentration (Cmin) and day was determined using a smoothing algorithm. There was no trend of increasing concentrations between Days 31-35 (Figure 5). This suggests that steady state for Fluoxetine or norfluoxetine had been attained on Day 31.



**Figure 5.** Mean plasma Fluoxetine concentration-time profile following multiple administration of with and without Clarinex 5 mg tablets.

The mean pharmacokinetic parameters of Fluoxetine and norfluoxetine are summarized in Table 5. Plasma Fluoxetine and norfluoxetine concentrations on Day 35 reflected moderate inter-subject variability as shown by %CV ranging between 19 to 56% for Cmax and AUC values.

**Table 5.** Mean (CV%) pharmacokinetic parameters of Fluoxetine and norfluoxetine on Day 35 following multiple administration of Clarinex 5mg with and without Fluoxetine

Parameter	Fluoxetine (Flu)				Norfluoxetine			
	Flu with placebo (n=17)		Flu with DL (n=18)		Flu with placebo (n=17)		Flu with DL (n=18)	
	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV
Cmax <sup>a</sup>	70.9	54	61.5	34	82.9	28	99.4	19
Tmax <sup>a</sup>	7.89	50	7.56	42	8.39	77	7.58	74
AUC(0-24h) <sup>a</sup>	1442	56	1191	32	1719	31	1981	22
AUC(0-24h)ratio <sup>a</sup>					145	43	184	41

a: Unit: Cmax-ng/mL; AUC-ng-hr/mL; Tmax-hr, AUC(tf) ratio (metabolite-to-parent)-%

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for Fluoxetine and its metabolite with and without Clarinex DL are presented in Table 6. Fluoxetine Cmax and AUC were reduced by 13% and 17%, respectively during co-administration with DL. The corresponding mean parameters of norfluoxetine increased by 22% and 18%, respectively, with co-administration of DL with Fluoxetine. According to the sponsor, these changes are considered to be pharmacokinetically and clinically insignificant. However, 90% CI for both Cmax and AUC point estimates, were out of the 80-125 BE guideline.

**Table 6.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of Fluoxetine and norfluoxetine with and without DL

Parameter	(Flu with DL) / (Flu with PL)		(Flu with DL) / (Flu with PL)	
	Ratio	90% CI	Ratio <sup>a</sup>	90% CI
	Fluoxetine		Norfluoxetine	
Cmax	91	72-115	122	107-139
AUC(0-24h)	89	69-113	118	101-136

### Pharmacodynamic Results

The mean differences between the maximum PR, QRS, QT, and QTc intervals and ventricular rate observed on Day 35 and baseline (Day -1) following DL plus Fluoxetine, DL alone or Fluoxetine alone are presented in Table 6.

**Table 6.** Mean<sup>b</sup> Difference Between Maximum ECG Parameters on Day 35 and Baseline (Day -1) for DL in Combination With Fluoxetine, DL Alone and Fluoxetine Alone (n=18/Group)

Parameter	DL Plus Flu	DL Plus Placebo	Placebo Plus Flu	Pooled Standard Deviation	p-Value DL Plus Flu vs. DL Plus PL	p-Value DL Plus Flu vs. Placebo Plus Flu
PR <sup>a</sup>	0.2	3.1	0.4	8.5	0.31	0.94
QRS <sup>a</sup>	-0.2	1.1	0.2	4.3	0.36	0.76
QT <sup>a</sup>	-0.7	-8.4	3.8	22.1	0.30	0.55
QTc <sup>a</sup>	8.2	6.9	6.4	10.6	0.71	0.61
Ventricular Rate <sup>a</sup>	4.7	7.3	-1.3	9.2	0.40	0.055

a: Units: PR, QRS, QT, QTc=msec; ventricular rate=bpm.

b: LS means and pairwise comparisons extracting source of variation due to treatment.

The results of the statistical analysis (Table 6) for PR, QRS, QT, and QTc show that there were no statistically significant differences between the combination of DL with Fluoxetine and DL alone. Similar, results were obtained when DL in combination

with Fluoxetine was compared with Fluoxetine alone. According to the sponsor, there was a marginally significant difference (p=0.055) in ventricular rate between DL in combination with Fluoxetine and Fluoxetine alone. The sponsor also stated that while there was not an equal distribution of males and females (38 males and 16 females) in each group, there appears to be no sex differences in the ECG parameters (Table 7).

**Table 7. Subgroup Analysis (By Sex) of the Mean Difference Between the Maximum ECG Parameters on Day 35 and Baseline (Day -1) Following DL/Placebo, DL/Flu or Flu/Placebo**

Parameter	Mean Difference Between Day 35 and Baseline (Day -1)			p-Value	
	DL 5 mg Plus Flu	DL 5 mg Plus Placebo	Placebo Plus Flu	DL/Flu vs. DL/PL	DL/ Flu vs. Placebo/Flu
<b>Males</b>					
PR	0.0	4.3	2.3	0.25	0.54
QRS	-0.9	1.5	-0.7	0.18	0.89
QT	-1.2	6.5	5.3	0.58	0.50
QTc	8.0	4.5	4.3	0.41	0.39
Ventricular Rate	5.5	7.2	1.5	0.65	0.07
<b>Females</b>					
PR	0.8	0.0	-3.3	0.81	0.21
QRS	1.6	0.0	2.0	0.50	0.86
QT	0.8	-14	0.7	0.24	0.99
QTc	8.8	13.2	10.7	0.49	0.76
Ventricular Rate	2.6	7.6	-0.8	0.40	0.54

Units: PR, QRS, QT, QTc=msec; ventricular rate=bpm.

The QTc intervals were also assessed by examining the mean difference between the maximum QTc at post-baseline and minimum QTc interval and the mean difference between the area under the QTc curve (AUC[0-10 hr] QTc) on Day 35 and baseline. None of the parameters showed any statistically significant differences between treatment groups (Table 8).

A listing of QTc intervals  $\geq 431$  msec for males and  $\geq 451$  msec for females at baseline and during treatment are shown in Table 9.

**Table 8. Statistical Evaluation of the Mean Difference Between the Maximum QTc on Day 35 and Minimum at Baseline and the Mean Change in AUC(0-10 hr) QTc on Day 35 and Baseline**

Parameter	DL 5 mg Plus Flu <sup>a</sup>	DL 5 mg Plus Placebo <sup>b</sup>	Placebo Plus Flu <sup>c</sup>	Pairwise Comparisons	
				A/B	A/C
Max QTc Day 35-Min QTc Baseline	40.1	36.9	33.7	0.45	0.14
AUC QTc (Day 35-Baseline)	63.1	68.4	17.9	0.87	0.15

a: DL 5 mg plus fluoxetine.

b: DL 5 mg plus placebo.

c: Placebo plus fluoxetine.

Table 9. Subjects with QTc > 450 msec for females and QTc > 430 msec for males

OBS	treatment	patno	QTc		Gender
			BASEMAX	POSTMAX	
1	DL5MG+PROZAC	000063			F
2	PROZAC	000040			F
3	PROZAC	000041			F
4	PROZAC	000044			F
5	PROZAC	000046			F
6	PROZAC	000062			F
7	DL5MG+PROZAC	000003			M
8	DL5MG+PROZAC	000004			M
9	DL5MG+PROZAC	000007			M
10	DL5MG+PROZAC	000013			M
11	DL5MG+PROZAC	000014			M
12	DL5MG+PROZAC	000029			M
13	DL5MG+PROZAC	000033			M
14	DL5MG+PROZAC	000036			M
15	DL5MG	000001			M
16	DL5MG	000002			M
17	DL5MG	000009			M
18	DL5MG	000017			M
19	DL5MG	000019			M
20	DL5MG	000021			M
21	DL5MG	000028			M
22	DL5MG	000030			M
23	PROZAC	000005			M
24	PROZAC	000008			M
25	PROZAC	000016			M
26	PROZAC	000018			M
27	PROZAC	000023			M
28	PROZAC	000036			M

## CONCLUSIONS

- Co-administration of Fluoxetine with DL caused increases in Cmax (15%) of DL and Cmax (17%) and AUC (13%) of 3-OH DL.
- Co-administration of Fluoxetine with DL reduce Fluoxetine Cmax and AUC by 9% and 11%, respectively and increased norfluoxetine Cmax and AUC 22% and 18%, respectively.
- There was no treatment effect in the difference between baseline maximum and Day 35 maximum for PR, QRS, QT, and QTc intervals and ventricular rate for DL in combination with Fluoxetine compared with DL alone.
- For the comparison of DL in combination with Fluoxetine and Fluoxetine alone there were no statistically significant changes in the ECG parameters except for ventricular rate which was marginally significant.

## GENERAL COMMENTS

- No elderly subjects were included in this study. The subjects were between the ages of 22 and 49 years (mean=37.1 years).
- Co-administration of fluoxetine with DL caused increases in mean Cmax (18%) of DL and mean Cmax (18%) and mean AUC (14%) of 3-OH DL. According to the sponsor, this change appears to be clinically insignificant. Although 90% CI for the DL PK parameters Cmax (95-135) were out of the guideline for BE, overall this reviewer is of the opinion that fluoxetine does not affect the PK of DL and its metabolite and viseversa. These findings are most likely due to the high variability of the data.

- Co-administration of fluoxetine with DL reduce fluoxetine Cmax and AUC by 13% and 17%, respectively and increased norfluoxetine Cmax and AUC 22% and 18%, respectively. According to the sponsor, this change appears to be clinically insignificant. This reviewer agrees with the sponsor's statement.
- For the comparison of DL in combination with fluoxetine and fluoxetine alone there were no statistically significant changes in the ECG parameters .
- There was a marginally significant difference ( $p=0.055$ ) in ventricular rate between DL in combination with fluoxetine (mean difference day 35 and baseline= 4.7 bpm) compared to fluoxetine alone (mean difference day 35 and baseline=-1.3 bpm). The clinical relevance of this finding should be evaluated by the medical reviewer.
- No poor metabolizers were identified in this study.

**APPEARS THIS WAY  
ON ORIGINAL**

---

**"EVALUATION OF THE PHARMACOKINETICS AND  
ELECTROCARDIOGRAPHIC PHARMACODYNAMICS OF DL WITH  
CONCOMITANT ADMINISTRATION OF AZITHROMYCIN"**

**Name of Sponsor:** Schering-Plough Corporation  
**Included Protocols:** P01381  
**Development Phase of Study:** I  
**Study Initiation Date:** Feb 18, 2000  
**Study Completion Date:** Mar 9, 2000  
**Sponsor's Project Director:** Christopher Banfield, Ph.D.  
**Sponsor's Project Physician:** Mark Marino, M.D.  
**Date of the Report:** Mar 15, 2000  
**Clinical Documentation  
Accession Number:** 1614606

---

**OBJECTIVE**

- To evaluate the effect of co-administration of desloratadine in combination with fexofenadine in combination with azithromycin on the pharmacokinetics of SCH 34117 (desloratadine or DL) and its' metabolite, SCH 45581 (3-hydroxydesloratadine or 3-OH DL) in healthy adult subjects.

**SUBJECTS**

A total of 90 subjects (45 males and 45 females) were enrolled into and completed this study. They had ages ranging between 19 and 46 years, inclusive (mean=34.8 years), heights of 150.5-198.1 cm (mean=171.7 cm), weights of 47.7-104.6 kg (mean=72.6 kg) and BMI of 19-27 (mean=24.5). There were a total of 80 Caucasians (89%) and ten Blacks (11%) subjects in this study. Subjects of comparable age, weight, and BMI were enrolled across the treatment group. The distribution of subjects by race and sex was similar across the treatment groups.

**STUDY DESIGN AND TREATMENT ADMINISTRATION**

Ninety healthy adults completed this randomized, open-label, parallel group, third-party blind multiple-dose study. Subjects were randomized to:

- Group A (DL with AZ):** 1 x 5-mg DL tablet administered once daily (AM) for 7 days. Concurrent administration of azithromycin (AZ) 500 mg (2 x 250 mg capsules) orally on Day 3 (AM) followed by once daily 250 mg (1 x 250 mg capsule) on Days 3-7 (AM); n=18 (9M, 9F).
- Group B (DL with Placebo):** 1 x 5-mg DL tablet administered once daily (AM) for 7 days. Concurrent administration of placebo (2 tablets) orally on Day 3 (AM) followed by once daily placebo (1 tablet) on Days 3-7 (AM); n=18 (9M, 9F).
- Group C (AZ with Placebo):** 1 x DL placebo tablet administered once daily (AM) for 7 days. Concurrent administration of azithromycin 500 mg

(2 x 250 mg capsules) orally on Day 3 (AM) followed by once daily 250 mg (1 x 250 mg capsule) on Days 3-7 (AM); n=18 (9M, 9F).

**Group D (FX with AZ):** 1 x 60-mg fexofenadine (FX) capsule administered twice daily (AM/PM) for 7 days. Concurrent administration of azithromycin 500 mg (2 x 250 mg capsules) orally on Day 3 (AM) followed by once daily 250 mg (1 x 250 mg capsule) on Days 3-7 (AM); n=18 (9M, 9F).

**Group E (FX with Placebo):** 1 x 60-mg fexofenadine capsule administered twice daily (AM/PM) for 7 days. Concurrent administration of placebo (2 tablets) orally on Day 3 (AM) followed by once daily placebo (1 tablet) on Days 3-7 (AM); n=18 (9M, 9F).

Subjects received their dose with 180 mL of non-carbonated water after a 10-hr fast.

### FORMULATION

The Clarinex 5mg bilayer tablets were manufactured by SPRI, Kenilworth, NJ, USA. The following formulation (Table 1) was used:

Table 1. Formulations for Clarinex 5mg Tablets

<b>Strength</b>	5 mg DL
<b>Formula. No.</b>	3408
<b>Batch No.</b>	38833-147
<b>FMR No.</b>	99592D09
<b>Manf. Date</b>	4/23/98
<b>Manf. Site</b>	Kenilworth, NJ
<b>Batch Size (tablets)</b>	<u>          </u>

Formula 3408 is the same as the to-be marketed formulation.

### Dissolution

The dissolution data and specifications are shown below. The batch used in this study was under dissolution specifications.

Method	Specification
<b>Apparatus:</b> USP apparatus II (paddle) <b>Speed:</b> 50 rpm <b>Temperature:</b> 37 °C <b>Medium:</b> 0.1 N HCL <b>Volume:</b> 500 mL	Q=85% at 30 min

Dissolution data for DL tablets 5 mg

Time (Minutes)	Dissolution Profile Results Percent 34117 Dissolved/Dosage Form												
	Avg.	1	2	3	4	5	6	7	8	9	10	11	12
15													
30													
45													
60													

**PHARMACOKINETIC MEASUREMENTS**

**Blood Sampling**

Blood samples (5 mL), for the determination of DL,3-OH DL and fexofenadine concentrations in plasma, were collected prior to dosing (0 hr) on Days 1, 4,5,6 and 7 and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hr following dosing on Day 7. At each time point, an additional 5 mL of blood were obtained for the determination of azythromycin concentrations.

**Analytical Method**

Plasma DL, 3-OH DL fexofenadine and azithromycin concentrations were determined using validated

methods with lower limits of quantitation (LOQ) of ng/mL (linear range: ng/mL) for DL and 3-OH DL, and 1 ng/mL (linear range: ng/mL) for fexofenadine and ng/mL (linear range: ng/mL) for azithromycin.

**SAFETY MEASUREMENTS**

Physical examinations, vital signs, electrocardiograms, and clinical laboratory tests were conducted at Screening and at the conclusion of the study (120 hours post-treatment) for safety evaluation. In addition, routine clinical laboratory safety tests were also monitored prior to treatment administration and vital signs were obtained daily.

**DATA ANALYSIS**

**Pharmacokinetic Data Analysis**

Individual plasma DL (SCH 34117), 3-OH DL (SCH 45581), fexofenadine and azithromycin concentration-time data were used to determine the pharmacokinetic parameters using model-independent methods.

**Statistical Analysis**

The Cmax and AUC values of SCH 34117 (and SCH 45581) or fexofenadine administered with azithromycin relative to SCH 34117 (and SCH 45581) or fexofenadine alone, as well as the Cmax and AUC values of azithromycin administered with SCH 34117 or fexofenadine relative to azithromycin alone, were expressed as the ratio of two treatments for log-transformed Cmax and AUC values. Confidence intervals for this difference and the power to detect a 20% difference between treatment means for a level of 0.05 (two-tailed) were also computed.

**Pharmacodynamics**

The primary pharmacodynamic parameter for this study was the difference between Day 7 maximum ventricular rate, PR, QRS, QT, and QTc intervals and baseline (Day -1) maximum ventricular rate, PR, QRS, QT, and QTc intervals. The electrocardiograph uses the Bazett formula to correct the QT intervals for heart rate.

ECGs were obtained at Screening, on Day -1 at approximately 8 AM, 9 AM, 9:30 AM, 10 AM, 11 AM, 12 PM, 1 PM, 2 PM, 4 PM, 6 PM, 12 AM (midnight), and 8 AM (ie, 24-hours postdose) and daily during the treatment phase (approximately two hours after the AM morning dose). Additionally, ECGs were obtained prior to blood sample collections at (zero hour) and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after the 8 AM dose on Day 7 of the treatment period

### **Pharmacodynamic Analysis**

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 7 maximum ventricular rate, PR, QRS, QT, and QTc intervals. This difference was analyzed using a linear model extracting source of variation due to treatment. The following pairwise comparisons were performed at the 0.05 level of significance:

- A vs. B,
- A vs. C,
- A vs. D,
- D vs. E,
- D vs. C.

where A=DL plus AZ, B=DL plus placebo, C=placebo plus AZ, D=FX plus AZ and E=FX plus placebo. Descriptive statistics for maximum ventricular rate and PR, QRS, QT, and QTc intervals are provided for baseline, Day 7 and Day 7 change from baseline.

Additional pharmacodynamic endpoints include the following:

- Area under the QTc intervals versus time curve (AUC) at baseline and Day 7 of treatment.
  - AUC for QTc was calculated for each subject at baseline using values collected on Day -1 and at Day 7 of treatment. Time 0-10 hours was the common time interval on Day -1 and Day 7.
  - Summary statistics were tabulated by treatment group for baseline AUC, Day 7 of treatment AUC and the changes of AUC (Day 7 AUC-baseline AUC). The change was analyzed using a linear model extracting source of variation due to treatment.
- Difference between the maximum QTc on Day 7 and minimum QTc at baseline.
  - The minimum QTc intervals were obtained for each subject at baseline from 12 QTc values collected on Day -1.
  - Summary statistics were tabulated by treatment group for the minimum at baseline and the difference from the maximum on Day 7. The changes in QTc (Day 7/8 maximum - baseline minimum) were analyzed using a linear model extracting source of variation due to treatment.

## RESULTS

### Analytical Method

#### In study Validation Results

**Table 2.** In-study validation information for DL, 3-OH DL, fexofenadine and azithromycin

	DL	3-OH DL	fexofenadine	Azithromycin
<b>Linearity</b>	Satisfactory: Standard	Satisfactory: Standard	Satisfactory:	Satisfactory:
<b>Accuracy</b>	Satisfactory:	Satisfactory: .	Satisfactory: -	Satisfactory:-
<b>Precision</b>	Satisfactory: )	Satisfactory:	Satisfactory:	Satisfactory:
<b>Specificity</b>	Satisfactory: submitted	Satisfactory: submitted	Satisfactory: submitted	Satisfactory: submitted

### Pharmacokinetic Results

#### DL and 3-OH DL

All 90 subjects (45 males and 45 females) completed the study. None was identified as slow metabolizers of SCH 34117, based on their AUC ratio values (3-OH DL to DL ratio >10%). Nine subjects had measurable pre-dose plasma concentrations of DL (Subject 67), fexofenadine (Subjects 44 and 88) and azithromycin (Subjects 44, 67, 71, 81, 84 and 87) on Day 1. These pre-dose concentrations varied from 1.4 to 146 times the LOQ. According to the sponsor, these pre-dose values on Day 1 are not expected to alter the Day 7 pharmacokinetics and therefore they should not affect the overall conclusions of the study.

The mean plasma concentration-time profiles for DL and its metabolite administration of the treatments are shown in Figures 1. Plasma DL and 3-OH DL samples were collected on Days 4, 5, 6, and 7 prior to dosing to determine if steady-state conditions were reached. The relationship between trough DL or 3-OH DL concentration (C<sub>min</sub>) and day was determined using a smoothing algorithm<sup>2</sup>. There was no trend of increasing concentrations between Days 5-7. This suggests that steady state for DL or 3-OH DL had been attained on Day 5 (Figure 2).

The mean pharmacokinetic parameters for DL and its metabolite are summarized in Table 3. The mean C<sub>max</sub> and AUC values of SCH 34117 increased by 8-19% with co-administration of azithromycin compared to DL alone (Figures 1,3,4 and Table 3). The corresponding mean parameters of 3-OH DL increased by 2-14% with co-administration of azithromycin (Figures 1, 3, 4 and Table 3).

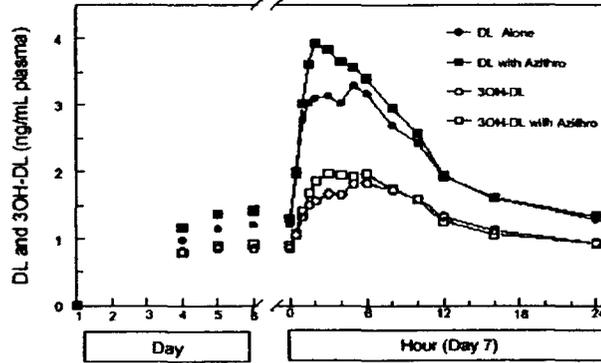


Figure 1. Mean plasma DL and 3-OH DL concentration-time profile following administration of Clarinex 5 mg tablets with and without azithromycin.

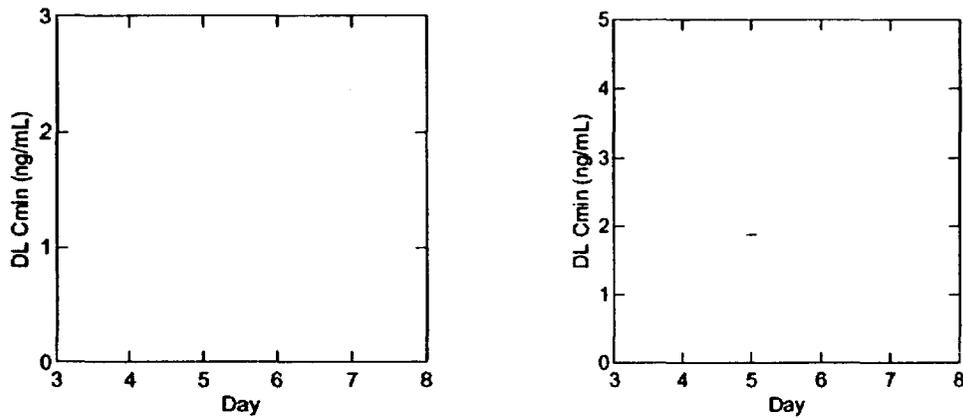
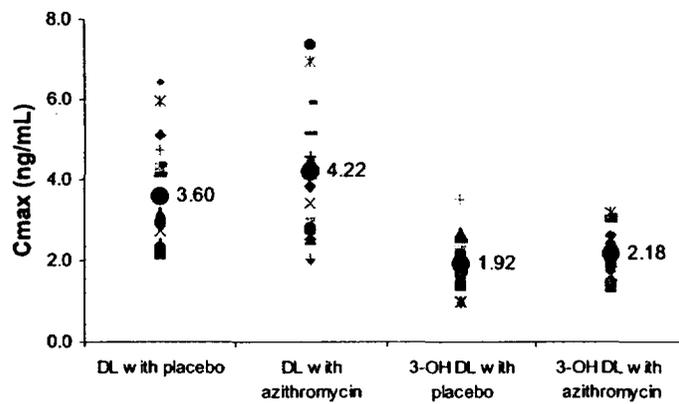


Figure 2. Relationship between individual DL Cmin and day following administration of Clarinex 5 mg without (left panel) and with (right panel) co-administration of azithromycin.

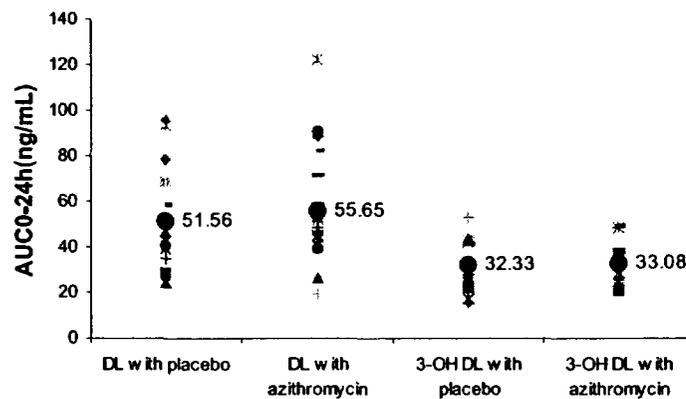
Table 3. Mean (CV%) pharmacokinetic parameters of DL and 3-OH on Day 7 following multiple administration of Clarinex 5mg with and without Azithromycin

Parameter	Desloratadine				3-OH DL			
	DL with placebo (n=18)		DL with Azithromycin (n=18)		DL with placebo (n=18)		DL with Azithromycin (n=18)	
	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV
Cmax <sup>a</sup>	3.6	37	4.3	46	1.92	31	2.18	27
Cmax (Geom mean)	3.39	-	3.9	-	1.8	-	2.11	-
Tmax <sup>a</sup>	3.75	48	3.2	57	4.8	38	4.11	38
AUC(0-24h) <sup>a</sup>	51.6	41	55.6	47	32.3	30	33.1	26
AUC(0-24h) <sup>a</sup> (geom mean)	47.9	-	50.2	-	30.9	-	32.1	-
AUC(0-24h)ratio <sup>a</sup>					72.9	50	74	70

a: Unit: Cmax-ng/mL; AUC-ng/hr/mL; Tmax-hr, AUC(tf) ratio (metabolite-to-parent)-%



**Figure 3.** Individual DL and 3-OH DL Cmax values on Day 7 following multiple administration of Clarinex 5mg tablets with and without Azithromycin. Data level represent mean values.



**Figure 4.** Individual DL and 3-OH DL AUC0-24h values on Day 5 following multiple administration of Clarinex 5mg tablets with and without Azithromycin. Data level represent mean values.

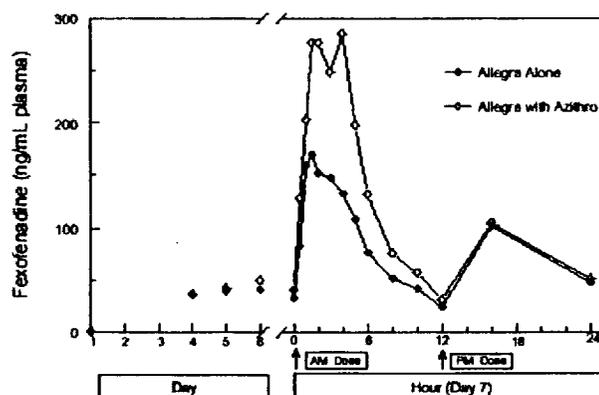
The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL, its metabolite with and without azytromycin are presented in Table 4. The point estimates (ratios) for AUC(I) and Cmax for DL and its metabolite indicate that co-administered of azytromycin with Clarinex 5 mg tablets caused increases in DL Cmax by (15%) and DL AUC by (5%) and 3-OH DL Cmax by (15%). According to the sponsor, these increments are clinically insignificant. However, 90% CI applied to Cmax and AUC were out of the 80-125% bioequivalence guideline.

**Table 4.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL, 3-OH DL with and without AZ

Parameter	(DL with AZ) / (DL with PL)		(DL with AZ) / (DL with PL)	
	Ratio	90% CI	Ratio <sup>a</sup>	90% CI
	DL		3-OH DL	
Cmax	115	95-144	115	98-136
AUC(0-24h)	100	82-134	104	88-122

### Fexofenadine

Plasma fexofenadine samples were collected on Days 4, 5, 6 and 7 prior to dosing to determine if steady-state conditions were reached. The relationship between trough fexofenadine concentration and day was determined using a smoothing algorithm. There was no trend of increasing concentrations between Days 4-7 (Figure 5). Thus, according to the sponsor, steady state for fexofenadine was attained on Day 4.



**Figure 5.** Mean plasma fexofenadine concentration-time profile following multiple administration of with and without AZ.

The mean PK parameters of fexofenadine are summarized in Table 5. Plasma fexofenadine concentrations reflected moderate inter-subject variability as shown by %CV ranging from 48 to 56% for Cmax and AUC (0-12 hr) values.

**Table 5.** Mean (CV%) pharmacokinetic parameters of fexofenadine on Day 7 following multiple administration of fexofenadine with and without AZ

Parameter	Fexofenadine			
	with placebo (n=17)		with AZ (n=18)	
	Arithmetic Mean	%CV	Arithmetic Mean	%CV
Cmax <sup>a</sup>	199	52	349	56
Cmax (geom mean)	174	-	294	-
Tmax <sup>a</sup>	4.56	119	3.81	87
AUC(0-12h) <sup>a</sup>	1041	48	1745	52
AUC(0-12h) (geom mean)	924	-	1547	-

a: Unit: Cmax-ng/mL; AUC-ng-hr/mL; Tmax-hr

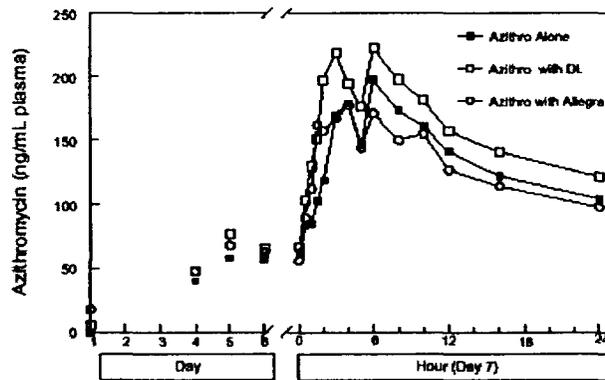
The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for fexofenadine with and without AZ are presented in Table 6. The statistical results indicate that when fexofenadine was administered with Azithromycin both the rate (Cmax) and extent of absorption of fexofenadine increased by 69 and 67%, respectively.

**Table 6.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of Fexofenadine with and without AZ

Parameter	(Allegra with AZ) / (Allegra with PL)	
	Ratio	90% CI
	DL	
Cmax	169	120-237
AUC(0-12h)	167	122-229

### Azithromycin

Plasma AZ samples were collected on Days 4, 5, 6 and 7 prior to dosing to determine if steady-state conditions were reached. The relationship between trough AZ concentration and day was determined using a smoothing algorithm. There was no trend of increasing concentrations between Days 5-7 (Figure 5). Thus, according to the sponsor, steady state for AZ was reached on Day 5.



**Figure 5.** Mean plasma AZ concentration-time profile following multiple administration of with and without DL or fexofenadine.

The mean PK parameters of AZ are summarized in Table 7. Plasma AZ concentrations reflected high inter-subject variability as shown by high %CV ranging from 43 to 91% for Cmax and AUC (0-12 hr) values.

**Table 7. Mean (CV%) pharmacokinetic parameters of AZ on Day 7 following multiple administration of AZ with and without DL or fexofenadine**

Parameter	AZ					
	with placebo (n=17)		with DL (n=18)		With fexofenadine	
	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV
C <sub>max</sub> <sup>a</sup>	241	47	338	56	249	91
C <sub>max</sub> (geom mean)	217	-	285	-	189	-
T <sub>max</sub> <sup>a</sup>	4.69	53	3.17	58	4.81	57
AUC(0-12h) <sup>a</sup>	3223	43	3845	46	3132	62
AUC(0-12h) (geom mean)	2980	-	3351	-	2620	-

a: Unit: C<sub>max</sub>-ng/mL; AUC-ng-hr/mL; T<sub>max</sub>-hr

The point estimates and the 90% CIs for the log-transformed C<sub>max</sub> and AUC(I) for AZ with and without DL or fexofenadine are presented in Table 8. Fexofenadine reduced Azithromycin C<sub>max</sub> by 13% and AUC by 12%. DL increased Azithromycin C<sub>max</sub> by 40% and AUC by 19%; According to the sponsor, these increases are considered to be clinically insignificant. However, 90% CI for both AZ C<sub>max</sub> and AZ AUC were out of the 80-125 BE guideline (Table 8).

**Table 8. Point estimates and 90% confidence intervals for the log-transformed C<sub>max</sub> and AUCinf values of AZ with and without DL or fexofenadine**

Parameter	(AZ with DL) / (AZ without DL)		(AZ with Fexofenadine) / (AZ without fexofenadine)	
	Ratio	90% CI	Ratio <sup>a</sup>	90% CI
C <sub>max</sub>	131	92-187	87	61-124
AUC(0-24h)	112	83-153	88	65-120

### Pharmacodynamic Results

The mean differences between the maximum PR, QRS, QT, and QTc intervals and ventricular rate observed on Day 7 and baseline (Day -1) following DL/{L, DL/AZ or PL/AZ are presented in Table 9.

**Table 9. Mean Difference Between Maximum ECG Parameters on Day 7 and Baseline (Day -1) for DL alone or in combination with AZ**

Parameter	DL Plus AZ	DL Plus Placebo	Placebo Plus AZ	p-Value DL/AZ vs DL/PL	p-Value DL/AZ vs PL/AZ
PR <sup>a</sup>	1.8	0.4	1.4	0.65	0.91
QRS <sup>a</sup>	-0.9	0	0	0.68	0.68
QT <sup>a</sup>	-7.4	-8.2	-10	0.9	0.7
QTc <sup>a</sup>	-4.2	-6.3	-0.1	0.61	0.32
Ventricular Rate <sup>a</sup>	4.8	5.3	4.5	0.85	0.92

a: Units: PR, QRS, QT, QTc=msec; ventricular rate=bpm.

The results of the statistical analysis (Table 9) for PR, QRS, QT, and QTc show that there were no statistically significant differences between the DL alone or in combination with AZ. Similar results were obtained when DL in combination with AZ was compared with placebo plus AZ. The sponsor stated that subgroup analysis (males

and females) did not show differences due to sex between DL alone or in combination with AZ (Table 10).

**Table 10.** Subgroup Analysis (By Sex) of the Mean Difference Between the Maximum ECG Parameters on Day 35 and Baseline (Day -1) Following DL/Placebo, DL/AZ or AZ/Placebo

Parameter	Mean Difference Between Day 35 and Baseline (Day -1)			p-Value	
	DL 5 mg Plus AZ	DL 5 mg Plus Placebo	Placebo Plus AZ	DL/AZ vs. DL/PL	DL/AZ vs. Placebo/AZ
<b>Males</b>					
PR	2.2	0.4	0.4	0.67	0.67
QRS	-0.9	-0.9	-0.9	1	1
QT	-3.2	-7.1	-15	0.72	0.29
QTc	-2.3	-8.9	1	0.29	0.59
Ventricular Rate	2.8	5	7.7	0.66	0.33
<b>Females</b>					
PR	1.3	0.4	2.4	0.82	0.78
QRS	-0.9	0.9	0.9	0.59	0.59
QT	-12	-9.3	-5.3	0.79	0.47
QTc	-6.1	-3.8	-1.2	0.69	0.4
Ventricular Rate	6.8	5.7	1.3	0.7	0.06

The QTc intervals were also assessed by examining 1) the mean difference between the maximum QTc on Day 7 and minimum QTc interval at baseline and 2) the mean difference between the area under the QTc curve (AUC[0-10 hr] QTc) on Day 7 and baseline. Seems that neither parameter showed any statistically significant differences for the interaction (DL and AZ) (Table 11).

**Table 11.** Statistical Evaluation of the Mean Difference Between the Maximum QTc on Day 7 and Minimum at Baseline and the Mean Change in AUC(0-10 hr) QTc on Day 7 and Baseline

Parameter	DL 5 mg Plus AZ <sup>a</sup>	DL 5 mg Plus Placebo <sup>b</sup>	Placebo Plus AZ <sup>c</sup>	FX Plus AZ <sup>d</sup>	FX Plus Placebo <sup>e</sup>	Pairwise Comparisons			
						A/B	A/C	D/E	C/D
Max QTc Day 7 – Min QTc Baseline	34.3	36.2	38.4	36.3	39.1	0.67	0.63	0.52	0.98
AUC QTc (Day 7- Baseline)	-2.7	-43.4	-5.0	-9.1	6.0	0.22	0.95	0.65	0.90

- a: DL 5 mg plus AZ.
- b: DL 5 mg plus placebo.
- c: Placebo plus AZ.
- d: FX plus AZ.
- e: FX plus placebo.

According to the sponsor, an evaluation of maximum QTc intervals at baseline and during the study for DL alone or in combination with AZ showed that the majority of the QTc values >440 msec were recorded at baseline. Moreover, the values either decreased or remained unchanged following treatment. For the four subjects with baseline QTc <440 msec, no increases exceeded 23 msec. The sponsor stated that these changes are not indicative of a drug effect.

With respect to fexofenadine, the sponsor has claimed no statistically significant treatment effect (interaction of FX and AZ) on any of the ECG parameters. Subgroup analysis by sex did not show any differences between treatments due to sex except for PR interval in males.

## **CONCLUSIONS**

- Co-administered of azythromycin with Clarinex 5 mg tablets caused increases in DL Cmax by (15%) and DL AUC by (5%) and 3-OH DL Cmax by (15%).
- Co-administration of fexofenadine with Azithromycin caused increases in both the rate (Cmax) and extent of absorption of fexofenadine by 69 and 67%, respectively.
- Fexofenadine reduced Azithromycin Cmax by 13% and AUC by 12%. DL increased Azithromycin Cmax by 31% and AUC by 12%.
- There were no statistically significant differences in ECG parameters (PR, QRS, QT, and QTc) between DL alone or in combination with AZ.

## **GENERAL COMMENTS**

- Co-administered of azythromycin with Clarinex 5 mg tablets caused increases in DL Cmax by (15%) and DL AUC by (5%) and 3-OH DL Cmax by (15%). 90% CI applied to Cmax and AUC were out of the 80-125% bioequivalence guideline. According to the sponsor, these increments are clinically insignificant and this reviewer agrees with this statement. The relatively wide CI is most likely due to variability of the data and the relatively small number of subjects included in the study.
- Fexofenadine reduced azithromycin Cmax by 13% and AUC by 12%. DL increased azithromycin Cmax by 40% and AUC by 19%. According to the sponsor, these increases are considered to be clinically insignificant. Although, 90% CI for both AZ Cmax and AZ AUC were out of the 80-125 BE guideline, this reviewer agrees with the sponsor's statements on the clinical insignificance of the findings.
- There were no statistically significant differences in ECG parameters (PR, QRS, QT, and QTc) between DL alone or in combination with AZ.
- According to the sponsor, fexofenadine has no statistically significant treatment effect (interaction of FX and AZ) on any of the ECG parameters. This reviewer agrees with this statement.
- Subgroup analysis (males and females) did not show differences in ECG parameters due to gender between DL alone or in combination with AZ.
- QTc intervals at baseline and during the study for DL alone or in combination with AZ showed that the majority of the QTc values >440 msec were recorded at baseline. The values either decreased or remained unchanged following treatment. For the four subjects with baseline QTc <440 msec, no increases exceeded 23 msec. The sponsor stated that these changes are not indicative of a drug effect.

---

**"EVALUATION OF THE PHARMACOKINETICS AND  
ELECTROCARDIOGRAPHIC PHARMACODYNAMICS OF DESLORATADINE  
WITH CONCOMITANT ADMINISTRATION OF CIMETIDINE"**

**Name of Sponsor:** Schering-Plough Corporation  
**Included Protocols:** P01868  
**Development Phase of Study:** I  
**Study Initiation Date:** May 31, 2000  
**Study Completion Date:** Jun 23, 2000  
**Sponsor's Project Director:** Sauzanne Khalilieh, Pharm.D.  
**Sponsor's Project Physician:** Mark Marino, M.D.  
**Date of the Report:** Jan 15, 2000  
**Clinical Documentation  
Accession Number:** 1656165

---

**OBJECTIVE**

- to compare the multiple-dose pharmacokinetic parameters of SCH 34117 (desloratadine or DL) and its metabolite, SCH 45581 (3-hydroxydesloratadine or 3-OH DL), following oral administration of DL alone or in combination with Cimetidine in healthy adult subjects.

**SUBJECTS**

Overall, 36 healthy volunteers, 18 male and 18 female, between the ages of 22 and 45 years inclusive (mean=35 years) weighing between 49 and 99 kg (mean=71.9 kg) were enrolled into the study. BMI's ranged from 19.8-27.2 kg/m<sup>2</sup> (mean=24.5 kg/m<sup>2</sup>). Thirty-four subjects were Caucasian (94%) and two were Black (6%).

**STUDY DESIGN AND TREATMENT ADMINISTRATION**

Thirty-six healthy adults (18 males and 18 females) completed this randomized, open-label, parallel group, multiple-dose study. Subjects were randomized to Treatments A or B as follows:

**Treatment A (DL alone):** DL 1 x 5-mg tablet QD on Day 1 and Days 3- 17; n=18

**Treatment B (DL with Cimetidine):** DL 1 x 5-mg tablet QD on Day 1 and Days 3-17 with Cimetidine 600-mg (2 x 300-mg tablets) Q12H Days 3-17; n=18

Subjects fasted for 10-hr prior to and 4-hr after dose administration on Days 1 and 17.

## FORMULATION

The Clarinex 5mg bilayer tablets were manufactured in Las Piedras PR. The following formulation (Table 1) was used:

Table 1. Formulations for Clarinex 5mg Tablets

Strength	5 mg DL
Formula. No.	3408
Batch No.	38833-142
FMR No.	98564D02
Manf. Date	3/23/98
Manf. Site	Las Piedras, PR
Batch Size (tablets)	_____

Formula 3408 is the same as the to-be marketed formulation.

## Dissolution

The dissolution method and dissolution data obtained from the batch used in this study are shown below.

Method	Specification
Apparatus: USP apparatus II (paddle) Speed: 50 rpm Temperature: 37 °C Medium: 0.1 N HCL Volume: 500 mL Detection: UV at 282nm	Q=80% at 30 min

Table D1. Dissolution data for DL tablets 5 mg

Time (Minutes)	Dissolution Profile Results Percent 34117 Dissolved/Dosage Form												
	Avg.	1	2	3	4	5	6	7	8	9	10	11	12
15													
30													
45													
60													

The data shows that the batch passes dissolution specifications.

## PHARMACOKINETIC MEASUREMENTS

### Blood Sampling

Blood samples (10 mL), for the determination of SCH 34117 and SCH 45581 concentrations in plasma, were collected prior to dosing (0 hr) and at 1, 2, 3, 4, 6, 8, 12, 24 and 48 hr post-dose following dosing on Day 1 (first dose) and 0 hr (pre-dose) on Day 14-17 and at 1, 2, 3, 4, 6, 8, 10, 12 and 24 hr following dosing on Day 17. Blood sample was also collected at 24 hr post-dose following administration of the second dose on Day 3.

### **Analytical Method**

Plasma SCH 34117 and SCH 45581 concentrations were determined using validated methods with lower limits of quantitation (LOQ) of  $\text{ng/mL}$  (linear range:  $\text{ng/mL}$ ) for SCH 34117 and SCH 45581.

### **SAFETY MEASUREMENTS**

Safety was assessed by monitoring adverse events, laboratory safety tests (CBC, blood chemistries, and urinalysis), pre- and poststudy physical examinations, vital signs, and electrocardiograms. The results were listed and reviewed.

### **Supplemental Analyses**

Additional analysis on AUC of QTc at baseline and Day 1, 3, and 17 of treatment and on the minimum and maximum QTc values were also provided. The area under the curve (AUC) for QTc was calculated for each subject at Day -1, 1, 3, and 17 using the four QTc readings collected at 2, 4, 8, and 12 hours postdose. Summary statistics were tabulated by treatment group for baseline Day -1, Day 1, 3, and 17 AUC, and the changes in AUC from baseline.

Additionally, summary statistics were tabulated by treatment group for the difference between minimum and maximum QTc values at Day -1 (baseline) and minimum and maximum post-treatment (Day 1, Day 3, and Day 17) QTc values as listed below:

1. Maximum QTc at baseline - Minimum QTc at baseline,
2. Maximum QTc at post-treatment - Minimum QTc at post-treatment,
3. Maximum QTc post-treatment - Minimum QTc at baseline.

### **DATA ANALYSIS**

#### **Pharmacokinetic Data Analysis**

Individual plasma DL (SCH 34117) and 3-OH DL (SCH 45581) concentration-time data were used to determine the pharmacokinetic parameters using model-independent methods.

#### **Statistical Analysis**

Means, standard deviations and coefficients of variation for the means were provided for the pharmacokinetic parameters based on treatments and also gender (male or female) within treatments. Means, standard deviations and %CV were also reported for the concentration data at each time point. The difference between Day 17 and Day 1 log-transformed AUC and Cmax values were statistically analyzed using a one-way (treatment) ANOVA. All other pharmacokinetic parameters (CL/F and Vz/F) were analyzed in their original scale.

## RESULTS

### Analytical Method

#### In study Validation Results

Table 2. In-study validation information for DL and 3-OH DL

	DL	3-OH DL
Linearity	Satisfactory: Standard	Satisfactory: Standard
Accuracy	Satisfactory:	Satisfactory:
Precision	Satisfactory:	Satisfactory:
Specificity	Satisfactory: submitted	Satisfactory: submitted

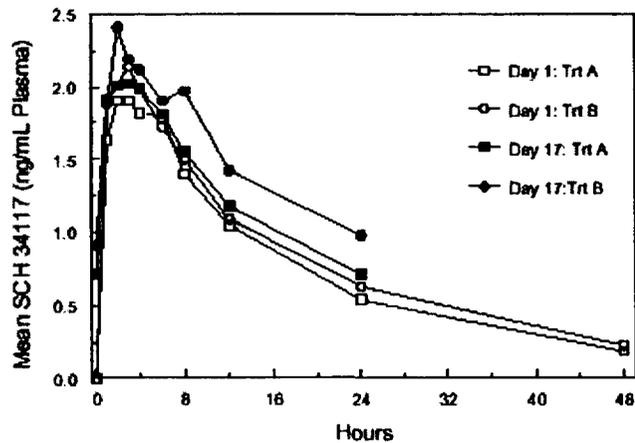
#### Pharmacokinetic Results

All 36 subjects completed the study and none were found to be slow metabolizers of SCH 34117, based on their AUC (tf) % ratio values (observed metabolite to parent ratio >10%) (Table 4).

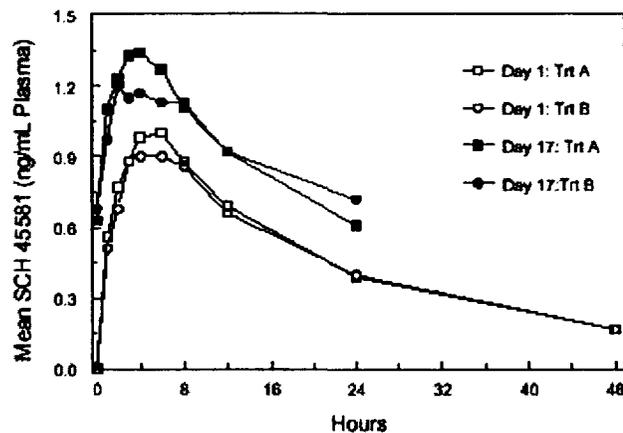
The mean plasma concentration-time profiles for DL and its metabolite on Day 1 and 17 are shown in Figure 1 and 2, respectively. Plasma SCH 34117 and SCH 45581 samples were collected on Days 14, 15, 16 and 17 prior to dosing to determine if steady-state conditions were reached.

Individual AUC<sub>t</sub> (day 17) following administration of DL once daily with or without 600 mg Cimetidine are presented in Figure 3. The relationship between mean trough SCH 34117 or SCH 45581 concentration (C<sub>min</sub>) and day is shown in Figure 4. There was no apparent increase in concentrations between Days 14-17. This suggests that steady state for DL and 3-OH DL was attained by Day 14.

The mean pharmacokinetic parameters for DL and its metabolite are summarized in Table 3. Plasma SCH 34117 and SCH 45581 concentrations reflected high inter-subject variability as shown by %CV ranging between 20 to 81%. Following multiple dosing, there was a small degree of accumulation (<1.5-fold) based on AUC(0-24 hr) ratio from Day 17 to Day 1. A small increase was observed for mean C<sub>max</sub> (~10%) and AUC (~19%) values of SCH 34117 at steady state after co-administration of Cimetidine compared to DL (Tables 3 to 5). The mean C<sub>max</sub> of SCH 45581 decreased by about 10% and the mean AUC of SCH 45581 remained unchanged at steady state with co-administration of Cimetidine (Tables 3 to 5). According to the sponsor, no statistically significant differences in any pharmacokinetic parameters were found between treatments for both DL and 3-OH DL on either Day 1 or Day 17.



**Figure 1.** Mean plasma DL concentration-time profile following administration of Clarinex 5 mg tablets with (trt B) and without Cimetidine (Trt A).



**Figure 2.** Mean plasma 3-OH DL concentration-time profile following administration of Clarinex 5 mg tablets with (trt B) and without Cimetidine (Trt A).

The Day 17 to Day 1 mean ratio of  $C_{max}$ , AUC,  $CL/F$  and  $V_z/F$  were similar between Treatments A and B for DL. Similarly, the Day 17 to Day 1 mean ratio of  $C_{max}$  and AUC were similar between Treatments A and B for 3-OH DL (Table 6). These results suggest no potential for pharmacokinetic interaction between DL and Cimetidine.

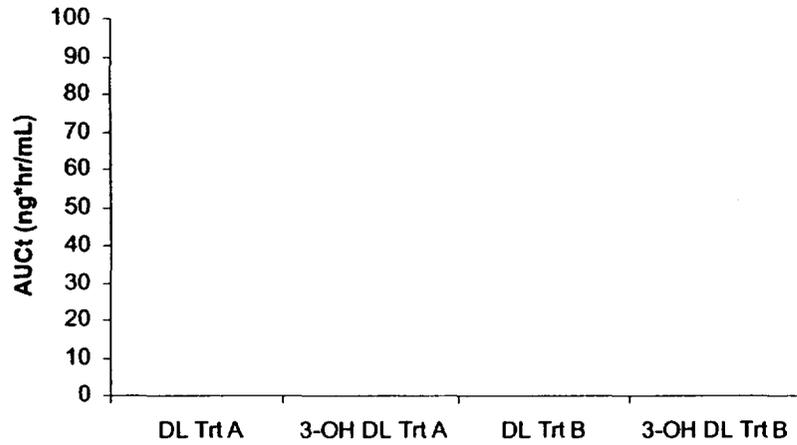


Figure 3. Individual AUCt (day 17) following administration of DL once daily with or without 600 mg Cimetidine.

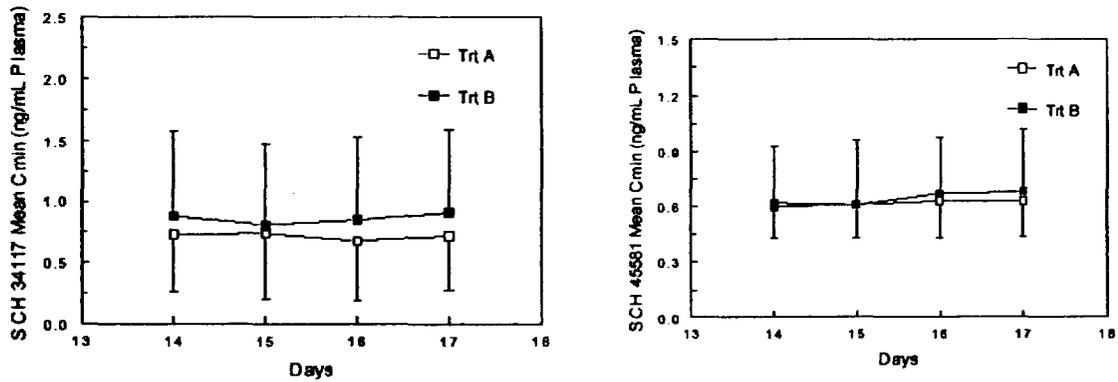


Figure 4. Relationship Between Mean DL (SCH 34117; left) or Mean 3-OH DL (SCH 45581; right) Cmin and Day Following 5 mg SCH 34117 Once Daily Oral Dosing Alone (Trt A) or With 600 mg Cimetidine (Trt B). Vertical error bars represent  $\pm$  SD.

**Table 3.** Mean (CV%) pharmacokinetic parameters of DL and 3-OH on Day 17 following multiple administration of Clarinex 5mg with (Trt B) and without Cimetidine (Trt A).

Parameter (Day 17)	Desloratadine				3-OH DL			
	Trt A (n=18)		Trt B (n=18)		Trt A (n=18)		Trt B (n=18)	
	Arithmetic Mean	%CV						
Cmax <sup>a</sup>	2.35	51	2.59	44	1.49	30	1.35	38
Cmax (Geom mean)	2.11		2.34		1.43		1.27	
Tmax <sup>a</sup>	2.61	48	3.06	78	3.94	56	4.44	66
AUC(0-24h) <sup>a</sup>	31.2	59	37.1	54	22.8	27	22.7	37
AUC(0-24h) <sup>a</sup> (geom mean)	27.2		32.3		22		21.4	
AUC(0-24h) ratio <sup>a</sup> (%)	-				72.8	37	67.5	48
Accumulation Index (R) <sup>b</sup>	1.1	25	1.28	40	1.42	23	1.48	31

a: Unit: Cmax-ng/mL; AUC-ng hr/mL; Tmax-hr, AUC(tf) ratio (metabolite-to-parent)-%, b: AUC(0-24 hr) ratio (Day 17:Day 1) with or without Cimetidine co-administration.

**Table 4.** Individual, Mean and Median AUC(tf) Values of DL (SCH 34117) and 3-OH DL (SCH 45581) on Day 17 Following 5 mg DL (SCH 34117) Once Daily Oral Dosing With or Without 600 mg Cimetidine

Subject	Treatment A <sup>a</sup> : AUC(tf) [ng.hr/mL]			Subject	Treatment B <sup>a</sup> : AUC(tf) [ng.hr/mL]		
	DL	3-OH DL	Ratio <sup>b</sup>		DL	3-OH DL	Ratio <sup>b</sup>
1	14.2	18.7	132	2	30.5	17.5	57.3
4	18.8	13.5	81.4	3	11.2	11.0	98.7
5	22.1	21.0	94.9	6	18.7	15.4	82.3
8	20.5	19.0	92.7	7	13.7	13.5	98.5
10	21.2	14.7	69.4	9	50.5	18.9	37.5
12	14.4	15.9	111	11	17.5	15.3	87.2
14	15.2	17.5	115	13	44.1	25.8	58.5
16	24.4	31.6	130	15	28.5	24.7	83.7
19	21.7	23.9	110	17	95.4	18.7	19.6
20	77.2	34.0	44.0	18	20.3	20.7	102
22	64.6	28.7	44.5	21	49.0	35.7	72.9
23	23.2	19.7	84.7	24	31.5	17.0	53.9
26	54.2	25.3	46.7	25	38.0	40.2	106
28	21.2	26.0	123	27	50.4	21.8	43.2
29	35.9	29.1	81.1	30	50.2	23.1	46.0
31	43.1	23.8	55.2	32	51.7	26.1	50.5
34	28.5	29.9	105	33	22.8	25.1	110
35	43.7	18.4	42.1	36	42.7	38.9	91.1
Arithmetic Mean	31.2	22.8	86.7		37.1	22.7	72.1
%CV	59	27	35		54	37	37
Geometric Mean	27.2	22.0	81.0		32.3	21.4	66.3
Median	22.7	22.4	88.7		34.8	21.2	77.6

a: Treatment A: DL 1 x 5-mg tablet QD on Day 1 and Days 3-17  
Treatment B: DL 1 x 5-mg tablet QD on Day 1 and Days 3-17 with cimetidine 600-mg (2 x 300-mg tablets) Q12H Days 3-17  
b: Calculated as AUC(tf) % ratio (SCH 45581: SCH 34117)

**Table 5 Mean Pharmacokinetic Parameters of DL and 3-OH DL on Day 1 and Day 17 Following 5 mg DL Once Daily Oral Dosing With or Without Cimetidine (n=18)**

Parameter	DL							
	Day 1				Day 17			
	Treatment A		Treatment B		Treatment A		Treatment B	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
Mean C <sub>max</sub> <sup>a</sup>	2.19	40	2.40	42	2.35	51	2.59	44
Median T <sub>max</sub> <sup>a</sup>	3.00	-	3.00	-	2.50	-	2.00	-
Mean AUC(0-24 hr) <sup>a</sup>	27.6	42	29.4	44	31.2	59	37.1	54
CL/F <sup>a</sup>	148	43	142	54	205	44	180	59
V <sub>z</sub> /F <sup>a</sup>	2972	41	2751	39	4157	49	3714	45

Parameter	3-OH DL							
	Day 1				Day 17			
	Treatment A		Treatment B		Treatment A		Treatment B	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
Mean C <sub>max</sub> <sup>a</sup>	1.13	33	1.01	29	1.49	30	1.35	38
Median T <sub>max</sub> <sup>a</sup>	6.00	-	6.00	-	3.00	-	3.50	-
Mean AUC(0-24 hr) <sup>a</sup>	16.2	21	15.5	24	22.8	27	22.7	37
Mean AUC(tf) ratio <sup>a</sup> (%)	72.8	37	67.5	48	86.7	35	72.1	37

a: Unit: C<sub>max</sub>-ng/mL; AUC-ng-hr/mL; CL/F-l/hr; V<sub>z</sub>/F-l; T<sub>max</sub>, and tf-hr, AUC(tf) % ratio (3-OH DL:DL).

%CV = Not determined when values are median, geometric means or when arithmetic mean=0.

Treatment A: DL 1 x 5 mg tablet QD on Day 1 and Days 3-17.

Treatment B: DL 1 x 5 mg tablet QD on Day 1 and Days 3-17 with cimetidine 600 mg (2 x 300 mg tablets) Q12H Days 3-17.

**Table 6. Mean Ratio (Day 17:Day 1) for Pharmacokinetic Parameters of DL (SCH 34117) and 3-OH DL (SCH 45581) Following 5 mg SCH 34117 Once Daily Oral Dosing With or Without 600 mg Cimetidine (n=18)**

	Desloratadine				3-OH DL			
	Trt A (n=18)		Trt B (n=18)		Trt A (n=18)		Trt B (n=18)	
	Arithmetic Mean	%CV						
Mean ratio (Day 17:Day 1)								
C <sub>max</sub>	1.07	23	1.09	22	1.37	27	1.37	29
AUC(0-24h) day 17: AUCinf Day1	0.76	19	0.86	40	0.83	16	0.85	22
AUC(0-24h) day 17: AUCt Day1	0.84	21	0.96	40	0.99	19	1.02	26
CL/F	1.38	21	1.29	29				
V <sub>z</sub> /F	1.4	32	1.36	24				

The 90% confidence intervals for C<sub>max</sub> and AUC based on the Day 17 DL log-transformed ratio of DL with Cimetidine to DL alone further indicates that the coadministration of Cimetidine with DL has no clinically meaningful affects of DL parameters (Table 7).

**Table 7. Ninety Percent Confidence Intervals for Day 17 DL and 3-OH DL PK Parameters**

Parameter	Treatment B/Treatment A			
	Ratio <sup>a</sup>	90% CI <sup>b</sup>	Ratio <sup>a</sup>	90% CI <sup>b</sup>
	DL		3-OH DL	
C <sub>max</sub>	112	88-145	88.8	73-107
AUC(0-24 hr)	119	88-161	97.2	81-116

a: Ratio of means expressed as a percent based on log-transformed values.

b: Ninety percent confidence interval (CI) based on log-transformed values.

Treatment A: DL 1 x 5 mg tablet QD on Day 1 and Days 3-17.

Treatment B: DL 1 x 5 mg tablet QD on Day 1 and Days 3-17 with cimetidine 600 mg (2 x 300 mg tablets) Q12H Days 3-17.

## Pharmacodynamic Results

The mean difference between maximum ECG parameters on Day 1, Day 3 and Day 17 and baseline (Day -1) for treatment A and treatment B, are presented in Tables 8, 9, and 10 respectively. According to the sponsor, there was no statistically significant difference between treatment groups for ventricular rate, PR, QRS, QT, and QTc intervals at each time point, for the maximum, changes and the percent changes from maximum baseline (Day -1) (p-value 0.07).

**Table 8. Mean Difference Between Maximum ECG Parameters on Day 1 and Baseline (Day -1) for Treatment A and Treatment B (n=18/group)**

Parameter	Treatment A	Treatment B	Pooled Std Deviation	p-value for Treatment A vs. Treatment B	95% Confidence Intervals for Treatment A vs. Treatment B
PR msec	-3.1	1.3	7.6	0.09	-9.6, 0.7
QRS msec	-0.2	0.2	3.5	0.70	-2.8, 1.9
QT msec	1.1	5.1	17.6	0.5	-15.9, 7.9
QTc msec	-1.1	-2.9	12.6	0.68	-6.8, 10.3
Ventricular Rate bpm	0.2	-0.9	7.2	0.65	-3.8, 6.0

**Table 9. Mean Difference Between Maximum ECG Parameters on Day 3 and Baseline (Day -1) for Treatment A and Treatment B (n=18/group)**

Parameter	Treatment A	Treatment B	Pooled Std Deviation	p-value Treatment A vs. Treatment B	95% Confidence Intervals for Treatment A vs. Treatment B.
PR msec	-2.4	0.4	8.0	0.29	-8.3, 2.5
QRS msec	-0.7	0.9	3.6	0.2	-4.0, 0.9
QT msec	-13	-2.7	16.2	0.07	-21.0, 1.0
QTc msec	1.4	-2.9	11.2	0.25	-3.2, 12.0
Ventricular Rate bpm	3.6	0.4	9.1	0.31	-3.0, 9.3

**Table 10. Mean Difference Between Maximum ECG Parameters on Day 17 and Baseline (Day -1) for Treatment A Treatment B (n=18/group)**

Parameter	Treatment A	Treatment B	Pooled Std Deviation	p-value Treatment A vs. Treatment B.	95% Confidence Intervals for Treatment A vs. Treatment B
PR msec	-3.6	1.3	9.2	0.12	-11.1, 1.3
QRS msec	0.2	0.7	10.1	0.9	-7.3, 6.4
QT msec	-9.1	-3.8	20.1	0.43	-19.0, 8.3
QTc msec	-0.8	-0.3	12.8	0.91	-9.2, 8.2
Ventricular Rate bpm	0.7	-0.7	9.2	0.65	-4.9, 7.6

a: Least square means and p-values from ANOVA extracting sources of variation due to treatment.

Treatment A: DL 1 x 5 mg tablet QD on Day 1 and Days 3-17.

Treatment B: DL 1 x 5 mg tablet QD on Day 1 and Days 3-17 with cimetidine 600 mg (2 x 300 mg tablets) Q12H Days 3-17.

Differences between treatment groups in maximum changes in PR on Day 1 and Day 3 were greater in females compared to males. Mean QTc values at baseline and post-treatment, were generally greater in females compared to males. However, according to the sponsor, no difference for any ECG parameter, was noted between treatment groups for either sex.

The sponsor stated that, there were 12 subjects with at least one QTc interval >440 ms, however, eight of these subjects had at least one elevated QTc value prior to receiving study medication (Screening and Day -1). The remaining four subjects (Subject Nos. 20, 28, 31, and 34) all in the DL alone treatment group, were reported to have a QTc value >440 ms only during the post-treatment period. Two subjects, one in the DL alone treatment group and one in the DL plus Cimetidine treatment group, had a QTc increase by  $\geq 30$  ms over baseline values during the treatment period. Subject No. 4 in the DL alone treatment group had a baseline QTc value of 435 ms and a maximum QTc value of 467 ms on Day 18 (approximately 24 hours post the Day 17 dose). Subject No. 11 in the DL plus Cimetidine treatment group had a maximum baseline QTc value of 403 ms and a maximum post-baseline QTc value of 433 on Day 17.

### **Conclusion**

- overall it seems that Cimetidine did not affect the PK of DL and its metabolite and viseversa.

### **COMMENTS TO MEDICAL OFFICER**

- An increase was observed for mean DL Cmax (~10%) and DL AUC (~19%) values at steady state after co-administration of Cimetidine compared to DL alone. The mean Cmax of 3-OH DL decreased by about 10% and the mean AUC of -OH DL remained unchanged at steady state with co-administration of Cimetidine.
- Although 90% CI for the DL PK parameters Cmax (Trt with Cimetidine/Trt without Cimetidine) (88-145) and AUC (88-161) were out of the guideline for BE, overall it seems that Cimetidine does not affect the PK of DL and its metabolite and viseversa. These findings are most likely due to the high variability of the data. However, the clinical significance of this variation in Cmax and AUC should be evaluated by the medical officer.
- It seems that no statistically significant difference between treatment groups (DL with and without Cimetidine) were observed for ventricular rate, PR, QRS, QT, and QTc intervals at each time point (Day 1, Day 3 and Day 17), for the maximum, changes and the percent changes from maximum baseline (Day -1).
- There were 12 subjects with at least one QTc interval >440 ms; however, eight of these subjects had at least one elevated QTc value prior to receiving study medication (Screening and Day -1).
- Four of the 12 subjects (Subject Nos. 20, 28, 31, and 34) all in the DL alone treatment group, were reported to have a QTc value >440 ms only during the post-treatment period.
- Two subjects, one in the DL alone treatment group and one in the DL plus Cimetidine treatment group, had a QTc increase by  $\geq 30$  ms over baseline values during the

treatment period. The clinical relevance of these findings should be evaluated by the medical officer.

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Sandra Suarez  
1/30/02 06:12:54 PM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
1/31/02 10:04:44 AM  
BIOPHARMACEUTICS  
I concur