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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-363

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-363
Proprietary Drug Name:	Clarinex 5 mg Tablets
Generic Name:	Desloratadine
Indication:	Treatment of Allergic Rhinitis (seasonal and perennial)
Dosage Form:	Tablet
Strength:	5mg
Route of Administration:	Oral
Dosage and administration:	Adults and children (age 12 years and older): One tablet twice daily
Applicant:	Schering Corporation
Clinical Division:	DPADP (HFD-570)
Submission Date:	April 9, 2001
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader :	Emmanuel Fadiran, Ph. D.

I. EXECUTIVE SUMMARY

Clarinex (desloratadine, DL) tablets 5 mg received an approval action on December 21, 2001 for the treatment of seasonal allergic rhinitis (SAR). In this submission (NDA 21-363) the sponsor, Schering Corporation, is seeking approval for a new indication, the treatment of perennial allergic rhinitis (PAR). In support of this application the sponsor conducted four safety and efficacy studies. These included two studies in subjects with PAR and two studies in subjects with SAR and concurrent asthma.

The Sponsor has previously reported (NDA 21-165) the results of the concomitant administration of DL with ketoconazole or erythromycin. To further characterize DL's interaction potential, Schering conducted four human pharmacokinetic studies as part of this NDA (21-363). The studies evaluated the effects of fluoxetine (Flu), azithromycin (AZ), cimetidine (CM) and grapefruit juice on the steady state pharmacokinetics/ pharmacodynamic (ECG parameters) of desloratadine and its metabolite, 3-OH desloratadine (3-OH DL).

While grapefruit juice does not alter the BA of DL or 3-OH DL, the effects of the other drugs on the PK of DL and its metabolite (and viceversa) are summarized in the following tables:

Table 1. Effects of Flu, AZ and CM on steady state DL and 3-OH DL parameters in healthy male and female volunteers

	Desloratadine		**3-OH desloratadine**	
	Cmax	**AUC0-24**	**Cmax**	**AUC0-24**
Azithromycin (500 mg Day1, 250 mcg QD x 4 days)	+19%	+8%	+14%	3%
Cimetidine (600 mg Q12h)	+12%	+19%	-11%	-3%
Fluoxetine (20 mg QD)	+18%	0%	+18%	+14%

Table 2. Effects of steady state DL (5 mg QD) on the pharmacokinetics of AZ, Flu and norfluoxetine in healthy male and female volunteers.

	Cmax	**AUC (0-24)**
Azithromycin (500 mg Day1, 250 mcg QD x 4 days)*	+40%	+19%
Fluoxetine (20 mg QD)	-13%	-17%
Norfluoxetine	+22%	+18%

*AUC0-12h. Cimetidine concentrations were not determined.

In general, no statistically significant changes in the ECG parameters (PR, QRS, QT, and QTc intervals and ventricular rate) were observed for the comparison of DL alone or in combination with the interacting drug (and viceversa). Overall, there were no clinically significant drug-drug interactions between DL and grapefruit juice and the tested drugs: azithromycin, cimetidine and fluoxetine.

COMMENTS TO THE MEDICAL OFFICER

- There were two subjects (#4: Caucasian, male; and #22:hispanic, female) identified as poor metabolizers (Study P1380). These subjects had AUCmet/AUCparent of less than 10%. These subjects did NOT appear to have the same effect on fexofenadine since the Cmax and AUCt values were close to the mean values (mean Cmax=201 ng/mL; mean AUCt=1130 ng*hr/mL).
- There was a marginally significant difference (p=0.055) in ventricular rate when DL was combined with fluoxetine (mean difference between day 35 and baseline= 4.7 bpm) compared to fluoxetine alone (mean difference between day 35 and baseline=-1.3 bpm). The clinical relevance of this finding should be evaluated by the medical reviewer.

- Four of the 12 subjects (Subject Nos. 20, 28, 31, and 34) all in the DL alone treatment group (cimetidine drug-drug interaction study), were reported to have a QTc value >440 ms (442, 445, 449, and 450 ms, respectivle7) only during the post-treatment period. Two subjects, one in the DL alone treatment group (435 ms at baseline and 467 ms on day 18) and one in the DL plus cimetidine treatment group (403 ms at baseline and 433 ms on day 15), had a QTc increase by ≥30 ms over baseline values during the treatment period. The clinical relevance of these findings should be evaluated by the medical officer.
- Study P01430, a drug-drug interaction with cimetidine (36 healthy subjects: 35 Hispanics and one black) was terminated earlier due to substantial gastrointestinal and cardiovascular side effects. The sponsor claims that the presence of side effects is not related to a pharmacokinetic interaction. This reviewer does not completely agree with the sponsor since the pharmacokinetic data provided is incomplete. It is recommended that the medical reviewer evaluates the clinical relevance of these findings.

The following comments have been conveyed to the sponsor:

- Provide a rationale for not including Hispanics in study P01868.
- Submit individual plasma concentrations for DL and its metabolite for all subjects from the study terminated before completion.
- If possible, submit individual cimetidine plasma concentrations for all subjects participated in the study terminated before completion.
- Submit all pharmacokinetic data generated for DL and its metabolite in the Hispanic population. Include a comparison across different races.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-363 submitted on April 9, 2001. The NDA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB. Please forward the labeling comments to the sponsor.

Reviewer
Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader

cc

NDA 21-363	:	Division File
HFD-870:		Malinowski, Hunt
HFD-570:		Fadiran, Nicklas, Chowdhury, Ladan, Suarez-Sharp

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III. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Desloratadine (DL) is an active metabolite of loratadine (Claritin) which possesses qualitatively similar pharmacodynamic activity with a relative oral potency 2 to 4 times that of loratadine. Like loratadine, DL is a selective, oral, peripheral H1-receptor antagonist. Pharmacokinetic studies have shown that administration of the proposed therapeutic dose of 5 mg DL gives the same systemic exposure (plasma AUC) of DL as administration of the marketed dose of 10-mg loratadine (NDA 21-165).

Clarinex tablets 5 mg received an approval action on December 21, 2001 for the treatment of seasonal allergic rhinitis (SAR). In this submission (NDA 21-363) the sponsor is seeking approval for a new indication, the treatment of perennial allergic rhinitis (PAR). In support of this application the sponsor conducted four safety and efficacy studies. These included two studies in subjects with PAR and two studies in subjects with SAR and concurrent asthma.

The Sponsor has previously reported the results of the concomitant administration of DL with ketoconazole or erythromycin, inhibitors of CYP3A4 (NDA 21-165). Neither ketoconazole nor erythromycin coadministered with DL resulted in clinically relevant alterations of the safety profile of DL. According to the sponsor, the results demonstrated that CYP3A4 does not play a major role in the metabolism of DL. To further characterize DL's interaction potential, Schering has conducted five additional human pharmacokinetic studies as part of this NDA 21-363. These studies (P01380, P01381, P01378 and P01868) evaluated the effects of potent inhibitors of CYP2D6 and potential inhibitors of absorption transporters on the PK/PD of DL and its metabolite. Although the sponsor submitted data for study P01430, this reviewer did not consider it since it was terminated earlier by the sponsor due to substantial side effect (see comments conveyed to the sponsor regarding this issue in the executive summary).

Study P1380 (four-way crossover study) assessed the effect of grapefruit juice on the bioavailability of desloratadine (5 mg) and fexofenadine (60 mg) in the same healthy adult population. From this study:

- Grapefruit juice had no effect on the Cmax and AUC values of DL or 3-OH DL (Table 1).
- Grapefruit juice reduced both Cmax and AUC values of fexofenadine by 30%.

Table 1. Mean pharmacokinetic parameters of DL and 3-OH DL following single administration of Clarinex 5mg with and without grapefruit juice

	DL (n = 23)				3-OH DL (n = 23)			
	DL Alone		DL with GFJ		DL Alone		DL with GFJ	
Parameter	Arithmetic Mean	Median	Arithmetic Mean	Median	Arithmetic Mean	Median	Arithmetic Mean	Median
Cmax[a]	2.06	2.10	2.14	2.13	0.923	0.930	0.980	0.930
Tmax[a]	3.41	2.50	3.57	2.50	4.96	6.00	5.48	6.00
AUC(tf)[a]	45.5	38.4	48.7	37.4	24.4	24.4	25.2	25.6
AUC(I)[a]	52.5		55.5		26.2		27.2	
AUC(tf) ratio[a]					78.1	71.2	75.1	74.5
a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax-hr, AUC(tf) ratio (metabolite-to-parent)-%								

Study P01378 (parallel group, multiple dose, 35 day administration) evaluated the effect of co-administration of desloratadine in combination with fluoxetine on the pharmacokinetics of DL and its' metabolite in healthy adult subjects (54 subjects). From this study:

- Co-administration of fluoxetine with DL caused increases in mean Cmax (15%) of DL and mean Cmax (17%) and mean AUC (13%) of 3-OH DL. Although 90% CI (Table 2) for the DL PK parameters Cmax (95-139) were out of the guideline for BE, this reviewer is of the opinion that fluoxetine does not affect the PK of DL and its metabolite and viseversa. The relatively wide CI observed is 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 (Table 3). 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 (Table 4).
- 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 (Table 4).

Table 2. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL, 3-OH DL with and without Fluoxetine

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

Table 3. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of fluoxetine and norfluoxetine with and without DL

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

Table 4. Mean[b] 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[a]	0.2	3.1	0.4	8.5	0.31	0.94
QRS[a]	-0.2	1.1	0.2	4.3	0.36	0.76
QT[a]	-0.7	-8.4	3.8	22.1	0.30	0.55
QTc[a]	8.2	6.9	6.4	10.6	0.71	0.61
Ventricular Rate[a]	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.

Study P1381 (parallel group, third-party blind, multiple-dose 7-day study) evaluated the effect of co-administration of desloratadine in combination with azithromycin on the pharmacokinetics of DL and its' metabolite (3-OH DL) in healthy adult subject (ninety subjects). From this study:

- 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 (Table 5). The sponsor claimed that 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%. Although 90% CI for both AZ Cmax and AZ

AUC were out of the 80-125 BE guideline (Table 6), this reviewer agrees with the sponsor's statements on the clinically insignificance of the findings. A communication letter has been sent to the special pathogens division to inform them about the effect of DL on the pharmacokinetics of azithromycin.

- There were no statistically significant differences in ECG parameters (PR, QRS, QT, and QTc) between DL alone or in combination with AZ.
- Fexofenadine has no statistically significant treatment effect (interaction of FX and AZ) on any of the ECG parameters.

Table 5. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL, 3-OH DL with and without AZ

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

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

	(AZ with DL) / (AZ without DL)		(AZ with Fexofenadine) / (AZ without fexofenadine)	
Parameter	**Ratio**	**90% CI**	**Ratio[a]**	**90% CI**
Cmax	131	92-187	87	61-124
AUC(0-24h)	112	83-153	88	65-120

Study P1868 (open-label, parallel group, multiple dose, 17-day study) compared the multiple-dose pharmacokinetic parameters of DL and its metabolite, following multiple oral administration of DL alone or in combination with cimetidine in healthy adult subjects (36 subjects). From this study:

- An increase was observed for mean DL Cmax (~10%) and mean 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 (Table 7) for DL 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.
- No statistically significant differences 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 ≥30 ms over baseline values during the treatment period. The clinical relevance of these findings should be evaluated by the medical officer.

- The sponsor did not determine the plasma concentration of cimetidine, therefore, the effect of DL on the pharmacokinetics of cimetidine is unknown.

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

Parameter	Treatment B/Treatment A			
	Ratio[a]	90% CI[b]	Ratio[a]	90% CI[b]
	DL		3-OH DL	
Cmax	112	86-145	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.

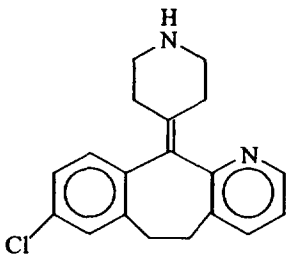
Treatment B: DL 1 x 5 mg tablet QD on Day 1 and Days 3-17 with cimetidine 600 mg (2 x 300 mg tablets) Q12H Days 3-17.

IV. QUESTION BASED REVIEW

Q1. What are the general attributes of Clarinex tablets?

DL Chemical name: The chemical name is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5H-benzo[5,6] cyclohepta [1,2-b]pyridine and has the following structural formula:

Structural formula:



Molecular formula: $C_{19}H_{19}ClN_2$

Molecular weight: 310.8

Solubility: DL is a white to off-white powder that is slightly soluble in water, but very soluble in ethanol and propylene glycol.

FORMULATION

The composition of the 5-mg tablet is the same as proposed in NDA 21-165.

INDICATION (as per proposed label)

CLARINEX Tablets are indicated for the relief of the nasal and non-nasal symptoms of allergic rhinitis (seasonal and perennial) in patients 12 years of age and older.

DOSAGE AND ADMINISTRATION (as per proposed label)

In adults and children 12 years of age and over, the recommended dose of CLARINEX Tablets is 5 mg once daily. In patients with liver or renal insufficiency, a starting dose of one 5 mg tablet every other day is recommended based on pharmacokinetic data.

Q2. What is known about the pharmacokinetics of desloratadine?

The following pharmacokinetics of DL and its metabolite were presented in NDA 21-165.

Absorption: Following oral administration of DL 5 mg once daily for 10 days to normal healthy volunteers, the mean time to maximum plasma concentrations (T_{max}) was approximately 3 hours and mean steady state peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) of 4 ng/mL and 56.9 ng·hr/ml were observed, respectively. Food had no effect on the bioavailability (C_{max} and AUC) of DL.

Distribution: DL and 3-hydroxy DL are 82 to 87% and 85 to 89%, bound to plasma proteins, respectively. Protein binding of DL and 3-hydroxy DL was unaltered in subjects with impaired renal function.

Metabolism: DL (a major metabolite of loratadine) is extensively metabolized to 3-hydroxy DL, an active metabolite, which is subsequently glucuronidated.

Disposition and Elimination: The mean elimination half-life of DL was 27 hours. C_{max} and AUC values increased in a dose proportional manner following single oral doses between 5 and 20 mg. The degree of accumulation after 14 days of dosing was consistent with the half-life of the drug. A human mass balance study documented a recovery of approximately 87% of the ^{14}C- DL dose, which was equally distributed in urine and feces as metabolic products. Analysis of plasma 3-hydroxy DL showed similar T_{max} and half-life values compared to DL.

Special Populations:

Geriatric: In older subjects (≥ 65 years old; n=17) following multiple-dose administration of CLARINEX Tablets, the mean C_{max} and AUC values for DL were 20% greater than in younger subjects (< 65 years old). The mean plasma elimination half-life of DL was 33.7 hr in subjects ≥ 65 years old. The pharmacokinetics for 3-OH DL appeared unchanged in older versus younger subjects. These age-related differences are unlikely to be clinically relevant and no dosage adjustment is recommended in elderly subjects.

Renally Impaired: pharmacokinetics following a single dose of 7.5 mg were characterized in patients with mild (n=7; creatinine clearance 51-69 mL/min/1.73m^2), moderate (n=6; creatinine clearance 34-43 mL/min/1.73m^2), and severe (n=6; creatinine clearance 5-29 mL/min/1.73m^2) renal impairment or hemodialysis dependent (n=6) patients. In patients with mild and moderate insufficiency, median C_{max} and AUC values increased by approximately 1.2 and 1.9-fold, respectively, relative to subjects with normal renal function. In patients with severe renal dysfunction or who were hemodialysis dependent, C_{max} and AUC values increased by approximately 1.7- and 2.5-fold, respectively. Minimal changes in 3-OH DL concentrations were observed. DL and 3-OH DL were poorly removed by hemodialysis. Dosage adjustment for patients with renal impairment is recommended.

Hepatically Impaired: DL pharmacokinetics were characterized following a single oral dose in patients with mild (n=4), moderate (n=4), and severe (n=4) hepatic dysfunction as defined by the Child-Pugh classification of hepatic dysfunction and 8 subjects with normal hepatic function. Patients with hepatic dysfunction, regardless of severity, had approximately a 2.4-fold increase in AUC as compared with normal subjects. The apparent oral clearance of DL in patients with mild, moderate, and severe hepatic dysfunction was 37, 36, and 28% of that in normal subjects, respectively. An increase in the mean elimination half-life of DL in patients with hepatic dysfunction was observed. For 3-OH DL, the mean C_{max} and AUC values for patients with hepatic dysfunction were not significantly different from subjects with normal hepatic function. Dosage adjustment for patients with hepatic impairment is recommended.

Drug Interactions: In two controlled clinical pharmacology studies in healthy male (n=12 in each study) and female (n=12 in each study) volunteers, DL 7.5 mg once daily was coadministered with erythromycin 500 mg every 8 hours or ketoconazole 200 mg every 12 hours for 10 days. Although increased plasma concentrations (Cmax and AUC 0-24 hrs) of DL and 3-OH DL were observed, there were no clinically relevant changes in the safety profile of DL, as assessed by electrocardiographic parameters (including the corrected QT interval), clinical laboratory tests, vital signs, and adverse events.

Q3. Was the to-be-marketed formulation used in the pharmacokinetic studies? Did the batches of Clarinex tables used in the PK studies meet dissolution specifications?

Yes, all the PK studies used formulation 3408 which corresponds to the to be marketed formulation.

All Clarinex tablets used dissolved more than [redacted]% in 30 min and therefore, met dissolution specifications. The dissolution method used was the one reported in previous NDA (21-165).

Q4. Does grapefruit juice affect the PK of desloratadine and its metabolite?

The sponsor conducted study P1380 to assess the effect of grapefruit juice on the bioavailability of desloratadine (5 mg) and fexofenadine (60 mg) in the same healthy adult population. Twenty-three (13 M, 10 F) healthy adults completed this randomized, open-label, 4 period crossover single-dose study. Subjects received four treatments separated by a 10 day washout period: DL alone, DL with GFJ, fexofenadine alone and fexofenadine with GFJ.

Subjects randomized to receive grapefruit juice were pretreated with 240 mL grapefruit juice for 2 days (at 8 am, 2 pm and 8 pm each day) prior to drug administration.

Figures Q4.1 and Q4.2 and Table Q4.1 show that the mean and the median Cmax and AUC values of DL were comparable with and without grapefruit juice. The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL, its metabolite and fexofenadine are presented in Table Q4.2. The CIs of AUC(I) and Cmax for DL and its metabolite after Clarinex 5mg indicate that when DL was administered with grapefruit juice there was no change in the rate and extent of absorption of DL or its metabolite. These results indicated that grapefruit juice does not affect the BA of DL and

its metabolite. GFJ reduced the BA of fexofenadine (both Cmax and AUC of fexofenadine were reduced by 30%).

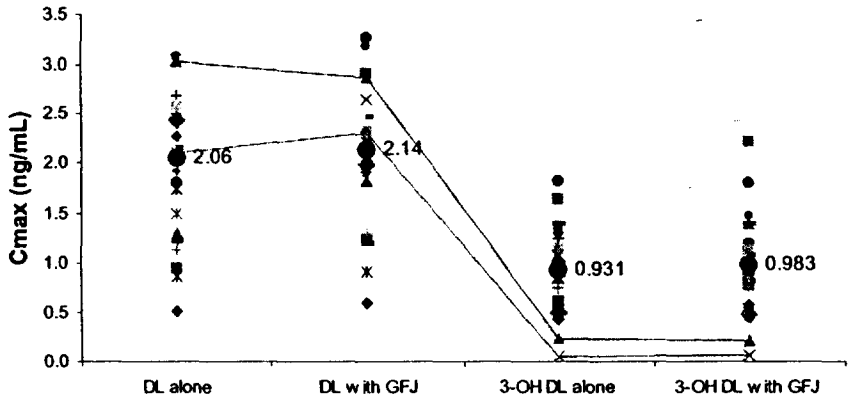


Figure Q4.1. Individual DL and 3-OH DL Cmax values following single administration of Clarinex 5mg tablets with and without grapefruit juice (GFJ). Linking lines represent Cmax values for poor metabolizers.

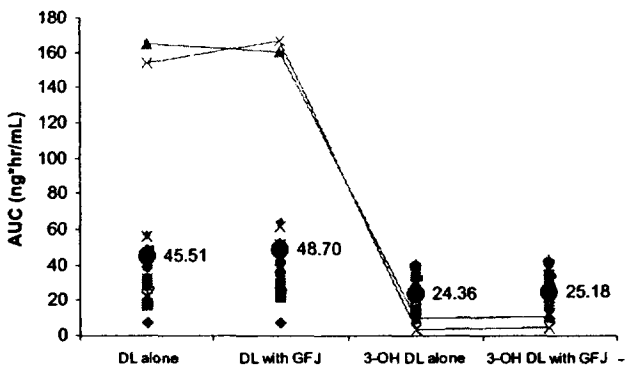


Figure Q4.2. Individual DL and 3-OH DL AUCtf values following single administration of Clarinex 5mg tablets with and without grapefruit juice. Linking lines represent AUCt values for poor metabolizers.

Table Q4.1. Mean pharmacokinetic parameters of DL and 3-OH following single administration of Clarinex 5mg with and without grapefruit juice

	DL (n = 23)				3-OH DL (n = 23)			
	DL Alone		DL with GFJ		DL Alone		DL with GFJ	
Parameter	Arithmetic Mean	Median	Arithmetic Mean	Median	Arithmetic Mean	Median	Arithmetic Mean	Median
Cmax[a]	2.06	2.10	2.14	2.13	0.923	0.930	0.980	0.930
Tmax[a]	3.41	2.50	3.57	2.50	4.96	6.00	5.48	6.00
AUC(tf)[a]	45.5	38.4	48.7	37.4	24.4	24.4	25.2	25.6
AUC(I)[a]	52.5		55.5		26.2		27.2	

AUC(tf) ratio[a]					78.1	71.2	75.1	74.5
a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax-hr, AUC(tf) ratio (metabolite-to-parent)-%								

Table Q4.2. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL, 3-OH DL and fexofenadine following single administration of the treatments

	(DL with GFJ) / (DL Alone)		(DL with GFJ) / (DL Alone)		(Allegra with GFJ/(Allegra Alone)	
Parameter	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
	SCH 34117		SCH 45581		Fexofenadine	
Cmax	107	100-115	105	100-111	69	59-80
AUC(tf)	110	104-116	105	99-111	69	61-77
AUC(I)	109	104-114	105	99-110	70	62-79

CONCLUSION

The data from this study showed that grapefruit juice had no effect on the Cmax and AUC values of DL or 3-OH DL, but reduced both Cmax and AUC values of fexofenadine by 30%.

COMMENTS TO THE MEDICAL OFFICER

- There were two subjects (4 and 22) identified as poor metabolizers. These subjects had AUCmet/AUCparent of less than 10%. These subjects did NOT appear to have the same effect on fexofenadine since the Cmax and AUCt values were close to the mean values (mean Cmax=201 ng/mL; mean AUCt=1130 ng*hr/mL).

Drug	DL		3-OH		Fexofenadine	
PK parameter	alone	With GFJ	alone	With GFJ	alone	With GFJ
	Subject 4					
Cmax (ng/mL)						
AUCt (ng*hr/mL)						
Ratio %						
	Subject 22					
Cmax (ng/mL)						
AUCt (ng*hr/mL)						
Ratio %						

- The subjects used on this study do not represent the population evenly since from the 23 subject completing the study 19 were Hispanic, 2 were Black and 3 were Caucasian.

Q5. Does Prozac affect the PK and PD (ECG parameters) of desloratadine and its metabolite?

The sponsor conducted study P01378 to evaluate the effect of co-administration of desloratadine in combination with fluoxetine on the pharmacokinetics of DL and its metabolite, 3-OH DL, in healthy adult subjects.

Fifty-four healthy adults completed this randomized, open-label, parallel group, third-party blind, multiple dose 35-day study. Subjects were randomized to receive: Group A (DL with Flu), Group B (DL with Placebo), Group C (Flu with Placebo).

The mean pharmacokinetic parameters for DL and its metabolite are summarized in Table Q5.1. The mean (arithmetic) Cmax value of DL increased by 18% with co-administration of fluoxetine compared to DL alone; however, fluoxetine had no effect on AUC of DL. The corresponding mean parameters of 3-OH DL increased by 14-18% with co-administration of fluoxetine. According to the sponsor, these increments are clinically insignificant, suggesting that DL is not a substrate of CYP2D6. However, 90% CI applied to DL Cmax were out of the 80-125% bioequivalence guideline (Table Q5.2).

Table Q5.1. Mean (CV%) pharmacokinetic parameters of DL and 3-OH on Day 35 following multiple administration of Clarinex 5mg with and without fluoxetine

	Desloratadine				3-OH DL			
	DL with placebo		DL with fluoxetine		DL with placebo		DL with fluoxetine	
Parameter	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV
Cmax[a]	3.6	26	4.25	32	1.57	26	1.86	34
Tmax[a]	2.42	50	1.83	61	5.11	45	4.08	62
AUC(0-24h)[a]	54.3	36	53.9	30	27.2	26	31.1	36
AUC(0-24h)ratio[a]					56.8	43	32.7	58
a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax-hr, AUC(tf) ratio (metabolite-to-parent)-%								

Table Q5.2. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of Dl, 3-OH DL with and without fluoxetine

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

Fluoxetine Cmax and AUC were reduced by 9% and 11%, respectively during co-administration with DL. The corresponding mean parameters of norfluoxetine increased by 22% and 18%, respectively (Table Q5.3). 90% CI for both Cmax and AUC point estimates, were out of the 80-125 BE guideline (Table Q5.4).

Table Q5.3. Mean (CV%) pharmacokinetic parameters of fluoxetine and norfluoxetine on Day 35 following multiple administration of Clarinex 5mg with and without fluoxetine

	Fluoxetine (Flu)				Norfluoxetine			
	Flu with placebo (n=17)		Flu with DL (n=18)		Flu with placebo (n=17)		FLu with DL (n=18)	
Parameter	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV
Cmax[a]	70.9	54	61.5	34	82.9	28	99.4	19
Tmax[a]	7.89	50	7.56	42	8.39	77	7.58	74
AUC(0-24h)[a]	1442	56	1191	32	1719	31	1981	22
AUC(0-24h)ratio[a]					145	43	184	41
a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax-hr, AUC(tf) ratio (metabolite-to-parent)-%								

Table Q5.4. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of fluoxetine and norfluoxetine with and without DL

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

The results of the statistical analysis (Table Q5.5) 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. There was a marginally significant difference ($p=0.055$) in ventricular rate between DL in combination with fluoxetine and fluoxetine alone. 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 Q5.5. Mean[b] 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[a]	0.2	3.1	0.4	8.5	0.31	0.94
QRS[a]	-0.2	1.1	0.2	4.3	0.36	0.76
QT[a]	-0.7	-8.4	3.8	22.1	0.30	0.55
QTc[a]	8.2	6.9	6.4	10.6	0.71	0.61
Ventricular Rate[a]	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 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 Q5.6).

Table Q5.6. 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[a]	DL 5 mg Plus Placebo[b]	Placebo Plus Flu[c]	Pairwise Comparisons A/B	Pairwise Comparisons 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.

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 13% and 17%, 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

- 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. 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 and this reviewer agrees with this 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.

Q6. Does azithromycin affect the PK and PD (ECG parameters) of desloratadine and its metabolite?

The sponsor conducted study P01381 to evaluate the effect of co-administration of desloratadine in combination with azithromycin on the pharmacokinetics of DL and its metabolite in healthy adult subjects. Ninety healthy adults completed this randomized, open-label, parallel group, third-party blind multiple-dose 7-day study. Subjects were randomized to receive: Group A (DL with AZ), Group B (DL with Placebo), Group C (AZ with Placebo), Group D (FX with AZ), and Group E (FX with Placebo).

Co-administered of azythromycin with Clarinex 5 mg tablets resulted in increases in DL Cmax by (19%) and DL AUC by (7.7%) and 3-OH DL Cmax by (14%) (Table Q6.1). 90% CI applied to Cmax and AUC were out of the 80-125% bioequivalence guideline (Q6.2).

Table Q6.1. Mean (CV%) pharmacokinetic parameters of DL and 3-OH on Day 7 following multiple administration of Clarinex 5mg with and without azithromycin

	Desloratadine				3-OH DL			
	DL with placebo (n=18)		DL with azithromycin (n=18)		DL with placebo (n=18)		DL with azithromycin (n=18)	
Parameter	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV
Cmax[a]	3.6	37	4.3	46	1.92	31	2.18	27
Cmax (Geom mean)	3.39	-	3.9	-	1.8	-	2.11	-
Tmax[a]	3.75	48	3.2	57	4.8	38	4.11	38
AUC(0-24h)[a]	51.6	41	55.6	47	32.3	30	33.1	26
AUC(0-24h)[a] (geom mean)	47.9	-	50.2	-	30.9	-	32.1	-
AUC(0-24h)ratio[a]				-	72.9	50	74	70
a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax-hr, AUC(tf) ratio (metabolite-to-parent)-%								

Table Q6.2. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of DL, 3-OH DL with and without AZ

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

The statistical results indicated that when fexofenadine was administered with azithromycin both the rate (Cmax) and extent of absorption of fexofenadine increased by 69 and 67%, respectively (Table Q6.3).

Table Q6.3. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of Fexofenadine with and without AZ

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

Fexofenadine reduced azithromycin Cmax by 13% and AUC by 12%. DL increased azithromycin Cmax by 40% and AUC by 19%. 90% CI for both AZ Cmax and AZ AUC were out of the 80-125 BE guideline (Table Q6.4).

Table Q6.4. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of AZ with and without DL or fexofenadine

	(AZ with DL) / (AZ without DL)		(AZ with Fexofenadine) / (AZ without fexofenadine)	
Parameter	Ratio	90% CI	Ratio[a]	90% CI
Cmax	131	92-187	87	61-124
AUC(0-24h)	112	83-153	88	65-120

The results of the statistical analysis (Table Q6.5) 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.

Table Q6.5. 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[a]	1.8	0.4	1.4	0.65	0.91
QRS[a]	-0.9	0	0	0.68	0.68
QT[a]	-7.4	-8.2	-10	0.9	0.7
QTc[a]	-4.2	-6.3	-0.1	0.61	0.32
Ventricular Rate[a]	4.8	5.3	4.5	0.85	0.92

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

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. This reviewer supports the sponsor's opinion.

With respect to fexofenadine, 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-administration 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 40% and AUC by 19%.
- 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. These increments are most likely clinically insignificant. 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%. 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 clinically insignificance of the findings. A communication letter has been sent to the special pathogens division to inform them on the effect of DL on the pharmacokinetics of azithromycin.
- There were no statistically significant differences in ECG parameters (PR, QRS, QT, and QTc) between DL alone or in combination with AZ.
- Fexofenadine has no statistically significant treatment effect (interaction of FX and AZ) on any of the ECG parameters.

Q7. Does cimetidine affect the PK and PD (ECG parameters) of desloratadine and its metabolite?

The sponsor conducted study P01868 to compare the multiple-dose pharmacokinetic parameters of DL and its metabolite following oral administration of DL alone or in combination with cimetidine in healthy adult subjects. Thirty-six healthy adults (18 males and 18 females) completed this randomized, open-label, parallel group, multiple-dose study. Subjects were randomized to: Treatment A (DL alone), and Treatment B (DL with cimetidine).

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 Cmax (~10%) and AUC (~19%) values of DL at steady state after co-

administration of cimetidine compared to DL alone. The mean Cmax of the metabolite decreased by about 10% and the mean AUC of the metabolite remained unchanged at steady state with co-administration of cimetidine (Tables Q7.1). 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.

Although 90% CI (Table Q7.2) 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 (Figure Q7.1).

Table Q7.1. 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).

	Desloratadine				3-OH DL			
	Trt A (n=18)		Trt B (n=18)		Trt A (n=18)		Trt B (n=18)	
Parameter (Day 17)	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV	Arithmetic Mean	%CV
Cmax[a]	2.35	51	2.59	44	1.49	30	1.35	38
Cmax (Geom mean)	2.11		2.34		1.43		1.27	
Tmax[a]	2.61	48	3.06	78	3.94	56	4.44	66
AUC(0-24h)[a]	31.2	59	37.1	54	22.8	27	22.7	37
AUC(0-24h)[a] (geom mean)	27.2		32.3		22		21.4	
AUC(0-24h) ratio[a] (%)	-				72.8	37	67.5	48
Accumulation Index (R) [b]	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 Q7.2. Ninety Percent Confidence Intervals for Day 17 DL and 3-OH DL PK Parameters

	Treatment B/Treatment A			
Parameter	Ratio[a]	90% CI[b]	Ratio[a]	90% CI[b]
	DL		3-OH DL	
Cmax	112	86-145	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.

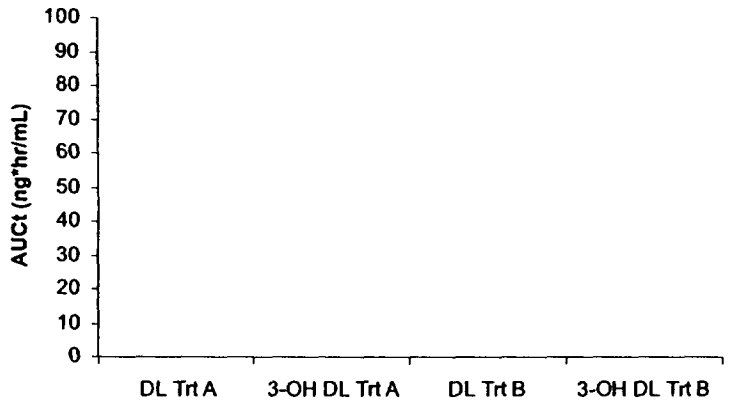


Figure Q7.1. Individual AUCt (day 17) following administration of DL once daily with or without 600 mg Cimetidine.

There was no statistically significant difference between treatment groups 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) (p-value 0.07) (Table Q7.3).

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 ≥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.

Table Q7.3 . 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.

CONCLUSION

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

GENERAL COMMENTS

- 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 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.
- 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 ≥30 ms over baseline values during the treatment period. The clinical relevance of these findings should be evaluated by the medical officer.
- The sponsor did not determine the plasma concentration of cimetidine, therefore, the effect of DL on the pharmacokinetics of cimetidine is unknown.

Q8. Did the sponsor send all the appropriate information to support the suitability of the analytical method?

Yes, the sponsor submitted all the appropriate information that supports that the analytical methods used in NDA 21-363 are accurate, precise, sensitive and specific. The lower limits of quantitation (LOQ) were: [redacted] ng/mL (linear range: [redacted] to [redacted] ng/mL) for DL and 3-OH DL, [redacted] ng/mL (linear range: [redacted] ng/mL) for fexofenadine, [redacted] ng/mL (linear range: [redacted] ng/mL) for azithromycin, and [redacted] ng/mL (linear range: [redacted] ng/mL) for Fluoxetine and norfluoxetine.

In study Validation Results

Table Q8.1. In-study validation information for DL and 3-OH DL (Study P01868)

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

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V. LABELING COMMENTS

The following comments to the label are recommended:

DRAFT

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

VI.2 INDIVIDUAL REPORTS

"INFLUENCE OF GRAPEFRUIT JUICE ON THE ORAL BIOAVAILABILITY OF DESLORATADINE AND FEXOFENADINE ADMINISTERED TO HEALTHY SUBJECTS: A FOUR-WAY CROSSOVER STUDY"

Name of Sponsor:	Schering-Plough Corporation
Included Protocols:	P01380
Development Phase of Study:	I
Study Initiation Date:	5 JAN 2000
Study Completion Date:	30 MAR 2000
Sponsor's Project Director:	Christopher Banfield, Ph.D.
Sponsor's Project Physician:	Mark Marino, M.D.
Date of the Report:	31 JUL 2000
Clinical Documentation Accession Number:	1513361

OBJECTIVE

- To assess the effect of grapefruit juice on the bioavailability of desloratadine (5 mg) and fexofenadine (60 mg) in the same healthy adult population.

SUBJECTS

Twenty-four subjects (13 males and 11 females) were enrolled in the study and 23 successfully completed this study (one female became pregnant and discontinued). The subjects were between the ages of 19 and 44 years (mean=32.6 years) and weighed between 53 and 95 kg (mean=71.4 kg). Nineteen subjects were Hispanic, 2 were Black and 3 were Caucasian.

STUDY DESIGN AND TREATMENT ADMINISTRATION

Twenty-three (13 M, 10 F) healthy adults completed this randomized, open-label, 4 period crossover single-dose study. Subjects received each of the following four treatments separated by a 10 day washout period:

Treatment A:	Desloratadine (DL) 1 x 5-mg tablet with 240 mL water following a 0-hr fast.
Treatment B:	Desloratadine (DL) 1 x 5-mg tablet with 240 mL grapefruit juice following a 10-hr fast.
Treatment C:	Fexofenadine (Allegra) 1 x 60-mg capsule with 240 mL water following 10-hr fast.
Treatment D:	Fexofenadine (Allegra) 1 x 60-mg capsule with 240 mL grapefruit juice following a 10-hr fast.

Subjects randomized to receive grapefruit juice (Treatments B and D) were pretreated with 240 mL grapefruit juice for 2 days (at 8 am, 2 pm and 8 pm each day) prior to drug administration (Treatment Day).

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

Strength	5 mg DL
Formula. No.	3408
Batch No.	38833-146
FMR No.	99592D09
Manf. Date	4/20/98
Manf. Site	Kenilworth, NJ
Batch Size (tablets)	[redacted]

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

PHARMACOKINETIC MEASUREMENTS

Blood Sampling

Blood samples for fexofenadine, DL and 3-OH DL determinations were drawn immediately prior to drug administration (0 hour) and then at, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96 and 120 hr post-dose.

Analytical Method

Plasma DL, 3-OH DL and fexofenadine concentrations were determined using validated [redacted] methods with lower limits of quantitation (LOQ) of [redacted] ng/mL (linear range: [redacted] ng/mL) for DL and 3-OH DL, and [redacted] ng/mL (linear range: [redacted] ng/mL) for fexofenadine, respectively.

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) and fexofenadine concentration-time data were used to determine the pharmacokinetic parameters using model-independent methods.

Statistical Analysis

Summary statistics (mean and %CV) were calculated for the concentration data at each sampling time and for the derived pharmacokinetic parameters. The

pharmacokinetic parameters were then subjected to statistical analysis by using a cross-over analysis of variance (ANOVA) model. Cmax and AUC values were log-transformed, and 90% confidence intervals (CI) for the mean difference between the treatments expressed as a percent of each treatment mean were calculated.

RESULTS

Analytical Method

Pre-Study Validation: The sponsor did not report data regarding pre-study validation, therefore, the % of recovery and stability are unknown for fexofenadine. The lower limit of quantitation (LOQ) for fexofenadine, using [redacted] mL of plasma, was the concentration of the lowest calibration standard curve, [redacted] ng/mL.

In study Validation Results

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

	DL	3-OH DL	Fexofenadine
Linearity	Satisfactory: Standard [redacted]	Satisfactory: Standard [redacted]	Satisfactory: Standard [redacted]
Accuracy	Satisfactory: [redacted]	Satisfactory: - [redacted]	Satisfactory: [redacted]
Precision	Satisfactory: [redacted]	Satisfactory:	Satisfactory:
Specificity	Satisfactory: [redacted] submitted	Satisfactory: [redacted] submitted	Satisfactory: [redacted] submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for DL and it metabolite and for fexofenadine following administration of clarinex 5mg tablets with and without grapefruit juice are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for DL and its metabolite and fexofenadine with and without the juice are summarized in Table 3 and 4, respectively. Figure 1 and Table 3 show that the mean and the median Cmax, Tmax and AUC values of SCH 34117 were comparable with and without grapefruit juice indicating that the grapefruit juice had no effect on rate and extent of absorption SCH 34117.

Individual DL and 3-OH DL Cmax and AUC(inf) values following the administration of the clarinex 5mg are shown in Figures 4 and 5, respectively. Likewise, individual Cmax and AUCinf for fexofenadine with and without the juice are represented in Figures 6. The rate of metabolism of SCH 34117 in Subjects 4 and 22 (Figures 4 and 5) appears to have been slower than that in the other subjects. These subjects were identified as slow metabolizers because their AUC ratios (metabolite-to-parent) were less than 10%.

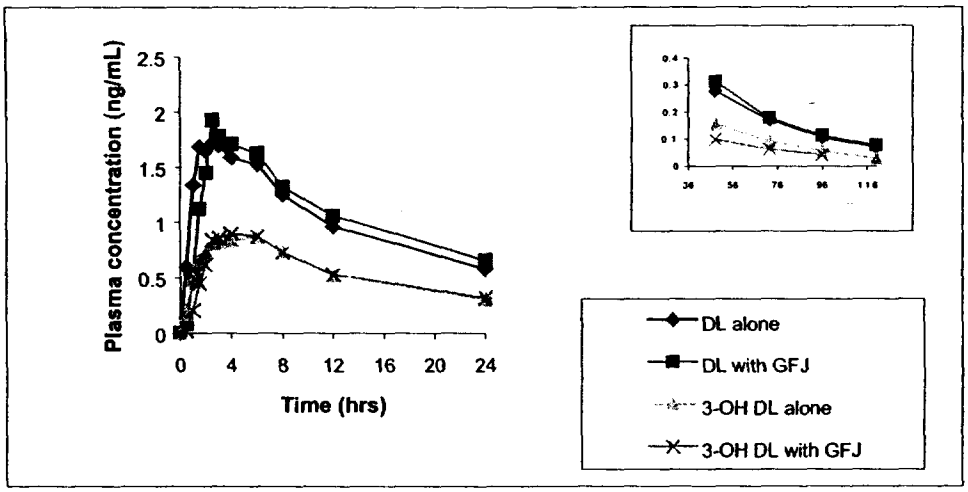

Figure 1. Mean DL and 3-OH DL plasma concentration-time profile following single administration of Clarinex 5 mg tablets with and without grape fruit juice. The insert represents the terminal phase of the profile.

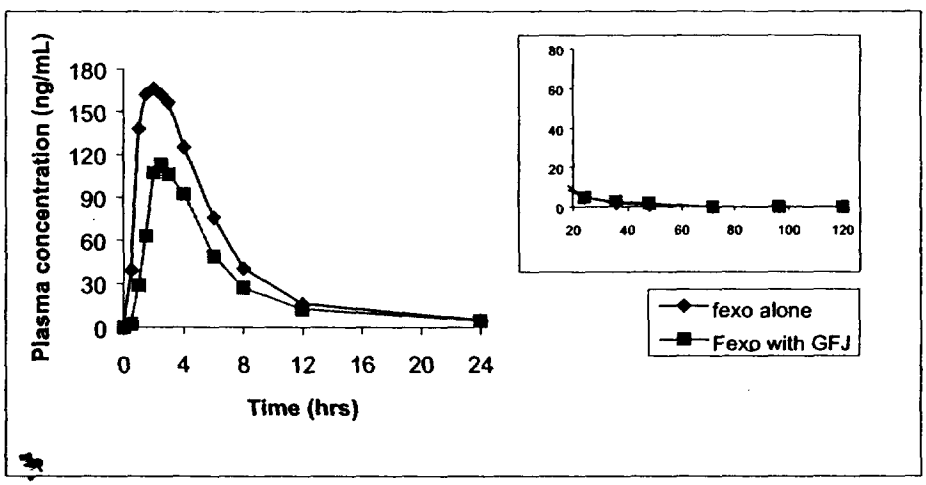

Figure 2. Mean fexofenadine plasma concentration-time profile following single administration of fexofenadine 60-mg capsules with and without grape fruit juice. The insert represents the terminal phase of the profile.

Table 3. Mean pharmacokinetic parameters of DL and 3-OH following single administration of Clarinex 5mg with and without grapefruit juice

	SCH 34117 (n = 23)				SCH 45581 (n = 23)			
	DL Alone		DL with GFJ		DL Alone		DL with GFJ	
Parameter	Arithmetic Mean	Median	Arithmetic Mean	Median	Arithmetic Mean	Median	Arithmetic Mean	Median

Cmax[a]	2.06	2.10	2.14	2.13	0.923	0.930	0.980	0.930
Tmax[a]	3.41	2.50	3.57	2.50	4.96	6.00	5.48	6.00
AUC(tf)[a]	45.5	38.4	48.7	37.4	24.4	24.4	25.2	25.6
AUC(I)[a]	52.5		55.5		26.2		27.2	
AUC(tf) ratio[a]					78.1	71.2	75.1	74.5
a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax-hr, AUC(tf) ratio (metabolite-to-parent)-%								

Table 4 and Figure 2, 5 and 6 show that the mean and median Cmax and AUC values of fexofenadine were reduced in the presence of grapefruit juice. In addition, the median Tmax value was 0.5 hr longer with GFJ. Table 5 indicates that indicate that when fexofenadine was administered with grapefruit juice both the rate (Cmax) and extent of absorption of fexofenadine was reduced by 30%.

Table 4. Mean pharmacokinetic parameters of fexofenadine following single administration of Allegra 60mg capsule with and without grapefruit juice

	Fexofenadine (n = 23)			
	Allegra Alone		Allegra with GFJ	
Parameter	Arithmetic Mean	Median	Arithmetic Mean	Median
Cmax[a]	201	181	128	132
Tmax[a]	2.28	2	2.57	2.5
AUC(tf)[a]	1130	987	756	717
AUC(I)[a]	1151		791	
a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax-hr, AUC(tf) ratio (metabolite-to-parent)-%				

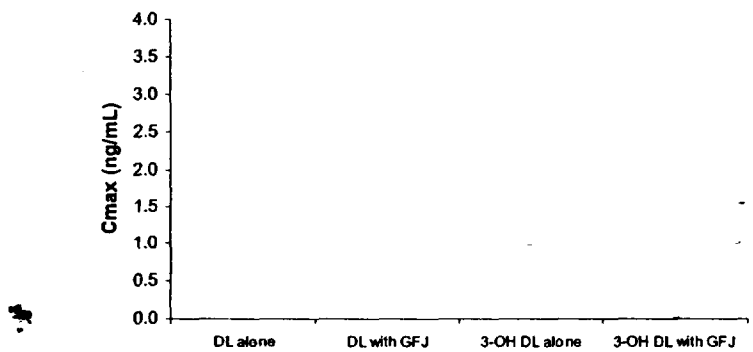

Figure 3. Individual DL and 3-OH DL Cmax values following single administration of Clarinex 5mg tablets with and without grapefruit juice (GFJ). Linking lines represent Cmax values for slow metabolizes.

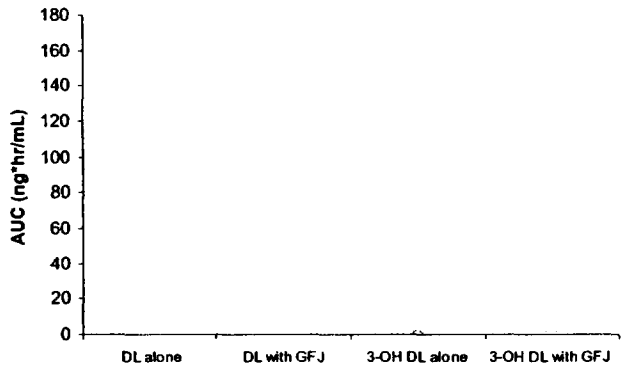

Figure 4. Individual DL and 3-OH DL AUCtf values following single administration of Clarinex 5mg tablets with and without grapefruit juice. Linking lines represent AUCt values for slow metabolizes.

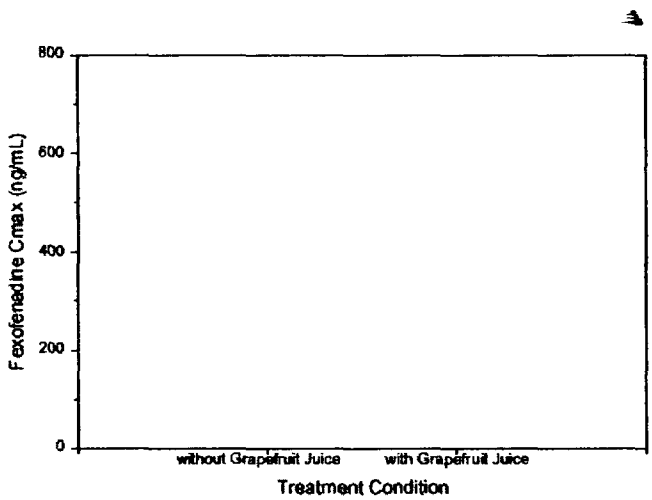

Figure 5. Individual Fexofenadine Cmax values following single administration of Allegra 60 mg capsules with and without grapefruit juice.

Preliminary statistical analysis was performed to examine the extreme pharmacokinetic values and the impact of outliers on the overall results. It was found that exclusion of outliers did not change the overall bioequivalence conclusion of the study. Therefore, all subjects were included in the final statistical analysis.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for DL, its metabolite and fexofenadine are presented in Table 5. The CIs of AUC(I) and Cmax for DL and its metabolite after Clarinex 5mg indicate that when SCH 34117 was administered with grapefruit juice there was no change in the rate and extent of absorption of DL or its metabolite.

The CIs of AUC(I) and Cmax for DL D-12 relative to Drixoral also met the 80-125% bioequivalence guideline.

The results indicated that grapefruit juice does not affect the BA of Dl and its

metabolite.

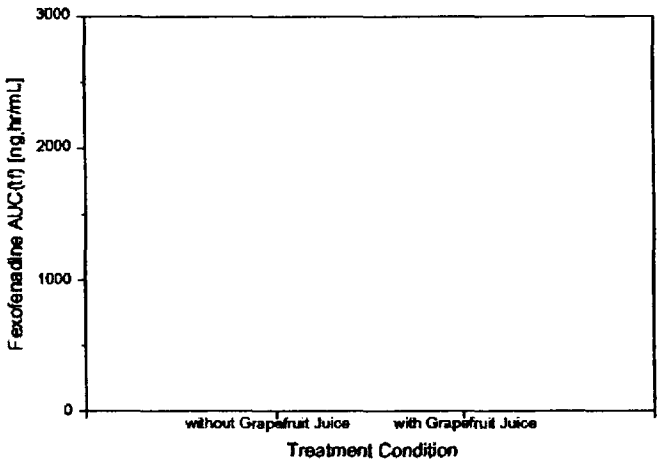

Figure 6. Individual Fexofenadine AUCt values following single administration of Allegra 60 mg capsules with and without grapefruit juice.

Table 5. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of Dl,3-OH DL and fexofenadine following single administration of the treatments

	(DL with GFJ) / (DL Alone)		(DL with GFJ) / (DL Alone)		(Allegra with GFJ/(Allegra Alone)	
Parameter	Ratio[a]	90% CI	Ratio[a]	90% CI	Ratio[a]	90% CI
	SCH 34117		SCH 45581		Fexofenadine	
Cmax	107	100-115	105	100-111	69	59-80
AUC(tf)	110	104-116	105	99-111	69	61-77
AUC(I)	109	104-114	105	99-110	70	62-79

CONCLUSION

- Grapefruit juice had no effect on the Cmax and AUC values of DL or 3-OH DL
- Grapefruit juice reduced both Cmax and AUC values of fexofenadine by 30%.

COMMENTS TO THE MEDICAL OFFICER

- There were two subjects (4 and 22) identified as poor metabolizers. These subjects had AUCmet/AUCparent of less than 10%. These subjects did appear to have the same effect on fexofenadine since the Cmax and AUCt values were close to the mean values (mean Cmax=201 ng/mL; mean AUCt=1130 ng*hr/mL).

Drug	DL		3-OH		Fexofenadine	
PK parameter	**alone**	**With GFJ**	**alone**	**With GFJ**	**alone**	**With GFJ**
	Subject 4					
Cmax (ng/mL)						
AUCt (ng*hr/mL)						
Ratio %						
	Subject 22					
Cmax (ng/mL)						
AUCt (ng*hr/mL)						
Ratio %						

- The subjects used on this study do not represent the population evenly since form the 23 subject completing the study 19 were Hispanic, 2 were Black and 3 were Caucasian.

"EVALUATION OF THE PHARMACOKINETICS AND ELECTROCARDIOGRAPHIC PHARMACODYNAMICS OF DL WITH CONCOMITANT ADMINISTRATION OF PROZAC®"

Name of Sponsor:	Schering-Plough Corporation
Included Protocols:	P01378
Development Phase of Study:	I
Study Initiation Date:	Mar 5, 2000
Study Completion Date:	April 20, 2000
Sponsor's Project Director:	Christopher Banfield, Ph.D.
Sponsor's Project Physician:	Mark Marino, M.D.
Date of the Report:	Dec 21, 2000
Clinical Documentation Accession Number:	1619477

OBJECTIVE

- To evaluate the effect of co-administration of desloratadine in combination with Fluoxetine 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

Fifty-four subjects (38 males and 16 females) were enrolled and completed this study. The subjects were between the ages of 22 and 49 years (mean=37.1 years) and weighed between 54 and 100 kg (mean=76.2 kg). Forty-nine subjects were Caucasian, four were Black and one was American Indian.

STUDY DESIGN AND TREATMENT ADMINISTRATION

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

Group A (DL with Flu):	One DL 5-mg tablet on Day 1 (AM) and once daily Fluoxetine (Flu) Pulvule ® 20 mg on Days 6-35 (AM) plus once daily DL 5-mg tablet on Days 29-35 (AM); n=18 (14M, 4F).
Group B (DL with Placebo):	One DL 5-mg tablet on Day 1 (AM) and once daily DL placebo on Days-6-35 (AM) plus once daily DL 5-mg tablet on Days 29-35 (AM); n=18 (13M, 5F).
Group C (Flu with Placebo):	One DL placebo tablet on Day 1 (AM) and once daily Fluoxetine (Flu) Pulvule ® 20 mg on Days 6-35 (AM) plus once daily DL placebo tablet on Days 29-35 (AM); n=17 (11M, 6F).

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