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*APPLICATION NUMBER:*

**21-300**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

# Clinical Pharmacology and Biopharmaceutics (OCPB) Review

**NDAs: 21-300**

**Date of Submission:** December 8, 2000 (Original)  
February 27, 2004 (current)  
July 9, 2004  
July 20, 2004  
August 10, 2004  
August 12, 2004

**Generic Name**

Desloratadine

**Brand Name:**

CLARINEX™ Syrup

**Formulations:**

Syrup (0.5 mg/ml)

**Route of Administration:**

Oral

**Indication:**

Seasonal Allergic Rhinitis (SAR) and Chronic Idiopathic Urticaria (CIU)

**Type of Submission:**

Response to the Approvable Letter/Resubmission

**Sponsor:**

Schering Corporation, Kenilworth, NJ

**Reviewer:**

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# 1. Executive Summary

## 1.1 Recommendation:

The office of Clinical Pharmacology and Biopharmaceutics found this NDA acceptable. Also, from OCPB perspective, this submission is considered a complete response to the approvable letter dated October 2, 2001.

## 1.2 Phase 4 Commitments

No Phase 4 commitments are applicable for this submission.

## 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor studied the response of 104 pediatric poor metabolizers treated with DL or loratadine in placebo-controlled trials of 2- to 5-weeks duration. This included three prospective multiple-dose studies in which DL was administered to children 2- to 11-years old, including 78 poor metabolizers (#P02798, P03016, and P02994).

Additional multiple-dose safety data in pediatric poor metabolizers were obtained from 16 children previously treated with DL in two safety studies (# P00302 and P00303), and 10 children previously treated with loratadine in Study (# C98-566). These subjects were *retrospectively* phenotyped for DL metabolizer status, and their safety including ECG were monitored (Study #P02781).

In these studies, patients were considered poor metabolizers based on the ratio of 3-OH DL/DL. Those with a ratio of <0.1 or <10% were considered poor metabolizers and those greater than >0.1 (or >10%) were considered normal. However, those patients who had a ratio of >0.25 (or >25%) were enrolled in further safety studies.

In terms of metabolism, the sponsor made extensive effort and conducted several *in vitro* studies to identify the isozymes or enzymes responsible for the metabolism of DL. The results of these studies were previously submitted and discussed at the meeting held with the sponsor on March 8, 2002.

### What are the Main Findings?

From these studies it can be concluded that the exposure to DL in poor metabolizers was **6 fold** higher than normal subjects (**Tables 1.1 and 1.2 and Figures 1.1 and 1.2**). Also, the exposure was similar in pediatric and adult subjects at age-appropriate doses. Therefore, the DL poor metabolizer phenotype is independent of age. The steady state level was achieved by Day 15 (**Table 1.3**).

Based on two phenotyping screening studies (#P02818 and P03031), the prevalence of poor metabolizers is expected to range from 10% to 20% in Blacks and 1% to 5% in Caucasians population.

In all *in vitro* experiments and all enzymes tested, none of the enzymes was found to be responsible for >3% of DL metabolism (ranged from <1 to <3%). Therefore, the enzymes responsible for the metabolism of DL are still unknown.

**Table 1.1. Exposure to DL in Poor Metabolizers Following Multiple Dose Administration of DL (Data from Study # P02798)**

Metabolizer Status	n	Children (2-5 yr)	n	Children (6-11 yr)	n	Adults (Multiple Dose) <sup>a</sup>
AUC(0-24 hr) (ng.hr/mL)						
DL Normal Metabolizer	8	23.4 (14.0-61.8)	12	30.4 (24.0-72.6)	364	44.3 (14.2-158)
DL Poor Metabolizer	4	143 (138-149)	13	223 (125-300)	33	271 (179-406)
Least Square Mean Ratio <sup>b</sup> Poor/Normal Metabolizer	-	5.61 (3.92, 8.04) <sup>c</sup>	-	6.45 (5.10, 8.16) <sup>c</sup>	-	6.01 (5.32, 6.78) <sup>c</sup>
Cmax (ng/mL)						
DL Normal Metabolizer	8	2.05 (1.10-4.31)	12	2.53 (1.71-3.89)	364	3.26 (0.55-11.6)
DL Poor Metabolizer	4	6.78 (6.53-7.04)	13	10.8 (5.94-14.6)	33	13.7 (8.85-23.7)
Least Square Mean Ratio <sup>b</sup> Poor/Normal Metabolizer	-	3.32 (2.40, 4.59) <sup>c</sup>	-	4.04 (3.27, 5.00) <sup>c</sup>	-	4.33 (3.81, 4.93) <sup>c</sup>

a: Dose normalized to 5 mg

b: ANOVA of log-transformed data extracting sources of variation due to age group and metabolizer status. The ratio is a contrast of metabolizer status.

c: Lower and upper 90% confidence interval based on log-transformed data.

**Table 1.2. Exposure to 3-OH DL in Poor Metabolizers Following Multiple Dose Administration of DL (Data from Study # P02798)**

	Children (2-5 yr, P02798)	Children (6-11 yr, P02798)	Adults
AUC(0-24 hr) ng.hr/mL. Median (Range; n)			
DL-Normal metabolizer	13.4 (8.81-17.0; n=8)	18.3 (11.9-28.7; n=12) <sup>b</sup>	28.8 (13.5-59.0; n=328)
DL-Poor metabolizer	2.40 (1.87-4.56; n=4)	3.58 (2.10-11.7; n=13)	4.86 (1.64-18.3; n=28)
Least Square Mean Ratio Poor/Normal Metabolizers	0.21 (0.14-0.31) <sup>c</sup>	0.21 (0.16-0.28) <sup>c</sup>	0.17 (0.16-0.19) <sup>c</sup>
Cmax (ng/mL). Median (Range; n)			
DL-Normal metabolizer	0.76 (0.55-0.97; n=8)	1.22 (0.70-1.76; n=12) <sup>b</sup>	1.64 (0.11-3.96; n=330) <sup>b</sup>
DL-Poor metabolizer	0.12 (0.09-0.37; n=4)	0.19 (0.11-0.77; n=13)	0.20 (0.03-3.63; n=28)
Least Square Mean Ratio Poor/Normal Metabolizers	0.20 (0.12-0.32) <sup>c</sup>	0.21 (0.15-0.29) <sup>c</sup>	0.13 (0.11-0.15) <sup>c</sup>

a: Data from studies P00117<sup>(12)</sup> (excluding Subject No. 22, had no 3-OH DL level), C98-352,<sup>(13)</sup> C98-353,<sup>(14)</sup> C98-356,<sup>(15)</sup> P00275,<sup>(16)</sup> P00272,<sup>(17)</sup> P00883,<sup>(18)</sup> P01858,<sup>(19)</sup> P01378,<sup>(20)</sup> P00884,<sup>(21)</sup> P01381,<sup>(22)</sup> P01430,<sup>(23)</sup> C98-013<sup>(11)</sup> was excluded because 3-OH DL was not measured.

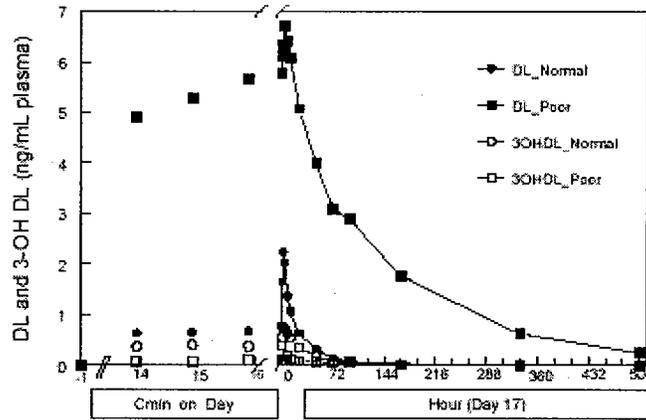
b: Subject No. 114 was excluded from this analysis (Section 9.8).

c: Lower and upper 90% confidence interval based on log-transformed data.

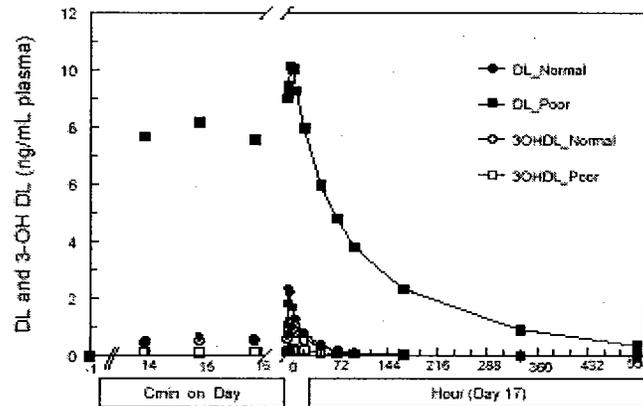
d: Subject No. 22 from Study P00117 had a Cmax value, but did not have an AUC (0-24 hr) value

**Figures 1.1 and 1.2 Mean Plasma Concentration-Time Profiles of DL and 3-OH DL in Children 2-5 years of age (top) and 6-11 years of age (bottom)**

**Figure 1.1: Age: 2-5 years**



**Figure 1.2: Age: 6-11 years**



**Table 1.3. Least Square Mean (95% CI) DL Through Concentrations by Metabolizers Status and by Age Group (Data from Study # P02798)**

Days	Least Square Mean (95% Confidence Interval) Cmin (ng/mL) <sup>d</sup>			
	DL-Normal <sup>a</sup> 2-5 yr n=8	DL-Poor <sup>b</sup> 2-5 yr n=4	DL-Normal <sup>a,c</sup> 6-11yr n=12	DL-Poor <sup>b</sup> 6-11 yr n=13
14	0.64 (0.45-0.84)	4.91 (4.58-5.23)	0.55 (0.36-0.74)	7.66 (7.03-8.29)
15	0.66 (0.46-0.86)	5.29 (4.97-5.62)	0.68 (0.49-0.87)	8.15 (7.52-8.77)
16	0.68 (0.48-0.88)	5.67 (5.35-6.00)	0.62 (0.43-0.81)	7.58 (6.95-8.20)
17	0.79 (0.59-0.99)	5.79 (5.46-6.11)	0.77 (0.57-0.96)	8.99 (8.36-9.62)
18	0.64 (0.44-0.84)	5.07 (4.75-5.40)	0.81 (0.62-1.00)	7.96 (7.33-8.59)

- a. DL-Normal=Normal metabolizer of desloratadine.
- b. DL-Poor=Poor metabolizer of desloratadine.
- c. Excludes Subject No. 114.
- d. ANOVA extracting sources of variability due to subject and day.

### Are There any Safety Concerns In Poor Metabolizers?

An analysis of the data for QTc was performed by OCPB (see Pharmacometric consult of Dr. He Sun). From the analysis of the data, no apparent signal of QTc prolongation has been observed in poor metabolizers compared to normal metabolizers and placebo treatments (Figures 1.3 and 1.4 and Table 1.4).

Overall, there was no difference in other safety parameters between poor and normal metabolizers or placebo. However, this safety observation is strictly limited to the summary data submitted to OCPB and should not be considered in anyway as final or complete. For complete safety assessment, please see the Medical Officer's review.

Figure 1.3

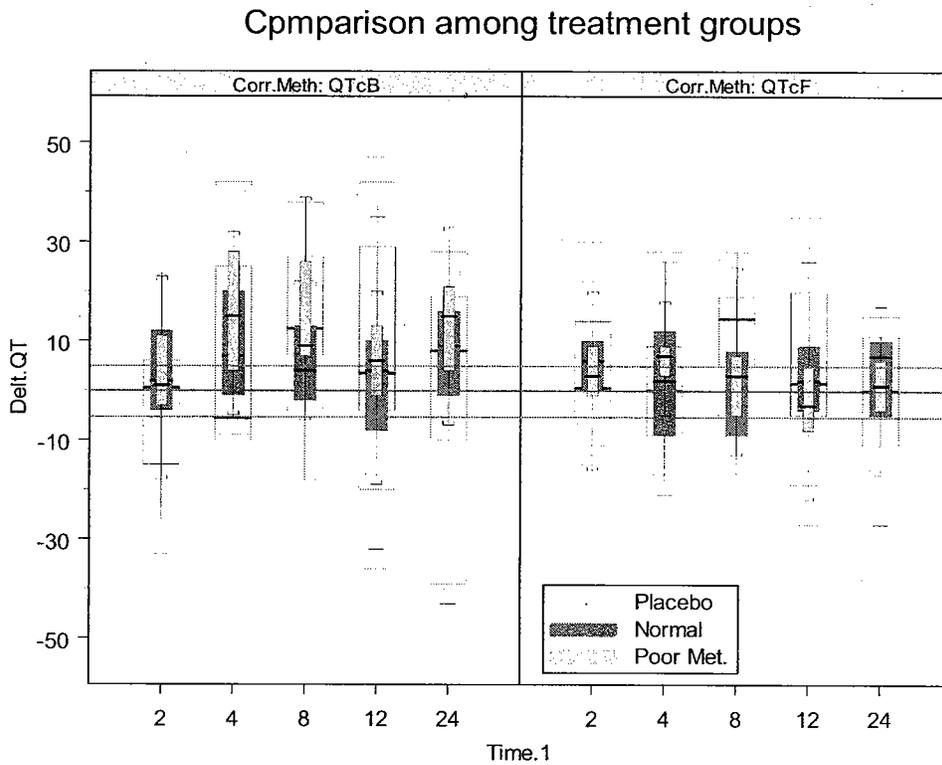


Figure 1.4

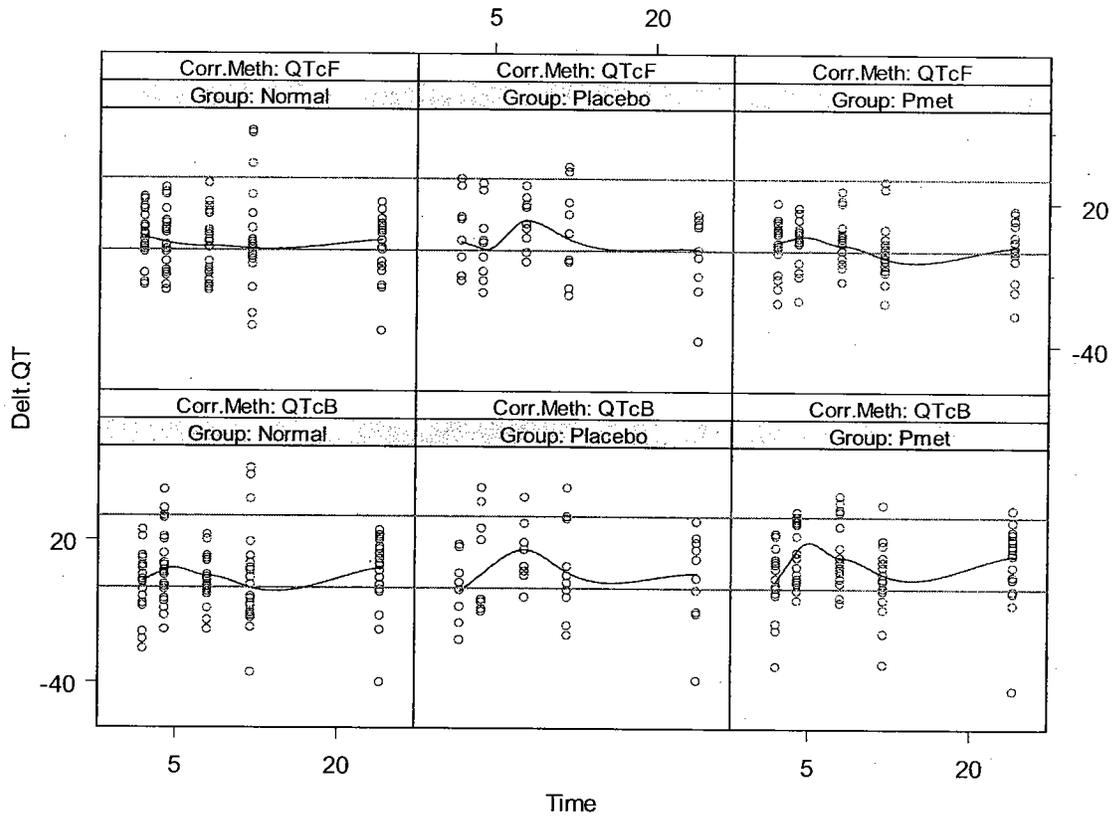


Table 1.4 Mean Change in QTc (msec) from Baseline at Specific Time Points

Time (h) (Correction Methods)	Normal Metabolizers	Placebo	Poor Metabolizers
2B	1.9	-1.6	1.9
2F	6.9	4.5	2.0
4B	8.7	7.7	16
4F	3.5	1.7	4.2
8B	4.0	16	14.0
8F	2	12.3	3.8
12B	4.5	7.6	4.6
12F	6.9	6.0	-0.06
24B	4.9	3.9	10.0
24F	1.9	-2	0.3

## **Overall Summary and Conclusions:**

Based on all the information submitted, the following main conclusions can be made:

- The exposure in poor metabolizers to DL is approximately **6 fold** higher than normal subjects. Overall, no apparent safety concern was observed in these subjects (see Medical Officer's review).
- The exposure was independent of age.
- The prevalence of poor metabolizers of DL appears to be higher in Blacks (10%-20%) compared to Caucasians (1%-5%).
- The isozymes and enzymes responsible for the conversion of DL to 3-OH DL remain unknown.
- Steady state concentration was achieved by Day 15.
- Overall, no apparent safety concern was noted in all populations.

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On Original**

## 2.0

# Clinical Pharmacology and Biopharmaceutics Review (Question Based Review)

### 2.1. What is the General Attribute to the Drug?

This is a response to the approvable letter. All the relevant clinical pharmacology and biopharmaceutics information for this drug product has been reviewed in the first review cycle. Therefore, only the pertinent information related to the sponsor's response to the approvable letter will be discussed in this review (please see the original OCPB review dated September 21, 2001).

### 2.2 What is the General Clinical Pharmacology?

As stated above, the general clinical pharmacology of this drug product has been reviewed in the first review cycle (please see the original OCPB review).

The main finding in this submission is that exposure to DL in poor metabolizers was **6 fold** higher than normal subjects. This exposure was independent of age and was also similar to adult subjects. In all studies, the steady state level was achieved by Day 15. In all studies, the prevalence of poor metabolizers was approximately 10% to 20% in Blacks and 1% to 5% in Caucasians population.

The sponsor conducted extensive research work to identify the enzymes responsible for the conversion of DL to 3-OH DL. Based on all experiments, no enzyme was found to be responsible for more than 3% of the conversion of DL to 3-OH DL. Therefore, the enzymes responsible for the metabolism of DL are unknown.

#### 2.2.1 Does this Drug Prolong the QT or QTc Interval?

No signals for prolongation in QTc intervals were noted in this submission. This conclusion was based on the analysis of the individual QTc data as shown in **Figures 2.2.1.1 and 2.2.1.2 and table 2.2.1.1** (see also the Medical Officer's Review and the pharmacometric consult section, 4.3).

In addition, no major adverse events were noted in OCPB submitted studies (please see the Medical Officer's review).

Figure 2.2.1.1

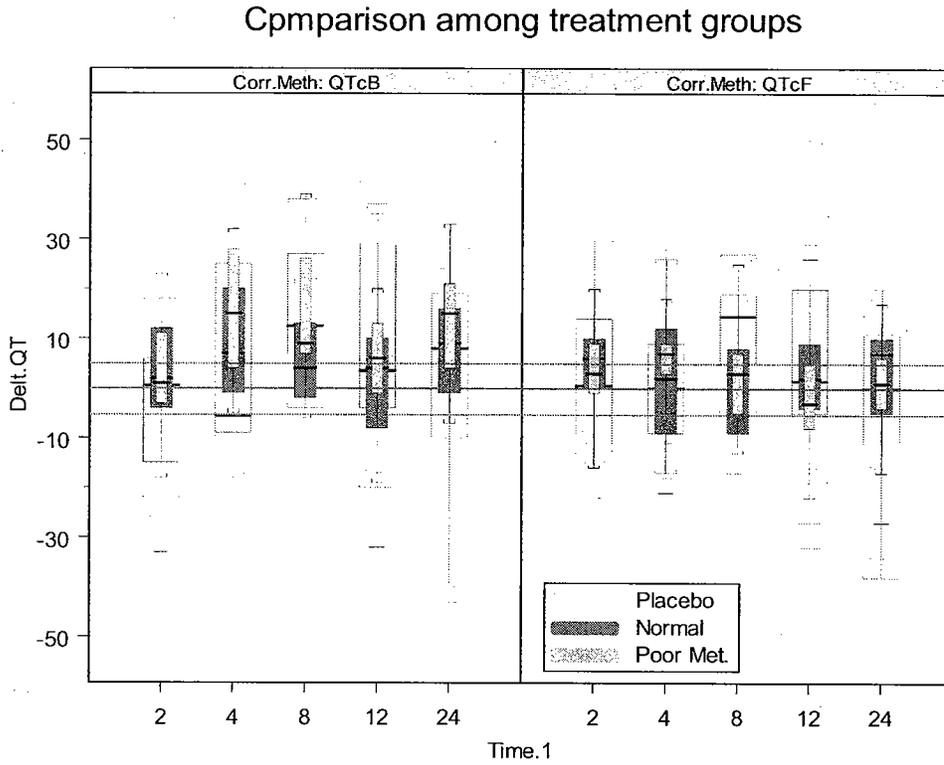
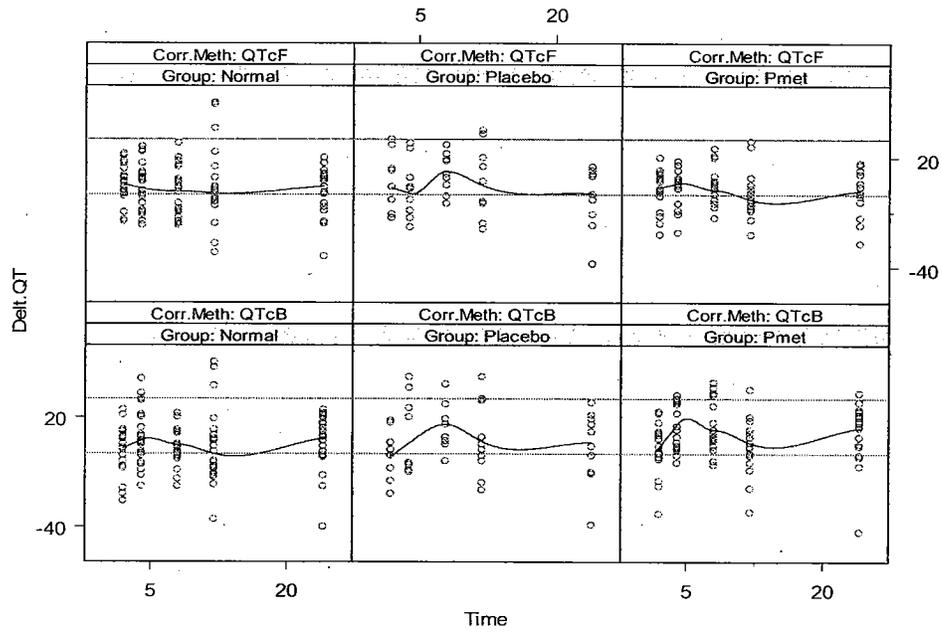


Figure 2.2.1.2



**Table 2.2.1.1 Mean Change in QTc (msec) from Baseline at Specific Time Points**

<b>Time (h) (Correction Methods)</b>	<b>Normal Metabolizers</b>	<b>Placebo</b>	<b>Poor Metabolizers</b>
<b>2B</b>	<b>1.9</b>	<b>-1.6</b>	<b>1.9</b>
<b>2F</b>	<b>6.9</b>	<b>4.5</b>	<b>2.0</b>
<b>4B</b>	<b>8.7</b>	<b>7.7</b>	<b>16</b>
<b>4F</b>	<b>3.5</b>	<b>1.7</b>	<b>4.2</b>
<b>8B</b>	<b>4.0</b>	<b>16</b>	<b>14.0</b>
<b>8F</b>	<b>2</b>	<b>12.3</b>	<b>3.8</b>
<b>12B</b>	<b>4.5</b>	<b>7.6</b>	<b>4.6</b>
<b>12F</b>	<b>6.9</b>	<b>6.0</b>	<b>-0.06</b>
<b>24B</b>	<b>4.9</b>	<b>3.9</b>	<b>10.0</b>
<b>24F</b>	<b>1.9</b>	<b>-2</b>	<b>0.3</b>

**2.3 Is there any Intrinsic Factors?**

DL is converted to 3-OH DL. The enzymes responsible for its conversion are not known at this time. In a subgroup of population the conversion of DL to 3-OH DL is markedly reduced. Subjects were classified based on their metabolic status as poor or normal metabolizers. This was based on the ratio of 3-OH DL to DL. Those with a ratio of <10% were classified as poor metabolizers, whereas those with a ratio of >10% were considered normals. However, those with a ratio of >25% were enrolled in further safety study (Study #02994). In the current submission, the safety and PK profiles of DL have been further characterized in the poor metabolizers sub-population following repeated doses of DL.

**2.4. Is there any Intrinsic Factor Affecting Exposure?**

The prevalence of poor metabolizers appears to be dependent on race and/or ethnic background. For example, the prevalence in Blacks is approximately 10 to 20 % higher than in Caucasians (1-5%). Therefore, the exposure to DL in Blacks is expected to be higher than in Caucasians.

Also, considering the variability in the data, the exposure to DL appears to be independent of age. In other word, the DL exposure in pediatric population appears to be comparable to adults.

**2.5 Is there any Extrinsic Factors?**

As stated above, the main factor affecting exposure is the  status in the conversion of DL to 3-OH DL.

**2.5 Is there any Biopharmaceutics Issues?**

As stated above, the general biopharmaceutics characteristic of the product have been reviewed by OCPB first review cycle. No new biopharmaceutics information and/or changes in formulation have been made since the submission of the original NDA.

## 2.6 Is there any Analytical issues?

Since the original NDA, no changes have been made to the analytical methodology for the determination of DL and 3-OH DL in plasma. The method is validated. For further detail, please see OCPB original review.

In the current submission, no analytical issues have been observed. However, it should be noted that in one study there was measurable plasma concentrations of DL and 3-OH DL in three subjects from the placebo group (Study # P02798). The sponsor believes that these observed concentrations could be due to the accidental use of Claritin by the subjects during the study.

## 2.7 What is the Rationale for the Current Submission? (Genetic and Metabolism of DL)?

This is a response to the Agency's Approvable letter date November 9, 2001. There were several comments to the sponsor in this letter. There were three comments that are directly related to OCPB (comments # 18, 19, and 20).

### Agency's Comment # 18:

"From the submitted pharmacokinetic data, it appears that a substantial number of children whose pharmacokinetic profiles were determined after a single dose had significantly higher exposure (AUC) than most patients to desloratadine and very low levels of 3-hydroxydesloratadine. The exposure to desloratadine resulting from multiple doses has not been determined in children, and in particular, those children with apparent poor metabolism. Moreover, there are no data provided to identify the underlying cause of these high exposure levels. Consequently, there is no means of prospectively identifying those patients who may have such high levels. If these patients are inherently poor metabolizers of desloratadine, then the number of patients who experience these high exposure levels may be much greater particularly if there is a deficient metabolic pathway involved that may be vulnerable to inhibition with concomitant medications."

"Therefore, it will be necessary for you to characterize the pharmacokinetics of repetitive-dose administration with desloratadine in a population determined to be "poor metabolizers" of desloratadine. Once an upper limit of exposure with repetitive dosing has been determined, the safety of this level of exposure will need to be adequately supported in order to gain approval."

### Summary of Sponsor's Response to Comment # 18:

- The sponsor has characterized the PK of repetitive-dose administration of DL and monitored its safety at steady-state in poor metabolizers ages 2-11 years.
- Overall, the exposure to DL in pediatric and adult poor metabolizers was approximately 6 times higher than that in normal metabolizers (Table 2.7.1). The DL poor metabolizer phenotype was independent of age.

**Table 2.7.1. Exposure in Poor Metabolizers Following Multiple Dose Administration of DL**

Metabolizer Status	n	Children (2-5 yr)	n	Children (6-11 yr)	n	Adults (Multiple Dose) <sup>a</sup>
AUC(0-24 hr) (ng.hr/mL)						
DL Normal Metabolizer	8	23.4 (14.0-61.8)	12	30.4 (24.0-72.6)	364	44.3 (14.2-158)
DL Poor Metabolizer	4	143 (138-149)	13	223 (125-300)	33	271 (179-406)
Least Square Mean Ratio <sup>b</sup>	-	-	-	-	-	-
Poor/Normal Metabolizer	-	5.61 (3.92, 8.04) <sup>c</sup>	-	6.45 (5.10, 8.16) <sup>c</sup>	-	6.01 (5.32, 6.78) <sup>c</sup>
C <sub>max</sub> (ng/mL)						
DL Normal Metabolizer	8	2.05 (1.10-4.31)	12	2.53 (1.71-3.89)	364	3.26 (0.55-11.6)
DL Poor Metabolizer	4	6.78 (6.53-7.04)	13	10.8 (5.94-14.6)	33	13.7 (8.85-23.7)
Least Square Mean Ratio <sup>b</sup>	-	-	-	-	-	-
Poor/Normal Metabolizer	-	3.32 (2.40, 4.59) <sup>c</sup>	-	4.04 (3.27, 5.00) <sup>c</sup>	-	4.33 (3.81, 4.93) <sup>c</sup>

a. Dose normalized to 5 mg.

b. ANOVA of log-transformed data extracting sources of variation due to age group and metabolizer status. The ratio is a contrast of metabolizer status.

c. Lower and upper 90% confidence interval based on log-transformed data.

- In terms of safety, there was no evidence that pediatric DL poor metabolizers experienced a different safety profile (please see Medical Officer's Review).

**Agency's Comment # 19:**

"You are encouraged to determine the mechanism accounting for higher levels of drug exposure observed in some patients, and to assess the potential for drug-drug interactions that might be expected based on the explanatory mechanism."

**Summary of Sponsor's Response to Comment # 19:**

The response to this question was discussed, in part, during the meeting held with the sponsor on March 8, 2002. Based on *in vitro* studies, the following conclusions were made by the sponsor:

- No 3-OH DL was detected *in vitro* in any liver tissue preparations. However, loratadine was readily converted to hydroxylated loratadine metabolites and to DL, but DL underwent only minimal metabolism. Thus, no conversion of DL to 3-OH DL was observed *in vitro*.
- No specific isozymes or enzymes were found responsible for the conversion of DL to 3-OH DL. The sponsor conducted several experiments using different CYP450 and other enzyme systems. None was found to have any significant effect. All the enzymes tested showed <1 to <3% effect.

**Reviewer's Comments:**

- It must be acknowledged that the sponsor has conducted several experiments and used the most current technology to identify the isozymes/enzymes responsible for the metabolism of DL to 3-OH DL.
- Therefore, it can be concluded that the sponsor has unsuccessfully been able to identify the enzyme(s). It is certain, however, that the formation of 3-OH DL is not catalyzed by any of the known CYP450s.

- Thus, the potential for drug interaction with DL as a substrate is low for the following reasons:
  - The formation of 3-OH DL is not mediated by any of the known metabolizing enzyme systems.
  - DL and 3-OH DL do not appear to inhibit CYP450 enzymes.
  - The unchanged drug and its metabolites are excreted mainly in urine and feces.

**Agency's Comment # 20:**

“The information requested in comments 18 and 19 above also will be pertinent to all other NDAs for desloratadine products (currently NDAs 21-165, 21-297, 21-300, 21-312, 21-313, and 21-363), although the relative proportion of affected patients may differ in adults compared to children.”

**Response to Comment # 20:**

No response was provided by the sponsor.

**2.8 What Studies Are Submitted in the Current NDA:**

The sponsor submitted 2 new multiple-dose PK studies # P02798 and P03016 in poor metabolizer pediatric population (ages 2-11 years). Among these, other supportive studies were included (Studies # P02818, P02994, P02781, and P03031) and various *in vitro* studies as shown in **Table 2.8.1**. In addition, as part of study #P02781, the sponsor conducted a retrospective safety analysis of Phase III studies that were submitted in the original NDA (Studies # 302 and 303).

It should be noted that some of these studies were submitted and reviewed during the previous review cycle and as part of the communication with the sponsor. Therefore, the focus of the review and discussion will be mainly on the most relevant studies and the new information submitted in the current review cycle.

**Table 2.8.1. List of studies in Pediatric Poor Metabolizers**

Study No.	Study Description	Study Design	Study Population	NDA/ Section
P02818	<b>Prospective Screening Study</b> Single-dose pharmacokinetic study to determine DL metabolic phenotype using loratadine syrup Age ≥2 to <12 years, Subjects received 10 mg loratadine (10 mL of 1 mg/mL loratadine syrup)	Phase-1 Single-dose, open-label	359 atopic subjects, screened to obtain DL poor metabolizers for subsequent safety studies P02798 and P03016	This submission
P02798	<b>Safety and Pharmacokinetics Study</b> Normal and poor DL metabolizers received 1.25 mg DL (≥2 to <6 years), 2.50 mg DL (≥6 year to <12 years), or placebo Duration 17 days.	Phase-1 Multiple-dose, randomized, investigator-blind, placebo-controlled	48 pediatric subjects with allergic rhinitis DL metabolic phenotype identified in Screening Protocol P02818	This submission
P03016	<b>Safety Study</b> Poor DL metabolizers received 1.25 mg DL (≥2 to <6 years), 2.50 mg DL (≥6 year to <12 years), Both normal and poor DL metabolizers received placebo Duration 4 weeks	Phase-3 Multiple-dose, third-party blind, placebo-controlled	42 pediatric DL poor and normal metabolizers with allergic rhinitis identified in Screening Protocol P02818	This submission
P02781	<b>Phenotyping Study</b> Single-dose pharmacokinetic study to determine the DL metabolic phenotype of loratadine-treated subjects from C98-566 and DL-treated subjects from P00302/P00303 Subjects from C98-566 received 5 mg of loratadine syrup Subjects from P00302/P00303, age ≥6 years received DL syrup, 5.0 mg age <6 years received DL syrup, 2.5 mg	Phase-1 Single-dose, open-label	162 total: 51 loratadine subjects enrolled in C98-566 age ≥2 to <6 yrs 60 DL-treated subjects enrolled in P00302 age ≥6 to <12 yrs 51 DL-treated subjects enrolled in P00303 age ≥2 to <6 yrs	This submission
P00302	<b>Safety Study</b> Safety and tolerability of DL syrup. Pediatric subjects received 2.5 mg DL syrup (60 subjects) or placebo syrup (60 subjects) once daily for 15 consecutive days	Phase-3 Randomized, placebo-controlled, parallel-group, double-blind	120 total: age ≥6 to <12 yrs, with a history of allergic rhinitis or chronic idiopathic urticaria,	NDA 21-300 Section 8
P00303	<b>Safety Study</b> Safety and tolerability of DL syrup. Pediatric subjects received 1.25 mg DL syrup (51 subjects) or placebo syrup (60 subjects) once daily for 15 consecutive days	Phase-3 Randomized, placebo-controlled, parallel-group, double-blind	111 total: age ≥2 to <6 yrs, with a history of allergic rhinitis or chronic idiopathic urticaria	NDA 21-300 Section 8

**Table 2.8.1. (continued). List of studies in Pediatric Poor Metabolizers**

Study No.	Study Description	Study Design	Study Population	NDA/ Section
C98-566	<b>Safety Study</b> Safety and tolerability of loratadine syrup. Pediatric subjects received 5.0 mg loratadine syrup (60 subjects) or placebo syrup (61 subjects) once daily for 14 consecutive days	Phase-3 Randomized, placebo- controlled, parallel- group, double-blind	121 total, age $\geq 2$ to $< 8$ yrs, with a history of allergic rhinitis or chronic idiopathic urticaria	NDA 20-641 Section 8
P00117	<b>Pharmacokinetics and Safety Study</b> Pharmacokinetics of DL, 3-OH DL, and 3-OH DL glucuronide determined and compared following oral administration of 5 mg and 7.5 mg DL, and 10 mg loratadine, once daily for 10 consecutive days	Phase-1 Open-label, randomized, multiple-dose, three-way crossover study.	25 total, age 19 to 41 years healthy subjects	NDA 21-165 Section 6
P01341	<b>Pharmacokinetics and Safety Study</b> Subjects received a single dose of 0.625 mg DL (age $\geq 6$ mos to $< 1$ yr) or 1.25 mg DL (age $\geq 1$ yr to $< 2$ yrs)	Single-dose, Randomized, Age Stratified, Parallel- Group, Open- Label study	58 total, age $\geq 6$ mos to $< 2$ yrs with allergic disorders	NDA 21-563 Section 8
P03031	<b>Screening/Phenotyping Study</b> Single-dose pharmacokinetic study to determine DL metabolic phenotype using loratadine syrup Age $\geq 2$ to $< 12$ years, Subjects received 10 mg loratadine (10 mL of 1 mg/mL loratadine syrup)	Phase-1 Single-dose, Open-label	Approximately 2300 pediatric atopic subjects or subjects with CIU screened to obtain DL poor metabolizers for subsequent safety study	Ongoing

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

## 4.2 Individual Study Review

### 4.2.1 Study # P02818:

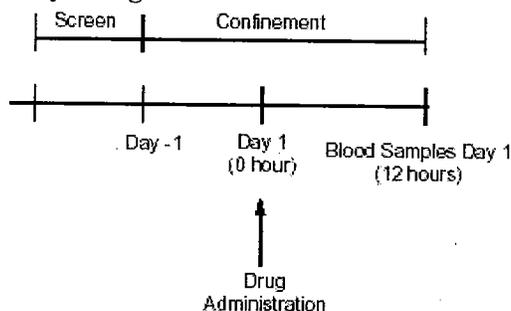
#### Objectives:

This is a one day screening protocol to determine the metabolic phenotype.

#### Design:

In this study, Claritin (loratadine) syrup was used. A single dose of 10 mg (10 ml) was administered to subjects between the ages of 2-12 years. A single blood sample was collected at 12 hours post dose for the determination of the plasma concentration ratio of 3-OH DL relative to DL (Table 4.2.1.1).

Table 4.2.1.1. Scheme of Study Design



#### What are the Study Criteria?

Those subjects with a ratio of <10% or >10% were considered Poor or normal metabolizers, respectively. It should be noted that subjects with a ratio of >25% were considered for subsequent safety studies. A total of 359 subjects were enrolled and completed the study (Table 4.2.1.1).

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**Table 4.2.1.2. Summary of Demographic Characteristics for All Subjects:**

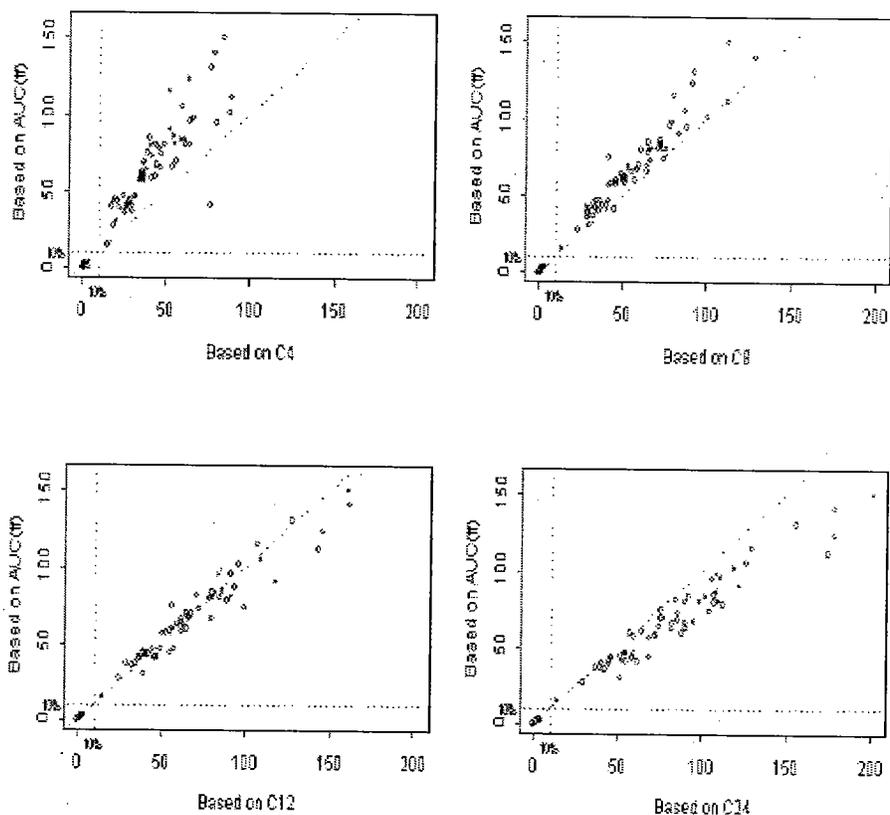
	EL Poor Metabolizer	EL Normal Metabolizer	All Subjects
<b>Number of Subjects</b>			
Number	53	306	359
<b>Age (Years)</b>			
Mean	7.0	6.3	6.4
Standard Deviation	2.74	2.64	2.67
Median	7.0	6.0	6.0
Range (min-max)	2-11	2-11	2-11
<b>Sex (N, %)</b>			
Female	29 (55%)	147 (48%)	176 (49%)
Male	24 (45%)	159 (52%)	183 (51%)
<b>Race (N, %)</b>			
Caucasian	5 (9%)	103 (34%)	108 (30%)
Black	48 (91%)	203 (66%)	251 (70%)
<b>Weight (kg)</b>			
Mean	31.6	26.8	27.5
Standard Deviation	14.78	11.0	11.73
Median	28.8	24.8	25.0
Range (min-max)	12.3-72.7	10.0-75.9	10.0-75.9

**How the Method Was Validated?**

The use of a single 12 hour blood samples instead of AUC was validated by the sponsor in 4 other studies that were submitted in the original NDA (Studies # P00270, P00225, P01125, and P01126). From these studies, the relationship between AUC and single plasma samples collected at 4, 8, 12, and 24 hours post loratadine administration were graphically plotted (**Figure 4.2.1.1**). Based on these plots, the best with AUC correlation was for 12 hour time-point.

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**Figure 4.2.1.1. Phenotype Validation Method: Correlation Between 3-OH/DL AUC and 3-OH DL/DL Concentration Ratio at Selected Time Points**



**Results:**

- Of the 359 subjects, 53 (14.8%) were identified as poor metabolizers with a ratio of <10% (Table 4.2.1.3). Of the 306 subjects determined to be normal metabolizers, 16 had a 3-OH DL to DL % ratio that was between 10% and 25%. Thus they were not eligible for subsequent safety studies.
- Based on this study, the prevalence of poor metabolizers was higher in the Blacks (19.1%) than Caucasians (4.6%).
- The use of a single 12 hours time point instead of AUC to determine the ratio seems to be adequate.

**Table 4.2.1.3: Summary of Ages Stratified by DL Metabolic Status**

	DL Poor Metabolizer	DL Normal Metabolizer	Total
Number of Subjects	53	306	359
Age (N, %)			
age 2 to <3 years	4 (8%)	22 (7%)	26 (7%)
age 3 to <4 years	3 (6%)	29 (9%)	32 (9%)
age 4 to <5 years	3 (6%)	42 (14%)	45 (13%)
age 5 to <6 years	6 (11%)	44 (14%)	50 (14%)
age 6 to <7 years	6 (11%)	27 (9%)	33 (9%)
age 7 to <8 years	7 (13%)	30 (10%)	37 (10%)
age 8 to <9 years	7 (13%)	33 (11%)	40 (11%)
age 9 to <10 years	5 (9%)	35 (11%)	40 (11%)
age 10 to <11 years	5 (9%)	27 (9%)	32 (9%)
age 11 to <12 years	7 (13%)	17 (6%)	24 (7%)

#### 4.2.2 Study # P03031:

##### Objectives:

This is also a screening study to determine the metabolic phenotype proceeding Study # P02994.

##### Design (Study # P03031):

This is similar to the above study # P02818 in which a single dose of 10 mg (10ml) of Claritin (loratadine) syrup was administered. Similar to the above study, a ratio of <10% was used to identify the poor metabolizer and that of >25% was for normal metabolizers and also for those to be eligible for a subsequent safety study (#P02994). The ratio of 3-OH DL to DL was determined at 12 hour single time point as described in the above screening study (#P02818). In this screening study, a total of 2075 subjects (957 females and 1118 males) in 24 centers across United States and Latin America were enrolled (Table 4.2.2.1).

**Table 4.2.2.1. Summary of Demographic Characteristics (Studies #P03031 and P02994)**

	P03031 (n=2075)					P02994 (n=97)				
	Total	DL Poor	DL Normal	Indeterminate <sup>a</sup>	NA <sup>b</sup>	DL (n=48)		Placebo (n=49)		
						DL Poor	DL Normal <sup>c</sup>	Total	DL Normal	DL Poor
Number of Subjects	2075	79 (4)	1917 (92)	37 (2)	42 (2)	48 (47)	2 (2)	49 (51)	39 (40)	10 (10)
Age (Years)										
Mean (SD)	6.6 (2.7)	6.5 (2.6)	6.7 (2.7)	5.7 (2.8)	6.2 (3.0)	6.8 (2.6)	2.5 (0.7)	6.7 (2.6)	6.6 (2.7)	6.3 (2.4)
Median	7.0	6.6	7.0	6.0	6.5	7.0	2.5	7.0	7.0	6.0
Range (min-max)	2-12	2-11	2-12	2-10	2-11	2-11	2-3	2-11	2-11	3-11
Age Group (N, %)										
Age 2 to <6 years	742	27	678	17	20	14	2	13	9	4
Age 6 to <12 years	1331	52	1237	20	22	32	0	36	30	6
Age 12	2	0	2	0	0	0	0	0	0	0
Age (N, %)										
Age 2 to <3 years	152 (7)	7 (9)	133 (7)	7 (19)	5 (12)	3 (7)	1 (50)	6 (12)	6 (15)	0
Age 3 to <4 years	179 (9)	4 (5)	166 (9)	4 (11)	5 (12)	3 (7)	1 (50)	2 (4)	1 (3)	1 (10)
Age 4 to <5 years	212 (10)	9 (11)	194 (10)	4 (11)	5 (12)	3 (7)	0	1 (2)	0	1 (10)
Age 5 to <6 years	199 (10)	7 (9)	185 (10)	2 (5)	5 (12)	5 (11)	0	4 (8)	2 (5)	2 (20)
Age 6 to <7 years	242 (12)	15 (18)	221 (12)	5 (14)	1 (2)	6 (13)	0	9 (18)	6 (15)	3 (30)
Age 7 to <8 years	246 (12)	7 (9)	224 (12)	3 (8)	6 (14)	5 (17)	0	6 (12)	6 (15)	0
Age 8 to <9 years	249 (12)	8 (10)	233 (12)	4 (11)	4 (10)	5 (11)	0	7 (14)	6 (15)	1 (10)
Age 9 to <10 years	233 (11)	12 (15)	217 (11)	3 (8)	1 (2)	6 (13)	0	8 (12)	5 (13)	1 (10)
Age 10 to <11 years	197 (9)	5 (6)	189 (9)	5 (14)	7 (17)	3 (7)	0	6 (12)	6 (15)	0
Age 11 to <12 years	176 (8)	5 (6)	162 (8)	0	3 (7)	4 (9)	0	2 (4)	1 (3)	1 (10)
Age 12	2 (<1)	0	2 (<1)	0	0	0	0	0	0	0

	P03031 (n=2075)					P02994 (n=97)				
	Total	DL Poor	DL Normal	Indeterminate <sup>a</sup>	NA <sup>b</sup>	DL (n=48)		Placebo (n=49)		
						DL Poor	DL Normal <sup>c</sup>	Total	DL Normal	DL Poor
Number of Subjects	2075	79 (4)	1917 (92)	37 (2)	42 (2)	48 (47)	2 (2)	49 (51)	39 (40)	10 (10)
Sex (N, %)										
Female	957 (46)	41 (52)	873 (46)	16 (43)	27 (64)	29 (63)	0	25 (51)	19 (49)	6 (60)
Male	1116 (54)	38 (48)	1044 (54)	21 (57)	15 (36)	17 (37)	2 (100)	24 (49)	20 (51)	4 (40)
Race (N, %)										
Caucasian	594 (29)	5 (6)	569 (30)	2 (5)	19 (45)	4 (9)	0	9 (18)	9 (23)	0
Black	386 (18)	50 (63)	299 (16)	14 (38)	3 (7)	33 (72)	2 (100)	24 (49)	18 (46)	6 (60)
Hispanic	899 (43)	12 (15)	842 (44)	19 (51)	17 (40)	5 (11)	0	14 (29)	11 (28)	3 (30)
American Indian	56 (2)	4 (5)	44 (2)	1 (3)	1 (2)	3 (7)	0	1 (2)	0	1 (10)
Asian	18 (1)	0	18 (1)	0	0	0	0	1 (2)	1 (3)	0
Other	157 (8)	8 (10)	149 (8)	1 (3)	2 (5)	1 (2)	0	0	0	0
Weight (kg)										
Mean	28.21	25.14	28.26	24.90	25.98	25.07	12.40	25.77	26.10	24.46
(SD)	(10.60)	(9.62)	(10.57)	(11.48)	(13.15)	(10.02)	(0.85)	(9.31)	(9.54)	(8.73)
Median	24.00	23.50	24.00	21.50	22.20	23.30	12.40	23.80	24.00	21.60
Range (min-max)	9.5-82.9	10.9-61.7	6.5-83.9	12.0-64.1	11.8-77.3	12.0-84.5	11.8-13.0	11.3-49.0	11.3-49.0	16.1-40.0
Missing	2	0	2	0	0	0	0	0	0	0

a: Subjects with a 3-OH DL to DL % ratio that was between ≥10% and <20%.

b: Not available (NA); metabolizer status was missing.

c: 2 subjects enrolled in P02994 as DL poor metabolizers based on the data from Screening Study P03031 were subsequently determined to be normal metabolizers based on the C<sub>min</sub> data from P02994.

**Results:**

- Of the 2075 subjects, 2058 completed the screening study and 2033 subjects were phenotyped for DL metabolizer status.
- 79 subjects (3.8%) were determined to be DL poor metabolizers (79/2033).
- Overall, the prevalence of the DL poor metabolizer phenotype in children 2 to 12 years of age was 3.9% (79/2033). The demographic distribution of these children are as follows: 13.6% Blacks (50/366), 1.3% Hispanics (12/890), and 0.84% Caucasians (5/594) (Table 4.2.2.2)
- A total of 97 subjects were randomized to treatment in Study # P02994 and 58 of these subjects were DL poor metabolizers (see Study # 02994).

**Table 4.2.2.2: DL Metabolism Status of Pediatric Subjects by Race (Study # P03031, updated/submitted July 9, 2004)**

	Total	DL Normal <sup>a</sup>	DL Poor <sup>b</sup>	Missing
Number of Subjects n (%)	2075 (100) <sup>c</sup>	1854 (94)	79 (4)	42 (2)
Race, n (%) <sup>d</sup>				
Black	366 (18)	313 (86)	50 (14)	3 (1)
Caucasian	584 (29)	570 (98)	5 (1)	19 (3)
Hispanic	890 (43)	861 (97)	12 (1)	17 (2)
Asian	18 (1)	18 (100)	0	0
American Indian	50 (2)	45 (90)	4 (8)	1 (2)
Other	157 (8)	147 (94)	8 (5)	2 (1)

- a. Includes normal metabolizers of DL and indeterminate.  
b. Poor metabolizers of DL.  
c. Percent in this column represents the percentage of subjects in each race category.  
d. Percent represents the percentage of the total number of subjects in that race category.

**Reviewer's Comments:**

- It appears that there is a little discrepancy between the previous screening study # P02818 and the current study. In the previous study, the prevalence of poor metabolizers was higher in both Blacks (19.1%) and Caucasians (4.6%) compared to the current study. The reason for this discrepancy could be due to the fact that there was high proportion of Blacks (70%) enrolled in Study # P02818 (251/359) compared to the current study (17.6%, 366/2075).
- Overall, the prevalence of poor metabolizers appears to be higher in Blacks than in Caucasians and other races.

**Conclusion:**

- Based on both screening studies, it can be concluded that the prevalence of poor metabolizers in Blacks is expected to range from approximately 10% to 20% and in Caucasians from 1% to 5%.

**4.2.3 Study # P02994:**

This is a subsequent study to the above screening study # P03031. The primary objective is to evaluate the safety and tolerance of DL in poor metabolizers following 5 weeks of repetitive dosing.

**Design:**

The metabolic status of all subjects enrolled in this study was previously identified in the screening study #P03031. This was a single daily dose, double-blind, placebo controlled study for 5 weeks.

## Demographic:

The total number of subjects enrolled in this study was 97 composed of 54 females and 43 males as shown in the previous table (Table 4.2.2.1). Of these 29 subjects were between the ages of 2 to 6 years and 68 between the ages of 6 to 12 years. A total of 48 subjects received DL and 49 received placebo treatments (10 poor metabolizers and 39 normal metabolizers).

## Doses:

There were two doses as follows:

- Group A (2-6 years old): 2.5 ml (1.25 mg) of DL syrup (0.5 mg/ml) daily X 5 weeks
- Group B (6-12 years old): 5 ml (2.5 mg) of DL syrup (0.5 mg/ml) daily x 5 weeks

## When Were the Blood Samples Collected?

Blood samples for the determination of trough concentration (C<sub>min</sub>) and ratio 3-OH DL to DL were collected at baseline, Day 15, and Day 36 prior to the scheduled dose at each of the respective days.

## Safety Monitoring:

The primary safety measures in this study were ECG readings. Other measures were included such as physical exams and vital signs that were monitored throughout the study.

## Results:

- A total of 87 subjects out of 97 completed the study (89.7%).
- Steady state was achieved on Day 15. Also, there was no difference between the C<sub>min</sub> on Day 15 and Day 36 (Table 4.2.3.18).
- It appears there was no significance safety concern, including QTc related changes (Table 9). However, there was a significant increase in ventricular rate in DL treated subjects compared to placebo. For further detail, please see the Medical Officer's review.

Table 4.2.3.1: Steady State

Analyte	Visit	Mean	%CV	Mean	%CV
		2 to 5 yr (n=11)		6 to 11 yr (n=32)	
DL <sup>b</sup>	Day 15	5.89	35	7.13	45
DL <sup>b</sup>	Day 36	5.18	49	6.11 <sup>a</sup>	62
3-OH DL <sup>b</sup>	Day 15	0.131	58	0.152	32
3-OH DL <sup>b</sup>	Day 36	0.121	85	0.126 <sup>a</sup>	76
Ratio 3-OH DL/DL	Day 15	2.43%	68	2.26%	32
Ratio 3-OH DL/DL	Day 36	2.19%	76	2.13% <sup>a</sup>	78

a: Subject 000267/Site 19 had missing Day 36 Visit data.

b: Unit: mg/mL

**Table 4.2.3.2. ECG Data: Mean Change and Mean Percent Change from Baseline**

Visit	DL Poor Metabolizer (A)			Placebo (B)			Analysis <sup>a</sup>		
	N	Mean <sup>b</sup>	Mean% Change <sup>c</sup>	N	Mean	Mean% Change	P <sub>std</sub> <sup>b</sup>	T <sub>tt</sub>	95% CI <sup>c</sup> A-B
<b>Ventricular Rate (bpm)</b>									
Baseline	45	85.8		48	85.4		13.9	0.889	(-5.3, 6.1)
Change from Baseline									
Day 8	44	3.7	(5.7%)	47	-3.5	(-2.7%)	13.7	0.014	(1.5, 12.9)
Day 15	44	7.9	(10.8%)	47	-1.8	(-0.7%)	13.1	<.001	(4.2, 15.1)
Day 22	42	3.3	(5.0%)	46	-0.7	(0.0%)	13.9	0.175	(-1.8, 10.0)
Day 29	40	2.3	(4.6%)	46	-2.2	(-1.5%)	12.1	0.088	(-0.7, 9.7)
Day 36	39	6.0	(8.5%)	46	1.2	(2.2%)	14.0	0.115	(-1.2, 11.0)
Endpoint <sup>d</sup>	45	5.8	(8.0%)	48	1.0	(1.9%)	13.6	0.094	(-0.8, 10.4)
<b>PR interval (msec)</b>									
Baseline	45	136.7		48	131.8		17.6	0.185	(-2.4, 12.1)
Change from Baseline									
Day 8	44	-0.8	(-0.2%)	47	0.6	(0.9%)	12.5	0.579	(-8.7, 3.7)
Day 15	44	1.5	(1.7%)	47	-1.7	(-0.8%)	12.8	0.243	(-2.2, 8.5)
Day 22	42	1.0	(1.2%)	46	-2.2	(-1.3%)	10.5	0.163	(-1.3, 7.6)
Day 29	40	-1.2	(-0.1%)	46	-0.8	(0.0%)	13.1	0.904	(-8.0, 5.3)
Day 36	39	-1.0	(-0.1%)	46	-0.1	(0.3%)	10.9	0.696	(-5.7, 3.8)
Endpoint <sup>d</sup>	45	-1.8	(-0.7%)	48	0.0	(0.4%)	11.2	0.442	(-6.4, 2.8)
<b>QRS interval (msec)</b>									
Baseline	45	75.9		48	77.0		6.0	0.362	(-3.6, 1.3)
Change from Baseline									
Day 8	44	-0.4	(-0.3%)	47	-0.5	(-0.5%)	5.8	0.948	(-2.3, 2.5)
Day 15	44	-0.7	(-0.7%)	47	0.6	(1.2%)	6.2	0.305	(-3.9, 1.3)
Day 22	42	-0.1	(0.1%)	46	-0.9	(-0.8%)	6.6	0.572	(-2.0, 3.6)
Day 29	40	-0.9	(-0.9%)	46	0.7	(1.2%)	5.8	0.196	(-4.1, 0.9)
Day 36	39	-0.1	(0.2%)	46	0.9	(1.5%)	5.5	0.420	(-3.3, 1.4)
Endpoint <sup>d</sup>	45	-0.4	(-0.1%)	48	0.9	(1.5%)	5.4	0.257	(-3.5, 0.9)
<b>QT interval (msec)</b>									
Baseline	45	338.7		48	342.3		28.6	0.550	(-15.3, 8.2)
Change from Baseline									
Day 8	44	-5.7	(-1.5%)	47	2.9	(1.2%)	24.5	0.101	(-18.8, 1.7)
Day 15	44	-10.0	(-2.7%)	47	2.7	(1.1%)	23.8	0.013	(-22.6, -2.8)
Day 22	42	-3.0	(-0.8%)	46	-0.4	(0.2%)	21.0	0.556	(-11.6, 6.3)
Day 29	40	-5.6	(-1.4%)	46	4.9	(1.8%)	21.2	0.025	(-19.6, -1.4)
Day 36	39	-7.2	(-1.8%)	46	-3.3	(-0.7%)	25.0	0.486	(-14.6, 7.0)
Endpoint <sup>d</sup>	45	-6.6	(-1.7%)	48	-3.3	(-0.7%)	24.4	0.515	(-13.4, 6.7)

**Table 4.2.3.2 (continued). ECG Data: Mean Change and Mean Percent Change from Baseline**

Visit	DL Poor Metabolizer (A)			Placebo (B)			Analysis <sup>a</sup>		
	N	Mean <sup>b</sup>	Mean% Change <sup>c</sup>	N	Mean	Mean% Change	Pstd <sup>d</sup>	Trt	95% CI <sup>e</sup> A-B
<b>Fridericia QTc Interval (msec)<sup>f</sup></b>									
Baseline	45	378.5		48	391.8		19.8	0.429	(-11.5, 4.9)
Change from Baseline									
Day 8	44	-0.5	(0.8%)	47	-2.0	(-0.4%)	17.6	0.682	(-5.8, 8.9)
Day 15	44	0.7	(0.3%)	47	0.7	(0.3%)	16.3	0.998	(-6.8, 6.8)
Day 22	42	1.8	(0.8%)	48	-2.7	(-0.8%)	16.8	0.209	(-2.8, 11.8)
Day 29	40	-1.4	(-0.2%)	48	2.5	(0.8%)	17.3	0.290	(-11.4, 3.5)
Day 36	39	1.0	(0.4%)	48	-2.6	(-0.8%)	19.1	0.400	(-4.8, 11.8)
Endpoint <sup>g</sup>	45	1.1	(0.8%)	48	-2.8	(-0.6%)	18.1	0.320	(-3.9, 11.8)
<b>Bazett QTc Interval (msec)<sup>f</sup></b>									
Baseline	45	400.8		48	403.6		21.2	0.491	(-11.8, 5.7)
Change from Baseline									
Day 8	44	2.5	(0.9%)	47	-4.9	(-1.1%)	20.8	0.093	(-1.3, 18.1)
Day 15	44	7.0	(1.9%)	47	-0.5	(0.0%)	19.3	0.067	(-0.5, 15.8)
Day 22	42	4.8	(1.4%)	48	-3.9	(-0.8%)	21.1	0.062	(-0.4, 17.5)
Day 29	40	0.7	(0.4%)	48	1.1	(0.4%)	21.5	0.937	(-9.8, 8.9)
Day 36	39	5.8	(1.7%)	48	-2.0	(-0.4%)	22.7	0.118	(-2.0, 17.8)
Endpoint <sup>g</sup>	45	5.7	(1.6%)	48	-2.4	(-0.5%)	22.6	0.686	(-1.2, 17.8)

- a: Subjects in the DL treatment group who were subsequently designated as Normal Metabolizers are excluded from this analysis.
- b: Means, pooled standard deviations (Pstd), and 95% Confidence Intervals (CI) of the treatment (Trt) differences were obtained from a one-way anova with treatment effects.
- c: Mean percent changes are raw means.
- d: Endpoint is the last post-baseline non-missing observation carried forward.
- e: FQTc interval based on Fridericia formula:  $QTc = QT / (RR/1000)^{0.75}$
- f: BQTc interval based on Bazett formula:  $QTc = QT / (RR/1000)^{0.5}$

### Conclusions:

- Overall, the drug was tolerated in poor metabolizers.
- Steady state was achieved in Day 15.

### 4.2.4 Study # P02798:

#### Objectives:

The primary objective of this study is to evaluate the PK profiles and safety of DL in poor metabolizers following multiple doses.

#### Design:

This was placebo-controlled, investigator-blind study in pediatric subjects with allergic rhinitis aged 2 to 11 years. Subjects were screened/phenotyped for metabolic status (poor or normal metabolizers) based on a separate protocol using loratadine/Claritin as probe (Study # P02818). **Tables 4.2.4.1 and 4.2.4.2** show the age distribution and demographics of the 48 subjects completed the study. Briefly, subjects were divided to receive the following treatments:

Group A (n=10): Placebo treatment

Group B (n=38): Active treatment (i.e., DL). These were divided as follows:

Group B1 (n= 21): normal metabolism status (n=8 ages 2-5 and n=13 ages 6-11 years)

Group B2 (n=17): poor metabolizers (n=4 ages 2-5 and n=13 ages 6-11 years)

**Table 4.2.4.1. Age Distribution of Subjects (Study # P02798)**

Age (Years)	DL Treated Subjects		Placebo Treated Subjects	
	Poor Metabolizer	Normal Metabolizer	Poor Metabolizer	Normal Metabolizer
2	0	3	0	0
3	0	1	1	1
4	1	1	0	1
5	3	3	0	1
6	3	2	1	1
7	0	2	1	0
8	4	2	0	1
9	2	2	0	0
10	2	3	0	1
11	2	2	0	1
Total	17	21	3	7

Subject's metabolizer status based on PK data from this study (P02798)

**Table 4.2.4.2. Demographic Characteristics by Treatment Status (Study # P02798)**

Age (Years)	Total	DL Poor	DL Normal	Placebo
n	48	17	21	10
Mean	6.9	7.6	6.7	6.3
Standard deviation	2.7	2.2	3.0	2.8
Median	7.0	8.0	7.0	6.0
Range (Min-Max)	2-11	4-11	2-11	3-11
Age Group (Number, %)				
Age 2 to 5 Years	16 (33.3)	4 (23.5)	8 (38.1)	4 (40)
Age 6 to 11 Years	32 (66.7)	13 (76.5)	13 (61.9)	6 (60)
Sex (Number, %)				
Female	21 (43.8)	7 (41.2)	10 (47.6)	4 (40)
Male	27 (56.3)	10 (58.8)	11 (52.4)	6 (60)
Race (Number, %)				
Caucasian	5 (10.4)	1 (5.9)	2 (9.5)	2 (20)
Black	43 (89.6)	16 (94.1)	19 (90.5)	8 (80)

A loading dose of DL equal to two times of the assigned daily doses was administered on Day 1 to normal DL metabolizers and for three days (Day 1, 2, and 3) to DL poor metabolizers. Then, daily doses of 1.25 or 2.5 mg were administered daily up to Day 17 in subjects ages 2-5 years and 6-11 years, respectively.

Blood samples for the determination of DL and 3-OH DL concentrations in plasma were collected on Day -1, and predose on Days 14, 15, and 16. In addition, multiple blood samples were obtained on Day 17. The plasma concentration data following administration of DL on Day 17 were used to estimate the DL and 3-OH DL PK parameters.

## Results:

- Mean DL and 3-OH DL concentration-time profiles of 2-5 year age group and 6-11 year group are shown in **Figures 4.2.4.1 and 4.2.4.2**. The mean PK data are shown in **Tables 4.2.4.3 and 4.2.4.4**.
- From these data it can be concluded that the exposure to DL in poor metabolizers is approximately **6 fold** higher than in normal metabolizers.
- In terms of the effect of children age, the plasma level of DL (i.e., exposure) in normal children 6-11 years old is approximately 10-15 % higher children of 2-5 years old. However, the difference appears to be greater in poor metabolizers relative to age by being approximately 50% higher in older children compared to young (**Tables 4.2.4.3 and 4.2.4.4**).
- Based on 5 mg dose normalization, the exposure in pediatric and adult normal and poor metabolizers appears to be comparable (**Table 4.2.4.5**) for C<sub>max</sub> (**Figures 4.2.4.3 and 4.2.3.4**) and AUC (**Figures 4.2.4.5 and 4.2.4.6**). In other words, both population show **6 folds** increase in exposure compared to corresponding normal subjects (**Table 4.2.4.6**).
- It should be noted that the concentrations achieved prior to dosing (C<sub>min</sub>) on Days 14-17 and 24 hours postdose on Day 17 (Days 18) are shown in **Figure 4.2.4.7**.
- The mean C<sub>min</sub> data suggest that all age groups of DL poor metabolizers were at steady state by Day 15 (**Table 4.2.4.7**).
- In terms of 3-OH DL, its formation is reduced in poor metabolizers compared to normal subjects (**Figures 4.2.4.1 and 4.2.4.1 and Tables 4.2.4.3, 4.2.4.8, and 4.2.4.9**). The mean ratio of the poor to normal metabolizers for either C<sub>max</sub> or AUC of 3-OH DL is <1 (**Table 4.2.4.9**). This is consistent with the decrease of 3-OH DL formation in poor metabolizers.
- As for DL, the magnitude of reduction in 3-OH DL formation is similar in pediatric and adult poor metabolizers.

## Safety:

- In terms of safety, it appears that there was some difference in ECG/QTc data among the groups. However, please see the Medical Officer's review for the detail discussion and analysis of ECG readings, QTc data, and all safety related information.
- The following three main observations were reported by the sponsor:
  - There was statistically significant difference (p=0.009) in change of PR interval from Day 9 to Day 17 between DL-treated poor metabolizers and DL-treated normal metabolizers (**Table 4.2.4.10**).
  - There was statistically significant difference in QT between DL-treated poor metabolizers and DL-treated normal metabolizers (**Table 4.2.4.11**).
  - An increase in ventricular rate (mean increase 9.8 bpm) from baseline in DL treated poor metabolizers was observed (**Table 4.2.4.12**).

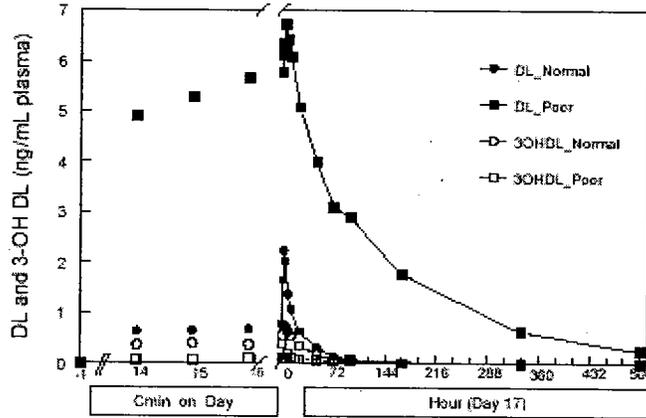
For all other safety related issues, please see the Medical Officer's review.

**Data Integrity:**

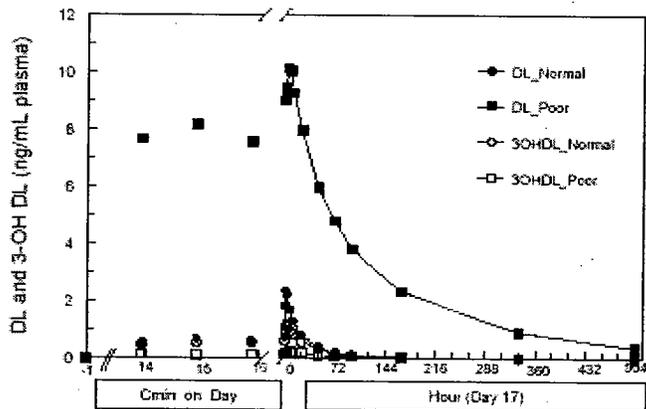
- In three placebo group subjects DL was detected at a concentration ranging from approximately 0.03 to 1.9 ng/ml. One subject had a concentration of 8.3 ng/ml at one time point. Similarly, 3-OH DL concentrations range from approximately 0.02 to 1.0 ng/ml in these subjects. Overall, the observed concentrations in these subjects are relatively high as the Cmax of DL in **all** subjects range from approximately 1 ng/ml to 15 ng/ml.
- Furthermore, one subject (#115) who is on placebo also had measurable DL concentrations. However, the sponsor believes that the samples from this subject were probably mislabeled for subject #114 who was treated with DL.

**Figures 4.2.4.1 and 4.2.4.2. Mean Plasma Concentration-Time Profiles of DL and 3-OH DL in Children 2-5 years of age (top) and 6-11 years of age (bottom)**

**Figure 4.2.4.1. Age: 2-5 years**



**Figure 4.2.4.2. Age: 6-11 years**



**Table 4.2.4.3. Mean (%CV) of PK Parameters of DL at Day 17 in Children 2-5 years of age and 6-11 years of age**

Parameter <sup>a</sup>	Mean	%CV	Range	Mean	%CV	Range
2-5 yr: DL-Normal Metabolizers (n=8)				2-5 yr: DL-Poor Metabolizers (n=4)		
C <sub>max</sub>	2.29	52	1.10-4.31	6.78	3	6.53-7.04
T <sub>max</sub>	2.50	37	2.0-4.0	2.75	55	1.0-4.0
AUC(0-24 hr)	29.5	59	14.0-61.8	143	4	138-149
t <sub>1/2</sub>	48.7	73	12.2-90.7	115	7	109-127
6-11 yr: DL-Normal Metabolizers (n=12) <sup>b</sup>				6-11 yr: DL-Poor Metabolizers (n=13) <sup>c</sup>		
C <sub>max</sub>	2.56	23	1.71-3.89	10.4	26	5.94-14.6
T <sub>max</sub>	2.67	67	2.0-8.0	5.54	61	0-12 <sup>c</sup>
AUC(0-24 hr)	34.7	37	24.0-72.6	220	24	125-300
t <sub>1/2</sub>	41.6	81	13.8-118	126	19	84.8-184

a: Units: C<sub>max</sub>: ng/mL; T<sub>max</sub>=hr; AUC: ng.hr/mL; t<sub>1/2</sub>: hr.

b: Excludes Subject No. 114

c: Subject No. 61 had a C<sub>min</sub> value higher than postdose values.

**Table 4.2.4.4. Median (Range) of AUC (0-24 h) and C<sub>max</sub> of DL and 3-OH DL in all Children 2-11 years of age (Normal and Poor Metabolizers)**

Metabolizer Status	n	DL	3-OH DL
		AUC(0-24 hr) (ng.hr/mL)	AUC(0-24 hr) (ng.hr/mL)
Normal Metabolizer	20	29.9 (14.0-72.6)	16.8 (8.81-28.7)
Poor Metabolizer	17	211 (125-300)	3.33 (1.87-11.7)
		C <sub>max</sub> (ng/mL)	C <sub>max</sub> (ng/mL)
Normal Metabolizer	20	2.39 (1.10-4.31)	0.97 (0.55-1.76)
Poor Metabolizer	17	9.28 (5.94-14.6)	0.17 (0.09-0.77)

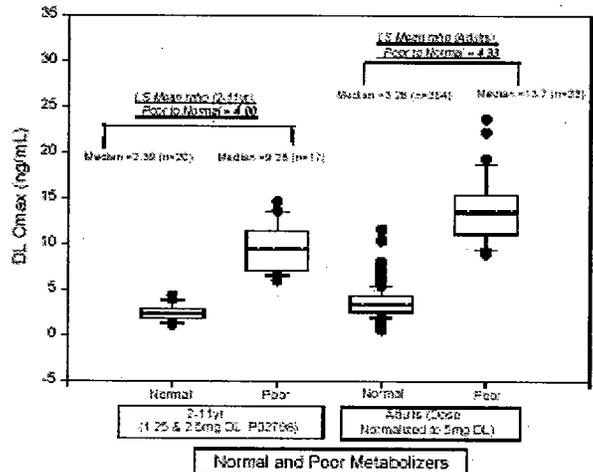
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**Table 4.2.4.5. Median (Range) DL AUC and Cmax in Children and in Adult Normal and Poor Metabolizers Following Multiple Dose Administration of DL**

Metabolizer Status	n	Children (2-5 yr)	n	Children (6-11 yr)	n	Adults (Multiple Dose) <sup>a</sup>
AUC(0-24 hr) (ng.hr/mL)						
DL-Normal Metabolizer	8	23.4 (14.0-61.8)	12	30.4 (24.0-72.6)	364	44.3 (14.2-158)
DL-Poor Metabolizer	4	143 (138-149)	13	223 (125-300)	33	271 (179-406)
Least Square Mean Ratio <sup>b</sup>	-	-	-	-	-	-
Poor/Normal Metabolizer	-	5.61 (3.92, 8.04) <sup>c</sup>	-	6.45 (5.10, 8.16) <sup>c</sup>	-	6.01 (5.32, 6.78) <sup>c</sup>
Cmax (ng/mL)						
DL-Normal Metabolizer	8	2.05 (1.10-4.31)	12	2.53 (1.71-3.89)	364	3.28 (0.55-11.6)
DL-Poor Metabolizer	4	6.78 (6.53-7.04)	13	10.8 (5.94-14.6)	33	13.7 (8.85-23.7)
Least Square Mean Ratio <sup>b</sup>	-	-	-	-	-	-
Poor/Normal Metabolizer	-	3.32 (2.40, 4.59) <sup>c</sup>	-	4.04 (3.27, 5.00) <sup>c</sup>	-	4.33 (3.81, 4.93) <sup>c</sup>

- a: Dose normalized to 5 mg. Data of adults from the following studies: C98-013,<sup>(11)</sup> P00117,<sup>(12)</sup> C98-352,<sup>(13)</sup> C98-353,<sup>(14)</sup> C98-356,<sup>(15)</sup> P00275,<sup>(16)</sup> P00272,<sup>(17)</sup> P00883,<sup>(18)</sup> P01868,<sup>(19)</sup> P01376,<sup>(20)</sup> P00884,<sup>(21)</sup> P01381,<sup>(22)</sup> and P01430.<sup>(23)</sup>
- b: ANOVA of log-transformed data extracting sources of variation due to age group and metabolizer status. The ratio is a contrast of metabolizer status.
- c: Lower and upper 90% confidence interval based on log-transformed data.

**Figure 4.2.4.3. Comparison of Children (2 to 11 years) and Adults Cmax Values**



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Figure 4.2.4.4. DL Cmax in and Adults

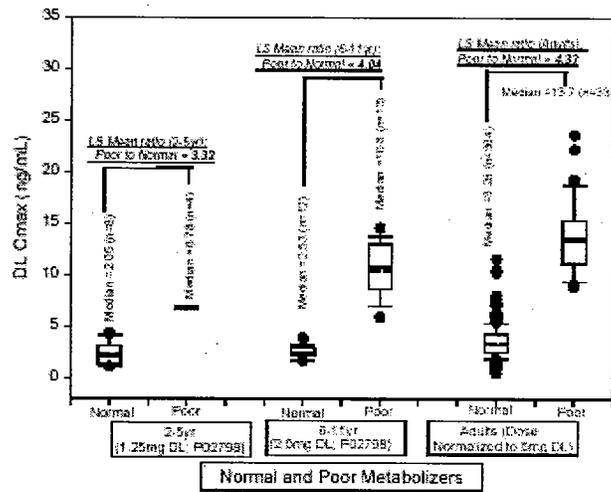
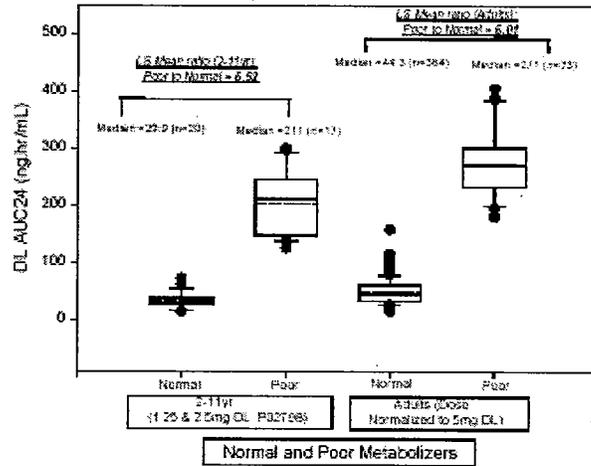


Figure 4.2.4.5. Comparison of Children (2 to 11 years) and Adults AUC Values



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Figure 4.2.4.6. DL AUC in Children and Adults

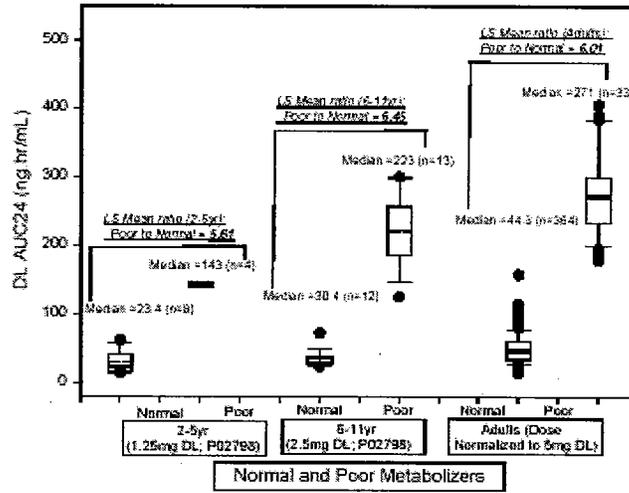
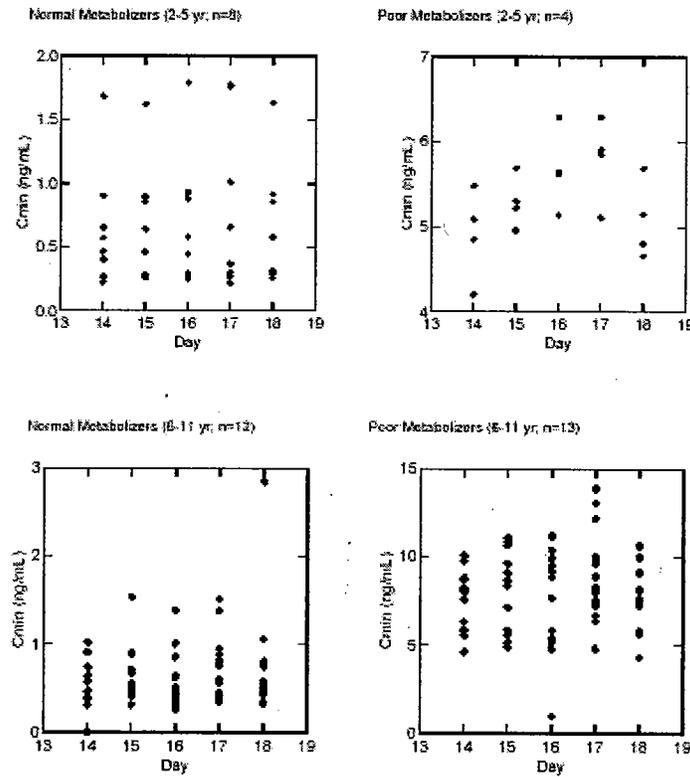


Figure 4.2.4.7. Trough (C<sub>min</sub>) DL Concentrations by Age Group and by Metabolizer Status (*note the difference in the y scales*)



**Table 4.2.4.7. Least Square Mean (95% CI) DL Through Concentrations by Metabolizers Status and by Age Group (Study # P02798)**

Days	Least Square Mean (95% Confidence Interval) C <sub>min</sub> (ng/mL) <sup>d</sup>			
	DL-Normal <sup>a</sup> 2-5 yr n=8	DL-Poor <sup>b</sup> 2-5 yr n=4	DL-Normal <sup>a,c</sup> 6-11yr n=12	DL-Poor <sup>b</sup> 6-11 yr n=13
14	0.64 (0.45-0.84)	4.91 (4.58-5.23)	0.55 (0.36-0.74)	7.66 (7.03-8.29)
15	0.66 (0.46-0.86)	5.29 (4.97-5.62)	0.68 (0.49-0.87)	8.15 (7.52-8.77)
16	0.68 (0.48-0.88)	5.67 (5.35-6.00)	0.62 (0.43-0.81)	7.58 (6.95-8.20)
17	0.79 (0.59-0.99)	5.79 (5.46-6.11)	0.77 (0.57-0.96)	8.99 (8.36-9.62)
18	0.64 (0.44-0.84)	5.07 (4.75-5.40)	0.81 (0.62-1.00)	7.98 (7.33-8.59)

- a: DL-Normal=Normal metabolizer of desloratadine.
- b: DL-Poor=Poor metabolizer of desloratadine.
- c: Excludes Subject No. 114.
- d: ANOVA extracting sources of variability due to subject and day.

**Table 4.2.4.8. Mean (%CV) and Range PK Parameters of 3-OH DL at Day 17 in Children 2-5 Years and 6-11 years of Age**

Parameter <sup>a</sup>	Mean	%CV	Range	Mean	%CV	Range
	2-5 yr: DL-Normal Metabolizers (n=8)			2-5 yr: DL-Poor Metabolizers (n=4)		
C <sub>max</sub>	0.75	19	0.55-0.97	0.17	77	0.09-0.37
T <sub>max</sub>	3.75	53	2.00-8.00	7.00	29	4.00-8.00
AUC(0-24 hr)	13.1	23	8.81-17.0	2.81	43	1.87-4.56
t <sub>1/2</sub>	34.0	41	20.8-57.4	91.3	32	52.6-122
Parameter <sup>a</sup>	Mean	%CV	Range	Mean	%CV	Range
	6-11 yr: DL-Normal Metabolizers (n=12)			6-11 yr: DL-Poor Metabolizers (n=13)		
C <sub>max</sub>	1.24	25	0.70-1.76	0.31	70	0.11-0.77
T <sub>max</sub>	5.00	121	2.00-24.0	9.31	99	0-24.0
AUC(0-24 hr)	20.5	25	11.9-28.7	4.88	58	2.10-11.7
t <sub>1/2</sub>	44.1	67	18.7-129	116	71	21.9-307

- a: Units: C<sub>max</sub>: ng/mL, T<sub>max</sub>=hr, AUC: ng.hr/mL, t<sub>1/2</sub>: hr.

**Table 4.2.4.9. Median (Range) 3-OH DL AUC (0-24h) and C<sub>max</sub> in Children and Adult Normal and Poor Metabolizers Following Multiple-Dose Administration of DL**

	Children (2-5 yr, P02798)	Children (6-11 yr, P02798)	Adults
AUC(0-24 hr) ng.hr/mL: Median (Range; n)			
DL-Normal metabolizer	13.4 (8.81-17.0; n=8)	18.3 (11.9-28.7, n=12) <sup>d</sup>	28.8 (13.5-59.0; n=329)
DL-Poor metabolizer	2.40 (1.87-4.56; n=4)	3.58 (2.10-11.7, n=13)	4.88 (1.64-18.3; n=28)
Least Square Mean Ratio: Poor/Normal Metabolizers	0.21 (0.14-0.31) <sup>e</sup>	0.21 (0.16-0.28) <sup>e</sup>	0.17 (0.16-0.19) <sup>e</sup>
C <sub>max</sub> (ng/mL): Median (Range; n)			
DL-Normal metabolizer	0.76 (0.55-0.97; n=8)	1.22 (0.70-1.76, n=12) <sup>d</sup>	1.64 (0.11-3.96; n=330) <sup>d</sup>
DL-Poor metabolizer	0.12 (0.09-0.37; n=4)	0.19 (0.11-0.77; n=13)	0.20 (0.03-3.63; n=28)
Least Square Mean Ratio: Poor/Normal Metabolizers	0.20 (0.12-0.32) <sup>e</sup>	0.21 (0.15-0.29) <sup>e</sup>	0.13 (0.11-0.15) <sup>e</sup>

- a: Data from studies P00117<sup>(1,2)</sup> (excluding Subject No. 22, had no 3-OH DL level), C98-352<sup>(13)</sup>, C98-353<sup>(14)</sup>, C98-355<sup>(15)</sup>, P00275<sup>(16)</sup>, P00272<sup>(17)</sup>, P00883<sup>(18)</sup>, P01868<sup>(19)</sup>, P01378<sup>(20)</sup>, P00884<sup>(21)</sup>, P01381<sup>(22)</sup>, P01430<sup>(23)</sup>, C98-013<sup>(11)</sup> was excluded because 3-OH DL was not measured.
- b: Subject No. 114 was excluded from this analysis (Section 9.8).
- c: Lower and upper 90% confidence interval based on log-transformed data.
- d: Subject No. 22 from Study P00117 had a C<sub>max</sub> value, but did not have an AUC (0-24 hr) value.

Table 4.2.4.10. PR internal (msec)

Time Point	DL Syrup								
	Poor Metabolizer			Normal Metabolizer			Placebo		
	(A)			(B)			(C)		
	N	LS Mean <sup>a</sup>	(Mean % Change) <sup>a</sup>	N	LS Mean	(Mean % Change)	N	LS Mean	(Mean % Change)
Baseline (Actual)	17	139.1		21	134.2		10	132.3	
Day 9 (Actual)	17	138.2		21	133.1		10	131.4	
Day 17 (Actual)	17	137.5		21	129.5		10	130.2	
Change from Baseline									
Day 9	17	-2.9	(-2.0%)	21	-1.2	(-0.6%)	10	-1.0	(-0.3%)
Day 17	17	-1.6	(-0.8%)	21	-4.7	(-3.2%)	10	-2.1	(-1.3%)
Change from Day 9									
Day 17	17	1.3	(1.5%)	21	-3.5	(-2.6%)	10	-1.2	(-0.9%)
Analysis Results <sup>a</sup>									
Time Point	Pooled SD	Pairwise Comparisons p-values							
		Treatment p-value	A-B	A-C	B-C				
Baseline (Actual)	17.3	0.557	0.394	0.331	0.774				
Day 9 (Actual)	15.6	0.706	0.538	0.439	0.779				
Day 17 (Actual)	14.2	0.200	0.090	0.199	0.906				
Change from Baseline									
Day 9	6.1	0.636	0.402	0.439	0.927				
Day 17	6.7	0.327	0.158	0.829	0.326				
Change from Day 9									
Day 17	5.4	0.003	0.009	0.259	0.270				
95% Confidence Intervals of Treatment Differences									
Time Point	A-B		A-C		B-C				
Baseline (Actual)	(-8.5, 16.2)		(-7.1, 20.6)		(-11.4, 15.3)				
Day 9 (Actual)	(-7.1, 13.4)		(-7.7, 17.4)		(-10.4, 13.8)				
Day 17 (Actual)	(-1.3, 17.3)		(-4.0, 18.7)		(-11.6, 10.3)				
Change from Baseline									
Day 9	(-5.7, 2.3)		(-6.8, 3.0)		(-4.9, 4.5)				
Day 17	(-1.3, 7.5)		(-4.6, 6.0)		(-7.7, 2.8)				
Change from Day 9									
Day 17	(1.2, 6.4)		(-1.9, 6.9)		(-6.6, 1.9)				

a: LS Means, pooled standard deviations, 95% confidence intervals, treatment and pairwise comparisons. p-values were obtained from an ANOVA model with treatment effects.

b: Mean Percent changes are unadjusted means.

Table 4.2.4.11. QT Intervals (msec)

QT Synop									
Time Point	Poor Metabolizer (A)			Normal Metabolizer (B)			Placebo (C)		
	N	LS	(Mean % Change) <sup>b</sup>	N	LS	(Mean % Change)	N	LS	(Mean % Change)
		Mean <sup>a</sup>			Mean			Mean	
Baseline (Actual)	17	347.1		21	331.4		10	330.7	
Day 9 (Actual)	17	336.9		21	329.4		10	329.3	
Day 17 (Actual)	17	335.8		21	329.3		10	332.9	
Change from Baseline									
Day 9	17	-8.5	(-2.4%)	21	-2.0	(-0.6%)	10	-1.5	(-0.4%)
Day 17	17	-11.3	(-3.2%)	21	-2.2	(-0.6%)	10	2.2	(0.7%)
Change from Day 9									
Day 17	17	-2.8	(-0.8%)	21	-0.2	(0.0%)	10	3.6	(1.2%)
Analysis Results <sup>a</sup>									
Time Point	Pooled SD	Treatment p-value	Pairwise Comparisons p-values						
			A-B	A-C	B-C				
Baseline (Actual)	21.2	0.054	0.028	0.059	0.951				
Day 9 (Actual)	23.0	0.420	0.228	0.313	0.964				
Day 17 (Actual)	21.5	0.047	0.356	0.732	0.665				
Change from Baseline									
Day 9	11.2	0.151	0.001	0.121	0.902				
Day 17	12.0	0.014	0.023	0.007	0.355				
Change from Day 9									
Day 17	10.2	0.293	0.429	0.120	0.359				
95% Confidence Intervals of Treatment Differences									
Time Point	A-B		A-C		B-C				
Baseline (Actual)	(-1.8, 29.6)		(-0.5, 33.4)		(-15.7, 17.1)				
Day 9 (Actual)	(-5.9, 24.3)		(-9.1, 27.8)		(-17.6, 18.0)				
Day 17 (Actual)	(-7.6, 20.6)		(-14.3, 20.2)		(-20.2, 13.0)				
Change from Baseline									
Day 9	(-13.9, 0.8)		(-16.1, 1.9)		(-9.2, 8.2)				
Day 17	(-17.1, -1.3)		(-23.1, -3.9)		(-13.6, 5.0)				
Change from Day 9									
Day 17	(-9.3, 4.0)		(-14.6, 1.7)		(-11.6, 4.1)				

a: LS Means, pooled standard deviations, 95% confidence intervals, treatment and pairwise comparisons p-values were obtained from an ANCOVA model with treatment effects.

b: Mean percent changes are unadjusted means.

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Table 4.2.4.12. Ventricular Rate (bpm)

Time Point	DL Syrup								
	Poor Metabolizer (A)			Normal Metabolizer (B)			Placebo (C)		
	N	LS Mean <sup>a</sup>	(Mean % Change) <sup>b</sup>	N	LS Mean	(Mean % Change)	N	LS Mean	(Mean % Change)
Baseline (Actual)	17	80.9		21	87.7		10	88.5	
Day 9 (Actual)	17	89.5		21	90.5		10	93.0	
Day 17 (Actual)	17	90.7		21	90.5		10	90.0	
Change from Baseline									
Day 9	17	8.6	(10.7%)	21	2.8	(3.5%)	10	4.5	(5.3%)
Day 17	17	9.8	(12.5%)	21	2.8	(3.5%)	10	1.4	(2.0%)
Change from Day 9									
Day 17	17	1.3	(1.7%)	21	0.0	(0.3%)	10	-3.1	(-2.9%)
Analysis Results <sup>a</sup>									
Time Point	Pooled SD	Treatment p-value	Pairwise Comparisons p-values						
			A-B	A-C	B-C				
Baseline (Actual)	10.4	0.090	0.052	0.072	0.832				
Day 9 (Actual)	10.9	0.713	0.780	0.417	0.544				
Day 17 (Actual)	9.7	0.981	0.940	0.845	0.888				
Change from Baseline									
Day 9	5.9	0.015	0.004	0.088	0.452				
Day 17	5.7	<.001	<.001	<.001	0.533				
Change from Day 9									
Day 17	5.7	0.172	0.509	0.054	0.166				
95% Confidence Intervals of Treatment Differences									
Time Point	A-B		A-C		B-C				
Baseline (Actual)	(-13.6, 0.1)		(-16.0, 0.7)		(-8.9, 7.2)				
Day 9 (Actual)	(-8.2, 8.2)		(-12.3, 5.2)		(-11.0, 5.9)				
Day 17 (Actual)	(-6.2, 6.6)		(-7.1, 8.8)		(-7.0, 8.1)				
Change from Baseline									
Day 9	(1.9, 9.8)		(-0.6, 8.8)		(-6.2, 2.8)				
Day 17	(3.3, 10.8)		(3.8, 13.0)		(-3.0, 5.8)				
Change from Day 9									
Day 17	(-2.5, 5.0)		(-0.3, 8.9)		(-1.3, 7.5)				

a: LS Means, pooled standard deviations. 95% confidence intervals, treatment and pairwise comparisons p-values were obtained from an ANCOVA model with treatment effects.  
b: Mean percent changes are unadjusted means.

Reviewer's Comments:

- Exposure was increased by approximately **6 fold** in poor metabolizers.
- Exposure was independent of age. In other words, the severity and magnitude of phenotype is similar in children and adults.
- The detectable DL concentrations in 3 placebo subjects could be due to accidental use of Claritin by the subjects.

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#### 4.2.5 Study # P03016:

##### Objectives:

The primary objective of this study is to evaluate the safety and steady state PK profiles of DL in poor metabolizers.

##### Design:

In some aspects, the design of the study was similar to the above study # P02798. This was Phase III, placebo-controlled, third-party blind, multiple dose study in 42 pediatric patients with allergic rhinitis aged 2 to 11 years. Patients were screened for metabolic status as described above.

Based on the data from screening study (# P02818) 20 subjects were enrolled for DL treatment, but 5 subjects in this group were determined to be normal metabolizers. Therefore, a total of 15 poor metabolizers and 5 normal metabolizers were treated with DL, respectively. The placebo group consists of 5 poor metabolizers and 17 normal metabolizers (**Table 4.2.5.1**).

**Table 4.2.5.1. Patients demographics**

	Total (n=42)	DL Poor <sup>a</sup> (n=15)	DL Normal <sup>a</sup> (n=5)	Placebo <sup>b</sup> (n=22)
<b>Age (Years)</b>				
mean	7.0	6.9	7.8	6.9
standard dev	2.8	2.8	0.8	2.8
median	7.0	6.0	8	7.0
range (min-max)	2-11	3-11	7-9	2-11
<b>Age Group (Number, %)</b>				
age 2 to 5 years	13 (31.0)	6 (40.0)	0 (0.0)	7 (31.8)
age 6 to 11 years	29 (69.0)	9 (60.0)	5 (100.0)	15 (68.2)
<b>Sex (Number, %)</b>				
female	22 (52.4)	9 (60.0)	4 (80.0)	9 (40.9)
male	20 (47.6)	6 (40.0)	1 (20.0)	13 (59.1)
<b>Race (Number, %)</b>				
Caucasian	5 (11.9)	3 (20.0)	0 (0.0)	2 (9.1)
Black	37 (88.1)	12 (80.0)	5 (100.0)	20 (90.9)

a: DL metabolizer status was classified according to the 3-OH:DL ratio from this study.

b: Consisting of 5 poor metabolizers and 17 normal metabolizers of DL.

No loading dose was administered in this study. Depending on age, patients received their assigned treatments of either 1.25 mg (age 2-5 years) or 2.5 mg (age 6-11 years) DL daily single doses for 29 days. Separate matched groups received placebos as follows:

Group A (2-5 years): 1.25 mg (2.5 mL of 0.5 mg/mL) QD X 29 Days

Group B (6-11 years): 2.5 mg (5 mL of 0.5 mg/mL) QD X 29 Days

Group C (2-5 years): 2.5 mL placebo syrup QD X 29 Days

Group D (6-11 years): 5 mL Placebo syrup QD X 29 Days

**When Blood Samples Were Collected?**

For the determination of DL and 3-OH DL steady state concentrations, blood samples were collected on Day -1, Days 15, 22, and 29. ECGs monitoring were performed for safety assessment on Day -1 and pre-dose and 3 hours post dose on Days 8, 15, 22, and 29.

**Results:**

- There was no clinically significant effect on ventricular rate, PR interval, or QRS interval. Thus it does not appear that there is any effect on QTc (Table 4.2.5.2-4.2.5.4). However, it appears that a slightly higher percentage of DL treated poor metabolizers had a >30 msec increase in QTcB, but not QTcF. For more details, see the Medical Officer’s review.
- Heart rate was increased in DL treated subjects compared to placebo (Table 4.2.5.5).

**Table 4.2.5.2. QTc intervals (msec)**

Visit	DL Poor Metabolizer (A) <sup>a</sup>		Placebo (B)		Analysis <sup>a</sup>		
	N	Mean <sup>b</sup>	N	Mean	Pstd <sup>b</sup>	95% CI <sup>b</sup> Trt A-B	
Baseline	15	341.5	22	341.9	25.0	0.989	(-17.4, 16.7)
Change from Baseline							
Day 8	15	-10.8	22	-7.0	18.7	0.547	(-16.5, 8.9)
Day 15	15	-1.7	22	2.9	16.7	0.419	(-15.9, 8.8)
Day 22	15	-2.1	22	11.7	20.1	0.048	(-27.5, -0.2)
Day 29	15	0.9	22	1.0	20.1	0.992	(-13.7, 13.6)

a: Subjects in the DL treatment group designated as Normal Metabolizers are excluded from this analysis.  
b: Means, pooled standard deviations (Pstd) and 95% Confidence Intervals (CI) of the treatment (Trt) difference are obtained from a one-way ANOVA model extracting effect due to treatment.

**Table 4.2.5.3. Bazett QTc intervals (msec)**

Visit	DL Poor Metabolizer (A) <sup>a</sup>		Placebo (B)		Analysis <sup>a</sup>		
	N	Mean <sup>b</sup>	N	Mean	Pstd <sup>b</sup>	95% CI <sup>b</sup> Trt A-B	
Baseline	15	406.6	22	406.2	18.0	0.697	(-9.9, 14.6)
Change from Baseline							
Day 8	15	8.7	22	7.1	19.9	0.959	(-13.8, 13.2)
Day 15	15	11.8	22	12.8	22.0	0.892	(-15.9, 13.9)
Day 22	15	18.5	22	10.0	22.7	0.274	(-7.0, 23.9)
Day 29	15	19.4	22	14.8	17.5	0.432	(-7.2, 16.5)

a: Subjects in the DL treatment group designated as Normal Metabolizers are excluded from this analysis.  
b: Means, pooled standard deviations (Pstd) and 95% Confidence Intervals (CI) of the treatment (Trt) difference are obtained from a one-way ANOVA model extracting effect due to treatment.

**Table 4.2.5.4. Changes in QTc B(Bazett) and QTcF (Fridericia)**

Changes	Changes	Number (%)							
		Day 8		Day 15		Day 22		Day 29	
		DL Poor	PL	DL Poor	PL	DL Poor	PL	DL Poor	PL
Changes in QTcB from baseline	<0	4 (27)	10(45)	4 (27)	8 (36)	4 (27)	8 (36)	2 (13)	4 (18)
	0-30	9 (60)	9 (41)	7 (47)	10 (45)	5 (33)	10 (45)	8 (53)	13 (59)
	31-60	2 (13)	3 (14)	4 (27)	4 (18)	5 (33)	4 (18)	5 (33)	5 (23)
	≥61	0	0	0	0	1 (7)	0	0	0
Changes in QTcF from baseline	<0	7 (47)	11(50)	5 (33)	6 (27)	3 (20)	6 (27)	3 (20)	4 (18)
	0-30	7 (47)	11 (50)	10 (67)	14 (64)	10 (67)	14 (64)	11 (73)	16(73)
	31-60	1 (7)	0	0	2 (9)	2 (13)	2 (9)	1 (7)	2 (9)
	≥61	0	0	0	0	0	0	0	0

**Table 4.2.5.5. Ventricular Hear Rate (Beats/min)**

Visit	DL Poor Metabolizer (A) <sup>a</sup>		Placebo (B)		Analysis <sup>a</sup>		
	N	Mean <sup>b</sup>	N	Mean	Pstd <sup>b</sup>	P-Value 95% CI <sup>b</sup>	
						Ttt	A-B
Baseline	15	86.5	22	86.3	12.6	0.980	(-8.4, 8.8)
Change from Baseline							
Day 8	15	8.7	22	7.0	9.8	0.591	(-4.9, 8.4)
Day 15	15	6.2	22	3.6	10.2	0.459	(-4.4, 9.5)
Day 22	15	9.4	22	-2.2	13.3	0.013	(2.6, 20.7)
Day 29	15	6.1	22	6.6	11.8	0.524	(-5.5, 10.6)

a: Subjects in the DL treatment group designated as Normal Metabolizers are excluded from this analysis.

b: Means, pooled standard deviations (Pstd) and 95% Confidence Intervals (CI) of the treatment (Ttt) difference are obtained from a one-way ANOVA model extracting effect due to treatment.

- Steady-state was achieved by Day 15 (Tables 4.2.5.6 and 4.2.5.7).
- The exposure in poor metabolizers was approximately 5-6 fold higher than that in the normal metabolizers (Tables 4.2.5.6 and 4.2.5.7).

**Table 4.2.5.6: Mean (%CV) Cmin of DL and 3-OH DL poor Metabolizers**

Analyte	Day	Mean %CV		Mean %CV	
		2 to 5 yr (n=6)		6 to 11 yr (n=9)	
DL	15	6.07	34	7.53	33
DL	22	6.14	33	7.51	32
DL	29	6.58	28	8.24	34
3-OH DL	15	0.11	44	0.18	78
3-OH DL	22	0.11	40	0.18	78
3-OH DL	29	0.11	22	0.18	99
Ratio 3-OH DL/DL	15	1.82%	50	2.88%	109
Ratio 3-OH DL/DL	22	1.99%	71	3.03%	123
Ratio 3-OH DL/DL	29	1.80%	55	2.13%	74

**Table 4.2.5.7: Mean (%CV) Cmin of DL and 3-OH DL Normal Metabolizers**

Day	DL (n=5) <sup>a</sup>		3-OH DL (n=5)		Ratio 3-OH DL/DL	
	Mean	%CV	Mean	%CV	Mean	%CV
-1	0.04 <sup>b</sup>	224	0.05 <sup>c</sup>	224	22.9%	224
15	1.38	90	0.54	22	58.3%	49
22	1.35	56	0.64	36	56.4%	51
29	1.36	60	0.59	26	53.3%	50

**Reviewer's Comments:**

It should be noted that 5 subjects enrolled in this study as poor metabolizers based on the data from the screening Study #P02818 were later determined to be normal metabolizers based on the Cmin data obtained in this trial. According to the sponsor, this discrepancy could be due to the use of the 12 hour single-point to determine the phenotypic status and the PK variability.

**Conclusions:**

- Steady-state was achieved by Day 15
- Exposure to DL in poor metabolizers was approximately **6 fold** higher than normal metabolizers.
- Although there was a slight trend of a longer QTc in poor metabolizers, the evidence may be subject to further analysis.

#### 4.2.6 Study # P02781:

##### Objective:

This is a retrospective analysis after characterization of the metabolic phenotype of DL in those subjects who participated in three previously conducted studies: C98-566, P00302, and P00303. After the determination of the metabolic status for DL, retrospective analysis of the safety data was conducted to compare its safety in "poor metabolizers" vs. "normal metabolizers".

##### Design:

Subjects received a single-dose of their assigned treatments on Day 1 of either 5 mg loratadine or 2.5 or 5 mg DL as they were administered in the original protocols (Table 4.2.6.1). Blood samples were collected at 4 and 12-hours postdose for the determination ratio of 3-OH DL to DL and at 12 hours postdose for safety evaluations.

**Table 4.2.6.1. Doses and Demographics in the Previous Studies**

Primary Protocol	Drug	Current Age	Dose
P00302/303	Desloratadine	<6	2.5 mg
		≥6	5 mg
C98-566	Loratadine	All	5 mg

##### Population:

- A total of 162 subjects were enrolled and completed this study. Of these 51, 60, and 51 subjects were from studies C98-566, P00302, and P00303, respectively (Table 4.2.6.2).
- All poor metabolizers were ≥6 years of age at the time of phenotyping. A total of 16 poor metabolizers were identified from among subjects who received DL, and 10 from those who received loratadine.

**Table 4.2.6.2. Number of % of Enrolled Subjects**

Protocol No. (Drug Dosed)	No. of Subjects Enrolled	No. of Subjects Who Received Active Treatment	No. of Subjects Phenotyped	Race <sup>a</sup>			No. of Poor Metabolizers Identified <sup>b</sup>		
				C	B	O	C	B	O
P00302 (DL)	120	60	60	28	30	2	4	4	0
P00303 (DL)	111	55	51 <sup>b</sup>	10	41	0	2	6	0
C98-566 (Loratadine)	121	60	51 <sup>c</sup>	43	8	0	6	4	0

a: C=caucasian, B=Black, O=other.

b: Four subjects did not participate in the phenotyping protocol.

c: Nine subjects did not participate in the phenotyping protocol.

**Results:**

- From the screening tests, the total number of poor metabolizers was as follows: 8 (13.3%) from study #P00302 (4 Blacks and 4 Caucasians), 8 (15.6%) in study #P00303 (6 Blacks and 2 Caucasians), and 10 (19.6%) from study #C98-566 (4 Blacks and 6 Caucasians). The individual demographic and % ratio of 3-OHDL/DL of each poor metabolizer subject is shown in **Table 4.2.6.3**.
- According to the sponsor, four of the 162 subjects reported at least one adverse event. One normal metabolizer in the 5 mg loratadine group; 2 normal metabolizers in the 5 mg DL group ( $\geq 6$  years); and one poor metabolizer in the 5 mg DL group ( $>6$  years).
- Based on the retrospective analysis of the safety data from studies # P00302, P00303, and C98-566, there were no serious or unexpected adverse events. All adverse events were mild to moderate in severity. Common adverse events included headache, viral infection and drowsiness.
- There was no apparent effect on QTc in poor metabolizers compared to either placebo or normal subjects (**Tables 4.2.6.4 and 4.2.6.5**). For further details on the QTc analysis and safety data, please see the Medical Officer's review.

**Table 4.2.6.3. Demographic Profile of Poor Metabolizers and Their Respective Ratios (%) of 3-OH DL to DL at 12 hours Postdose**

Protocol No.	Subject No.	Age/Gender	Race	Ratio (%) 12 HR
P00302	302006	11/F	Black	2.52
	302019	9/M	Black	9.32
	302020	10/F	Caucasian	2.12
	302062	10/M	Caucasian	2.39
	302074	12/F	Black	0.00
	302081	10/M	Caucasian	1.37
	302096	8/F	Black	0.00
	302098	8/M	Caucasian	2.89
P00303	303056	6/M	Black	2.59
	303087	7/M	Black	0.64
	303089	6/M	Black	1.63
	303094	7/F	Black	2.60
	303095	7/M	Black	0.62
	303110	7/F	Black	1.77
	303125	6/F	Caucasian	2.69
	303126	7/F	Caucasian	3.07
C98-566	566030	6/F	Caucasian	3.54
	566033	6/M	Black	1.28
	566051	8/F	Caucasian	1.09
	566052	8/F <sup>a</sup>	Black	0.00
	566056	8/F	Black	1.05
	566070	6/F	Caucasian	2.04
	566073	6/F	Caucasian	3.22
	566107	6/M	Caucasian	3.44
	566125	7/F	Black	1.33
	566133	7/M	Caucasian	1.72

a: Following lock of the database, it was determined that the gender of Subject No. 566052 should have been recorded as male.

**Table 4.2.6.4. ECG Data in Children Ages 2 to 5 Years Old**

Study Period	DL 1.25 mg QD Normal Metabolizers			DL 1.25 mg QD Poor Metabolizers			Placebo QD		
	n	Mean	STD	n	Mean	STD	n	Mean	STD
<b>Ventricular Rate (bpm)</b>									
Baseline	43	104.5	21.7	8	88.38	8.77	56	104.8	17.3
Change	43			8			56		
Day 8		3.84	20.0		5.5	12.8		-2.14	13.8
Day 15		-1.44	19.4		2.38	10.7		-8.8	14.5
% Change	43			8			56		
Day 8		5.0	-		7.0	-		-1.2	-
Day 15		0	-		3.6	-		-7.3	-
<b>PR Interval (msec)</b>									
Baseline	43	127.4	12.6	8	131.0	5.55	56	127.8	14.5
Change	43			8			56		
Day 8		-3.16	10.1		-2.5	10.2		-0.18	10.7
Day 15		-1.51	12.4		1.5	11.3		-1.05	12.5
% Change	43			8			56		
Day 8		-2.0	-		-2.0	-		0.3	-
Day 15		-0.6	-		1.2	-		-0.3	-
<b>QRS Interval (msec)</b>									
Baseline	43	72.28	8.11	8	71.0	7.63	56	72.64	9.21
Change	43			8			56		
Day 8		-1.30	6.15		-1.5	4.75		-1.14	6.37
Day 15		-0.09	7.01		1.5	5.21		-0.07	7.01
% Change	43			8			56		
Day 8		-1.6	-		-1.7	-		-1.0	-
Day 15		0.1	-		2.2	-		0.5	-
<b>QT Interval (msec)</b>									
Baseline	43	316.8	27.3	8	339.5	16.1	56	318.3	25.4
Change	43			8			56		
Day 8		-1.58	23.3		-8.0	17.6		2.61	20.2
Day 15		4.47	27.2		-1.0	22.0		13.0	23.9
% Change	43			8			56		
Day 8		-0.2	-		-2.2	-		1.0	-
Day 15		1.7	-		-0.1	-		4.4	-
<b>QTc Interval (msec) Bazett Formula</b>									
Baseline	43	412.8	15.1	8	410.9	12.9	56	416.9	18.5
Change	43			8			56		
Day 8		5.38	22.5		2.43	23.4		-1.08	17.0
Day 15		2.48	23.7		4.8	16.3		-0.86	20.1
% Change	43			8			56		
Day 8		1.4	-		0.7	-		-0.2	-
Day 15		0.7	-		1.2	-		-0.1	-

Study Period	DL 1.25 mg QD Normal Metabolizers			DL 1.25 mg QD Poor Metabolizers			Placebo QD		
	n	Mean	STD	n	Mean	STD	n	Mean	STD
<b>QTc Interval (msec) Fridericia Formula</b>									
Baseline	43	377.8	13.9	8	385.5	11.1	56	380.7	16.4
Change	43			8			56		
Day 8		2.61	18.7		-1.57	16.8		0.40	14.9
Day 15		3.23	20.9		2.67	15.6		4.66	18.0
% Change	43			8			56		
Day 8		0.8	-		-0.3	-		0.2	-
Day 15		1.0	-		0.7	-		1.4	-

DL-Normal=Normal metabolizer of DL.  
DL-Poor=Poor metabolizer of DL.

**Table 4.2.6.5. ECG Data in Children Ages 6 to 11 Years Old**

Study Period	DL 2.5 mg QD Normal Metabolizers			DL 2.5 QD Poor Metabolizers			Placebo QD		
	n	Mean	STD <sup>a</sup>	n	Mean	STD <sup>a</sup>	n	Mean	STD <sup>a</sup>
<b>Ventricular Rate (bpm)</b>									
Baseline	52	81.75	12.1	8	88.75	6.3	60	80.4	9.66
Change	52			8			60		
Day 8		-1.15	10.2		-4.75	8.51		-3.10	9.05
Day 15		-0.6	9.26		-7.0	7.75		-3.65	10.4
% Change	52			8			60		
Day 8		-0.5	-		-5.2	-		-3.4	-
Day 15		-0.2	-		-7.8	-		-4.1	-
<b>PR Interval (msec)</b>									
Baseline	52	132.2	13.2	8	125.5	11.9	60	133.0	16.8
Change	52			8			60		
Day 8		-1.31	9.81		-4.5	5.42		0	9.51
Day 15		1.27	14.0		2.5	9.30		-0.60	11.4
% Change	52			8			60		
Day 8		-0.7	-		-3.6	-		0.2	-
Day 15		1.2	-		2.0	-		-0.1	-
<b>QRS Interval (msec)</b>									
Baseline	52	79.77	9.75	8	81.5	4.24	60	77.47	7.02
Change	52			8			60		
Day 8		-0.77	5.32		-1.5	7.69		0.40	6.99
Day 15		-1.92	6.16		0.50	4.99		-0.67	6.84
% Change	52			8			60		
Day 8		-0.8	-		-1.6	-		0.8	-
Day 15		-2.0	-		0.7	-		-0.6	-
<b>QT Interval (msec)</b>									
Baseline	52	356.5	20.1	8	345.0	16.5	60	359.5	22.4
Change	52			8			60		
Day 8		3.62	20.6		15.5	17.7		6.80	16.1
Day 15		1.0	21.6		18.0	16.6		7.93	18.8
% Change	52			8			60		
Day 8		1.1	-		4.4	-		2.0	-
Day 15		0.4	-		5.4	-		2.3	-
<b>QTc Interval (msec) Bazett Formula</b>									
Baseline	52	413.8	20.5	8	419.1	18.9	60	414.4	20.2
Change	52			8			60		
Day 8		1.26	24.3		5.52	21.4		-0.84	17.6
Day 15		-1.14	23.0		3.61	17.8		-1.51	21.8
% Change	52			8			60		
Day 8		0.5	-		1.4	-		-0.1	-
Day 15		-0.1	-		1.0	-		-0.2	-
<b>QTc Interval (msec) Fridericia Formula</b>									
Baseline	52	393.5	14.7	8	392.7	17.0	60	395.1	17.9
Change	52			8			60		
Day 8		2.17	19.9		9.2	17.0		1.92	13.6
Day 15		-0.37	20.0		8.94	14.8		1.84	16.6
% Change	52			8			60		
Day 8		0.7	-		2.4	-		0.6	-
Day 15		0	-		2.4	-		0.6	-

a: Standard Deviation of the Mean.  
DL-Normal=Normal metabolizer of DL.  
DL-Poor=Poor metabolizer of DL.

## Conclusions:

- Out of 162 subjects, 26 subjects were identified as poor metabolizers (16%).
- The exposure to DL was approximately **6 fold** higher in poor metabolizers as compared to normal subjects.
- According to the sponsor, retrospective analysis showed no clinically significant adverse to DL in poor metabolizers compared to placebo.

## Clinical Studies:

The sponsor cross referenced the originally submitted Phase III studies #: 302 and 303. As described above, a retrospective analysis of these studies was performed in poor metabolizers who were enrolled in these studies (study # P02781). It should be noted that Studies #302 and 303 were submitted and reviewed in the first review cycle (please also see the Medical Officer's review). Therefore, these studies were not reviewed by OCPB in the current review cycle.

### 4.2.7 *In vitro* Studies:

The sponsor has conducted a series of *in vitro* studies to characterize the enzymes/isozymes responsible for the metabolism of DL. These studies were discussed at March 8, 2002 meeting with the sponsor. The synopses of these studies are included in this submission as part of the sponsor's response to comment # 19 in the approvable letter dated October 2, 2001.

Overall, the sponsor conducted extensive *in vitro* studies to characterize the isozymes and enzymes responsible for the metabolism of DL and its conversion to 3-OH DL. As of today, the enzymes responsible for the metabolism of DL and its conversion to 3-OH DL are unknown. All the tested enzymes were found to be responsible for <1% to <3% of the metabolism and conversion of DL to 3-OH DL. As stated above, these studies were, in part, discussed at the meeting held with the sponsor on March 8, 2002 (see also response to Comment #19).

Since the sponsor has provided a very extensive justification and effort to identify the enzymes responsible for the metabolism of DL, no further studies are required from the sponsor at this time. The sponsor efforts and justification in this area are acknowledged and acceptable to OCPB.

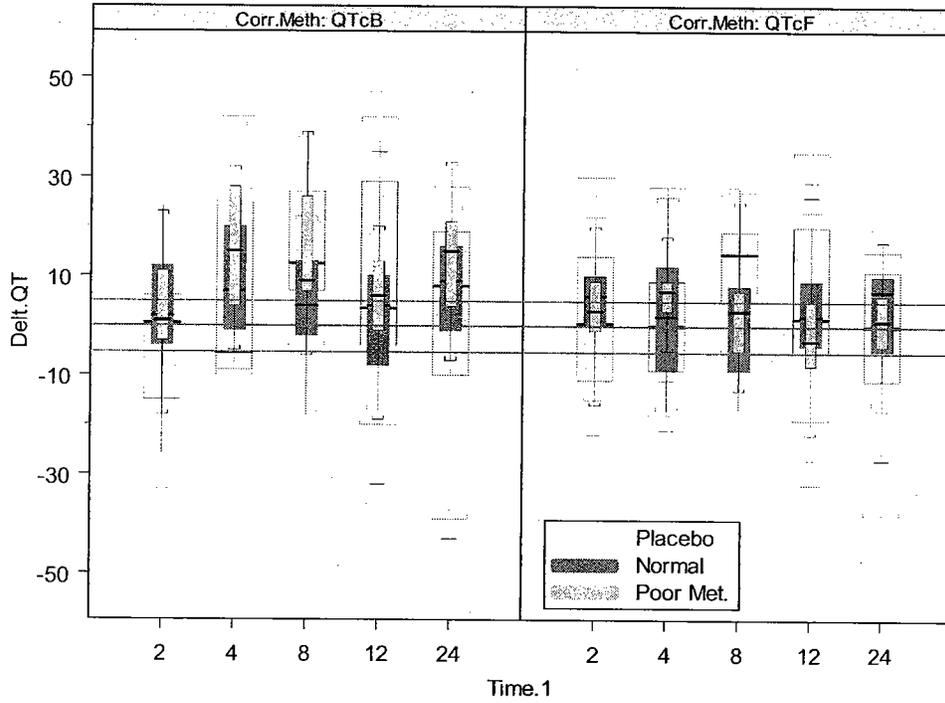
### 4.3 Consult Review (Pharmacometric)

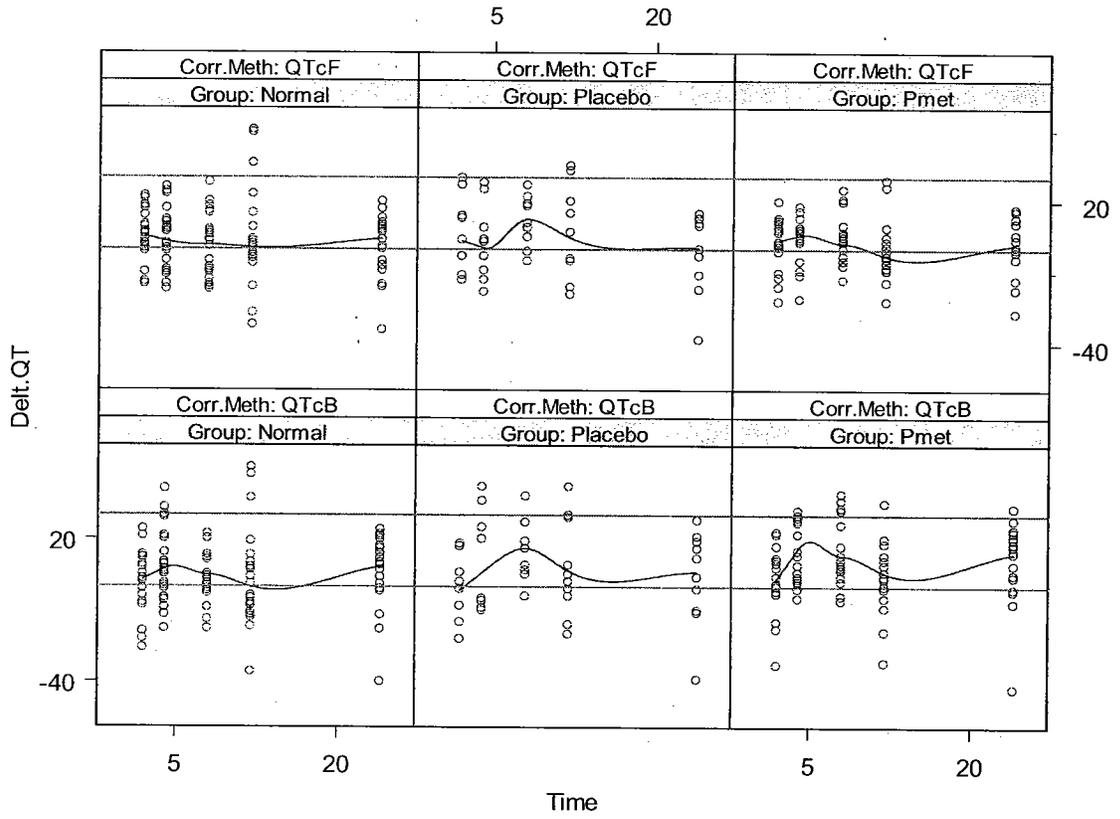
Dr. He Sun, a senior pharmacometric analyst in OCPB, was consulted with QTc data. A copy of his analysis is attached.

1. Data is limited.
2. Variability are comparable among three trt arms

QTcB or QTcF depends on QT-RR plot, which we do not have data. If we consider QTcF (Fredericia correction method) as the appropriate method, then no QTc prolongation signal is seen.

### Comparison among treatment groups





Appears This Way  
On Original

\*\*\* Summary  
**Based on treatment arm  
only (both methods and all  
time points)**

Group:Normal  
Delt.QT  
Mean: 4.161905  
Std Dev.: 14.917716  
----

Group:Placebo  
Delt.QT  
Mean: 5.66000  
Std Dev.: 17.03367  
----

Group:Pmet  
Delt.QT  
Mean: 5.747059  
Std Dev.: 14.064964

\*\*\* Summary  
**Based on Method and  
treatment arm (all time  
points)**

Group:Normal  
Corr.Meth:QTcB  
Delt.QT  
Mean: 4.866667  
Std Dev.: 15.658659  
----

Group:Placebo  
Corr.Meth:QTcB  
Delt.QT  
Mean: 6.80000  
Std Dev.: 18.25332  
----

Group:Pmet  
Corr.Meth:QTcB  
Delt.QT  
Mean: 9.447059  
Std Dev.: 15.618598  
----

Group:Normal  
Corr.Meth:QTcF  
Delt.QT  
Mean: 3.457143  
Std Dev.: 14.178144  
----

Group:Placebo  
Corr.Meth:QTcF

Delt.QT  
Mean: 4.52000  
Std Dev.: 15.82331  
----

Group:Pmet  
Corr.Meth:QTcF  
Delt.QT  
Mean: 2.047059  
Std Dev.: 11.240770

\*\*\* Summary  
For each time point, each  
method and each treatment

Group:Normal  
Corr.Meth:QTcB  
Time:2  
Delt.QT  
Mean: 1.952381  
Std Dev.: 13.868944  
----

Group:Placebo  
Corr.Meth:QTcB  
Time:2  
Delt.QT  
Mean: -1.6000  
Std Dev.: 13.4594  
----

Group:Pmet  
Corr.Meth:QTcB  
Time:2  
Delt.QT  
Mean: 1.882353  
Std Dev.: 14.473607  
----

Group:Normal  
Corr.Meth:QTcF  
Time:2  
Delt.QT  
Mean: 4.904762  
Std Dev.: 10.304876  
----

Group:Placebo  
Corr.Meth:QTcF  
Time:2  
Delt.QT  
Mean: 4.50000  
Std Dev.: 15.93215  
----

Group:Pmet  
Corr.Meth:QTcF  
Time:2  
Delt.QT  
Mean: 2.00000

Std Dev.: 11.24722  
----  
Group:Normal  
Corr.Meth:QTcB  
Time:4  
Delt.QT

Mean: 8.666667  
Std Dev.: 15.688637  
----

Group:Placebo  
Corr.Meth:QTcB  
Time:4  
Delt.QT  
Mean: 7.70000  
Std Dev.: 20.73671  
----

Group:Pmet  
Corr.Meth:QTcB  
Time:4  
Delt.QT  
Mean: 16.0000  
Std Dev.: 12.8938  
----

Group:Normal  
Corr.Meth:QTcF  
Time:4  
Delt.QT  
Mean: 3.52381  
Std Dev.: 12.92137  
----

Group:Placebo  
Corr.Meth:QTcF  
Time:4  
Delt.QT  
Mean: 1.70000  
Std Dev.: 15.45639  
----

Group:Pmet  
Corr.Meth:QTcF  
Time:4  
Delt.QT  
Mean: 4.235294  
Std Dev.: 10.431499  
----

Group:Normal  
Corr.Meth:QTcB  
Time:8  
Delt.QT  
Mean: 4.380952  
Std Dev.: 11.227093  
----

Group:Placebo  
Corr.Meth:QTcB  
Time:8  
Delt.QT

Mean: 16.40000  
 Std Dev.: 14.12799  
 ----  
 Group:Pmet  
 Corr.Meth:QTcB  
 Time:8  
     Delt.QT  
     Mean: 14.23529  
     Std Dev.: 13.96213  
 ----  
 Group:Normal  
 Corr.Meth:QTcF  
 Time:8  
     Delt.QT  
     Mean: 2.0000  
     Std Dev.: 12.9499  
 ----  
 Group:Placebo  
 Corr.Meth:QTcF  
 Time:8  
     Delt.QT  
     Mean: 12.30000  
     Std Dev.: 10.33925  
 ----  
 Group:Pmet  
 Corr.Meth:QTcF  
 Time:8  
     Delt.QT  
     Mean: 3.764706  
     Std Dev.: 10.592034  
 ----  
 Group:Normal  
 Corr.Meth:QTcB  
 Time:12  
     Delt.QT  
     Mean: 4.47619  
     Std Dev.: 20.80293  
 ----  
 Group:Placebo

Corr.Meth:QTcB  
 Time:12  
     Delt.QT  
     Mean: 7.64000  
     Std Dev.: 20.30435  
 ----  
 Group:Pmet  
 Corr.Meth:QTcB  
 Time:12  
     Delt.QT  
     Mean: 4.647059  
     Std Dev.: 15.499763  
 ----  
 Group:Normal  
 Corr.Meth:QTcF  
 Time:12  
     Delt.QT  
     Mean: 4.952381  
     Std Dev.: 20.836209  
 ----  
 Group:Placebo  
 Corr.Meth:QTcF  
 Time:12  
     Delt.QT  
     Mean: 6.10000  
     Std Dev.: 19.14535  
 ----  
 Group:Pmet  
 Corr.Meth:QTcF  
 Time:12  
     Delt.QT  
     Mean: -0.05882353  
     Std Dev.: 12.83291952  
 ----  
 Group:Normal  
 Corr.Meth:QTcB  
 Time:24  
     Delt.QT  
     Mean: 4.857143

Std Dev.: 15.913157  
 ----  
 Group:Placebo  
 Corr.Meth:QTcB  
 Time:24  
     Delt.QT  
     Mean: 3.90000  
     Std Dev.: 19.98027  
 ----  
 Group:Pmet  
 Corr.Meth:QTcB  
 Time:24  
     Delt.QT  
     Mean: 10.47059  
     Std Dev.: 17.70282  
 ----  
 Group:Normal  
 Corr.Meth:QTcF  
 Time:24  
     Delt.QT  
     Mean: 1.904762  
     Std Dev.: 12.688202  
 ----  
 Group:Placebo  
 Corr.Meth:QTcF  
 Time:24  
     Delt.QT  
     Mean: -2.0000  
     Std Dev.: 16.4587  
 ----  
 Group:Pmet  
 Corr.Meth:QTcF  
 Time:24  
     Delt.QT  
     Mean: 0.2941176  
     Std Dev.: 11.6176843

#### **4.4. Signature Page**

##### **Reviewer**

Sayed (Sam) Al Habet, R.Ph., Ph.D.  
Office of Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader-----

cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

## 4.5 Filing Memo

# Clinical Pharmacology and Biopharmaceutics Filing Memo

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<b>NDA:</b> 21-605	<b>Date of Submission:</b> December 8, 2000 ( <b>Original</b> ) February 27, 2004 (current)
<b>Generic Name</b>	Desloratadine
<b>Brand Name:</b>	CLARINEX™ Syrup
<b>Formulations:</b>	Syrup (0.5 mg/ml)
<b>Route of Administration:</b>	Oral
<b>Indication:</b>	Seasonal Allergic Rhinitis (SAR) and Chronic Idiopathic Urticaria (CIU)
<b>Type of Submission:</b>	Response to the Approvable Letter/Resubmission
<b>Sponsor:</b>	Schering Corporation, Kenilworth, NJ
<b>Reviewer:</b>	Sayed (Sam) Al Habet, R.Ph., Ph.D.
<b>Team Leader</b>	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.
<b>Date of Submission:</b>	February 27, 2004
<b>Date Received:</b>	March 5, 2004
<b>Review Date:</b>	March 10, 2004
<b>First Draft</b>	March 19, 2004
<b>Second Draft</b>	March 22, 2004
<b>DFS Draft:</b>	March 22, 2004

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### Background:

According to the sponsor, this is a complete response to the approvable letter dated October 2, 2001. The main objective of this response is to establish the safety, PK profile, and exposure of Desloratadine (DL) in poor metabolizer pediatric population.

Desloratadine (DL) is an active metabolite of loratadine (Claritin). It is currently marketed under the trade name Clarinex for the relief of the nasal and non-nasal symptoms of allergic rhinitis and

chronic idiopathic urticaria in patients 12 years of age and older. In terms of formulation, it is currently available as film coated tablets and orally-disintegrating tablets (REDITABS).

In December 8, 2000 the sponsor submitted the current NDA (21-300) for Clarinex syrup containing 0.5 mg/ml DL. An approvable action letter was issued on October 2, 2001 with the following main deficiencies:

- 1) There were numerous CMC related issues.
- 2) The drug appears to be metabolized very slowly in subjects that believed to be poor metabolizers. In a few subjects, the level of the drug was >2-3 folds higher than the majority of the subjects who participated in the PK studies. Therefore, it was suspected that these subjects could be poor metabolizers.

Based on these observations, the sponsor was requested to conduct additional studies to establish the safety and PK profiles of the drug after exposure to multiple doses. In addition, the sponsor was encouraged to characterize the isozymes responsible for the metabolism of the drug.

#### **What Studies Are Submitted in the Current NDA:**

##### **A. PK Studies:**

The sponsor submitted two new multiple-dose PK studies # P02798 and P03016 in poor metabolizer pediatric population (ages 2-11 years). Other supportive studies were included (Studies # P02818, P02994, P02781, and P03031) and various *in vitro* studies. The following is a summary of each study:

##### **Study # P02798:**

##### **Objectives:**

The primary objective of this study is to evaluate the PK profiles and safety of DL in poor metabolizers following multiple doses.

##### **Design:**

This was placebo-controlled, investigator-blind study in pediatric subjects with allergic rhinitis aged 2 to 11 years. Subjects were screened/phenotyped for metabolic status (poor or normal metabolizers) based on a separate protocol using loratadine/Claritin as probe (Study # P02818).

A loading dose of DL equal to two times of the assigned daily doses was administered on Day 1 to normal DL metabolizers and for three days (Day 1, 2, and 3) for DL poor metabolizers. Then, daily doses of 1.25 or 2.5 mg were administered daily up to Day 17 in subjects ages 2-5 years and 6-11 years, respectively.

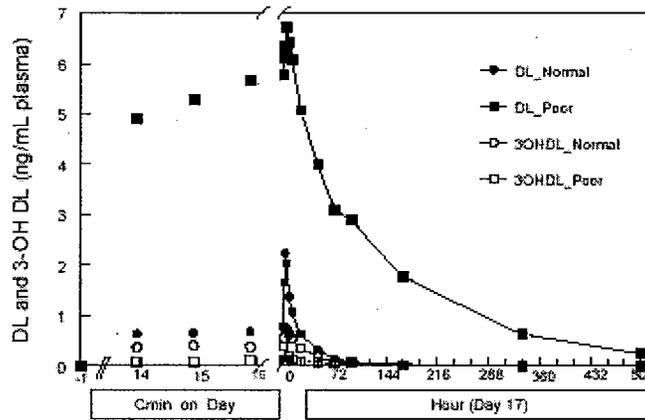
Blood samples for the determination of DL and 3-OH DL concentrations in plasma were collected on Day -1, and predose on Days 14, 15, and 16. In addition, multiple blood samples were obtained on Day 17. The plasma concentration data following administration of DL on Day 17 were used to estimate the DL and 3-OH DL PK parameters.

**Results:**

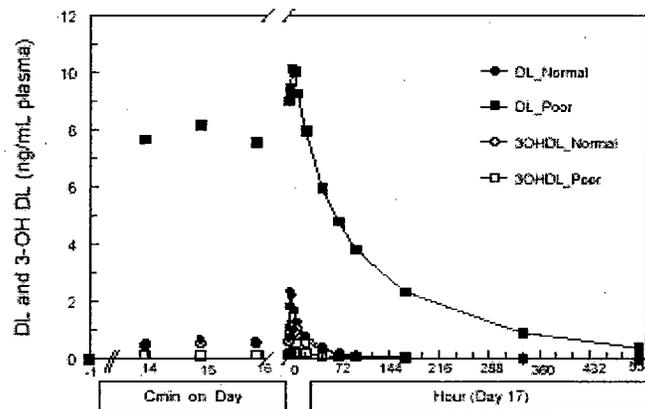
- The results are summarized in **Figure 1** and **Tables 1,2**.
- The data clearly shows that the exposure to DL in poor metabolizers is approximately 6 times that of normal metabolizers.

**Figure 1. Mean Plasma Concentration-Time Profiles of DL and 3-OH DL in Children 2-5 years of age (top) and 6-11 years of age (bottom)**

Age: 2-5 years



Age: 6-11 years



**Table 1. Mean (%CV) of PK Parameters of DL at Day 17 in Children 2-5 years of age and 6-11 years of age**

Parameter <sup>a</sup>	Mean	%CV	Range	Mean	%CV	Range
2-5 yr: DL-Normal Metabolizers (n=8)				2-5 yr: DL-Poor Metabolizers (n=4)		
C <sub>max</sub>	2.29	52	1.10-4.31	6.78	3	6.53-7.04
T <sub>max</sub>	2.50	37	2.0-4.0	2.75	55	1.0-4.0
AUC(0-24 hr)	29.5	59	14.0-61.8	143	4	138-149
t <sub>1/2</sub>	48.7	73	12.2-80.7	115	7	106-127
6-11 yr: DL-Normal Metabolizers (n=12) <sup>b</sup>				6-11 yr: DL-Poor Metabolizers (n=13) <sup>c</sup>		
C <sub>max</sub>	2.56	23	1.71-3.89	10.4	26	5.94-14.6
T <sub>max</sub>	2.67	67	2.0-8.0	5.54	61	0-12 <sup>c</sup>
AUC(0-24 hr)	34.7	37	24.0-72.6	220	24	125-300
t <sub>1/2</sub>	41.6	81	13.8-118	126	19	84.8-184

a: Units: C<sub>max</sub>: ng/mL; T<sub>max</sub>=hr; AUC: ng.hr/mL; t<sub>1/2</sub>: hr

b: Excludes Subject No. 114

c: Subject No. 61 had a C<sub>min</sub> value higher than postdose values.

**Table 2. Median (Range) of AUC (0-24 h) and C<sub>max</sub> of DL and 3-OH DL in all Children 2-11 years of age (Normal and Poor Metabolizers)**

Metabolizer Status	n	DL	3-OH DL
		AUC(0-24 hr) (ng.hr/mL)	AUC(0-24 hr) (ng.hr/mL)
Normal Metabolizer	20	29.9 (14.0-72.6)	16.8 (8.81-28.7)
Poor Metabolizer	17	211 (125-300)	3.33 (1.87-11.7)
		C <sub>max</sub> (ng/mL)	C <sub>max</sub> (ng/mL)
Normal Metabolizer	20	2.39 (1.10-4.31)	0.97 (0.55-1.76)
Poor Metabolizer	17	9.28 (5.94-14.6)	0.17 (0.09-0.77)

### Conclusions:

Based on this study, dose adjustment in poor metabolizers may be recommended. Details will be discussed when all data are thoroughly reviewed.

### Study # P03016:

### Objectives:

The primary objective of this study is to evaluate the safety and steady state PK profiles of DL in poor metabolizers.

### Design:

In some aspects, the design of the study was similar to the above study # P02798. It was placebo-controlled, third-party blind, multiple dose study in pediatric patients with allergic rhinitis aged 2 to 11 years. Patients were screened for metabolic status as described above.

No loading dose was administered in this study. Depending on age, patients received their assigned treatments of either 1.25 mg (age 2-5 years) or 2.5 mg (age 6-11 years) DL daily single doses for 29 days. Separate matched groups received placebos.

Blood samples were collected for the determination of DL and 3-OH DL concentrations in plasma. ECGs monitoring were performed for safety assessment on day -1 and pre-dose and 3 hours post dose on Days 8, 15, 22, and 29. Blood was collected on Day -1, and predose on Days 14, 15, and 16 and multiple samples on Day 17. The plasma concentration data following administration of DL on Day 17 were used to estimate the DL and 3-OH DL PK parameters.

**Results:**

- According to the sponsor, there was no clinically significant effect on ventricular rate, PR interval, or QRS interval (Table 3).

**Table 3. Changes in QTc B(Bazett) and QTcF (Fridericia)**

Changes	Changes	Number (%)							
		Day 8		Day 15		Day 22		Day 29	
		DL Poor	PL	DL Poor	PL	DL Poor	PL	DL Poor	PL
Changes in QTcB from baseline	<0	4 (27)	10(45)	4 (27)	8 (36)	4 (27)	8 (36)	2 (13)	4 (18)
	0-30	9 (60)	9 (41)	7 (47)	10 (45)	5 (33)	10 (45)	8 (53)	13 (59)
	31-60	2 (13)	3 (14)	4 (27)	4 (18)	5 (33)	4 (18)	5 (33)	5 (23)
	≥61	0	0	0	0	1 (7)	0	0	0
Changes in QTcF from baseline	<0	7 (47)	11(50)	5 (33)	6 (27)	3 (20)	6 (27)	3 (20)	4 (18)
	0-30	7 (47)	11 (50)	10 (67)	14 (64)	10 (67)	14 (64)	11 (73)	16(73)
	31-60	1 (7)	0	0	2 (9)	2 (13)	2 (9)	1 (7)	2 (9)
	≥61	0	0	0	0	0	0	0	0

- Steady-state was achieved by Day 15 (Tables 4 and 5).
- The exposure in poor metabolizers was approximately 5-6 fold higher than that in the normal metabolizers (Tables 4 and 5).

**Table 4: Mean (%CV) Cmin of DL and 3-OH DL poor Metabolizers**

Analyte	Day	Mean %CV		Mean %CV	
		2 to 5 yr (n=6)		6 to 11 yr (n=9)	
DL	15	6.07	34	7.53	33
DL	22	6.14	33	7.51	32
DL	29	6.58	28	8.24	34
3-OH DL	15	0.11	44	0.18	78
3-OH DL	22	0.11	40	0.18	78
3-OH DL	29	0.11	22	0.18	99
Ratio 3-OH DL/DL	15	1.82%	50	2.88%	109
Ratio 3-OH DL/DL	22	1.99%	71	3.03%	123
Ratio 3-OH DL/DL	29	1.80%	55	2.13%	74

**Table 5: Mean (%CV) Cmin of DL and 3-OH DL Normal Metabolizers**

Day	DL (n=5) <sup>a</sup>		3-OH DL (n=5)		Ratio 3-OH DL/DL	
	Mean	%CV	Mean	%CV	Mean	%CV
-1	0.04 <sup>b</sup>	224	0.05 <sup>b</sup>	224	22.9%	224
15	1.38	90	0.54	22	56.3%	49
22	1.35	58	0.64	36	56.4%	51
29	1.36	60	0.59	26	53.3%	50

**Conclusions:**

From OCPB perspective, no conclusions can be made at this time. The data has not yet been reviewed.

**Study # P02818:**

**Objectives:**

This is a screening protocol to determine the metabolic phenotype.

**Design:**

In this study, Claritin (loratadine) syrup was used. A single dose of 10 mg (10 ml) was administered to subjects between the ages of 2-12 years. A single blood sample was collected at 12 hours post dose for the determination of the plasma concentration ratio of 3-OH DL relative to DL. Those subjects with a ratio of <10% or >10% were considered Poor or normal metabolizers, respectively. It should be noted that subjects with a ratio of >25% were considered for subsequent safety studies. A total of 359 subjects were enrolled and completed the study

**Results:**

- Of the 359 subjects, 53 (14.8%) were identified as poor metabolizers with a ratio of <10% (Table 6).
- The prevalence of poor metabolizers is higher in the blacks than Caucasians.
- According to the sponsor, the use of a single 12 hours post dose blood sample to determine the ratio was well validated.

**Table 6: Summary of Ages Stratified by DL Metabolic Status**

	DL Poor Metabolizer	DL Normal Metabolizer	Total
Number of Subjects	53	306	359
Age (N, %)			
age 2 to <3 years	4 (8%)	22 (7%)	26 (7%)
age 3 to <4 years	3 (6%)	29 (9%)	32 (9%)
age 4 to <5 years	3 (6%)	42 (14%)	45 (13%)
age 5 to <6 years	6 (11%)	44 (14%)	50 (14%)
age 6 to <7 years	6 (11%)	27 (9%)	33 (9%)
age 7 to <8 years	7 (13%)	30 (10%)	37 (10%)
age 8 to <9 years	7 (13%)	33 (11%)	40 (11%)
age 9 to <10 years	5 (9%)	35 (11%)	40 (11%)
age 10 to <11 years	5 (9%)	27 (9%)	32 (9%)
age 11 to <12 years	7 (13%)	17 (6%)	24 (7%)

**Study # P03031:**

**Objectives:**

This is also a screening protocol to determine the metabolic phenotype.

**Design:**

This is similar to the above study # P02818 by using a single dose of 10 mg (10ml) of Claritin (loratadine) syrup. Similar to the above study, a ratio of <10% was used to identify the poor metabolizer and that of >25% was for normal metabolizers and also for those to be eligible for a subsequent safety study (#P02994). A total of 2075 subjects were enrolled.

**Results:**

- Of the 2075 subjects, 2058 completed the screening study and 2033 subjects were phenotyped for DL metabolizer status.
- 79 subjects were determined to be DL poor metabolizers.
- The prevalence of the DL poor metabolizer phenotype is shown **Table 7**.
- A total of 97 subjects were randomized to treatment in Study # P02994 and 58 of these subjects were DL poor metabolizers.

**Table 7: Number and % of Enrolled Subjects**

	DL Poor (n=79)	DL Normal (n=1917)	Indeterminate <sup>a</sup> (n=37)	NA <sup>b</sup> (n=42)
Number (%) Completed	79 (100)	1916 (100)	37 (100)	26 (62)
Number (%) Discontinued	0	1 (<1)	0	16 (38)
Reason for Discontinuation				
Lost to Follow-up	0	0	0	3 (7)
Non-compliance	0	1 (<1)	0	11 (26)
Did Not Wish to Continue for Reasons Unrelated to Assigned Study Treatment	0	0	0	2(5)

a: Subjects with a 3-OH DL to DL % ratio that was ≥10% and <20%.

b: Not available (NA); metabolizer status was missing due to incomplete or missing assay data.

## Study # P02994:

This is a subsequent study to the above screening study # P03031. The primary objective is to evaluate the safety and tolerance of DL in poor metabolizers following 5 weeks of repetitive dosing.

### Design:

The metabolic status of all subjects enrolled in this study was previously identified in the screening study #P03031. This was a single daily dose, double-blind, placebo controlled study for 5 weeks.

The total number of subjects enrolled in this study was 97 (54 females, and 43 males). A total of 48 received DL and 49 received placebo treatments. There were two doses: 2.5 ml (1.25 mg) of DL syrup (0.5 mg/ml) was administered to the young children ages 2-6 years and 5 ml (2.5 mg) to the older children ages >6 to <12 years. For each dose there was a matching placebo. All treatments continued daily for 5 weeks.

Blood samples for the determination of trough concentration (C<sub>min</sub>) of DL and 3-OH DL were collected at baseline, Day 15, and Day 36 prior to the scheduled dose at each of the respective days. Physical exams, ECG, and vital signs were monitored throughout the study for safety and tolerance.

### Results:

- According to the sponsor, there was no significance safety concern, including QTc related changes.
- According to the sponsor, steady state was achieved on Day 15. Also, there was no difference between the C<sub>min</sub> on day 15 and day 36 (**Table 8**).

**Table 8: Number and % of Enrolled Subjects**

Analyte	Visit	Mean	%CV	Mean	%CV
		2 to 5 yr (n=11)		6 to 11 yr (n=32)	
DL <sup>b</sup>	Day 15	5.89	35	7.13	45
DL <sup>b</sup>	Day 36	5.18	49	6.11 <sup>a</sup>	62
3-OH DL <sup>b</sup>	Day 15	0.131	58	0.152	32
3-OH DL <sup>b</sup>	Day 36	0.121	85	0.126 <sup>a</sup>	76
Ratio 3-OH DL/DL	Day 15	2.43%	68	2.26%	32
Ratio 3-OH DL/DL	Day 36	2.19%	76	2.13% <sup>a</sup>	76

a. Subject 000267/Site 19 had missing Day 36 Visit data.

b. Unit: mg/mL

### Conclusions:

According to the sponsor, the drug was tolerated in poor metabolizers. Also, the steady state was achieved in Day 15. From OCPB perspective, no comments can be made at this time.

**Study # P02781:**

**Objective:**

This is a retrospective analysis after characterization of the metabolic phenotype of DL in those subjects who participated in three previously conducted studies: C98-566, P00302, and P00303. After the determination of the metabolic status for DL, retrospective analysis of the safety data was conducted to compare its safety in "poor metabolizers" vs. "normal metabolizers".

**Design:**

Subjects received a single-dose of their assigned treatment on Day 1 of either 5 mg loratadine or 2.5 or 5 mg DL as they were administered in the original protocol. Blood samples were collected at 4 and 12-hours postdose for the determination of DL and 3-OH DL plasma concentrations and at 12 hours postdose for safety evaluations.

**Results:**

- A total of 162 subjects were enrolled and completed this study. Of these 51, 60, and 51 subjects were from studies C98-566, P00302, and P00303, respectively.
- All poor metabolizers were  $\geq 6$  years of age at the time of phenotyping. A total of 16 poor metabolizers were identified from among subjects who received DL, and 10 from those who received loratadine (Table 9).

**Table 9: Number and % of Enrolled Subjects**

Protocol No. (Drug Dosed)	No. of Subjects Enrolled	No. of Subjects Who Received Active Treatment	No. of Subjects Phenotyped	Race <sup>a</sup>			No. of Poor Metabolizers Identified <sup>a</sup>		
				C	B	O	C	B	O
P00302 (DL)	120	60	60	28	30	2	4	4	0
P00303 (DL)	111	55	51 <sup>b</sup>	10	41	0	2	6	0
C98-566 (Loratadine)	121	60	51 <sup>c</sup>	43	8	0	6	4	0

a: C=caucasian, B=Black, O=other.

b: Four subjects did not participate in the phenotyping protocol.

c: Nine subjects did not participate in the phenotyping protocol.

- According to the sponsor, in this study, four of the 162 subjects reported at least one adverse event. One normal metabolizer in the 5 mg loratadine group; 2 normal metabolizers in the 5 mg DL group ( $\geq 6$  years); and one poor metabolizer in the 5 mg DL group ( $>6$  years).
- Based on the retrospective analysis of the safety data from studies # P00302, P00303, and C98-566, there were no serious or unexpected adverse events. All adverse events were mild to moderate in severity. Common adverse events included headache, viral infection and drowsiness.

**Conclusion:**

- Out of 162 subjects, 26 subjects were identified as poor metabolizers (16%).
- The exposure to DL was approximately 6 fold higher in poor metabolizers as compare to normal subjects.
- According to the sponsor, retrospective analysis showed no clinically significant adverse to DL in poor metabolizers compared to placebo.

**B. Clinical Studies:**

The sponsor crossed referenced the originally submitted Phase III studies #: 302 and 303. Retrospective analysis of these studies was conducted in poor metabolizers who were enrolled in these studies (study # P02781).

**C. In vitro Studies:**

The sponsor has conducted a series of *in vitro* studies to characterize the enzymes/isozymes responsible for the metabolism of DL. These studies were discussed at March 8, 2002 meeting with the sponsor. The synopses of these studies are included in this submission as part of the sponsor's response to comment # 19 in the approvable letter dated October 2, 2001.

**General Comments:**

None of the observation and data in the above summary review has been verified by the office of Clinical Pharmacology and Biopharmaceutics (OCPB). All conclusions and observations stated in this filing memo were based on the sponsor's statements. Therefore, no comments can be made at this time until all data are thoroughly reviewed. The purpose of this filing memo is only to list the content of the NDA with a synopsis of each study.

**RECOMMENDATION:**

The NDA is fileable. See also the attached filing form.

**Reviewer**

Sayed (Sam) Al Habet, R.Ph., Ph.D.  
Office of Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader-----

cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

Office of Clinical Pharmacology and Biopharmaceutics  
New Drug Application Filing and Review Form

General Information About the Submission				
	Information		Information	
NDA Number	21-300	Brand Name	CLARINEX™ Syrup	
OCPB Division I	HFD-870	Generic Name	Desloratadine	
Medical Division	HFD-570	Drug Class	Antihistamine	
OCPB Reviewer	Sayed (Sam) Al Habet, R.Ph., Ph.D.	Indication(s)	Seasonal Allergic rhinitis (SAR) and Chronic Idiopathic Urticaria (CIU)	
OCPB Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.	Dosage Form	Syrup (0.5 mg/ml)	
		Dosing Regimen	Once daily (1.25 to 5 mg)	
Date of Submission	February 27, 2004	Route of Administration	Oral	
Estimated Due Date of OCPB Review	October 27, 2004	Sponsor	Schering Corporation	
PDUFA Due Date	February 27, 2005	Priority Classification	S	
Division Due Date	November 27, 2004			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:	X	5		
Blood/plasma ratio:				
Plasma protein binding:				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<i>Healthy Volunteers-</i>				
single dose:	X	2		
multiple dose:	X	2		
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:			
<b>Population Analyses -</b>			
Data rich:			
Data sparse:			
<b>II. Biopharmaceutics</b>			
<b>Absolute bioavailability:</b>			
<b>Relative bioavailability -</b>			
solution as reference:			
alternate formulation as reference:			
<b>Bioequivalence studies -</b>			
traditional design; single / multi dose:			
replicate design; single / multi dose:			
<b>Food-drug interaction studies:</b>			
<b>Dissolution:</b>			
<b>(IVIVC):</b>			
<b>Bio-wavier request based on BCS</b>			
BCS class			
<b>III. Other CPB Studies</b>			
<b>Genotype/phenotype studies:</b>			
<b>Chronopharmacokinetics</b>			
<b>Pediatric development plan</b>			
<b>Literature References</b>			
<b>Total Number of Studies</b>	7		
<b>Filability and QBR comments</b>			
	"X" if yes	Comments	
<b>Application filable ?</b>	<b>Yes</b>	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
<b>Comments sent to firm ?</b>		Comments have been sent to firm (or attachment included). FDA letter date if applicable.	
<b>QBR questions (key issues to be considered)</b>	<p>This is a response to the Agency's approvable letter dated October 2, 2001. The sponsor submitted information on the PK profiles after a single and multiple doses of the drug in children considered to be poor metabolizers. Also, the sponsor provided additional <i>in vitro</i> studies to characterize the isozymes responsible for the metabolism of the drug. The <i>in vitro</i> information were included as part of the sponsor's response, specifically to comment # 19 in the approvable letter.</p> <p>According to the sponsor, these studies are considered a complete response to OCPB comments provided in the action letter dated October 2, 2001.</p>		
<b>Other comments or information not included above</b>			
<b>Primary reviewer Signature and Date</b>	Sayed (Sam) Al Habet, R.Ph., Ph.D.		
<b>Secondary reviewer Signature and Date</b>	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.		

CC: NDA HFD-570, HFD-870 (Al Habet, Fadiran, Malinowski), CDR (B. Murphy, biopharm file)

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

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Sayed Al-Habet  
8/24/04 09:11:04 AM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
8/24/04 09:23:20 AM  
BIOPHARMACEUTICS  
I concur

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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**NDA:** 21-300  
**Proprietary Drug Name:** Clarinex™ Syrup  
**Generic Name:** Desloratadine  
**Indication:** Treatment of Seasonal Allergic Rhinitis (SAR) and Chronic Idiopathic Urticaria (CIU)  
**Dosage Form:** Syrup  
**Strength:** 0.5 mg/mL  
**Route of Administration:** Oral  
**Dosage and administration:** **Adults and children (age 12 and older):** 2 teaspoonfuls (5mg) of syrup once daily.  
**Children 6 to 11 years of age:** 1 teaspoonful (2.5 mg) once daily.  
**Children 2- to 5-years of age:** 1/2 teaspoonful (1.25 mg) once daily.  
**Applicant:** Schering Corporation  
**Clinical Division:** DPADP (HFD-570)  
**Submission Date:** December 8, 2000  
**Reviewer:** Sandra Suarez-Sharp, Ph.D.  
**Team Leader :** Emmanuel Fadiran, Ph. D.

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**Table 1.** BE of DL syrup (5 mg) and tablet (5mg) formulations in healthy volunteers under fed and fasted conditions

Formulation		Point estimates (%)		90% Confidence Intervals	
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
<b>Desloratadine</b>					
Trt B/ Trt A	AUC(inf)	95.4	102.35	84-108	90.06-116.3
	Cmax	92.5	100.51	84-102	90.7-111.4
Trt C/ Trt B	AUC(inf)	104	98.6	92-118	86.8-112.1
	Cmax	94.1	92.0	85-104	83.0-101.9
<b>3-OH Desloratadine</b>					
Trt B/ Trt A	AUC(inf)	94.9	100.7	89-101	94.4-107.5
	Cmax	96.5	98.7	89-104	91.2-106.9
Trt C/ Trt B	AUC(inf)	101	101.76	95-108	95.4-108.6
	Cmax	87.2	95.9	81-94	88.6-103.8

Clarinet tablets 5 mg (treatment A), syrup 5 mg (fasted conditions; treatment B) and syrup 5 mg (fed conditions; treatment C).

The pharmacokinetic studies conducted in children 2-5 years of age indicated that a single dose of clarinex syrup 1.25 mg (study P01125) had comparable AUCt and Cmax values for DL, but NOT for the metabolite 3-OH DL, to those obtained in adults (data from bioequivalence study: P00213) receiving clarinex syrup 5 mg (Table 2). The 3-OH DL AUCt and Cmax values obtained in adults receiving clarinex syrup 5 mg were statistically significantly higher (1.5-fold higher for both parameters) than those observed in this children population receiving a single dose of clarinex syrup 1.25 mg.

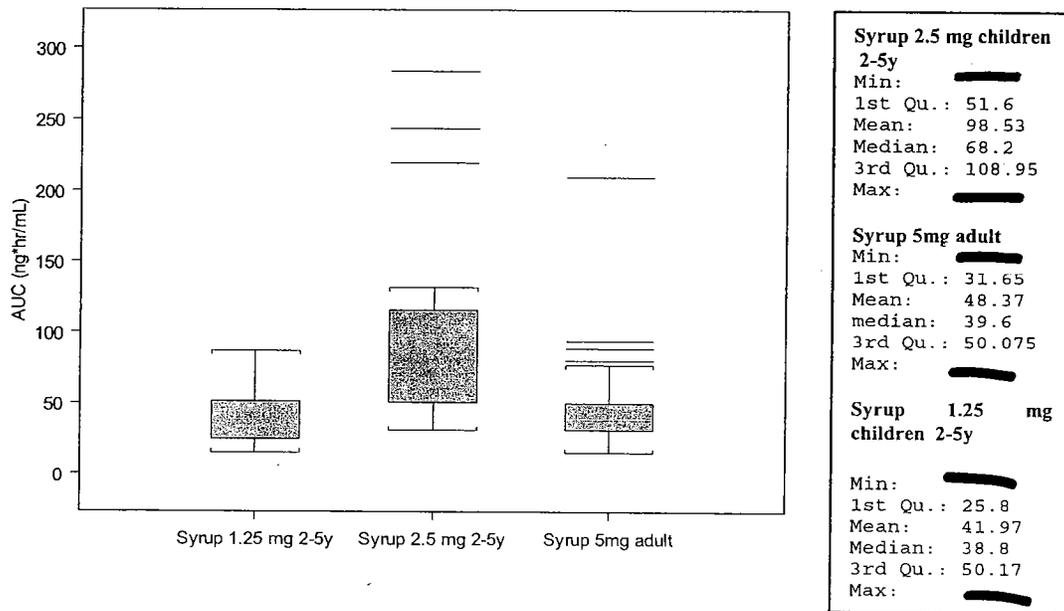
**Table 2.** Mean pharmacokinetic parameters of DL and 3-OH DL following administration of the treatments in children 2-5 years of age and adults

<b>Desloratadine</b>					
PK parameter	Children Data		Adult data	Ratio A/C	Ratio B/C
	Syrup 2.5mg (A) <sup>1</sup>	Syrup 1.25 mg (B) <sup>2</sup>	Syrup 5mg (C) <sup>3</sup>		
AUCt (ng*hr/mL)	98.6 (76)	42.0 (49)	46.22 (71)	2.13	0.91
AUCinf (ng*hr/mL)	111 (90)	45.1 (56)	48.36 (54)	2.30	0.93
Cmax (ng/mL)	5.36 (41)	2.68 (50)	2.3 (51)	2.33	1.17
Tmax (hr)	2.94 (79)	3.17 (63)	3.58 (45)		
T1/2 (hr)	18.7 (60)	16.4 (55)	24.03 (23)		
<b>3-OH desloratadine</b>					
PK parameter	Children Data		Adult data	Ratio A/C	Ratio B/C
	Syrup 2.5mg (A) <sup>1</sup>	Syrup 1.25 mg (B) <sup>2</sup>	Syrup 5mg (C) <sup>3</sup>		
AUCt (ng*hr/mL)	33.7 (51)	17.3 (42)	25.98 (28)	1.30	0.67
AUCinf (ng*hr/mL)	35.9 (47)	18.6 (35)	27.83 (28)	1.29	0.67
Cmax (ng/mL)	1.27 (61)	0.64 (49)	1.03 (38)	1.23	0.62
Tmax (hr)	4.44 (63)	4.89 (35)	4.73 (39)		
T1/2 (hr)	28.4 (67)	26.2 (78)	30.71 (21)		
AUCt ratio (%)*	34.1	41.19	56.2		

Calculated as the ratio of AUCt of 3-OH DL/DL\*; <sup>1</sup> Study P00225; <sup>2</sup> study P01125; <sup>3</sup> study P00213

The administration of a single dose of 2.5 mg of clarinex syrup to children 2-5 years of age (study P00225) resulted in DL AUCt and Cmax values, which were 2.13-fold and 2.33-fold higher, respectively, than those observed in healthy adults receiving 5 mg of syrup (Figure 1, Table 2).

*Based on these data, the appropriate dose of clarinex syrup for pediatric patients 2 to 5 years of age would be 1.25 mg.*



**Figure 1.** Box plot comparing the DL AUCt obtained following administration of a 5 mg syrup in healthy adults (from study P00213), and 1.25 mg (study P01125) and 2.5 mg (study P00225) clarinex syrup in children 2-5 years old.

The pharmacokinetic studies conducted in children 6 to 11 years of age indicated that a single dose of clarinex syrup 2.5 mg (study P01126) had comparable AUCt and Cmax values for DL, but NOT for the metabolite 3-OH DL, to those obtained in adults receiving clarinex syrup 5 mg (Table 3). The 3-OH DL AUCt and Cmax values obtained in adults receiving clarinex syrup 5 mg (data from study P00213) were statistically significantly higher (1.27- and 1.35-fold higher, respectively) than those observed in this children population receiving a single dose of clarinex syrup 2.5mg.

The administration of a single dose of 5 mg of clarinex syrup (study P00270) to this population of children resulted in AUCt and Cmax values which were 2.19-fold and 1.66 fold higher, respectively, than those observed in healthy adults receiving 5 mg of syrup (Figure 2, Table 3).

*Based on these data, the appropriate dose for pediatric patients 6 to 11 years of age would be 2.5 mg.*

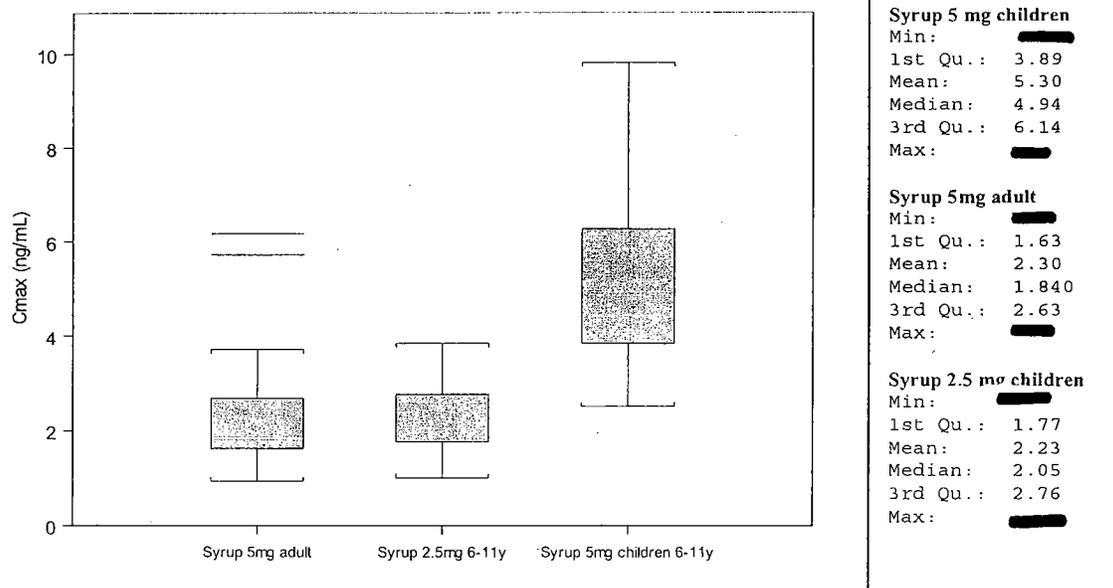
**Table 3.** Mean pharmacokinetic parameters of DL and 3-OH DL following administration of the treatments in children 6-11 years of age and adults

<b>Desloratadine</b>					
PK parameter	Children Data		Adult data	Ratio A/C	Ratio B/C
	Syrup 5 mg <sup>1</sup> (A)	Syrup 2.5 mg <sup>2</sup> (B)	Syrup 5mg <sup>3</sup> (C)		
AUCt (ng*hr/mL)	101 (89)	48.6 (88)	46.22 (71)	2.19	1.05
AUCinf (ng*hr/mL)	111 (102)	55.5 (100)	48.36 (54)	2.30	1.15
Cmax (ng/mL)	5.3 (41)	2.23 (35)	2.3 (51)	2.30	0.97
Tmax (hr)	2.78 (73)	3.67 (79)	3.58 (45)		
T1/2 (hr)	18.6 (49)	19.4 (61)	24.03 (23)		

<b>3-OH desloratadine</b>					
PK parameter	Children Data		Adult data	Ratio A/C	Ratio B/C
	Syrup 5mg <sup>1</sup> (A)	Syrup 2.5 mg <sup>2</sup> (B)	Syrup 5mg <sup>3</sup> (C)		
AUCt (ng*hr/mL)	43.0 (45)	20.5 (50)	25.98 (28)	1.66	0.79
AUCinf (ng*hr/mL)	45.9 (42)	23.2 (38)	27.83 (28)	1.65	0.83
Cmax (ng/mL)	1.77 (57)	0.764 (54)	1.03 (38)	1.72	0.74
Tmax (hr)	4.44 (63)	4.44 (42)	4.73 (39)		
T1/2 (hr)	26.8 (43)	28.1 (65)	30.71 (21)		
AUCt ratio (%)*	42.6	42.2	56.2		

\*Calculated as the ratio of AUCt of 3-OH DL/DL; <sup>1</sup>data from P00270; <sup>2</sup>data from P01126; <sup>3</sup> data from P00213



**Figure 2 .** Box plot for DL Cmax values following single administration of Clarinex syrup 5 mg in adults (P00213), syrup 2.5 mg in children 6-11 years old (P01126) and syrup 5 mg in children 6 to 11 years old (P00270).

## 2. COMMENTS TO SPONSOR

- The sponsor should not use interchangeably relative bioavailability (%) and point estimates (%). For BE purposes, point estimates are calculated as the ratio of the log-transform means for the AUC and Cmax. The determination of relative BA is based on non-log transformed data.
- The sponsor is encouraged to include patients rather than healthy volunteers in future studies concerning pediatrics.

## 3. COMMENTS TO THE MEDICAL OFFICER

- The tablet and syrup formulations were bioequivalent and a high-fat and high-caloric meal (total calories: 841; 31.6 g of proteins, 53.8 g of fat and 57.4 g of carbohydrates) had no effect on the bioavailability of DL from the syrup formulation.
- Pediatric subjects 2 to 5 years of age receiving a single dose of clarinex syrup 1.25 mg had comparable AUCt and Cmax values for DL, but NOT for the metabolite (3-OH DL), to those obtained in adults receiving clarinex syrup 5 mg. Cmax and AUCt values for the metabolite were statistically significantly lower for the 1.25mg dose (ratio of 1.25mg/5mg= 0.62, 0.67, respectively) to those obtained for the 5mg dose in adults when compared by this reviewer using the ANOVA method.
- Pediatric subjects 6 to 11 years of age receiving a single dose of clarinex syrup 2.5 mg had comparable AUCt and Cmax values for DL, but NOT for the metabolite (3-OH DL), to those obtained in adults receiving clarinex syrup 5 mg. Cmax and AUCt values for the metabolite were statistically significantly lower for the 2.5 mg dose (ratio of 2.5mg/5mg= 0.74, 0.79, respectively) to those obtained for the 5mg dose in adults when compared by this reviewer using the ANOVA method.
- Since DL is more potent (anti-histamine effect) than its metabolite, 1.25 mg and 2.5 mg of clarinex syrup administered to children 2-5 and 6-11 years of age, respectively may have the same efficacy as 5 mg of the syrup administered to adults, despite the lower 3-OH DL plasma concentrations found in the children population.
- Previous studies conducted in healthy adults (NDA 21-297) showed that DL and its metabolite (3-OH DL) have an accumulation factor that range from 1.64 to 1.75 and from 2.19 to 2.37, respectively, following administration of the Clarinex 5 mg tablet formulation daily for 28 days. Therefore, multiple dose PK of DL and its metabolite in children may be predicted based on these findings.
- Two to three subjects from every PK study had DL Cmax and AUC values, which were 2- to 6-fold higher and 3-OH DL Cmax and AUC values, which were 2- to more than 10-fold lower than the median Cmax and AUC observed for the rest of the group. Low AUC % ratios of 3-OH DL/DL have been identified in previous clarinex NDAs (21-312 and 21-313) suggesting the existence of DL slow metabolizers. The clinical relevance of these observations on the safety of clarinex should be evaluated by the medical reviewer.
- A graphic representation of Cmax as a function of weight revealed a clear correlation between these two parameters. Therefore, weight seems to be an important covariate that affects the pharmacokinetics of desloratadine in children.

#### 4. LABELING COMMENTS

[REDACTED]

#### 5. RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-300 submitted on December 8, 2000. The NDA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB. However, the clinical relevance of the existence of desloratadine slow metabolizers on the safety of clarinex should be evaluated by the medical reviewer. Please forward the above comments to the sponsor.

Reviewer

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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

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cc  
NDA 21-300/N-000: Division File  
HFD-870: Malinowski, Hunt

HFD-570:

Fadiran, Nicklas, Trout, Suarez-Sharp

**Appears This Way  
On Original**

The present review has been focused on the following issues.

## 6. QUESTION BASED REVIEW

### Q1. Was the to-be-marketed formulation used in the pharmacokinetic studies?

YES.

The sponsor used the following clarinex syrup formulation in all the PK studies:

**Table 1.** Formulation for Desloratadine 0.5 mg/mL Syrup

Syrup Strength	0.5 mg/mL
Formula. No.	3518
Batch No.	53266-003-B
FMR No.	99513D09
Manf. Date	2/23/99
Recertification Date	11/99

Batch No. 53266-003-B is the same as the to-be marketed formulation. The batch size used in this study was [REDACTED] which is [REDACTED] of the size of a full production batch [REDACTED]. The DL syrup was packaged and supplied to the investigator by [REDACTED] [REDACTED] which is an approved manufacturing site.

### Q2. Is the clarinex syrup formulation (5mg) equivalent to the 5-mg tablet formulation? Did food affect the bioavailability of DL from the syrup formulation?

The tablet and syrup formulations were bioequivalent. High-fat and high-caloric meal had no effect on the bioavailability of DL from the syrup formulation.

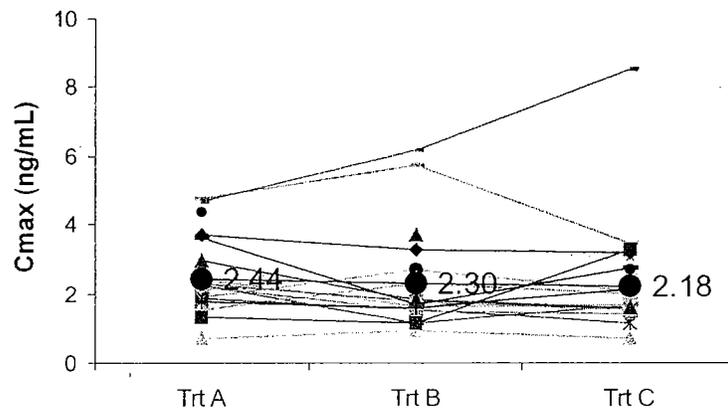
The point estimates (%) and the 90% CIs for the log-transformed C<sub>max</sub> and AUC(inf) for DL and its metabolite (3-OH DL) are presented in Table 2. Figures 1 and 2 showed the individual DL C<sub>max</sub> and AUC<sub>inf</sub> for the 3 test treatments, respectively. Preliminary analysis was performed to examine the extreme pharmacokinetic values and the impact of outliers (Subjects 25 and 29, see Figures 1 and 2) on the overall results. It was found that exclusion of these subjects from the statistical analysis did not change the overall bioequivalence conclusion of the study. As a result, Subjects 25 and 29 were included in the final statistical analysis.

According to the sponsor, the CIs for AUC(I) and C<sub>max</sub> of DL and 3-OH DL for Treatment B (clarinex syrup fasted) relative to Treatment A (clarinex tablet 5mg), and Treatment C (clarinex syrup fed) relative to Treatment B met the 80-125 bioequivalence guideline. This reviewer calculated 90% CIs for C<sub>max</sub> and AUC using the WinNonlin program and the findings are contrasted in Table 2. The 90% CIs calculated by this reviewer are similar to the ones reported by the sponsor. This indicates that the tablet and syrup formulations were bioequivalent, and that a high-fat and high-caloric meal (total calories: 841; 31.6 g of proteins, 53.8g of fat and 57.4g of carbohydrates) had no effect on the bioavailability of DL from the syrup formulation.

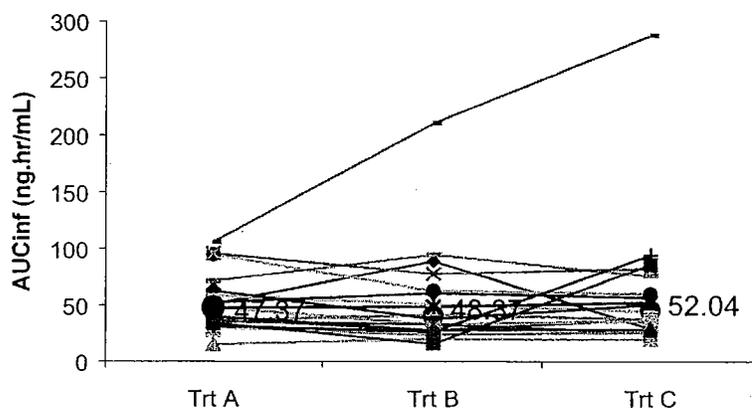
**Table 2.** Bioequivalence of DL syrup (5 mg) and tablet (5mg) formulations in healthy volunteers under fed and fasted conditions (study P00213)

Formulation		Point estimates (%)		90% Confidence Interval	
<b>Desloratadine</b>					
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
<b>Trt B/ Trt A</b>	AUC(inf)	95.4	102.35	84-108	90.06-116.3
	Cmax	92.5	100.51	84-102	90.7-111.4
<b>Trt C/ Trt B</b>	AUC(inf)	104	98.6	92-118	86.8-112.1
	Cmax	94.1	92.0	85-104	83.0-101.9
<b>3-OH-Desloratadine</b>					
<b>Trt B/ Trt A</b>	AUC(inf)	94.9	100.7	89-101	94.4-107.5
	Cmax	96.5	98.7	89-104	91.2-106.9
<b>Trt C/ Trt B</b>	AUC(inf)	101	101.76	95-108	95.4-108.6
	Cmax	87.2	95.9	81-94	88.6-103.8

Clarinex tablets 5 mg (treatment A), syrup 5 mg (fasted conditions; treatment B) and syrup 5 mg (fed conditions; treatment C).



**Figure 1.** Individual DL Cmax values following single administration of Clarinex tablets 5 mg (treatment A), syrup 5 mg (fasted conditions; treatment B) and syrup 5 mg (fed conditions; treatment C). Data levels correspond to mean values



**Figure 2.** Individual DL AUC<sub>0→inf</sub> values single following administration of Clarinex tablets 5 mg (treatment A), syrup 5 mg (fasted conditions; treatment B) and syrup 5 mg (fed conditions; treatment C). Data levels correspond to mean values.

**Q3. Is the proposed dose of 1.25mg QD in children 2-5 years of age supported by the pharmacokinetic studies?**

**YES.**

The sponsor conducted two pharmacokinetic studies in children 2-5 years of age. Study P00225 used a single dose of clarinex syrup 2.5 mg and study P01125 use a single dose of 1.25mg. Both PK studies were open-label Phase I studies in 18 healthy pediatric subjects (different subjects for each study).

Table 3 shows the mean PK parameters for the following treatments: single dose of clarinex syrup 1.25mg and 2.5 mg administered to children 2-5 years of age and single dose of clarinex syrup 5mg administered to healthy adults (from P00213). There was high intersubject variability in DL plasma concentrations as shown in Figures 3 and 4 and the associated pharmacokinetic parameters (Table 3). A stepwise regression procedure conducted by the sponsor did not detect significant relationships between age or body weight and the pharmacokinetic parameters for the 1.25 mg dose; however for the 2.5 mg dose, the stepwise regression procedure detected a significant relationship between body weight and C<sub>max</sub> (p=0.05), explaining 22% of the variability among subjects.

A single dose of syrup 2.5 mg in these children resulted in C<sub>max</sub> and AUC<sub>t</sub> values for DL which were more than 2-fold higher (2.3-, 2.13-fold, respectively) and approximately equal (1.29- and 1.3-fold, respectively) for the metabolite than those obtained in the adult population receiving 5mg of the syrup formulation (Table 3).

A single dose of syrup 1.25mg in children 2-5 years resulted in C<sub>max</sub> and AUC<sub>t</sub> values for DL which were very similar to those obtained in the adult population receiving 5mg of the syrup formulation (Table 3). However, C<sub>max</sub> and AUC<sub>t</sub> for the metabolite were statistically significantly lower for the 1.25mg dose than those obtained for the 5mg

dose in adults when compared by this reviewer using the ANOVA method (see Table 4). Since DL is more potent than its metabolite, 1.25mg of clarinex syrup administered to children 2-5 years of age may have the same efficacy than 5 mg of the syrup administered to adults.

Previous studies conducted in healthy adults (NDA 21-297) showed that DL and its metabolite (3-OH DL) have accumulation factors that range from 1.64 to 1.75 and from 2.19 to 2.37, respectively, following administration of the Clarinex 5 mg tablet formulation daily for 28 days. Therefore, the PK of DL and 3-OH DL in children after multiple dosing may be predicted based on these findings.

**Table 3.** Mean pharmacokinetic parameters of DL and 3-OH DL following administration of the treatments in children 2-5 years of age

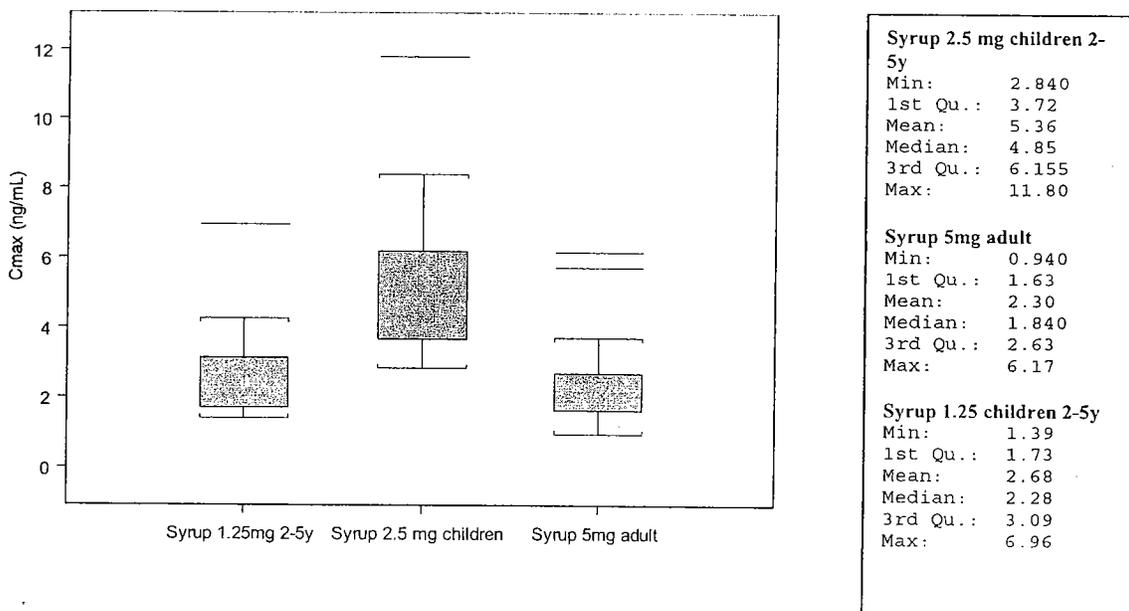
<b>Desloratadine</b>					
PK parameter	Children Data		Adult data	Ratio A/C	Ratio B/C
	Syrup 2.5mg <sup>1</sup> (A)	Syrup 1.25 mg <sup>2</sup> (B)	Syrup 5mg <sup>3</sup> (C)		
AUCt (ng*hr/mL)	98.6 (76)	42.0 (49)	46.22 (71)	2.13	0.91
AUCinf (ng*hr/mL)	111 (90)	45.1 (56)	48.36 (54)	2.30	0.93
Cmax (ng/mL)	5.36 (41)	2.68 (50)	2.3 (51)	2.33	1.17
Tmax (hr)	2.94 (79)	3.17 (63)	3.58 (45)		
T1/2 (hr)	18.7 (60)	16.4 (55)	24.03 (23)		
<b>3-OH desloratadine</b>					
PK parameter	Children Data		Adult data	Ratio A/C	Ratio B/C
	Syrup 2.5mg (A)	Syrup 1.25 mg (B)	Syrup 5mg (C)		
AUCt (ng*hr/mL)	33.7 (51)	17.3 (42)	25.98 (28)	1.30	0.67
AUCinf (ng*hr/mL)	35.9 (47)	18.6 (35)	27.83 (28)	1.29	0.67
Cmax (ng/mL)	1.27 (61)	0.64 (49)	1.03 (38)	1.23	0.62
Tmax (hr)	4.44 (63)	4.89 (35)	4.73 (39)		
T1/2 (hr)	28.4 (67)	26.2 (78)	30.71 (21)		
AUCt ratio (%)*	34.1	41.2	56.2		

\*Calculated as the ratio of AUCt of 3-OH DL/DL; <sup>1</sup> study P00225; <sup>2</sup> study P01125; <sup>3</sup> study P00213

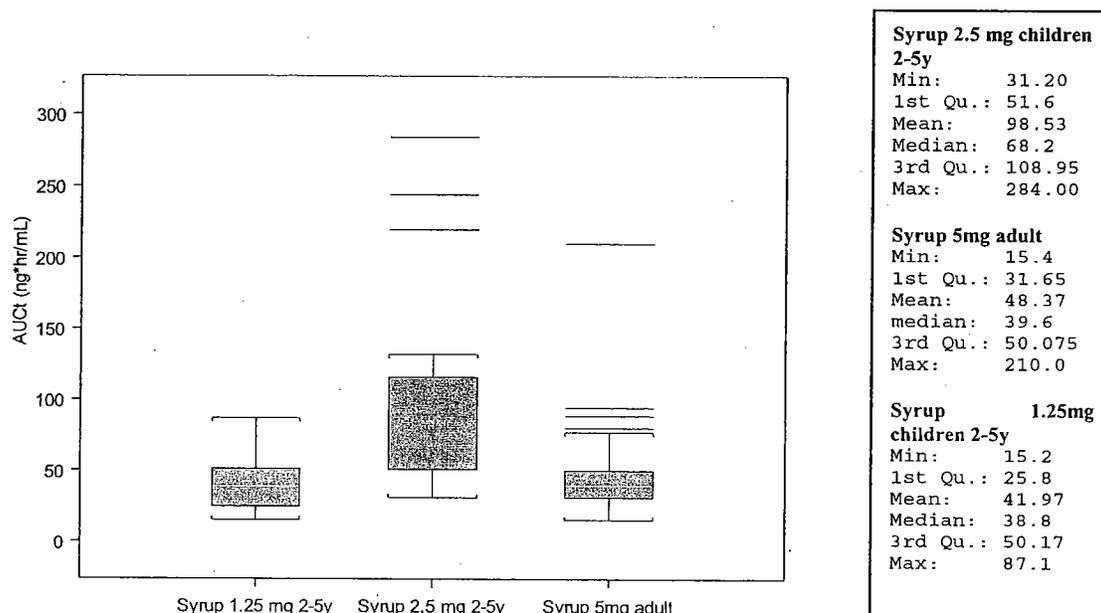
**Table 4. ANOVA analysis for AUCt and Cmax obtained from children 2-5 years of age and adults**

<b>Desloratadine</b>			
PK parameter	Children Data	Adult data	P value (A vs. B)
	Syrup 1.25 mg <sup>1</sup> (A)	Syrup 5mg <sup>2</sup> (B)	
AUCt (ng*hr/mL)	42.0 (49)	46.22 (71)	0.4516
Cmax (ng/mL)	2.68 (50)	2.3 (51)	0.31
<b>3-OH desloratadine</b>			
PK parameter	Children data	Adult data Syrup 5mg	P value (A vs. B)
	Syrup 1.25mg (A)	(B)	
AUCt (ng*hr/mL)	17.3 (42)	25.98 (28)	<<<<<0.05
Cmax (ng/mL)	0.64 (49)	1.03 (38)	0.001

<sup>1</sup>study P01125; <sup>2</sup>study P00213



**Figure 3.** Box plot comparing the DL Cmax obtained following administration of a 5 mg syrup in healthy adults (from study P00213), and 1.25 mg (study P01125) and 2.5 mg (study P00225) clarinex syrup in children 2-5 years old.



**Figure 4.** Box plot comparing the DL AUCt obtained following administration of a 5 mg syrup in healthy adults (from study P00213), and 1.25 mg (study P01125) and 2.5 mg (study P00225) clarinex syrup in children 2-5 years old.

**Q4. Is the proposed dose of 2.5mg QD in children 6-11 years of age supported by the pharmacokinetic studies?**

**YES.**

The sponsor conducted two pharmacokinetic studies in children 6-11 years of age. Study P00270 used a single dose of clarinex syrup 5.0 mg and study P01126 use a single dose of 2.5 mg. Both PK studies were open-label Phase I studies in 18 healthy pediatric subjects (different subjects for each study).

Table 5 shows the mean PK parameters for the following treatments: single dose of clarinex syrup 2.5 mg and 5 mg administered to children 6-11 years of age and single dose of clarinex syrup 5mg administered to healthy adults (data from study P00213). There was high intersubject variability in DL plasma concentrations as shown in Figures 5 and 6 and the associated pharmacokinetic parameters (Table 5). A stepwise regression procedure conducted by the sponsor detected a significant relationship between age and Cmax (p=0.024), explaining 45% of the variability among subjects for the 5 mg dose and a significant relationship between body weight and Cmax (p=0.01) explaining 34% of the variability among pediatric subjects for the 2.5 mg dose.

A single dose of syrup 5 mg in these children resulted in DL Cmax and AUCt values which were more than 2-fold higher (2.3, 2.19-fold, respectively) and

approximately 2-fold higher (1.7- and 1.66-fold, respectively) for the metabolite than those obtained in the adult population receiving 5mg of the syrup formulation.

A single dose of syrup 2.5 mg in children 6 to 11 years resulted in Cmax and AUCt values for DL which were similar to those obtained in the adult population receiving 5mg of the syrup formulation. However, Cmax and AUCt for the 3-OH DL were statistically significantly lower for the 2.5 mg dose than those obtained for the 5mg dose in adults when compared by this reviewer using the ANOVA method (see Table 6).

Since DL is more potent than its metabolite, 2.5 mg of clarinex syrup administered to children 6-11 years of age may have the same efficacy than 5 mg of the syrup administered to adults, despite the lower 3-OH DL plasma concentrations found in the children population.

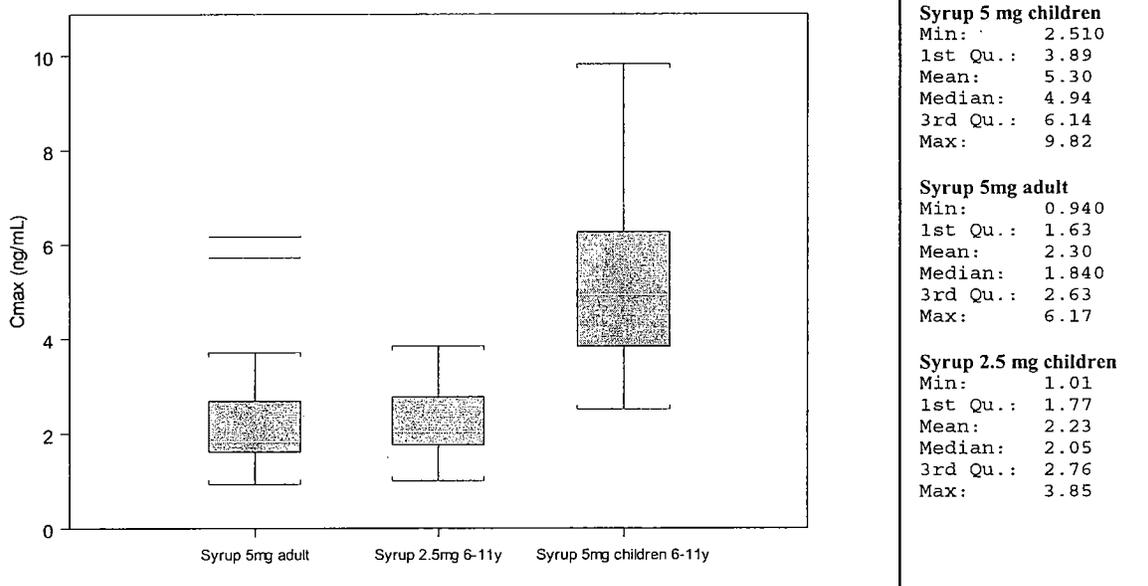
**Table 5.** Mean pharmacokinetic parameters of DL and 3-OH DL following administration of the treatments in children 6-11 years of age.

<b>Desloratadine</b>					
PK parameter	Children Data		Adult data	Ratio A/C	Ratio B/C
	Syrup 5 mg <sup>1</sup> (A)	Syrup 2.5 mg <sup>2</sup> (B)	Syrup 5mg <sup>3</sup> (C)		
AUCt (ng*hr/mL)	101 (89)	48.6 (88)	46.22 (71)	2.19	1.05
AUCinf (ng*hr/mL)	111 (102)	55.5 (100)	48.36 (54)	2.30	1.15
Cmax (ng/mL)	5.3 (41)	2.23 (35)	2.3 (51)	2.30	0.97
Tmax (hr)	2.78 (73)	3.67 (79)	3.58 (45)		
T1/2 (hr)	18.6 (49)	19.4 (61)	24.03 (23)		
<b>3-OH desloratadine</b>					
PK parameter	Children Data		Adult data	Ratio A/C	Ratio B/C
	Syrup 5mg (A)	Syrup 2.5 mg (B)	Syrup 5mg (C)		
AUCt (ng*hr/mL)	43.0 (45)	20.5 (50)	25.98 (28)	1.66	0.79
AUCinf (ng*hr/mL)	45.9 (42)	23.2 (38)	27.83 (28)	1.65	0.83
Cmax (ng/mL)	1.77 (57)	0.764 (54)	1.03 (38)	1.72	0.74
Tmax (hr)	4.44 (63)	4.44 (42)	4.73 (39)		
T1/2 (hr)	26.8 (43)	28.1 (65)	30.71 (21)		
AUCt ratio (%)*	42.6	42.1	56.2		

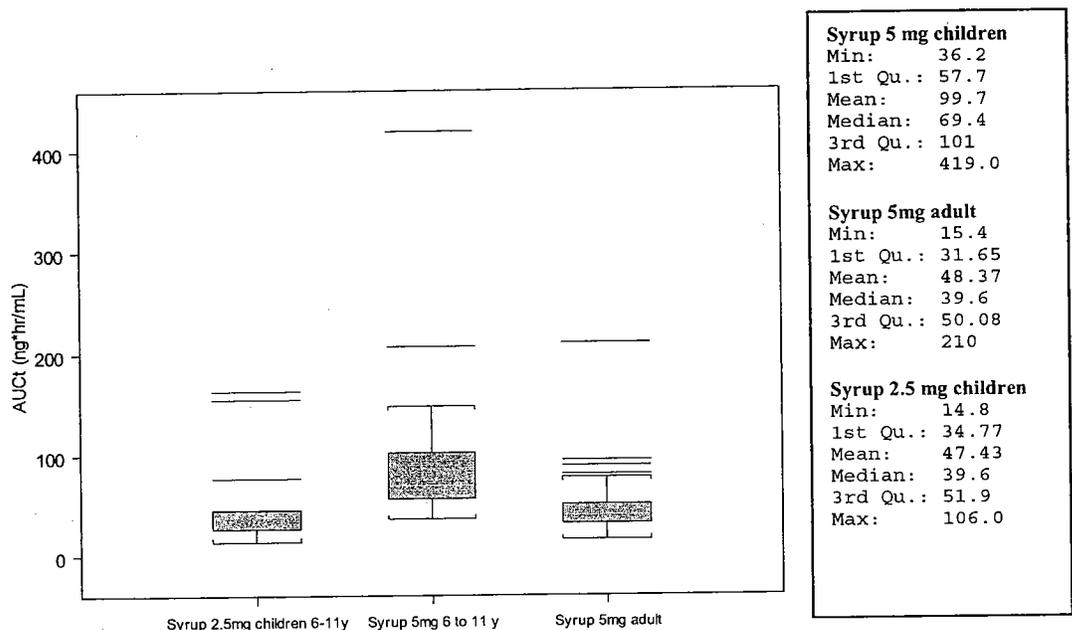
\*Calculated as the ratio of AUCt of 3-OH DL/DL; <sup>1</sup>data from study P00270; <sup>2</sup>from study P01126; <sup>3</sup>from study P00213.

**Table 6.** ANOVA analysis for AUCt and Cmax obtained from children 6-11 years of age

<b>Desloratadine</b>			
PK parameter	Children Data	Adult data	P value (A vs. B)
	Syrup 2.5 mg (A)	Syrup 5mg (B)	
AUCt (ng*hr/mL)	48.6 (88)	46.22 (71)	0.97
Cmax (ng/mL)	2.23 (35)	2.3 (51)	0.82
<b>3-OH desloratadine</b>			
PK parameter	Children data	Adult data	P value (A vs. B)
	Syrup 2.5 mg (A)	Syrup 5mg (B)	
AUCt (ng*hr/mL)	20.5 (50)	25.98 (28)	<<<<<<0.05
Cmax (ng/mL)	0.764 (54)	1.03 (38)	0.03



**Figure 5 .** Box plot comparing the DL Cmax values obtained following administration of a 5 mg syrup in healthy adults (from study P00213), and 2.5 mg (study P01126) and 5 mg (study P00270) clarinex syrup in children 6-11 years old.



**Figure 6.** Box plot comparing the DL AUCt values obtained following single administration of Clarinex syrup 5 mg in adults (study P00213), syrup 2.5 mg in children 6-11 years old and syrup 5 mg in children 6 to 11 years old (study P00270).

## 7. BACKGROUND AND RATIONALE

Desloratadine (DL, SCH 34117; formerly known as descarboethoxyloratadine, DCL) is an active metabolite of loratadine (SCH 29851, 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 H<sub>1</sub>-receptor antagonist. Pharmacokinetic studies have shown that administration of the proposed therapeutic dose of 5.0-mg DL gives the same systemic exposure (plasma AUC) of DL as administration of the marketed dose of 10-mg loratadine (NDA 21-165).

The safety and efficacy data obtained for desloratadine in adolescents and adults during clinical trials revealed that it is effective in the treatment of SAR or CIU, well tolerated, and characterized by an adverse event profile similar to that previously observed with loratadine.

The conditions of allergic rhinitis and CIU are similar in adults and children, from pathology mechanisms to symptoms; therefore, a similar plasma exposure should provide comparable efficacy in both populations. According to the sponsor, pediatric effectiveness may be extrapolated from adequate and well-controlled efficacy studies in adults, and can be supplemented with other information, such as pharmacokinetic studies in pediatric subjects.

In support of this application, the sponsor has submitted the results of two clinical safety as well as the results of five pharmacokinetic studies. The integrated summary of safety focuses on the results of 2 Phase-III, randomized, double-blind, placebo-controlled, single-center, parallel-group studies in children 2 to 5 years of age (Study **P00303**) and 6 to 11 years of age (Study **P00302**) with a history of allergic rhinitis or CIU, conducted

under similar protocols. A total of 231 subjects were randomized and received at least 1 dose of study drug for two weeks: 55 subjects received DL 1.25 mg QD, 60 received DL 2.5 mg QD, and 116 received placebo. All 231 subjects were included in the safety evaluations.

#### **Clinical Safety and Efficacy Studies**

**Study P00302:** Phase-III, single-center, randomized, Double-blind, placebo-controlled, parallel- group, randomized safety study in children 6 to 11 years of age (120, DL 2.5 mg: 60 ; Placebo: 60) with AR or CIU: DL2.5 mg QD vs. placebo for 2 weeks.

**Study P00303:** Phase-III, single-center, randomized, Double-blind, placebo-controlled, parallel-group, randomized safety study in children 2 to 5 years of age (111, DL 1.25 mg: 55 Placebo: 56) with AR or CIU: DL1.25 mg QD vs. placebo for 2 weeks.

#### **Pharmacokinetic Studies**

**Study P00213:** Bioavailability of Desloratadine Syrup and Tablet Formulations in Healthy Volunteers.

**Study P00225:** Single-Dose Pharmacokinetic Study of Desloratadine in Normal Pediatric Volunteers Age 2-5 Years.

**Study P00270:** Single Dose Pharmacokinetic Study of Desloratadine Syrup in Normal Pediatric Volunteers Age 6-11 Years

**Study P01125:** Single-Dose Pharmacokinetic Study of Desloratadine Syrup in Normal Pediatric Volunteers Age 2-5 Years.

**Study P01126:** Single Dose Pharmacokinetic Study of Desloratadine in Normal Pediatric Volunteers Age 6-11 Years

### **7.1 INTRODUCTION**

#### **7.1.1 PHARMACOKINETICS**

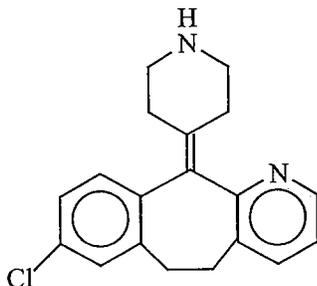
The pharmacokinetics of DL and its metabolite have been presented in detail in a previous NDA for clarinet (NDA 21-165).

**Pharmacokinetic/Pharmacodynamic Correlation.** No studies have been conducted.

#### **7.1.2 CHEMISTRY OVERVIEW**

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

**Structural formula:**



**Figure 1.** Structural formula of DL.

**Molecular formula:** C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>

**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.

**7.1.3 FORMULATION**

CLARINEX Syrup is a clear orange colored liquid containing 0.5 mg/1ml desloratadine. The following formulation of clarinex syrup was used in all the PK studies and is the same as the to-be-marketed formulation.

INGREDIENTS	mg/mL
Desloratadine (SCH 34117), Micronized	
Propylene Glycol USP	
Sorbitol Solution USP	
Citric Acid Anhydrous USP	
Sodium Citrate Dihydrate USP	
Sodium Benzoate NF	
Edetate Disodium USP	
Sugar Granulated	
Natural & Artificial Flavor for Bubble Gum : —	
Dye FD&C Yellow No. 6	
Water Purified USP q.s. ad	

**7.1.4 INDICATION (as per proposed label)**

CLARINEX is indicated for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 2 years of age and older. Symptoms treated in chronic idiopathic urticaria were pruritus, number of hives and the size of the largest hive.

**7.1.5 DOSAGE AND ADMINISTRATION (as per proposed label)**

The recommended dose of CLARINEX syrup in adults and children 12 years of age and over is 2 teaspoonfuls (5mg) once daily.

Children 6- to 11-years of age: The recommended dose of CLARINEX Syrup is 1 teaspoonful (2.5 mg) once daily.

Children 2- to 5-years of age: The recommended dose of CLARINEX Syrup is 1 /2 teaspoonful (1.25 mg) once daily.

**8. SAFETY**

Pending.....

**Appears This Way  
On Original**



**Table 1.** Formulation for Desloratadine 5 mg Tablet (Protocol P00213)

Tablet Strength	5 mg
Formula. No.	3408
Batch No.	38833-142
FMR No.	98564D02
Manf. Date	3/23/98
Manufacturing site	██████████
Batch size	████████████████████
Recertification Date	3/00

**Table 2.** Formulation for Desloratadine 0.5 mg/mL Syrup (Protocol P00213)

Syrup Strength	0.5 mg/mL
Formula. No.	3518
Batch No.	53266-003-B
FMR No.	99513D09
Manf. Date	2/23/99
Recertification Date	11/99

Batch No. 38833-142 (tablet) and 53266-003-B (syrup) are the same as the to-be marketed formulation. The batch size for the syrup used in this study was ██████ which is ██████ of the size of a full size batch (██████████). See page 19 for information regarding tablet formulation, dissolution method and dissolution data.

## PHARMACOKINETIC MEASUREMENTS

### Blood Sampling

Blood samples were taken at predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours post-dose.

### Analytical Method

Plasma samples were assayed for DL and 3-OH DL concentrations using a LC/MS/MS method.

## 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.

## DATA ANALYSIS

### Pharmacokinetic Data Analysis

The mean and %CV were calculated for plasma concentrations of desloratadine and 3-OH desloratadine at each time point. Concentration values less than the assay LOQ (██████████) were reported as and set to zero in the calculations. The plasma concentration-time data for desloratadine and 3-OH desloratadine were then subjected to pharmacokinetic analysis by noncompartmental methods using WinNonlin.

### 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 using a crossover analysis of variance (ANOVA) model. The effects due to subject, period and treatment were extracted. Cmax and AUC values were log-transformed and ninety percent (90%) confidence intervals (CI) for the mean difference between the treatments expressed as a percent of each treatment mean.

### Reviewer's remarks

This reviewer used WinNonlin program to calculate 90% confidence intervals for the ratio of the means (Cmax and AUC) between treatments (A vs. B and B vs. C; see Table 5).

## RESULTS

### Analytical Method

**Pre-Study Validation:** The sponsor did not report data regarding pre-study validation, therefore, the % of recovery and stability are unknown.

### In-Study Validation

#### Limit of Quantitation

The lower limit of quantitation and upper limit of quantitation were 0.025 ng/mL and 10.0 ng/mL, respectively, for both SCH 34117 and SCH 45581.

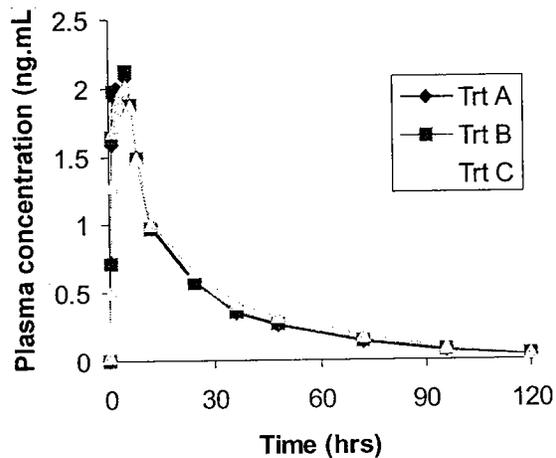
Table 3. In-study validation information for SCH 34711 and SCH 45581

	SCH 34711 (DL)	SCH 45581 (3-OH DL)
<b>Linearity</b>	Satisfactory: Standard curve range from 0.025 to 10.0 ng/mL; $r^2 \geq 0.99$	Satisfactory: Standard curve range from 0.025-10 ng/mL; $r^2 \geq 0.99$
<b>Accuracy</b>	Satisfactory: 9.1% (% Bias) at 0.075 ng/mL; 7.2% at 0.998 ng/mL; -2.5% at 6.1 ng/mL.	Satisfactory: -9.2% (% Bias) at 0.075 ng/mL; -7.0% at 1.0 ng/mL; -7.5% at 7.5 ng/mL.
<b>Precision</b>	Satisfactory: (%CV) 7.2 at 0.075 ng/mL; 3.2 at 0.998 ng/mL; 3.0 at 7.48 ng/mL.	Satisfactory: 6.2% at 0.075 ng/mL; 4.1% at 1.0 ng/mL; 2.6% at 7.5 ng/mL.
<b>Specificity</b>	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted

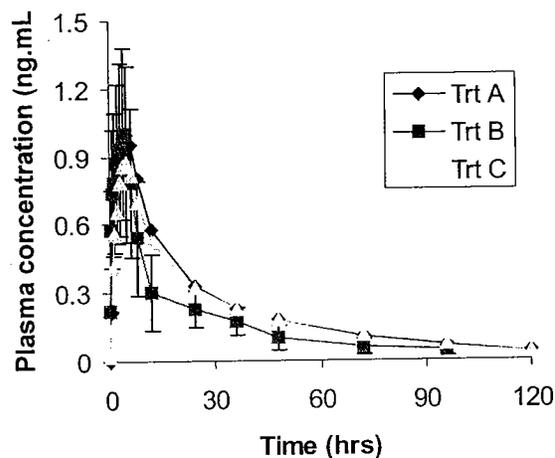
### Pharmacokinetic Results

The mean plasma concentration-time profiles for DL and its metabolite following administration of the three treatments are presented in Figures 1 and 2 respectively. The mean pharmacokinetic parameters for DL and its metabolite are summarized in Table 4. The individual Cmax and AUC(inf) values for DL and its metabolite following the

administration of the three treatments are shown in Figures 3 and 4, respectively. SCH 34117 exhibited high inter-subject variability with %CV values for C<sub>max</sub> and AUC(I) ranging from 31 to 93% (Table 4 and figures 3 and 4). The sponsor did not provide any explanation for this high variability.



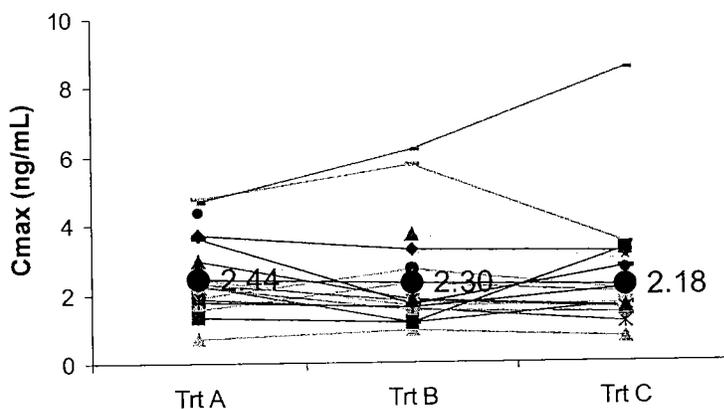
**Figure 1.** Mean DL plasma concentration-time profiles following single administration of Clarinex tablets 5 mg (treatment A), syrup 5 mg (fasted conditions; treatment B) and syrup 5 mg (fed conditions; treatment C).



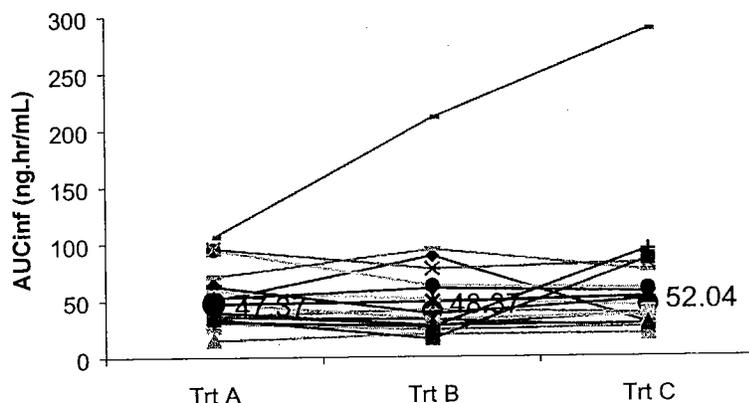
**Figure 2.** Mean 3-OH DL plasma concentration-time profiles following single administration of Clarinex tablets 5 mg (treatment A), syrup 5 mg (fasted conditions; treatment B) and syrup 5 mg (fed conditions; treatment C). Bars represent mean ± SD.

**Table 4.** Mean pharmacokinetic parameters of DL and 3-OH DL following single administration of the treatments.

<b>Desloratadine</b>			
<b>PK parameter</b>	<b>Tablet</b>	<b>Syrup fasted</b>	<b>Syrup fed</b>
AUCt (ng*hr/mL)	45.78 (44)	46.2 (71)	49.9 (90)
AUCinf (ng*hr/mL)	47.35 (45)	48.36 (54)	52.02 (93)
Cmax (ng/mL)	2.44 (41)	2.3 (51)	2.19 (62)
Tmax (hr)	4.17 (50)	3.58 (45)	3.47 (44)
T1/2 (hr)	22.28 (21)	24.03 (23)	23.4 (19)
CL/F (L/hr)	124.59 (44)	134.63 (46)	128.67 (41)
<b>3-OH desloratadine</b>			
AUCt (ng*hr/mL)	27.03 (25)	25.98 (28)	25.72 (31)
AUCinf (ng*hr/mL)	29.01 (24)	27.83 (28)	28.28 (31)
Cmax (ng/mL)	1.06 (34)	1.03 (38)	0.91 (38)
Tmax (hr)	4.72 (41)	4.73 (39)	4.6 (23)
T1/2 (hr)	31.75 (21)	30.71 (21)	34.55 (31)



**Figure 3.** Individual DL Cmax values following single administration of Clarinex tablets 5 mg (treatment A), syrup 5 mg (fasted conditions; treatment B) and syrup 5 mg (fed conditions; treatment C).



**Figure 4.** Individual DL  $AUC_{0 \rightarrow \infty}$  values single administration of Clarinex tablets 5 mg (treatment A), syrup 5 mg (fasted conditions; treatment B) and syrup 5 mg (fed conditions; treatment C).

**Table 5.** Bioequivalence of DL syrup (5 mg) and tablet (5mg) formulations in healthy volunteers under fed and fasted conditions

Formulation		Point estimates (%)		90% Confidence Intervals	
		Desloratadine			
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
<b>Trt B/ Trt A</b>	AUC(inf)	95.4	102.35	84-108	90.06-116.3
	Cmax	92.5	100.51	84-102	90.7-111.4
<b>Trt C/ Trt B</b>	AUC(inf)	104	98.6	92-118	86.8-112.1
	Cmax	94.1	92.0	85-104	83.0-101.9
		3-OH Desloratadine			
<b>Trt B/ Trt A</b>	AUC(inf)	94.9	100.7	89-101	94.4-107.5
	Cmax	96.5	98.7	89-104	91.2-106.9
<b>Trt C/ Trt B</b>	AUC(inf)	101	101.76	95-108	95.4-108.6
	Cmax	87.2	95.9	81-94	88.6-103.8

### GENERAL COMMENTS

The blood sample at 0-hr time point for Subject 25 (Treatment C) contained SCH 34117 and SCH 45581 at concentrations of 1.06 and 0.663 ng/mL, respectively. These concentrations were considered to have no impact on the overall results of the study. Preliminary analysis was performed to examine the extreme pharmacokinetic values and the impact of outliers (Subjects 25 and 29, see Figures 3 and 4) on the overall results. According to the sponsor, it was found that exclusion of Subjects 25 and 29 from the

statistical analysis did not change the overall bioequivalence conclusion of the study. As a result, Subjects 25 and 29 were included in the final statistical analysis.

Statistical comparisons of C<sub>max</sub> and AUC(inf) values for Treatment A versus Treatment B, and Treatment B versus Treatment C were performed for both SCH 34117 and SCH 45581. According to the sponsor, no period effect was detected ( $p > 0.05$ ). The lack of period effect was confirmed by this reviewer using the WinNonlin program, however, this reviewer found no period effect for DL AUC, but a sequence and a subject (sequence) effect for C<sub>max</sub> ( $p \gg 0.05$ ).

According to the sponsor, the ANOVA test showed statistically significant differences among treatments ( $p < 0.05$ ) for C<sub>max</sub>. Pairwise comparisons revealed that the mean AUC(I) values for Treatments A, B and C were not statistically different from each other ( $p > 0.05$ ), and the mean C<sub>max</sub> value for Treatment A was not significantly different from that for Treatment B ( $p > 0.05$ ). According to the sponsor, even though the C<sub>max</sub> value for Treatment B was statistically greater than that for Treatment C ( $p < 0.05$ ), the difference was small (<12%) and may not be clinically relevant. This reviewer agrees with this statement.

The relative bioavailability and the 90% CIs for the log-transformed C<sub>max</sub> and AUC(I) for SCH 34117 and SCH 45581 are presented in Table 5. According to the sponsor, the CIs of AUC(I) and C<sub>max</sub> of SCH 34117 and SCH 45581 for Treatment B relative to Treatment A, and Treatment C relative to Treatment B met the 80-125 bioequivalence guideline. This reviewer calculated 90% CIs for C<sub>max</sub> and AUC using the WinNonlin program. The values found are contrasted in Table 4. The 90% CIs calculated by this reviewer are in agreement with the ones reported by the sponsor. This indicates that the tablet and syrup formulations were bioequivalent, and that a high-fat and high-caloric meal had no effect on the bioavailability of SCH 34117 from the syrup formulation.

#### **COMMENTS TO SPONSOR**

- The sponsor should not use interchangeably relative bioavailability (%) and point estimates (%) which, for BE purposes, is calculated as the ratio of the log-transform means for the AUC and C<sub>max</sub>. The determination of relative BA is base on non-transformed data.

#### **CONCLUSION**

1. The tablet and syrup formulations were bioequivalent.
2. High-fat and high-caloric meal had no effect on the bioavailability of DL from the syrup formulation.



  1   Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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**“SINGLE-DOSE PHARMACOKINETIC STUDY OF DESLORATADINE  
SYRUP IN NORMAL PEDIATRIC VOLUNTEERS 2-5 YEARS OF AGE”**

**Included Protocol:** P00225

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**OBJECTIVE**

- To determine the pharmacokinetics of desloratadine (SCH 34117) and its metabolite, 3-OH desloratadine (SCH 45581), following a single 2.5-mg dose of SCH 34117 syrup in healthy pediatric volunteers ranging in age from 2-5 years.

**SUBJECTS**

Eighteen (18) subjects (12 males and 6 females) were enrolled and successfully completed this study. Subjects were between the ages of 2 and 5 years (mean=3.4 years) and weighed between 13 and 22.3 kg (mean=17.3 kg). Seven (7) subjects were black and 11 were Caucasian.

At least 4 subjects of each of the following age groups were enrolled, except in the 3 to 5 year old age group where only 3 subjects were enrolled.

- 2 but <3,
- 3 but <4,
- 4 but <5,
- 5 but <6.

**STUDY DESIGN AND TREATMENT ADMINISTRATION**

This was a single-dose, open-label Phase I study of clarinet syrup. All subjects received a single 2.5-mg oral dose of SCH 34117, administered as SCH 34117 syrup (0.5 mg/mL). The study medication was administered by having the subject drink the entire 5 mL of SCH 34117 syrup followed by a 10-mL tap water rinse of the dose container (oral syringe, etc) to ensure complete dose intake. Subjects were required to fast for 10 hr prior to dose administration.

**FORMULATION**

The DL syrup was packaged and supplied to the Investigator by                       
                     The following formulation (Table 1) was used:

**Table 1.** Formulation for Desloratadine 0.5 mg/mL Syrup (Protocol P00225)

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Syrup Strength	0.5 mg/mL
Formula. No.	3518
Batch No.	53266-003-B
Batch size	<u>                    </u>
FMR No.	99513D09
Manf. Date	2/23/99
Recertification Date	11/99

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Batch No. 53266-003-B is the same as the to-be marketed formulation. The batch size used in this study was [REDACTED], which is [REDACTED], of the size of a full size batch.

## **PHARMACOKINETIC MEASUREMENTS**

### **Blood Sampling**

Blood samples (2.5 mL), for the determination of SCH 34117 and SCH 45581 concentrations in plasma, were collected at 0 hr (pre-dose) and at 1, 1.5, 2, 4, 8, 12, 24, 48, 72 and 96 hr post-dose, as described in the protocol.

### **Analytical Method**

Plasma SCH 34117 and SCH 45581 concentrations were determined using a validated LC/MS/MS method with a lower limit of quantitation (LOQ) of 0.025 ng/mL for each analyte. The method has a linear range of 0.025 to 10 ng/mL of plasma for each analyte.

## **SAFETY MEASUREMENTS**

For safety evaluation, physical examinations, vital signs, electrocardiograms and clinical laboratory tests were conducted at screening and at the conclusion of the study (96 hours post-treatment). 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 SCH 34117 and SCH 45581 concentration-time data were used to determine the pharmacokinetic parameters using model-independent methods.

### **Statistical Analysis**

Summary statistics including means, standard deviations, coefficients of variation and 95% confidence intervals for the means were provided for the pharmacokinetic parameters. Means, standard deviations and %CV were reported for the concentration data at each time point.

The individual pharmacokinetic parameters were plotted against demographic factors (e.g., age, and body weight), and the resulting graphs examined for correlations. In order to confirm the influence of demographic factors on the pharmacokinetics of SCH 34117, these covariates were then included in a stepwise linear regression model to assess the relationship between these factors and the pharmacokinetic parameters (e.g., C<sub>max</sub>, AUC, etc). Demographic factors were entered at the 10% level and removed at the 5% level of probability. The p-values of the regression method are presented in the text.

## **RESULTS**

### **Analytical Method**

**Pre-Study Validation:** The sponsor did not report data regarding pre-study validation, therefore, the % of recovery and stability are unknown.

## In-Study Validation

### Limit of Quantitation

The lower limit of quantitation and upper limit of quantitation were 0.025 ng/mL and 10.0 ng/mL, respectively, for both SCH 34117 and SCH 45581.

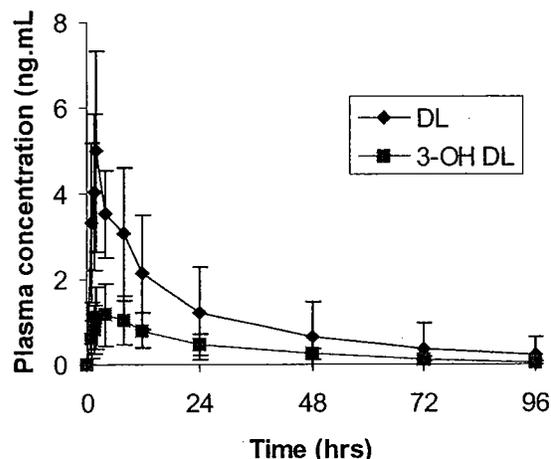
Table 3. In-study validation information for SCH 34711 and SCH 45581

	SCH 34711	SCH 45581
<b>Linearity</b>	Satisfactory: Standard curve range from 0.025 to 10.0 ng/mL; $r^2 \geq 0.996$	Satisfactory: Standard curve range from 0.025-10 ng/mL; $r^2 \geq 0.99$
<b>Accuracy</b>	Satisfactory: 8.3% (% Bias) at 0.075 ng/mL; 8.4% at 0.998 ng/mL; 5.2% at 7.48 ng/mL.	Satisfactory: -11.1% (% Bias) at 0.075 ng/mL; -6.6.0% at 1.0 ng/mL; -7.1% at 7.5 ng/mL.
<b>Precision</b>	Satisfactory: (%CV) 4.8 at 0.075 ng/mL; 4.5 at 0.998 ng/mL; 2.2 at 7.48 ng/mL.	Satisfactory: 8.1% at 0.075 ng/mL; 2.3% at 1.0 ng/mL; 4.5% at 7.5 ng/mL.
<b>Specificity</b>	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted

### Pharmacokinetic Results

The mean plasma concentration-time profiles for DL and its metabolite following single administration of clarinex syrup 2.5 mg are shown in Figure 1. A comparison of the mean pharmacokinetic parameters for DL and its metabolite following administration of a 5 mg tablet and 5 mg syrup in healthy adults (from study P00213) and syrup 2.5 mg in children 2-5 years old is summarized in Table 4.

The individual C<sub>max</sub> and AUC<sub>t</sub> values for DL and its metabolite following the administration of 2.5 mg syrup in children 2-5 years of age are presented in Figures 2 and 3, respectively. Figures 4 and 5 are box plots comparing the DL AUC<sub>t</sub> obtained following administration of a 5 mg tablet in healthy adults, 5mg syrup in healthy adults and 2.5 mg syrup in children 2-5 years old. There was high intersubject variability in DL plasma concentrations as shown in Figures 2-5 and the associated pharmacokinetic parameters (Table 4). According to the sponsor, the stepwise regression procedure detected a significant relationship between body weight and C<sub>max</sub> (p=0.05), explaining 22% of the variability among subjects.



**Figure 1.** Mean DL and 3-OH DL plasma concentration-time profiles following single administration of clarinex syrup 2.5 mg in children 2-5 years of age. Bars represent mean  $\pm$  SD.

**Table 4.** Mean pharmacokinetic parameters of DL and 3-OH DL following administration of the treatments.

<b>Desloratadine</b>				
PK parameter	Adult Data		Children data	Ratio 5mg/ 2.5 mg syrup
	Tablet 5 mg**	Syrup 5mg**	Syrup 2.5mg	
AUCt (ng*hr/mL)	45.78 (44)	46.22 (71)	98.6 (76)	2.13
AUCinf (ng*hr/mL)	47.35 (45)	48.36 (54)	111 (90)	2.3
Cmax (ng/mL)	2.44 (41)	2.3 (51)	5.36 (41)	2.33
Tmax (hr)	4.17 (50)	3.58 (45)	2.94 (79)	
T1/2 (hr)	22.28 (21)	24.03 (23)	18.7 (60)	
CL/F (L/hr)	124.59 (44)	134.63 (46)		
<b>3-OH desloratadine</b>				
PK parameter	Adult Data**		Children data	Ratio 5mg/ 2.5 mg syrup
	Tablet 5 mg**	Syrup 5mg**	Syrup 2.5mg	
AUCt (ng*hr/mL)	27.03 (25)	25.98 (28)	33.7 (51)	1.29
AUCinf (ng*hr/mL)	29.01 (24)	27.83 (28)	35.9 (47)	1.29
Cmax (ng/mL)	1.06 (34)	1.03 (38)	1.27 (61)	1.33
Tmax (hr)	4.72 (41)	4.73 (39)	4.44 (63)	
T1/2 (hr)	31.75 (21)	30.71 (21)	28.4 (67)	
AUCt ratio (%)	59.04	56.2	34.2	

\* Calculated as the ratio of AUCt of 3-OH DL/DL; \*\* Data from study P00213

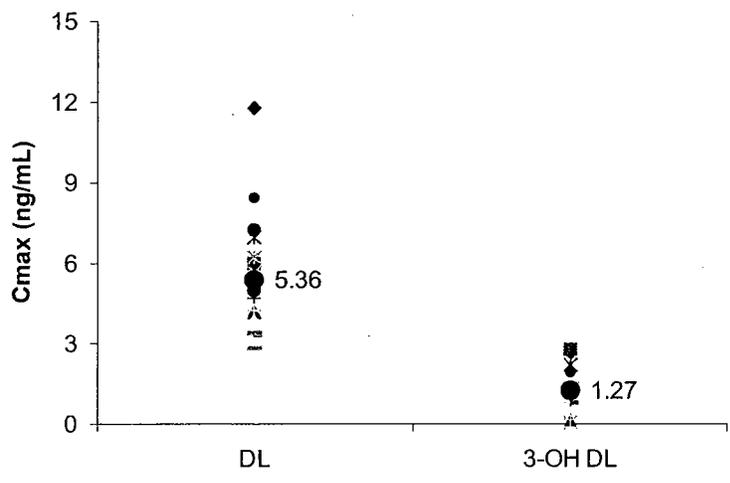


Figure 2. Individual DL Cmax values following single administration of Clarinex syrup 2.5 in children 2-5 years of age.

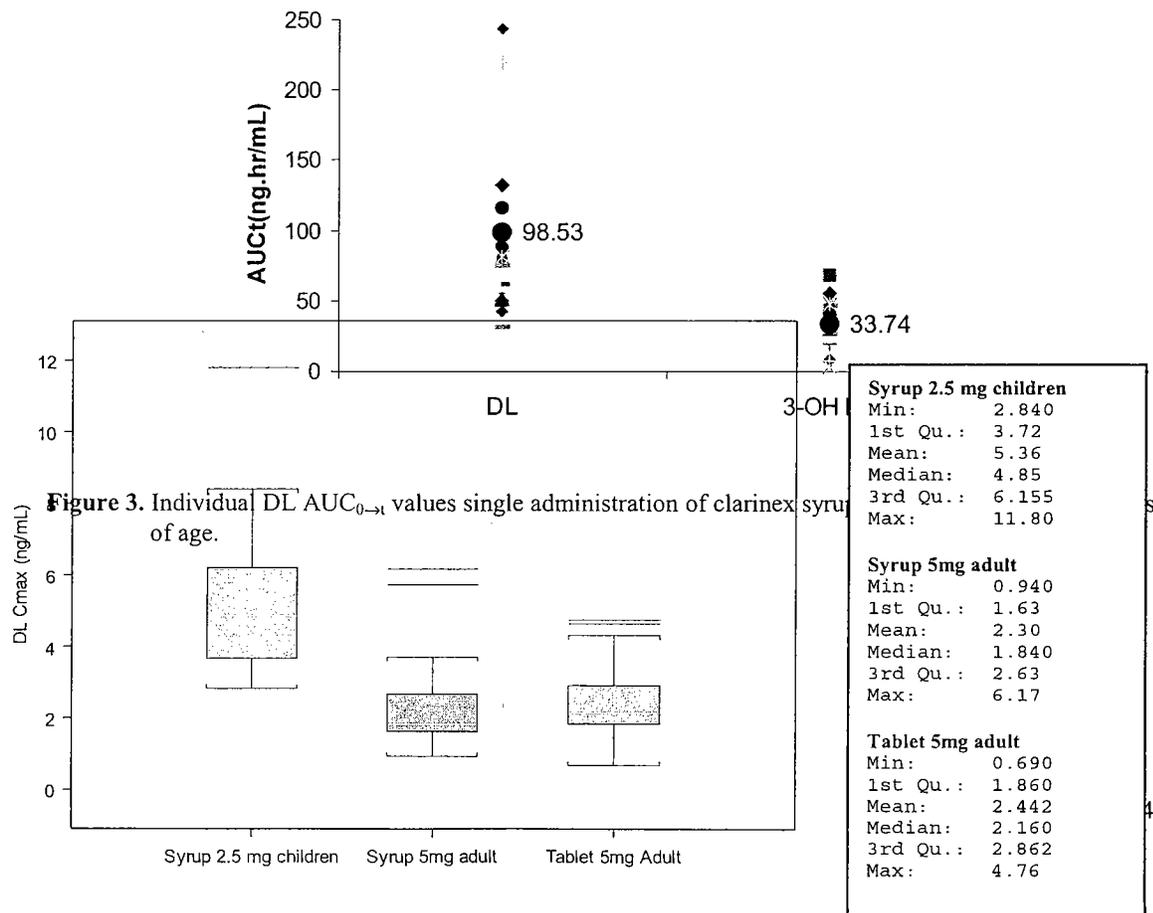
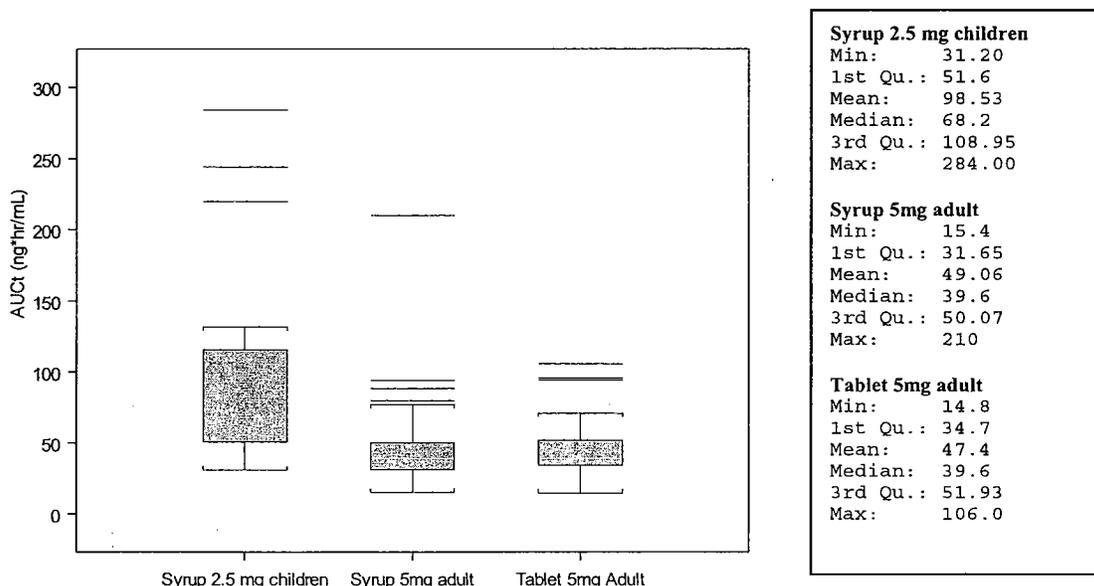


Figure 3. Individual DL AUC0->t values single administration of clarinex syrup of age.

**Figure 4.** Box plot comparing the DL Cmax values obtained following administration of a 5 mg tablet and 5mg syrup in healthy adults (study P00213) and 2.5 syrup in children 2-5 years old.



**Figure 5.** Box plot comparing the DL AUCt values obtained following administration of a 5 mg tablet and 5mg syrup in healthy adults (study P00213) and 2.5 syrup in children 2-5 years old.

#### COMMENTS

A 2.5 mg oral dose of DL syrup was associated with a mean DL AUC(tf) value that was >2-fold greater in pediatric subjects aged 2 to 5 years compared to adults who also received a 5 mg dose of DL syrup or tablet (Table 4, Figure 5). According to the sponsor, a similar relationship was observed between the 3-OH DL data of pediatric subjects and in adults. However, this reviewer calculated the ratios for 3-OH DL AUCt and Cmax (syrup 2.5 mg in children/syrup 5 mg in adults) and they were found to be approximately 1.3 (Table 4).

The systemic exposure and plasma concentrations in Subjects 4, 8 and 16 were higher for DL and lower for 3-OH DL than those in the other subjects (Figures 2 and 3). The sponsor believes that the rate of metabolism of DL in these subjects appears to be lower than that in other subjects. The AUC(tf) of DL in these subjects (apparently slow metabolizers) were 220, 244 and 284 ng\*hr/mL and the corresponding values for 3-OH DL were 7.25, 8.28 and 2.75 ng\*hr/mL. This is in contrast to the AUC(tf) values of DL (3-OH DL) in the other subjects ranging from 31 to 132 ng\*hr/mL (19 to 68 ng\*hr/mL). The mean AUC ratio of metabolite to parent was 55.4% for all subjects (Table 4), compared to about 2.55% in slow metabolizers (n=3). The mean AUC ratio (metabolite to parent) increased to 65% when slow metabolizers were excluded. According to the sponsor none of the slow metabolizers reported an adverse event.

In summary, for pediatric subjects to obtain similar DL exposure as adults, pediatric subjects 2 to 5 years of age should receive approximately 50% of the 2.5-mg dose administered in this study.

#### **CONCLUSION**

- To obtain similar systemic exposure of DL (not considering 3-OH DL) in pediatric subjects ages 2-5 years as observed in adults administered 5 mg, it is recommended that the 2.5-mg dose be reduced by approximately 50%.

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On Original**

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**“SCH 34117: SINGLE-DOSE PHARMACOKINETIC STUDY OF  
DESLORATADINE SYRUP IN NORMAL PEDIATRIC VOLUNTEERS AGE 2-5  
YEARS”**

**Included Protocol:** P01125

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**OBJECTIVE**

- To determine the pharmacokinetics of desloratadine (SCH 34117) and its metabolite, 3-OH desloratadine (SCH 45581), following a single 1.25-mg dose of SCH 34117 syrup in healthy pediatric volunteers ranging in age from 2-5 years.

**SUBJECTS**

Eighteen subjects (10 males and 8 females) were enrolled and successfully completed this study. Subjects were between the ages of 2 and 5 years (mean=3.4 years) and weighed between 13 and 22 kg (mean=16.9 kg). Two subjects were black and 16 were Caucasians.

**STUDY DESIGN AND TREATMENT ADMINISTRATION**

This was a single-dose, open-label Phase I study of clarinex 1.25-mg syrup . All subjects received a single 1.25-mg oral dose of SCH 34117, administered as SCH 34117 syrup (0.5 mg/mL). The study medication was administered by having the subject drink the entire 2.5 mL of SCH 34117 syrup followed by a 5-mL tap water rinse of the dose container (oral syringe, etc.) to ensure complete dose intake. Subjects were required to fast for 10 hr prior to morning dose administration.

**FORMULATION**

The DL syrup was packaged and supplied to the investigator by ██████████

██████████ The following formulation (Table 1) was used:

**Table 1** Formulation for Desloratadine 0.5 mg/mL Syrup (Protocol P01125)

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Syrup Strength	0.5 mg/mL
Formula. No.	3518
Batch No.	53266-003-B
Batch size	<span style="background-color: black; color: black;">██████████</span>
FMR No.	99513D09
Manf. Date 2	2/23/99
Recertification Date	11/99

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Batch No. 53266-003-B is the same as the to-be marketed formulation. The batch size used in this study was 550 L, which is 10% of the size of a full size batch (5500L).

## **PHARMACOKINETIC MEASUREMENTS**

### **Blood Sampling**

Blood samples (2.5 mL), for the determination of SCH 34117 and SCH 45581 concentrations in plasma, were collected at 0 hr (pre-dose) and at 1, 1.5, 2, 4, 8, 12, 24, 48, 72 and 96 hr post-dose, as described in the protocol

### **Analytical Method**

Plasma SCH 34117 and SCH 45581 concentrations were determined using a validated LC/MS/MS method with a lower limit of quantitation (LOQ) of 0.025 ng/mL for each analyte. The method has a linear range of 0.025 to 10 ng/mL of plasma for each analyte.

## **SAFETY MEASUREMENTS**

For safety evaluation, physical examinations, vital signs, electrocardiograms and clinical laboratory tests were conducted at Screening and at the conclusion of the study (96 hours post-treatment). 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 SCH 34117 and SCH 45581 concentration-time data were used to determine the pharmacokinetic parameters using model-independent methods.

### **Statistical Analysis**

Summary statistics including means, standard deviations, coefficients of variation and 95% confidence intervals for the means were provided for the pharmacokinetic parameters. Means, standard deviations and %CV were reported for the concentration data at each time point.

The individual pharmacokinetic parameters were plotted against demographic factors (e.g., age, and body weight), and the resulting graphs examined for correlations. In order to confirm the influence of demographic factors on the pharmacokinetics of SCH 34117, these covariates were then included in a stepwise linear regression model to assess the relationship between these factors and the pharmacokinetic parameters (e.g., C<sub>max</sub>, AUC, etc). Demographic factors were entered at the 10% level and removed at the 5% level of probability. The p-values of the regression method are presented in the text.

## **RESULTS**

### **Analytical Method**

**Pre-Study Validation:** The sponsor did not report data regarding pre-study validation, therefore, the % of recovery and stability are unknown.

## In-Study Validation

### Limit of Quantitation

The lower limit of quantitation and upper limit of quantitation were 0.025 ng/mL and 10.0 ng/mL, respectively, for both SCH 34117 and SCH 45581.

**Table 3.** In-study validation information for SCH 34711 and SCH 45581

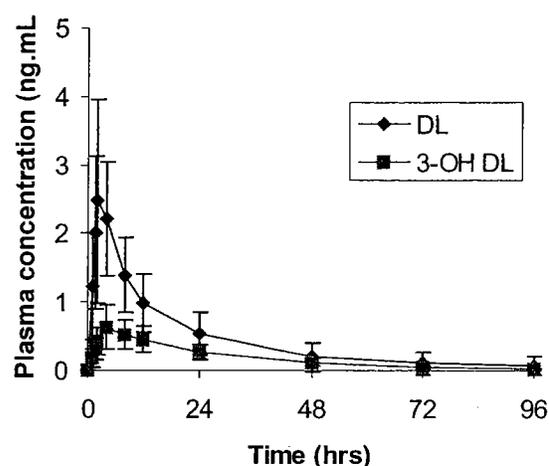
	SCH 34711	SCH 45581
<b>Linearity</b>	Satisfactory: Standard curve range from 0.025 to 10.0 ng/mL; $r^2 \geq 0.996$	Satisfactory: Standard curve range from 0.025-10 ng/mL; $r^2 \geq 0.99$
<b>Accuracy</b>	Satisfactory: -0.29 % (% Bias) at 0.075 ng/mL; 3.67 % at 0.775 ng/mL; -2.33 % at 7.50 ng/mL.	Satisfactory: 7.91% (% Bias) at 0.075 ng/mL; 3.91% at 0.75 ng/mL; -0.245% at 7.5 ng/mL.
<b>Precision</b>	Satisfactory: (%CV) 6.0 at 0.075 ng/mL; 3.22 at 0.75 ng/mL; 6.63 at 4.5 ng/mL.	Satisfactory: 12.9% at 0.075 ng/mL; 3.91% at 0.75 ng/mL; -0.245% at 7.5 ng/mL.
<b>Specificity</b>	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted

### Pharmacokinetic Results

The mean plasma concentration-time profiles for DL and its metabolite following single administration of clarinex syrup 1.25 mg are shown in Figure 1. A comparison of the mean pharmacokinetic parameters for DL and its metabolite following administration of syrup 1.25 mg in children 2-5 years of age, syrup 5mg in healthy adults (from study P00213) and syrup 2.5 mg in children 2-5 years old (from study P00225) is summarized in Table 4.

The individual C<sub>max</sub> and AUC<sub>t</sub> values for DL and its metabolite following the administration of syrup 1.25 mg in children 2-5 years of age and syrup 5 mg in adults (from study P00213) are presented in Figures 2 and 3, respectively. Figures 4 and 5 are box plots comparing the DL C<sub>max</sub> and AUC<sub>t</sub> obtained following administration of syrup 1.25 mg in children 2-5 years of age, syrup 5 mg in healthy adults and syrup 2.5 mg in children 2-5 years old. There was high intersubject variability in DL plasma concentrations as shown in Figures 2 to 5 and the associated pharmacokinetic parameters (Table 4). The stepwise regression procedure did not detect significant relationships between age or body weight and the pharmacokinetic parameters.

The pharmacokinetic parameters (AUC<sub>t</sub>, C<sub>max</sub>) obtained following the administration of syrup 1.25 mg in children 2-5 years of age and syrup 5 mg in adults were subjected by this reviewer to statistical analysis using an analysis of variance (ANOVA) model. The results are shown in Table 5.

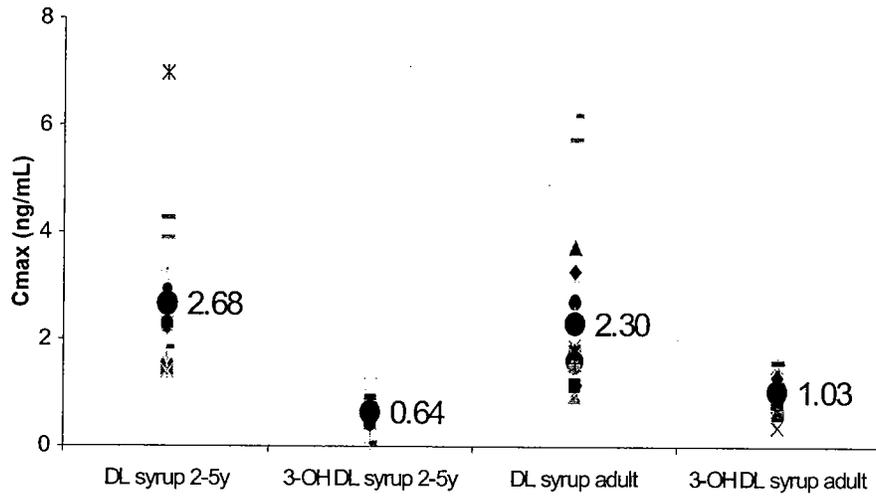


**Figure 1.** Mean DL and 3-OH DL plasma concentration-time profiles following single administration of clarinex syrup 1.25 mg in children 2-5 years of age. Bars represent mean  $\pm$  SD.

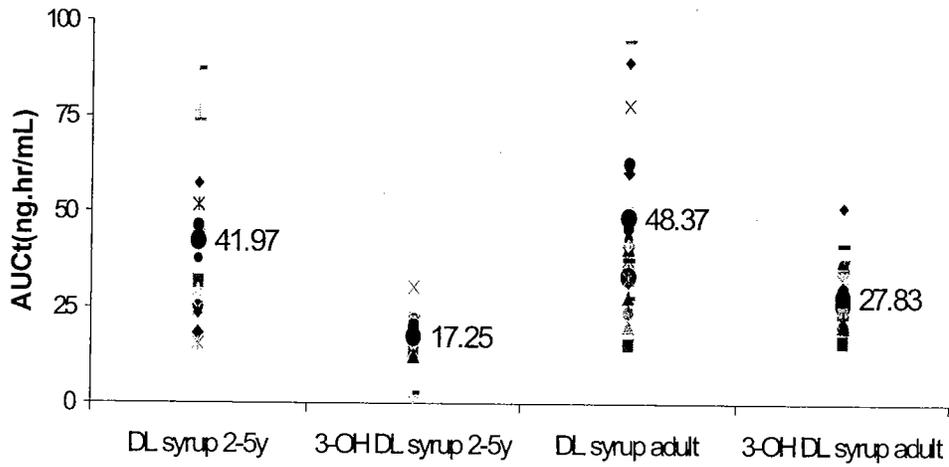
**Table 4.** Mean pharmacokinetic parameters of DL and 3-OH DL following administration of the treatments.

<b>Desloratadine</b>				
PK parameter	Children Data		Adult data	Ratio 5mg/ 1.25 mg syrup
	Syrup 2.5mg <sup>1</sup>	Syrup 1.25 mg	Syrup 5mg <sup>2</sup>	
AUCt (ng*hr/mL)	98.6 (76)	42.0 (49)	46.22 (71)	1.1
AUCinf (ng*hr/mL)	111 (90)	45.1 (56)	48.36 (54)	1.17
Cmax (ng/mL)	5.36 (41)	2.68 (50)	2.3 (51)	0.86
Tmax (hr)	2.94 (79)	3.17 (63)	3.58 (45)	
T1/2 (hr)	18.7 (60)	16.4 (55)	24.03 (23)	
CL/F (L/hr)			134.63 (46)	
<b>3-OH desloratadine</b>				
PK parameter	Children Data		Adult data	Ratio 5mg/ 1.25 mg syrup
	Syrup 2.5mg <sup>1</sup>	Syrup 1.25 mg	Syrup 5mg <sup>2</sup>	
AUCt (ng*hr/mL)	33.7 (51)	17.3 (42)	25.98 (28)	1.5
AUCinf (ng*hr/mL)	35.9 (47)	18.6 (35)	27.83 (28)	1.5
Cmax (ng/mL)	1.27 (61)	0.64 (49)	1.03 (38)	1.61
Tmax (hr)	4.44 (63)	4.89 (35)	4.73 (39)	
T1/2 (hr)	28.4 (67)	26.2 (78)	30.71 (21)	
AUCt ratio (%)*	34.2	41.2	56.2	

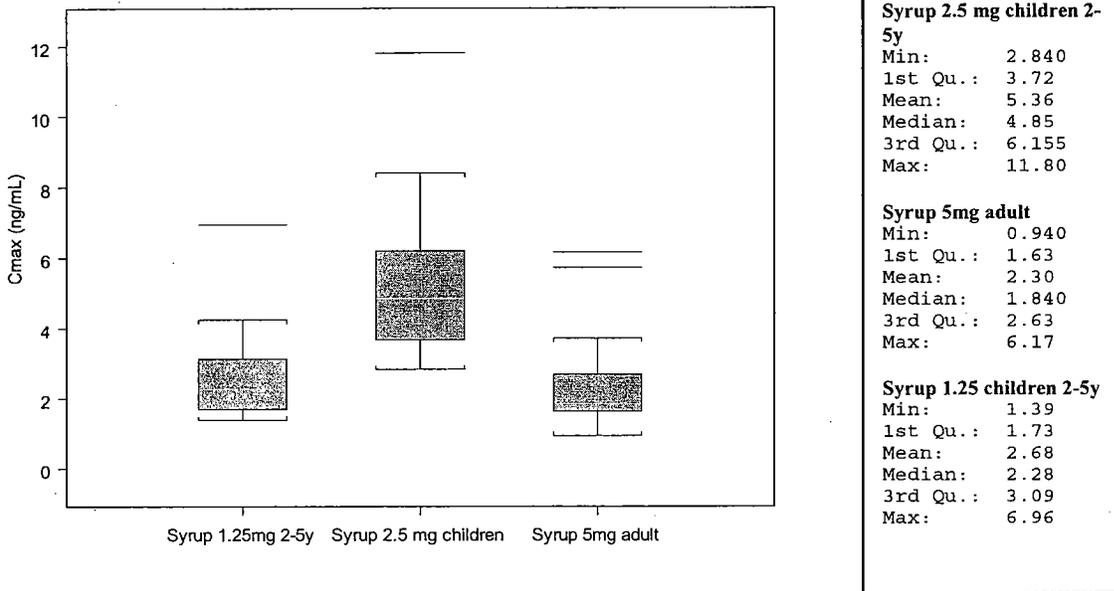
\* Calculated as the ratio of AUCt of 3-OH DL/DL; <sup>1</sup> Data from study P00225; <sup>2</sup> data from study P00213



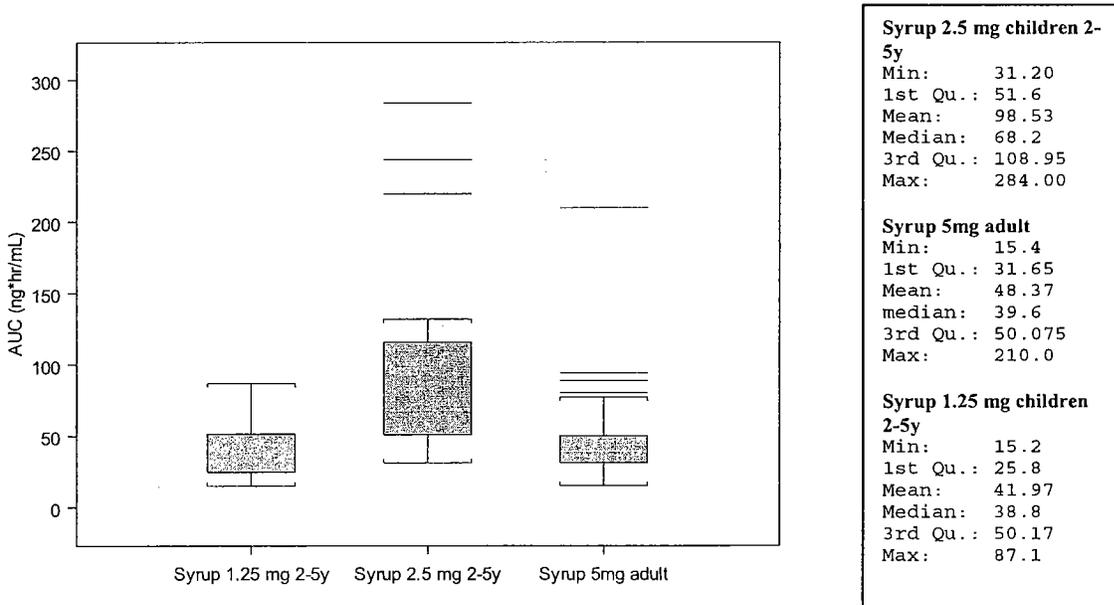
**Figure 2.** Individual DL and 3-OH DL C<sub>max</sub> values following single administration of Clarinex syrup 1.25 mg in children 2-5 years of age and single administration of Clarinex syrup in adults (study P00213).



**Figure 3.** Individual DL and 3-OH DL AUC<sub>0-t</sub> values following single administration of Clarinex syrup 1.25 mg in children 2-5 years of age and single administration of Clarinex syrup in adults (study P00213).



**Figure 4.** Box plot comparing the DL Cmax values obtained following administration of a 5 mg syrup in healthy adults (from study P00213), and 1.25 mg (study P01125) and 2.5 mg (study P00225) clarinex syrup in children 2-5 years old.



**Figure 5.** Box plot comparing the DL AUCt values obtained following administration of a 5 mg syrup in healthy adults (from study P00213), and 1.25 mg (study P01125) and 2.5 mg (study P00225) clarinex syrup in children 2-5 years old.

**Table 5.** ANOVA analysis for AUCt and Cmax

<b>Desloratadine</b>			
<b>PK parameter</b>	<b>Children Data Syrup 1.25 mg (A)</b>	<b>Adult data Syrup 5mg (B)</b>	<b>P value (A vs. B)</b>
AUCt (ng*hr/mL)	42.0 (49)	46.22 (71)	0.4516
Cmax (ng/mL)	2.68 (50)	2.3 (51)	0.31
<b>3-OH desloratadine</b>			
	<b>Children data Syrup 1.25mg (A)</b>	<b>Adult data Syrup 5mg (B)</b>	<b>P value (A vs. B)</b>
AUCt (ng*hr/mL)	17.3 (42)	25.98 (28)	<<<<<0.05
Cmax (ng/mL)	0.64 (49)	1.03 (38)	0.001

**COMMENTS**

According to the sponsor, a 1.25-mg oral dose of clarinex syrup was associated with a mean DL AUC(tf) value for pediatric subjects aged 2 to 5 years old, similar to that observed in adults who received a 5-mg dose of clarinex syrup (Table 4). The ANOVA analysis conducted by this reviewer revealed that in fact, there are not statistically significant differences between these 2 treatments (Table 5). The sponsor stated that the metabolite data of pediatric and adult subjects were also comparable. However, Table 5 shows statistically significant differences in AUCt and Cmax between treatments.

The systemic exposure and plasma concentrations in Subjects 16 and 17 were higher for DL and lower for 3-OH DL than those in the other subjects (Figures 2 and 3). The sponsor believes that the rate of metabolism of DL in these subjects appears to be lower than that in other subjects. The AUC(tf) of DL in these subjects (apparently slow metabolizers) were 75.9 and 87.1 ng\*hr/mL and the corresponding values for 3-OH DL were 1.57 and 2.60 ng\*hr/mL with AUC ratios (metabolite to parent) of 2 and 3%, respectively. This is in contrast to AUC ratio values in the other subjects (normal metabolizers) ranging from 28 to 123%. The mean AUC ratio (metabolite to parent) increased to 59% when slow metabolizers were excluded. According to the sponsor none of the slow metabolizers reported an adverse event.

The presence of slow metabolizers in the children population may explain the smaller values of Cmax for the metabolite compared to those obtained in adults.

**CONCLUSION**

Pediatric subjects aged 2 to 5 years of age receiving a single dose of clarinex syrup 1.25 mg had comparable AUCt and Cmax values of DL, but NOT for the metabolite 3-OH DL, to those obtained in adults receiving clarinex syrup 5 mg.

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**“SINGLE-DOSE PHARMACOKINETIC STUDY OF DESLORATADINE  
SYRUP IN NORMAL PEDIATRIC VOLUNTEERS 6 to 11 YEARS OF AGE”**

**Included Protocol:** P00270

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**OBJECTIVE**

- To determine the pharmacokinetics of desloratadine (SCH 34117) and its metabolite, 3-OH desloratadine (SCH 45581), following a single 5-mg dose of SCH 34117 syrup in healthy pediatric volunteers ranging in age from 6 to 11 years.

**SUBJECTS**

Eighteen (18) subjects (10 males and 8 females) were enrolled and successfully completed the study. Subjects were between the ages of 6 and 11 years (mean=8.5 years) and weighed between 19.1 and 56.8 kg (mean=31.1 kg). Ten (10) subjects were Black and eight (8) were Caucasian.

**STUDY DESIGN AND TREATMENT ADMINISTRATION**

This was a single-dose, open-label Phase I study of DL in 18 healthy pediatric subjects. All subjects received a single 5-mg dose of DL (10 mL) as syrup following an overnight fast.

**FORMULATION**

The DL syrup was packaged and supplied to the Investigator by [REDACTED].  
[REDACTED] The following formulation (Table 1) was used:

**Table 1** Formulation for Desloratadine 0.5 mg/mL Syrup (Protocol P00225)

Syrup Strength	0.5 mg/mL
Formula. No.	3518
Batch No.	53266-003-B
Batch size	[REDACTED]
FMR No.	99513D09
Manf. Date	2/23/99
Recertification Date	11/99

Batch No. 53266-003-B is the same as the to-be marketed formulation. The batch size used in this study was [REDACTED] which is 10% of the size of a full size batch [REDACTED].

**PHARMACOKINETIC MEASUREMENTS**

**Blood Sampling**

Blood samples (2.5 mL), for the determination of SCH 34117 and SCH 45581 concentrations in plasma, were collected at 0 hr (pre-dose) and at 1, 1.5, 2, 4, 8, 12, 24, 48, 72 and 96 hr post-dose, as described in the protocol.

### **Analytical Method**

Plasma SCH 34117 and SCH 45581 concentrations were determined using a validated LC/MS/MS method with a lower limit of quantitation (LOQ) of 0.025 ng/mL for each analyte. The method has a linear range of 0.025 to 10 ng/mL of plasma for each analyte.

### **SAFETY MEASUREMENTS**

For safety evaluation, physical examinations, vital signs, electrocardiograms and clinical laboratory tests were conducted at Screening and at the conclusion of the study (72 hours post-treatment). 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 SCH 34117 and SCH 45581 concentration-time data were used to determine the pharmacokinetic parameters using model-independent methods.

#### **Statistical Analysis**

Summary statistics including means, standard deviations, coefficients of variation and 95% confidence intervals for the means were provided for the pharmacokinetic parameters. Means, standard deviations and %CV were reported for the concentration data at each time point.

The individual pharmacokinetic parameters were plotted against demographic factors (e.g., age, and body weight), and the resulting graphs examined for correlations. In order to confirm the influence of demographic factors on the pharmacokinetics of SCH 34117, these covariates were then included in a stepwise linear regression model to assess the relationship between these factors and the pharmacokinetic parameters (e.g., C<sub>max</sub>, AUC, etc). Demographic factors were entered at the 10% level and removed at the 5% level of probability. The p-values of the regression method are presented in the text.

### **RESULTS**

#### **Analytical Method**

**Pre-Study Validation:** The sponsor did not report data regarding pre-study validation, therefore, the % of recovery and stability are unknown.

#### **In-Study Validation**

##### **Limit of Quantitation**

The lower limit of quantitation and upper limit of quantitation were 0.025 ng/mL and 10.0 ng/mL, respectively, for both SCH 34117 and SCH 45581.

**Table 3.** In-study validation information for SCH 34711 and SCH 45581

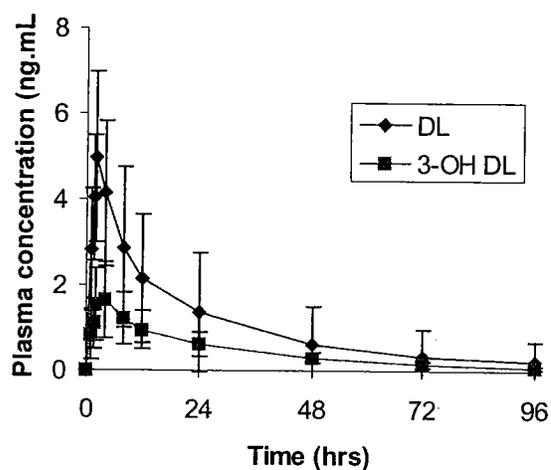
	DL	3-OH DL
<b>Linearity</b>	Satisfactory: Standard curve range from 0.025 to 10.0 ng/mL; $r^2 \geq 0.996$	Satisfactory: Standard curve range from 0.025-10 ng/mL; $r^2 \geq 0.99$
<b>Accuracy</b>	Satisfactory: 8.0% (% Bias) at 0.075 ng/mL; 8.0% at 0.998 ng/mL; 7.0% at 7.48 ng/mL.	Satisfactory: -3.1% (% Bias) at 0.075 ng/mL; -6.7.0% at 1.0 ng/mL; -6.1% at 7.5 ng/mL.
<b>Precision</b>	Satisfactory: (%CV) 5.4 at 0.075 ng/mL; 3.7 at 0.998 ng/mL; 3.0 at 7.48 ng/mL.	Satisfactory: 8.7% at 0.075 ng/mL; 3% at 1.0 ng/mL; 2.4% at 7.5 ng/mL.
<b>Specificity</b>	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted

### Pharmacokinetic Results

The mean plasma concentration-time profiles for DL and its metabolite following single administration of clarinex syrup 5-mg (10mL) in children 6-11 years old are shown in Figure 1. A comparison of the mean pharmacokinetic parameters for DL and its metabolite following administration of a 5 mg tablet and 5 mg syrup in healthy adults (study P00213) and syrup 5 mg in children 6 to 11 years old is summarized in Table 4.

The individual C<sub>max</sub> and AUC<sub>t</sub> values for DL and its metabolite following the administration of syrup 5 mg in children 6 to 11 years of age are presented in Figures 2 and 3, respectively. Figures 4 and 5 are box plots comparing the DL AUC<sub>t</sub> obtained following administration of a 5-mg tablet in healthy adults, syrup 5mg in healthy adults and syrup 5mg in children 6 to 11 years old. There was high intersubject variability in DL plasma concentrations as shown in figures 2, 3, and 5 and the associated pharmacokinetic parameters (Table 4). The stepwise regression procedure detected a significant relationship between age and C<sub>max</sub> (p=0.024), explaining 45% of the variability among subjects.

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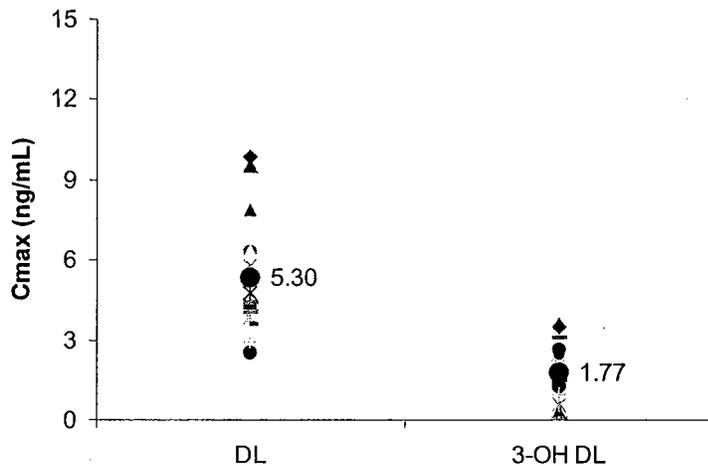


**Figure 1.** Mean DL and 3-OH DL plasma concentration-time profiles following single administration of clarinex syrup 5 mg in children 6 to 11 years of age. Bars represent mean  $\pm$  SD.

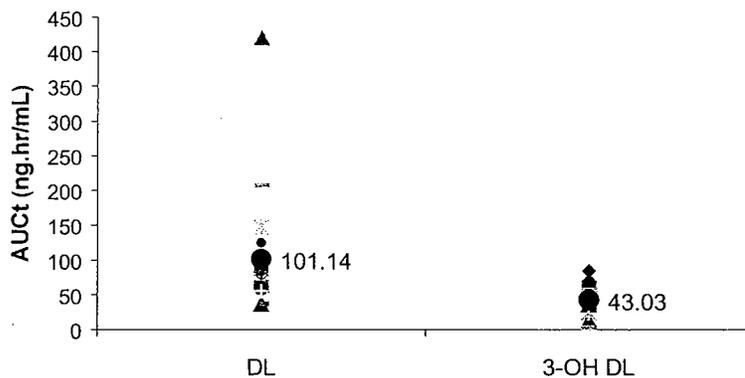
**Table 4.** Mean pharmacokinetic parameters of DL and 3-OH DL following administration of the treatments.

<b>Desloratadine</b>				
PK parameter	Adult Data		Children data	Ratio 5mg 6-11y/ 5mg syrup
	Tablet 5 mg <sup>1</sup>	Syrup 5mg <sup>1</sup>	Syrup 5 mg	
AUCt (ng*hr/mL)	45.78 (44)	46.22 (71)	101 (89)	2.19
AUCinf (ng*hr/mL)	47.35 (45)	48.36 (54)	111 (102)	2.30
Cmax (ng/mL)	2.44 (41)	2.3 (51)	5.3 (41)	2.30
Tmax (hr)	4.17 (50)	3.58 (45)	2.78 (73)	
T1/2 (hr)	22.28 (21)	24.03 (23)	18.6 (49)	
CL/F (L/hr)	124.59 (44)	134.63 (46)		
<b>3-OH desloratadine</b>				
PK parameter	Adult Data <sup>1</sup>		Children data	Ratio 5mg 6-11y/ 5mg syrup
	Tablet 5 mg <sup>1</sup>	Syrup 5mg <sup>1</sup>	Syrup 5 mg	
AUCt (ng*hr/mL)	27.03 (25)	25.98 (28)	43.0 (45)	1.66
AUCinf (ng*hr/mL)	29.01 (24)	27.83 (28)	45.9 (42)	1.65
Cmax (ng/mL)	1.06 (34)	1.03 (38)	1.77 (57)	1.72
Tmax (hr)	4.72 (41)	4.73 (39)	4.44 (63)	
T1/2 (hr)	31.75 (21)	30.71 (21)	26.8 (43)	
AUCt ratio (%)*	59.04	56.2	42.6	

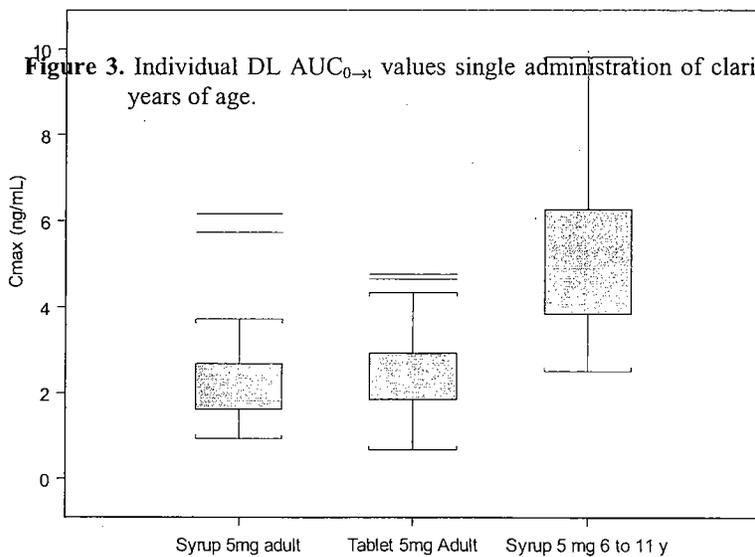
\* Calculated as the ratio of AUCt of 3-OH DL/DL; <sup>1</sup>Data from study P00213.



**Figure 2.** Individual DL Cmax values following single administration of Clarinex syrup 5mg in children 6 to 11 years of age.



**Figure 3.** Individual DL AUC<sub>0-∞</sub> values single administration of clarinex 5mg in children 6 to 11 years of age.



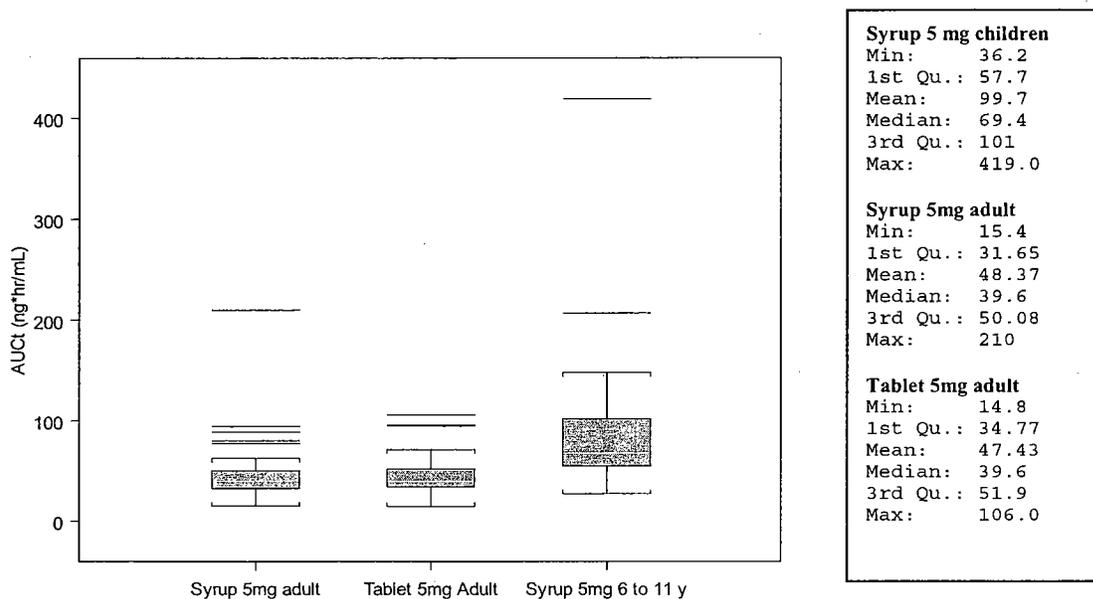
**Syrup 5 mg children**  
 Min: 2.510  
 1st Qu.: 3.89  
 Mean: 5.30  
 Median: 4.94  
 3rd Qu.: 6.14  
 Max: 9.82

**Syrup 5mg adult**  
 Min: 0.940  
 1st Qu.: 1.63  
 Mean: 2.30  
 Median: 1.840  
 3rd Qu.: 2.63  
 Max: 6.17

**Tablet 5mg adult**  
 Min: 0.690  
 1st Qu.: 1.860  
 Mean: 2.442  
 Median: 2.160  
 3rd Qu.: 2.862  
 Max: 4.76

to 11

**Figure 4.** Box plot for DL Cmax values following single administration of Clarinex tablets 5 mg in adults, syrup 5 mg (fasted conditions) in adults (from study P00213) and syrup 5 mg in children 6 to 11 years old.



**Figure 5.** Box plot comparing the DL Acute obtained following administration of a 5-mg tablet in healthy adults, 5mg syrup in healthy adults (from study P00213) and 5 mg syrup in children 6 to 11 years old.

## COMMENTS

A 5-mg oral dose of SCH 34117 syrup was associated with a mean DL AUC(tf) value that was 2.2-fold higher in pediatric subjects aged 6 to 11 y compared to adults who also received a 5-mg dose of SCH 34117 syrup (Figure 5, Table 4). Acute values for the metabolite were 1.6 times lower for the pediatric population compared to the adult population (Table 4).

The systemic exposure and plasma concentrations in two of the 18 subjects (Subjects 3 and 18) were higher for SCH 34117 and lower for SCH 45581 than those in the other subjects; the rate of metabolism of SCH 34117 in these subjects appears to be slower than that in other subjects. The mean AUC ratio of metabolite to parent was 62.7% for all subjects (n=18, Table 4), compared to about 2.3% in slow metabolizers (n=2). According to the sponsor, the mean AUC ratio (metabolite to parent) increased to 70% when slow metabolizers were excluded.

## **CONCLUSION**

- Compared to the adults, pediatric subjects had higher AUC values of DL (2.2-fold higher) and 3-OH DL (1.6-fold higher) following a single oral 5-mg of clarinex syrup. Therefore, to maintain the similar systemic exposure to clarinex syrup in pediatric subjects as in adults, the dosage regimen should be decreased by 50% (5 mg to 2.5 mg).

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**“SINGLE-DOSE PHARMACOKINETIC STUDY OF DESLORATADINE  
SYRUP IN NORMAL PEDIATRIC VOLUNTEERS AGE 6-11 YEARS”**

**Included Protocol:** P01126

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**OBJECTIVE**

- To determine the pharmacokinetics of desloratadine (SCH 34117) and its metabolite, 3-OH desloratadine (SCH 45581), following a single 2.5-mg dose of SCH 34117 syrup in healthy pediatric volunteers ranging in age from 6 to 11 years.

**SUBJECTS**

Eighteen (18) subjects (9 males and 9 females) were enrolled and successfully completed the study. Subjects were between the ages of 6 and 11 years (mean=8.5 years) and weighed between 18.6 and 50.5 kg (mean=30.7 kg). Two subjects were Black and 16 were Caucasian.

**STUDY DESIGN AND TREATMENT ADMINISTRATION**

This was a single-dose, open-label Phase I study of clarinex syrup. All subjects received a single 2.5-mg oral dose of clarinex syrup, administered as SCH 34117 syrup (0.5 mg/mL). The study medication was administered by having the subject drink the entire 5 mL of SCH 34117 syrup followed by two 10-mL tap water rinses of the dose container (oral syringe, etc.) to ensure complete dose intake. Subjects were required to fast for 10 hr prior to morning dose administration.

**FORMULATION**

The DL syrup was packaged and supplied to the Investigator by [REDACTED]. The following formulation (Table 1) was used:

**Table 1.** Formulation for Desloratadine 0.5 mg/mL Syrup (Protocol P00225)

Syrup Strength	0.5 mg/mL
Formula. No.	3518
Batch No.	53266-003-B
Batch size	[REDACTED]
FMR No.	99513D09
Manf. Date 2	2/23/99
Recertification Date	05/00

Batch No. 53266-003-B is the same as the to-be marketed formulation. The batch size used in this study was 550 L, which is 10% of the size of a full size batch (5500L).

## **PHARMACOKINETIC MEASUREMENTS**

### **Blood Sampling**

Blood samples (2.5 mL), for the determination of DL and 3-OH DL concentrations in plasma, were collected at 0 hr (pre-dose) and at 1, 1.5, 2, 4, 8, 12, 24, 48, 72 and 96 hr post-dose, as described in the protocol.

### **Analytical Method**

Plasma DL and 3-OH DL concentrations were determined using a validated LC/MS/MS method with a lower limit of quantitation (LOQ) of 0.025 ng/mL for each analyte. The method has a linear range of 0.025 to 10 ng/mL of plasma for each analyte.

## **SAFETY MEASUREMENTS**

For safety evaluation, physical examinations, vital signs, electrocardiograms and clinical laboratory tests were conducted at Screening and at the conclusion of the study (72 hours post-treatment). 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 and 3-OH DL concentration-time data were used to determine the pharmacokinetic parameters using model-independent methods.

### **Statistical Analysis**

Summary statistics including means, standard deviations, coefficients of variation and 95% confidence intervals for the means were provided for the pharmacokinetic parameters. Means, standard deviations and %CV were reported for the concentration data at each time point.

The individual pharmacokinetic parameters were plotted against demographic factors (e.g., age, and body weight), and the resulting graphs examined for correlations. In order to confirm the influence of demographic factors on the pharmacokinetics of SCH 34117, these covariates were then included in a stepwise linear regression model to assess the relationship between these factors and the pharmacokinetic parameters (e.g., C<sub>max</sub>, AUC, etc). Demographic factors were entered at the 10% level and removed at the 5% level of probability. The p-values of the regression method are presented in the text.

## **RESULTS**

### **Analytical Method**

**Pre-Study Validation:** The sponsor did not report data regarding pre-study validation, therefore, the % of recovery and stability are unknown.

## In-Study Validation

### Limit of Quantitation

The lower limit of quantitation and upper limit of quantitation were 0.025 ng/mL and 10.0 ng/mL, respectively, for both DL and 3-OH DL.

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

	DL	3-OH DL
<b>Linearity</b>	Satisfactory: Standard curve range from 0.025 to 10.0 ng/mL; $r^2 \geq 0.996$	Satisfactory: Standard curve range from 0.025-10 ng/mL; $r^2 \geq 0.99$
<b>Accuracy</b>	Satisfactory: 0.0168% (% Bias) at 0.075 ng/mL; 3.02% at 0.75 ng/mL; -1.97 % at 7.5 ng/mL.	Satisfactory: 10% (% Bias) at 0.075 ng/mL; 4.29% at 0.75 ng/mL; -0.467 % at 7.5 ng/mL.
<b>Precision</b>	Satisfactory: (%CV) 6.8 at 0.075 ng/mL; 3.4 at 0.75 ng/mL; 6.09 at 7.5 ng/mL.	Satisfactory: (%CV) 10.8 at 0.075 ng/mL; 3.83 at 0.75 ng/mL; 5.6 at 7.5 ng/mL.
<b>Specificity</b>	Satisfactory: Chromatograms submitted	Satisfactory: chromatograms submitted

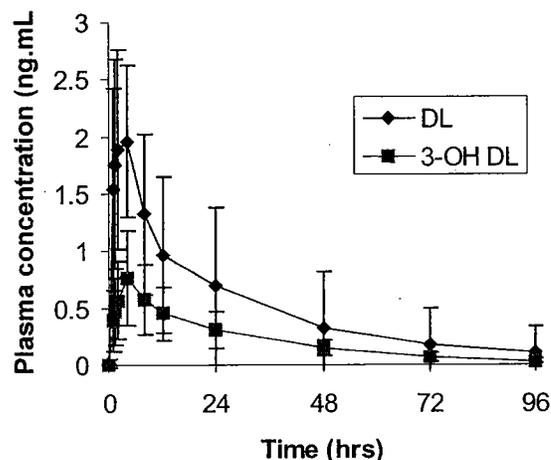
### Pharmacokinetic Results

The mean plasma concentration-time profiles for DL and its metabolite following single administration of clarinex syrup 2.5-mg in children 6-11 years old are shown in Figure 1. Subject 13 had measurable 0-hr DL concentration of 0.176 ng/mL (~7-times the assay LOQ). According to the sponsor, the reason for this is unknown, but this value was judged to not affect the overall conclusions of the study.

A comparison of the mean pharmacokinetic parameters for DL and its metabolite following administration of syrup 2.5 mg in children 6-11 years of age, syrup 5mg in healthy adults (from study P00213) and syrup 5 mg in children 6-11 years old (from study P00270) is summarized in Table 4.

The individual  $C_{max}$  and  $AUC_t$  values for DL and its metabolite following the administration of 2.5 mg syrup in children 6 to 11 years of age and syrup 5 mg in adults are presented in Figures 2 and 3, respectively. Figures 4 and 5 are box plots comparing the DL  $AUC_{inf}$  obtained following administration of syrup 2.5 mg syrup in healthy children 6-11 years old, syrup 5mg in healthy adults and syrup 5mg in children 6 to 11 years old. There was high intersubject variability in DL plasma concentrations as shown in figures 2, 3, and 5 and the associated pharmacokinetic parameters (Table 4). The stepwise regression procedure detected a significant relationship between body weight and  $C_{max}$  ( $p=0.01$ ) explaining 34% of the variability among pediatric subjects

The pharmacokinetic parameters ( $AUC_t$ ,  $C_{max}$ ) obtained following the administration of syrup 1.25 mg in children 2-5 years of age and syrup 5 mg in adults then subjected by this reviewer to statistical analysis using an analysis of variance (ANOVA) model. The results are shown in Table 5.

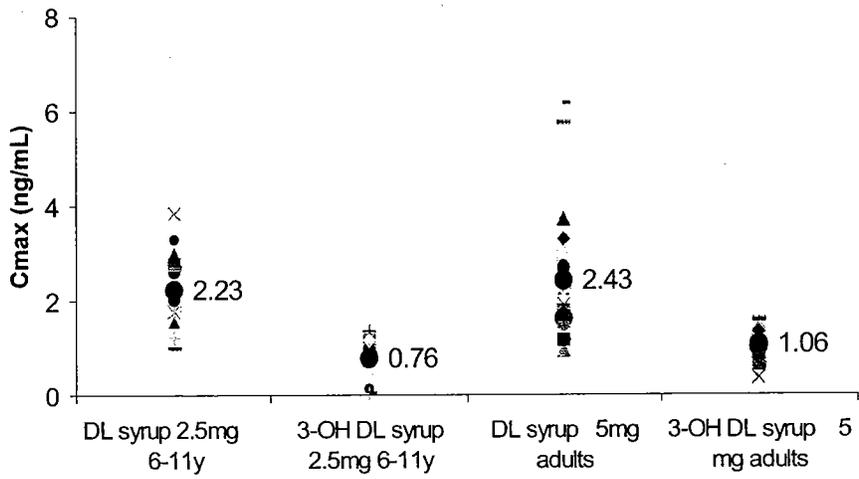


**Figure 1.** Mean DL and 3-OH DL plasma concentration-time profiles following single administration of clarinex syrup 2.5 mg in children 6 to 11 years of age. Bars represent mean  $\pm$  SD.

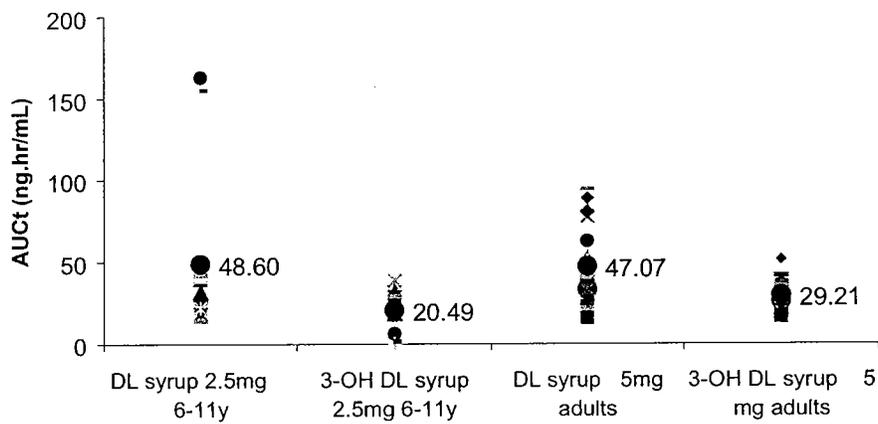
**Table 4.** Mean pharmacokinetic parameters of DL and 3-OH DL following administration of the treatments.

<b>Desloratadine</b>				
PK parameter	Children 6- 11y Data		Adult data <sup>1</sup>	Ratio 2.5mg 6-11y/ 5 mg adult syrup
	Syrup 2.5mg	Syrup 5 mg <sup>2</sup>	Syrup 5mg	
AUCt (ng*hr/mL)	48.6 (88)	101 (89)	46.22 (71)	1.05
AUCinf (ng*hr/mL)	55.5 (100)	111 (102)	48.36 (54)	1.15
Cmax (ng/mL)	2.23 (35)	5.3 (41)	2.3 (51)	0.97
Tmax (hr)	3.67 (79)	2.78 (73)	3.58 (45)	
T1/2 (hr)	19.4 (61)	18.6 (49)	24.03 (23)	
CL/F (L/hr)			134.63 (46)	
<b>3-OH desloratadine</b>				
PK parameter	Children 6-11y Data		Adult Data <sup>1</sup>	Ratio 2.5mg 6-11y/ 5 mg adult syrup
	Syrup 2.5mg	Syrup 5 mg <sup>2</sup>	Syrup 5 mg	
AUCt (ng*hr/mL)	20.5 (50)	43.0 (45)	25.98 (28)	0.79
AUCinf (ng*hr/mL)	23.2 (38)	45.9 (42)	27.83 (28)	0.83
Cmax (ng/mL)	0.764 (54)	1.77 (57)	1.03 (38)	0.74
Tmax (hr)	4.44 (42)	4.44 (63)	4.73 (39)	
T1/2 (hr)	28.1 (65)	26.8 (43)	30.71 (21)	
AUCt ratio (%)*	42.2	42.6	56.2	

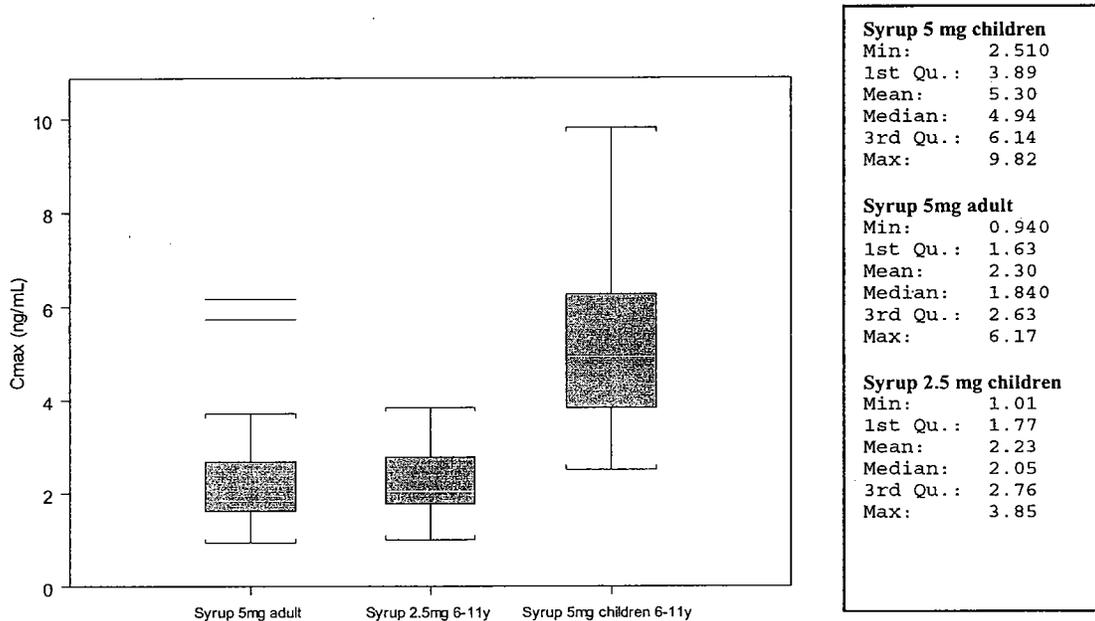
\* Calculated as the ratio of AUCt of 3-OH DL/DL; <sup>1</sup> Data from study P00213; <sup>2</sup> data from study P00270.



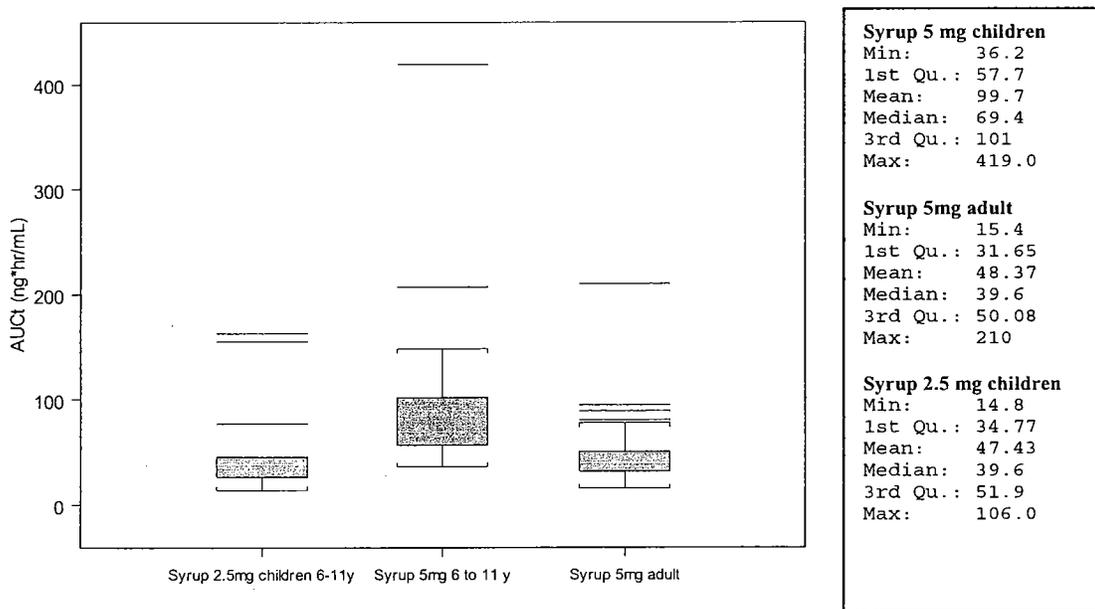
**Figure 2.** Individual DL Cmax values following single administration of clarinex syrup 2.5 mg and 5mg to children 6 to 11 years of age and adults, respectively.



**Figure 3.** Individual DL and 3-OH DL AUC<sub>0-t</sub> values following single administration of clarinex syrup 2.5 mg and 5mg to children 6 to 11 years of age and adults, respectively.



**Figure 4 .** Box plot comparing the DL Cmax values obtained following administration of a 5 mg syrup in healthy adults (from study P00213), and 2.5 mg and 5 mg (study P00270) clarinex syrup in children 6-11 years old.



**Figure 5.** Box plot comparing the DL AUCt values obtained following single administration of Clarinex syrup 5 mg in adults (study P00213), syrup 2.5 mg in children 6-11 years old and syrup 5 mg in children 6 to 11 years old (study P00270).

**Table 5.** ANOVA analysis for AUCt and Cmax

<b>Desloratadine</b>			
<b>PK parameter</b>	<b>Children Data Syrup 2.5 mg (A)</b>	<b>Adult data Syrup 5mg (B)</b>	<b>P value (A vs. B)</b>
AUCt (ng*hr/mL)	48.6 (88)	46.22 (71)	0.97
Cmax (ng/mL)	2.23 (35)	2.3 (51)	0.82
<b>3-OH desloratadine</b>			
<b>PK parameter</b>	<b>Children data Syrup 1.25mg (A)</b>	<b>Adult data Syrup 5mg (B)</b>	<b>P value (A vs. B)</b>
AUCt (ng*hr/mL)	20.5 (50)	25.98 (28)	<<<<<<0.05
Cmax (ng/mL)	0.764 (54)	1.03 (38)	0.03

**COMMENTS**

According to the sponsor, a 2.5-mg oral dose of clarinex syrup was associated with a mean DL AUC(tf) value for pediatric subjects aged 6 to 11 years old, similar to that observed in adults who received a 5-mg dose of clarinex syrup (Table 4). The ANOVA analysis conducted by this reviewer revealed that in fact, there are not statistically significant differences between these 2 treatments (Table 5). The sponsor stated that the metabolite data of pediatric and adult subjects were also comparable. However, Table 5 shows statistically significant differences in AUCt and Cmax between treatments.

The systemic exposure and plasma concentrations in Subjects 13, 16 and 17 were higher for DL and lower for 3-OH DL than those in the other subjects. Thus, according to the sponsor the rate of metabolism of SCH 34117 in these subjects appears to be slower than that in other subjects. The AUC(tf) of DL in these slow metabolizers were 163, 77.1 and 155 ng·hr/mL and the corresponding values for 3-OH DL were 6.0, 0.04 and 1.39 ng·hr/mL with AUC ratios (metabolite to parent) of 3.7, 0.05 and 0.9%, respectively. This is in contrast to the AUC ratio values in the other subjects (normal metabolizers) ranging from 39.9 to 140%. The mean AUC ratio increased to 82% (from 67%) when the slow metabolizers were excluded.

**CONCLUSION**

Pediatric subjects aged 6 to 11 years of age receiving a single dose of clarinex syrup 2.5 mg had comparable AUCt and Cmax values of DL, but NOT for the metabolite 3-OH DL, to those obtained in adults receiving clarinex syrup 5 mg.

**Office of Clinical Pharmacology and Biopharmaceutics**  
*New Drug Application Filing and Review Form*

General Information About the Submission			
	Information		Information
NDA Number	21-300	Brand Name	Clarinet Syrup
OCPB Division (I, II, III)	II	Generic Name	Desloratadine (DL)
Medical Division	DPADP	Drug Class	Antihistamine
OCPB Reviewer	Sandra Suarez-Sharp	Indication(s)	SAR, CIU
OCPB Team Leader	Young Moon Choi (acting)	Dosage Form	Syrup
		Dosing Regimen	1.25mg/2.5mg QD 2-5/6-11 years old
Date of Submission	December 8, 2000	Route of Administration	Oral
Estimated Due Date of OCPB Review	September 2001	Sponsor	Schering Corp.
PDUFA Due Date	October 8, 2001	Priority Classification	Standard
Division Due Date	September 8, 2001		

**3 Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	5	5	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	4	4	
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>	X	1		
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:	X	1		
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	SINGLE	1	
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
Literature References	X			
<b>Total Number of Studies</b>		5	5	
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. <ul style="list-style-type: none"> <li><b>Please submit pre-study validation data for the analysis of DL and its metabolite.</b></li> </ul>		
<b>QBR questions (key issues to be considered)</b>	<ol style="list-style-type: none"> <li>Was the to-be-marketed formulation used in the pharmacokinetic studies?</li> <li>Is the clarinex syrup formulation (5mg) equivalent to the 5 mg tablet formulation? Did food affect the BA of DL from the clarinex syrup?</li> <li>Is the proposed dose of 1.25 QD mg in children 2-5 years of age supported by the PK studies?</li> <li>Is the proposed dose of 2.5 mg QD in children 6-11 years of age supported by the PK studies?</li> </ol>			
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>				
<b>Secondary reviewer Signature and Date</b>				

CC: NDA 21-300, HFD-850 (Electronic Entry or Lee), HFD-570 (Trout), HFD-870 (Fadiran, Hunt, Malinowski), CDR (B. Murphy)

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

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Sandra Suarez  
9/21/01 10:35:10 AM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
9/21/01 11:22:17 AM  
BIOPHARMACEUTICS  
I concur