EFFICACY RESULTS TABLE

Study P00221

		DL		Placebo		P-value
	N	Mean (% Change)	N	Mean (% Change)	*	
Pruritus Score Analysis-AM/PM PRIOR 12 (PRIMARY EFFICACY MEASURE)						
Baseline	95	2.24 (0)	94	2.22 (0)	0.02	
Day 1	95	-0.21 (-11.0)	94	-0.10 (-5.3)	0.11	0.176
Day 2	95	-0.94 (-45.2)	94	-0.30 (-14.0)		
Day 3	95	-1.09 (-50.2)	93	-0.32 (-14.2)		
Day 4	95	-1.26 (-57.4)	91	-0.62 (-25.6)		
Days 1-8	**95**	**-1.22 (-56.0)**	**94**	**-0.49 (-21.5)**		
Days 9-15	89	-1.53 (-69.3)	76	-0.79 (-34.1)		
Days 16-22	81	-1.59 (-70.5)	69	-0.91 (-40.7)		
Days 23-29	79	-1.66 (-74.9)	67	-1.00 (46.8)		
Days 30-36	77	-1.64 (-73.9)	62	-1.07 (49.2)		
Days 37-42	77	-1.63 (-56.0)	62	-1.07 (-48.7)		
Pruritis Score Analysis-AM NOW						
Baseline	95	1.99 (0)	94	2.11 (0)	-0.12	
Day 2	95	-0.86 (-45.1)	93	-0.18 (-3.5)		
Day 3	95	-0.89 (-49.3)	92	-0.15 (-3.3)		
Day 4	95	-0.96 (-50.0)	91	-0.53 (-20.8)	0.43	
Days 2-8	95	-1.05 (-55.1)	94	-0.41 (-14.5)		
Days 9-15	89	-1.27 (-64.9)	76	-0.69 (-26.7)		
Days 16-22	81	-1.34 (-64.9)	69	-0.85 (-36.8)	0.49	
Days 23-29	79	-1.39 (-70.8)	67	-0.96 (-45.1)	0.43	
Days 30-36	77	-1.37 (-70.5)	62	-0.97 (-44.8)	0.40	
Days 37-42	77	-1.36 (-68.9)	62	-1.02 (-46.0)	0.34	
Total Symptom Score Analysis-AM NOW						
Days 2-8	95	-2.69 (-49.2)	94	-0.97 (-12.7)		
Total Symptom Score Analysis-AM/PM PRIOR						
Days 1-8	95	-3.17 (-51.6)	94	-1.14 (-19.3)		
Number of Hives Analysis-AM/PM Prior						
Days 1-8	95	-0.98 (-48.4)	94	-0.33 (-15.8)		
Size of the Largest Hive Analysis-AM/PM PRIOR						
Days 1-8	95	-0.97 (-49.7)	94	-0.32 (-17.0)		
Interference with Sleep Analysis						
Day 2-8	95	-0.71 (-53.0)	94	-0.39 (-18.4)	0.32	
Overall Condition of CIU Analysis: Joint Investigator and Subject-Evaluated						
Last Visit	95	-1.17 (-48.2)	95	-0.52 (21.8)		
Evaluation of Therapeutic Response: Joint Investigator and Subject-Evaluated						
Last Visit	95	2.76	95	3.78		
Interference with Daily Activities Analysis Results						
Day 1-8	95	-0.94 (-50.2)	93	-0.28 (-20.0)		

* 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 56.0% and 21.5% respectively. The mean pruritus baseline score in the drug treated, at the day-8 evaluation time point, decreased from 2.24 to 1.02 (Δ-1.22). The mean baseline pruritus score in the placebo group, at the day 8 evaluation time point, decreased from 2.22 to 1.73 (Δ-0.49). Therefore the mean absolute pruritus score difference in baseline pruritus scores at the one week interval of drug over placebo is 1.73-1.02 = **0.71** units. The difference in mean change from baseline symptom scores between treatment groups is **0.73**.

It is important to note that, during the conduct of the study, almost twice as many placebo patients (n=21, 22.1%) as drug patients (n=13, 13.7%) 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, 13 subjects treated with drug and 21 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 six of therapy. Also, the pre-specified difference between treatment groups of mean change of 0.5 units or more was demonstrated from day 2 to day 42. The greatest number of data discontinuations occurred between the first and second week of therapy for the placebo group and between week two and three for the drug group.

Site number 03 had a greater difference between the mean percent change of pruritus for the drug group compared to placebo group than was observed at other sites. This site also had 8% of the patients in the

study. However, elimination of this site from data analysis of the primary endpoint had little effect on the level of statistical significance (<.001) or on the mean percentage change differential (30.3%) between the drug group compared to the placebo group. The difference in mean change from baseline symptom scores between treatment groups without this site is 0.64.

Placebo vs. DL treatment categorical analysis responder shift charts demonstrating the actual percentage of subjects moving from one categorical treatment group to another have been constructed. Treatment shift charts compare Day 1 AM PRIOR to Day 8 AM PRIOR and are included in the appendix. These charts indicate a uniform shift of subjects treated with DL from a more symptomatic group with regard to pruritus score to a less symptomatic group. This shift for DL was greater than that for placebo, which is 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 6 patients randomized to drug and 3 patients randomized to placebo. The >65 year old age group had 3 patients randomized to drug and 6 patients randomized to placebo. These groups had too few subjects about which to make meaningful inferences. There were 27 males randomized to drug and 21 males randomized to placebo. The sponsor did not perform statistical testing on this group. There were 14 Non-Caucasians randomized to drug and 10 Non-Caucasians randomized to placebo.

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 throughout the study duration. The difference in mean change from baseline symptom scores between treatment groups at days 1-8 is **0.64**. The sponsor also

evaluated AM PRIOR, PM PRIOR, AM/PM PRIOR, AM/PM NOW and PM NOW for all time points. 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: The 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. The statistical significance was demonstrated by day 2 and continued throughout the study duration. The difference between treatment groups in mean change from baseline in the AM NOW TSS treatment group at days 1-8 is **1.72**. These data also support a 24-hour dosing regimen.

   AM/PM PRIOR TSS also demonstrated statistical significance at days 1-8 and the mean score for each week of the study retained statistical significance. The difference between treatment groups in mean change from baseline symptom scores for the AM/PM PRIOR TSS variable is **2.03**. Other TSS analysis variables were not evaluated in depth. [Clinstat\P00221\8D pg.161]

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 throughout the duration of the study. The mean baseline number of hives score in the drug group at the day 8 time point decreased to 1.24(=2.22-0.98). The baseline mean number of hives score in the placebo group decreased to 1.81(=2.14-0.33). The difference in mean change from baseline symptom scores between treatment groups was **0.65**.

   Although the mean difference is statistically significant, it provides no information about the absolute number of patients who benefited from treatment. A categorical or "shift" analysis was therefore performed to determine the approximate number of patients who shifted from a group with more hives to a group with fewer hives (see appendix). Groups were classified as follows: Group 3 (>12 hives), Group 2 (7-12

hives), and Group 1 (1-6 hives). This chart demonstrates that during the first week of treatment, both DL and the placebo patients tended to shift from a group with more hives toward a group with fewer numbers of hives. Although the shift was seen for both placebo and DL patients, the shift was greater for the DL group.

The sponsor's analyses of other parameters were not evaluated in depth. [Clinstat\P00221\8D pg. 162]

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 decrease from baseline in mean score in the treatment group at day-8 was 1.21(=2.18-0.97). The decrease from baseline in mean score in the placebo group at day-8 was 1.83(=2.15-0.32). The difference between treatment groups was **0.65**. Although there is statistical significance in these values, the clinical significance is not readily demonstrated. The same criticism applies to this analysis as to item #1 and #3 above. The sponsor's analyses of other parameters were not evaluated in depth. [Clinstat\P00221\8D pg. 163]

5. Interference with Sleep: At the primary efficacy time point, the drug group had statistically significant less interference with sleep than the placebo group. The statistical significance was noted from day 2 throughout the study duration. 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. A statistically significant difference was noted at all time points throughout the study. A site effect was not noted as it was in study P00-220. All daily entries for overall condition were noted after the previous week's diary 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. The sponsor found this difference to be statistically significant. The clinical relevance has not been established. A site effect was not noted as in study P00-220.

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. A statistically significant difference was noted throughout the study duration.

(4) Safety Results

(a) 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\P00221\8D, pg. 74]

EXTENT OF EXPOSURE
Study P00221

	Number of Subjects	
Length of Exposure	DL 5.0 mg QD (n=116)	Placebo (n=110)
1 to 7 days	95 (100)	95 (100)
8 to 14 days	92 (96.8)	80 (84.2)
15 to 21 days	88 (92.6)	74 (77.9)
22 to 28 days	80 (84.2)	69 (72.6)
29 to 35 days	78 (82.1)	66 (69.5)
36 to 42 days	**78 (82.1)**	**64 (67.4)**
43 to 49 days	62 (65.3)	52 (54.7)
50 or more days	2 (2.1)	0
Mean (days)	38.2	32.6
Median	43	43
Range (min-Max)	[redacted]	

(b) Adverse Events

i. Deaths-None.

ii.Serious or life-threatening adverse events-None.

One subject (04/140) had an anaphylactic reaction to naproxen sodium during the screening period prior to randomization. This patient recovered and completed the study after being randomized to drug. One subject (02/068) experienced back pain and had surgical removal of a kidney stone. Subject No. 07/125 reported an unintended pregnancy after completion of the placebo arm of the study.

iii. Severe adverse events

Three subjects, one in the DL group (02/068-kidney stone) and two in the placebo group, reported severe adverse events. Five subjects discontinued treatment because of adverse events: 3 (3.2%) treated with drug and 2 (2.1%) treated with placebo. Subject 02/068

discontinued the study after 15 days on treatment because of a kidney stone removal. This patient also received multiple antibiotics (prohibited medication). Subject 04/141 discontinued the study after 40 days on treatment for an "Anxiety attack", "Panic attack" and agitation. Patient 23/205 discontinued the study after 4 days on treatment. This subject developed an infection in her wrist after puncturing her wrist with a thorn while grooming a dog. This infection required antibiotics (prohibited medication) for therapy. The discontinuations are summarized below. [Clinstat\P00221\8D, pg. 83].

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					
02/068	F/37/C	16/22 18/18	15/29	Back Pain Renal Stone Remove	Severe
04/141	M/40/C	40/46 40/46	40/45 40/45	Agitation Agitation	Moderate
23/205	F/48/C	2/24	4/4	Infection	Moderate
Placebo					
03/083	F/73/C	6/Ongoing	6/4	Kidney Infection	Moderate
11/041	F/39/C	40/Ongoing	42/67	Injury	Moderate

Subjects 10/068 and 23/205 events were unlikely to be related to drug exposure. There is not enough information on subject 10/141 to make an assessment.

iv) Non-Serious adverse events

Treatment-emergent adverse events were reported for 53 (55.8%) of patients exposed to drug and 41 (43.2%) of patients exposed to placebo. The most common adverse events were headache (DL-12.6%, P-16.8%), fatigue (DL-8.4%, P-0%), viral infection (DL-7.4%, P-8.4%), pharyngitis (DL-6.3%, P-3.2%) URI (DL-5.3%, P-4.2%) and dizziness (DL-5.3%, P-2.1%).

Incidence of Treatment-Emergent adverse events ≥ 2% are summarized in the table below. [Clinstat\P00221\8D, pg. 76]

ADVERSE EVENTS
Study P00221

Body System/Organ Class	Number (%) of Subjects DL 5.0 mg QD (n=95)	Placebo (n=95)
Any Adverse Event	53 (55.8)	41 (43.2)
Body As a Whole	21 (18.1)	13 (11.8)
Back Pain	**3 (3.2)**	**1 (1.1)**
Fatigue	**8 (8.4)**	**0**
Headache	12 (12.6)	16 (16.8)
Headache Aggravated	2 (2.1)	0
Central and Peripheral Nervous System	5 (5.3)	5 (5.3)
Dizziness	**5 (5.3)**	**2 (2.1)**
Gastrointestinal System Disorders	11 (11.6)	6 (6.3)
Diarrhea	**3 (3.2)**	**1 (1.1)**
Dyspepsia	**3 (3.2)**	**1 (1.1)**
Nausea	**4 (4.2)**	**1 (1.1)**
Vomiting	1 (1.1)	2 (2.1)
Musculoskeletal System Disorders	3 (3.2)	2 (2.1)
Myalgia	2 (2.1)	2 (2.1)
Psychiatric Disorders	4 (4.2)	3 (3.2)
Somnolence	2 (2.1)	2 (2.1)
Resistance Mechanism Disorders	8 (8.4)	8 (8.4)
Infection Viral	7 (7.4)	8 (8.4)
Respiratory System Disorders	19 (20.0)	13 (13.7)
Coughing	1 (1.1)	3 (3.2)
Dyspnea	**2 (2.1)**	**0**
Nasal Congestion	**2 (2.1)**	**0**
Pharyngitis	**6 (6.3)**	**3 (3.2)**
Rhinitis	**2 (2.1)**	**0**
Sinusitis	0	2 (2.1)
Upper Respiratory Tract Infection	0	2 (2.1)
Skin and Appendages Disorders	5 (5.3)	2 (2.1)
Acne	**2 (2.1)**	**0**
Vision Disorders	3 (3.2)	0
Conjunctivitis	**3 (3.2)**	**0**

Although infrequent, back pain, fatigue, dizziness, diarrhea, dyspepsia, nausea, dyspnea, nasal congestion, rhinitis, acne and conjunctivitis were noted to occur > 2% (Bolded in table above) in the DL subjects compared to placebo. There were no clear adverse events related to demographic variables (age, sex, race), although there were too few minority subjects about which to draw inferences.

(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: 05, 14, 15, 16, 17, 18, 25, and 27. Calculated QTc interval category classifications were the same as in study P00-220. The sponsor presents mean ECG data [Clinstat\P00221\8D, pg. 89]. Table 24 [Clinstat\P00221\8D, pg. 91] indicates that no patients receiving drug had ≥20% change in their QTc-F. The sponsor also indicates [Clinstat\P00221\8D, pg. 609] that 4 patients had a change in baseline of 31 to 60 milliseconds, but retained a normal QTc-F interval. One patient had a change in baseline QTc-F of 61 milliseconds or more, but retained a normal QTc-F interval. The absolute value for QTc in these patients also was not listed. The sponsor states that one subject (28/232) in the drug group had a QTc-F interpretation of 452 msec (pretreatment QTc-F=411msec). This patient was at site 28, which did not include overreading of the ECG. No other prolongation of ECG was noted by my own evaluation of the databank [crt\datasets\P00221\L18ECG].

The same comments apply to this section as to the ECG section of study P00220.

vi) CONCLUSIONS

(1) Efficacy

Efficacy of DL 5 mg in CIU is supported by the data from this clinical trial. Efficacy of DL was assessed using the primary endpoint of mean pruritus AM/PM PRIOR 12 hour score for days 1-8. Effect size was 24.5% over placebo or 0.71 units of absolute change. Mean pruritus AM NOW score for days 1-8 time point supports a 24 hour dosing interval with a mean difference between treatment groups of > 0.5 units. Total symptom score, number of hives and size of the largest hive also demonstrated numerical superiority over placebo compared to the drug therapy group. Interference with sleep, overall condition of CIU, evaluation of therapeutic response and interference with daily activities also demonstrated numerical superiority in active treatment compared to placebo at the one-week time point evaluation. There were more patients in the placebo group that discontinued prematurely, which is supportive of drug efficacy. Dose ranging data were not provided in this submission, however, it is likely that the dose effective for SAR would also be effective for CIU since this has been shown to be true of the parent drug, loratadine. Dose-ranging data were provided in NDA 21-165 in support of the SAR indication.

(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 drug related deaths during this study. Two of the 3 adverse events noted in the DL group were not likely to be drug-related. There was not enough information about the third adverse event in patient 04/141 to evaluate if this reaction was secondary to drug. The most common adverse events in the drug group were headache, fatigue, viral infection, pharyngitis and dizziness. Also, back pain, fatigue, pharyngitis, diarrhea, dyspepsia, nausea, dyspnea, nasal congestion, rhinitis, acne and conjunctivitis were noted to occur at a greater frequency in the DL subjects compared to placebo. 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. No treatment emergent adverse events unique to the CIU population were identified by this study.

(1) Labeling Comments

Under **Clinical Trials** section: Line 185 states that efficacy and safety of CLARINEX was [redacted] This is inaccurate. Efficacy and safety of CLARINEX was studied and the word [redacted] should be deleted. Also, although the study was of six week 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. Interference with sleep 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 and this study does not support that claim.

APPEARS THIS WAY
ON ORIGINAL

STUDY P01196 (Safety analysis only)

i) TITLE

A Study Evaluating The Suppression Of Wheal And Flare Following Multiple-Dose Administration Of Desloratadine (5mg) To Normal Volunteers.

ii) OBJECTIVES

This study 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.

iii) END POINT

(1) Safety: Vital signs and adverse event monitoring.
(2) Efficacy: The primary variable is the minimum wheal area at Day 28 in drug group compared to placebo group.

iv) SETTING/CENTERS

This was a single-center study that enrolled 28 subjects.

v) POPULATION

Healthy normal male and female volunteers between 18-45 years of age, inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests. Subjects needed to have a positive skin reaction to histamine and negative skin reaction to saline. Subjects should not have used any drugs (except acetaminophen) within 2 weeks prior to the study and no antihistamines or oral decongestants within at least 60 days prior to skin testing.

vi) DESIGN

(1) Overall statement

This is a investigator-subject (third-party) blind, placebo-controlled, single-center, multiple-dose, study in healthy male and female subjects.

(2) Summary of protocol

Physical examinations were performed at screening and at the conclusion of the study. Electrocardiograms and clinical laboratory test were performed at screening and Day –1. In the morning of Day 1 through Day 28, each subject

received, under directly observed therapy, a single 5 mg dose of DL or matching placebo via oral administration. Subjects were allowed to consume breakfast one hour after administration of the treatment. A pharmacist at the site dispensed DL and placebo according to the randomization schedule. Neither the subjects nor the investigator were aware of the treatment assignment. Adverse events were recorded throughout the study. Subjects were given baseline applications of histamine via skin prick at predose, and 1, 3, 6, 12 and 24 hours after dosing. Wheal and flare areas were measured using a tape and pen method. Repeated histamine applications occurred at specified times on days 1, 7, 14, 21 and 28. Serial blood samples were collected on these days for DL and 3-OH DL concentrations. Histamine reactions were assessed by measuring the area of the wheal and flare 10 minutes after the application of histamine and by the measurement of skin blood flow at 0, 5 and 10 minutes with a laser doppler flow meter. Subjects were confined for the duration of the study.

vii) RESULTS

(1) Patient Disposition

Twenty-eight subjects (3F/25M) between the ages of 20-44 years were enrolled and 24 subjects completed the study. Ten subjects were Caucasian, 12 were African-American, 3 were Asian, 2 were Hispanic and 1 was other. Four subjects dropped out of the study, 2 for personal reasons not related to the study (Subject No. 28 who received 5 mg DL and Subject No. 20 who received placebo) and 2 due to adverse events. Subject No. 15 (placebo) experienced a viral syndrome and Subject No. 9 (placebo) experienced prostatitis. Fourteen subjects receiving drug completed the study.

Caucasian females were the predominant demographic group studied for the two pivotal CIU studies, therefore the subjects studied in this trial were not representative of the subjects studied in the two pivotal trials, although there was no evidence that DL PK parameters showed any gender differences (see below).

(2) Safety Results

(a) Adverse Events

i) Deaths-None
ii) Serious or life-threatening adverse events-None
ii) Severe adverse events-None
iv) Non-Serious adverse events

Sixteen subjects reported 33 adverse events. Events are summarized in the table below. [Clinstat\P01196.pdf\pgs. 11-12]

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STUDY P01196 ADVERSE EVENT TABLE

Body System/Organ Class	Number (%) of Subjects DL 5.0 mg QD (n=14)	Placebo (n=14)
Subjects Reporting Adverse Event	6 (43)	10 (71)
Autonomic Nervous System	0	2 (14%)
Dry Mouth	0	2 (14%)
Body As a Whole	1 (7%)	4 (29%)
Headache	1 (7%)	4 (29%)
Pain	1 (7%)	0
Central and Peripheral Nervous System	1 (7%)	1 (7%)
Dizziness	1 (7%)	1 (7%)
Gastrointestinal System Disorders	2 (14%)	1 (7%)
Abdominal Pain	1 (7%)	0
Constipation	0	1 (7%)
Dyspepsia	1 (7%)	0
Hearing and Vestibular Disorders	1 (7%)	0
Earache	1 (7%)	0
Heart Rate and Rhythm Disorders	0	1 (7%)
Arrhythmia	0	1 (7%)
Platelet, Bleeding and Clotting Disorder	0	1 (7%)
Hematoma	0	1 (7%)
Psychiatric Disorders	2 (14%)	1 (7%)
Insomnia	2 (14%)	1 (7%)
Reproductive Disorders, Male	0	1 (8%)
Prostatitis	0	1 (8%)
Resistance Mechanism Disorders	0	1 (7%)
Viral Infection	0	1 (7%)
Respiratory System Disorders	0	1 (7%)
Dyspnea	0	1 (7%)
Skin and Appendages Disorders	4 (29%)	2 (14%)
Dermatitis Contact	1 (7%)	0
Laceration, Skin	1 (7%)	1 (7%)
Pruritis	2 (14%)	1 (7%)
Rash	1 (7%)	0
Skin Disorder	1 (7%)	0
Urinary System Disorders	1 (7%)	0
Dysuria	1 (7%)	0
Vascular (Extracardiac) Disorders	0	1 (7%)
Hemorrhage Nose	0	1 (7%)
White Cell and RES Disorders	1 (7%)	0
Lymphadenopathy	1 (7%)	0

(b) Adverse laboratory events

There were no clinically significant laboratory abnormalities at screening or on day –1. No clinical laboratory tests were performed while the subjects were receiving drug or at study endpoint.

(c) Electrocardiogram Results

The sponsors only performed ECGs at screening (Day –21 to –2) and with visit 1 (Day –1). Therefore, no ECGs were performed while subjects were receiving drugs. Sponsors do not indicate whether ECGs were machine or hand read.

The sponsors indicate that ECGs and clinical laboratory tests were performed for safety evaluations. However, with this protocol ECGs and clinical laboratory tests were used only to exclude subjects with abnormalities, not to monitor for possible adverse effects of drug and safety evaluations.

(a) Pharmacokinetic Results

This area will be reviewed in depth by the clinical pharmacology reviewer. However, one subject (no. 10) was noted to be an outlier with significantly higher serum concentrations of DL than the remainder of the group. Metabolite-to-parent ratios revealed that this subject was not a slow metabolizer of DL based on previously defined criteria for the identification of slow metabolizers (Metabolite-to-parent ratio <10%). See appendix for individual subject AUC and Cmax sponsor derived graph [Clinstat\P01196pdf\pg 229]. The table below demonstrates subject no. 10 compared to subject no. 16 (lowest values) and group mean. [Clinstat\P01196.pdf\pgs. 302-303, 318-319]

STUDY P01196-TABLE OF PHARMACOKINETIC RESULTS*

Phase	AUC 24 (ng*hr/ml)	Cmax (ng/ml)	T ½ (Hrs)
Day 1			
Subject no. 10			
Subject no. 16			
Group Mean	29.59 (SD=10.61)	2.83 (SD=1.10)	14.18 (SD=3.21)
Day 28			
Subject no. 10			
Subject no. 16			
Group Mean	53.97 (SD=29.38)	3.89 (SD=1.69)	14.50 (SD-3.46)

* Demonstrating subjects with max-min values compared to group mean

This demonstrates that at steady state, subject no. 10 (M/39/H) has an AUC 5.6 times greater than the subject with the lowest AUC. Subject no. 10 also has an AUC that is 2.7 times greater than the group mean. Subject no. 10 attains Cmax levels 4.1 times greater than subject no. 16 and 2.2 times greater than the group mean. The accumulation index for DL ranged from 1.6 to 1.8 over the 28-day dosing period.

Subject no. 10 demonstrated much higher levels than the other subjects in this study. It is unfortunate that the sponsor did not included ECG and clinical laboratory evaluations

on day 28 as part of the safety evaluation. The sponsor provided a box and whisker plot [clinstat\P01196.pdf\pg. 231] demonstrating that subject AUC and Cmax levels in study P00117 from NDA submission 21-165 exceeded subject no. 10 AUC and Cmax levels. The original NDA submission for DL included a PK/PD study with timed ECGs that exceeded this patient's Cmax and AUC. No adverse effects were noted. Subject no. 10 reported pruritus and rash beginning on day 9 and resolving by day 15 for the pruritus and day 17 for the rash. No other adverse events were reported by subject no. 10. Review of patient No. 10 case report forms did not reveal any adverse reactions that could be correlated to Cmax. Review of pharmacokinetic data from NDA 21-165 revealed that this patient was within the Cmax range noted for the population studied in DL's original submission.

i) CONCLUSIONS

The safety of desloratadine as assessed by self-reported adverse events is in general supported by this trial given the limits of the study. Safety assessments included adverse events, vital signs and physical examination. ECGs and clinical laboratory testing were not performed while patients were receiving drug. There was one outlier in the study group for AUC and Cmax levels of DL, whose elevated steady state level of DL did not appear to correlate with any specific adverse event(s). There were no deaths, serious or severe adverse events. The four early withdraws from the study did not appear to be drug related.

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IX. INTEGRATED SUMMARY OF EFFICACY

a) Overview

The Integrated Efficacy and Safety Summaries will provide an overview of the combined data from studies P00220 and P00221 which are identical Phase-III, multicenter, randomized, placebo-controlled, double-blinded, parallel-group studies.

The efficacy of desloratadine in CIU is supported by the primary endpoint of mean pruritus AM/PM PRIOR 12 hour score for days 1-8 of the six-week trial period for each study. Effect size of DL was greater than placebo and statistically significant in both studies. The sponsor has pooled demographic data but has presented the efficacy results side-by-side for the two studies without pooling data.

This ISE summary contains data on a total of 416 patients, 211 exposed to desloratadine 5 mg for 6 weeks during the 2 multicenter studies. These studies were conducted in 58 centers with 46 in the U.S.A and 12 internationally in Canada, Europe and South America.

b) Demographic summary

A summary of the demographic data is presented in the table below. [Clinstat\ise.pdf\pg. 17]

DEMOGRAPHIC DATA
Studies P00220 and P00221

Demographic	DL 5.0 mg QD (n=211)	Placebo (n=205)
Age (years)		
Mean	40.5	40.5
Median	40	40
Range (Min-Max)	12-80	13-84
Age Subgroup, N (%)		
12 to <18 years	13 (6)	9 (4)
18 to <65 years	190 (90)	187 (91)
	8 (4)	9 (4)
Sex, n (%)		
Male	58 (27)	46 (22)
Female	153 (73)	159 (78)
Race, n (%)		
Caucasian	167 (79)	159 (78)
Black	10 (5)	8 (4)
Asian	10 (5)	9 (4)
American Indian	1 (<1)	0
Hispanic	20 (9)	26 (13)
Other	3 (1)	3 (1)
Duration of CIU (years)		
Mean	4.9	6.3
Median	2.0	1.9

Range (Min-Max)	[redacted]

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c) Onset of efficacy

In both studies, onset of efficacy, as demonstrated by a absolute mean numerical difference of >0.5 units between treatment groups for the primary efficacy variable pruritus AM/PM Prior was demonstrated by day 2. This and additional variables are summarized in the following table.

ISE SUMMARY TABLE
Studies P00220 and P00221

		DL		Placebo		P-value
	N	Mean (% Change)	N	Mean (% Change)	*	
Pruritus Score Analysis-AM/PM PRIOR 12						
Days 2 (P00220)	114	-0.96 (-40.3)	110	-0.44 (-13.8)		
Days 2 (P00221)	95	-0.94 (-45.2)	94	-0.30 (-14.0)		
Pruritus Score analysis-Day 1 PM PRIOR 12						
Day 1 (P00220)	112	-0.44 (-17.6)	109	-0.24 (10.8)	0.24	0.100
Day 1 (P00221	94	-0.46 (-23.9)	92	-0.23 (11.2)	0.23	0.090
Pruritus Score Analysis-Day 1 PM NOW						
Day 1 (P00220)	111	-0.74 (-29.7)	109	-0.39 (-11.4)	0.35	
Day 1 (P00221)	93	-0.72 (-36.3)	91	-0.20 (-7.7)		
Pruritus Score Analysis-Day 2 AM NOW						
Day 2 (P00220)	111	-0.82 (-36.6)	110	-0.46 (-14.8)	0.36	
Day 2 (P00221)	95	-0.86 (-45.1)	93	-0.18 (-3.5)		

*= DL timepoint mean change from Baseline-Placebo mean timepoint change from Baseline

Study P01196 indicated that sustained inhibition of histamine-induced wheal activity was demonstrated by DL 12 hours after the day 1 oral dosage when compared to placebo (These results were not covered in this document. Please see OCBP review). [Clinstat\P01196.pdf\pg. 406]

Therefore efficacy, as demonstrated by attainment of the pre-specified AM/PM Prior endpoint, was demonstrated by day 2 in both studies P00220 and P00221.

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d) Duration of efficacy

Day 2-8 mean pruritus AM NOW results for study P00220 do not support 24 hours duration dosing, while the results of study P00221 do. Day 2-8 Mean Total Symptom AM NOW scores also would support a 24 hour dosing interval. Data suggests that the duration of efficacy for SAR would also apply to CIU and this has been shown to be true of the parent drug, loratadine. In both studies mean AM/PM PRIOR pruritus, pruritus NOW, TSS AM NOW and AM/PM PRIOR, number and size of the largest hive AM/PM Prior are all similar and show the same trend toward improvement for subjects receiving drug therapy at the primary efficacy time point. Please see the following table.

EFFICACY RESULTS TABLE
Studies P00220 and P00221

		DL		Placebo		P-value
	N	Mean (% Change)	N	Mean (% Change)	*	
Pruritus Score Analysis-AM/PM PRIOR 12 (PRIMARY EFFICACY MEASURE) Study P00220						
Days 1-8 (P00220)	**115**	**-1.05 (-47.9)**	**110**	**-0.52 (-21.9)**		
Days 1-8 (P00221)	**95**	**-1.22 (-56.0)**	**94**	**-0.49 (-21.5)**		
Pruritis Score Analysis-AM NOW						
Days 2-8 (P00220)	115	-0.89 (-45.1)	110	-0.55 (-24.8)	0.34	
Days 2-8 (P00221)	95	-1.05 (-55.1)	94	-0.41 (-14.5)		
Total Symptom Score Analysis-AM NOW						
Days 2-8 (P00220)	115	-2.40 (-42.8)	110	1.53 (24.3)		
Days 2-8 (P00221)	95	-2.69 (-49.2)	94	-0.97 (-12.7)		
Total Symptom Score Analysis-AM/PM PRIOR						
Days 1-8 (P00220)	115	-2.84 (-43.3)	110	-1.50 (-21.4)		
Days 1-8 (P00221)	95	-3.17 (-51.6)	94	-1.14 (-19.3)		
Number of Hives Analysis-AM/PM Prior						
Days 1-8 (P00220)	115	-0.88 (-40.8)	110	-0.44 (-19.9)	0.44	
Days 1-8 (P00221)	95	-0.98 (-48.4)	94	-0.33 (-15.8)		
Size of the Largest Hive Analysis-AM/PM PRIOR						
Days 1-8 (P00220)	115	-0.90 (-39.0)	110	-0.52 (19.3)	0.38	
Days 1-8 (P00221)	95	-.0.97 (-49.7)	94	-0.32 (-17.0)		
Interference with Sleep Analysis						
Days 2-8 (P00220)	115	-0.70 (-44.0)	110	-0.39 (-14.4)	0.31	
Days 2-8 (P00221)	95	-0.71 (-53.0)	94	-0.39 (-18.4)	0.32	
Overall Condition of CIU Analysis: Joint Investigator and Subject-Evaluated						
Last Visit (P0020)	115	-1.13 (-48.3)	110	-0.59 (27.3)		
Last Visit (P0021)	95	-1.17 (-48.2)	95	-0.52 (21.8)		
Evaluation of Therapeutic Response: Joint Investigator and Subject-Evaluated						
Last Visit (P00220)	115	2.74	110	3.62	-0.88	
Last Visit (P00221)	95	2.76	95	3.78	-1.02	
Interference with Daily Activities Analysis Results						
Days 1-8 (P00220)	114	-0.73 (-46.9)	110	-0.36 (-17.2)	0.37	
Days 1-8 (P00221)	95	-0.94 (-50.2)	93	-0.28 (-20.0)		

*= DL mean timepoint change from Baseline-Placebo mean timepoint change from Baseline

Study P01196 demonstrated inhibition of histamine induced wheal activity, a pharmacodynamic endpoint, by DL for twenty-four hours in the group receiving DL compared to placebo.

Therefore, a 24-hour interval is supported by study P00221, study P001196 (indirect evidence) and evidence from NDA 21-165.

e) Efficacy in subgroups

Response by age, sex, and race was also examined. Overall, DL was numerically more effective than placebo in reducing mean AM/PM PRIOR pruritus scores in both male and female subjects and Caucasian and non-Caucasian subjects. The sponsor performed numerical comparisons only. Mean changes and mean percent changes were similar between sexes. The limited number of subjects in the 12 to < 18 years old or the ≥ 65 years old groups do not permit inferential conclusions. This data is summarized in the table below. Time points achieving ≥ 0.5 unit difference favoring DL over placebo are bolded.

Demographic Summary Data [Clinstat\ise.pdf\pgs. 53-66]

Interval	DL			Placebo			
Day 1-8	N	Mean (SD)	Mean % Change	N	Mean (SD)	Mean % Change	*
Pruritus AM/PM PRIOR-12-17 years old							
P00220	7	-1.28 (1.0)	-55.9%	6	-0.30 (0.7)	-12.4%	**0.98**
P00221	6	-1.36 (0.3)	-57.3%	3	-0.67 (0.8)	-31.0%	**0.69**
Pruritus AM/PM PRIOR-18-64 years old							
P00220	103	-1.09 (0.8)	-49.0%	101	-0.55 (0.7)	-22.7%	**0.54**
P00221	86	-1.25 (0.8)	-55.9%	85	-0.50 (0.7)	-20.7%	**0.75**
Pruritus AM/PM PRIOR-≥65 years old							
P00220	5	-0.32 (0.3)	-14.4%	3	-0.38 (0.5)	-16.0%	-0.06
P00221	3	-1.37 (0.3)	-56.9%	6	-0.58 (0.5)	-28.1%	**0.79**
Pruritus AM/PM PRIOR-Male							
P00220	31	-1.07 (0.7)	-50.9%	25	-0.35 (0.6)	-12.7%	0.48
P00221	27	-1.09 (0.8)	-48.8%	21	-0.58 (0.7)	-26.4%	**0.51**
Pruritus AM/PM PRIOR-Female							
P002200	84	-1.07 (0.9)	-46.8%	85	-0.59 (0.8)	-24.6%	0.48
P00221	68	-1.33 (0.7)	-58.9%	73	-0.49 (0.7)	-20.2%	**0.84**
Pruritus AM/PM PRIOR-Caucasian							
P00220	85	-1.05 (0.8)	-47.6%	74	-0.58 (0.7)	-24.4%	0.47
P00221	81	-1.26 (0.7)	-57.2%)	84	-0.52 (0.7)	-22.0%	**0.74**
Pruritus AM/PM PRIOR- Non-Caucasian							
P00220	14	-1.24 (0.9)	-49.2%	10	-0.48 (0.7)	-18.1%	**0.76**
P00221	30	-1.12 (0.8)	-48.8%	36	-0.45 (0.8)	-16.8%	**0.67**

*= DL mean timepoint change from Baseline-Placebo mean timepoint change from Baseline

The Non-Caucasian group was not further subdivided by racial heritage.

Therefore, conclusions regarding efficacy reflect predominantly 18-64 year old Caucasian females. No inferences can be drawn at age extremes or in different gender or ethnic groups.

f) Study audit and review of financial disclosure forms

An audit of study sites was not performed for this application. There was not a preponderance of patients recruited at a single site. Subjects receiving drug did not have an inordinate response rate at any site.

g) Summary statement

The data are conclusive that desloratadine 5 mg daily provides a numerical and statistically significant reduction in pruritus for patients diagnosed with CIU after a one week treatment interval within the limitations of the study. Limitations include limited evaluation in populations other than Caucasians and limited evaluations in age groups outside the range of 18-64 years old. There was also limited evaluation in male gender, although the study demographics did reflect the population demographics of the disease. Based on the totality of the data and on placebo drop-out rates, desloratadine 5 mg daily also provides a clinical improvement in CIU patients. Desloratadine's clinical effects are demonstrated by day 2 based on AM/PM PRIOR scores.

h) Labeling comments

Please see comments under studies P00220 and P00221.

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X. INTEGRATED SUMMARY OF SAFETY

a) Overview

A total of 416 subjects were randomized into studies P00220 and P00221. All subjects were combined and included in the safety evaluation.

b) Demographics

A summary of the demographic data is presented in the table below. [Clinstat\ise.pdf\pg. 17]

DEMOGRAPHIC SUMMARY DATA
STUDIES P00220 AND P00221

Demographic	DL 5.0 mg QD (n=211)	Placebo (n=205)
Age (years)		
Mean	40.5	40.5
Median	40	40
Range (Min-Max)	12-80	13-84
Age Subgroup, N (%)		
12 to <18 years	13 (6)	9 (4)
18 to <65 years	190 (90)	187 (91)
	8 (4)	9 (4)
Sex, n (%)		
Male	58 (27)	46 (22)
Female	153 (73)	159 (78)
Race, n (%)		
Caucasian	167 (79)	159 (78)
Black	10 (5)	8 (4)
Asian	10 (5)	9 (4)
American Indian	1 (<1)	0
Hispanic	20 (9)	26 (13)
Other	3 (1)	3 (1)
Duration of CIU (years)		
Mean	4.9	6.3
Median	2.0	1.9
Range (Min-Max)		

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c) Duration of Exposure/Extent of Exposure

The overall extent of exposure is summarized in the table below. [clinstat\iss.pdf\pg. 21]

SUMMARY OF EXTENT OF DRUG EXPOSURE
STUDIES P00220 AND P00221

	Number (%) of Subjects	
Day Interval	DL 5.0 mg N=211	Placebo N=205
1-7	211 (100.0)	205 (100.0)
8-14	202 (95.7)	178 (86.8)
15-21	192 (91.0)	159 (77.6)
22-28	181 (85.8)	150 (73.2)
29-35	177 (83.9)	146 (71.2)
36-42	176 (83.4)	138 (67.3)
43-49	132 (62.6)	108 (52.7)
≥ 50	7 (3.3)	1 (<1)
Mean (days	38.5	33.0
Median	43	43
Range (Min-Max)	[redacted]	

In study P01196, twenty-eight subjects were enrolled and 24 subjects completed the study. Subjects receiving DL were exposed for 28 `days.

i) Patient disposition

A total of 105 subjects discontinued from the studies prior to completing the protocol 38 (18%)-DL, 67 (32.7%)-placebo. Ten subjects discontinued in association with adverse events (6-DL, 4-placebo). Overall the percentage of discontinuations was 18% for the DL group and 32.7% for the placebo group. The most common reason for discontinuation was treatment failure (12.8%-DL, 24.4%-P). [clinstat\iss.pdf\pg. 13]

Four subjects discontinued therapy in study P01196. Two subjects for personal reasons and two subjects (both placebo) for adverse events (prostatitis and a viral syndrome).

d) Deaths/Serious Adverse Events/Adverse Events/Pregnancies

All the adverse events reported were treatment-emergent defined as beginning on or after the first day of treatment through 30 days after the last day of subject participation. There were no deaths. Serious or life-threatening adverse events and severe adverse events are summarized under each individual study. There was one reported pregnancy in a patient who had received placebo. Pooled non-serious adverse events data reveals that the most frequently reported adverse event was headache followed by viral infection, nausea and fatigue. These results are presented in the table below. [clinstat\iss.pdf\pg. 26]

POOLED NON-SERIOUS ADVERSE EVENT
STUDIES P00220 AND P00221

	Number (%) of Subjects	
Body System/Organ Class	DL 5.0 mg QD (n=211)	Placebo (n=205)
Any Adverse Event	103 (48.8)	83 (40.5)
Autonomic Nervous System Disorders	9 (4.3)	6 (2.9)
Mouth Dry	**7 (3.3)**	**6 (2.9)**
Body As a Whole	42 (19.9)	32 (15.9)
Fatigue	**11 (5.2)**	**1 (<1)**
Fever	1 (<1)	4 (2.0)
Headache	**30 (14.2)**	**27 (13.2)**
Central and Peripheral Nervous System	9 (4.3)	10 (4.9)
Dizziness	**8 (3.8)**	**6 (2.9)**
Gastrointestinal System Disorders	26 (12.3)	17 (8.3)
Diarrhea	**5 (2.4)**	**3 (1.5)**
Dyspepsia	**6 (2.8)**	**1 (<1)**
Nausea	**11 (5.2)**	**3 (1.5)**
Vomiting	3 (1.4)	4 (2.0)
Musculoskeletal System Disorders	10 (4.7)	4 (2.0)
Myalgia	**7 (3.3)**	**2 (1.0)**
Psychiatric Disorders	10 (4.7)	9 (4.4)
Somnolence	7 (3.3)	8 (3.9)
Resistance Mechanism Disorders	13 (6.2)	12 (5.9)
Infection Viral	12 (5.7)	12 (5.9)
Respiratory System Disorders	28 (13.3)	23 (11.2)
Coughing	2 (<1)	5 (2.4)
Pharyngitis	**6 (2.8)**	**4 (2.0)**
Upper Respiratory Tract Infection	8 (3.8)	8 (3.9)

Fatigue occurred in 5.2% of subjects receiving DL compared to 1% of subjects receiving placebo. Although infrequent, dyspepsia, nausea and myalgia were noted to occur > 2% (Bolded in table above) in the DL subjects compared to placebo. Other AE's occurring at a greater frequency in DL compared to placebo subjects included dry mouth, headache, dizziness, diarrhea, and pharyngitis.

The sponsor also displayed body system/organ class treatment-emergent adverse

events summarized for age, race and sex. No appreciable differences were noted in any of these demographic subgroups, however there were too few subjects in the age 12 to <18 years or ≥ 65 years, or who were non-Caucasian, from which to make meaningful conclusions.

Study P01196 revealed no unique safety findings compared to studies P00220 or P00221.

e) Laboratory Studies

There were no clinically meaningful laboratory abnormalities in the subjects receiving drug.

f) Special Studies

There were no clinically meaningful ECG abnormalities in the subjects receiving drug. However, ECG determinations were only made at baseline and at study completion. ECG for the final visit were to be obtained approximately 1 to 3 hours after the last dose of study drug which would roughly correlate with C_{max}.

g) Labeling Comments

Please see comments under studies P00220 and P00221.

XI. CONCLUSIONS

The sponsor has submitted 2, multicenter safety and efficacy studies and one pharmacokinetic study to support the indication of desloratadine 5 mg every day in the treatment of chronic idiopathic urticaria. The two efficacy studies had identical trial designs and were randomized, double-blind, parallel-group, placebo-controlled studies. Both of these studies attained the numerical pre-specified mean endpoint difference and statistical significance favoring DL over placebo in improvement of pruritus in CIU subjects at the primary time point of one week. In evaluating data regarding improvement in the size and number of hives mean score at the one week time point, study P00220 did not attain a ≥0.5 unit numerical endpoint difference between the subjects in the DL group compared to subjects in the placebo group, but did demonstrate statistical significance. Study P00221 did attain a ≥0.5 unit numerical endpoint difference and statistical significance between the subjects in the DL group compared to subjects in the placebo group in improving the size and number of hives mean score at the one week time point. The body of evidence indicates that DL is effective in the treatment of CIU.

The use of desloratadine in patients with chronic idiopathic urticaria did not reveal any unique safety concerns. There did not appear to be an inordinate risk of adverse events in the limited number of patients in this study compared to the benefit experienced by drug

responders. The safety of DL was not established in this NDA submission in special populations of patients with clinically significant hematological, cardiovascular, hepatic, renal, neurologic, psychiatric or autoimmune diseases.

XII. LABELING COMMENTS

DRAFT

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

Cc: Original NDA/21,297
HFD 570/Division File
HFD 570/Purucker
HFD 570/Meyer
HFD 570/Gebert
HFD 570/Rosebraugh
HFD 570/Ostroff

References:

1. Greaves MW. Chronic Urticaria. NEJM 1995; 332(26):1767-1772.
2. Nelson HS, Reynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. Ann Allergy Asthma Immunol 2000; 84(5):517-22.
3. Greaves MW, Sabroe RA. BMJ 1998; 316:1147-50.
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6. Ring J, Brockow K, Ollert M, Engst R. Antihistamines in urticaria. Clin Exp Allergy 1999 Mar;29 Suppl 1:31-7.
7. Erel F, Sener O, Erdil A, Karaayvaz M, Gur G, Caliskaner Z, Ozangue N. Impact of Helicobacter pylori and Giardia lamblia infections on chronic urticaria. J Investig Allergol Clin Immunol 2000 Mar-Apr; 10(2):94-7.

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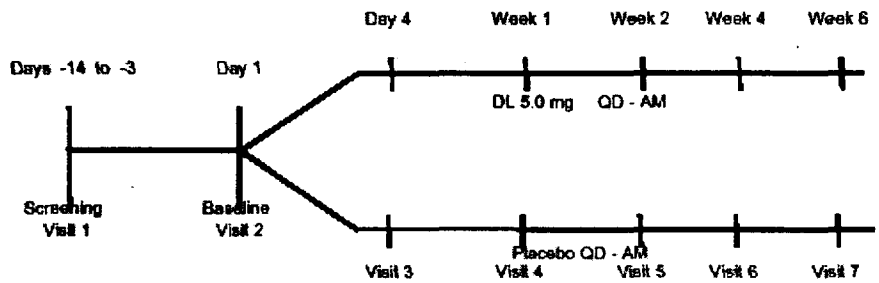
XIII. APPENDIX

Schematic representation of the study design. [Clinstat\P00220\8D, pg. 20]



Postbaseline visits were on Day 4, and Weeks 1, 2, 4 and 6:
(Visits 3 ,4, 5, 6 and 7)

Allowed Visit windows:
Day 4 and Week 1: +/- 1 day
Weeks 2, 4 and 6: +/- 2 days

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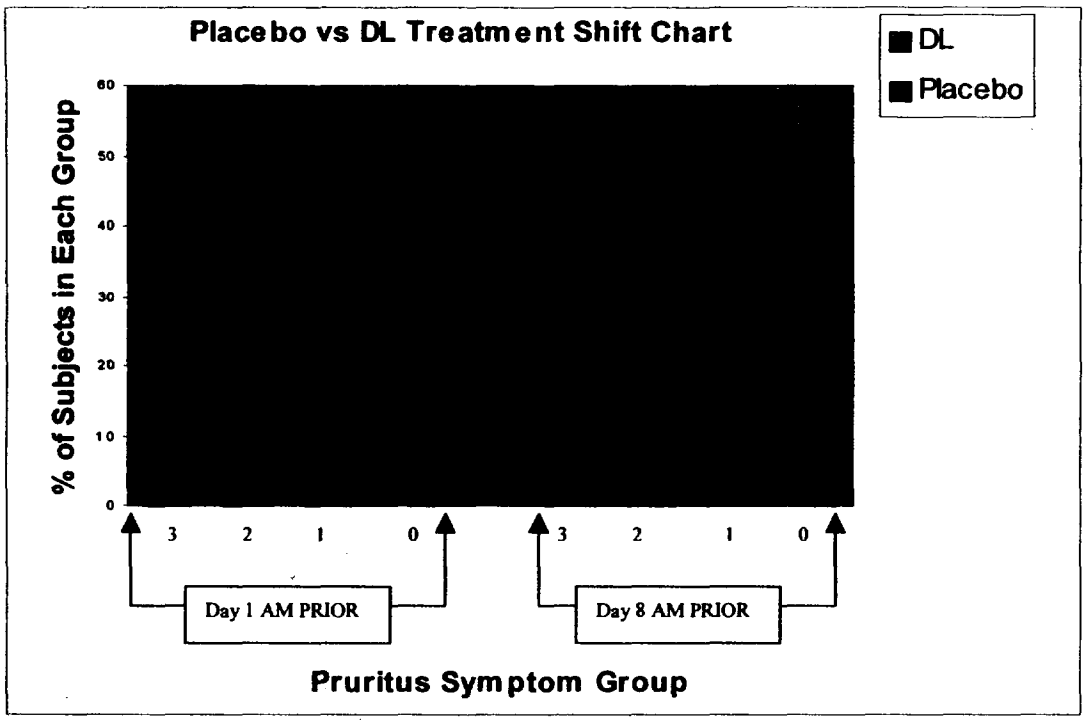

Study P00-220: Placebo vs DL Treatment Categorical Analysis Responder Shift Chart for Day 1 (Baseline) vs Day 8 AM PRIOR Scores
Group 3=Severe Pruritus, Group 0=No Pruritus
DL group had a 7% (n=8) drop out rate between day 1 and day 8
Placebo group had a 9% (n=10) drop out rate between day 1 and day 8

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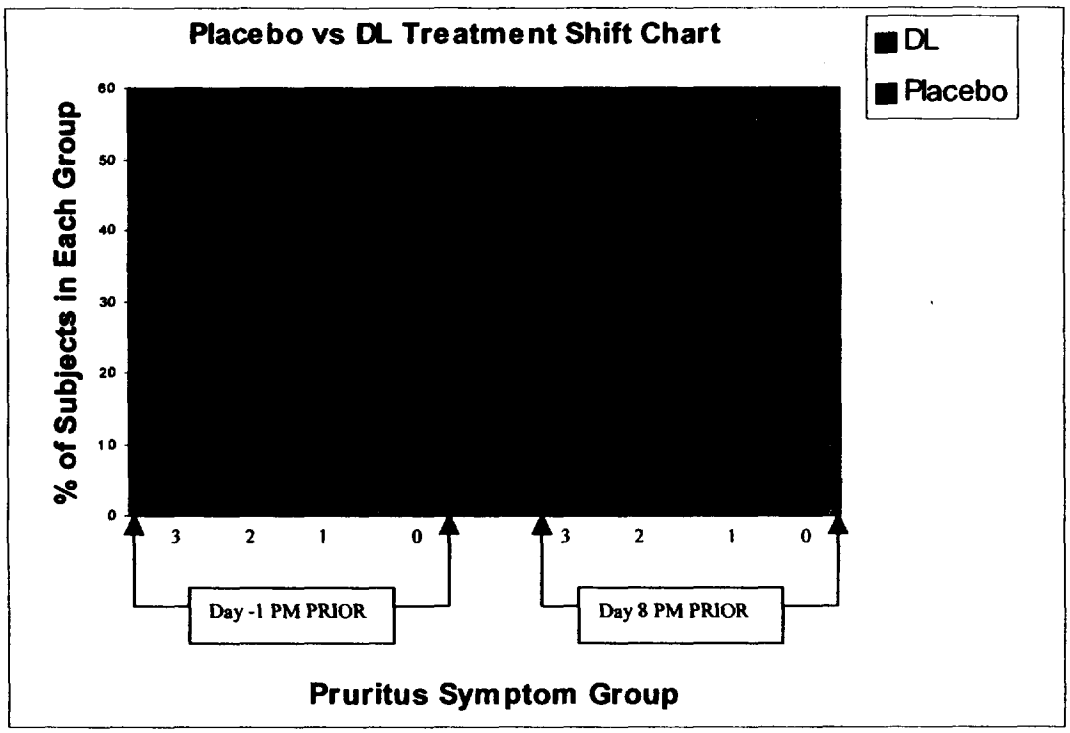
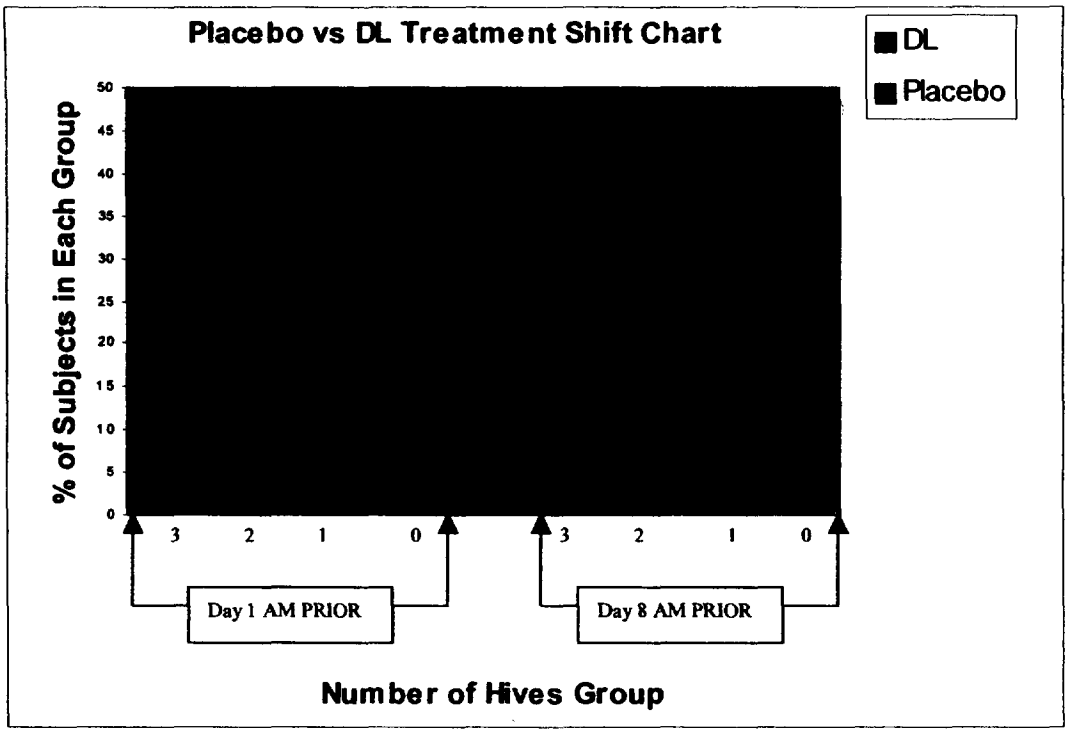
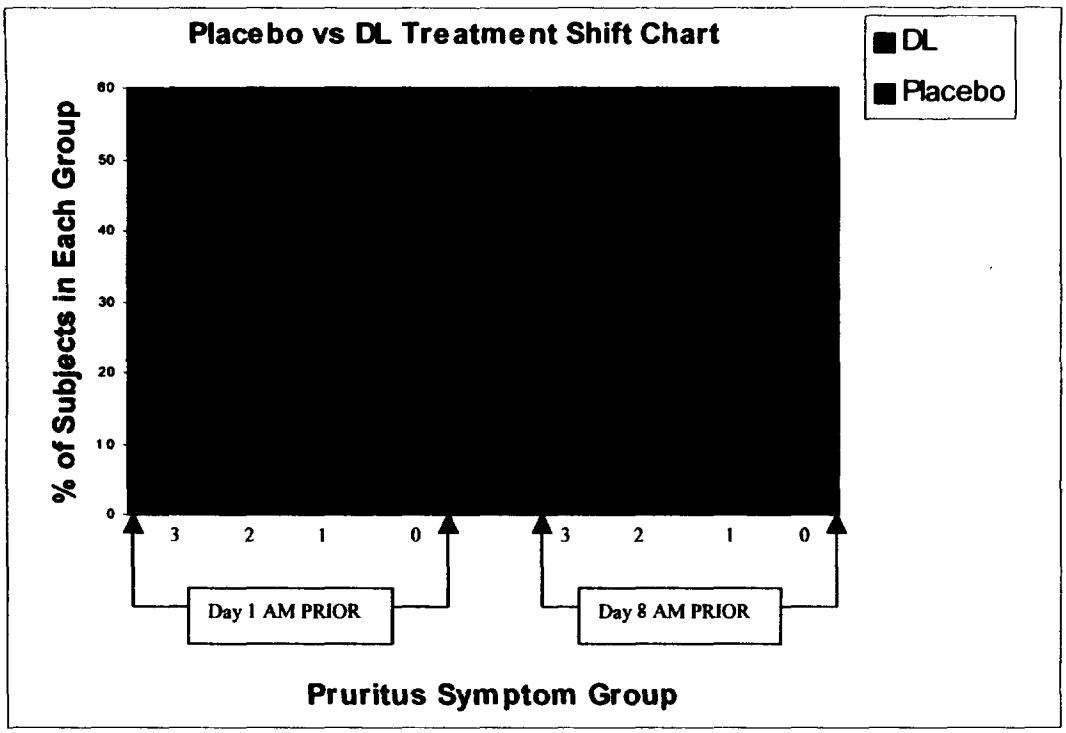


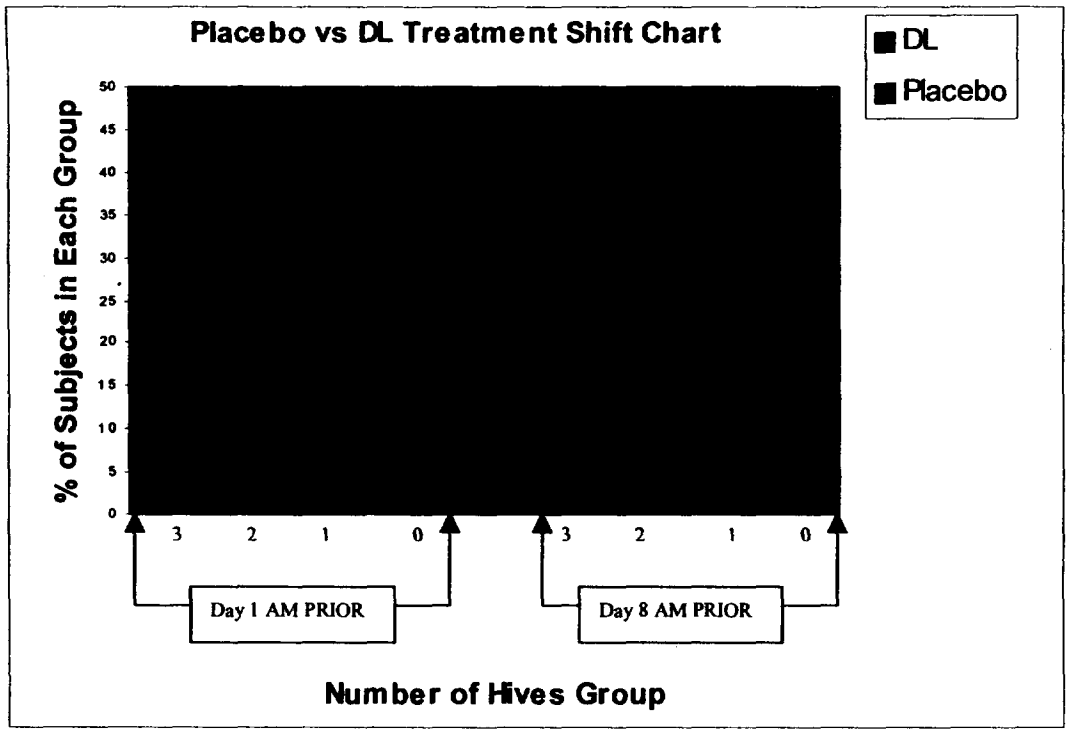
Study P00-220: Placebo vs DL Treatment Categorical Analysis Responder Shift Chart for Day -1 (Baseline) vs Day 8 PM PRIOR Scores
Group 3=Severe Pruritus, Group 0=No Pruritus
DL group had a 10% (n=12) drop out rate between day -1 and day 8
Placebo group had a 19% (n=21) drop out rate between day -1 and day 8



Study P00-220: Placebo vs DL Treatment Categorical Analysis Responder Shift Chart for Day 1 (Baseline) vs Day 8 AM PRIOR Scores
Group 3=>12 hives, Group 0=None
DL group had a 6% (n=7) drop out rate between day 1 and day 8
Placebo group had a 9% (n=10) drop out rate between day 1 and day 8



Study P00-221: Placebo vs DL Treatment Categorical Analysis Responder Shift Chart for Day 1 (Baseline) vs Day 8 AM PRIOR Scores
Group 3=Severe Pruritus, Group 0=No Pruritus
DL group had a 3% (n=3) drop out rate between day 1 and day 8
Placebo group had a 16% (n=17) drop out rate between day 1 and day 8



Study P00-221: Placebo vs DL Treatment Categorical Analysis Responder Shift Charts for Day 1 (Baseline) vs Day 8 AM PRIOR Scores
Group 3=>12 hives, Group 0=None
DL group had a 3% (n=3) drop out rate between day 1 and day 8
Placebo group had a 17% (n=16) drop out rate between day 1 and day 8

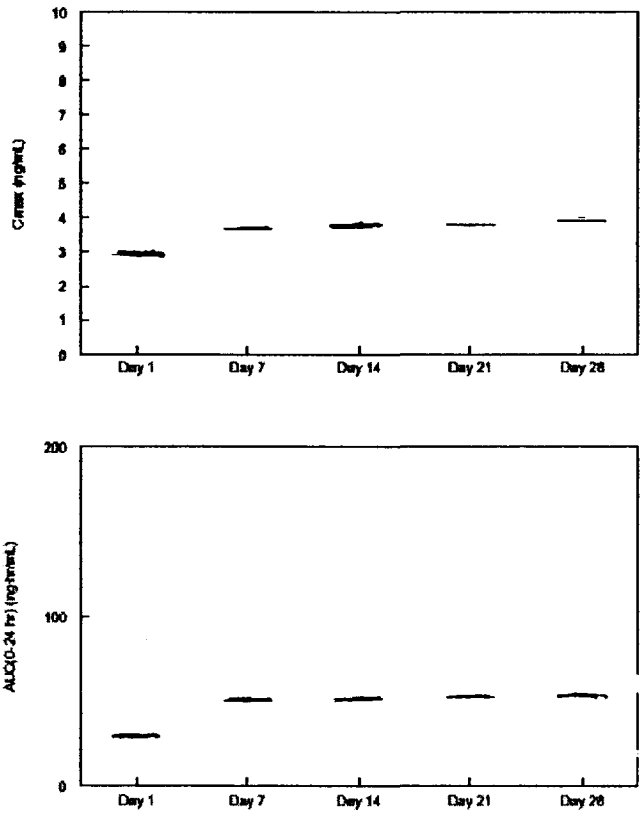


Figure 3 Cmax and AUC(0-24 hr) of SCH 34117 Following Oral Administration of 5 mg SCH 34117 in Individual Subjects
The horizontal lines represent the mean. The high Cmax and AUC values are for Subject 10 (see text for details).

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/s/

Curtis Rosebraugh
6/15/01 06:43:14 AM
MEDICAL OFFICER

Mary Purucker
6/15/01 10:12:49 AM
MEDICAL OFFICER
Concur. See also TL memo.