CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-165

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-165 (000)
Drug Substance	Desloratadine
Drug Product(s)	Clarinex Tablet (desloratadine 5 mg)
Sponsor	Schering Corp.
Type of submission	General Correspondence (Response to reviewer's request)
Date of submission	3/6/2001
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D. OCPB/DPE-2

Synopsis

Desloratadine (SCH 34117; DCL) is a tricyclic antihistamine with selective peripheral histamine H1-receptor antagonist activity. It is an active metabolite of loratadine (Claritin ®) which is marketed as 10 mg tablet in the U.S. Relative oral potency of DCL is two to four times greater than loratadine in animals.

The sponsor developed a tablet formulation (5-mg strength) of DCL for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis, including nasal congestion, in patients 12 years of age and older. The proposed dosage regimen is 5-mg oral, Q.D. for adults and children 12 years of age and over.

On 10/20/1999, the sponsor submitted the data from a complete safety/efficacy program (four multiple dose studies for safety and four single dose studies for onset of action) and 14 clinical pharmacology studies.

This reviewer completed the review of the clinical pharmacology and biopharmaceutics data and found that the systemic exposure was 18-32 % higher in African –American than in Caucasian. Similarly, five subjects with high systemic exposure in Study C98357 are all African-Americans. It was noted that the sponsor investigated the genotype of the subjects with the 5 alleles (A,B, D, E, and T) for 2D6 in that study. However, allele Z(*17) which is abundant in African-Americans and Asians was not studied. Therefore, the sponsor was asked to investigate the genotype for allele Z (*17) for the subjects in Study C98357.

The present submission dated 3/12/2001 is the sponsor's response to the above Agency's request on the genotype study.

The sponsor's response was acceptable. The sponsor investigated the 48 samples from 4 studies for CYP2D6 genotype. CYP2D6 *2, *3, *4, *5, *7, *8, *9, *10. *11, *12, *15, *17, and *18 alleles, as well as CYP2D *29 allele (See the appendix for detailed methods) were tested. Among the 48 samples, 12 samples were from the subjects with poor DCL 3- hydroxylation function (i.e., appeared high systemic exposure of DCL than average). Other 36 samples were from the subjects with normal DCL 3-hydroxylation function.

The genotype results indicate that there is a lack of correlation in between 2D6 genotype and 3-OH DCL formation:

(1) Four individuals (Subjects 11588, 12108, 11743, and 11747) possess two- non functional or "null" CYP2D6 alleles (i.e., * 4/ *4, * 4/ *5, and *3 / *4), but exhibited normal 3-OH DCL formation (See Table 1).
(2) Eleven out of 12 subjects with the poor 3-OH DCL formation ability appeared to possess at least one functional allele, either CYP 2D6 *1 or *2, (i.e., possess 2D6 phenotype of

extensive metabolizer). One exception was an individual (i.e., Subject ID No. 511073) with a novel CYP 2D6 genotype, *17ins/*29.

Also, there was a lack of correlation between allele *17 and poor formation of 3-OH DCL:

(1) The results of CYP2D6 genotyping showed that a total of 10 out of 48 samples possess *17. Among them, half showed normal DCL 3-hydroxylation formation and the other half are poor DCL 3-hydroxylation function.
(2) It was noted that two individuals appeared to possess CYP 2D6 *17 allele out of the 14 individuals from the Study CI98-357. One was identified as a normal and the other had high systemic exposure of DCL (i.e., poor DCL 3 hydroxylation function).
(3) It is also noted that the various combination of alleles (i.e., * 1/ * 17, *1/ *29, *4/ *17, *2/ *5, and * 2/ *17) appeared both in the samples from the poor and normal DCL 3-hydroxylation metabolizer (See Table 1 in the appendix).

Conclusions

From this study, following two conclusions were made.

- The genotype results indicate that there is a lack of correlation in between 2D6 genotype and 3-OH DCL formation.
- Also, there was a lack of correlation between allele *17 and poor formation of 3-OH DCL.

Recommendation: No Action Indicated

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II has reviewed the sponsor's response and found that the provided data are acceptable from a pharmacokinetic perspective. No more action is needed at present.

/S/

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

/S/

Emmanuel Fadiran, Ph.D.
Team Leader
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Appendix 1. Genotype study

Background
General Information
Method
Results
Reviewer's comments

cc NDA 21-165, Division File
HFD-870: Emmanuel Fadiran, Young Moon Choi, Shiew-Mei Huang
HFD-570: Sandra Barns, Anthony Zeccola

Appendix 1. Genotyping for CYP 2D6

1. Background

Descarboxyethoxyloratadine(SCH34117; DCL) is an active, N-desalkyl metabolite of loratadine. A major metabolite of DCL in humans is the glucuronide conjugate of 3-hydroxy DCL (3-OH-DCL).

Clinical pharmacology studies showed that the systemic exposure of DCL was 18-32 % higher in African –American than in Caucasian. Similarly, five subjects with high systemic exposure in Study C98357 are all African-Americans.

It is noted that the sponsor investigated the genotyping of the subjects with the 5 alleles (A,B, D, E, and T) for 2D6 in that study. However, allele Z(*17) which is abundant in African-Americans and Asians was not studied. Therefore, the sponsor was asked to investigate the genotype for allele Z (*17) for the subjects in Study C98357.

In this context, the review is focused on whether or not there is any correlation of *17 allele with poor DCL 3-hydroxy metabolism.

2. General information on CYP2D6 gene locus:

CYP2D6 gene locus is highly polymorphic with more than 50 variant forms of the gene (allele) described to data. Inheritance of two non-functional or null alleles results in inefficient metabolism [i.e., poor-metabolizer (PM)] of many drugs including several beta receptor antagonist, anti-arithimics, anti-depressants, anti-psychotics and morphine derivatives.

This PM phenotype of CYP2D6 is found in 5-10 % of Caucasians and about 1-2 % of Asian and African-Americans. In Caucasians, the *3, *4, *5, and *6 alleles are the most common loss of functional alleles and account for approximately 98 % of PM phenotypes. Compared to Caucasians, Asian and African-Americans tend to have lower CYP2D6 activities even though the actual incidence of PM is less than in Caucasians.

This may be partially explained by a lower frequency of non-functional alleles and a relatively high frequency of population-selective alleles that are associated with decreased activity relative to the wild type *1 allele. For example, CYP2D6 *10 allele occurs at a frequency of 50 % in Asians, and *17 alleles is reported at a frequency of 30-35 % in black Africans and 21 % in African-Americans.

3. Method of genotyping

A polymerase chain reaction (PCR) / restriction fragment length polymorphism –based genotyping strategy is employed to detect alleles associated with the extensive and poor metabolizer status.

(1) Genomic DNA was isolated from white blood cells.

(2) The isolated DNA is quantitated and qualitated by

Subsequently extra long polymerase chain reaction is used to specifically amplify the CYP 2D6 gene:

(3) A series of reamplification assays are then performed followed by restriction enzyme digestions.:

(4) The resulting DNA fragments are analyzed by agarose gel electrophoresis, and assignment of the genotype is made by interpretation of the banding patterns. If necessary, additional

long polymerase chain reactions are performed to detect large gene deletions and gene duplications:

Additional XL-PCR reactions have been established to detect CYP2D6 alleles carrying duplications (*1x2, *2x2, and *4x2) and tile *16 gene rearrangement. [redacted] methods were also developed for two new alleles. These are described in detail below.

Assay for the CYP2D6*29 allele

Assay for the 18 bp insertion in the CYP2D6*17 allele

4. Results

Table 1 presents the final genotype.

Table1. Demographic data, 2D6 genotype, anticipated CYP2D6 phenotype, and desloratadine 3-hydroxylation phenotype

Study No.	Subjects ID	Gender	Race	CYP2D6 genotype	CYP 2D6 Phenotype	DCL 3-hydroxylation phenotype
C98-357	11413	M	B	*2x2/ *29	EM	PM
	11414	M	B	*1 / *17	EM	N
	11415	M	B	*2 / *17	EM	PM
	11417	M	B	*1 / *2	EM	PM
	11418	M	C	*1 / *2	EM	N
	11419	M	C	*1 / *4	EM	N
	11420	M	B	*1 / *29	EM	PM
	11421	M	B	*2 / * 3	EM	N
	11423	M	C	*1 / * 5	EM	N
	11425	F	C	*1 / *4	EM	N
	11426	F	B	*1 / * 29	EM	N
	11427	F	B	*1 / * 5	EM	N
	11429	F	C	*1 / * 4	EM	N
	11434	F	B	*1 / *2	EM	PM
C98-356	11569	M	C	*2 / *4	EM	N
	11570	F	C	*2 / *4	EM	N
	11572	M	B	*2 / *17	EM	PM
	11574	M	C	*1 / *4	EM	N
	11575	F	B	*2 / *29	EM	N
	11577	M	B	*1 / *29	EM	N
	11579	M	C	*1 / *29	EM	N
	11580	M	B	*4 / *17	EM	PM
	11581	M	B	*4 / *17	EM	N
	11583	F	C	*1 / *29	EM	N
	11588	F	B	*4 / *4	PM	N
	11589	F	C	*1 / *4	EM	N
	11590	F	B	*1 / *2 X 2	EM	N
	11591	M	B	*2 / *5	EM	N
	11605	M	C	*1 / * 4	EM	NA
	11628	F	B	*1 / *4 X 2	EM	N
	11650	F	B	*2 / * 5	EM	PM
	12108	M	B	*4 / *5	PM	N
	12109	F	C	*1 / * 4	EM	N
	12885	F	C	*1 / *4	EM	N
C98-354	11670	M	C	*2 / * 7	EM	N
	11671	F	B	*3 / *10	EM	N
	11672	F	B	*2 / * 2X 2	EM	N
	11675	M	B	*2 / * 17	EM	N
	11676	M	B	*3 / *17	EM	N
	11678	M	C	NA	-	N
	11741	M	B	*1 / * 10	EM	N
	11742	M	C	*1 / * 2	EM	PM
	11743	M	C	*3 / * 4	PM	N
	11745	M	B	* 2/ * 17	EM	N
	11746	M	B	*1 / * 17	EM	PM
	11747	M	C	*4 / *4	PM	N
	11749	F	B	*2 / *17	EM	N
C98-097	511073	M	B	* 17 ins/ *29	PM (?)	PM

B represents African-American; C represents Caucasian;
M is male and F is female;
N is normal, PM is poor metabolizer and NA is not available.

5. Reviewer's comments

The sponsor responded adequately to the agency's request with respect to 2D6 genotyping. The sponsor provided 2D6 genotype of the five individuals whose systemic exposure is unusually higher than the others in Study C98-357 (The evaluation of the electrocardiographic pharmacodynamic effects following administration of multiple high-dose of SCH34117).

Furthermore, the sponsor provided 2D6 genotype of samples from Studies C98-356 (A multiple dose pharmacokinetic study in healthy subjects), C98-354 (Single dose pharmacokinetics in subjects with various degrees of chronic liver disease), and C98-07 (The absorption, metabolism and excretion of 14C-SCH 34117 in healthy male volunteers).

The genotype results indicate that there is a lack of correlation in between 2D6 genotype and 3-OH DCL formation:

- Four individuals (Subjects 11588, 12108, 11743, and 11747) possess two- non-functional or "null" CYP2D6 alleles (i.e., * 4/ *4, * 4/ *5, and *3 / *4), but exhibited normal 3-OH DCL formation.

- The 11 out of 12 subjects with the poor 3-OH DCL formation ability appeared to possess at least one functional allele, either CYP 3D6 *1 or *2, (i.e., possess 2D6 phenotype of extensive metabolizer).

Also, the above results indicates a lack of correlation between allele *17 and poor formation of 3-OH DCL:

- The results of CYP2D6 genotyping showed that a total of 10 out of 48 samples possesses *17. Among them, half showed normal DCL 3-hydroxylation formation and the other half is poor DCL 3-hydroxylation function.

- It was noted that two individuals appeared to possess CYP 2D6 *17 allele out of the 14 individuals from the Study CI98-357. One was identified as a normal and the other had high systemic exposure of DCL (i.e., poor DCL 3 hydroxylation function).

- It is also noted that the various combination of alleles (i.e., * 1/ * 17, *1/ *29, *4/ *17, *2/ *5, and * 2/ *17) appeared both in the samples from the poor and normal DCL 3-hydroxylation metabolizer (See Table 1 in the appendix).

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-165	Reviewer: Young Moon Choi, Ph.D.
Drug: Desloratadine Tablet	Submission: 3/20/00 and 5/18/00
Sponsor: Schering Corp	
Type of submission: Original NDA	PDUFA due date: 11/21/00
	Div due date : 9/21/00
Review Code: 1S	

1. SYNOPSIS

This short review is for the two submissions dated 3/20/00 and 5/18/00.

The sponsor submitted the original NDA 21-165 on 10/20/00 for desloratadine tablet. After the filing meeting, this reviewer requested the information of in vitro human metabolism, protein binding, and the final study report for the study C98-335, "Single dose pharmacokinetics of SCH 34117 in subjects with various degree of chronic renal insufficiency."

The submission dated 3/20/00 included the in vitro study information and the submission dated 5/18/00 is the final study report for study C98-355.

This information has been reviewed and signed-off (paper copy) on 9/20/00.

2. REVIEWER'S COMMENT. No action is indicated.

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed the submission dated 3/20/00 and 5/18/00. The review can be found in Clinical Pharmacology and Biopharmaceutics review dated 9/20/00 (paper copy).

11-21-00

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

12/7/00

John Hunt
Deputy Director
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-165; Div file; HFD-570 (Trout),
HFD-870(Huang, Hunt, Choi), CDR (B. Murphy)

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-165	Reviewer: Young Moon Choi, Ph.D.
Drug: Desloratadine Tablet	Submission: 10/20/99
Sponsor: Schering Corp	Reviewed: 9/16/00
Type of submission: Original NDA	PDUFA due date: 11/21/00
	Div due date : 9/21/00
Review Code: 1S	

1. Synopsis

Desloratadine (SCH 34117; DCL) is a tricyclic antihistamine with selective peripheral histamine H1-receptor antagonist activity. It is an active metabolite of loratadine (Claritin ®) which is marketed as 10 mg tablet in the U.S. Relative oral potency of DCL is two to four times greater than loratadine in animals.

The sponsor developed a tablet formulation (5-mg strength) of DCL to indicate the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis, in patients 12 years of age and older. The proposed dosage regimen is 5-mg oral, Q.D. for adults and children 12 years of age and over.

In support of the proposed indications and dosage regimen, the sponsor has submitted eight safety/efficacy studies (four multiple dose studies for safety and four single dose studies for onset of action).

In addition, the sponsor submitted 14 clinical pharmacology studies for the following information:

- Absorption/Distribution/Metabolism/Excretion (One single dose study using C14 labeled DCL tablet)
- Dose proportionality (two single dose studies and a multiple dose study for the range of 2.5 – 20 mg doses)
- Drug interaction (Ketoconazole and erythromycin coadministration studies)
- In vitro metabolism/transport studies
- Food effect
- Race, age and gender effect (one multiple dose study for age, one multiple dose study for race and gender effect)
- Special populations (Hepatic and renal impairment)
- Comparative study with Claritin 10 mg
- Comparative study of polymorphs of drug substance (Form 1 and 2) to investigate the in vivo performance since inter-conversion of the polymorphs can occur during tablet formulation.
- Cardiac effect following multiple administration of 45 mg dose QD (9 times of the recommended daily dose for 10 days)

The sponsor requested a deferral of pediatric studies with the tablet formulation, since they intended to study pediatrics with product.

The above clinical pharmacology studies were reviewed following a question-based review format.

- What is the fate of DCL following oral administration?
- What is the dose-systemic exposure relationship ?
  - Does the systemic exposure increase with dose proportionally?
  - How does the systemic exposure after multiple dose compare to single dose?
- How does the DCL exposure from 5 mg DCL tablet compare to 10 mg Claritin tablets?
- Is the systemic exposure related to untoward cardiac effect, (e.g., ventricular rate, QRS, and QTc)?

- How does the exposure change in the presence of intrinsic and extrinsic patient factors?
  - Should the dose be adjusted in renally impaired patients?
  - Should the dose be adjusted in hepatically impaired patients?
  - Should the dose be adjusted in the elderly?
  - Should the dose be adjusted by gender?
  - Is there any food effect on the bioavailability of DCL?
  - Is there any drug-drug interaction?
- Are the proposed dissolution method and specification appropriate?
- What is the impact of the polymorphism of DCL on pharmacokinetics?

2. COMMENTS TO THE MEDICAL OFFICER

(1) The fate of DCL after oral administration.

- Absolute oral bioavailability has not been determined in human. Based on the Tmax (on the average 3.5 hour) and T1/2 (approximately 31 hours), it could be concluded that DCL is slowly absorbed and eliminated. Based on the urinary and feces recovery of radioisotope, absorption seems to be more than 40 %.
- Once absorbed, DCL appeared to undergo enterohepatic recirculation and was extensively metabolized to 3-OH desloratadine and then glucuronidated and excreted into urine (major route of elimination). Approximately half of the dose may be eliminated into the feces (either unabsorbed or excreted into gastrointestinal lumen through bile or other mechanism).
- The in vitro and in vivo data suggest that CYP 2D6, CYP1A2, CYP2B6, and CYP 3A4 may be responsible for its metabolism.
- In vitro data suggest that DCL does not inhibit CYP 1A2, 2C9, 2C19, 3A4, and 2D6.
- Protein binding of DCL is moderate (85.6%) and its distribution to red blood cell was minimal (Plasma/Blood ratio=
- The pharmacokinetics of DCL followed linear pharmacokinetics, i.e., the systemic exposure of DCL increased with dose proportionally.

(2) Comparison of systemic exposure with Claritin 10 mg tablet

A comparative study of systemic exposure after multiple dose administration has been conducted with a three way cross over design (Study P00117). The results showed that the systemic exposure of DCL after 5 mg multiple dose administration of DCL (multiple dose) was comparable to that after 10 mg Claritin.

The metabolic profile of DCL is appeared similar to that after loratadine administration (Reference: Study Report # C98-284 : The absorption, metabolism and excretion of 14C-SCH 29851 in healthy male volunteers)

Based on the results, this reviewer is of the opinion that the available safety data after 10 mg Claritin oral administration may be used in the evaluation of the safety after DCL 5 mg dose.

(3) Systemic exposure and cardiac effect (Ventricular rate, QRS, and QTc change)

The relationship between the systemic exposure and this adverse effect was examined in study C98357 using a dose (45 mg) which was 9-times of the proposed dose (5 mg).

The Cmax and AUC were more than 10 times those of the 5 mg dose. Linear regression suggested that there was no substantial correlation between these cardiac parameters vs. DCL concentration. However, the data submitted were not optimal (e.g., QT data were machine read), these data will be re-examine when additional data became available.

(4) Systemic exposure in renally impaired patients

In renal impairment (CLcr<80ml/min), the systemic exposure is increased more than 2 times compared to healthy subjects. DCL was not removed by hemodialysis.

A regression analysis may be needed to determine at what point of the renal impairment warrants a dosage adjustment.

(5) Systemic exposure in hepatically impaired patients
Subjects with all level of the hepatic dysfunction exhibited greater exposure (more than 2 times) to desloratadine than normal subjects.
Based on the results, this reviewer recommends that the dose be reduced to half in hepatic patients group (Child-Pugh score ≥5).

(6) Effect of age, race, and gender on DCL systemic exposure
The DCL systemic exposure increased (20 %) in elderly (>65 years).
Female subjects treated for 14 days with desloratadine had 10% and 3% higher desloratadine C_{max} and AUC values, respectively, compared with male subjects. The 3-hydroxy desloratadine C_{max} and AUC values were also increased by 45% and 48%, respectively, in females compared with males.
The systemic exposure was higher (18-32 %) in black subjects than in Caucasian subjects.

Similarly, the subjetcs with high systemic exposure in study C98357 are all African–Americans. The sponsor investigated the genotyping of the subjects with the 5 alleles (A, B, D, E, and T) for Cyp 2D6 in Study C98357. However, allele Z (*17) is more abundant in African-Americans and Asians. Therefore, the sponsor may need to investigate the genotype for allele Z for the subjects in Study C98357.

(7) Food effect
Food did not affect on the bioavailability of DCL.

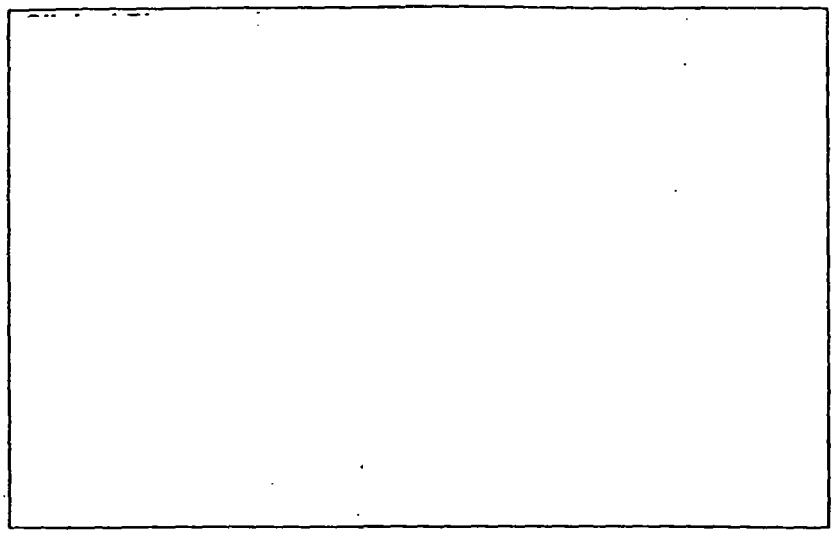
(8) Drug-drug interaction
Coadministration of therapeutic doses of ketoconazole (200 mg bid) or erythromycin (500 mg tid) increased DCL systemic exposure 20 –45 % or 14 – 24 %, respectively.
(The degree of the interaction is approximately ½ of loratadine; Refer to the Claritin labeling).

3. COMMENTS TO THE CHEMIST
(1) The effect of polymorphism on bioavailability
The two polymorphs appeared to be bioequivalent indicating no in vivo impact of the polymorphism.

(2) Dissolution method and specification
The proposed method is acceptable. However, upon reviewing the dissolution data of biobatch, this reviewer recommends a dissolution specification of Q= % at 30 min for desloratadine tablet.
The dissolution data of biobatch and all the stability data are supportive of Q= % at 30 min.
This reviewer recommends the following dissolution method and specification:

Method
Apparatus: USP apparatus II (paddle)
Speed: 50 rpm
Temperature: 37 °C
Medium: 0.1 N HCl
Volume: 500 ml
Specification
Q= % at 30 min

4. Labeling Comments
(1) The sponsor is asked to reframe the structure of the labeling under the section of Clinical Pharmacology/ Pharmacokinetics. It is recommended that the following standard format be used.



(2) Under Clinical Pharmacology section: The statement,
:" needs additional information of dosing.

(3) Under the section of pharmacokinetics, for pharmacokinetic (PK) parameters, the sponsor needs to provide a range of the values since PK parameters appeared to be highly variable.

(4) The sponsor should include renal failure information under the clinical pharmacology section/special population. Based on increased systemic exposure by renal failure, the sponsor should state the dose adjustment. The sponsor is asked to perform a regression analysis to determine at what point of the renal impairment warrants a dosage adjustment.

(5) The information of increased systemic exposure by hepatic and renal failure should be reflected in other labeling section, e.g., precaution, and dosage and administration section, appropriately.

(6) Following is the recommended labeling of Clinical Pharmacology section:

CLINICAL PHARMACOLOGY:
Pharmacokinetics:

DRAFT

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

DRAFT

5. COMMENTS TO THE SPONSOR

done 9/14/00 submission

(1) The dissolution method proposed by the sponsor is acceptable. However, the dissolution specification should be changed to [redacted] at 30 min.

(2) It is noted that the systemic exposure was higher (18-32 %) in African-American than in Caucasian (Study C98356). Similarly, the subjects with high systemic exposure in study C98357 are all African–Americans. The sponsor investigated the genotyping of the subjects with the 5 alleles (A, B, D, E, and T) for CYP 2D6 in Study C98357. However, allele Z (*17) is abundant in African-Americans and Asians. Therefore, the sponsor is asked to investigate the genotype for allele Z for the subjects in Study C98357.

6. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed and found NDA 21-165 to be acceptable provided that the above "Labeling Comments" are addressed satisfactorily and dissolution specifications are modified by the sponsor. Please forward the above "Labeling comments" and "Comments to the sponsor", as appropriate.

9/20/00.

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

9/20/00

Shiew-Mei Huang, Ph.D.
Acting Division Director
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-165; Div file; HFD-570 (Trout, Swiss, and Nicklas),
HFD-870(Uppoor, Huang, Hunt, Choi), CDR (B. Murphy)

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8. BACKGROUND

Desloratadine (SCH 34117; DCL) is a long acting tricyclic antihistamine with selective peripheral histamine H1-receptor antagonist activity. It is an active metabolite of loratadine (Claritin ®) which is marketed as 10 mg tablets in the U.S. Relative oral potency of DCL is two to four times greater than loratadine in animal models.

The sponsor developed a tablet formulation (Please refer to the following composition of drug product) using desloratadine for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR), in patients 12 years of age and older.
Proposed dosage regimen is 5-mg oral, Q.D. for adults and children 12 years of age and over.

In support of the above indications and dosage regimen, the sponsor has conducted a complete safety and efficacy program for SAR patients 12 years or older (a total of 8 clinical trials; 4 for safety and 4 for onset of action). For pediatric patients, the sponsor intended to use formulation.

In addition to the clinical trials, a total of 14 clinical pharmacology studies have been reported (Please refer to Appendix biopharmaceutic study summary table).

The sponsor also conducted an alcohol performance study (single dose; 7.5 mg of DCL and placebo; four-way crossover with/without alcohol). However, this study was not reviewed because there was no pharmacokinetic information.

9. DRUG SUBSTANCE AND DRUG PRODUCT

9-1. Drug substance

Generic name: Desloratadine
Code name: SCH 34117
Chemical name: 8-chloro-6,11-dihydro-11-(1-piperidinylidene)-5H-benzo-[5,6]-cyclohepta [1,2-6]pyridine
Molecular weight: 310.8
Molecular formula: C19H19ClN2
Physical from: white to off-white powder
Melting point: 154-157 °C
Solubility: DCL is very soluble in methanol (>400 mg/ml), ethanol (>100 mg/ml), and propylene glycol (>100 mg/ml). It is soluble in acetone (20 mg/ml) and 0.1 N HCl (40 mg/ml). It is slightly soluble in water (0.1 mg/ml) and 0.1 N NaOH (0.08 mg/ml).
With increasing pH, the solubility is decreased (Refer to the following table).

Solvent	Solubility (mg/ml) at ambient temperature
0.1 N HCl	37.6
0.05 sodium acetate buffer (pH 4.5)	26.2
0.05 M phosphate buffer (pH 6.8)	10.3
0.05 M phosphate buffer (pH7.4)	1.5
Distilled water	0.35 (Data from tablet)

Dissociation constant: pKa's of pyridine nitrogen and piperidine nitrogen were 4.3 and 9.7, respectively.

Partition coefficient (Ko/w) between n-octanol and buffer: 5.4 x 10 –3 at pH 1 and 10.5 at pH 7.

Polymorphism: It should be noted that two polymorphs of DCL have been identified. Although one drug substance form is predominantly produced, there is interconversion between two forms during tabulating process. Accordingly, it is difficult to determine how much each form is in the

final tablet and what is its impact on the bioavailability of DCL. Therefore, a bioequivalence study was performed comparing capsule formulations for each form with a to-be-marketed tablet formulation which contains both forms. It appeared that those formulations are bioequivalent.

9-2. Drug product

Following table summarizes the composition of 5-mg tablet.

Core Ingredient	mg/Tablet
Desloratadine (SCH 34117)	5.00
Corn Starch NF	
Dibasic Calcium Phosphate Dihydrate USP	
Microcrystalline Cellulose NF	
Talc USP	
Blue	
Clear	
Carnauba Wax NF	
White Wax NF	
Core weight	**106.61**

Reviewer's comment: ~~The to-be-marketed formulation (5-mg tablet) was used~~ In all the clinical pharmacology studies. For other strengths, i.e., 2.5, 7.5, 10, and 20 mg/tablet, the cellulose amount was adjusted. This is acceptable.

It was noted that the sponsor used only one biobatch throughout the study for 7.5 mg strength (batch number #38833 140) and 5 mg strength (Batch number 398833-142; dissolution data provided for specification), except the Study C98-013 (5 mg strength; Batch number 38833-077).

10. Analytical method

Reviewer's comment on the analysis:

The analytical method employed in the present submission is acceptable. For the analytical performance in individual studies, please refer to the individual study review. For pre-study validation, please refer to the attached "summary of the pre-study validation".

11. pharmacokinetics

Q1: What is the fate of DCL following oral administration? How is DCL eliminated from the body?

To answer this question, a C14 labeled pharmacokinetic study (C98-097), in vitro metabolism studies, and an in vitro protein binding study, as well as overall single and multiple dose studies in healthy volunteers were evaluated.

Throughout the studies, a large intersubject variation was observed (Refer to the following tables). The exact reason(s) of the large variation in pharmacokinetic parameters after oral administration is not known.

Plasma blood ratios ranged from suggesting minimal partitioning of drug into the red blood cells. DCL binds to plasma protein moderately (85.6 %).

After a single oral administration of C14-DCL 10 mg (Study C98-097), the plasma AUC of DCL was 8 % of the plasma AUC of total C14. This suggests extensive metabolism of DCL. In the same study, a mean total of 87.1 % (urine 40.6 % and feces 46.5 %) of the radioactive dose was recovered in the excreta in 10 days.

The metabolite profiles in plasma, urine and feces indicates that 3-OH DCL formulation and its subsequent glucuronidation is the major pathway of metabolism. A proposed biotransformation pathway is summarized in the figure.

From in vitro human metabolism studies (Refer to the attachment), CYP1A1, CYP1A2, CYP 3A4, CYP2B6, CYP 2C19, and CYP 2D6 appeared to be involved in the metabolism of desloratadine.

It was noted that the pharmacogenotype of 2D6 and 2C19 does not correlate with systemic exposure. For example in the study C98-357, the five subjects predicted to be slow metabolizer based on unusually high systemic exposure of DCL turned out to be extensive metabolizers by genotyping. However, this reviewer noted that these five subjects are all blacks and that allele Z(*17), a common allele found in blacks were not tested in this study.

The following tables summarizes the results from the clinical pharmacology studies of DCL after administration of loratadine or desloratadine.

Desloratadine 2.5 mg single dose

Study Number	Cmax (ng/ml)	Tmax (hour)	T1/2 (hour)	AUC 0-24 (ng.hr/ml)	AUC tf (ng.hr/ml
I97 248	0.8 (51)	3.5 (61)		9.77 (93)	

Values are arithmetic means.
AUC tf represent AUC timezero to the last measurable concentration.
The values in parenthesis are CV %.

Desloratadine Dose 5 mg single dose

Study number	Cmax (ng/ml)	Tmax (hour)	T1/2 (hour)	AUC 0-24 (ng.hr/ml)	AUC tf (ng.hr/ml)
I97-248; n=10	1.67 (40)	1.7 (25)	-	-	20.7 (39)
C98-013; n=10	1.83 (35)	6.0 (50)	33.4 (85)	29.4 (42)	32.5; AUC is up to infinity
P00311; n=53	1.9 (31)	3.26 (55)	-	-	32.1 (36)
P00311; n=53	1.9 (36)	3.14 (59)	-	-	35.0 (78)
P00311; n=53	2.05 (36)	2.65 (55)	-	-	34.2 (35)
C98-214; n=20	2.18 (33)	4.5 (70)	29.4 (86)	-	78.0 (127)

Values are arithmetic means.
AUC tf represent AUC time to measurable concentration.
The values in parenthesis are CV %.

Desloratadine Dose7.5 mg single dose

Study number		Cmax (ng/ml)	Tmax (hour)	T1/2 (hour)	AUC 0-24 (ng.hr/ml	AUC tf (ng.hr/ml)
C98355 n=12		3.65 (31)	2.63 (65)	19.3 (17)	-	62.4 (36)
C98356 N=12 for each group	WM	3.46 (44)	3.04 (104)	27.5 (100)	-	59.7 (35)
	WF	3.57 (33)	2.54 (47)	20.7 (16)	-	65.8 (37)
	BM	3.0 (32)	5.58 (66)	30.6 (74)	-	44.6 (34)
	BF	4.05 (37)	3.42 (61)	23.1 (43)		53.3 (29)
C98354 n=8		2.95 (21)	5.50 (22)	54.3 (74)	-	181.0 (95)
C98215 n=17	Fasted	3.3 (36)	3.36 (60)	20.9 (86)	-	63.5 (45)
	fed	3.53 (33)	4.75 (108)	22.0 (100)	-	62.5 (40)
C98214 n=20		3.03 (31)	4.1 (72)	31.4 (80)	-	104.0 (93)
C98013 n=10		2.28 (31)	2.95 (41)	19.0 (24)	26.6 (29)	43.7 (40.7)

Values are arithmetic means.
AUC tf represent AUC time to measurable concentration.
The values in parenthesis are CV %.
W=Caucasian; B=Black; M=male; F=Female

Desloratadine Dose 10 mg single dose

Study Number	Cmax (ng/ml)	Tmax (hour)	T1/2 (hour)	AUC 0-24 (ng.hr/ml	AUC tf (ng.hr/ml)
C98-097 n=5	4.32	5.8	19.5	-	77.7
I97248 n=10	4.26 (73)	2.15 (68)	-	-	70.4 (75)
C98-013	4.08 (22)	2.95 (78)	34.6 (81)	55.0 (36)	71.1 (27)
C98214	3.8 (29)	4.4 (71)	31.7 (96)	-	126 (98)

Values are arithmetic means.
AUC tf represent AUC time to measurable concentration.
The values in parenthesis are CV %.

Desloratadine Dose 20 mg single dose

Study Number	Cmax (ng/ml)	Tmax (hour)	T1/2 (hour)	AUC 0-24 (ng.hr/ml	AUC tf (ng.hr/ml)
I97248 n=10	8.36 (22)	2.2 (66)	24.6 (70)		158 (92)
C98-013	7.08 (39)	3.95 (59)	19.2 (26)	97.5 (39)	169 (46)
C98214	8.08 (26)	3.9 (71)	32.3 (76)		290 (92)

Values are arithmetic means.
AUC tf represent AUC time to measurable concentration.
The values in parenthesis are CV %.

DCL 5 mg multiple dose

After Multiple dose		Cmax (ng/ml)	Tmax (hour)	T1/2	AUC (ng·hr/ml) 0-24
P00117; n=25		4.89 (72)	3.08 (72)	34.9 (93)	71.9 (107)
P00275	19-45 yrs (n=65)	3.83 (57)	3.35 (55)	25.3 (53	55.4 (83)
	46-64 yrs (n=30)	3.92 (46)	2.98 (56)	26.1 (13)	54.1 (43)
	65-70 yrs (n=17)	4.69 (44)	2.76 (63)	33.7 (62)	67.8 (72)
	Overall n=123	3.98 (52)	3.17 (56)	26.8 (50)	56.9 (73)
C98013; n=10		6.33 (95)	6.4 (20)	40.4 (85)	113 (107)

Values are arithmetic means.
The values in parenthesis are CV %.

DCL 7.5 mg Multiple dose

After Multiple dose		Cmax (ng/ml)	Tmax (hour)	T1/2	AUC (ng·hr/ml) 0-24
P00117 n=25		7.30 (75)	3.23 (86)	33.5 (79)	104.0 (105)
C98013 n=10		4.18 (19)	4.6 (29)	18.8 (18)	57.1 (28)
C98352 n=24		12.4 (61)	6.1 (65)	-	225.0 (74)
C98353 n=24		6.51 (54)	2.88 (63)	-	100.0 (78)
C98356	WM n=12	6.05 (99)	2.29 (82)	36.0 (51)	98.1 (136)
	WF n=12	5.46 (36)	2.5 (62)	29.9 (14)	74.5 (44)
	BM n=12	7.52 (103)	5.08 (57)	42.0 (53)	135.0 (122)
	BF n=12	6.73 (48)	3.33 (78)	35.4 (42)	107.0 (73)

Values are arithmetic means.
The values in parenthesis are CV %.
W=Caucasian; B=Black; M=male; F=Female

DCL 10 mg Multiple dose

After Multiple dose	Cmax (ng/ml)	Tmax (hour)	T1/2	AUC (ng·hr/ml) 0-24
C98013; n=10	7.81 (73)	9.5 (148)	37.4 (65)	135 (92)

Values are arithmetic means.
The values in parenthesis are CV %.

DCL 20 mg Multiple dose

After Multiple dose	Cmax (ng/ml)	Tmax (hour)	T1/2	AUC (ng·hr/ml) 0-24
C98013; n=10	12.3 (39)	4.35 (71)	26.7 (26)	185 (35)

Values are arithmetic means.
The values in parenthesis are CV %.

DCL 45 mg Multiple dose

After Multiple dose	Cmax (ng/ml)	Tmax (hour)	T1/2	AUC (ng·hr/ml) 0-24
C98-357 n=24	63.8 (85)	4.54 (58)	–	1057 (100)

LORATADINE 10 mg Multiple dose

After Multiple dose	Cmax (ng/ml)	Tmax (hour)	T1/2	AUC (ng·hr/ml) 0-24
P00117 n=25	6.03 (63)	1.25 (121)	32.7 (72)	74.9 (103)

Values are arithmetic means.
The values in parenthesis are CV %.

Q2. What is the "dose-systemic exposure relationship" ?

- Does increasing dose proportionally increase the systemic exposure?
- How is the systemic exposure after multiple doses compared to single dose?

Two single-dose studies and one multiple-dose study provides dose proportionality information for the dose – systemic exposure relationship from 2.5 to 20 mg.

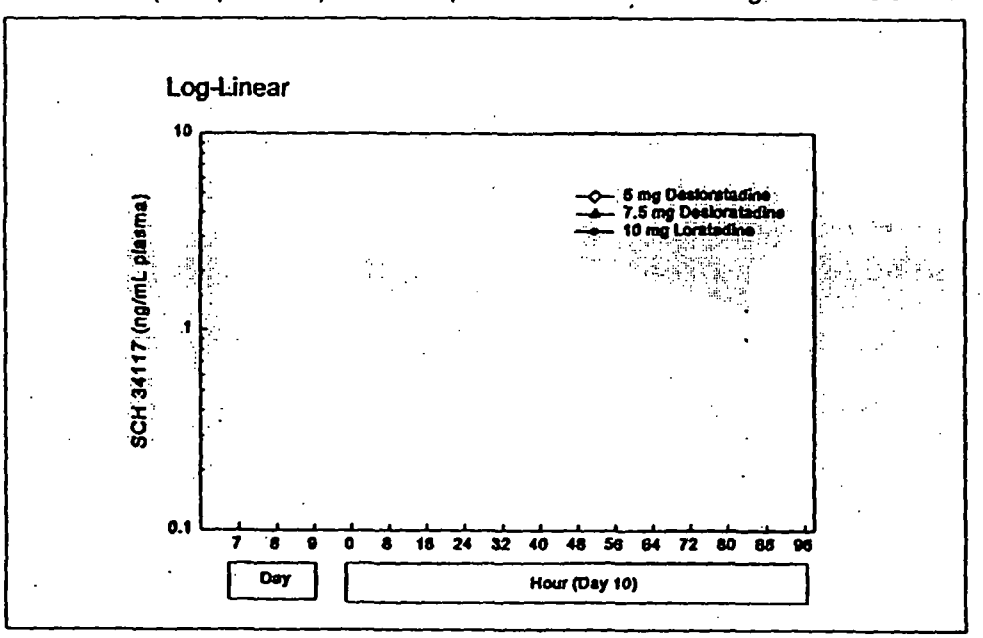
By linear regression of the mean Cmax and AUC values over dose, the dose proportionality has been shown in single-dose and multiple-dose studies (Refer to the above tables).

It could be concluded that, within the studied dose range, systemic exposure is proportionally increased by the dose.

After multiple dosing, the degree of accumulation of systemic exposure was 2.5 to 3.4 (please refer to the above discussion) agreed well with the theoretical value 2.4-2.5, indicating that the systemic exposure after multiple doses could be expected from single-dose data.

Q3. How does the DCL exposure after the administration of 5 mg DCL tablets compare to that after the 10 mg Claritin tablets administration?

A comparative study of systemic exposure after multiple doses has been conducted by a three-way cross over design (Study P00117). The results showed that the systemic exposure after 5 mg doses of DCL (multiple dose) were comparable to that after 10 mg dose of Claritin.



Based on the results, this reviewer is of the opinion that the available safety data after 10 mg Claritin oral administration may be used in the evaluation of the safety after 5 mg doses of DCL.

Q4. How does the systemic exposure relate to the untoward cardiac effects, such as ventricular rate, QRS, and QTc changes?

The relationship between systemic exposure and adverse effect were examined in the study C98357 using a 9-time DCL dose (45 mg) than proposed dose (5 mg).

The following table summarizes the results.

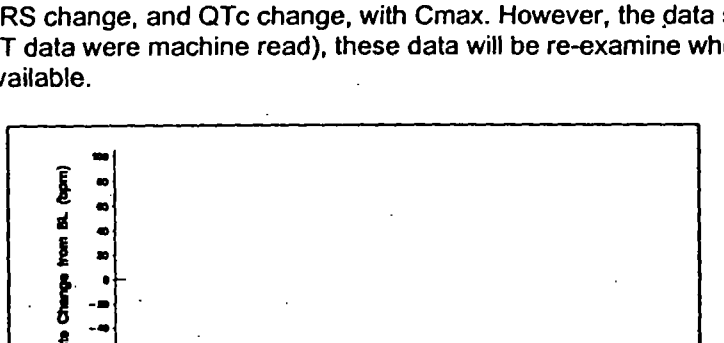
Table Mean Pharmacokinetic Parameters of Desloratadine (SCH 34117) and 3-OH Desloratadine (SCH 45581) on Day 10 (Protocol C98-357)

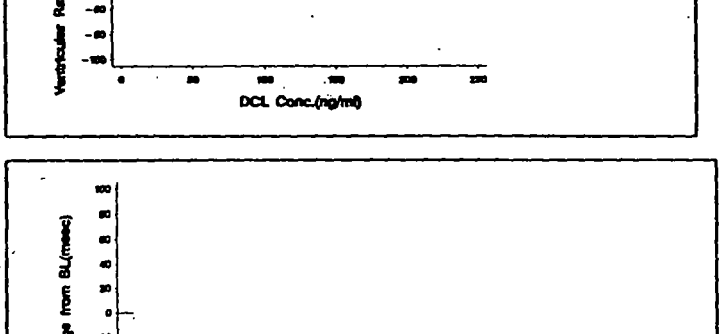
Parameter	Unit	SCH 34117	%CV	SCH 45581	%CV
Cmax	ng/mL	63.8	85	12.2	56
Cmax[a]	ng/mL	57.3	79	12.6	52
Cmax (geometric mean)	ng/mL	50.1	–	8.95	–
Tmax	hr	4.54	58	4.04	47
Tmax[a]	hr	4.52	59	3.96	48
Tmax (median)	hr	5.0	–	4.0	–
AUC(0-24hr)	ng·hr/mL	1057	100	185	52
AUC(0-24hr)[a]	ng·hr/mL	944	97	192	49
AUC(0-24hr)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

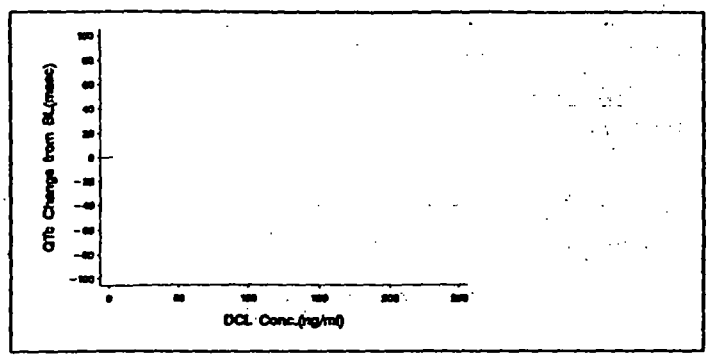
n=24
a: n=23, excluding Subject 22
%CV were not calculated for non-arithmetic means

The above Cmax and AUC were more than 10 times of those of 5 mg dose.

There appeared to be no apparent correlation of cardiac effects, i.e., ventricular rate change, QRS change, and QTc change, with Cmax. However, the data submitted were not optimal (e.g., QT data were machine read), these data will be re-examine when additional data became available.







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Q5. Should the dose be adjusted in renally impaired patients?

The degree of systemic exposure after a 7.5 mg DCL single dose was evaluated in various degrees of stable (i.e., nonacute and nonrapidly progressive) chronic renal insufficiency (CRI) and in patients with severe CRI who undergoe hemodialysis.

The following table summarizes the results.

	Group 1 (N=12) (CLcr: >80 ml/min)		Group 2 (N=7) (CLcr: 51-80 ml/min		Group 3 (N=6) (CLcr: 30-50 ml/min		Group 4 (N=6) (CLcr<30 ml/min)		Group 5 (N=6) (Hemodialysis dependent) Off dialysis	
	Arith. Mean	Median	Arith. Mean	Media	Arith. Mean	Median	Arith. Mean	Median	Arith. Mean	Median
Cmax [a]	3.65 (31)	3.41	4.56 b (35)	4.02	5.39 (48)	4.00	6.20 (21)	6.15	5.97 (47)	5.20
Cmax [b]			4.08 (25)		5.70 (44)					
Tmax [a]	2.63 (65)	2.00	4.64 (53)	6.00	4.00 (76)	4.00	2.42 (75)	2.00	2.58 (43)	3.00
Tmax [b]			4.50 (42)	6.00	3.2 (72)	2.00				
AUC tf [a]	62.4 (36)	55.1	160 (70)	105	132 (57)	93.5	143 (35)	138	116 (35)	109
AUC tf [b]			100 (48)		111 (51)					
T1/2 [a]	19.3 (17)	18.8 c	37.0 (84)	27.5	45.8 (101)	30.7	30.1 (18)	29.3		
CL/F [a]	2115 (26		1081(68)		1068 (56)		882 (37)		1037 (38	
CLcr [a]	107 (20)		60.7 (12)		39.2 (8)		19.0 (43)			

a: Unit: Cmax-ng/mL; AUC-ng-hr/mL; Tmax and tl/2-hr, CLF and CLcr-ml/min.
b: Excludes Subject Nos. 5 and 23 from the mild impairment group and Subject No. 1 1 from the moderate impairment group.
c: Harmonic mean tl/2.

The above results indicate that
(1) The systemic exposure is increased more than 2 times in the renal failure.
(2) DCL is not removed by hemodialysis.

Based on the results, this reviewer recommends the dose be reduced to half in renal patients.

Q6. Should the dose be adjusted in hepatically impaired patients?

The degree of systemic exposure after a single dose (7.5 mg DCL) was evaluated in various degrees of stable chronic liver disease.

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

a Median
b: Harmonic mean
c: Tmax for 2 subjects was within the first 1.5 hr and at least 12 hr for the other 2 subjects.
Mild=Child Pugh score 5-6; moderate=7-9; Severe=10-15

Subjects with hepatic dysfunction exhibited greater exposure (more than 2 times) to desloratadine than normal subjects.
Based on the results, this reviewer recommends that the dose be reduced to half in hepatic patients (Child-Pugh score ≥ 5).

Q7. Should the dose be adjusted in elderly?

Study P00275, a pivotal study, used 112 subjects for PK after multiple doses (5 mg QD for 10 days). The ages were between 19-70 years. Therefore, the subjects were divided by three age groups (19-45 years; n=65, 46-64 years; n=30, and 65-70 years; n=17), and the systemic exposure was compared.

Parameter[a]	Age Group: 19-45 yr[b] Mean (%CV)	Age Group: 46-64 yr[c] Mean (%CV)	Age Group: 65-70 yr[d] Mean (%CV)
		DL	
Cmax	3.83 (57)	3.92 (46)	4.69 (44)
Tmax	3.35 (55)	2.98 (56)	2.76 (63)
AUC(0-24 hr)	55.4 (83)	54.1 (43)	67.8 (72)
t1/2	25.3 (53)	26.1 (13)	33.7 (62)
CL/F·kg	20.4 (26)	16.8 (28)	19.7 (34)
		3-OH DL	
Cmax	1.92 (30)	2.12 (33)	2.05 (30)
Tmax	4.80 (41)	4.90 (34)	4.35 (48)
AUC(0-24 hr)	30.7 (30)	34.3 (32)	34.6 (30)
t1/2	34.7 (36)	35.6 (11)	41.8 (42)

a:Unit: Cmax-pg/mL; AUC-pg·hr/mL; Tmax and t1/2-hr; CL/F kg-mL/hr/kg
b:n=65
c:n=30
d:n=17

The mean Cmax and AUC values were 20 % greater in the elderly group (65-70 years of age) that in younger subjects (<65 years old).
This reviewer is of the opinion that dose adjustment is not warranted for elderly patients.

Q7. Should the dose be adjusted by gender/race?

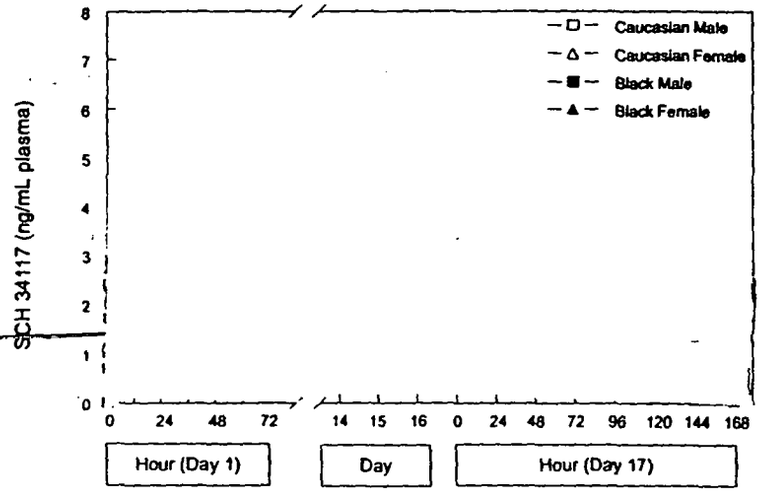
The sponsor conducted a multiple-dose study (7.5 mg dose QD) in 48 subjects (12 Caucasian males 12 Caucasian female, 12 black males, 12 black females) for evaluation of the systemic exposure (Study C98356).

On the average, the plasma exposure (Cmax and AUC) for DCL was higher in females compared with males. (10 % for Cmax and 3 % for AUC).

Mean pharmacokinetic parameters for DCL were higher in black compared with Caucasian subjects (18-32 %).

Based on the degree of difference, this reviewer is of the opinion that the dose adjustment may not be warranted by gender/race.

Linear:linear



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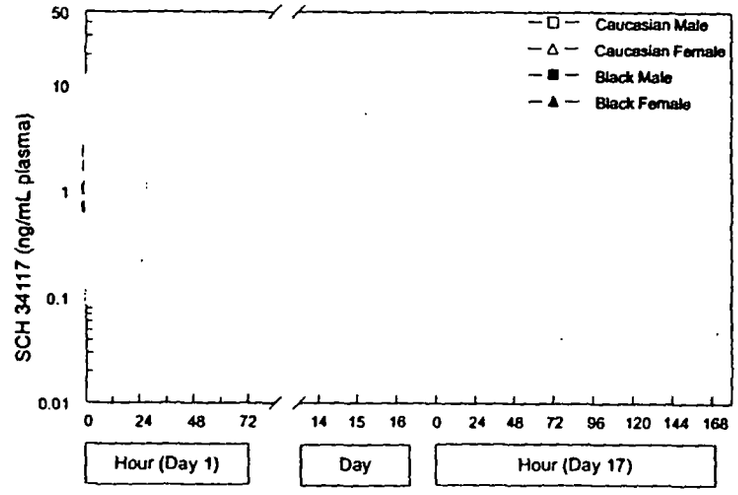


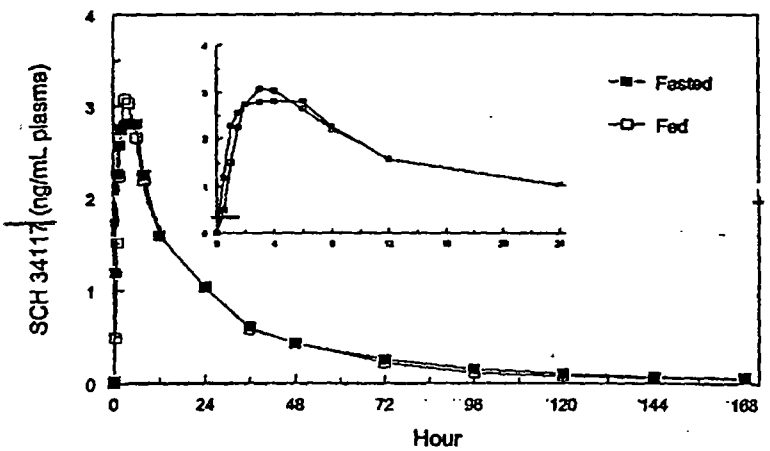
Q8. Is there any food effect on bioavailability of DCL?

Study C98215 was conducted to evaluate the food effect on DCL PK.

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

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

Linear:linear



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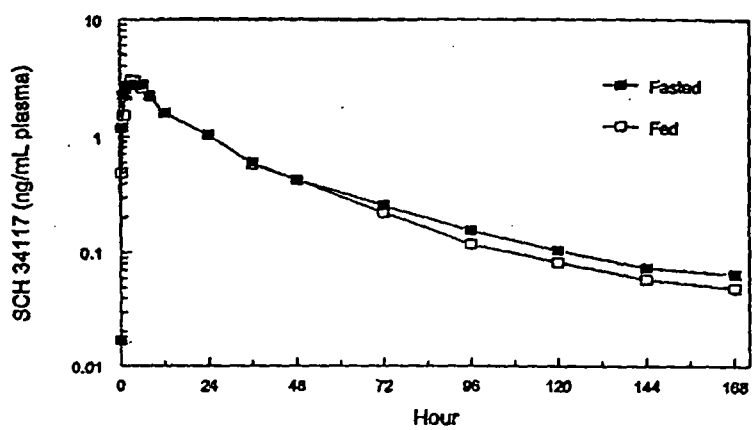


The above figure describes the mean plasma profiles of DCL with/without food.

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

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

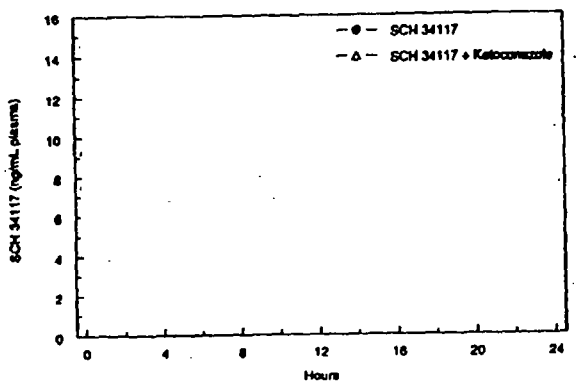
a: n=18
b: n=17
c: Ratio of the mean value for fed vs fasted. α=0.05 (two-tailed)
d: α=0.05 (two-tailed)

The results indicate that food had no effect on the oral bioavailability of desloratadine.

Q9. Is there any drug-drug interaction?

Two in vivo drug interaction studies have been conducted in normal healthy volunteers (n=24). DCL(7.5 mg QD) was coadministered with ketoconazole 200 twice daily or erythromycin 500 mg every eight hours for 10 days.

Linear:linear



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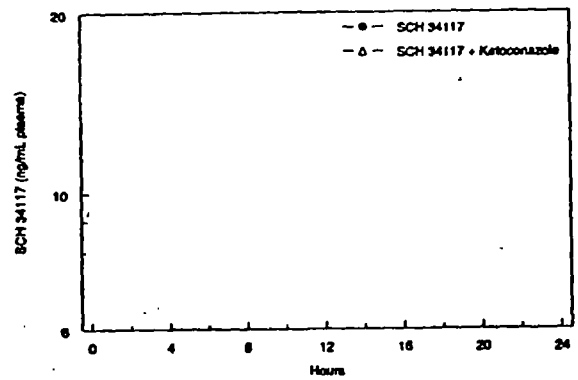


The mean pharmacokinetic parameters of desloratadine and 3-OH desloratadine on Day 10 are summarized below:

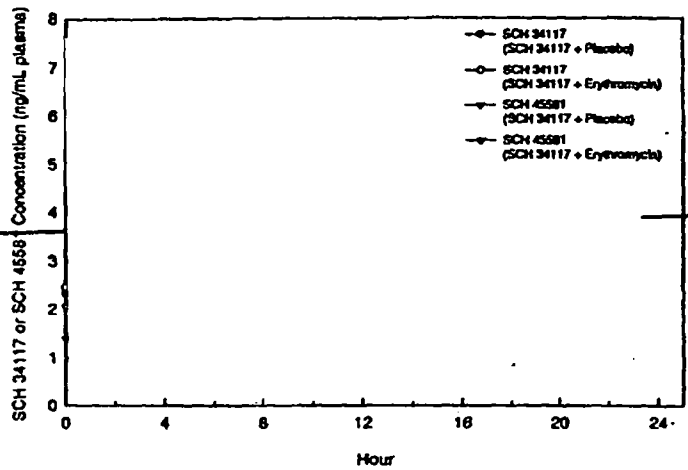
	Desloratadine					
	Treatment A Desloratadine with Placebo			Treatment B Desloratadine with Ketoconazole		
Parameter	Arithmetic Mean	%CV	Geometric Mean	Arithmetic Mean	%CV	Geometric Mean
Cmax (ng/mL)	12.4	61	10.1	15.8	63	13.1
Tmax[a] (hr)	6.10	65	5.5[a]	5.94	59	5.0[a]
AUC(0-24hr) (ng·hr/mL)	225	74	168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

a: Median Tmax.

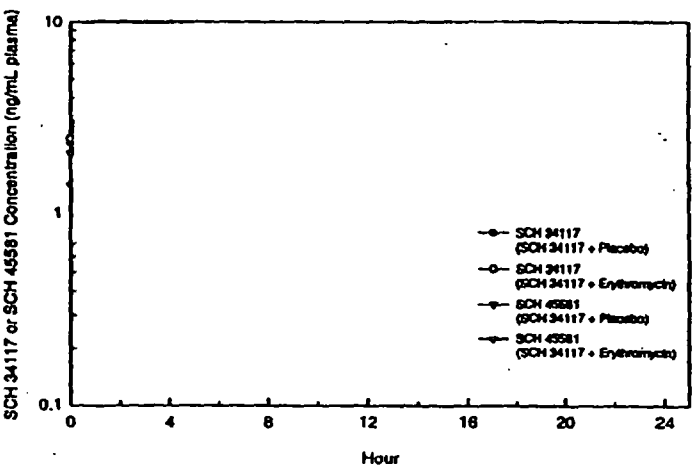
Desloratadine was slowly absorbed with a median Tmax value of 5 hours for both treatments. Steady-state geometric means for Cmax and AUC(0-24hr) of desloratadine and 3-OH desloratadine increased with concomitant administration of ketoconazole.

After Coadministration of ketoconazole, mean desloratadine Cmax and AUC 0-24 values at steady state were increased by 29-45 % % and 21-39 %, respectively.

Linear:linear



Log:linear



Above figures represent plasma profile with/without erythromycin coadministration.

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

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

a: Median Tmax.

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

After Coadministration of erythromycin, mean desloratadine Cmax and AUC 0-24 values at steady state were increased by 24 % % and 14 %, respectively.

These results suggest that there may be CYP3A4, p-glycoprotein (pGp), or other mechanisms of interactions. The degree of interaction also suggests that CYP3A4 is not the major metabolizing enzyme. This is consistent with in vitro findings.
Based on the degree of difference, this reviewer is of the opinion that the dose adjustment is not warranted by ketoconazole, erythromycin, or other CYP3A4 inhibitors.

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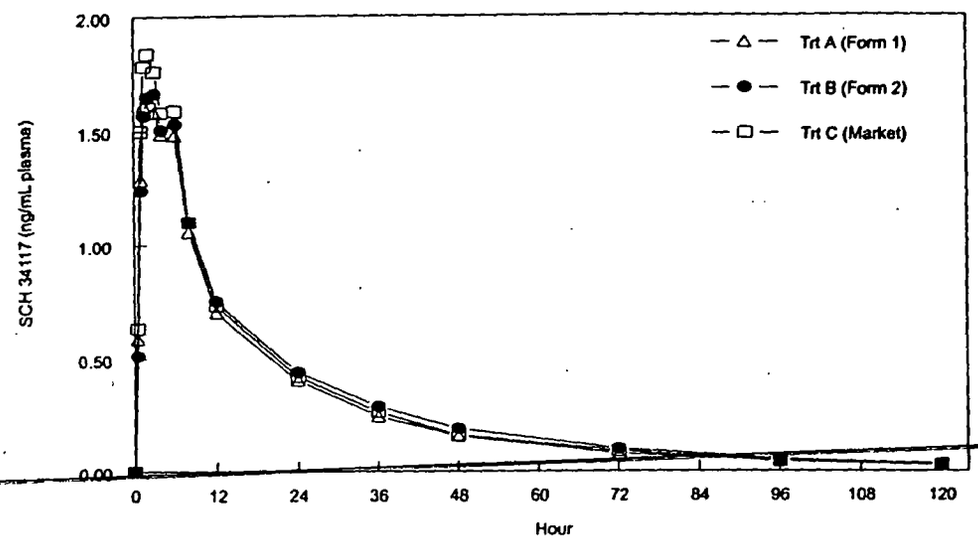
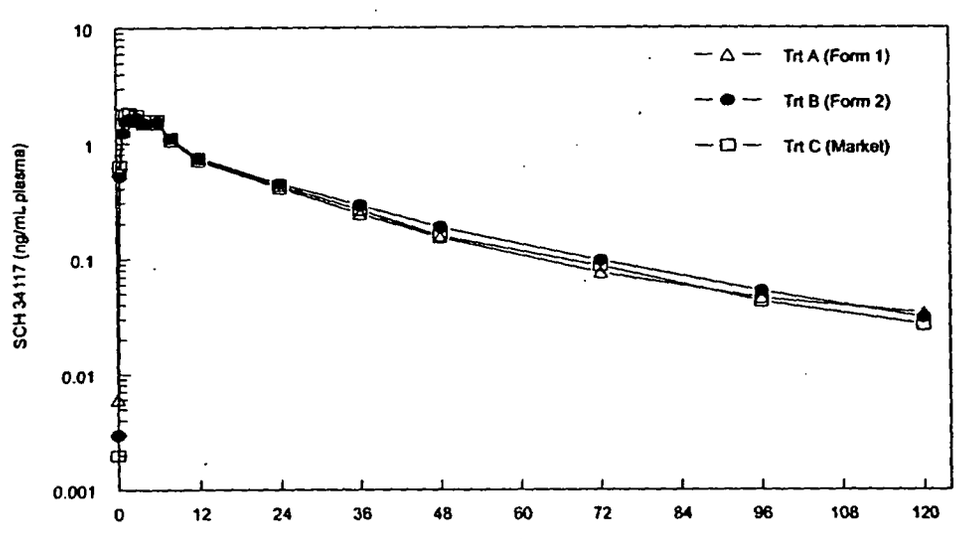
Q10. What is the impact of the polymorphism of DCL on pharmacokinetics

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

Linear:linear



Log:linear



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

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

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

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

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

- DL 5 mg tablet and DL 5 mg capsule (mainly DL polymorph Form 2) were bioequivalent.
- DL 5 mg capsule (mainly DL polymorph Form 1) and DL 5 mg capsule (mainly DL polymorph Form 2) were bioequivalent.

These results suggest the lack of pharmacokinetic relevance of the 2 solid state polymorphs of DL.

12. Dissolution

The following table compares the sponsor's proposed dissolution method and specification with this reviewer's recommendation:

Sponsor's proposal	Reviewer's recommendation
Method Apparatus: USP apparatus II (paddle) Speed: 50 rpm Temperature: 37 °C Medium: 0.1 N HCl Volume: 500 ml	Method is acceptable.
Specification Q=ζ ϒ% at 45 min	Q=ζ /% at 30 min

Following is the sponsor's rationale of the above proposal:
For apparatus: In a comparative dissolution study using both basket and paddle method at the same condition, i.e., in 0.1 N HCl at 50 rpm speed, the paddle method showed a slower dissolution profile than basket method, indicating better discriminating capability.(Refer to the attached figure)

Reviewer's comment: The selection of the paddle method is acceptable. This reviewer agrees with the sponsor's rationale.

For dissolution medium: The sponsor selected 0.1 N HCl as a medium by considering solubility and dissolution profile at various pH solution (0.02, 0.05, 0.1, 0.2, 0.5 N HCl, pH 4.5 of 0.05M sodium acetate buffer, pH 6.8 of 0.05M potassium phosphate buffer).

Time (min)	0.02 N HCl	0.05 N HCl	0.1 N HCl	0.2N HCl	0.5 N HCl	Na acetate Buffer pH 4.5	phosphate buffer pH 6.8
15	78±5	79±15	84±10	94±10	96±3	68±10	49±7
30	90±4	91±12	94±7	101±5	101±1	79±9	64±7
45	96±3	96±10	97±5	103±3	102±1	85±8	73±8
60	100±2	100±8	100±4	104±2	103±1	89±6	79±8

Please refer to the attached figure for comparison of average values.

Reviewer's comment: This reviewer is of the opinion that the selection of 0.1 N HCl as the dissolution medium is acceptable, considering the high solubility and similarity of in vivo condition. A large inter-tablet variability was observed in all the media.

For dissolution specification: The sponsor's rationale for the proposed specification (Q=ζ /% at 45 min) is to meet the following objectives: (1) a reasonable level of discrimination as evidenced

by periodic Stage 2 testing (approximately 10 %), (2) a performance standard set around the clinical batch, and (3) assurance of batch-to-batch consistency of the "to-be-marketed product"

Reviewer's comment:
Upon reviewing the dissolution data of biobatch (See following table), this reviewer recommends a dissolution specification of Q= % at 30 min for desloratadine tablet. The stability data (Please refer to the attached graph extracted from the review of Chemist (Dr. Swiss)) are supportive Q= % at 30 min.

Individual Dissolution Release Data for pivotal biobatch 38833-142 (Tested on 5/11/98)

Tablet	15 min	30 min	45 min	60 min
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	88	99	102	104
Range				

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Appendix 1. Summary of individual study

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Title of the Study: SCH 34117: A Multiple-Dose Pharmacokinetic Evaluation of Desloratadine in Healthy Subjects Differing in Gender and Race (C98-356)

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

Studied Period: 15 SEP 1998 – 21 DEC 1998

Clinical Phase: I

Objective(s): To characterize the multiple-dose pharmacokinetic profile of desloratadine following administration of desloratadine 7.5 mg to healthy subjects differing in gender and race.

Methodology: Open-label, multiple-dose, parallel-group study. Forty-eight (48) healthy subjects (12 caucasian males, 12 black males, 12 caucasian females, 12 black females). ECGs were recorded on Day – 1 (Baseline), Day 1, daily on Days 4-17 and on Day 24 (follow-up). Blood samples were collected at pre-specified times for pharmacokinetic (PK) and safety evaluations. Vital signs were obtained at pre-specified times for safety evaluation. Volunteers were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events.

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

Number of Subjects: Forty-eight healthy subjects (24 male and 24 female)

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

Test Product, Dose, Mode of Administration, Batch No(s): SCH 34117, 7.5 mg tablets, Batch No. 38833-140. Treatments were administered orally.

Reference Therapy: None.

Duration of Treatment: SCH 34117 7.5 mg administered once on Day 1 and daily in the morning on Days 4-17.

Criteria for Evaluation: Blood samples were collected for determination of pharmacokinetic parameters (AUC and Cmax) for desloratadine and 3-OH desloratadine.

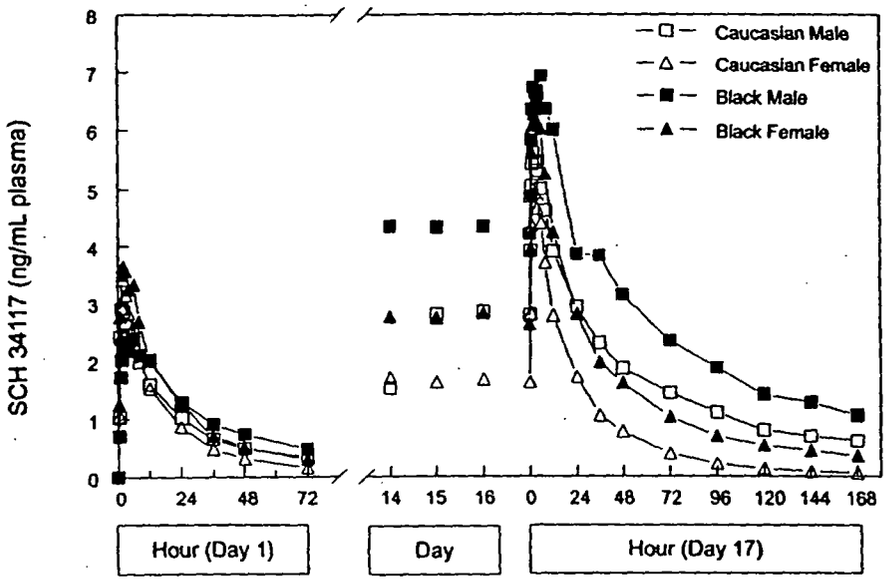
Statistical Methods:
Summary statistics, means and standard deviations, are provided for the concentration data at each timepoint and the PK parameters. The PK parameters (log transformed AUC and Cmax) were analyzed using an ANOVA model extracting effects due to gender, race and the gender race interaction. The difference between males and females (gender effect) and between Caucasian and Blacks (race effect) were the comparisons of interest. The 90% confidence intervals for the difference between gender and between races and the power to detect a 20% difference (a=0.05, two-tailed) were computed. Steady state was assessed using and ANOVA model, extracting effects due to subject and day for the Cmin concentrations from Days 14 to 17.

RESULTS:
Subject Disposition: Forty-eight subjects were enrolled and completed treatment.

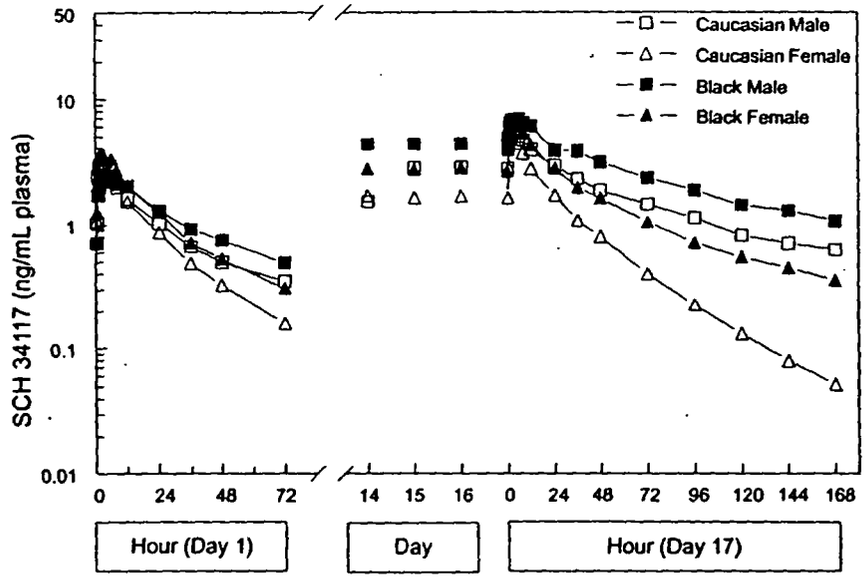
Demographic and Baseline Characteristics: Forty-eight volunteers [24 males (12 Caucasian, 12 Black) and 24 females (12 Caucasian, 12 Black)] between the ages of 19 and 45 years (mean = 32.4 years) and weighing between 50.5 and 108 kilograms (mean = 72.5 kg) were enrolled into the study. All subjects were determined to be in good health.

Pharmacokinetics:
Mean Plasma profiles of DCL after oral administraiton of DCL 7.5 mg tablet described in the following figurres.

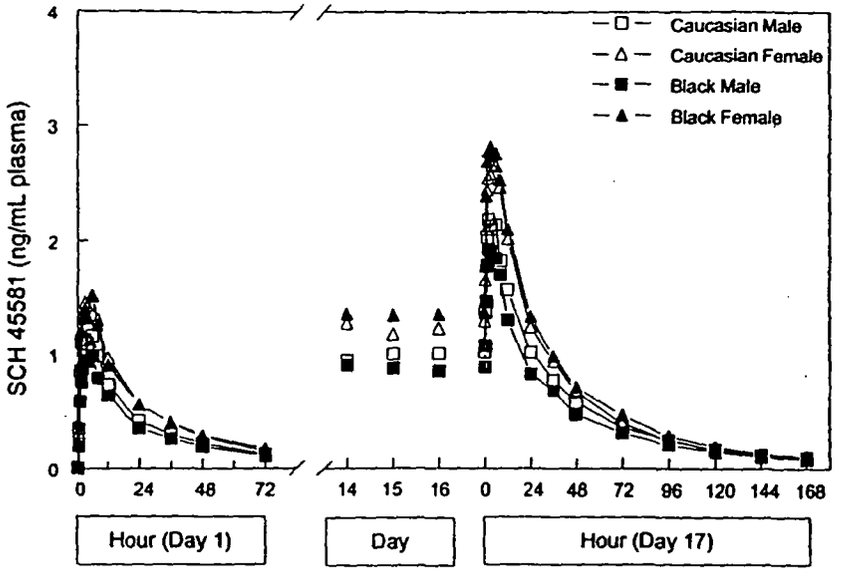
Linear:linear



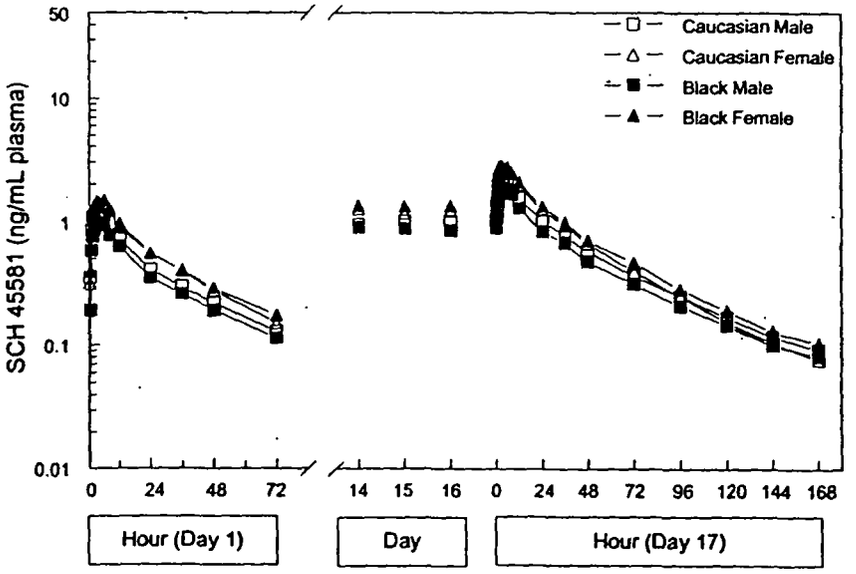
Log:linear



Linear:linear



Log:linear



Above figure reprents the mean Plasma SCH 45581 Concentration-Time Profiles after 7.5 mg SCH 34117 Single and Once Daily Oral Dosing to Healthy Adult Subjects Differing in Gender and Race.

Single-Dose Pharmacokinetics: The associated arithmetic (% CV) and geometric mean derived pharmacokinetic parameters for desloratadine and 3-OH desloratadine following a single-dose are presented in the table.

Subjects Differing in Gender and Race								
	Caucasian				Black			
	Male (n=12)		Female (n=12)		Male (n=12)		Female (n=12)	
Parameter[a] (Single Dose)	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean
				SCH 34117				
Cmax	3.46 (44)	3.13	3.57 (33)	3.40	3.00 (32)	2.86	4.05 (37)	3.83
AUC(0-24 hr)	41.2 (37)	38.7	42.2 (31)	40.6	44.6 (34)	42.5	53.3 (29)	51.3
AUC(I)	59.7[b] (35)	56.7[b]	65.8 (37)	62.1	67.9[c] (36)	64.8[c]	81.0[d] (32)	77.2[d]
Tmax	3.04 (104)	1.75[e]	2.54 (47)	2.00[e]	5.58 (66)	2.00[e]	3.42 (61)	3.00[e]
t1/2	27.5 (100)	20.7[f]	20.7 (16)	20.3[f]	30.6 (74)	23.7[f]	23.1 (43)	21.1[f]
				SCH 45581				
Cmax	1.45 (49)	1.19	1.66 (26)	1.61	1.07 (63)	0.692	1.62 (49)	1.36
AUC(0-24 hr)	18.5 (39)	15.8	23.8 (25)	23.1	15.4 (56)	10.4	23.0 (38)	20.0
AUC(I)	38.0[b] (25)	37.0[b]	44.3 (29)	42.6	35.8[c] (26)	34.6[c]	48.6[d] (32)	46.6[d]
Tmax	3.46 (71)	3.00[e]	4.50 (42)	4.00[e]	5.92 (44)	6.00[e]	5.00 (43)	6.00[e]
t1/2	33.2 (53)	29.5[f]	24.9 (16)	24.3[f]	52.1 (103)	34.0[f]	30.5 (45)	27.9[f]

a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax and t1/2-hr.
b: n=11 [Excluding Subject 27. This subject was excluded because the extrapolated area (from time tf to infinity) was >25% of AUC(tf)].
c: n=10 [Excluding Subjects 4 and 13. These subjects were excluded because the extrapolated area (from time tf to infinity) was >25% of AUC(tf)].
d: n=11 [Excluding Subject 19. This subject was excluded because the extrapolated area (from time tf to infinity) was >25% of AUC(tf)].
e: Median Tmax.
f: Harmonic mean t1/2.

The PK parameters (Cmax and AUC) for both analytes showed moderate intersubject variability (25-3%CV). Four subjects (1 Caucasian male, 2 black males, 1 black female) showed concentrations of desloratadine which were higher than the majority of the group. There was no correlation between the predicted phenotype (rapid metabolizer) for CYP2D6 and CYP2C19 and desloratadine metabolizing capacity.

The results of the statistical evaluation are summarized in the table below.

Analyte	Parameter[a] (Single Dose)	Degrees of Freedom	Female (n=24)	Male (n=24)	Ratio (Female/Male)	90% Confidence Interval[b]
SCH 34117	Cmax	44	3.61	2.99	121	101 – 145
	AUC(I)	40[d]	69.2	60.6	114	97 – 135
SCH 45581	Cmax	44	1.48	0.907	163	107 – 249
	AUC(I)	40[d]	44.5	35.8	124[c]	108 – 143

			Black (n=24)	Caucasian (n=24)	Ratio (Black/Caucasian)	
SCH 34117	Cmax	44	3.31	3.26	101	85 – 122
	AUC(I)	40[d]	70.7	59.3	119	101 – 141
SCH 45581	Cmax	44	0.970	1.38	70	46 – 107
	AUC(I)	40[d]	40.2	39.7	101	88 – 116

a: Unit: Cmax-ng/mL; AUC(I)-ng·hr/mL
b: 90% confidence interval based on log-transformed data
c: Statistically significant, p=0.012
d: Subjects 4, 13, 19 and 24 excluded.

With the exception of Cmax for SCH 45581, the ratio of females/males and Blacks/Caucasian was less than 25%.

Multiple-Dose Pharmacokinetics: Cmin values (0 hour) for Days 14 through 17 were analyzed for each group for attainment of steady state. The results indicate that steady state was attained by Day 15 (11 doses) following once daily dosing.

The arithmetic (% CV) and geometric mean derived pharmacokinetic parameters after multiple dosing (daily x 14 days) are provided below.

	Caucasian				Black			
	Male (n=12)		Female (n=12)		Male (n=12)		Female (n=12)	
Parameter[a] (Multiple Dose)	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean
				SCH 34117				
Cmax	6.05 (99)	4.80	5.46 (36)	5.21	7.52 (103)	5.57	6.73 (48)	6.19
AUC(0-24 hr)	98.1 (136)	68.3	74.5 (44)	69.2	135 (122)	88.8	107 (73)	92.4
Tmax	2.29 (82)	2.00[b]	2.50 (62)	2.00[b]	5.08 (57)	5.00[b]	3.33 (78)	2.00[b]
t1/2	36.0 (51)	31.8	29.9 (14)	29.4[c]	42.0 (53)	36[c]	35.4 (42)	32.6[c]
R	1.13 (39)		1.14 (12)		1.24 (49)		1.16 (28)	
				SCH 45581				
Cmax	2.31 (34)	2.14	2.85 (21)	2.79	2.09 (54)	1.73	2.98 (33)	2.78
AUC(0-24 hr)	38.1 (32)	36.0	48.1 (22)	47.0	32.7 (44)	28.7	50.6 (31)	47.9
Tmax	5.04 (123)	2.50[b]	4.67 (47)	4.00[b]	4.17 (41)	3.5[b]	3.75 (49)	3.5[b]
t1/2	47.7 (46)	43[c]	36.5 (12)	35.9[c]	51.7 (55)	44.8[c]	46.2 (74)	38.4[c]
R	1.25 (53)		1.11 (12)		1.65 (86)		1.28 (43)	

a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax and t1/2-hr.
b: Median Tmax
c: Harmonic means t1/2.

The mean degree of accumulation of desloratadine and 3-OH desloratadine was similar between the groups, and ranged from 1.1 to 1.6. This degree of accumulation was judged not to be clinically relevant. Statistical evaluation of the PK parameters following QD dosing for 14 days are summarized in the table below.

Analyte	Parameter[a] (Multiple Dose)	Degrees of Freedom	Female (n=24)	Male (n=24)	Ratio (Female/Male)	90% Confidence Interval[b]
SCH 34117	Cmax	44	5.68	5.17	110	85 – 143
	AUC(0-24 hr)	44	80.0	77.9	103	75 – 140
SCH 45581	Cmax	44	2.79	1.93	145[c]	114 – 183
	AUC(0-24 hr)	44	47.5	32.1	148[d]	121 – 181

			Black (n=24)	Caucasian (n=24)	Ratio (Black/Caucasian)	90% Confidence Interval[b]
SCH 34117	Cmax	44	5.87	5.00	118	91 – 152
	AUC(0-24 hr)	44	90.6	68.8	132	97 – 179
SCH 45581	Cmax	44	2.20	2.45	90	71 – 114
	AUC(0-24 hr)	44	37.1	41.1	90	74 – 110

a: Unit: Cmax-ng/mL; AUC(0-24 hr) -ng·hr/mL
b: 90 % confidence interval based on log-transformed data
c: Statistically significant, p=0.011
d: Statistically significant, p=0.002

On average the gender/race differences for desloratadine were generally not more than 35%. The exception is 3-OH desloratadine where female levels were 45-50% higher than males.

Safety: Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects. Overall, 11 of 48 (23%) subjects reported treatment-emergent adverse events. The most frequently reported adverse event was headache. The incidence of reported adverse events was similar by race (Caucasian 21% and Blacks 25%). Female subjects reported more adverse events than male subjects (38% vs 8%), respectively. The most common adverse event reported by female subjects was headache.

No subject discontinued participation in the study due to adverse events and no intervention was required to treat any adverse event .

SPONSOR'S CONCLUSIONS:

- Multiple oral doses of desloratadine 7.5 mg administered to healthy adults differing in gender and race was safe and well tolerated.
- On average, pharmacokinetic parameters (AUC, Cmax) for desloratadine and 3-OH desloratadine were higher in females (3-10% and 45-48%, respectively) compared with males.
- Mean pharmacokinetic parameters (AUC, Cmax) for desloratadine were higher in Black compared with Caucasian subjects (18-32%), while 3-OH desloratadine pharmacokinetic parameters were lower (10%).
- Comparison of the AUC and Cmax values following 14 days of treatment with desloratadine indicate that no dose adjustment is needed for race or gender.

REVIEWRE'S COMMENTS:

The sponsor conducted the present study appropriately. The data are acceptable.
This reviewer agrees with the sponsor's conclusion.

Title of Study: SCH 34117: Single Dose Pharmacokinetics of SCH 34117 in Subjects With Various Degrees of Chronic Renal Insufficiency (C98-355)

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

Study Center(s): Orlando, USA

Studied Period: 9 DEC 98 - 16 NOV 99
Clinical Phase: I

Objective(s): The primary objective of this single-dose study was to evaluate the pharmacokinetics of desioratadine (DL) and 3-OH desloratadine (3-OH DL) in subjects with normal renal function and with various degrees of stable (ie, nonacute and nonrapidly progressive) chronic renal insufficiency (CRI) and in patients with severe CRI who are undergoing hemodialysis.
The secondary objective of this study was to evaluate the safety and tolerability of single doses of desloratadine in subjects with chronic renal insufficiency based on safety laboratory tests and reported adverse events.

Desgn/ procedure: This was a Phase 1, open-label, single-dose, parallel-group study of desioratadine in healthy volunteers and those with various degrees of chronic renal insufficiency including severe CRI (those who require hemodialysis). During Screening, subjects were confined for approximately 36 hours for the determination of creatinine clearance. After a Screening phase of up to 3 weeks, subjects were admitted within 24 hours prior to dosing (Day -1). After receiving a single-dose of desioratadine, subjects in Groups 1-4 were followed for 96 hours (confined for 48 hours; at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hr); subjects in Group 5 were followed for 72 hours following the nonhemodialysis and the hemodialysis periods (confined for 48 hours in each period). Additional blood samples were collected from group 5 subjects (period 2) during dialysis at 4.5, 5, 6, 7,8, (or end of dialysis), 8.25, 8.5, and 9 hours post dose.Arterial blood samples were collected from Group 5 subjects during dialysis at 4.5, 5, 6, 7, and 8 hours (or end of the dialysis) post dose for determination of plasma of DL and 3-OH DL concentrations.

Number of Subjects: A total of 37 adult subjects (12 normal, 7 mild, and 6 subjects in each of the remaining CRI group) were empanelled for this study.

Diagnosis and Criteria for Inclusion: Subjects with chronic renal insufficiency (N=25) or with normal renal function (N=12) between the ages 18-70 years were included. Subjects were assigned to the following treatment groups based upon creatinine clearance (CLCr).

Group	Creatinine Clearance		N
1	Creatinine clearance >80 mUmin/1.73M2		12
2	Creatinine clearance 51-80 mUmin/1.73M2	inclusive	7
3	Creatinine clearance 30-50 mUmin/1.73M2	inclusive	6
4	Creatinine clearance <30 mUmin/1.73M2	inclusive	6
5	Subjects who are hemodialysis-dependent		6

Test Product, Dose, Mode of Administration, Batch No(s): Desioratadine tablets, 7.5 mg, oral, Batch No. 38833-140.

Duration of Treatment: Single-dose administered in AM Day 1. Group 5 treated in Periods 1 and 2.

Criteria for Evaluation: The primary pharmacokinetic endpoints were the following parameters; Cmax, Tmax and AUC time 0 to the last measureable concentration time point (AUCtf). In addition, the amount of drug removed during hemodialysis and the degree of plasma protein binding were determined. Safety

was assessed based on the result of the Screening and post study physical examinations, laboratory safety tests, vital signs and adverse experiences.

Statistical Methods: Summary statistics including means, standard deviations, coefficients of variation for the means were provided for the pharmacokinetic parameters. Means, standard deviations and %CV were also reported for the concentration data at each time point. Linear regression analysis was used to explore the relationship between creatinine clearance (CLcr) and apparent total plasma clearance (CL/F) of DL.

Clinical Pharmacology:

Subject Disposition: All 37 subjects enrolled completed treatment.

Subject Demography: Twenty five Caucasians, 9 Blacks, 1 Asian and 2 Hispanics between the ages of 26 to 70 years and weighing between 49 kg and 116 kg participated in the study. There were 26 males and 11 females. The mean age and weights were similar for all groups.

Pharmacokinetics: The mean (%CV) and median DL pharmacokinetic parameters for Groups 1 to 5 are provided in the table below:

	Group 1 (N=12) (CLcr: >80 mumin)		Group 2 (N=7) (CLcr: 51-80 mumin		Group 3 (N=6) (CLcr: 30-51 mumin		Group 4 (N=6) (CLcr<30 mumin)		Group 5 (Hemodialysis dependent) Off dialysis	
	Arith. Mean	Median	Arith. Mean	Media	Arith. Mean	Median	Arith. Mean	Median	Arith. Mean	Median
Cmax [a]	3.65 (31)	3.41	4.56 b (35)	4.02	5.39 (48)	4.00	6.20 (21)	6.15	5.97 (47)	5.20
Cmax [b]			4.08 (25)		5.70 (44)					
Tmax [a]	2.63 (65)	2.00	4.64 (53)	6.00	4.00 (76)	4.00	2.42 (75)	2.00	2.58 (43)	3.00
Tmax [b]			4.50 (42)	6.00	3.2 (72)	2.00				
AUC tf [a]	62.4 (36)	55.1	160 (70)	105	132 (57)	93.5	143 (35)	138	116 (35)	109
AUC tf [b]			100 (48)		111 (51)					
T1/2 [a]	19.3 (17)	18.8 c	37.0 (84)	27.5	45.8 (101)	30.7	30.1 (18)	29.3		
CL/F [a]	2115 (26		1081(68)		1068 (56)		882 (37)		1037 (38	
CLcr [a]	107 (20)		60.7 (12)		39.2 (8)		19.0 (43)			

a: Unit: Cmax-ng/mL; AUC-ng-hr/mL; Tmax and tl/2-hr, CUF and CLcr-mUmin.

b: Excludes Subject Nos. 5 and 23 from the mild impairment group and Subject No. 1 1 from the moderate impairment group.

c: Harmonic mean tl/2.

Three subjects (2 with mild renal impairment and 1 with moderate impairment) had higher exposure to D but lower 3-OH DL than other subjects in the groups. The DL exposure was in the same range as subjects in other studies with normal renal function who were classified as slow metabolizers. The relationship between CUF and CLcr explains 49% of the variability. This value increased to 55% when the slow metabolizers were excluded. For DL, median AUC and Cmax values were higher for subjects with renal impairment than for subjects with normal renal function. However, for normal metabolizers, there was considerable ovedap between the individual Cmax and AUC values. There was little difference between the responses for subjects with mild (Group 2) and moderate (Group 3) impairment. In severe renal impairment the increase in median was -1.8- fold for Cmax and -2.5-fold for AUC. The arithmetic (%CV) mean and median 3-OH DL pharmacokinetic parameters are summarized below:

	Group 1 (N=12) (CLcr: >80 mumin)		Group 2 (N=7) (CLcr: 51-80 mumin		Group 3 (N=6) (CLcr: 30-51 mumin		Group 4 (N=6) (CLcr<30 mumin)		Group 5 (Hemodialysis dependent) Off dialysis	
	Arith. Mean	Median	Arith. Mean	Media	Arith. Mean	Median	Arith. Mean	Median	Arith. Mean	Median
Cmax [a]	1.63 (25)	1.65	1.06(55)	1.30	1.74(61)	1.72	1.79 (33)	1.76	1.42(50)	1.35
Cmax [b]			1.39(9)		2.04(37)					
Tmax [a]	4.33 (48)	6.00	15.0(168)	6.00 d	3.92(61)	4.5	4.83(79)	3.50	3.42(44)	3.00
Tmax [b]			5.00(25)	6.00	3.50(61)	3.00				
AUC tf [a]	40.0 (21)	39.9	26.7(45)	33.2	44.5(44)	48.0	61.6(50)	56	34.4(43)	29.2
AUC tf [b]			33.6(9)		51.3(20)					
T1/2 [a]	25.6 (12)	25.4 c	43.8(63)	34.7 c	51.6(86)	36.5	35.4(13)	34.8		
AUC tf Ratio a,d	68.3 (28)		28.7(71)		44.4(57)		44.0(40)		35.7 (75)	

a: Unit: Cmax-ng/mL; AUC-ng-hr/mL; Tmax and tl/2-hr; AUC(tf) ratio-%.
b: Excludes Subject Nos. 5 and 23 from the mild impairment group and Subject No. 1 1 from the moderate impairment group.
c: Harmonic mean tl/2.
d Calculated as the ratio of AUC(tf) of 3-OH DL to DL.

The changes in pharmacokinetics of 3-OH DL were minimal in subjects with renal insufficiency when compared with subjects with normal renal function.
The mean amount of DL removed during the 4-hour dialysis was low (0.3% of the dose) which is consistent with no or minimal difference in arterial and venous concentration-time profiles during dialysis. Plasma protein binding of DL was unaltered by renal impairment (renal impairment: mean 81%-84% bound vs. normal renal function: 83% bound). Similarly, there was no change for 3-OH DL (renal impairment: mean 86% bound vs. normal renal function: 87% bound).

Safety: Six (16%) of the 37 subjects reported at least one adverse event (AE) in this study. Most adverse events were mild to moderate in severity; one unrelated, serious adverse event requiring hospitalization (exacerbation of chronic obstructive pulmonary disease) was reported. No adverse events were reported by subjects in Groups 1 and 2. The follow-up physical examination and vital signs for all patients were within the ranges seen in adult. No patients showed any clinically relevant changes in his follow-up ECG compared with Screening. There were also no clinically relevant changes in clinical laboratory safety test results reported for any subject.

SPONSOR'S CONCLUSIONS:
Subjects with chronic renal insufficiency including dialysis-dependent experienced a 1.7 to 2.5 fold increase in DCL median AUC with minimal change in 3-OH DCL concentrations.

Both Cmax and AUC of DL increased (<9.5-fold) in subjects with renal dysfunction following a single oral 7.5 mg desioratadine as tablet.

DL and 3-OH DL were not removed by hemodialysis.

Slow metabolizers with renal dysfunction (mild and moderate) had AUC values of DL comparable to slow metabolizers with normal renal function in other studies.

Protein binding of DL and 3-OH DL was unaltered in subjects with impaired renal function.

REVIREWER' COMMENT

The systemic exposure is increased 2 fold in renal patients. Since DCL is not removable by hemodyalisis, this reviewer recommends the dose should be reduced to half in renal patients group.
The results from this study should be stated in package insert under Precautions, and Dosage and Administratin section as described in Claritin labeling.

APPEARS THIS WAY
ON ORIGINAL

Title of the Study: SCH 34117: Evaluation of the Pharmacokinetics of Desloratadine and 3-OH Desloratadine (Protocol No. P00117).

Investigator(s): Regine Rouzier-Panis, M.D.

Studied Period: 11 Feb 99 – 08 May 99

Clinical Phase: I

Objective(s): To characterize the pharmacokinetic profile of desloratadine (DL), 3-OH desloratadine (3-OH DL, SCH 45581) and 3-OH DL glucuronide following multiple-dose administration of 5 mg and 7.5 mg DL and 10 mg loratadine tablets.

Methodology: Randomized, three-way crossover, open-label, multiple-dose study. Twenty-four (24) healthy subjects (18 males and 6 females) each received multiple-dose treatment during three separate treatment periods. The order in which subjects received treatments was assigned according to a computer-generated random code provided by SPRI. Blood samples were collected at pre-specified times for pharmacokinetic and safety evaluations. ECGs were recorded on Day –1 (Baseline), and on Day 1 (follow-up). Vital signs were obtained at pre-specified times for safety evaluation. Volunteers were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events. Plasma samples were assayed for DL, 3-OH DL and loratadine using assays (LOQ= ng/mL). Total 3-OH concentrations (glucuronide conjugate plus free) were determined using method with LOQ of ng/mL.

Number of Subjects: Twenty-five healthy subjects (18 males and 7 females) were enrolled and 24 subjects completed all 3 treatment periods.

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

Test Product, Dose, Mode of Administration, Batch No(s): DL 5.0 and 7.5 mg tablets, Batch Nos. 38833-142 and 38833-140 respectively. Treatments were administered orally.

Reference Therapy, Dose, Mode of Administration, Batch No(s): SCH 29851 (Claritin) 10 mg tablets, Batch 8026. Treatment was administered orally.

Duration of Treatment: All treatments were administered for 10 days during each of the 3 treatment periods. Each treatment period was separated by at least a 14 day washout period.

Criteria for Evaluation: Blood samples were collected over 96 hours for determination of pharmacokinetic parameters (AUC and Cmax) on Day 10. Pending possible determination of DL, 3-OH DL, 3-OH-DL glucuronide, urine samples were obtained over 12 hours prior to and 24 hours after completion of each treatment period.

Statistical Methods: The derived pharmacokinetic parameters were statistically analyzed using a crossover analysis of variance model. The effects due to subject, period and treatment were to be extracted. Pairwise comparisons were also provided. No adjustment was made for multiple comparisons.
The bioavailability of DL, 3-OH DL and 3-OH DL glucuronide following administration of 5 and 7.5 mg DL compared to l0 mg loratadine was expressed as the ratio of the treatments, based on log-transformed AUC and Cmax values.
Confidence intervals for these estimates of bioavailability and the power to detect a 20% difference between treatment means for an α level of 0.05 (two-tailed) were computed. The pooled residual error and associated degrees of freedom from the analyses of variance was used in the calculation of the confidence interval and power.
Summary statistics for DL, 3-OH DL, 3-OH DL glucuronide and loratadine, e.g., means and standard deviations were provided for the concentration data at each time point and the pharmacokinetic parameters.

RESULTS:
Clinical Pharmacology:
Subject Disposition: Twenty-five subjects (18M/7F) were enrolled into the study and 24 subjects (18M/6F)

completed all 3 treatment periods. Subject No. 18 dropped out of the study after receiving 2 doses in treatment period 1 for reasons not associated with an adverse event. This subject is included in the safety analysis only.

Demographic and Baseline Characteristics: Twenty-five subjects (18M/7F) between the ages of 19 and 41 years inclusive (mean = 26.0 years) with body mass index between 19-27 (mean = 22.2) were enrolled into the study. Twenty subjects were Caucasian, 4 were Black and 1 was Asian.

Pharmacokinetics: Cmin values (0-hr) for Days 7 through 10 were analyzed for DL, 3-OH DL, 3-OH DL glucuronide and loratadine (following administration of Claritin®) for each treatment.

Day	5 mg DL		7.5 mg DL		10 mg Loratadine	
	DL (ng/mL)[a]					
7	1.37	(128)	2.76	(117)	1.79	(135)
8	1.78	(144)	2.53	(127)	2.16	(160)
9	1.85	(142)	2.70	(135)	1.99	(143)
10	1.86	(143)	2.25	(140)	2.08	(140)
	3-OH DL (ng/mL)[a]					
7	0.56	(47)	0.79	(55)	0.56	(49)
8	0.55	(51)	0.84	(47)	0.58	(55)
9	0.57	(52)	0.87	(51)	0.59	(48)
10	0.57	(50)	0.91	(43)	0.62	(58)
	3-OH DL Glucuronide (ng/mL)[a]					
7	11.3	(52)	15.9	(48)	12.2	(59)
8	10.9	(42)	16.4	(48)	11.3	(52)
9	10.7	(43)	16.0	(43)	10.3	(39)
10	12.1	(47)	18.1	(40)	11.5	(46)
	SCH 29851 (ng/mL)[a]					
7	NA		NA		0.099	(60)
8	NA		NA		0.11	(64)
9	NA		NA		0.11	(63)
10	NA		NA		0.12	(74)

NA = not appropriate for loratadine after 5 mg and 7.5 mg DL administration; a: n=24

The results indicate that steady state was attained by Day 10 following administration of each treatment.

The mean (%CV) DL, 3-OH DL and 3-OH DL glucuronide pharmacokinetic parameters on Day 10 are summarized below:

Table
Arithmetic (%CV) and Geometric Mean Desloratadine Pharmacokinetic Parameters on Day 10 Following Multiple-Dose Administration of Desloratadine 5 mg and 7.5 mg and Loratadine 10 mg Once Daily for 10 days. (Protocol P00117)

Parameter[a]	5 mg DL		7.5 mg DL		10 mg Loratadine	
Cmax (ng/mL)	4.89	(72)	7.30	(75)	6.03	(63)
Cmax (Geometric Mean) (ng/mL)	4.03	( )	5.97	( )	5.10	( )
Tmax (hr)	3.08	(72)	3.23	(86)	2.17	(121)
Tmax (Median with Range) (hr)	2	(1-8)	2	(1-10)	1.25	(1-12)
AUC(0-24hr) (ng·hr/mL)	71.9	(107)	104	(105)	74.9	(103)
AUC(0-24hr) (Geometric Mean) (ng·hr/mL)	50.6	( )	75.0	( )	53.1	( )
t1/2 (hr)	34.9	(93)	33.5	(79)	32.7	(72)
t1/2 (Harmonic Mean) (hr)	25.2	( )	25.7	( )	26.0	( )

a: n=24

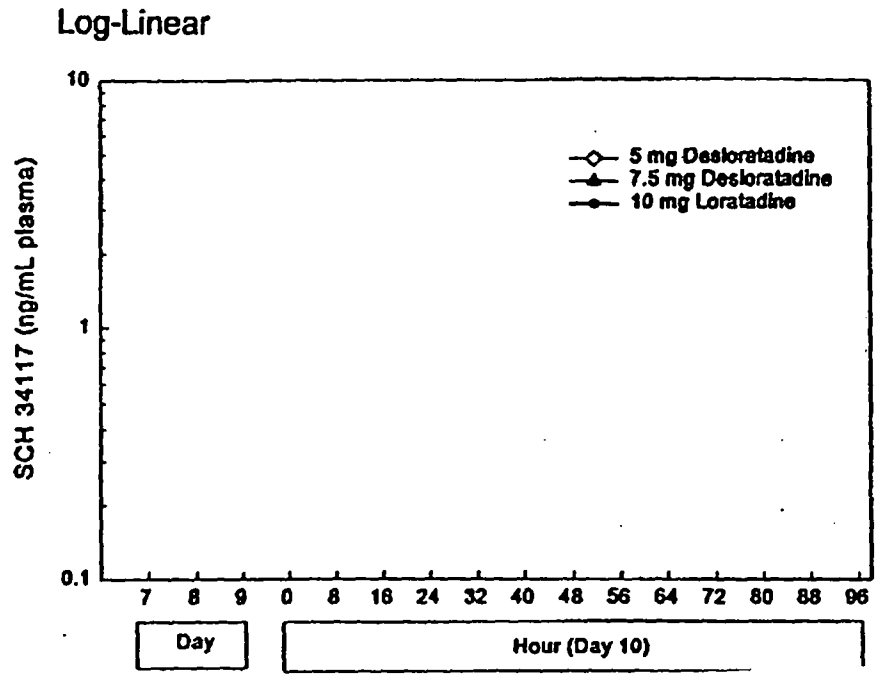


Table Mean (%CV) 3-OH-Desloratadine and 3-OH-Desloratadine Glucuronide Pharmacokinetic Parameters on Day 10 Follow Once Daily Administration of Desloratadine 5 mg and 7.5 mg and Loratadine 10 mg for 10 Days (Protocol P00117)

Parameter [a]	5 mg DL		7.5 mg DL		10 mg Loratadine	
3-OH DL						
Cmax (ng/mL)	1.62	(50)	2.30	(41)	1.73	(54)
Cmax (Geometric Mean) (ng/mL)	1.35	()	1.99	()	1.40	()
Tmax (hr)	5.06	(59)	4.38	(54)	3.29	(81)
Tmax (Median with Range) (hr)	5		5		2	
AUC(0-24hr) [b] (ng·hr/mL)	23.1	(44)	34.3	(42)	23.4	(47)
AUC(0-24hr) (Geometric Mean) (ng·hr/mL)	20.1	()	29.5	()	20.0	()
AUC [b] (%)	56.5	(52)	56.2	(49)	53.7	(49)
t1/2 (hr)	49.1	(85)	46.7	(72)	44.8	(58)
t1/2 (Harmonic Mean) (hr)	37.6	()	37.5	()	38.2	()
3-OH DL glucuronide						
Cmax (ng/mL)	29.4	(43)	46.0	(43)	29.9	(56)
Cmax (Geometric Mean) (ng/mL)	25.4	()	40.1	()	24.7	()
Tmax (hr)	8.04	(30)	7.38	(39)	7.48	(37)
Tmax (Median with Range (hr)	8		8		8	
AUC(0-24hr) [b] (ng·hr/mL)	488	(41)	735	(41)	489	(47)
AUC(0-24hr) (Geometric Mean) (ng·hr/mL)	427	()	641	()	419	()
AUC ratio [b] ( )	22.0	(26)	22.5	(26)	22.0	(34)
t1/2 (hr)	34.9	(79)	36.5[c]	(131)	27.5	(31)
t1/2 (Harmonic Mean) (hr)	27	()	26.1	()	26.1	()

a: n=24

b: n=23. Subject 22 following Treatment A, the AUC (0-24 hr) was not calculated because the 24 hr plasma concentration was not determined.

c: n=20

There were proportional increases in the pharmacokinetic parameters (AUC and Cmax) of DL, 3-OH DL and 3-OH DL glucuronide as the dose of DL was increased from 5 mg to 7.5 mg.
The results of statistical evaluation of the relative bioavailability based on log transformed AUC and Cmax values for DL, 3-OH DL and 3-OH DL glucuronide are presented below.

Parameter	Test Treatment	Relative Bioavailability (%)[a]	Confidence Interval[b]	Power[c] (%)
		DL		
Cmax	5 mg DL	79.0	73-85	98
	7.5 mg DL	117	109-126	
AUC(0-24 hr)	5 mg DL	95.2	91-100	100
	7.5 mg DL	141	135-147	
		3-OH DL		
Cmax	5 mg DL	96.6	88-106	89
	7.5 mg DL	142	130-156	
AUC(0-24 hr)	5 mg DL	100	95-105	100
	7.5 mg DL	147	140-155	
		3-OH DL Glucuronide		
Cmax	5 mg DL	103	96-110	99
	7.5 mg DL	163	152-174	
AUC(0-24 hr)	5 mg DL	102	97-107	100
	7.5 mg DL	153	146-160	

a: Expressed as a percent of 5 mg and 7.5 mg DL to 10 mg loratadine
b: 90% confidence interval based on log-transformed data.
c: To detect a 20% difference

Statistical evaluations show that for DL AUC values and for 3-OH DL and 3-OH DL glucuronide Cmax and UC values met the criteria for bioequivalence following administration of 5 mg DL and 10 mg loratadine.

Safety: Blood pressure, pulse rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects. Overall, 4 of 25 (16%) subjects reported treatment-emergent adverse events. Reported adverse events included; back pain 1 (4), fever 1 (4), headache 1 (4), and throat pain 1 (4). All reported adverse events were mild in severity. No subject discontinued participation in the study due to adverse events. One subject, 18 (BOU) dropped out of the study after 2 doses in Phase I for reasons not associated with an adverse event.

SPONSOR'S CONCLUSIONS:

- DL 5 mg and 7.5 mg administered once daily for 10 days was safe and well tolerated.
- The bioavailability of DL, 3-OH DL and 3-OH DL glucuronide were similar following oral administration of 5 mg DL and 10 mg loratadine; the relative bioavailability based on AUC was 95, 100, and 102%, respectively.
- The administration of DL 7.5 mg results in a higher bioavailability of DL compared with administration of 10 mg loratadine.
- Increases in DL, 3-OH DL and conjugated 3-OH DL glucuronide, Cmax and AUC values appeared dose-proportional following administration of 5 and 7.5 mg DL.
- 3-OH DL was extensively glucuronidated; exposure to 3-OH DL glucuronide was ~ 22-fold higher than unconjugated 3-OH DL.

REVIEWER'S COMMENT:
The sponsor conducted the present study appropriate. The results are acceptable. High intersubject variability was oberved; For Cmax and AUC, CV was in the range of . . % and . %, respectively. The reason of the high intersubject variability is not known.

The systmic exposure following 7.5 mg dose appeared to be larger than that following 10 mg loratadine. On the other hand, the systmic exposure following 5 mg dose appeared to be smaller than that following 10 mg loratadine. Although DCL is more potent antihistamine agent, loratadine also have antihistaminic effect. Therefore, the effect or safety profile may be different , even though there are similar systmic exposure of DCL after DCL administration and loratadine administration.

It should be noted that there were second peak in plasma indicating enterohepatic recirculation of DCL. Tthis second peak is blunted after averaged.

APPEARS THIS WAY
ON ORIGINAL

Title of Study: SCH 34117: Multiple-Dose Pharmacokinetics of Desloratadine and 3-OH Desloratadine in Healthy Subjects (Protocol P00275).

Investigator(s): Albert Cohen, M.D., Thomas Maybury, M.D., Casey Johnson, D.O.

Study Center(s):

Studied Period: 11 MAR 1999 to 20 APR 1999

Clinical Phase: I

Objective(s): To characterize the pharmacokinetic profiles of desloratadine (DL) and 3-OH desloratadine (3-OH DL) following multiple dose administration of 5 mg DL to a population representative of that studied in the clinical efficacy and safety SAR program.

Design / procedure : Open-label, multiple-dose study. One hundred and thirteen healthy subjects each received multiple dose treatment with DL 5 mg. Blood samples were collected at pre-specified times for safety and pharmacokinetic evaluations (at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96 and 120 hr). Subjects were continually observed and questioned throughout the study for possible occurrence of adverse events.

Assay: Plasma samples were assayed for DL and 3-OH DL concentrations using assay (LOQ = ' ng/mL).

Number of Subjects: 114 projected. One hundred and thirteen healthy subjects (57 males and 56 females) were enrolled.

Diagnosis and Criteria for Inclusion: Male and female Caucasian and African American subjects between 18-70 years of age, inclusive, in good health based on medical history, physical examination, electrocardiogram and routine laboratory tests (blood chemistry, hematology and urinalysis) and having a BMI between 19-27 were empanelled for this study.

Test Product, Dose, Mode of Administration, Batch No(s): DL 5 mg tablets, oral, Batch No. 38833-142.

Duration of Treatment: For 10 days, 5 mg of DL was administered once daily at approximately 8 a.m.

Criteria for Evaluation: Physical examinations, electrocardiograms, clinical laboratory tests were performed at screening and at the conclusion of the study and adverse events throughout the study were recorded for safety evaluation. Blood samples were collected over 120 hours following dosing on Day 10 for determination of pharmacokinetic parameters. Supplemental analysis of the relationship between age and the pharmacokinetics of DL was conducted.

Statistical Methods: The pharmacokinetic parameters were listed and summarized using means, standard deviations and coefficients of variation.

RESULTS:
Clinical Pharmacology:
Subject Disposition: 113 subjects were enrolled and 112 subjects completed treatment. One subject (Subject No. 38) dropped out after 7 doses for personal reasons.

Demographic and Baseline Characteristics: Overall, 113 subjects (57 males and 56 females) between the ages of 19 and 70 years (mean=43.5 years) and weighing between 46 and 98.6 kg (mean=72.9 kg) were enrolled into the study. Ninety-five were Caucasian (48 males and 47 females) and 18 were African American (9 male and 9 female).
Pharmacokinetics: The mean plasma trough concentration data are within 10 % of one another suggesting the steady state conditions were attained by day 7 following administration of DCL 5 mg.

Table
Mean Minimum Plasma Concentrations (Cmin) of DL and 3-OH DL Following Multiple Oral Dosing of DL 5 mg to Healthy Subjects on Days 7, 8, 9 and 10 (Protocol P00275)

		Cmin (ng/mL)			
Compound		Day 7	Day 8	Day 9	Day 10
		All Subjects			
DL	Arithmetic Mean (%CV)	1.26 (96)	1.31 (104)	1.33 (107)	1.38 (114)
	Geometric Mean	1.02	1.04	1.05	1.07
3-OH DL	Arithmetic Mean (%CV)	0.792 (35)	0.811 (35)	0.808 (35)	0.845(36)
	Geometric Mean	0.738	0.755	0.756	0.786

%CV were not calculated for non-arithmetic means

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

Pharmacokinetic Parameters								
Analyte		Cmax	Tmax	AUC(0-24hr)	CL/F	tf	t1/2	
DL		(ng/mL)	(hr)	(ng·hr/mL)	(L/hr)	(hr)	(hr)	Ratio[d]
				All Subjects				
	Arithmetic Mean	3.98	3.17	56.9	112	118	26.8	[b]
	%CV	52	56	73	43	7	50	[b]
	Geometric Mean	3.63	2.00[a]	49.4	101	117	24.2[c]	[b]
3-OH DL	Arithmetic Mean	1.99	4.76	32.3	[b]	120	36.0	71.0
	%CV	31	40	31	[b]	0	33	63.4
	Geometric Mean	1.87	5.00[a]	30.4	[b]	120	34.0[c]	[b]

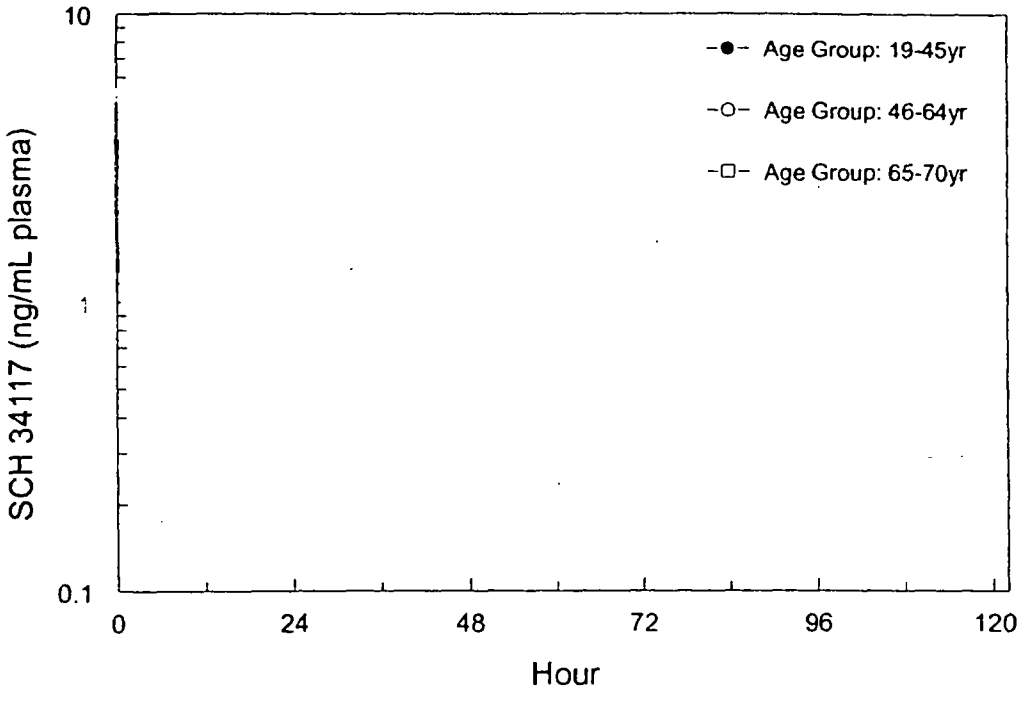
a: Median.
b: Value not calculated.
c: Harmonic mean.
d: Ratio of AUC(0-24 hr) for 3-OH DL to DL.
%CV were not calculated for non-arithmetic means.

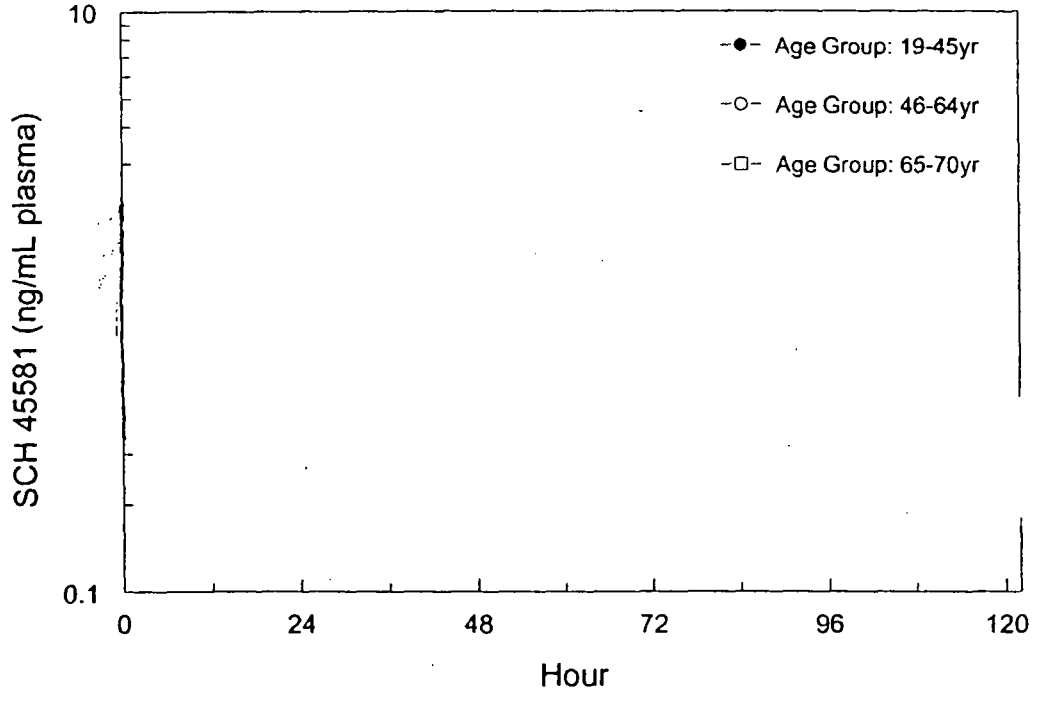
DL was absorbed with a median Tmax of 2 hours. The value for 3-OH DL was 5 hours.
Mean apparent total body clearance was high.
The mean half-life of 26.8 hours is similar to that reported in previous studies. Mean (%CV) pharmacokinetic parameters of D and 3-OH DL by age groups are presented below:

Parameter[a]	Age Group: 19-45 yr[b] Mean (%CV)	Age Group: 46-64 yr[c] Mean (%CV)	Age Group: 65-70 yr[d] Mean (%CV)
		DL	
Cmax	3.83 (57)	3.92 (46)	4.69 (44)
Tmax	3.35 (55)	2.98 (56)	2.76 (63)
AUC(0-24 hr)	55.4 (83)	54.1 (43)	67.8 (72)
t1/2	25.3 (53)	26.1 (13)	33.7 (62)
CL/F·kg	20.4 (26)	16.8 (28)	19.7 (34)
		3-OH DL	
Cmax	1.92 (30)	2.12 (33)	2.05 (30)
Tmax	4.80 (41)	4.90 (34)	4.35 (48)
AUC(0-24 hr)	30.7 (30)	34.3 (32)	34.6 (30)
t1/2	34.7 (36)	35.6 (11)	41.8 (42)

a:Unit: Cmax-pg/mL; AUC-pg·hr/mL; Tmax and t1/2-hr; CL/F kg-mL/hr/kg
b:n=65
c:n=30
d:n=17

There appeared to be a 30% increase in t1/2 in Subject ≥65 years old compared with younger subjects (Refer to the following Figure)


10
1
0.1
SCH 34117 (ng/mL plasma)
Age Group: 19-45yr
Age Group: 46-64yr
Age Group: 65-70yr
0
24
48
72
96
120
Hour


10
0.1
SCH 45581 (ng/mL plasma)
Age Group: 19-45yr
Age Group: 46-64yr
Age Group: 65-70yr
0
24
48
72
96
120
Hour

Safety:
Blood pressure, pulse rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects. Overall, 30 of 113 (27%) subjects reported treatment – emergent adverse events. The most frequently reported adverse events were headache 8 (7%) and constipation 8 (7%). All reported adverse events were mild to moderate in severity. Subject 57 had a SGPT value of 88 IU which was classified as Grade 1 on the Common Toxicity Criteria. All other liver function tests were within the normal range. Subject No. 103 complained of a "racing heart" which was decoded as tachycardia. However, the heart rate was recorded as being 96 bpm, which is not consistent with the clinical definition of tachycardia Twelve subjects required additional treatment for adverse events (10 subjects received acetaminophen, 1 received glycerin suppository and 1 received Pepto-Bismol). There were no discernible differences in the AE profiles for male and female subjects. Three subjects . 65 years old reported AEs. Two subjects reported constipation while the other reported back pain, all of which were considered unrelated to treatment and were mild in severity. No subject discontinued participation in the study due to an adverse event. No serious nor unexpected adverse events were reported.

SPONSOR'S CONCLUSIONS:

- Five mg DL administered once daily for 10 days was safe and well tolerated.
- Following multiple dose oral administration of 5 mg DL steady state Cmax and AUC values for all subjects were 3.98 ng/mL and 56.9 nγVhr/mL, respectively, for DL with a mean (arithmetic) t1/2 of 26.8 hours.
- DL was absorbed with a median Tmax value of 2 hr.
- DL was eliminated with a mean (arithmetic) t1/2 of 26.8 hours.
- Arithmetic mean 3-OH DL plasma AUC was 71% of DL AUC.
- DL has a high apparent total body clearance.
- No dosage modification is warranted in elderly subjects.

REVIEWER'S COMMENTS:
The sponsor conducted the present study appropriately. Data are acceptable.

The sposnor's statement of "high apparent total body clearance" is not correct. The low AUC value can be a result of poor absorption.

The four outliers were observed (Subjects No. 4, 45, 83, and 85) . Their systemic exposure is much larger than others; (i.e., Cmax . 10 ng/ml; AUC > 200 ng hr/ml). There seems no correlation of race, gender, and age to the high Cmax and large AUC. The reason of the outlier has not been known.

In elferly subjects, it was noted that there were 20 % or 30 % increase of systemic exposure (Cmax and AUC) or elimination t1/2, respectively. This reviewer agrees the sponsor's conclusion that no dosage modification is warranted in elderly subjects, based on the result of C98-357: Evaluation of the electrocardiographic pharmacodynamic effects following administration of multiple high dose (Please refer to the individual study review).

Title of the Study: SCH 34117: Bioavailability of Desloratadine Polymorphs Administered to Healthy Subjects: A Three-Way Crossover Study (Protocol P00311).

Investigator(s):

Studied Period: 25 March 1999 - 22 June 1999

Clinical Phase: I

Objective(s): To evaluate the bioavailability of the to be marketed 5 mg tablet formulation of desloratadine (DL) and DL 5 mg capsules formulated with mainly DL polymorph Form 1 or DL polymorph Form 2 as well as the bioequivalence of capsules formulated with mainly DL polymorph Form 1 or DL polymorph Form 2, based on log-transformed Cmax and AUC.
Design/ Procedure: Randomized open-label, single-dose, three-way crossover study. Healthy adult subjects received each treatment, one in each period. The order in which subjects received each treatment was determined by a computer-generated random code provided by SPRI. Blood samples were collected at pre-specified times for pharmacokinetic and safety evaluations (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hour after administration). ECG's and vital signs were obtained at pre-specified times for safety evaluation. Volunteers were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events.

ASSAY: Plasma samples were assayed for DL and 3-OH DL content using assay (LOQ = ng/mL).

Number of Subjects: Sixty healthy subjects planned; 63 were enrolled.

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

Test Product, Dose, Mode of Administration, Batch No(s): DL: 5 mg (Form 1), Batch No. 52782-090; 5 mg (Form 2), Batch No. 52782-091; 5 mg tablet, Batch No.38833-142. All treatments were administered orally after an overnight fast.

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

Duration of Treatment: Single doses were administered in the morning (approximately 8 a.m.) during each treatment period and subjects were followed for 120 hours postdose.

Criteria for Evaluation: Blood samples were collected over 120 hours for determination of PK parameters. Log-transformed AUC and Cmax of DL and 3-OH DL.

Statistical Methods: The derived pharmacokinetic parameters were statistically analyzed using a crossover analysis of variance model. The effects due to subject, period and treatment were extracted. Bioequivalence was assessed by the 90% confidence intervals for the mean difference between the treatments for log-transformed AUC and Cmax. The mean difference was expressed as a percent of each treatment mean. The power to detect a 20% difference in treatment means for an alpha level of 0.05 (two-tailed) was also computed. The pooled residual error and associated degrees of freedom from the analyses of variance were used in the calculation of the confidence interval and power. The pharmacokinetic parameters were analyzed for extreme values by reviewing the studentized ranges of deviations from the expected value derived from the analysis of variance to see if any value exceeded 3.

RESULTS:
Clinical Pharmacology:
Subject Description: Sixty-three subjects were enrolled into the study and 53 subjects completed all three treatment periods. Subjects were discontinued for reasons of non-compliance (Subject Nos. 12, 13, 32, 42, 51 and 55), administrative (Subject Nos. 63, 64 and 65) and one subject (Subject No 43) did not meet protocol eligibility criteria. Subject Nos. 59 and 60 were not used.

Demographic and Baseline Characteristics: Sixty-three healthy male subjects between the ages of 19 and 41 years, inclusive (mean = 26.3 years) and having a BMI between 19 and 29 (mean = 23) were enrolled into the study. Sixty-one subjects were Caucasian, 1 was Asian and 1 was American Indian.