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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-297**

Medical Review(s)

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #: 21,297

APPLICATION TYPE: NDA

SPONSOR: Schering

PRODUCT/PROPRIETARY NAME: Clarinex

INDICATION: Chronic Idiopathic
Urticaria

USAN / Established Name: Desloratadine

CATEGORY OF DRUG: Antihistamine

ROUTE OF ADMINISTRATION: Oral

MEDICAL REVIEWER: C Rosebraugh MD MPH

REVIEW DATE: 2 October 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date/CDER
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31 August 2000

N21,297

45-Day Review of Original Application

RELATED APPLICATIONS (if appropriate)

Document Date:

Document ID #:

Comments:

21,165

Desloratadine initial NDA

Overview of Application/Review: The submission is in both electronic and paper media and is comprised of 27 paper volumes in addition to 2 CD's and one diskette. The 45 day filing and planning meeting for desloratadine 5 mg tablets was held on 17 October 2000. The sponsor has provided data intended to support the safety and efficacy of this drug product for the treatment of chronic idiopathic urticaria (CIU). Included in the submission are: PO1196: a clinical pharmacology wheal and flare study in 28 healthy volunteers. Primary review of this study will be conducted by the Biopharmacologist reviewer, Dr. Saurez. The medical review will cover safety issues related to the trial. There are two efficacy and safety studies, P00-220, P00-221, conducted with a total of 416 adult and adolescent subjects with CIU. These studies had identical 6 week evaluation protocols and randomized approximately 100 patients per treatment arm, per study. All study subjects received desloratadine 5 mg orally, or placebo. The primary efficacy variable was change from baseline in average AM/PM reflective (PRIOR) pruritus score over the first week of treatment (Days 1-8). There are several secondary efficacy variables evaluated which included pruritis, number and size of hives, total symptom scores (sum of pruritus, number of hives and size of the largest hive), interference with sleep, interference with daily activities and investigator-subject-evaluated condition. No investigators were chosen for audit. On it's face, from the clinical perspective, the submission appears complete and filable. There are no clinical filing issues. The key studies are the 2 clinical efficacy studies, review of which will be completed by 15 December 2000. The clinical pharmacology study review will be completed by 19 January 2001. The ISE will be completed by 16 February 2001 and the ISS and labeling by 16 March 2001.

Outstanding Issues: None

Recommended Regulatory Action:

N drive location:

New Clinical Studies: _____ Clinical Hold

_____ Study May Proceed

NDAs:

Efficacy / Label Supp.: _____ Approvable

_____ Not Approvable

Signed: Medical Reviewer: _____

Date: _____

Medical Team Leader: _____

Date: _____

MEDICAL OFFICER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #: NDA 21297	APPLICATION TYPE: Original NDA
SPONSOR: Schering	PRODUCT/PROPRIETARY NAME: Clarinex
INDICATION: Chronic Idiopathic Urticaria	USAN / Established Name: Desloratadine
CATEGORY OF DRUG: Antihistamine	ROUTE OF ADMINISTRATION: Oral
MEDICAL REVIEWER: C. Rosebraugh, MD, MPH	REVIEW DATE:

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date/CDER Stamp Date	Document ID #:	Submission type/Comments/Due date (if appropriate):
31 August 2000	N21-297	Original Application

RELATED APPLICATIONS (if appropriate)

Document Date:	Document ID #:	Comments:
	N21-165	Desloratadine initial NDA

Overview of Application/Review:
 See executive summary

Outstanding Issues:
 See comments to the sponsor

Recommended Regulatory Action:	N drive location:
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New Clinical Studies: _____	Clinical Hold _____	Study May Proceed _____
NDA's:		
Efficacy / Label Supp.: <input checked="" type="checkbox"/>	Approvable _____	Not Approvable _____

Signed:	Medical Reviewer: _____	Date: _____
	Medical Team Leader: _____	Date: _____

TABLE OF CONTENTS

I. GLOSSARY OF TERMS	3
II. EXECUTIVE SUMMARY AND RECOMMENDATIONS	4
RECOMMENDED AGENCY ACTION	7
III. MATERIAL REVIEWED	9
IV. BACKGROUND	9
V. CHEMISTRY	10
VI. PRECLINICAL PHARMACOLOGY	10
VII. CLINICAL PHARMACOLGY	10
VIII. CLINICAL TRIALS	11
Pivotal Study P00-220	11
Pivotal Study POO-221	33
STUDY P01196 (Safety analysis only)	47
IX. INTEGRATED SUMMARY OF EFFICACY	53
X. INTEGRATED SUMMARY OF SAFETY	59
XI. CONCLUSIONS	62
XII. LABELING COMMENTS	63
XIII. APPENDIX	67

I. GLOSSARY OF TERMS

AUC-24:	Area under the curve from 0 to 24 hours
C _{max} :	Max observed plasma concentration
T _½ :	Half-Life of drug
DL:	Desloratadine
CIU:	Chronic Idiopathic Urticaria
ITT:	Intention to Treat
NOW:	Status at the time of assessment
PRIOR:	AM/PM 12 hour reflective (PRIOR) scores
SAR:	Seasonal Allergic Rhinitis
QT _c -F:	Q-T interval rate correction-Fridericia's
QT _c -B:	Q-T interval rate correction-Bazett's

II. EXECUTIVE SUMMARY AND RECOMMENDATIONS

The sponsor has submitted an original NDA for desloratadine tablets (Clarinet[®]) for use in the treatment of chronic idiopathic urticaria (CIU) in adults and adolescents age 12 years and older. A separate NDA for Clarinet[®] (NDA 21-165) for the seasonal allergic rhinitis (SAR) indication was previously submitted to this Division and has received an approvable action. Desloratadine is the active metabolite of loratadine (Claritin[®], Schering-Plough), an antihistamine approved for both indications. In support of the CIU indication, the sponsor has submitted clinical efficacy and safety data from two controlled clinical studies and one clinical pharmacology study. The two clinical studies (P00220, P00221) were phase-III pivotal trials of identical design, which were randomized, double-blinded, placebo-controlled, parallel-group, efficacy and safety studies of desloratadine 5.0 mg every day versus placebo every day for up to 6 weeks. The supporting clinical pharmacology study (P01196) was a single-center, multiple-dose, double-blind, randomized, parallel-group study of desloratadine 5.0 mg once daily versus placebo for 28 days in the suppression of wheal and flare and the determination of pharmacokinetic parameters. Safety data for study P01196 will be presented in this review.

The two clinical studies enrolled a total of 416 adult and adolescent subjects aged ≥ 12 years with CIU. Randomization resulted in 211 subjects receiving treatment with desloratadine and 205 subjects receiving treatment with placebo. The studies were conducted in 58 medical centers with 46 of these centers in the United States and 12 centers internationally. Approximately 75% of the subjects in these two studies were women with ages ranging from 12 to 84 years. Evaluation of efficacy was based primarily on subjects' self-assessments of CIU symptoms. Subjects assessed the severity of the signs and symptoms of CIU (three individual symptom scores for pruritus, number of hives, and size of largest hive) twice daily in a diary, both reflective over 12 hours (PRIOR) and at the time of assessment (NOW). The sample size was chosen to detect a difference between treatment groups of ≥ 0.5 unit, on a four-unit scale, in the mean change from baseline diary symptom score for pruritus (only). Subjects also assessed

interference with sleep and daily activities. Subjects and investigators reviewed the subject's diary and jointly assessed the overall condition of CIU and therapeutic response to therapy. **The primary efficacy variable in both studies was the average AM/PM reflective (PRIOR) pruritus score, expressed as a change from baseline value, over the first week of treatment (Days 1-8).** The primary efficacy variable was analyzed on the intention to treat (ITT) population, using a two-way ANOVA that extracted sources of variation due to treatment and center. Specific time points and the amount of unit change considered significant were not specified *a priori* for secondary efficacy variables. Secondary efficacy variables included other individual symptom scores, total symptom scores of the 3 individual symptoms, assessment of interference with sleep, interference with daily activities, overall condition of CIU and therapeutic response. Entry criteria defined minimum baseline pruritus entrance scores (subject blinded) that were necessary for subject study entrance and participation.

Study P00220 was conducted at 29 medical centers: 23 in the United States and 6 internationally. A total of 226 subjects were randomized at 25 centers. One hundred sixteen (116) subjects were randomized to active drug and 110 subjects were randomized to placebo. A total of 54 (23.8%) subjects failed to complete the study: 19 (16.4%) subjects in the DL group and 35 (31.8%) in the placebo group. Fourteen subjects in the DL group and 29 subjects in the placebo group discontinued the study prematurely due to treatment failure. Desloratadine 5.0 mg demonstrated a mean numerical difference ≥ 0.5 units and a statistically significant response ($p < 0.001$) compared to placebo for the primary efficacy endpoint at the primary time point. This response was noted as early as day two and continued through day 8. The mean pruritus reduction score of drug and placebo at day 8 were 47.9% and 21.9% respectively. The difference in mean change from baseline symptom scores between treatment groups was **0.53**. The numerical difference was < 0.5 units from day 9 until the completion of the study, however statistical significance between the groups was maintained through day 29.

Evaluation of the secondary variables revealed that at the one week time point, there was also a statistically significant difference favoring the drug group compared to the placebo group in the secondary variable pruritus AM NOW, although the mean change from baseline symptom scores between treatment groups was only **0.34**. This would not, by itself, support the 24 hour dosing interval purposed by the sponsor. Total symptom score AM/PM PRIOR and overall condition of CIU scores demonstrated >0.5 unit change and $p < 0.001$. Number of hives, size of largest hive, interference with sleep and interference with daily activities all demonstrated <0.5 unit change between DL and placebo groups but demonstrated statistical significance at the one week evaluation time point.

There were no significant laboratory, ECG or safety issues identified and there were no treatment emergent adverse events unique to the CIU population compared to the allergic rhinitis population identified by this study.

Study P00221 was conducted at 29 medical centers: 23 in the United States and 6 internationally. A total of 190 subjects were randomized at 29 centers. Ninety-five subjects were randomized to active drug and 95 subjects were randomized to placebo. A total of 51 (26.8%) subjects failed to complete the study: 19 (20%) subjects in the DL group and 32 (33.7%) in the placebo group. Thirteen subjects in the DL group and 21 subjects in the placebo group discontinued the study prematurely due to treatment failure. Desloratadine 5.0 mg once daily did show a numerical >0.5 unit and statistically significant response ($p < 0.001$) compared to placebo in the primary efficacy endpoint. This difference was noted as early as day two and continued through day 42. The relative pruritus reduction score of drug and placebo at day 8 were 56.0% and 21.5% respectively. The difference in mean change from baseline symptom scores between treatment groups was **0.73**.

Evaluation of the secondary variables revealed that at the one week time point, there was a numerical difference of **0.64** and statistical significance between treatment groups favoring desloratadine for pruritus AM NOW supporting a 24 hour dosing interval. All

other secondary efficacy variables, except interference with sleep analysis, demonstrated a numerical difference >0.5 units and statistical significance of the drug therapy group compared to placebo at the 7 day time point. Interference with sleep analysis revealed a numerical difference of 0.32 with $p < 0.001$.

There were no significant laboratory, ECG or safety issues identified in this study and there were no treatment emergent adverse events unique to the CIU population identified by this study. The most frequent adverse events were headache (DL-14.2%, Placebo 13.2%), viral infection (DL-5.7%, Placebo-5.9%), nausea (DL-5.2%, Placebo-1.5%) and fatigue (NA-5.2%, Placebo <1%).

Study P01196 was a single-center study that enrolled 28 subjects and was designed to assess the ability of desloratadine 5 mg, given daily for 28 days, to suppress the wheal and flare reaction induced by a skin prick application of histamine in normal volunteers. Safety monitoring endpoints included blood pressure, pulse rate, oral body temperature and adverse events. There were no significant safety issues identified in this study although clinical laboratory and ECG parameters were not monitored during the study.

RECOMMENDED AGENCY ACTION

The recommended agency action is **approvable**. The data are conclusive that desloratadine 5 mg once daily provides a statistical significant reduction in pruritus after a one week interval. Based on the totality of the data and on placebo dropout rates, desloratadine 5 mg once daily also provides clinical improvement in CIU patients. Medication risks are appropriate for the degree of clinical benefit derived (*see above*). Mean pruritus AM NOW scores for days 1-8 time point provide questionable support for a 24 hour dosing interval since the difference between placebo and DL did not meet or exceed 0.5 units in study P00220, although it did in study P00221. However, it may be reasonable to extrapolate this information from SAR data (NDA 21-165). Also, the to-be-marketed dose of 5 mg once daily is not fully supported by a dose-ranging pharmacodynamic component in this submission (only the 5 mg dosage was studied).

However, data suggest that the dose shown to be effective for SAR would also likely be effective for CIU, as has been shown to be true of the parent drug, loratadine.

Final approval of desloratadine for the CIU indication will require satisfactory resolution of all deficiencies identified for the SAR indication, primarily CMC and GMP in nature, in addition to the indicated revisions to the product label (see comments to sponsor).

**APPEARS THIS WAY
ON ORIGINAL**

III. MATERIAL REVIEWED

Assessment of this NDA was initiated with a review of the sponsor's overall clinical program for this drug. Minutes of meetings and teleconferences with the sponsor were reviewed, as well as notes from previous reviewers. Financial disclosure statements were reviewed. Previous Agency history with other chemical entities seeking approval in the treatment of CIU was reviewed. A literature review on CIU was performed^(1, 2, 3, 4, 5, 6). Input was obtained from other disciplines, especially statistics and biopharmaceutics. The two key studies identified as pivotal in support of the sponsor's claim for safety and effectiveness were reviewed first. A safety review of the clinical pharmacology study was performed next. Finally, the sponsor's integrated summaries of efficacy and safety were reviewed. Medical officer comments are written in *Italics*. References to pages in the application are in square brackets [].

IV. BACKGROUND

a) Indications

ClarinetTM (desloratadine) tablets are being developed by Schering for the treatment of chronic idiopathic urticaria in adolescents and adults 12 years of age and above. The safety and efficacy of desloratadine in SAR has already been demonstrated in clinical trials, therefore the main questions in this review were (1) whether desloratadine was efficacious in the treatment of CIU compared to placebo, and (2) whether desloratadine usage in CIU patients presents unique safety concerns.

b) Related NDA

On October 20, 1999 (CDER stamp date October 21, 1999), Schering submitted an NDA (21-165) seeking approval for desloratadine 5 mg tablets for the treatment of seasonal allergic rhinitis in adults. ClarinetTM (desloratadine) was found to be approvable based on data from clinical trials conducted in 3282 patients with SAR. Final approval awaits satisfactory resolution of labeling and other issues. At the time of this NDA submission, the sponsor had completed 20 multiple-dose, double-blind, controlled trials of two to six weeks duration, 11 single-dose trials, and 41 clinical pharmacology studies in approximately 5000 patients.

c) Administrative history

A pre-IND meeting was held on January 12, 1998 and subsequently an IND was filed on March 9, 1998. The following meetings have been held with the sponsor:

1) August 7, 1998-Toxicology meeting, 2) November 18, 1998-Toxicology meeting, 3) January 20, 1999-Teleconference, 4) March 30, 1999-Teleconference, 5) May 4, 1999-Teleconference, 6) May 10, 1999-Teleconference, 7) May 11, 1999- Pre-NDA meeting, 8) August 3, 1999-Toxicology meeting, 9) September 14, 1999-Toxicology Policy Group, 10) January 18, 2000-Pre-NDA.

Although appropriate as an efficacy supplement to an approved NDA, the sponsor has chosen to submit a separate NDA (21-297) for the CIU indication because of the unapproved status of NDA 21-165. In support of this application, the sponsor has submitted clinical efficacy and safety data from two multicenter studies. Data from a pharmacodynamic single center wheal and flare suppression study has also been submitted as supportive evidence.

- d) Foreign marketing history
There is no foreign marketing experience with this drug.

V. CHEMISTRY

The molecular formula for desloratadine is $C_{19}H_{19}ClN_2$. The CMC section of this NDA cross references NDA 21,165.

VI. PRECLINICAL PHARMACOLOGY

The preclinical section of this NDA cross references NDA 21,165.

VII. CLINICAL PHARMACOLGY

The clinical pharmacology section of this NDA cross references NDA 21,165. The mean C_{max} for DL 5 mg as a single dose is between 2.8 ng/ml and 3.9 ng/ml. Maximum plasma drug concentrations are achieved at approximately 3.5 hours post dose. The mean accumulation factor ranged from 1.64 to 1.75. The $T_{1/2}$ is approximately 17 hours.

**APPEARS THIS WAY
ON ORIGINAL**

VIII. CLINICAL TRIALS

Pivotal Study P00-220

i) TITLE

Efficacy and safety of desloratadine (SCH 34117) in the treatment of chronic idiopathic urticaria.

ii) OBJECTIVES

The primary objective of this study was to evaluate the efficacy of desloratadine (DL, SCH 34117) 5.0 mg QD compared with placebo QD in subjects with chronic idiopathic urticaria (CIU). The secondary objective was to characterize the safety profile of DL using the following parameters: Adverse events, electrocardiograms (ECGs), vital-sign evaluations, and laboratory results.

iii) ENDPOINTS

- (1) Efficacy: Subject-evaluated pruritus score analysis results, confirmatory analyses of the efficacy-evaluable data set, response by age, sex, and race, and response by study center.
- (2) Safety: Subject reported treatment-emergent adverse events along with vital signs and laboratory parameters.

iv) SETTING/CENTERS

The study was design to recruit approximately 10 to 12 subjects at each of approximately 30 domestic and international study centers to meet the projected sample size of approximately 200 subjects. Twenty-nine centers were initiated in this study; of these, 25 enrolled subjects and 4 (Center Nos. 4, 26, 27, and 30) did not enroll subjects.

v) POPULATION

(1) Inclusions:

- 12 years of age or older, of either sex and of any race.
- History of signs and symptoms for ≥ 6 weeks prior to the screening visit.
- Subjects were to have experienced a current flare of their CIU for ≥ 3 weeks prior to the screening visit. Hives were to have been present on at least 3 days per week during this current flare prior to the screening visit.
- Overall condition at least moderate (score of ≥ 2) at screening and at baseline.

- ❑ Moderate pruritus (score of ≥ 2), and hives present (score of ≥ 1) at screening.
- ❑ Total score for pruritus of ≥ 14 at baseline, the sum of AM and PM reflective diary scores (Describing their status over the previous 12 hours-PRIOR) for the 3 days prior to baseline and the AM reflective diary score on Day 1.
- ❑ Capacity to assess their symptom scores accurately and consistently.
- ❑ Good general health as confirmed by routine clinical and laboratory testing. Clinical laboratory tests (CBC, blood chemistries, urinalysis) were to be within normal limits or clinically acceptable.
- ❑ Free of any clinically significant disease other than chronic idiopathic urticaria.
- ❑ Subject and/or parent or guardian was willing to give written informed consent and able to adhere to dosing and visit schedules and meet study requirements.
- ❑ For females of childbearing potential, a negative serum pregnancy test (β -HCG) at screening.
- ❑ Female subjects were to have used a medically accepted method of birth control, i.e., double barrier method, oral contraceptive, Depo-Provera or Norplant, prior to baseline and during the study. Women of childbearing potential were to be counseled in the appropriate use of birth control while in this study. Women who were not currently sexually active were to agree and consent to use 1 of the above-mentioned methods if they became sexually active while participating in the study. If the subject had a tubal ligation, used an intra-uterine device, or the husband/partner had a vasectomy, another method was to be used. [Clinstat\P00220\8D, pg. 22]

(2) Exclusion

- ❑ Subjects with asthma requiring chronic use of inhaled or systemic corticosteroids.
- ❑ Subjects who were unresponsive to antihistamine treatment in the past.
- ❑ Subjects with a history of allergies to more than 2 classes of medication or who were allergic to or could not tolerate antihistamines.
- ❑ Subjects who had been treated with any investigational drug in the last 30 days prior to baseline.
- ❑ Food or drug allergies manifesting as skin reactions. Physical urticaria or other known etiology.
- ❑ Pregnant or nursing females.
- ❑ History of hypersensitivity to the study drug or its excipients.
- ❑ Family member of the investigational study staff who was involved with this study.
- ❑ Subjects previously randomized into the study.
- ❑ Subjects with current evidence of clinically significant hematopoietic, cardiovascular, hepatic, renal, neurologic, psychiatric, autoimmune disease or other disease that precluded the subject's participation in the study. Particular attention was given to subjects with conditions that would have interfered with

the absorption, distribution, metabolism or excretion of the study drug or with the subject's ability to reliably complete the diary card.

- Subjects whose ability to provide informed consent was compromised.
- Subjects with a history of noncompliance with medications or treatment protocols.

[Clinstat\P00220\8D, pg. 23]

Although autoimmune disease is listed as an exclusion criteria, the sponsor did not perform any collagen vascular or vasculitis serology. Additionally, thyroid serologies were not performed. Therefore I am less secure that these patients fulfill the criteria of CIU. However, the randomization scheme would help to decrease any bias that would be introduced by disease misclassification.

(3) Proscribed Medications

Subjects who had taken the following medications prior to screening must have followed the minimum washout periods prior to Day -3. These medications were prohibited for the duration of the study.[Clinstat\P00220\8D, pg. 29]

Medication	Washout period
Corticosteroids	
Nasal, ocular, oral, inhaled, intravenous, or rectal	1 month
Intramuscular or intra-articular	3 months
Any dermatological	2 weeks
Antihistamines	
Short-acting (e.g., chlorpheniramine)	12 hours
Long-acting OTC forms of chlorpheniramine	48 hours
Long-acting antihistamines (e.g., cetirizine, terfenadine, fexofenadine, hydroxyzine)	10 days
Clemastine	48 hours
Loratadine	10 days
Azelastine	10 days
Astemizole	3 months
Systemic antibiotics (unless on a stable dose for prophylactic therapy)	2 weeks
H ₂ -receptor antagonists (cimetidine, ranitidine)	7 days
Non-steroidal anti-inflammatory drugs	7 days
Montelukast, zafirlukast, zileuton	10 days

The washout period for some of the above drugs may be too short, however this should decrease the effect size.

vi) DESIGN

(1) Overall statement

This is a multicenter, phase III, randomized, double-blind, placebo-controlled, parallel-group study of desloratadine 5.0 mg in subjects with Chronic Idiopathic Urticaria.

(2) Summary of protocol

- (a) This was a Phase III, randomized, placebo-controlled, parallel-group, multicenter, double-blind study of DL 5.0 mg QD in subjects with CIU. The study was conducted at 29 medical centers: 23 in the United States and 6 internationally. Of these 29 centers, 25 enrolled subjects and 4 (Center Nos. 4, 26, 27, and 30) did not enroll subjects. Duration of treatment was up to 6 weeks. There were no amendments. Subjects assessed the severity of the signs and symptoms of CIU (pruritus, number of hives, and size of largest hive) twice daily in a diary, describing their status over the previous 12 hours (PRIOR) and their status at the time of assessment (NOW). Subjects were to participate in a Screening phase of 3 to 14 days, during which they (with assistance from their parents/guardians, if appropriate) were to complete diary cards with evaluations of their CIU symptoms. The sum of AM and PM reflective diary scores for pruritus for the 3 days prior to the Baseline visit and the AM reflective score for pruritus at Baseline (Day 1) was to have been ≥ 14 to qualify for randomization. Subjects were not aware of the symptom scores required for randomization. At the baseline visit, after randomization to study drug, a new set of diaries were provided. On the daily cards, subjects evaluated pruritus, number of hives, size of largest hive, interference with sleep and interference with daily activities

A schematic representation of the study design is provided in the appendix [Clinstat\P00220\8D, pg. 20].

- (b) Study sequence: Randomization was performed in blocks of 4 using random numbers generated by SAS function UNIFORM. The schedule of basic study procedures is shown in the following table [Clinstat\P00220\8D, pg. 21].

Schedule of study procedures table

Study Days	Screening	Baseline	Treatment Period				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Days -14 to -3	Day 1	Day 4	Week 1	Week 2	Week 4	Week 6
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Medical/Disease History	X						
Concomitant Medications Review	X	X	X	X	X	X	X
Vital Signs (temperature, blood pressure, pulse, respiration rate)	X	X	X	X	X	X	X
12-Lead Electrocardiogram	X						X
Pregnancy Test, Serum (female subjects)	X						X
Complete Blood Count, Blood Chemistry, Urinalysis	X						X
Assessment of Urticaria Signs and Symptoms	X						
Overall Condition of Chronic Idiopathic Urticaria	X	X	X	X	X	X	X
Evaluation of Therapeutic Response			X	X	X	X	X
Dispense Diaries	X	X		X	X	X	
Provide Instruction on Symptom Diary	X	X	X	X	X	X	
Collect/Review Symptom Diary		X	X	X	X	X	X
Administration of Study Drug in Office		X					X
Dispense Study Drug		X		X	X	X	
Collect/Count Study Drug				X	X	X	X
Adverse Events Evaluation		X	X	X	X	X	X

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(3) Assessments

(a) Efficacy

The primary efficacy variable was the average AM/PM 12 hour reflective (PRIOR) pruritus score from subject diaries, expressed as a change from the Baseline value, over the first week of treatment. Pruritus intensity was scaled as: 0=None, not present, 1=Mild, clearly present but minimal awareness, easily tolerated, 2=Moderate, definite awareness which was bothersome but tolerable, 3=Severe, hard to tolerate. [Clinstat\P00220\8D, pg. 32]

The number of hives was evaluated as 0= None, 1= One to six, 2= Seven to twelve, 3= More than twelve. [Clinstat\P00220\8D, pg. 33]

Size of the largest hive was evaluated as: 0=None, 1=<1.25 cm, 2=1.25-2.5 cm, 3= >2.5 cm. [Clinstat\P00220\8D, pg. 33]:

Interference with sleep (AM reflective only) was scored according to the following criteria: 0=No interference at all, 1=Not annoying or troublesome, adequate amount of sleep, 2=Interfered somewhat with sleep, average sleep, woke up a few times, 3=Substantially interfered with sleep, poor sleep. [Clinstat\P00220\8D, pg. 33]

Interference with daily activities (PM reflective only) was scored according to the following criteria: 0=None, 1=Mild, not annoying or troublesome, 2=Moderate, interfered somewhat, 3=Severe, substantially interfered with activities. [Clinstat\P00220\8D, pg. 34]

Joint physician/subject evaluation was scored according to the following criteria: 0=None, 1=Mild, signs/symptoms were clearly present but minimal awareness, 2=Moderate, definite awareness of signs/symptoms, 3=Severe, signs/symptoms were hard to tolerate. [Clinstat\P00220\8D, pg. 34]

Joint physician/subject evaluation of therapeutic response was scored according to the following criteria: 1=Complete relief, 2=Marked relief, greatly improved, 3=Moderate relief, 4=Slight relief, 5=Treatment failure. [Clinstat\P00220\8D, pg. 35] The sponsor evaluated six sets of data for each symptom and total symptom scores at the listed time points in the table below. [Clinstat\P00220\8D, pg. 35]

Time Interval	Day 1	Day 2	Day 3	Day 4	Wk1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
VARIABLE	Days Included									
AM NOW		2	3	4	2-8	9-15	16-22	23-29	30-36	37-42
AM PRIOR		2	3	4	2-8	9-15	16-22	23-29	30-36	37-42
PM NOW	1	2	3	4	2-8	9-15	16-22	23-29	30-36	37-42
PM PRIOR	1	2	3	4	2-8	9-15	16-22	23-29	30-36	37-42
Mean AM/PM NOW	1	2	3	4	2-8	9-15	16-22	23-29	30-36	37-42
Mean AM/PM PRIOR	1	2	3	4	2-8	9-15	16-22	23-29	30-36	37-42

Secondary efficacy endpoints included the following:

1. Pruritus [NOW]
2. Number of hives [PRIOR and NOW]
3. Size of largest hive [PRIOR and NOW]
4. Total symptom scores (sum of scores for the above 3 individual signs and symptoms of CIU)
5. Assessment of interference with sleep
6. Interference with daily activities, overall condition of CIU, and evaluation of therapeutic response

(b) Safety

Body temperature, systolic and diastolic blood pressure, pulse, and respiration were measured at each visit. A standard 12-lead ECG was recorded as defined above. The final ECG was obtained 1 to 3 hours after the last dose of study drug. All adverse events were recorded in the subject's medical records and on the case report forms. Subjects who experienced adverse events were to be followed to satisfactory resolution or stabilization of the event. Subjects were to be removed from the study when; 1) It was considered necessary for their welfare, 2) Subjects who had intolerable symptoms, 3) Noncompliance with the protocol, 4) The occurrence of a significant adverse event or intercurrent illness, or a laboratory abnormality based on investigator's discretion. Patients who withdrew early were to have all the final visit procedures done.

(c) Compliance

Compliance was evaluated at each post-baseline visit by asking the subject and/or the parent or guardian, tablet counts and by reviewing diary comment cards for study drug use. The sponsor states that the majority of subjects were $\geq 95\%$ compliant with the dosing regimen.

Studies have shown tablet counts to poorly reflect true compliance. Few studies have a true compliance rate this high. However, the sponsor's randomization scheme should minimize bias.

vii) STATISTICAL AND ANALYTICAL PLAN

(1) Efficacy

(a) Power Analysis- The sample size was chosen to detect a difference between treatment groups of 0.5 units or more in the mean change from baseline diary symptoms score for pruritus (PRIOR), assuming a pooled standard deviation of 1.0, with a power of 90% and 5% two-sided significance level. Therefore a sample was designed to enroll 200 subjects or 100 subjects per treatment group.

(b) Planned analysis- The primary analysis was to use the intent-to-treat (ITT) population. Analysis was also performed on the evaluable (*sponsor defined prior to breaking the blind*) population. The ITT population was defined as all subjects randomized. The evaluable population included all randomized subjects who met criteria established prior to unblinding, and was based on baseline symptom scores, compliance and concomitant medication. The primary and secondary efficacy variables were analyzed using a two-way ANOVA that extracted sources of variation due to treatment and center. The average of the first-week treatment period was the primary time point, which included all subjects with any follow-up data. For subject inclusion in the secondary efficacy variables, endpoint week analyses was defined as the last available week average for each subject.

Note: This Reviewer performed an in-depth analysis on the ITT population data only. A correction for multiply comparisons was not stated.

(2) Safety

(a) An ECG was obtained at screening and visit 7. ECG recordings were machine read at all study centers with the following exceptions: 01, 11, 14, 15, 17, 18, 19 and 22. Fridericia and Bazett QTc corrections were performed. Calculated QTc intervals (in msec) were categorized as follows: Normal ≤ 430 (Males), ≤ 450 (Females); Borderline 431-450 (Males), 451-470 (Females); Prolonged > 450 (Males), > 470 (Females). Changes from baseline were assigned to the following categories: < 0 , 0-30 msec, 31-60 msec, or ≥ 61 msec.

viii) RESULTS

(1) Patient Disposition

A total of 226 subjects were randomized at 25 centers. One hundred sixteen subjects were randomized to active drug and 110 subjects were randomized to placebo. A total of 54 (23.9%) subjects failed to complete the study: 19 (16.4%) subjects in the DL group and 35 (31.8%) in the placebo group. The sponsor derived the following table to summarize subject disposition.[Clinstat\P00220\8D, pg. 53]

PATIENT DISPOSITION, N (%), Study P00200

	DL 5.0 mg QD	Placebo
Number Randomized	116 (100)	110 (100)
Number (%) Completed	97 (83.6)	75 (68.2)
Number (%) Discontinued	19 (16.4)	35 (31.8)
Reason for Discontinuation		
Treatment Failure	14 (12.1)	29 (26.4)
Adverse Event	3 (2.6)	2 (1.8)
Non-compliance	1 (0.9)	1 (0.9)
Lost to Follow-up	1 (0.9)	2 (1.8)
Did Not Wish to Continue	0	1 (0.9)

Treatment failure was not defined by the sponsor, although mention is made of withdrawing subjects, at the investigators' discretion, with intolerable symptoms.
[Clinstat\P00220\8D, pg. 24]

(2) Patient Demographics

Patient demographics are summarized in the following table. The majority of subjects for both groups were female and Caucasian.[Clinstat\P00220\8D, pg. 56]

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PATIENT DEMOGRAPHICS, N (%)
Trial P00-220

Demographic	DL 5.0 mg QD (n=116)	Placebo (n=110)
Age (years)		
Mean	41.8	39.2
Median	42	39
Range (Min-Max)	13-80	13-84
Age Subgroup, N (%)		
12 to <18 years	7 (6)	6 (5)
18 to <65	104 (90)	101 (92)
≥65 years	5 (4)	3 (3)
Sex, n (%)		
Male	31 (27)	25 (23)
Female	85 (73)	85 (77)
Race, n (%)		
Caucasian	86 (74)	74 (67)
Black	5 (4)	4 (4)
Asian	7 (6)	8 (7)
Hispanic	16 (14)	21 (19)
Other	2 (2)	3 (3)
Duration of CIU (years)		
Mean	5.4	6.1
Median	3.0	2.5
Range (Min-Max)	0-12	0-12

A finite and relatively high number of CIU patients have spontaneous remissions within one year. It is important that there is similarity between groups in regards to the mean and median duration of CIU, which there appears to be.

(3) Efficacy Results

Efficacy results were analyzed for the ITT population only. One subject lacked post-baseline diary data and was excluded from efficacy analysis. The total symptom score was defined to be the sum of the 3 individual symptom scores; whenever any one of these 3 individual symptom scores was missing, then the total was missing. Each individual symptom score was evaluated each morning and evening. These evaluations were recorded in daily diaries (AM or PM as appropriate). For the derived intervals, the corresponding values were averaged over all non-missing days in the interval. Subjects missing either the baseline or the post-baseline interval value for a given variable and interval had no change or from baseline calculation. Therefore, they were not included in any of the efficacy analyses or summaries of that variable for that interval. Data from 225 patients from the ITT population were analyzed. The primary efficacy endpoint (bolded in Efficacy Table) and selected data from the secondary endpoints are presented in the table below. Statistically significant endpoints are highlighted in the p-value column. Value differences between treatment groups attaining 0.5 units or more in mean

change from baseline are also highlighted. [Clinstat\P00220\8D, pgs. 59, 61, 62, 64, 68, 158, 159, 207, 219, 226]

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EFFICACY RESULTS TABLE

Study P00220

Pruritus Score Analysis-AM/PM PRIOR 12 (PRIMARY EFFICACY MEASURE)						
	DL		Placebo		*	P-value
	N	Mean (% Change)	N	Mean (% Change)		
Baseline	115	2.19 (0)	110	2.21 (0)	-0.02	0.190
Day 1	115	-0.23 (-8.7)	110	-0.13 (-5.5)	0.10	
Day 2	114	-0.96 (-40.3)	110	-0.44 (-13.8)		
Day 3	112	-1.08 (-47.4)	110	-0.46 (-16.2)		
Day 4	112	-1.08 (-48.5)	108	-0.57 (-23.3)		
Days 1-8	115	-1.05 (-47.9)	110	-0.52 (-21.9)		
Days 9-15	107	-1.28 (-59.1)	90	-0.85 (-39.8)	0.43	
Days 16-22	103	-1.37 (-63.3)	83	-1.03 (-48.1)	0.34	
Days 23-29	100	-1.44 (-67.0)	80	-1.13 (-52.9)	0.31	
Days 30-36	99	-1.44 (-66.1)	78	-1.27 (-59.1)	0.17	0.224
Days 37-42	96	-1.54 (-69.2)	73	-1.28 (-58.6)	0.26	0.076
Pruritus Score Analysis-AM NOW						
Baseline	115	1.97 (0)	110	2.02 (0)	-0.05	
Day 2	111	-0.82 (-36.6)	110	-0.46 (-14.8)	0.36	
Day 3	109	-0.92 (-45.7)	109	-0.52 (-20.0)	0.40	
Day 4	111	-0.96 (-49.0)	108	-0.61 (-27.4)	0.35	
Days 2-8	115	-0.89 (-45.1)	110	-0.55 (-24.8)	0.34	
Days 9-15	107	-1.13 (-56.7)	90	-0.81 (-37.0)	0.32	
Days 16-22	103	-1.11 (-58.5)	83	-0.95 (-49.0)	0.16	0.228
Days 23-29	100	-1.17 (-62.9)	80	-1.01 (-51.9)	0.16	0.245
Days 30-36	99	-1.16 (-62.8)	78	-1.16 (-61.2)	0	0.958
Days 37-42	96	-1.24 (-63.0)	73	-1.22 (-61.2)	0.02	0.921
Total Symptom Score Analysis-AM NOW						
Days 2-8	115	-2.40 (-42.8)	110	-1.53 (-24.3)		
Total Symptom Score Analysis-AM/PM PRIOR						
Days 1-8	115	-2.84 (-43.3)	110	-1.50 (-21.4)		
Number of Hives Analysis-AM/PM Prior						
Days 1-8	115	-0.88 (-40.8)	110	-0.44 (-19.9)	0.44	
Size of the Largest Hive Analysis-AM/PM PRIOR						
Days 1-8	115	-0.90 (-39.0)	110	-0.52 (-19.3)	0.38	
Interference with Sleep Analysis						
Day 2-8	115	-0.70 (-44.0)	110	-0.39 (-14.4)	0.31	
Overall Condition of CIU Analysis: Joint Investigator and Subject-Evaluated						
Last Visit	115	-1.13 (-48.3)	110	-0.59 (-27.3)		
Evaluation of Therapeutic Response: Joint Investigator and Subject-Evaluated						
Last Visit	115	2.74	110	3.62	-0.88	
Interference with Daily Activities Analysis Results						
Day 1-8	114	-0.73 (-46.9)	110	-0.36 (-17.2)	0.37	

* Difference between DL and Placebo in mean change from baseline- to-endpoint

(a) Primary Efficacy Endpoint

The primary endpoint was the mean change in pruritus score after one week of therapy. Efficacy results were reviewed for the ITT population only. Published studies have used the same symptom-centered primary endpoint, but have used an endpoint time of 4 weeks (Nelson et al, *Ann Allergy Asthma Immunol* 2000 May; 84(5):517-22). A review of Pulmonary-Allergy Division history reveals that a pre-specified one-week time endpoint has been acceptable. Desloratadine 5.0 mg did show a statistically significant response, as compared to placebo, in the primary efficacy endpoint. The statistical significance was noted as early as day two. The relative pruritus reduction score of drug and placebo were 47.9% and 21.9% respectively. The mean pruritus baseline score in the drug treated group, at the day-8 evaluation time point, decreased from 2.19 to 1.14 ($\Delta -1.05$). The mean baseline pruritus score in the placebo group, at the day 8 evaluation time point, decreased to from 2.21 to 1.69 ($\Delta -0.52$). Therefore the mean absolute pruritus score difference in baseline pruritus scores at the one week interval of drug over placebo is $1.69-1.14 = 0.55$ units. The difference in mean change from baseline symptom scores between treatment groups is **0.53**.

While the clinical relevance of this change may be questioned, it is important to note that, during the conduct of the study, almost twice as many placebo patients ($n=35$, 31.8%) as drug patients ($n=19$, 16.4%) discontinued the study early. The high number of placebo discontinuations noted in this study has been consistent with other CIU studies submitted to the Agency. The leading and predominant cause of early discontinuation, 14 subjects treated with drug and 29 subjects treated with placebo, was due to treatment failure. This would indicate that the drug had a clinically important effect in this study.

The differential discontinuation rate would also probably introduce bias toward the null hypothesis. In order to account for this bias, the sponsor states that they performed "endpoint week" analyses for each subject's last available week average. This reveals that the primary efficacy endpoint was statistically significant through week four of therapy, but not through weeks 5 and 6. Also, the pre-specified difference between treatment groups of mean change of 0.5 units or more was not demonstrated beyond the day 1-8 interval. The greatest number of patient discontinuations occurred between the first and second week of therapy for both the placebo and drug group. Placebo vs. DL categorical analysis responder shift charts demonstrating the actual percentage of subjects moving from one symptom severity group to another has been constructed. Placebo vs. DL treatment shift charts comparing Day 1 AM PRIOR to Day 8 AM PRIOR and

comparing Day -1 PM PRIOR to Day 8 PM PRIOR are included in the appendix. These charts indicate a uniform shift of subjects treated with DL from categories of greater symptom severity (higher numbers) to categories with lesser symptom severity compared to subjects who received placebo, and are also supportive of efficacy.

Subgroup analysis for the two individual pivotal studies was also performed using the demographic parameters age, sex, and race. In general, there were too few individuals in each of the subgroups to justify a by-study analysis. The reader is referred to the *Integrated Summary of Efficacy* for a more comprehensive discussion of each of these subgroups. The 12-17 year old age group had 7 patients randomized to drug and 6 patients randomized to placebo. The >65 year old age group had 5 patients randomized to drug and 3 patients randomized to placebo. These groups had too few subjects about which to make meaningful inferences. There were 31 males randomized to drug and 25 males randomized to placebo. The sponsor did not perform statistical testing on this group. [Clinstat\P00220\8D, pg. 164] There were 30 Non-Caucasians randomized to drug and 36 Non-Caucasians randomized to placebo. The majority of the minority patients were composed of Hispanic patients with 16 randomized to drug and 21 randomized to placebo. The sponsor did not perform statistical testing on this group. All other minority groups had too few enrollees to draw inferences from.

The sponsor only tested one dosage strength in this study, therefore a dose-response relationship was not evaluated. Treatment by study center was not statistically significant for the primary parameter.

(b) Secondary Efficacy Endpoints

1. Pruritus: Group mean pruritus AM NOW scores are presented in the Efficacy Results Table. The AM NOW scores reflect subject symptoms present at the end of the dosing interval. The sponsor plans to use these data to support a 24 hour dosing interval. Statistical significance is demonstrated by day two and extends through week two of the study for the treatment group. However, a mean change from baseline symptom scores between treatment groups of 0.5 units or more was never demonstrated (actual value=0.34 at days 1-8). Drawing further inferences would be subject to bias due to the excessive patient discontinuation demonstrated in the placebo group. The sponsor also evaluated AM PRIOR, PM PRIOR, AM/PM PRIOR, AM/PM NOW and PM NOW for all time points (see table on page 15). These points will not be reviewed in depth.

The sponsor did not pre-specify which time points would be examined for the secondary efficacy endpoints. The sponsor also never stated the power analysis for mean change difference in baseline between treatment groups for any of the secondary efficacy endpoints. Clinically significant differences were not pre-specified for any secondary efficacy endpoints. No correction for multiple comparisons was stated, however, the demonstrated level of significance (0.001 in most cases) makes this issue less relevant.

2. Total Symptom Score (TSS) Analysis: TSS is comprised of pruritus, hive size and hive number. Statistical significance was demonstrated for days 2-8 AM NOW TSS in the treatment group. Statistical significance was demonstrated by day 2 and continued through until day 15. The difference between treatment groups in mean change from baseline symptom scores for AM NOW TSS at days 2-8 is **0.87**. Days 16-42 failed to demonstrate statistical significance. These data also support a 24-hour dosing regimen.

AM/PM PRIOR TSS also demonstrated statistical significance at days 1-8. The difference between treatment groups in mean change from baseline symptom in AM/PM PRIOR TSS score was **1.34**. Other TSS variables were not evaluated in depth.

3. Number of Hives: AM/PM Prior number of hives analysis reveals a statistically significant decrease in the number of hives for days 1-8 in the treatment group. This change was noted by day 2 and continued through day 29. The difference in mean change from baseline symptom scores between treatment groups at days 1-8 is **0.44**. The mean baseline number of hives score in the drug group at the day 8 time point decreased to 1.33 (=2.21-0.88). The baseline mean number of hives score in the placebo group decreased to 1.69 (=2.21-0.52).

Although there is a statistically significant mean difference, it does not indicate the absolute number of patients who shift from one group, such as group 3 (>12 hives) or group 2 (7-12 hives) or group 1 (1-6 hives), to a lesser group in the patients receiving drug compared to those receiving placebo. A Placebo vs. DL categorical analysis responder shift chart comparing Day 1 AM PRIOR to Day 8 AM PRIOR from data sent by the sponsor has been included in the appendix. This chart demonstrates that a shift from a group with more severe symptoms to one with lesser symptoms occurred during the first week of treatment in both placebo and active treatment groups, with a greater shift occurring in the active treatment group. Other variable analyses were not evaluated in depth.

4. Size of the Largest Hive: AM/PM Prior size of the largest hive analysis reveals a statistically significant decrease in the largest hives

for day 1-8 in the treatment group. The baseline mean score in the treatment group at the day 8 time point decrease was 1.30 (=2.20-0.90). The baseline mean score in the placebo group at the day 8 time point decrease was 1.70 (=2.20-0.52). The difference in mean change from baseline symptom scores between treatment groups is **0.38**. Although there is statistical significance in these values, the clinical significance is not readily demonstrated. The same criticism applies to this analysis as to items #1 and #3 above. Other variable analyses were not evaluated in depth.

5. Interference with Sleep Analysis: At the primary time point, the drug group had statistically significant less interference with sleep than the placebo group. The statistical significance was noted from day 2 through day 29 and was not present for days 30-42. This study was not designed to demonstrate whether this was due to a sedating effect of the medication, or a therapeutic effect due to decreased symptoms.
6. Overall Condition of CIU (Joint Investigator and Subject evaluated): At the primary time point, the drug group demonstrated statistically significant improvement over the placebo group. Statistical significance was noted at all time points throughout the study. A site effect, that does not drive statistical significance, was also noted at all time points. All daily entries for overall condition were noted after the previous week's diaries entries were reviewed. This could introduce a significant bias in the evaluation. The same criticisms as in #1 and #3 above apply to this efficacy variable.
7. Evaluation of Therapeutic Response (Joint investigator and subject-evaluated): Unlike the other secondary endpoints, this was evaluated on a five point scale instead of a four point scale. This endpoint also demonstrates statistical significance at the primary time point as well as at all time points evaluated. A site effect, that does not drive statistical significance, was also noted at all time points.
8. Interference with Daily Activities: At the primary time point, the drug group demonstrated statistically less interference with daily activities as compared to the placebo group. This difference was noted through day 15. Days 16-42 did not demonstrate a statistically significant difference. The same criticisms as in #1 and #3 apply to this efficacy variable.

(2) Safety Results

1. Extent of exposure

All patients who were randomized and received at least one dose of the study medication were included in the safety analysis. The extent of exposure is summarized in the table below. [Clinstat\P00220\8D, pg. 72]

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EXTENT OF EXPOSURE
Study P00220

Length of Exposure	Number of Subjects	
	DL 5.0 mg QD (n=116)	Placebo (n=110)
1 to 7 days	116 (100)	110 (100)
8 to 14 days	110 (94.8)	98 (89.1)
15 to 21 days	104 (89.7)	85 (77.3)
22 to 28 days	101 (87.1)	81 (73.6)
29 to 35 days	99 (85.3)	80 (72.7)
36 to 42 days	98 (84.5)	74 (67.3)
43 to 49 days	70 (60.3)	56 (50.9)
50 or more days	5 (4.3)	1 (0.9)
Mean (days)	38.7	33.4
Median	43	43
Range (min-Max)		

(b) Adverse Events

- i) Deaths: none
- ii) Serious Adverse Events: none
- iii) Severe Adverse Events:

Three subjects, one in the DL group and two in the placebo group, reported severe adverse events. Five subjects discontinued treatment because of adverse events: 3 (2.6%) treated with drug and 2 (1.8%) treated with placebo. Subject 20/153 discontinued the study after two days of therapy after being diagnosed with an URI by her primary care physician. Subject 22/404 discontinued after 4 days of therapy because of nausea felt by the investigator to be secondary to DL. Subject 23/177 discontinued early because of bronchitis and sinusitis. The case report form states that the subject discontinued study medication as he was placed on an antibiotic/prohibited medication, but he was listed under adverse events. The subject discontinuations are summarized in the table below. [Clinsta\p00220\8D, pg. 81].

SUBJECTS DISCONTINUING TREATMENT

Center/Subject	Sex/Age/Race	Onset/End Day	Days on Tx/Last Contact	Adverse Event(s)	Severity
DL 5.0 mg QD					
20/153	F/49/C	1/8	2/9	URI	Moderate
22/404	F/29/C	2/4	4/5	Nausea	Moderate
23/177	F/44/C	8/41	14/15	Bronchitis Sinusitis	Moderate Moderate
Placebo					
15/416	F/27/H	16/16	21/31	Vomiting	Moderate
17/362	F/37/C	3/3	3/6	Somnolence	Moderate

Two subjects treated with drug had adverse events resulting in interruption of treatment. Subject No. P00220-19/439 experienced palpitations and severe fatigue. The sponsor states that this patient subsequently discontinued the study due to treatment failure and therefore was not included as a subject discontinuing treatment because of a severe adverse event. The sponsor states that the subject had a normal ECG at screening and at the final visit. There is no indication in the record that an ECG was performed during the event. The second subject, No. P00220-23/235 experienced pneumonia after 34 days of treatment with study drug.

This patient may have been mis-classified. An ECG should have been obtained in this patient at the time of symptoms. A normal ECG at baseline and Final visit, in a patient who discontinued therapy, would indicate that the ECG's were obtained when the patient was not actively taking drug. Furthermore, a more thorough evaluation of the symptoms of fatigue should have occurred in this patient to rule out common drug causes such as vasculitis and rhabdomyolysis. At present, however, there is no other indication in the pre-marketing database that DL may pose a safety risk due to these particular adverse events.

iv) Non-Serious adverse events

Treatment-emergent adverse events were reported for 50 (43.1%) of patients exposed to drug and 42 (38.2%) of patients exposed to placebo. The most common adverse events were headache (DL-15.5%, P-10.0%), nausea (DL-6.0%, P-1.8%) and dry mouth (DL-5.2%, P-4.5%).

Incidence of Treatment-Emergent adverse events $\geq 2\%$ are summarized in the table below. [Clinstat\P00220\8D, pg. 74]

ADVERSE EVENTS
Study P00220

Body System/Organ Class	Number (%) of Subjects	
	DL 5.0 mg QD (n=116)	Placebo (n=110)
Any Adverse Event	50 (43.1)	42 (38.2)
Autonomic Nervous System Disorders	7 (6.0)	5 (4.5)
Mouth Dry	6 (5.2)	5 (4.5)
Body As a Whole	21 (18.1)	13 (11.8)
Fatigue	3 (2.6)	1 (0.9)
Fever	0	3 (2.7)
Headache	18 (15.5)	11 (10.0)

Central and Peripheral Nervous System	4 (3.4)	5 (4.5)
Dizziness	3 (2.6)	4 (3.6)
Gastrointestinal System Disorders	15 (12.9)	11 (10.0)
Dyspepsia	3 (2.6)	0
Nausea	7 (6.0)	2 (1.8)
Musculoskeletal System Disorders	7 (6.0)	2 (1.8)
Myalgia	5 (4.3)	1 (0.9)
Psychiatric Disorders	6 (5.2)	6 (5.5)
Somnolence	5 (4.3)	4 (3.6)
Resistance Mechanism Disorders	5 (4.3)	4 (3.6)
Infection Viral	5 (4.3)	4 (3.6)
Respiratory System Disorders	9 (7.8)	10 (9.1)
Nasal Congestion	2 (1.7)	3 (2.7)
Upper Respiratory Tract Infection	3 (2.6)	4 (3.6)

Headache was also the most common adverse event noted in NDA 21-165. Adverse events occurring more commonly among DCL patients compared to placebo include dry mouth, fatigue, headache, dyspepsia, nausea, myalgia, somnolence, and viral infection. There were no clear adverse events related to demographic variables (age, sex, race) except for somnolence which was experienced by 4 male subjects in the drug group (12.9%) compared to no male subjects in the placebo group.

In light of the experience of patient 00220-19/439 described above, it is interesting to note the incidence of fatigue (DL-2.6%, P-0.9%) and myalgia (DL-4.3%, P-0.9) present in this study.

- (c) Adverse laboratory events
There were several laboratory abnormalities, none of which were clinically significant.

- (d) Electrocardiogram Results

Electrocardiogram recordings were machine-read in all study centers except: 01, 11, 14, 15, 17, 18 19, and 22. Calculated QTc intervals were categorized as normal (≤ 430 msec-Males, ≤ 450 msec-Females), borderline (431msec to 450 msec-Males, 451 msec-470 msec-Females) and prolonged (>450 msec-Males, >470 msec-Females). [Clinstat\P00220\8D, pg. 52] The sponsor presents mean ECG data [Clinstat\P00220\8D, pg. 88]. Table 26 [Clinstat\P00220\8D, pg. 90] indicates that 2 patients receiving drug had $\geq 20\%$ change in their QTc-F, but does not indicate what their final QTc interval is. The sponsor also indicates [Clinstat\P00220\8D, pg. 593] that 7 patients had a change in

baseline of 31 to 60 milliseconds and 2 patients had a change in baseline of 61 milliseconds or more. These determinations were made by Fridericia formula, which is more conservative than Bazetts formula at faster heart rates. The absolute value for QTc in these patients also was not listed. The sponsor states that 2 subjects in the drug group had QTc-F interpretations of 480 msec or more (No. 220-14/076-537 msec, 220-25/185-455msec). The sponsor states that a review of the ECG of subject 220-14/076 by an independent cardiologist was interpreted as 394 msec. This patients initial QTc-F was 401 msec. My own evaluation of the databank [crt\datasets\P00220\L18ECG] revealed the two patients described above. Additionally two other patients 220-00/433 and 220-00/405 had baseline QTc-B values of 462 msec and 465 msec respectively that decreased to 450msec and 444 msec respectively, at the end of therapy.

Drugs being primarily evaluated for QTc interval changes require human overread of all ECG's. Machine-interpreted ECG data is unacceptable for primary safety evaluation. However, because the effect of desloratadine on QTc was extensively studied during trials submitted under a previous NDA (NDA 21,165, where >2000 patients were studied) it is unlikely that an additional 100 - 200 patients exposed to DL during studies conducted in support of this NDA will contribute substantially to the overall pre-marketing safety profile of this drug .

i) CONCLUSIONS

(1) Efficacy

Efficacy of DL 5 mg in CIU is supported by the data submitted in this application. Efficacy of DL was assessed using the primary endpoint "mean pruritus AM/PM PRIOR 12 hour score" for days 1-8. The effect size was 26% over placebo or 0.52 units of absolute change. Mean pruritus AM NOW score measured on days 1-8 supports but is not definitive for a 24 hour dosing interval, since the difference between placebo and DL did not exceed the pre-specified clinically significant difference of 0.5 units. It may be reasonable to extrapolate this information from the 24-hour dosing interval demonstrated for the SAR indication, however. Total symptom score, number of hives and size of the largest hive demonstrated numerical superiority of the drug therapy group compared to placebo. Interference with sleep, overall condition of CIU, evaluation of therapeutic response and interference with daily activities showed numerical superiority of the drug treatment groups compared to placebo during the day 1-8 time point evaluation. There were more subjects in the placebo group that discontinued prematurely, which is supportive of drug efficacy. The dosage chosen by the sponsor is not

supported by a dose-ranging pharmacodynamic component in this study. However, data suggests that the dose effective for SAR would also be effective for CIU, which has been shown to be true of the parent drug, loratadine.

(2) Safety

Safety of DCL 5mg in general is supported by this trial. The once daily administration of desloratadine 5mg was generally safe and well tolerated. Safety assessments included adverse events, vital signs, physical examination, clinical laboratory tests and ECGs. Clinical laboratory tests and ECGs were done at baseline and at the last visit. There were no deaths or severe adverse events reported during this study. Two of the 3 serious adverse events noted in the DL subjects were unlikely to be drug related. Interpretation of the third (nausea) is limited by lack of information but was felt by the investigator to be drug related. It is impossible to evaluate whether or not the interruption of therapy in patient P00220-19/439 secondary to weakness and palpitations was due to drug therapy because of inadequate evaluation of his symptoms and lack of re-exposure to the drug. The most common adverse events in the drug group were headache, dry mouth and nausea. Nausea, dyspepsia and myalgia in the DL group, while infrequent, exceeded the placebo group by > 2%. None of these symptoms necessitated drug withdrawal. No ECG effects were noted although the analysis was inadequate. The cardiovascular safety of desloratadine is generally supported by studies conducted for NDA 21-165. Although qualitatively similar, the adverse event profile defined by the CIU population studied in this application may indicate sufficient differences to justify labeling distinct from that provided for the SAR population in NDA 21-165 (see ISS, below).

(1) Labeling Comments

Under **Clinical Trials** section: Please see labeling comments in SECTION 10. Line 185 states that efficacy and safety of CLARINEX was . This is inaccurate. Efficacy and safety of CLARINEX was studied and the word should be deleted. Also, although the study was of six weeks duration, the primary time end point evaluation for reduction of associated itching and hives was at one week. The sponsor should insert a sentence clarifying this. The categories pruritus AM NOW, number of hives, size of largest hive, interference with sleep and interference with daily activities did not achieve a pre-specified change ≥ 0.5 (although there was no clearly stated unit change that was considered significant for secondary endpoints) at the one week time interval evaluation. Therefore the results of this study does not support this claim in the label.

Pivotal Study POO-221

i) TITLE

Efficacy and safety of desloratadine (SCH 34117) in the treatment of chronic idiopathic urticaria.

ii) OBJECTIVES

This study is identical in objective, design and population criteria to study P00-220. Differences are noted under the appropriate section.

iii) ENDPOINTS

This study has identical efficacy and safety endpoints as study P00-220. Please refer to that study for more information.

iv) SETTING/CENTERS

The study was design to recruit approximately 10 to 12 subjects at each of approximately 30 domestic and international study centers to meet the projected sample size of approximately 200 subjects. The study ultimately enrolled 190 total patients, 48 males and 142 females. The age range was 12-79 years. There were 95 patients in the DL group and 95 patients in the placebo group. [Clinstat\PO0221\8D, pg. 3,4, 23]

v) POPULATION

(1) Inclusions:

Please refer to the review of study P00-220 for criteria and reviewer's comments.

(2) Exclusion Criteria:

Please refer to the review of study P00-220 for criteria and reviewer's comments.

(3) Proscribed Medications:

Please refer to the review of study P00-220 for criteria and reviewer's comments.

vi) DESIGN

(1) Overall statement

This was a Phase III, randomized, placebo-controlled, parallel-group, multicenter, double-blind study of DL 5.0 mg QD in subjects with Chronic Idiopathic Urticaria.

(2) Summary of protocol

(a) The study was conducted at 29 medical centers: 23 in the United States and 6 internationally. Of these 29 centers, 27 enrolled subjects and 2 (Center Nos. 26 and 29) did not enroll subjects. Duration of treatment was up to 6 weeks. Study center P00221-18 amended their protocol to limited enrollment to subjects ≥ 18 years of age. For further details, please refer to study P00-220.

(b) Study sequence: Please refer to study P00-220 for criteria and reviewer's comments.

(3) Assessments

(a) Efficacy

For efficacy assessment details, please refer to study review P00220.

(b) Safety

For safety assessment details, please refer to study review P00220.

(c) Compliance

For compliance details, please refer to study review P00220.

vii) STATISTICAL AND ANALYTICAL PLAN

(1) Efficacy

Please refer to study review P00220 for criteria and reviewer's comments regarding this section.

(2) Safety

Please refer to study review P00220 for criteria and reviewer's comments regarding this section.

viii) RESULTS

(1) Patient Disposition

A total of 190 subjects were randomized at 29 centers from July 12 1999 to March 16, 2000. Ninety-five subjects were randomized to active drug and 95 subjects were randomized to placebo. A total of 51 (26.8%) subjects failed to complete the study: 19 (20%) subjects in the DL group and 32 (33.7%) in the placebo group. The sponsor derived the following table to summarize subject disposition. [Clnstat\P00221\8D, pg. 54]

DISPOSITION OF PATIENTS, N (%)

Study P00221

	DL 5.0 mg QD	Placebo
Number Randomized	95 (100%)	95 (100%)
Number (%) Completed	76 (80)	63 (66.3)
Number (%) Discontinued	19 (20)	32 (33.7)
Reason for Discontinuation		
Treatment Failure	13 (13.7)	21 (22.1)
Adverse Event	3 (3.2)	2 (2.1)
Non-compliance	3 (3.2)	6 (6.3)
Lost to Follow-up	1 (0.9)	2 (1.8)
Did Not Wish to Continue	0	1 (0.9)

Treatment failure was not defined by the sponsor, although mention is made of withdrawing subjects, at the investigators' discretion, with intolerable symptoms. [Clinstat\P00221\8D, pg. 25,26]

(2) Patient Demographics

Patient demographics are summarized in the following table. The majority of subjects for both groups were female and Caucasian. [Clinstat\P00220\8D, pg. 56]

DEMOGRAPHICS

Study P00221

Demographic	DL 5.0 mg QD (n=116)	Placebo (n=110)
Age (years)		
Mean	38.9	42.0
Median	39	43
Range (Min-Max)	12-75	14-79
Age Subgroup, N (%)		
12 to <18 years	6 (6)	3 (3)
18 to <65 years	86 (91)	86 (91)
3 (3)	3 (3)	6 (6)
Sex, n (%)		
Male	27 (28)	21 (22)
Female	68 (72)	74 (78)
Race, n (%)		
Caucasian	81 (85)	85 (89)
Black	5 (5)	4 (4)
Asian	3 (3)	1 (1)
American Indian	1 (1)	0
Hispanic	4 (4)	5 (5)
Other	1 (1)	0
Duration of CIU (years)		
Mean	4.3	6.4
Median	1.8	1.5
Range (Min-Max)		

A finite and relatively high number of CIU patients have spontaneous remissions within one year. It is important that there is similarity between groups in regards to the mean and median duration of CIU, which there appears to be.

(3) Efficacy Results

Efficacy results were analyzed for the ITT population only. One subject (placebo group) lacked baseline diary data and was excluded from efficacy analysis. Data from 189 patients from the ITT population were analyzed. The primary efficacy endpoint (bolded in Efficacy Table) and selected data from the secondary endpoints are presented in the table below. Statistically significant endpoints are highlighted in the p-value column. Value differences between treatment groups attaining 0.5 units or more in mean change from baseline are also highlighted. Other criteria are outlined under study P00220. [Clinstat\P00221\8D, pgs. 60, 62, 64, 66, 70, 162, 163, 213, 225, 232]

**APPEARS THIS WAY
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