CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER 21-165

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

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

APPLICATION #NDA	21,165	APPLICATION TYPE:	Original NDA
SPONSOR:	Schering	PRODUCT/PROPRIETARY NAME:	Clarinex
		USAN Established Name:	Desloratadine
CATEGORY OF DRUG:	Antihistamine	ROUTE OF ADMINISTRATION:	Oral (tablet)
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	29 September 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
20 October 1999	21 October 1999	Original NDA	see overview below

Overview of Application/Review: This NDA is approvable since the sponsor has submitted data to support the efficacy and safety of desloratadine at a dose of 5 mg given once a day. The cardiac safety is demonstrated by animal studies, in-vitro channel studies, lack of significant cardiac effects with repetitive administration, measurement of ECG parameters after administration of a dose 9 times the recommended dose, and interaction studies with ketoconazole and erythromycin. The labeling will need to be revised in regard to onset of effectiveness, dosage for patients with renal or hepatic impairment, and other issues.

Outstanding Issues: labeling

Recommended Regulatory Action: approvable

NDAs:

Efficacy / Label Supp.: x Approvable _____ **Not Approvable**

Signed: **Medical Reviewer:** _____ **Date:** 9/29/2000

Medical Team Leader: _____ **Date:** 9/29/00

(Please also see the Memorandum)

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INTROBACK - 1

Introduction: Desloratadine is the active metabolite of loratadine (Claritin) which is a marketed as a 10 mg tablet in the United States, and is a non-sedating H-1 receptor antagonist. When administered orally, loratadine (Claritin) is rapidly metabolized to descarboethoxyloratadine (desloratadine)(DCL), which is the major metabolite of loratadine and is pharmacologically active. Based on antihistaminic activity in studies in rats, DCL is four times more potent than loratadine. Studies in animals suggest that there is poor access of DCL to central histamine (H1) receptors in the brain. Preclinical studies have shown that DCL has similar pharmacodynamic activity to loratadiine.

Desloratadine is proposed for treatment of patients 12 years of age and older with seasonal allergic rhinitis at a dose of 5 mg once a day.

The sponsor has an extensive clinical program for the tablet formulation of desloratadine that includes: 1) a work productivity study; 2) a study of the effectiveness of DCL in relieving nasal congestion; 3) a study of the effectiveness of DCL in patients who have not responded to fexofenadine; 4) a study of the effectiveness of DCL in the treatment of perennial allergic rhinitis; 5) a study assessing its prophylactic effectiveness in seasonal allergic rhinitis; 6) a study assessing the effectiveness of DCl for asthma in patients with allergic rhinitis; and 7) a study evaluating the ability to improve sleep quality.

Since loratadine is rapidly metabolized to desloratadine, exposure to desloratadine is greater than exposure to the parent compound. The elimination half-life and AUC for desloratadine are significantly greater than for loratadine.

The inactive ingredients in the DCL tablet include dibasic calcium phosphate dihydrate, microcrystalline cellulose, corn starch, and talc. The tablets are coated with FDC Blue #2 Lake,

carnauba wax and white wax. Tablets are supplied in HDPE bottles and in unit dose blisters.

Desloratadine was developed because of an improved pharmacokinetic profile over loratadine, based on less extensive first-pass metabolism and a longer plasma elimination half-life. Oral administration of DCL results in significant absorption without any food effect. After oral absorption, DCL is hydoxylated at the 3 position with subsequent glucuronidation and is excreted to a similar extent in urine and feces. The long plasma elimination half-life supports once daily dosing.

With increasing awareness of the sedative risks involved with use of first generation antihistamines and driving, the importance of second generation non-sedating antihistamines in the management of conditions such as allergic rhinitis is well established.

Background: The Pre-IND meeting for desloratadine was held on 12 January 1998 and the IND was submitted on 9 March 1998. The sponsor submitted the NDA for desloratadine tablets on 20 October 1999. The pre-NDA meeting with the sponsor had been held on 11 May 1999. Based on that meeting, total symptom scores (TSS) and total nasal symptom scores were analyzed with and without nasal congestion. The sponsor had previously agreed to analyze the TSS and non-nasal symptom scores with and without cough. With this submission, the sponsor requested deferral of pediatric studies with this formulation.

Desloratadine has not been approved for use in any country.

The sponsor was told that long-term (6-12 month) studies would not be required provided the systemic exposure of 5 mg of DCL was less than the systemic exposure of 10 mg of loratadine. Pharmacokinetic studies comparing these two drug products show that the Cmax and AUC after administration of 5 mg of DCL is less than that seen after administration of 10 mg of loratadine.

EXECSUM - 3

NDA 21,165
Desloratadine Tablets

Executive Summary

I. Recommendations: Based on the clinical data submitted by the sponsor, this NDA is approvable for the clinical indications proposed. The efficacy and safety of desloratadine (DCL) at the dose proposed for clinical use have been demonstrated in well controlled studies. Labeling changes will be needed to provide for appropriate clinical use of this drug.

II. Summary of Clinical Findings: The sponsor has submitted four multicenter, double-blind, placebo-controlled, randomized, parallel, repetitive dose studies of 2-4 weeks duration in patients 12 years of age and older with seasonal allergic rhinitis to support the efficacy and safety of desloratadine.

Three of these studies (studies 223, 224, and 225) compared DCL at daily doses of 5 mg and 7.5 mg with placebo in adult and adolescent patients with seasonal allergic rhinitis. A total of 487 patients received DCL 5 mg, 489 received DCL 7.5 mg and 487 received placebo in these studies, 158, 159 and 158 of whom received DCL 5 mg, DCL 7.5 mg and placebo, respectively, for 4 weeks. The primary efficacy variable in all 3 studies was change from baseline in average reflective 12 hour AM/PM total symptom score over 2 weeks of treatment (the first two weeks in the 4 week study). Total symptom score in all 3 studies included four nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing), and five non-nasal symptoms (itchy eyes, tearing, eye redness, itching of the ears and palate and cough). Analyses were performed excluding nasal congestion and cough. A categorical scale of 0-3 was used in assessing symptoms on both a reflective and point-in-time basis.

In the fourth study (study 001), 173 patients, 172 patients, 173 patients, 172 patients, 172 patients and 174 adult and adolescent patients with seasonal allergic rhinitis received 2.5 mg, 5 mg, 7.5 mg, 10 mg, 20 mg and placebo, respectively, over a period of 2 weeks. The primary efficacy variable in this study was also change from baseline in the average over the two week

treatment period in reflective AM/PM total symptom score based on patient assessment of symptoms using a categorical scale of 0-3 on a reflective and point-in-time basis. The total symptom score consisting of four nasal symptoms (rhinorrhea, sneezing, itching nose and nasal congestion), and four non-nasal symptoms (itching of the eyes, tearing of the eyes, redness of the eyes, and itching of the ears/palate).

The sponsor performed 4 single dose onset of action studies, 3 in an environmental exposure unit (EEU) and one outside. In addition, studies were done in patients with renal and hepatic impairment and in patients concomitantly receiving erythromycin and desloratadine and ketoconazole and desloratadine. A number of pharmacokinetic studies were performed evaluating the systemic exposure from desloratadine after food ingestion, in specific ethnic groups and in comparison with loratadine. Cardiac effect was assessed in one study in which patients received 45 mg/day for 10 days.

These studies were designed to address key issues related to the safe and effective use of desloratadine. These issues in relation to the results of these studies are discussed below with comments.

Issue 1: Efficacy of DCL at a dose of 5 mg per day: Of the 3 studies comparing 5 mg and 7.5 mg daily doses of DCL with placebo (studies 223, 224, and 225), based on the primary outcome variable (change from baseline in TSS), efficacy was demonstrated to 7.5 mg but not 5 mg in one study (study 225), 5 mg but not 7.5 mg in one study (study 224) and to both 5 and 7.5 mg in the third study (study 223).

The fact that the efficacy of 7.5 mg per day was not demonstrated in study 224 raises doubt about the validity of the data in this study, since logically a dose of 7.5 mg per day should demonstrate at least as great an effect as 5 mg/day under the same study conditions. The efficacy of the 5 mg daily dose of DCL was not demonstrated in one study (study 225). If studies 224 and 225 can not be used to support the efficacy of the 5 mg/day dose of DCL, only one of these three studies (study 223) can be used to support the efficacy of 5 mg per day of DCL, the dose recommended for clinical use.

However, the efficacy of DCL at doses of 5 mg per day and higher was demonstrated in study 001.

Conclusion: There are two well designed studies that demonstrate the efficacy of DCL at a dose of 5 mg daily.

Issue 2: Safety of DCL at recommended dose: No clinically significant adverse events, changes in laboratory values, changes in vital signs or ECG changes were consistently seen after the administration of DCL 5 mg per day. A slightly greater incidence of adverse events consistent with sedation (e.g. fatigue, somnolence) was seen after the administration of 5 mg per day of DCL. The difference between the incidence of this type of adverse effect after administration of desloratadine and administration of placebo is not clinically significant. There were no clinically significant changes in laboratory values associated with age, gender or ethnic background.

Pre-clinical, in-vitro and clinical studies were done to assess the cardiac effect of desloratadine. The pre-clinical studies showed no adverse effect on cardiac parameters. There was no greater effect seen from desloratadine than was seen with loratadine based on in-vitro channel studies. A dose of 45 mg of desloratadine was given to healthy volunteers for 10 days and produced a 4 msec greater prolongation of the QTc interval than placebo based on machine reading of the QTc interval and maximum QTc from serial ECGs. Because of the method of reading and the outcome variable used, as well as the greater increase in QTc interval after administration of DCL than was seen after administration of placebo, it can not be concluded from this study that the change in QTc interval was not clinically significant. Interaction studies with concomitant administration of DCL and erythromycin in one study and DCL and ketoconazole in another study failed to show any adverse cardiac effect.

Conclusion: There is no reason to believe, based on the data submitted, that there are any safety concerns related to the use of DCL.

Issue 3: Onset of effectiveness: Onset of effectiveness should be considered in two ways: 1) the onset of effectiveness after a single dose; and 2) the length of time after starting treatment that effectiveness can be demonstrated.

In regard to onset of effectiveness after a single dose of desloratadine, the sponsor did one large outdoor study (study 226) where no difference between desloratadine and placebo was seen. One large study was done in an EEU (study 367). This study demonstrated an onset of effectiveness of 2 hours after administration of 5 mg of desloratadine. It is unclear why no onset of effectiveness was seen until 3.5 hours after administration of 7.5 mg of desloratadine in this study. Two small studies were also done in a Vienna Challenge Chamber (studies 448 and 287). Onset of effectiveness of 5 mg desloratadine in these studies was 1.25 and 1.75 hours.

The onset of effectiveness with repetitive administration of 5 mg of DCL (studies 223, 224, 225 and 001) was 1 day or less in 2 studies (the first time point for evaluation was 24 hours after administration of the first dose) compared with 2 days and greater than 3 days in the other 2 studies.

Conclusion: ~~The sponsor~~ has not provided sufficient data to support a claim for the onset of effectiveness of 5 mg of DCL, based on single dose studies. This conclusion is based on the following: 1) a large outdoor study showed no effectiveness of DCL; and 2) the study results are open to question because of the longer time required to demonstrate effectiveness of 7.5 mg of DCL than 5 mg of DCL. The sponsor has demonstrated that onset of effectiveness can occur as early as 24 hours after drug administration in the repetitive dose studies of 2-4 weeks duration.

Issue 4: appropriate dose for patients with renal or hepatic impairment: Studies evaluating the pharmacokinetics of DCL in patients with liver and renal impairment showed that patients with liver and renal impairment have greater systemic exposure to DCL and may require lower doses of DCL. The labeling should be changed to indicate that dosage adjustment may be necessary in patients with hepatic and renal impairment.

Issue 5: Cardiac effect, especially effect on QTc interval: Patients received 45 mg of DCL for 10 days with a 4 msec greater prolongation of the QTc interval after DCL than after placebo. ECGs were machine-read and results were based on maximum QTc intervals from serial ECGs. No significant difference from placebo was seen in QTc interval or ventricular rate when DCL was given concomitantly with either erythromycin or ketoconazole. Preclinical and in-vitro studies do not demonstrate any potential for an adverse cardiac effect in humans who receive DCL. Furthermore, there were no significant differences between the group that received 5 mg DCL and the group that received placebo in terms of any electrocardiographic parameter in the pooled data from the multiple dose studies, in which AEs related to the cardiovascular system occurred with a similar frequency in patients who received DCL and those who received placebo. Finally, animals studies and in-vitro tests do not demonstrate any adverse effect of DCL on the heart.

CONCLUSIONS:

1. The sponsor has submitted data to adequately support the safety and efficacy of desloratadine at a dose of 5 mg given once a day.

2. The onset of effectiveness studies submitted by the sponsor do not provide acceptable data to support a claim for onset of action. The repetitive 2-4 week studies can be used to support a claim that a statistically significant improvement in symptoms was seen within 24 hours after initiation of treatment.

3. The cardiac safety of desloratadine is demonstrated by: 1) animal studies; 2) in-vitro channel studies; 3) lack of significant cardiac effects with repetitive administration; 4) clinically insignificant change in QTc and other ECG parameters with a dose 9 times the proposed clinical dose; and 5) lack of any significant increase in the QTc interval when desloratadine was given concomitantly with erythromycin in one study and ketoconazole in another study.

4. There is significant increase in systemic availability of desloratadine when given to patients with renal or hepatic impairment. This will require dose adjustment in this patient population.

5. Labeling changes are required in regard to claims of

Desloratadine

Key repetitive dose efficacy and safety studies

NDA 21,165
Drug: desloratadine
Formulation: Oral tablet
Sponsor: Schering
Indication: Seasonal allergic rhinitis

Efficacy and Safety Studies;

1. **001 – 2 weeks; volumes 120-123**

2. **223 – 2 weeks; volumes 124-126**

3. **224 – 2 weeks; volumes 127-129**

4. **225 – 4 weeks; volumes 130-132**

Study 225:

METHODS: Study 225 was a parallel, double-blind, placebo-controlled, randomized, multicenter, repetitive dose study in 475 adult and adolescent patients (approximately 158 per arm) who had seasonal allergic rhinitis with an established baseline severity. Patients received either 5 mg or 7.5 mg of desloratadine in comparison with placebo for 4 weeks. The primary outcome variable was change from baseline in average reflective 12 hour AM/PM total symptom score (TSS) over the first two weeks of treatment. There were 4 nasal (rhinorrhea, nasal congestion, nasal itching and sneezing) and 5 non-nasal symptoms (itchy eyes, tearing, eye redness, itching ears/palate and cough) included in the total symptom score. Secondary outcome variables included change in total nasal symptoms, change in total non-nasal symptoms, change in individual symptoms, overall evaluation of the patient by the patient and physician, evaluation by patient and physician of therapeutic response, and quality of life assessment. Evaluation of symptoms were made by patients on a reflective and point-in-time basis using a 0-3 categorical scale. Safety was assessed by evaluating adverse events, change in laboratory tests, change in vital signs and change in ECGs. Two patient populations were analyzed: 1) an intent-to-treat population; and 2) an evaluable for efficacy population. Analyses were done including and excluding nasal congestion and cough.

RESULTS: A statistically significant improvement in TSS was noted after administration of 5 mg of desloratadine on days 2 and 3 (24 and 48 hours after initiating treatment)($p = 0.01, 0.02$) but not at any other time point, including the first two weeks of treatment ($p = 0.35$). The AM point-in-time assessment by patients who received desloratadine was not significantly different than the assessment made by patients who received placebo, indicating that there was no clinical effect at the end of the dosing interval. None of the secondary outcome variables indicated that the 5 mg dose of desloratadine produced a significantly greater change from baseline than placebo. On the other hand, a dose of 7.5 mg of desloratadine produced a significantly greater improvement in TSS ($p = 0.04$) over the first two weeks of treatment than did placebo. A statistically

significant difference favoring desloratadine 7.5 mg compared to placebo was seen for most parameters at most time points. Interestingly, over the third and fourth weeks of the study, there was no statistically significant difference between the 7.5 mg dose of desloratadine and placebo ($p = 0.16$, $p= 0.58$, respectively). Effectiveness of the 7.5 mg dose of desloratadine was seen as early as the end of the dosing interval after the first dose (day 2). Although there were more patients who developed diarrhea, vomiting, nervousness and dry mouth after taking the 7.5 mg dose of desloratadine, and overall more treatment-related adverse events in the 5 mg desloratadine group, there were no safety concerns raised by the data in this study.

DISCUSSION: This study supports the effectiveness of the 7.5 mg dose of desloratadine over two weeks of treatment but did not demonstrate the efficacy of the 5 mg dose of desloratadine. There were no issues raised about the safety of 5 mg of desloratadine in this study.

APPEARS THIS WAY
ON ORIGINAL

Study 225: 10 centers

Study objective: to characterize the efficacy and safety of two different dose levels of DSL

Number of patients: 475; 158 received 5 mg of DSL; 159 received 7.5 mg and 158 received placebo

Age range: 12-75 years

Patient population: SAR; clinically symptomatic not on corticosteroids; rhinorrhea score of at least 2; total nasal symptom score of at least 6; total non-nasal score of at least 5; overall condition of 2 or greater; on the 3 days prior to baseline, total reflective scores must total 36 or more for total nasal score, 30 for total non-nasal score and 12 for rhinorrhea score

Study design: multicenter, parallel (3 arm), double-blind, placebo-controlled, randomized, dose-level study

Drug administration: DSL 5 mg per day and 7.5 mg per day as a tablet (given once daily orally in the AM)

Periods of study: 4 weeks of randomized treatment; 1 week screening; assessment of patients on day 1 (baseline), and days 4, 8, 15, and 25.

Parameters evaluated:

> **primary efficacy variable = change from baseline in average reflective 12 hour AM/PM total symptom score over the first two weeks of treatment based on ITT population; evaluation was done without cough.**

total symptom score = rhinorrhea + nasal congestion + nasal itching + sneezing + itchy eyes + tearing + eye redness + itching ears/palate + cough (9 nasal and non-nasal symptoms); severity was based on a categorical scale from 0-3 (none-severe)

secondary efficacy variables include the following:

total nasal symptom score = sum of nasal congestion, rhinorrhea, sneezing and itching of nose (4 symptoms)

total non-nasal symptom score = sum of itching/burning eyes, watering eyes, redness eyes, itching ears/palate and cough (5 symptoms); evaluation was done without cough.

analyses were done for mean AM/PM scores, AM reflective scores, PM reflective scores, AM point-in-time scores and PM point-in-time scores

overall condition of the patient (using a categorical scale of 0-3 [none-severe])and evaluation of therapeutic response (using a categorical scale of 1-5 [complete relief-treatment failure]) were made jointly be the patient and the physician from baseline to the last visit.

Analyses were also made based on all patients who met key eligibility criteria; efficacy evaluable data set.

Pollen counts at least several times weekly measured in counts/mm

Determination of patient exposure to outside air was also made.

Quality of life assessment using the Short Form Health Summary (HRQOL) at baseline and on day 14 and the Juniper Rhino-conjunctivitis QOL questionnaire in patients 18 years and older.

safety parameters included AEs, change from baseline in labs (screening and visit 6 [day 29]), VSs (at each visit) and 12 lead ECGs at screening and visit 6 (day 29);

Study results:

Discontinuations: 37 patients; 11 in the 5 mg DSL group, 11 in the 7.5 mg DSL group and 15 in the placebo group (see Table 1; tab 7, v1.130, p51)

Protocol deviation: 34 (27 in the first 2 weeks)(see Table 2; tab 8, v1.130, p52)

Patient Distribution Analysis Subset (see Table 3; tab9, v1.130, p53)

Demographics: see table 4;tab 10, v1.130, p55)

Efficacy:

In terms of the primary efficacy variable (average AM/PM reflective TSS change from baseline over the first 2 weeks of the study), the 5 mg dose of DSL, the dose that is proposed for treatment, was not statistically significantly ($p > 0.41$) or clinically significantly better than placebo, whether cough was included or excluded, using either the ITT or efficacy evaluable data set. When the change from baseline in TSS was analyzed for different time periods, there was a statistically significant difference between 5 mg DSL and placebo only on days 2 and 3 ($p = 0.01$, $p = 0.03$)(see Table 5; tab 12, v1.130, p59 and table below). There was no treatment-by-center effect ($p = 0.72$). There were 10 centers. At 5 centers, there was a significantly greater response to DSL 5 mg than placebo, while at the other 5 centers, there was a comparable (2) or greater response (3) in the placebo group. Any trend favoring DSL 5 mg is being driven by data on women patients, since men who received placebo did better than men who received DSL 5 mg.

In terms of secondary efficacy variables, similar results were obtained. For example, based on the ITT population: 1) for AM point-in-time analysis of TSS over the first two weeks of treatment, the 5 mg DSL dose "was numerically equivalent to placebo" (p = 0.97). Mean percent reduction in AM point-in-time TSS was 21% for both the 5 mg DSL and the placebo groups (see table 6; tab14, v1.130, p63); 2) reflective AM/PM total nasal symptom scores (TNSS) over the first two weeks of treatment, decreased 21% in the 5 mg DSL group and 20% in the placebo group, and the results, except for days 2 and 3 (p = 0.02) were not statistically significantly different from placebo (p = 0.44 over the first two weeks of treatment); 3) TNSS AM point-in-time showed no statistically significant difference between 5 mg DSL and placebo, with 18% improvement in both groups; 4) total non-nasal symptom scores, including or excluding cough, showed no statistically significant difference between 5 mg DSL and placebo (p = 0.31) except on days 2 and 3 (p = 0.01 and p = 0.03); 5) individual nasal and non-nasal symptom evaluation showed a similar pattern (see table 7; tab 18, v1.130, pgs70-72). There was not a statistically significant difference between DSL 5 mg and placebo for any nasal or ocular symptom; 6) based on the joint global evaluation by patients/physicians, "The 5.0 mg dose group was nopt significantly different from placebo at any time point." (table 8; tab19, v1.130, p74); 7) in regard to joint patient and physician evaluation of therapeutic response, "The 5.0 mg dose was significantly different from placebo only on day 4 (p = 0.01)(table 9; tab20, v1.130, p76); and 8) in regard to QOL assessment, "No statistically significant difference between the active treatment groups and placebo in the mean changes from baseline across any of the SF-36 domains were, however, observed.", and "no significant difference in the mean changes from baseline in the disease specific domains were observed between the treatment groups.".

Therefore, the sponsor has not demonstrated the efficacy of the 5 mg dose of DSL, based on the fact that there is not a statistically significant difference between this dose and placebo for the primary efficacy parameter or any other parameter evaluated.

The sponsor has demonstrated the efficacy of the 7.5 mg dose of DSL in terms of the primary efficacy variable and most other efficacy parameters (see tables below).

Statistical comparison of desloratadine with placebo at various timepoints

Interval	5 mg DCL	7.5 mg DCL
Day 2	P = 0.01	P < 0.01
Day 3	P = 0.02	P = 0.02
Day 4	P = 0.15	P = 0.14
Days 2-8	P = 0.13	P = 0.03
Days 9-15	P = 0.73	P = 0.05
Days 16-22	P = 0.71	P = 0.18
Days 23-29	P = 0.74	P = 0.58
Days 2-15	P = 0.35	P = 0.04

Table
7.5 mg DSL

parameter	time measured	p value (DSL – placebo)
TSS with cough	Mean AM/PM reflective	P = 0.04 (ITT)
TSS without cough	Mean AM/PM reflective	P = 0.03 (ITT)
TSS with cough	Mean AM/PM point-in-time	P = 0.04 (ITT)
TSS without cough	Mean AM/PM point-in-time	P = 0.03 (ITT)
TSS	Mean AM reflective	P = 0.07 (ITT)
TSS with cough	Mean PM reflective	P = 0.03 (ITT)
TSS without cough	Mean PM reflective	P = 0.02 (ITT)
TSS	Mean PM point-in-time	P = 0.02 (ITT)
TSS	Mean AM point-in-time	P = 0.06 (ITT)
TNSS	Mean AM/PM reflective	P = 0.03 (ITT)
TNSS	Mean AM reflective	P = 0.07 (ITT)
TNSS	Mean PM reflective	P = 0.02 (ITT)
TNSS	Mean AM point-in-time	P = 0.02 (ITT)
TNSS	Mean AM/PM point-in-time	P = <0.01 (ITT)
TNSS	Mean PM point-in-time	P = <0.01 (ITT)
Tnon-nasal SS c cough	Mean AM/PM reflective	P = 0.06 (ITT)
Tnon-nasal SS s cough	Mean AM/PM reflective	P = 0.05 (ITT)
Tnon-nasal SS c cough	Mean AM/PM point-in-time	P = 0.13 (ITT)
Tnon-nasal SS s cough	Mean AM/PM point-in-time	P = 0.12 (ITT)
Tnon-nasal SS c cough	Mean AM reflective	P = 0.10 (ITT)
Tnon-nasal SS s cough	Mean AM reflective	P = 0.12 (ITT)
Tnon-nasal SS c cough	Mean PM reflective	P = 0.04 (ITT)
Tnon-nasal SS s cough	Mean PM reflective	P = 0.03 (ITT)
Tnon-nasal SS c cough	Mean AM point-in-time	P = 0.19 (ITT)
Tnon-nasal SS s cough	Mean AM point-in-time	P = 0.20 (ITT)
Nasal congestion	Mean AM/PM reflective	P = 0.08 (ITT)
Nasal congestion	Mean AM/PM point-in-time	P = 0.10 (ITT)
Nasal congestion	Mean AM reflective	P = 0.21 (ITT)
Nasal congestion	Mean PM reflective	P = 0.05 (ITT)
Nasal congestion	Mean AM point-in-time	P = 0.14 (ITT)
Nasal congestion	Mean PM point-in-time	P = 0.09 (ITT)
Rhinorrhea	Mean AM/PM reflective	P = 0.21 (ITT)
Rhinorrhea	Mean AM/PM point-in-time	P = 0.15 (ITT)

Rhinorrhea	Mean AM reflective	P = 0.15 (ITT)
Rhinorrhea	Mean AM point-in-time	P = 0.34 (ITT)
Rhinorrhea	Mean PM reflective	P = 0.45 (ITT)
Rhinorrhea	Mean PM point-in-time	P = 0.07 (ITT)
Nasal itching	Mean AM/PM reflective	P = <0.01 (ITT)
Nasal itching	Mean AM/PM point-in-time	P = <0.01 (ITT)
Nasal itching	Mean AM reflective	P = 0.03 (ITT)
Nasal itching	Mean AM point-in-time	P = <0.01 (ITT)
Nasal itching	Mean PM reflective	P = <0.01 (ITT)
Nasal itching	Mean PM point-in-time	P = <0.01 (ITT)
Sneezing	Mean AM/PM reflective	P = 0.05 (ITT)
Sneezing	Mean AM/PM point-in-time	P = <0.01 (ITT)
Sneezing	Mean AM reflective	P = 0.11 (ITT)
Sneezing	Mean AM point-in-time	P = <0.01 (ITT)
Sneezing	Mean PM reflective	P = 0.04 (ITT)
Sneezing	Mean PM point-in-time	P = <0.01 (ITT)
Itching/burning eyes	Mean AM/PM reflective	P = 0.02 (ITT)
Itching/burning eyes	Mean AM/PM point-in-time	P = 0.05 (ITT)
Itching/burning eyes	Mean AM reflective	P = 0.06 (ITT)
Itching/burning eyes	Mean AM point-in-time	P = 0.23 (ITT)
Itching/burning eyes	Mean PM reflective	P = <0.01 (ITT)
Itching/burning eyes	Mean PM point-in-time	P = 0.01 (ITT)
Tearing eyes	Mean AM/PM reflective	P = 0.26 (ITT)
Tearing eyes	Mean AM/PM point-in-time	P = 0.44 (ITT)
Tearing eyes	Mean AM reflective	P = 0.65 (ITT)
Tearing eyes	Mean AM point-in-time	P = 0.64 (ITT)
Tearing eyes	Mean PM reflective	P = 0.09 (ITT)
Tearing eyes	Mean PM point-in-time	P = 0.34 (ITT)
Eye redness	Mean AM/PM reflective	P = 0.12 (ITT)
Eye redness	Mean AM/PM point-in-time	P = 0.17 (ITT)
Eye redness	Mean AM reflective	P = 0.15 (ITT)
Eye redness	Mean AM point-in-time	P = 0.25 (ITT)
Eye redness	Mean PM reflective	P = 0.14 (ITT)
Eye redness	Mean PM point-in-time	P = 0.17 (ITT)
Itching ears/palate	Mean AM/PM reflective	P = 0.08 (ITT)
Itching ears/palate	Mean AM/PM point-in-time	P = 0.19 (ITT)
Itching ears/palate	Mean AM reflective	P = 0.12 (ITT)
Itching ears/palate	Mean PM reflective	P = 0.09 (ITT)
Itching ears/palate	Mean AM point-in-time	P = 0.15 (ITT)

No safety concerns for either the 5 mg or the 7.5 mg dose are raised by this study, although there were more patients who developed diarrhea, vomiting, nervousness and dry mouth after taking the 7.5 mg dose of DSL(see below).

Safety Data:

✦ **Adverse Events:**

- **overall incidence of AEs: 63% in 5 mg group; 57% in 7.5 mg group and 51% in placebo group**

- **Of AEs reported by at least 2% of patients, those AEs that occurred with at least a 2% greater incidence than placebo in either of the active treatment groups were; 1) flu-like symptoms (6% of 5 mg group, 3% of 7.5 mg group and 1% of placebo group); 2) post procedure pain (2% of the 5 mg group and none in the 7.5 mg and placebo groups); 3) dizziness (4% in the 5 mg group, 1% in the 7.5 mg group and 2% in the placebo group); 4) diarrhea (4% in the 7.5 mg group, and < 1% in the 5 mg group and the placebo group); 5) vomiting (3% in the 7.5 mg group and < 1% in the 5 mg group and none in the placebo group); 6) nervousness (3% in the 7.5 mg group and none in the 5 mg group and < 1% in the placebo group); 7) dysmenorrhea (6% in the 5 mg group, 8% in the 7.5 mg group and 2% in the placebo group); 8) asthma (3% in the 7.5 mg group, and < 1% in the other two groups); 9) nasal disorders (2% in the 5 mg group, 1% in the 7.5 mg group and none in the placebo group); 10) pharyngitis (6% in the 5 mg group, 7% in the 7.5 mg group and 1% in the placebo group); 11) upper respiratory infections (4% in the 5 mg group and 1% in the other two groups; and 12) migraine (3% in the 7.5 mg group, 1% in the 5 mg group and < 1% in the placebo group).**

- **treatment-related AEs: 20% in 5 mg group, 21% in the 7.5 mg group and 15% in the placebo group**

- using the same criteria as for overall AEs, significant treatment-related AEs reported by 2% or more of patients were: 1) headache (9% of both active treatment groups and 4% of the placebo group; and 2) nervousness (3% of the 7.5 mg group and none of the other two groups.

- severe AEs: 14% of 5 mg group, 15% of 7.5 mg group, and 13% of the placebo group. There were no significant differences between the treatment groups for any individual AEs, either overall or treatment-related.

- discontinuations because of AEs: 1% of 5 mg group, 4% of 7.5 mg group and 3% of placebo group.

✦ Laboratory values: There were no clinically significant changes from baseline in median laboratory values. One patient who received 5 mg of desloratadine developed an increase in SGOT from 17 U/L at screening to 227 U/L on day 29. One week later, the patient's SGOT was 23 U/L. In the same patient, the LDH increased from 212 U/L at screening to 822 U/L on day 29, and returned to 243 U/L one week after discontinuing treatment. This suggests that an occasional patient can develop a transient increase in liver enzymes after receiving desloratadine. In addition, one patient who received 7.5 mg of DCL developed a serum glucose level of 209 IU/L after treatment for 4 weeks, but one patient who received placebo had a serum glucose level of 232 IU/L on day 15.

✦ ECGs: There were no patients who received desloratadine and developed clinically significant ECG changes.

There was a mean decrease in both QT and QTc interval in patients who received desloratadine at either dose (-1.1 and –3.8 msec for 5 and 7.5 mg in regard to QT; and –0.4 and –6.4 msec for 5 and 7.5 mg in regard to QTc), compared to patients who received placebo, where there was a slight increase (0.8 msec for QT and 2.8 msec for QTc).

In terms of percent increase from baseline in QT and QTc intervals, there was a 10-14% increase in the QT interval in 6% of patients receiving 5 mg, 4% of patients receiving 7.5 mg and 3% of placebo patients. One 5 mg patient had a 15-19% increase in the QT interval, whereas no 7.5 mg patient had such an increase and 3% of placebo patients did have this degree of prolongation. No patients receiving loratadine had a 20% or greater increase in the QT interval. For findings in regard to the QTc interval, see the table below, taken from tab35, p102, v1.130.

QTc interval	10-14% increase	15-19% increase	≥ 20% increase
5 mg DCL	6%	5%	3%
7.5 mg DCL	8%	5%	3%
Placebo	7%	3%	4%

✦ <u>vital signs</u>: **no clinically significant change in vital signs was seen in either the group that received 5 mg or the group that received 7.5 mg of desloratadine.**

Study 224:

METHODS: Study 224 was a parallel, double-blind, placebo-controlled, randomized, multicenter, repetitive dose study in 489 adult and adolescent patients (164 per arm) who had seasonal allergic rhinitis with an established baseline severity. Patients received either 5 mg or 7.5 mg of desloratadine in comparison with placebo for 2 weeks. The primary outcome variable was change from baseline in average reflective 12 hour AM/PM total symptom score (TSS) over the two weeks of treatment. There were 4 nasal (rhinorrhea, nasal congestion, nasal itching and sneezing) and 5 non-nasal symptoms (itchy eyes, tearing, eye redness, itching ears/palate, and cough) included in the total symptom score. Secondary outcome variables included change in total nasal symptoms, change in total non-nasal symptoms, change in individual symptoms, overall evaluation of the patient by the patient and physician, evaluation by patient and physician of therapeutic response, and quality of life assessment. Evaluation of symptoms were made by patients on a reflective and point-in-time basis using a 0-3 categorical scale. Safety was assessed by evaluating adverse events, change in laboratory tests, change in vital signs and change in ECGs. Two patient populations were analyzed: 1) an intent-to-treat population; and 2) an evaluable for efficacy population. Analyses were done including and excluding nasal congestion and cough.

RESULTS: A statistically significant improvement in TSS was noted after administration of 5 mg of desloratadine after 1 week of treatment and there was a statistically significant improvement in TSS compared to placebo for the two weeks of treatment ($p = 0.02$). By contrast, the group that received 7.5 mg of desloratadine showed no improvement in mean TSS at any time point in comparison with placebo ($p = 0.68$ for the two weeks of treatment). A statistically significant difference between the group that received 5 mg of desloratadine and the group that received placebo was not seen for the individual symptoms of nasal congestion or rhinorrhea. The difference in improvement in TSS between the 5 mg desloratadine and placebo groups is of questionable clinical significance. There were no safety concerns raised as a result of the data generated in this study.

DISCUSSION: This study demonstrated effectiveness of 5 mg of desloratadine but did not demonstrate effectiveness of 7.5 mg of desloratadine. There is no apparent scientific basis for this finding. Therefore, the validity of the data from this study is questionable making this study unacceptable as support for the effectiveness of 5 mg of desloratadine. There were no issues related to the safety of 5 mg of desloratadine in this study.

Study 224: 10 centers

Study objective: to assess the efficacy and safety of DCL at two dose levels compared with placebo

Number of patients: 164 patients in each of the three treatment groups; 489 patients were included in the ITT population

Age range: 12 years of age and older

Patient population: SAR; in order to qualify at screening: rhinorrhea score 2 or greater; total nasal symptom score of 6 or greater; total non-nasal symptom score of 5 or greater; all based on 12 hour reflective scoring by patient and physician; in order to quality for randomization, for the six 12 hour scores over the 3 days prior to baseline – total rhinorrhea score of 12 or greater; total nasal symptom score of 36 or greater; total non-nasal symptom score of 30 or greater; patient had to have a global evaluation of 2 at baseline in order to be randomized.

Study design: randomized, placebo-controlled, parallel, double-blind, multicenter, repetitive dose study

Drug administration: 5.0 and 7.5 mg DCL once a day in the AM

Periods of study: screening (visit 1 was 4-14 days before baseline evaluation); visit 2 was day 1 (baseline); visits 3, 4, and 5 were on days 4, 8, and 15 respectively of the study; 2 weeks of randomized treatment.

Parameters evaluated:

- **efficacy: several times weekly to daily pollen counts; primary efficacy variable – average AM/PM 12 hour reflective total symptom score (sum of 9 nasal and non-nasal symptom scores) change from baseline over the two weeks of treatment; secondary efficacy variables included total nasal symptom score; total non-nasal symptom score reflective and time of assessment; all**

individual symptom scores reflective and at time of assessment; in addition, analyses were performed of non-nasal symptom scores without cough and nasal symptom scores without nasal congestion; analysis will be based on ITT population; consistency across centers will be analyzed; analysis of average AM/PM instantaneous; AM reflective prior 12 hours; AM instantaneous; PM reflective prior 12 hours; PM instantaneous.

- **nasal symptoms: rhinorrhea, nasal congestion, nasal itching, sneezing; reflective and time of assessment; scoring in AM before medication and in PM approximately 12 hours later**

- **non-nasal symptoms: itching/burning eyes, watering eyes, redness of eyes, itching ears/palate, cough; reflective and time of assessment; scoring in AM before medication and in PM approximately 12 hours later**

  scoring system for all combinations of and individual symptoms

  0 = none
  1 = present, minimal, easily tolerated
  2 = aware, bothersome, tolerable
  3 = hard to tolerate, interference with activities

- **global evaluation jointly by patient and physician on study days 4, 8, and 15 days, reflective of the entire time interval since the last evaluation**

  0 = none
  1 = mild
  2 = moderate
  3 = severe

◆ evaluation of therapeutic response by patient/physician on visits 3, 4, and 5 (days 4, 8, and 15)

1 = complete relief
2 = marked relief
3 = moderate relief
4 = slight relief
5 = no relief

☛ safety:

● AEs:

● ECGs: at screening and after 2 weeks of treatment

● vital signs: screening, baseline, and on days 4, 8, and 15

● laboratory tests: at screening and after 2 weeks of treatment

☛ QOL: at baseline and after 2 weeks of treatment; consisting of generic SF-36 health Survey and Rhinoconjunctivitis QOL questionnaire based on 1 week recall

Results:

◆ There were 13 (8%), 3 (2%) and 9 (5%) patients who discontinued the study in the DCL 5 mg, DCL 7.5 mg and placebo groups, respectively. Of these, 4 (2%), 3 (2%) and 2 (1%) discontinued because of an adverse event in the DCL 5 mg, DCL 7.5 mg and placebo groups, respectively. There were 7 patients (4%) in the DCL 5 mg group who discontinued because of treatment failure compared with none in the DCL 7.5 mg group and 4 (2%) in the placebo group (see tab7, p50, v1.127)

- There were no significant differences between the three treatment groups in terms of protocol violations for various reasons (see tab8, p51, v1.127).

- The number of patients in the ITT analysis were 164 in each of the two active treatment groups and 161 in the placebo group. There were 154, 157, and 151 patients in the efficacy evaluable subset of patients for the DCL 5 mg, DCL 7.5 mg and placebo groups, respectively (see tab9, p52, v1.127).

- There were no significant differences in age, gender, ethnic background or duration of SAR between the three treatment groups (see tab10, p53, v1.127). The demographics of the three groups were comparable.

- The primary efficacy variable was the average reflective 12 hour AM/PM total symptom score (including cough) based on change from baseline over the 2 week treatment period (i.e. days 2-15) in the ITT population. There was a statistically significant difference between 5 mg DCL/day and placebo ($p = 0.02$) averaged over days 2-15. The was no statistically significant difference between 7.5 mg DCL/day and placebo averaged over days 2-15 ($p = 0.68$) or at any other time point in the study (see tab11, p56, v1.127). When cough was excluded from the total symptom score, the same response was seen, i.e. the 5 mg dose of DCL/day was statistically more efficacious than placebo ($p = 0.02$) but the 7.5 mg dose of DCL/day was not ($p = 0.64$) averaged over days 2-15 (see tab12, p57, v1.127). The results appear to be consistent across centers. The mean decrease in symptoms after receiving 5 mg/day of DCL (- 5.57) and after receiving placebo (- 4.23), a mean difference of 1.34 or 0.15 per symptom (assuming the same degree of improvement in each of the nine symptoms that were included in the total symptom score) is not clinically significant.

- Instantaneous AM scores: this score reflects an assessment of symptoms 24 hours after the last dose of DCL. The instantaneous mean AM scores indicated that there was a treatment effect 24 hours after taking a 5 mg dose of DCL but not a 7.5 mg dose. The

instantaneous mean AM total symptom score was significantly better for days 2-15 after 5 mg of DCL/day than after placebo, including cough ($p = 0.03$) or excluding cough ($p = 0.03$), but 7.5 mg of DCL/day was not statistically better than placebo ($p = 0.55$, $p = 0.48$)(see tabs13,14, pgs60,61, v1.127). The mean decrease in symptoms after receiving 5 mg/day of DCL (- 4.96) and after receiving placebo (- 3.76), a mean difference of 0.13 per symptom, assuming the same degree of improvement for each of the nine symptoms included in the total symptom score, is not clinical significant.

- Reflective mean total nasal symptom scores for AM/PM over 12 hours, based on ITT population: A statistically significant difference was seen between the group that received DCL 5 mg/day and the group that received placebo, based on the average scores over days 2-15 ($p = 0.02$). This effect was seen as early as the first week of treatment ($p = 0.05$) and was greater after the second week of treatment ($p = < 0.01$). There was no statistically significant difference between the groups that received 7.5 mg/day of DCL and placebo ($p = 0.50$). There was a mean difference of 0.61 in nasal symptom score improvement between the group that received 5 mg/day of DCL and the group that received placebo (a difference of 0.15 for each of 4 nasal symptoms if the response to each of the nasal symptoms was the same). There is no clinically significant difference in mean improvement in nasal symptom score between either of the groups that received DCL and the group that received placebo (see tab15, p63, v1.127).

- Reflective mean total non-nasal symptom scores AM/PM over 12 hours with inclusion and exclusion of cough, based on ITT population: A statistically significant difference was seen between the group that received DCL 5 mg/day and the group that received placebo, based on the average scores over days 2-15 including cough ($p = 0.02$). This effect was seen as early as the first week of treatment ($p = 0.03$) and was greater after the second week of treatment ($p = 0.01$). There was no statistically significant difference between the groups that received 7.5 mg/day of DCL and placebo ($p = 0.84$).

There was a mean difference of 0.74 in non-nasal symptom score between the group that received 5 mg DCL/day and the group that received placebo (a difference of 0.15 for each of 5 non-nasal symptoms if the response to each of the nasal symptoms was the same). There is no clinically significant difference in mean improvement in non-nasal symptom score between either of the groups that received DCL and the group that received placebo (see tabs 16,17, p 654-66, v1.127).

- Mean change in individual symptoms based on reflective scoring over previous 12 hours AM/PM over the 2 weeks of the study: As might be expected neither dose of DCL showed a statistically significantly greater reduction in nasal congestion ($p = 0.27$ for 5 mg, $p = 0.55$ for 7.5 mg) or cough ($p = 0.09$ for 5 mg, $p = > 0.99$ for 7.5 mg). Interestingly, neither 5 mg of DCL/day nor 7.5 mg of DCL/day produced a statistically significantly greater improvement in rhinorrhea that placebo ($p = 0.19$ for 5 mg, $p = 0.82$ for 7.5 mg). The mean differences between the group that received 5 mg DCL/day and the group that received placebo in terms of total symptom scores and nasal symptom scores was driven by improvement in sneezing in the DCL group ($p = < 0.01$ over days 2-15 with statistically significant improvement in sneezing beginning as early as day 2. Other symptoms where there was a statistically significant difference between 5 mg DCL/day and placebo over the two weeks of treatment were: 1) nasal itching ($p = 0.03$); 2) itching/burning eyes ($p = 0.03$); 3) redness of the eyes ($p = 0.04$); and 4) itching of the ears/palate ($p = 0.05$)(see tab18, pgs68-70, v1.127)

- global evaluation by patient/physician: There was a statistically significant difference between the group that received 5 mg DCL/day and the group that received placebo after 2 weeks of treatment ($p = 0.05$). A statistically significant difference was not seen between the group that received DCL 7.5 mg/day and the group that received placebo ($p = 0.52$) at any time point. The 0.22 difference in improvement between the 5 mg/day and placebo groups is unlikely to be a clinically significant difference (see tab19, p72, v1.127). The percentage of patients that improved one category and sustained that

improvement during the study was 62% of the group that received 5 mg DCL, 52% of the group that received placebo and 47% of the group that received 7.5 mg DCL.

- **<u>therapeutic response</u>: Both the 5 mg/day and 7.5 mg/day DCL groups showed a statistically significantly greater therapeutic response than the placebo group ($p = < 0.01$ for both groups) after 2 weeks of treatment. An improvement of 0.12 and 0.07 on a categorical scale of 0-5 is probably of little clinical significance (see tab20, p73, v1.127)**

Parameter	time measured	P value (DCL vs placebo) 5 mg DCL	7.5 mg DCl
TSS with cough	AM/PM reflective	0.02	0.68
TSS without cough	AM/PM reflective	0.02	0.64
TSS with cough	AM/PM point in time	0.01	0.44
TSS without cough	AM/PM point in time	0.01	0.40
TSS	AM reflective	0.03	0.84
TSS with cough	PM reflective	0.01	0.57
TSS without cough	PM reflective	<0.01	0.51
TSS	PM point in time	<0.01	0.33
TSS	AM point in time	0.03	0.55
TNSS	AM/PM reflective	0.02	0.50
TNSS	AM reflective	0.05	0.54
TNSS	PM reflective	0.01	0.53
TNSS	AM point in time	0.04	0.19
TNSS	AM/PM point in time	0.01	0.24
TNSS	PM point in time	<0.01	0.30
TSS non-nasal c cough	AM/PM reflective	0.02	0,84
TSS non-nasal s cough	AM/PM reflective	0.02	0.80
TSS non-nasal c cough	AM/PM point in time	0.01	0.69
TSS non-nasal s cough	AM/PM point in time	0.02	0.66
TSS non-nasal c cough	AM reflective	0.04	0.89
TSS non-nasal s cough	AM reflective	0.05	0.89
TSS non-nasal c cough	PM reflective	0.01	0.60
TSS non-nasal s cough	PM reflective	0.01	0.51
TSS non-nasal c cough	AM point in time	0.04	0.99
TSS non-nasal s cough	AM point in time	0.04	0.96
TSS non-nasal c cough	PM point in time	<0.01	0.41
TSS non-nasal s cough	PM point in time	0.01	0.40
Nasal congestion	AM/PM reflective	0.27	0.55
Nasal congestion	AM/PM point in time	0.11	0.88
Nasal congestion	AM reflective	0.45	0.46
Nasal congestion	PM reflective	0.19	0.70
Nasal congestion	AM point in time	0.20	0.82
Nasal congestion	PM point in time	0.08	0.95
Rhinorrhea	AM/PM reflective	0.19	0.82
Rhinorrhea	AM/PM point in time	0.15	0.82
Rhinorrhea	PM point in time	0.19	0.67
Rhinorrhea	AM reflective	0.25	0.85
Rhinorrhea	AM point in time	0.18	0.38
Rhinorrhea	PM reflective	0.18	0.78
Nasal itching	AM/PM reflective	0.03	0.14
Nasal itching	AM/PM point in time	0.01	0.08
Nasal itching	PM reflective	<0.01	0.11
Nasal itching	AM reflective	0.11	0.27
Nasal itching	AM point in time	0.10	0.24
Nasal itching	PM point in time	<0.01	0.03
Sneezing	AM/PM reflective	<0.01	0.12
Sneezing	AM/PM point in time	<0.01	0.08

Table (continued)

Parameter	time measured	P value DCL vs placebo DCL 5 mg	DCL 7.5 mg
Sneezing	PM point in time	<0.01	0.14
Sneeziing	AM reflective	<0.01	0.08
Sneezing	AM point in time	<0.01	0.05
Itching eyes	PM reflective	<0.01	0.30
Itching eyes	AM/PM reflective	0.03	0.84
Itching eyes	AM/PM point in time	<0.01	0.48
Itching eyes	PM point in time	<0.01	0.29
Itching eyes	AM reflective	0.13	0.74
Itching eyes	AM point in time	0.04	0.76
Tearing eyes	PM reflective	<0.01	0.42
Tearing eyes	AM/PM reflective	0.07	0.59
Tearing eyes	AM/PM point in time	0.07	0.44
Tearing eyes	AM reflective	0.14	0.77
Tearing eyes	PM reflective	0.03	0.45
Tearing eyes	AM point in time	0.14	0.40
Eye reddness	PM point in time	0.05	0.54
Eye reddness	AM/PM reflective	0.04	0.63
Eye reddness	AM/PM point in time	0.03	0.81
Eye reddness	PM reflective	0.04	0.48
Eye reddness	AM reflective	0.05	0.83
Eye reddness	AM point in time	0.03	0.88
Itching ears/palate	PM point in time	0.04	o.48
Itching ears/palate	AM/PM reflective	0.05	0.81
Itching ears/palate	AM/PM point in time	0.12	0.77
Itching ears/palate	PM point in time	0.08	0.61
Itching ears/palate	AM reflective	0.08	0.50
Itching ears/palate	PM reflective	0.07	0.80
Cough	AM point in time	0.23	0.33
Cough	AM/PM reflective	0.09	>0.99
Cough	AM/PM point in time	0.06	0.94
Cough	PM point in time	0.02	0.68
Cough	AM reflective	0.11	0.90
Cough	AM point in time	0.16	0.81
	PM reflective	0.11	0.93

◆ safety:

☛ Adverse events: overall 49% of group that received 5 mg of DCL, 3% of the group that received 7.5 mg DCL and 52% of the group that received placebo had adverse events. The incidence of adverse events considered related to study drug was 12% in the DCL 5 mg group, 11% in the 7.5 mg DCL group and 10% in the placebo group. In terms of adverse events that occurred with an incidence of 2% or greater in at least one treatment group, there were 6 types of adverse events that occurred with an overall incidence of 2% or more in one of the DCL groups than in the placebo group (see table below).

Overall Adverse Events

Adverse event	DCL 5 mg	DCL 7.5 mg	placebo
Dry mouth	5%	2%	1%
Dry throat	3%	1%	< 1%
Myalgia	2%	< 1%	0
Nervousness	< 1%	2%	0
Dyspnea	2%	< 1%	0
Pharyngitis	7%	4%	3%

There were 3%, 2% and 2% of patients in the DCL 5 mg, DCL 7.5 mg and placebo groups, respectively, who discontinued because of an adverse event. Only one patient in the 5 mg DCL group had an adverse event that required discontinuation that was felt to be probably related to the study drug (44 female with dyspepsia probable and fatigue possible).

COMMENT: Because of the structure of DCL, which is similar to the non-sedating antihistamine Optimine (azatadine), the greater incidence of dry mouth and dry throat are of interest, suggesting that there may be a significant anticholinergic effect produced by DCL.

- Laboratory tests: There were a few patients who had a clinically significant change in any laboratory test. This included two patients in the 5 mg DCL group who had normal serum glucose levels at screening and levels of 316 and 192 U/L after two weeks of treatment (N = 70-125). There were 4 patients in the DCL 7.5 mg group whose serum glucose levels went from normal at baseline to 151, 142, 145, and 147 U/L after two weeks of treatment, as well as 3 patients in the placebo group, 142, 143, and 157 U/L. In addition, one patient had a screening serum glucose of 219 U/L. The mean change in serum glucose was not significantly different between the three treatments. There were 11 patients in the 7.5 mg DCL group who had a normal serum glucose at baseline and an elevated level after drug administration compared to 4 patients in both the 5 mg DCL and the placebo groups. There is, nevertheless, no reason to believe that DCL causes an increase in serum glucose. There were 7 patients in the 7.5 mg DCL group that had a normal bilirubin at baseline and an elevated bilirubin after drug administration compared to 2 patients in both the 5 mg DCL and placebo groups. There were 7 patients in the 5 mg DCL group who had a normal alkaline phosphatase at baseline and an elevated level after drug administration, compared to 1 patient in each of the other two groups. Two patients in the 5 mg DCL group had increased WBC of 14.47 and 13.74 (N = 4-10.50), after treatment, while no patients in the other two groups had an elevated WBC after treatment. The significance, if any, of these findings is unclear. There were more patients in the 7.5 mg DCL group that had protein in the urine (35 [24%]), than in the 5 mg DCL (19 [10%]) or placebo groups (27 [16%]). The clinical significance of this difference, if any, is unclear.

- ECGs: The sponsor states that "Due to the use of different formulas for calculating QTc intervals by the computerized ECG tracing machines used at the centers, all QTc intervals were recalculated by Schering-Plough using the cube root (Fridericia) formula. This was done so that consistently derived QTc interval values could be pooled across the multicenter study." There were no patients who had had a normal baseline ECG who had a clinically significantly abnormal

ECG after either treatment with either dose of DCL. There was a decrease in the mean QT and QTc interval after all treatments. The only patient who had a 20% or greater increase in the QT interval was a patient who received placebo and there were more patients who had received placebo who developed a 20% or greater increase in the QTc interval than patients who received either dose of DCL.
There were more patients in the 5 mg DCL and the 7.5 mg DCL groups (4% and 2%, respectively) who had a 15-19% increase in the QTc interval, than in the placebo group (none).

- Vital signs: There were no clinically significant changes in vital signs after administration of any of the 3 treatments.

Conclusions: The sponsor has demonstrated a statistically significant difference between 5 mg of DCL and placebo, based on the primary efficacy variable, total symptom score, as well as most other parameters. The statistically significant difference in total symptom scores between the group that received 5 mg DCL and the group that received placebo appears to have been driven in large part by a greater improvement in sneezing in the active treatment group. No statistically significant difference between 5 mg DCL and placebo was seen for rhinorrhea. There was no statistically significant difference between the 7.5 mg dose of DCL and placebo. It is unclear why the larger dose did not beat placebo. The difference between the improvement seen in the group that received 5 mg/day of DCL and the group that received placebo is of questionable clinical significance. No safety concerns were raised by the data from this study.

Study 223:

METHODS: Study 223 was a parallel, double-blind, placebo-controlled, randomized, multicenter, repetitive dose study in 496 adult and adolescent patients (approximately 165 per arm) who had seasonal allergic rhinitis with an established baseline severity. Patients received either 5 mg or 7.5 mg of desloratadine in comparison with placebo for 2 weeks. The primary outcome variable was change from baseline in average reflective 12 hour AM/PM total symptom score (TSS) over the two weeks of treatment. There were 4 nasal (rhinorrhea, nasal congestion, nasal itching and sneezing) and 5 non-nasal symptoms (itchy eyes, tearing, eye redness, itching ears/palate, and cough) included in the total symptom score. Secondary outcome variables included change in total nasal symptoms, change in total non-nasal symptoms, change in individual symptoms, overall evaluation of the patient by the patient and physician, evaluation by patient and physician of therapeutic response, and quality of life assessment. Evaluation of symptoms were made by patients on a reflective and point-in-time basis using a 0-3 categorical scale. Safety was assessed by evaluating adverse events, change in laboratory tests, change in vital signs and change in ECGs. Two patient populations were analyzed: 1) an intent-to-treat population; and 2) an evaluable for efficacy population. Analyses were done including and excluding nasal congestion and cough.

RESULTS: Efficacy was demonstrated in this study for both the 5 mg and the 7.5 mg dose of desloratadine, based on a statistical comparison with placebo. Over the two weeks of treatment, the improvement in mean TSS was significantly greater in the 5 mg DCL group ($p = 0.04$) and the 7.5 mg DCL group ($p < 0.01$) compared to placebo. A statistically significant degree of improvement occurred within the first 2 days in the group that received 5 mg desloratadiine per day. The effectiveness demonstrated by the7.5 mg desloratadine group was consistently greater for the parameters evaluated at all time points than the effectiveness seen in the 5 mg desloratadine group. Interestingly, effectiveness of the 5 mg dose of desloratadine was demonstrated during the second week of treatment ($p = 0.10$). The 5 mg dose of DCL was not effective for nasal congestion or rhinorrhea. There was no significant increase in the incidence of adverse

events in either the 5 mg or 7.5 mg DCL groups, although there was a slightly greater incidence of fatigue and somnolence. There were no clinically significant changes in laboratory values, vital signs or ECGs.

DISCUSSION: The efficacy of the 5 mg dose of desloratadine was demonstrated in this study, although the onset of effectiveness was not seen until 48 hours after initiation of treatment and effectiveness was lost after the first week of treatment. There were no safety concerns raised by the data from this study.

Study 223:

- Number of patients: 496 patients (165 in the 5 mg DCL group, 166 in the 7.5 mg DCL group and 165 in the placebo group)

- Age range: 12-75 years

- Patient population: SAR; reflective rhinorrhea score of 2 or greater and total nasal symptom score of 6 or greater and total non-nasal symptom score of at least 5 at screening; to qualify for randomization, for the 3 days prior to baseline (3 AM and 3 PM assessments; 6 assessments) rhinorrhea of at least 12, total nasal symptom score of at least 36 and total non-nasal symptom score of at least 30

- Study design: randomized, placebo-controlled, parallel, multicenter, double-blind, repetitive dose study

- Drug administration: 5 and 7.5 mg once a day in the AM

- Periods of study: 14 days of randomized treatment; visit 3 (day 4), visit 4 (day 8) and visit 5 (day 15); visit 2 (baseline); screening 4-14 days

- Parameters evaluated: primary efficacy variable = change from baseline as the average over the two week treatment period in reflective (AM/PM) total symptom score; total symptom score = nasal symptoms (rhinorrhea, stuffiness, itching and sneezing) and non-nasal symptoms (itching eyes, tearing eyes, redness of the eyes, itching ears/palate with and without cough); primary analyses were based on the ITT population (efficacy-evaluable patients, i.e. patients who met key eligibility and evaluability criteria were utilized for confirmatory analyses of efficacy); secondary efficacy variables included nasal, non-nasal and individual symptom scores (both reflective and point-in-time), overall condition as assessed by the patient and physician (based on a categorical scale of 0-3), and response to therapy (based on a categorical scale of 1-5); supplemental analyses were done of the primary efficacy and total nasal symptoms were done without nasal congestion. Symptoms were graded on a categorical scale of 0-3; QOL was determined assessments were also

made; pollen counts daily to several times per week; hours exposed to outside air was recorded daily;

- Safety parameters:
  - AEs:
  - ECGs: at screening and at the conclusion of the study (1-3 hours after drug administration
  - vital signs: at each visit
  - Laboratory tests: at screening and the conclusion of the study

- Study Results:

- Discontinuations: There were more patients in the placebo group who discontinued than in either of the DCL groups.

- Demographics: There was no significant difference in the demographics of the three groups.

- total symptom score reflective over the preceding 12 hours for mean AM and PM values over the two weeks of treatment: Mean improvement in both the 5 and the 7.5 mg per day DCL groups was statistically significantly greater than placebo ($p = 0.04$ and $p < 0.01$, respectively). At 9 of the 10 centers, the 7.5 mg DCL per day group had more improvement than placebo, while at 8 of the 10 centers, the 5 mg DCL per day group had more improvement than placebo.

- total symptom score point-in-time in AM (end of dosing interval) over the two weeks of treatment: For this parameter there was not a statistically significant difference in the mean change over time between the group that received 5 mg per day of DCL and the group that received placebo ($p = 0.09$). There was a statistically significant difference between the group that received 7.5 mg per day of DCL and the group that received placebo ($p = 0.02$).

Mean change from baseline over two weeks

Parameter	time measured	P value (DCL vs placebo) 5 mg DCL	7.5 mg DCl
TSS with cough	AM/PM reflective	0.04	< 0.01
TSS without cough	AM/PM reflective	0.03	< 0.01
TSS with cough	AM/PM point in time	0.08	0.02
TSS without cough	AM/PM point in time	0.05	< 0.01
TSS with cough	AM point in time	0.09	0.02
TSS without cough	AM point in time	0.06	< 0.01
TSS with cough	AM reflective	0.05	< 0.01
TSS without cough	AM reflective	0.05	< 0.01
TSS with cough	PM reflective	0.04	< 0.01
TSS without cough	PM reflective	0.03	< 0.01
TSS with cough	PM point in time	0.09	0.02
TSS without cough	PM point in time	0.06	0.02
**********	**********	**********	**********
TNSS	AM/PM reflective	0.06	< 0.01
TNSS	AM/PM point in time	0.10	0.02
TNSS	AM reflective	0.08	< 0.01
TNSS	PM reflective	0.06	< 0.01
TNSS	AM point in time	0.10	0.02
TNSS	PM point in time	0.15	0.03
**********	**********	**********	**********
TSS non-nasal c cough	AM/PM reflective	0.04	< 0.01
TSS non-nasal s cough	AM/PM reflective	0.03	< 0.01
TSS non-nasal c cough	AM/PM point in time	0.08	0.02
TSS non-nasal s cough	AM/PM point in time	0.04	< 0.01
TSS non-nasal c cough	AM reflective	0.05	< 0.01
TSS non-nasal s cough	AM reflective	0.04	< 0.01
TSS non-nasal c cough	PM reflective	0.05	< 0.01
TSS non-nasal s cough	PM reflective	0.03	< 0.01
TSS non-nasal c cough	AM point in time	0.10	0.03
TSS non-nasal s cough	AM point in time	0.05	< 0.01
TSS non-nasal c cough	PM point in time	0.09	0.03
TSS non-nasal s cough	PM point in time	0.04	0.02
**********	**********	**********	**********
Nasal congestion	AM/PM reflective	0.25	0.03
Nasal congestion	AM/PM point in time	0.38	0.16
Nasal congestion	AM reflective	0.28	0.03
Nasal congestion	AM point in time	0.57	0.26
Nasal congestion	PM reflective	0.31	0.07
Nasal congestion	PM point in time	0.27	0.14
**********	**********	**********	**********
Rhinorrhea	AM/PM reflective	0.19	< 0.01
Rhinorrhea	AM/PM point in time	0.23	0.11
Rhinorrhea	AM reflective	0.42	0.02
Rhinorrhea	AM point in time	0.31	0.11
Rhinorrhea	PM reflective	0.09	< 0.01
Rhinorrhea	PM point in time	0.23	0.18

TABLE (continued)

Parameter	time measured	P value (DCL vs placebo) 5 mg DCL	7.5 mg DCL
Nasal itching	AM/PM reflective	0.07	< 0.01
Nasal itching	AM/PM point in time	0.14	0.04
Nasal itching	AM reflective	0.05	0.01
Nasal itching	AM point in time	0.07	0.08
Nasal itching	PM reflective	0.16	< 0.01
Nasal itching	PM point in time	0.36	0.05
**********	**********	**********	**********
Sneezing	AM/PM reflective	0.02	< 0.01
Sneezing	AM/PM point in time	0.04	< 0.01
Sneezing	AM reflective	0.03	< 0.01
Sneezing	AM point in time	0.03	< 0.01
Sneezing	PM reflective	0.02	< 0.01
Sneezing	PM point In time	0.11	0.03
**********	**********	**********	**********
Itching eyes	AM/PM reflective	0.05	0.01
Itching eyes	AM/PM point in time	0.01	< 0.01
Itching eyes	AM reflective	0.05	< 0.01
Itching eyes	AM point in time	0.02	< 0.01
Itching eyes	PM reflective	0.10	0.04
Itching eyes	PM point In time	0.02	0.02
**********	**********	**********	**********
Tearing eyes	AM/PM reflective	0.03	< 0.01
Tearing eyes	AM/PM point in time	0.11	0.07
Tearing eyes	AM reflective	0.03	0.01
Tearing eyes	AM point in time	0.08	0.05
Tearing eyes	PM reflective	0.07	0.01
Tearing eyes	PM point in time	0.21	0.16
**********	**********	**********	**********
Eye reddness	AM/PM reflective	0.02	0.01
Eye reddness	AM/PM point in time	0.03	0.03
Eye reddness	AM reflective	0.02	0.02
Eye reddness	AM point in time	0.06	0.02
Eye reddness	PM reflective	0.02	0.02
Eye reddness	PM point in time	0.03	0.11
**********	**********	**********	**********
Itching ears/palate	AM/PM reflective	0.20	< 0.01
Itching ears/palate	AM/PM point in time	0.35	0.02
Itching ears/palate	AM reflective	0.43	< 0.01
Itching ears/palate	AM point in time	0.43	0.03
Itching ears/palate	PM reflective	0.08	< 0.01
Itching ears/palate	PM point in time	0.27	0.02
**********	**********	**********	**********
Cough	AMPM reflective	0.69	0.28
Cough	AM/PM point in time	0.90	0.83
Cough	AM reflective	0.57	0.24
Cough	AM point in time	0.91	0.96
Cough	PM reflective	0.89	0.38
cough	PM point in time	0.89	0.58

TSS = total symptom score
TNSS = total nasal symptom score

As noted in the table above, the improvement in the group that received 5 mg DCL per day was not statistically significantly different than placebo for total nasal symptom scores, nasal congestion, rhinorrhea, nasal itching (except AM reflective), itching of the ears/palate or cough at any time point. There was a statistically significant difference between the group that received 5 mg of DCL per day and the placebo group in regard to the primary efficacy variable, total symptom scores over the preceding 12 hours for the entire two week period of treatment. The group that received 7.5 mg of DCL per day consistently showed statistical significance over placebo, except for nasal congestion, rhinorrhea and cough. Since the difference in improvement in total symptom scores between the group that received 5 mg DCL per day and the placebo group was not clinically significant, in the opinion of this reviewer, the conclusion is that the 7.5 mg DCL dose has been shown to be effective but the 5 mg DCL dose has not, in this study.

- **overall evaluation of symptoms; joint evaluation by patient and investigator: No statistically significant difference in overall improvement in SAR was seen between the 5 mg DCL and placebo groups (p = 0.59) or the 7.5 mg DCL and placebo groups (p = 0.33). The joint patient/investigator assessment of therapeutic response did show a statistically significant difference between the 7.5 mg DCL group and the placebo group (p = 0.02) but not the 5 mg DCL and placebo groups (p = 0.19)**

- **safety parameters:**

  - **adverse events: AEs were reported in 46% of the 5 mg DCL group, 44% of the 7.5 mg DCL group and 41% of the placebo group. In terms of AEs reported by 2% or more of patients, there was no clinically significant difference between the three groups in terms of any AE, although severe headache was more frequently reported in the 7.5 mg DCL group (6%) as compared to the placebo group (2%), fatigue was more frequently reported in both the 5 and 7.5 mg DCL groups (2%)**

than in the placebo group (<1%), and somnolence was reported in 3% and 4% of the 5 mg and 7.5 mg DCL groups, respectively compared to 1% of the placebo group. Based on 23-26 patients per treatment group, dysmenorrhea was reported by 15% (2 patients) and 17% (1 patient) in the 5 mg and 7.5 mg DCL groups, respectively, compared to no patients in the placebo group.

- **laboratory tests: There was no clinically relevant changes in median laboratory values. One patient who received 7.5 mg DCL per day, had an increase in SGOT from 34 to 155 U/L after 2 weeks of treatment. On the other hand, one patient in the 5 mg DCL group had a baseline value of 152 U/L. There were 4 patients receiving DCL who had a normal serum potassium at baseline and a low level after treatment (3 in the 5 mg group and 1 in the 7.5 mg group) compared to none in the placebo group. There were 6 patients in the 5 mg DCL group, 8 patients in the 7.5 mg DCL group and one patient in the placebo group who had a normal SGPT at baseline and an elevated SGPT after treatment. Similar differences were not seen in SGOT.**

- **ECGs: The mean QT and QTc intervals increased after treatment in the 7.5 mg DCL group (1.9 and 2.4 msec, respectively) compared with a decrease in both the QT and the QTc interval in the 5 mg DCL and placebo groups. There was a slightly greater percentage of patients in the 7.5 mg DCL group who had a prolongation of the QT interval of 10-14% or 15-19% (5% and 2%) and/or the QTC interval (11% and 6%) after treatment than in the 5 mg DCL (3% in the 10-14% range and none in the 15-19% range for QT and 8% in the 10-14% range and 2% in the 15-19% range) or placebo groups (see table below).**

Percent change from baseline in QT and QTC intervals

Parameter	10-14%	15-19%	20% or more
QT interval	**********	**********	**********
5 mg DCL	3%	None	None
7.5 mg DCL	5%	2%	None
Placebo	2%	1%	1%
QTc interval	**********	**********	**********
5 mg DCL	8%	2%	1%
7.5 mg DCL	11%	6%	2%
Placebo	4%	4%	2%

☛ **vital signs: There were no clinically significant changes in mean systolic or diastolic blood pressure or heart rate and no significant difference in either of the DCL groups from placebo. There were 5 patients (3 in the 5 mg group and 2 in the 7.5 mg group) who had a 40% or greater change in heart rate from baseline, compared to none in the placebo group.**

CONCLUSIONS:

1. **The 7.5 mg/day dosage of DCL was efficacious, and was as safe as the 5 mg/day dosage.**

2. **Since the 5 mg/day dosage produced a statistically significantly greater improvement in the primary efficacy variable (TSS) than placebo (p = 0.03), it would be reasonable to conclude that this dosage is efficacious as well. However, this reviewer feels that this result is more than offset by the lack of a statistically significant difference from placebo in regard to total nasal symptoms, rhinorrhea, nasal itching, and itching of the ears/palate. In addition, this reviewer interprets the data arbitrarily as lacking any indication of a clinically significant effect.**

3. **No safety issue were raised in regard to the data reported on this study, although further review of the ECG data will be discussed following review of the sponsor's recent submission of the analysis of this data.**

Study 001:

METHODS: Study 001 was a parallel, double-blind, placebo-controlled, randomized, multicenter, repetitive dose study in 1036 adult and adolescent patients (172-174 per arm) who had seasonal allergic rhinitis with an established baseline severity. Patients received either 2.5 mg, 5 mg, 7.5 mg, 10 mg or 20 mg of desloratadine in comparison with placebo for 2 weeks. The primary outcome variable was change from baseline in average reflective 12 hour AM/PM total symptom score (TSS) over the two weeks of treatment. There were 4 nasal (rhinorrhea, nasal congestion, nasal itching and sneezing) and 4 non-nasal symptoms (itchy eyes, tearing, eye redness and itching ears/palate) included in the total symptom score. Secondary outcome variables included change in total nasal symptoms, change in total non-nasal symptoms, change in individual symptoms, ~~overall evaluation of the patient~~ by the patient and physician, evaluation by patient and physician of therapeutic response, and quality of life assessment. Evaluation of symptoms were made by patients on a reflective and point-in-time basis using a 0-3 categorical scale. Safety was assessed by evaluating adverse events, change in laboratory tests, change in vital signs and change in ECGs. Two patient populations were analyzed: 1) an intent-to-treat population; and 2) an evaluable for efficacy population. Analyses were done including and excluding nasal congestion and cough.

RESULTS: The efficacy of all doses of desloratadine except for the 2.5 mg dose were demonstrated for all parameters at most time points. There was no dose-response seen in the groups that received 5 mg to 20 mg of desloratadine. The difference in improvement in TSS from baseline in the group that received 5 mg DCL was not clinically significantly different than the difference seen in the placebo group. There was a slightly greater incidence of adverse events in the desloratadine treatment groups than in the placebo group and a slightly greater incidence of fatigue and somnolence. In terms of fatigue, a dose response was seen beginning at a dose of 5 mg of desloratadine. There were no clinically significant changes in laboratory values, vital signs or ECGs in the patients who received 5 mg of desloratadine.

DISCUSSION: The efficacy and safety of a dose of 5 mg of desloratadine is supported by the statistically significant difference in improvement in symptoms seen in the 5 mg DCL group in this study and the lack of any clinically significant changes in safety parameters. The improvement in symptoms was, however, not clinically significant, in the opinion of this reviewer.

Study 001:

☛ Study Characteristics:

☛ number of patients:1036 (173 received 2.5 mg DCL, 172 received 5 mg DCL, 173 received 7.5 mg DCL, 172 received 10 mg DCL, 172 received 20 mg DCL, 174 received placebo)

☛ age range: 12-75

☛ patient population: SAR; rhinorrhea at least 2, TNSS at least 6 and total non-nasal symptom score at least 5 at both screening and baseline

☛ study design: multicenter (29 centers), US, placebo-controlled, randomized, parallel, double-blind study

☛ drug administration: DCL 2.5, 5, 7.5, 10, and 20 mg once a day in AM

☛ periods of study: approximately 1 week screening period; followed by 2 weeks of randomized treatment; evaluation at days 4, 8, and 15

☛ parameters evaluated:

efficacy:

☛ the primary efficacy variable was change from baseline (3 days prior to randomization) in the average over the two week treatment period of reflective AM/PM total symptom scores (4 nasal and 4 non-nasal symptoms)(analyzed with and without nasal congestion) (0-3 categorical scale)

☛ nasal symptom scores (with and without nasal congestion) (rhinorrhea, itching nose, sneezing) (0-3 categorical scale)

- ☛ non-nasal symptom scores (itching eyes, tearing eyes, redness eyes, itching ears/palate) (0-3 categorical scale)
- ☛ individual symptom scores
- ☛ overall condition (joint physician/patient evaluation) (0-3 scale)
- ☛ response to therapy (joint physician/patient evaluation) (1-5 scale)

☛ safety:

- ☛ laboratory tests: screening and after 2 weeks of treatment
- ☛ vital signs: each study visit
- ☛ 12 lead ECG: screening and after 2 weeks of treatment
- ☛ adverse events:

☛ study results:

- ☛ discontinuations: The percentage of patients who discontinued because of an adverse event or because of treatment failure was no greater in any of the active treatment groups than in the placebo group. The overall percentage of patients in the placebo group who discontinued was 5%. This is essentially the same as the groups that received 2.5 and 5 mg of DCL (6% and 7%, respectively) and the same as the other treatment groups.
- ☛ protocol deviations: There were more patients excluded from the efficacy evaluable subset because of protocol violations in the 5 mg, 10 mg, and 20 mg DCL groups than in the placebo group. The difference (11 in the placebo group, 12, 14 and 15 in the 3 DCL groups) was not great enough to have influenced the study results.

- **demographics: The percentage of males was significantly greater in the placebo group than in any of the DCL groups. Review of the data does not demonstrate any significant difference in response based on gender. The duration of SAR was not significantly different among the treatment groups.**

- **primary efficacy outcome variable: No dose-response was seen. There was a statistically significant difference in terms of improvement in symptoms in each of the DCL groups ($p < 0.01$) than in the placebo group (tab 12, p 53, v 1.120) The reduction in symptoms in the 5 mg DCL group over the two week treatment period was 28% and in the 7.5 mg group was 27% (tab 11, p 52, v 1.120)(see table below). The mean change in TSS over the change seen after administration of placebo for the 14 days of treatment of 0.2-0.3 per symptom in the DCL groups is not, in this reviewer's opinion, a clinically significant change.**

- **secondary efficacy outcome variables: The mean change in TSS AM point in time, total nasal symptoms and total non-nasal symptoms for the DCL groups over the effect seen with placebo for the entire two weeks of the study per symptom (0.2-0.3) is not, in this reviewer's opinion, a clinically significant change. See table below.**

TABLE

Mean change from baseline over 2 weeks (ITT population)

Parameter	time measured	2.5 mg DCL	5 mg DCL	7.5 mg DCL	10 mg DCL	20 mg DCL
TSS	AM/PM reflective (t11, 12, p 52,53, v1.120)	-3.2 (0.19) ** placebo –2.5	-4.3 (< 0.01)	-4.3 (< 0.01)	-3.9 (< 0.01)	-4.8 (< 0.01)
TSS	AM/PM point in time (t1b, p557, v1.121)	-3.5 (0.04) placebo –2.5	-4.1 (< 0.01)	-4.4 (< 0.01)	-4.0 (< 0.01)	-4.7 (< 0.01)
TSS	AM point in time (t13, 14, p 55,56, v1.120)	-3.2 (0.10) ** placebo –2.4	-3.8 (< 0.01)	-4.2 (< 0.01)	-3.8 (< 0.01)	-4.4 (< 0.01)
TSS	AM reflective (t1b, p583, v1.121)	-2.8 (0.34) ** placebo –2.3	-4.1 (< 0.01)	-3.9 (< 0.01)	-3.6 (< 0.01)	-4.5 (< 0.01)
TSS	PM reflective	-3.7 (0.12) ** placebo –2.9	-4.6 (< 0.01)	-4.9 (< 0.01)	-4.3 (< 0.01)	-5.2 (< 0.01)
TSS	PM point in time	–3.8 (0.02) placebo –2.6	-4.3 (< 0.01)	-4.7 (< 0.01)	-4.1 (< 0.01)	-5.0 (< 0.01)
********	********	********	********	********	********	********
TNSS	AM/PM point in time (t1a, p559, v 1.121)	-1.7 (0.13) ** placebo –1.3	-2.1 (< 0.01)	-2.2 (< 0.01)	-2.1 (< 0.01)	-2.5 (< 0.01)
TNSS	AM/PM reflective (t 15, 16, p57,58, v1.120)	-1.6 (.40)** placebo –1.4	-2.2 (<0.01)	-2.3 (< 0.01)	-2.0 (< 0.01)	-2.5 (< 0.01)
TNSS	AM reflective (t1b, p586, v1.121)	-1.4 (0.64) ** placebo –1.3	-2.1 (0.01)	-2.0 (< 0.01)	-1.8 (0.03)	-2.3 (< 0.01)
TNSS	AM point in time (t1b, p609, v1.121)	-1.5 (0.34) ** placebo –1.3	-1.9 (0.01)	-2.1 (< 0.01)	-2.0 (< 0.01)	-2.4 (< 0.01)
TNSS	PM reflective	-1.9 (0.23) ** placebo –1.6	-2.5 (< 0.01)	-2.6 (< 0.01)	-2.3 (< 0.01)	-2.8 (< 0.01)
TNSS	PM point in time	-1.8 (0.06) ** placebo –1.3	-2.2 (< 0.01)	-2.3 (< 0.01)	-2.1 (< 0.01)	-2.6 (< 0.01)
********	********	********	********	********	********	********
Total non-nasal symptom score	AM/PM point in time (t1b, p 563, v1.121)	-1.8 (0.02) placebo –1.2	-2.0 (< 0.01)	-2.2 (< 0.01)	-1.9 (< 0.01)	-2.2 (< 0.01)
Total non-nasal symptom score	AM/PM reflective (t17 18, p59,60. v 1.120	-1.6 (0.10) ** placebo –1.2	-2.1 (< 0.01)	-2.1 (< 0.01)	-1.9 (0.01)	-2.3 (0.01)
Total non-nasal symptom score	AM reflective (t1b, p589, v1.121)	-1.4 (0.18) ** placebo –1.1	-2.0 (< 0.01)	-1.9 (< 0.01)	-1.8 (< 0.01)	-2.2 (< 0.01)
Total non-nasal symptom score	AM point in time (1b,p 612 v1.121)	-1.7 (0.04) placebo –1.1	-1.8 (0.01)	-2.1 (< 0.01)	-1.8 (0.01)	-2.1 (< 0.01)
Total non-nasal symptom score	PM reflective	-1.8 (0.08) placebo –1.4	-2.1 (< 0.01)	-2.3 (< 0.01)	-2.0 (0.02)	-2.4 (< 0.01)
Total non-nasal symptom score	PM point in time	-2.0 (0.01) placebo –1.3	-2.1 (< 0.01)	-2.3 (< 0.01)	-2.0 (< 0.01)	-2.3 (< 0.01)