7 INTEGRATED REVIEW OF SAFETY

Integrated review of safety data supporting this application follows below.

7.1 Methods and Findings

A clinical program was performed because the desloratadine in Clarinex-D 24 Hour extended release tablets failed to show bioequivalence to the individual desloratadine 5 mg mono-product (i.e. Clarinex 5 mg) in two bioequivalence studies. Systemic exposure with 5 mg desloratadine in this long-acting combination was less than with approved desloratadine 5 mg formulations. While the lower clinical exposure has implications for the clinical program from an efficacy perspective, this is less of a concern from a safety perspective.

The applicant submitted data from two clinical studies, P01875 and P01884, to support the (efficacy and) safety for Clarinex-D® 24 Hour Tablets. A total of 2852 subjects were randomized into the two Phase 3 studies and received at least one dose of study drug. There were no unexpected or unusual adverse event findings in the two clinical studies. The most frequently reported adverse events (reported for ≥ 5% of patients in any treatment group) were dry mouth, headache, and insomnia, and these AEs were more prevalent in the DL D-24, DL D-24, and PSE treatment group indicating the known sympathomimetic side effects of PSE.

The applicant submitted a safety update for desloratadine from published literature and post-marketing adverse events for the period between December 21, 2001 and September 30, 2004 for patients 12 years of age and older. The applicant also conducted a literature search and a search of the AERS database for adverse events reported for pseudoephedrine from December 21, 2001 to December 31, 2003.

Review of the safety findings in this application revealed no new or unusual safety trends. There were no deaths, and no serious and unexpected adverse events that were attributed by an investigator to study drug. The adverse event profile is similar to what might be expected from use of an antihistamine and a decongestant in combination, with the most common adverse events being dry mouth, headache, and insomnia. Of note, there was no placebo group to allow placement of the incidence of adverse events into perspective.

7.1.1 Deaths

There were no deaths from DL D-24 in the two Phase 3 clinical studies, P01875 and P01884 for patients.

In the safety update, the applicant noted that there were nine cases of death or death as an outcome reported in patients taking desloratadine. Case summaries were reviewed, and two are of interest. In one instance, attribution of the event was possibly related to desloratadine

use. In a second, causality assessment was not made, but attribution of this reviewer is that the event was possibly related to desloratadine use. The summaries are presented below.

> Patient 2002-04-1104, a 42-year-old female with a history of hypertension, was initiated on DL tablet for an unspecified indication. On the same day, the patient complained of not feeling well, and later collapsed and went into cardiac arrest, and subsequently died. The AEs reported were myocarditis, cardiac arrest, coma, ventricular fibrillation, and cerebrovascular accident.
>
> Patient 2002-04-2093, a 12-year old boy, took a 5-mg DL tablet for 1 day. He experienced asthma, cardiac arrest, ventricular fibrillation, hypotension, brain hypoxia, and fatigue. The outcome was death, which was assessed to be unrelated to the drug.

Most of the deaths for the other seven patients were due to predisposed disease states (i.e. liver cancer, Factor X deficiency, congestive heart failure, neuropsychiatric disorder). In the literature review, there were three spontaneous abortions reported: a twin gestation that occurred at 10 weeks, a one-month gestation in a female with an ovarian cyst, and a 7-week normal gestation [safety update.pdf, pages 29-31]. There were no reported deaths with pseudoephedrine or with the combination of DL and PSE.

7.1.2 Other Serious Adverse Events

There were a total of five serious adverse events during the treatment phases of the two clinical studies, 0 in the DL D-24, 2 in the DL D-24 AF, 1 in the DL, and 3 in the PSE treatment groups. All events (i.e. 1 asthma, 1 pneumonia, 2 cases of cholelithiasis, 1 acute sinusitis and lower respiratory tract infection) were considered by the investigators to be unrelated to study drug treatment. The events are discussed in Sections 10.1.1.11.4.5 and 10.1.2.5.5.5 of this review, and are therefore not discussed in depth in this section of the review. In addition, one patient was hospitalized during the screening phase of Study P01875 with a head injury from falling off a moving vehicle.

Three pregnancies occurred during Study P01875 (1 DL D-24 AF, 2 PSE). Two patients electing to abort (1 DL D-24 AF, 1 PSE), and one delivered a healthy baby boy (PSE). In Study P01875, one patient with a negative screening pregnancy test was positive of a test performed at randomization. The patient was randomized and took one dose of study drug (DL) prior to being discontinued from the study. Seven patients had positive pregnancy tests during screening and were not randomized. [ISS, 8.H.6.1.9, p 44-5, iss.pdf]

In the safety update, the Applicant reported on AEs reported for DL and PSE. Three SAEs reported to AERS were considered to be associated with the use of PSE. They were thyroid disorder, convulsion (with intentional overdose), and loss of consciousness [12/2/2004, Section 5.3, pp 50-51, safety update.pdf].

In the applicant's safety database for desloratadine there were 5181 adverse event reports in 3110 patients ≥12 years of age. Of the 5181 adverse events reports, 317 (6%) were considered serious adverse events (SAEs). Review of serious adverse events showed a wide scatter over many body systems and disorders. The most frequent occurring in five or more patients were syncope (13), hypersensitivity (10), anaphylactic reaction (10), angioneurotic edema (9), tachycardia (8), tachyarrhythmia (7), grand mal convulsion (7), convulsion (7), hepatitis (7), hallucination (6), bronchospasm (6), urinary retention (5), Stevens-Johnson syndrome (5), and ventricular extrasystoles (5). A total of 47 cases of cardiovascular SAEs were reported, among which were 3 deaths. There were two cases of QT prolongation, one in a 79 year old female and one in a 60 year old male. The degree of QT prolongation was not known for either case. Twenty-one cases of SAEs related to hepatobiliary disorders were reported, the most common being hepatitis. Seven cases of hepatitis and one case of fulminant hepatitis were reported. Seven renal and urinary SAEs were reported; five of them being urinary retention. A total of 52 cases of SAEs related to nervous system disorders were reported, with the most common being syncope, Grand mal convulsion, and convulsion. At the Division's request, brief descriptions of all cases of convulsion were submitted with the safety update, and these were reviewed. Many of the events were attributed to having possibly been related to desloratadine use. Three cases of spontaneous abortion were reported. [12/2/2004, Section 5.3, safety update.pdf]

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A total of 190 (6.6%) patients out of 2852 randomized patient failed to complete the study. There was no pattern to dropouts, except those related to AEs as noted below.

7.1.3.2 Adverse events associated with dropouts

Details of the patients who were randomized, experienced and adverse event, completed, discontinued, or discontinued due to adverse events are shown in Table 7. A total of 102 (3.6%) patients were dropped from the study due to adverse events, 14 (0.5%) due to treatment failures, and 21 (0.7%) were lost to follow-up. Of the 102 patients discontinued due to one or more AEs, AEs were similar in frequency among treatment groups (DL D-24: 3.4%; DL D-24 AF: 4.5%; PSE: 3.5%, and DL: 2.9%). Consistent with the incidence of all types of adverse events in the two studies, there were numerically less dropouts (and specifically, due to any AE or an SAE) in the DL-alone group compared with the other groups. Most AEs that were associated with discontinuation were not unexpected and can reasonably be considered treatment-related to PSE, such as headache, insomnia, nausea, psychomotor activity, and dizziness.

Four patients experienced adverse events leading to discontinuation that were considered to be serious: one each due to hyperpyrexia (DL D-24 AF); cholelithiasis (DL D-24 AF); and

asthma (PSE); and one due to diarrhea, nausea, vomiting, bronchitis, and sinusitis (PSE), all considered by the investigator to be severe and unlikely related to study medication.

Table 7. ISS: Incidence of Adverse Events and Discontinuations due to Adverse Events, Studies P01875 and P01884, MITT*

	DL D-24	DL D-24 AF	DL	PSE
Randomized (N)	708	713	712	719
Any adverse event[a]	263 (37.1)	299 (41.9)	196 (27.5)	269 (37.4)
Any treatment-related adverse event[b]	172 (24.3)	197 (27.6)	93 (13.1)	183 (25.5)
Any severe adverse event	50 (7.1)	60 (8.4)	29 (4.1)	50 (7.0)
Any severe treatment-related adverse event*	27 (3.8)	42 (5.9)	11 (1.5)	30 (4.2)
Completed (N, %)	665	663	671	666
Discontinued (N, %)	43	50	41	53
due to any adverse event	24 (3.4)	32 (4.5)	21 (2.9)	25 (3.5)
due to severe adverse event	15 (2.1)	11 (1.5)	6 (0.8)	11 (1.5)

* MITT = All patients randomized *and* who received at least one dose of study drug.
[a] Number of patients reporting an adverse event at least once during the study. Some patients may have reported more than 1 adverse event.
[b] Considered by the investigator to be possibly or probably related to treatment.

Source; Section 3H6, Table 10, p 185 and Table 13, p 190, summary.pdf

7.1.3.3 Other significant adverse events

No other significant adverse events were noted in the two clinical studies, and no serious or unexpected adverse events were reported in any of the clinical pharmacology studies.

A published report regarding DL concerned a 38 year old female with a history of recurrent lymphoma who had received a stem cell transplant and a variety of chemotherapeutic regimens and developed severe hepatotoxicity after the administration of DL and fluconazole. Although fluconazole treatment was temporally associated with the reported hepatotoxicity, it was impossible for the investigators to impute causation to any one of the drugs alone or in combination with fluconazole.[1]

7.1.4 Other Search Strategies

No other special safety studies or searches were conducted for this NDA.

7.1.5 Common Adverse Events

The proportion of patients reporting a treatment-emergent adverse event in the two clinical trials was similar in the DL D-24 (37.1%), DL D-24 AF (41.9%), and PSE (37.4%) groups, and slightly lower in the DL (27.5%) group, as shown in Table 7. The majority of adverse events in any of the PSE-containing formulations were similar between treatment groups, with most related to the sympathomimetic effects of PSE, presumably accounting for the

lower rate of AEs reported in the DL-alone group. Most events were mild or moderate in severity.

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were elicited by patient reports on daily diary cards kept during the baseline and treatment periods, as captured and evaluated at each clinic visit.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant grouped closely related investigator or patient reported terms using a MedDRA dictionary of preferred terms. While these dictionaries leave considerable discretion to the classifier for choosing the term that best describes what has been reported, the applicant's categorization of events was not assessed by comparing the preferred terms to the terms used by investigators and patients. The only term for which this might have been a concern was fatigue, which can encompass many different terms and types of AEs. However, since rates were similar among treatment groups, with most differences occurring in the one group without PSE, and since all of the common events that were reported were expected based on drug class, this was not explored further in the NDA safety review.

7.1.5.3 Incidence of common adverse events

No substantial difference in the pattern of adverse events among treatment groups was evident in any of the demographic subgroups, as seen in Table 8. In general, when differences in incidence of AEs were noted between groups, it was the DL-alone group that had fewer events, implying that many of the events were related to the PSE component. Among PSE-containing treatment groups, AE incidence was quite similar. However, note that there was no placebo group to provide a background rate and comparator group against which one could assess the laboratory results.

7.1.5.4 Common adverse event tables

Table 8. ISS: Incidence of Treatment-Emergent Adverse Events Reported by ≥2% of Patients in Any Treatment Group, Pooled Studies P01875 and P01884, MITT*

	DL D-24 N = 708	DL D-24 AF N = 713	DL N = 712	PSE N = 719
Any adverse event[a]	263 (37.1)	299 (41.9)	196 (27.5)	269 (37.4)
Autonomic nervous system	63 (8.9)	86 (12.1)	21 (2.9)	84 (11.7)
Dry mouth	59 (8.3)	81 (11.4)	17 (2.4)	77 (10.7)
Body As a Whole	71 (10.0)	68 (9.5)	68 (9.6)	74 (10.3)
Fatigue	18 (2.5)	16 (2.2)	19 (2.7)	14 (1.9)
Headache	45 (6.4)	37 (5.2)	37 (5.2)	47 (6.5)
Nervous system disorders	34 (4.8)	46 (6.5)	16 (2.2)	31 (4.3)
Dizziness	14 (2.0)	22 (3.1)	6 (0.8)	13 (1.8)
Psychomotor hyperactivity	17 (2.4)	19 (2.7)	2 (0.3)	16 (2.2)
Gastrointestinal System Disorders	66 (9.3)	55 (7.7)	32 (4.5)	62 (8.6)
Anorexia	12 (1.7)	14 (2.0)	2 (0.3)	12 (1.7)
Nausea	12 (1.7)	17 (2.4)	7 (1.0)	18 (2.5)
Psychiatric Disorders	79 (11.2)	80 (11.2)	28 (3.9)	86 (12.0)
Insomnia	35 (4.9)	40 (5.6)	5 (0.7)	54 (7.5)
Nervousness	16 (2.3)	7 (1.0)	5 (0.7)	9 (1.3)
Somnolence	24 (3.4)	27 (3.8)	12 (1.7)	18 (2.5)
Respiratory System Disorders	50 (7.1)	45 (6.3)	43 (6.0)	54 (7.5)
Pharyngitis	18 (2.5)	9 (1.3)	11 (1.5)	20 (2.8)

* MITT = All patients randomized *and* who received at least one dose of study drug.
[a] Number of patients reporting a treatment-emergent adverse event at least once during the study, without regard to relationship to treatment. Some patients may have reported more than 1 adverse event.

Source; Section 3H6, Table 11, p 186, summary.pdf

For comparative purposes only, the labels for Clarinex and Claritin D-24 (which uses the same PSE 240 mg core) were evaluated. These are shown in Table 9 and Table 10. No unusual trends are noted.

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On Original

Percent AEs	DL D-24 studies (%)			Clarinex Label (%)	
	DL D-24 N = 708	DL N = 712	PSE N = 719	Clarinex N = 1655	Placebo N = 1652
Dry mouth	8.3	2.4	10.7	3.0	1.9
Myalgia				2.1	1.8
Fatigue	2.5	2.7	1.9	2.1	1.2
Headache	6.4	5.2	6.5		
Dizziness	2.0	0.8	1.8		
Psychomotor hyperactivity	2.4	0.3	2.2		
Anorexia	1.7	0.3	1.7		
Nausea	1.7	1.0	2.5		
Insomnia	4.9	0.7	7.5		
Nervousness	2.3	0.7	1.3		
Somnolence	3.4	1.7	2.5	2.1	1.6
Pharyngitis	2.5	1.5	2.8	4.1	2.0
Dysmenorrhea				2.1	1.6

Table 9. ISS: Adverse events in ≥2% compared to Clarinex label

Percent AEs	DL D-24 studies (%)			Claritin D-24 Label (%)		
	DL D-24 N = 708	DL N = 712	PSE N = 719	Claritin D-24 N = 605	PSE N = 220	Placebo N = 605
Dry mouth	8.3	2.4	10.7	8	7	2
Fatigue	2.5	2.7	1.9	3	1	2
Headache	6.4	5.2	6.5			
Dizziness	2.0	0.8	1.8	4	3	2
Psychomotor hyperactivity	2.4	0.3	2.2			
Anorexia	1.7	0.3	1.7	2	2	0
Nausea	1.7	1.0	2.5	3	4	2
Insomnia	4.9	0.7	7.5	5	9	1
Nervousness	2.3	0.7	1.3	3	4	1
Somnolence	3.4	1.7	2.5	6	5	4
Pharyngitis	2.5	1.5	2.8	5	5	5
Dysmenorrhea				2	2	1
Coughing				3	3	1

Table 10. ISS: Adverse events in ≥2% compared to Claritin D-24 label

7.1.5.5 Identifying common and drug-related adverse events

The adverse events reported as occurring in ≥2% of patients in any treatment group were evaluated with respect to other labels or both desloratadine and pseudoephedrine, and for expected adverse event profiles based on drug class and known effects. No unexpected trends were noted.

7.1.5.6 Additional analyses and explorations

In the applicant's safety database for desloratadine, there were 5181 adverse event reports in 3110 patients ≥12 years of age. A total of 627 patients (20% of all reported AEs) experienced a total of 1026 nervous system AEs. The most common AEs reported were headache, somnolence and dizziness. [12/2/2004, Section 5.3, safety update.pdf]

Reviewer's Note: While somnolence and dizziness are two of the AEs reported at ≥2% in the two clinical trials, and therefore will be in the adverse event table in the label, headache was not. This reviewer suggests that all three be included in the section of the PI entitled Adverse Events Observed in Clinical Practice.

A total of 344 cardiovascular AEs (6.6% of all reported AEs) were experienced by 222 patients 12 years and over, and in patients where age was not reported. The most common AEs reported were palpitations (n=118), tachycardia (n=94), and blood pressure increased (n=37), which are already listed in the desloratadine label. A total of 52 patients (1.6% of all reported AEs) experienced 81 hepatobiliary AEs. The most commonly reported AEs were hepatic enzyme increased (n=15), gamma-glutamyltransferase increased (n=10), hepatitis (n=9), transaminases increased (n=8), jaundice (n=7), and liver function test abnormal (5). A total of 50 patients (1.2% of all reported AEs) experienced 62 renal and urinary AEs. The most common AEs reported were pollakiuria and urinary retention. A total of 40 patients experienced 50 AEs reproductive system and breast AEs. The most common AEs reported were amenorrhea (n=7) and erectile dysfunction (n=6). [12/2/2004, Section 5.3, safety update.pdf]

7.1.6 Less Common Adverse Events

Exploration for incidence of less common adverse events was not necessary or applicable for two short studies employing two well-known drugs and drug classes.

7.1.7 Laboratory Findings

In the two clinical studies, there were no clinically relevant changes in median laboratory test values observed across the four treatment groups. [8.H.6.2, iss.pdf]

7.1.7.1 Overview of laboratory testing in the development program

As was appropriate for this clinical program, in the two clinical studies clinical labs were obtained during screening (Baseline) and at the end of the two-week treatment period (Endpoint). No specific trends in laboratory values were noted for the treatment groups. However, note that there was no placebo group to provide a background rate and comparator group against which one could assess the laboratory results.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not Applicable

7.1.7.3 Standard analyses and explorations of laboratory data

Median percent changes from Baseline (the last value prior to the start of treatment) to Endpoint (the last post-baseline measurement during the study) in laboratory test values were evaluated for any clinically relevant change for each treatment group in the pooled dataset. The distribution of subjects by categories of change was also examined for trends of change. No clinically relevant changes in median laboratory values were observed across the four treatment groups.

Laboratory results were also stratified by age, sex, and race. Analyses of these variables by age, gender, and race did not indicate any differential response to treatment between sexes, ages, and between Caucasians, Blacks, and Hispanics. There were too few patients of Asian, American Indian, or "Other" ethnic groups to adequately assess the differential response to treatment for these subgroups.

7.1.7.3.1 Analyses focused on measures of central tendency

See above.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The change in laboratory values from Baseline to Endpoint was evaluated for each test relative to the reference range. The majority of patients remained within the reference range at Endpoint, and no clinically meaningful trends were observed.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Clinically meaningful abnormalities were defined as a blood chemistry (liver function) parameters ≥2.6 times the upper limit of normal, hemoglobin concentration ≤9.4 g/dL (94 g/L), platelet count ≤74,000 µL, or white blood cell count (WBC) ≤2,900/µL. A total of 36 subjects (8 treated with DL D-24, 12 treated with DL D-24 AF, 9 treated with PSE, and 7 treated with DL) had values that met at least one of these criteria.

Eight patients (1/697 treated with DL D-24, 3/694 treated with DL D-24 AF, 2/700 treated with DL, and 2/703 treated with PSE) had worsening liver function parameters at the Final visit (Endpoint). None of these subjects had a history of liver disease or risk factors for liver

disease. All repeat laboratory test results for these subjects were either within or approximated normal reference range values.

Only one patient (Subject P01875-19/6799; DL D-24 AF) experienced elevated liver function values that were reported as an adverse event. This was a 34-year-old Caucasian female, who had normal ALT and AST values (16 U/L and 18 U/L, respectively) at Baseline, but elevated values at Endpoint (133 U/L and 129 U/L, respectively). The elevated values were considered by the investigator to be adverse events of moderate severity and possibly related to study medication. Repeat laboratory tests performed 8 days later revealed ALT and AST values (41 U/L and 22 U/L, respectively) that were within the reference ranges.

Nineteen of the 2778 patients (6/692 treated with DL D-24, 4/693 treated with DL D-24 AF, 5/700 treated with PSE, and 4/693 treated with DL) had WBC values ≤2,900/μL. Three of the 2778 subjects (2/693 treated with DL D-24 AF and 1/700 treated with PSE) had platelet counts ≤74,000 μL at Screening or Endpoint. Twelve of these 22 subjects had values within the normal reference range at Screening that decreased to clinically meaningful values at the Final visit, or had elevated values at Screening that worsened during the study.

7.1.7.4 Additional analyses and explorations

Not Applicable

7.1.7.5 Special assessments

Not Applicable

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

As was appropriate for this clinical program, in the two clinical studies vital signs were obtained at each visit: during screening, at baseline and at both on-treatment visits (days 8 and 15).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Data were pooled from the two clinical studies.

7.1.8.3 Standard analyses and explorations of vital signs data

Diastolic and systolic blood pressure, heart rate, and respiration rat were examined for the mean change from baseline and the distribution of patients among percentiles of change.

7.1.8.3.1 Analyses focused on measures of central tendencies

There were no clinically relevant changes in mean values for vital signs observed across the four treatment groups.

7.1.8.3.2 Marked outliers and dropouts for vital sign abnormalities

Analysis of outliers and dropouts was not performed.

7.1.8.4 Additional analyses and explorations

Not Applicable

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Twelve-lead ECGs were obtained at screening (Baseline) and at the end of the last visit (Endpoint) in both clinical studies. This is appropriate, given the fact that both of these drugs have previously been extensively evaluated for ECG effects.

The ECG performed at the final visit was performed in the 2-6 hour post-dosing time interval. Ventricular rate, PR, QRS, QT, and QTc intervals were reported using "Cardiac Alert" telephonic technology, a monitoring service that provides centralized ECG readings for clinical trials. The information provided in the Appendix of the protocols states that ECG interpretations were based on strict criteria, taking into account the patients medical status. Results were 'flagged' as normal, insignificant ECG abnormality, significant ECG abnormality, or exclusion criteria met (i.e. one or more significant ECG anomalies were detected, corresponding to the protocol's exclusion criteria – in this case none were specified). Of interest, nowhere in the protocol was the methodology for evaluation of QTc intervals specified, nor were limits specified for the upper limits of normal for the QTc interval. However, the ISS reports that QTc intervals were calculated using both Bazett and Fridericia formulae. [Study P01875, 9.5.1.3.2, p 43; 16.1.1.1, Appendix 3, p 1460-78; P01875.pdf; ISS, 8.H.6.3.2, p62, iss.pdf]

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Data were pooled from the two clinical studies.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Tables were prepared for ECG interval data, including ventricular rate, PR, QRS, QT, and calculated QTcF or QTcB (Fridericia and Bazett formulae) intervals, and presented overall

and by sex. Mean ventricular rate increased by 6.7, 6.4, 2.8, and 5.4 in the DL D-24, DL D-24 AF, DL, and PSE groups, respectively. Among patients who received DL D-24 or DL D-24 AF, the increase from Baseline in ventricular rate was slightly greater among females (7.5 bpm and 7.0 bpm, respectively) than males (5.4 bpm in each treatment group). Most of the increases in ventricular rate were in patients treated with a formulation containing PSE, and slight increases in ventricular rate are a known side effect of PSE treatment. No clinically relevant effects on PR, QRS, QT, or QTc intervals were noted. Subgroup analyses of ECG interval data based on age and race showed no apparent differences among treatment groups. [ISS, 8.H.6.3.2, p62-5, iss.pdf]

A table was prepared of the distribution of subjects by percent change from Baseline in ECG intervals. For ventricular rate, 28% DL D-24, 29% DL D-24 AF, and 21% PSE subjects, demonstrated a ≥20% increase in rate compared with 13% of DL subjects. For PR, QRS, QT, and QTc intervals, there were no apparent differences among treatment groups, with the majority of subjects having a ≤10% change from Baseline. [ISS, 8.H.6.3.2, p65-7, iss.pdf]

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.2.1 Shifts from normal to abnormal

A shift table was prepared for shifts in ECG values from Baseline to Endpoint, based on the centralized reading of the ECG as normal, abnormal with no clinically significant (NCS) abnormality, abnormal with clinically significant (CS) ECG abnormality (Table 11). There were no differences of note among treatment groups. As noted previously, it is very difficult to interpret any changes in ECG findings in the clinical without the presence of a placebo group. Nevertheless, information from the shift table is presented below. [ISS, 8.H.6.3.2, p58-62, iss.pdf]

Table 11. ISS: Summary of ECG Shifts, Pooled Studies P01875 and P01884

Baseline Evaluation	Endpoint Evaluation	Number (%) of Subjects[a] DL D-24 QD (N=702)	DL D-24 AF QD (N=698)	DL 5 mg QD (N=699)	PSE 240 mg QD (N=702)
Normal	Normal	306 (44)	317 (45)	302 (43)	304 (43)
	Abnormal, NCS	85 (12)	77 (11)	90 (13)	86 (12)
	Abnormal, CS	8 (1)	4 (<1)	7 (1)	4 (<1)
	Missing	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Abnormal, NCS	Normal	101 (14)	111 (16)	81 (12)	109 (16)
	Abnormal, NCS	156 (22)	145 (21)	158 (23)	147 (21)
	Abnormal, CS	5 (<1)	9 (1)	11 (2)	7 (<1)
	Missing	0	0	1 (<1)	1 (<1)
Abnormal, CS	Normal	6 (<1)	5 (<1)	6 (<1)	6 (<1)
	Abnormal, NCS	20 (3)	16 (2)	23 (3)	25 (4)
	Abnormal, CS	13 (2)	11 (2)	12 (2)	7 (<1)
	Missing	0	1 (<1)	1 (<1)	0
Missing	Normal	0	1 (<1)	1 (<1)	1 (<1)
	Abnormal, NCS	1 (<1)	0	0	2 (<1)
	Abnormal, CS	0	0	2 (<1)	1 (<1)
	Missing	0	0	2 (<1)	0
Total		702	698	699	702

a: Represents the number of subjects in each treatment group who have Baseline and postbaseline ECG data.

Note: NCS=not clinically significant; CS=clinically significant.

Source: ISS, 8.H.6.3.2, Table 24, p59, iss.pdf

There were 85 (12%), 77 (11%), 90 (13%), and 86 (12%) shifts from *normal* to *abnormal NCS* ECGs in the DL D-24, DL D-24 AF, DL, and PSE groups, respectively. One patient in this shift group had an abnormal ECG reported as an adverse event, (Subject P01875-09/5560), a 46-year-old Caucasian female treated with DL D-24 who had an abnormal ECG reading of right axis deviation at the Final visit on Day 15. This abnormal ECG was considered by the investigator to be an adverse event of mild severity and unlikely to be related to study medication. At a visit on Day 29, follow-up ECG was normal.

There were 8 (1%), 4 (<1%), 7 (1%), and 4 (<1%) shifts from *normal* to *abnormal CS* ECGs in the DL D-24, DL D-24 AF, DL, and PSE groups, respectively. Four patients in this shift group had an abnormal ECG reported as an adverse event, described below. None of the patients has a history of cardiovascular disease. The narratives below are taken directly from the Applicant's ISS. [ISS, 8.H.6.3.2, p60, iss.pdf]

- "Subject P01875-21/5095 (DL), an 18-year-old Black male, had a normal (sinus bradycardia) ECG evaluation at Baseline. At Endpoint (Day 15), the subject had an abnormal, clinically significant ECG (sinus bradycardia, T-wave inversion suggestive of ischemia). The subject did not report any symptoms. The ischemia was reported as an adverse event, which was considered by the investigator to be moderate and possibly related to study medication. At an unscheduled visit (Day 22), the subject had an abnormal, not clinically significant ECG (early repolarization – normal variant).

- Subject P01884-41/5500 (DL), a 45-year-old Caucasian female, had a normal (sinus bradycardia, indeterminate) ECG evaluation at Baseline. At Endpoint (Day 14), the subject had an abnormal, clinically significant ECG (AV block/left posterior hemiblock; late R-wave transition). The AV block was reported as an adverse event, which was considered by the investigator to be mild and possibly related to the study medication. An unscheduled follow-up ECG for this subject was still abnormal, clinically significant (left posterior hemiblock; late R-wave transition). No additional follow-up information on this subject is available.

- Subject P01884-34/6970 (DL D-24 AF), a 31-year-old Caucasian male, had a normal (normal sinus rhythm) ECG evaluation at Baseline. At Endpoint (Day 15), the subject had an abnormal, clinically significant ECG (first degree AV block; incomplete right bundle branch block [RBBB]). The AV block was reported as an adverse event, which was considered by the investigator to be mild and possibly related to the study medication. At an unscheduled follow-up visit, the subject had an abnormal ECG (first degree AV block) which was not considered clinically significant.

- Subject P01884-39/6525 (DL D-24 AF), a 64-year-old Caucasian male, had a normal (normal sinus rhythm) ECG evaluation at Baseline. At Endpoint (Day 15), the subject had an abnormal, clinically significant ECG (atrial fibrillation; prolonged QT interval). The atrial fibrillation was reported as an adverse event, which was considered by the investigator to be moderate and probably related to the study medication. An unscheduled follow-up ECG for this subject was still abnormal, clinically significant (atrial fibrillation). No additional follow-up information on this subject is available."

There were 5 (<1%), 9 (1%), 11 (2%), and 7 (<1%) shifts from *abnormal NCS* to *abnormal CS* ECGs in the DL D-24, DL D-24 AF, DL, and PSE groups, respectively. Four patients in this shift group had an abnormal ECG reported as an adverse event, described below. The narratives below are taken directly from the Applicant's ISS. [ISS, 8.H.6.3.2, p61-2, iss.pdf]

- "Subject P01875-02/7244 (DL), a 69-year-old Caucasian male, had an abnormal, not clinically significant ECG at Baseline (normal sinus rhythm, specific T-wave changes, incomplete RBBB, early repolarization, normal variant). The subject was randomized and initiated treatment on 17 OCT 2000. He reported ankle edema as an adverse event 5 days after initiation of treatment, and completed the study per protocol on 31 OCT 2000. At the Final visit, there were ECG abnormalities (quadrigeminy) that were not present at Screening. Five days after study completion ( ), the subject was hospitalized and diagnosed with congestive heart failure. Initially, the investigator considered the event to be possibly related to study medication. The subject was discharged on ( ), but was readmitted to the hospital o ( ) with reports of "not feeling well". The subject was discharged o ( ) (no diagnostic work-up was performed), and hospitalized a third time on ( ), and reported that he had been diagnosed

with pericarditis (unconfirmed). The subject was discharged on [redacted] and had a repeat ECG performed on site on [redacted], which was abnormal but not clinically significant. Subsequently, after re-evaluation and consultation with the treating cardiologist, the relationship to study medication was changed to unlikely. The subject was diagnosed with congestive heart failure due to an underlying cardiomyopathy of unknown etiology. The congestive heart failure was categorized as a serious event.

- Subject P01875-15/7392 (DL), a 31-year-old Black male, experienced a moderate ECG abnormality on Day 8 of treatment. The subject had a medical history of hypertension. The subject had an abnormal, not clinically significant ECG evaluation at Baseline (non-specific T-wave changes, ST elevation, early repolarization, normal variant) and an abnormal clinically significant ECG at Endpoint (non-specific T-wave changes, ST elevation) as documented by the Principal Investigator. The event was considered by the investigator to be possibly related to study medication.

- Subject P01875-02/7223 (PSE), a 42-year-old Caucasian female, experienced mild myocardial ischemia on Day 15 of treatment, ending the same day. The subject had no history of cardiovascular disease. The subject had an abnormal, not clinically significant ECG evaluation at Baseline (sinus bradycardia, RAD), and an abnormal, clinically significant ECG at Endpoint (T-wave inversion suggestive of ischemia, RAD). The event was considered by the investigator to be possibly related to study medication.

- Subject P01884-11/5593 (DL D-24), a 12-year-old Black female, with no history of cardiovascular disease, had an abnormal, not clinically significant ECG evaluation at Baseline (incomplete RBBB; non-specific T-wave changes). At Endpoint (Day 15), the subject had an abnormal, clinically significant ECG (left posterior hemiblock; LV strain/ischemia; incomplete RBBB). The AV block (left posterior hemiblock) was reported as an adverse event, which was considered by the investigator to be mild and unlikely related to the study medication. No additional follow-up information is available for this subject."

Changes from Baseline in QTc interval data (Fridericia formula) were summarized based on the following categories: less than 0 msec, 0 to 30 msec, 31 to 60 msec, or 61 or more msec. The majority of patients experienced either no change or a 0-30 msec change from Baseline for Fridericia QTc interval. Seventy (10%) patients in the DL D-24 group, 76 (11%) in the DL D-24 AF group, 69 (10%) in each of the DL and PSE groups had a change from Baseline between 31 and 60 msec. Outliers of ≥61 msec for changes in QTcF are discussed below.

7.1.9.3.2.2 Outlier analyses

Less than 1% of patients in each of the DL D-24 (3), DL (4), and PSE (6) groups had changes of ≥61 msec in QTcF, and 10 (1%) treated with DL D-24 AF had changes of ≥61 msec. Results are reproduced below in Table 12. [ISS, 8.H.6.3.2, p70, iss.pdf]

Table 12. ISS: Summary of Changes from Baseline in QTcF, Pooled Studies P01875 and P01884

Treatment	Baseline Evaluation[b]	N	Missing	Change from Baseline (milliseconds)[a] <0	0 to 30	31 to 60	≥61
DL D-24 QD[c]	Normal	694	9	338 (49)	274 (39)	70 (10)	3 (<1)
	Borderline	11	0	10 (91)	1 (9)	0	0
	Prolonged	1	0	1 (100)	0	0	0
	Missing	2	2	0	0	0	0
	Overall	708	11	349 (49)	275 (39)	70 (10)	3 (<1)
DL D-24 AF QD[c,d]	Normal	698	14	330 (47)	269 (39)	76 (11)	10 (1)
	Borderline	12	1	11 (92)	0	0	0
	Prolonged	1	0	0	1 (100)	0	0
	Missing	2	2	0	0	0	0
	Overall	713	17	341 (48)	270 (38)	76 (11)	10 (1)
DL 5 mg QD	Normal	698	18	352 (50)	255 (37)	69 (10)	4 (<1)
	Borderline	5	0	5 (100)	0	0	0
	Prolonged	2	0	2 (100)	0	0	0
	Missing	7	7	0	0	0	0
	Overall	712	25	359 (50)	255 (36)	69 (10)	4 (<1)
PSE 240 mg QD	Normal	696	21	332 (48)	268 (39)	69 (10)	6 (<1)
	Borderline	16	0	16 (100)	0	0	0
	Prolonged	3	0	3 (100)	0	0	0
	Missing	4	4	0	0	0	0
	Overall	719	25	351 (49)	268 (37)	69 (10)	6 (<1)

a: Baseline represents the last non-missing value occurring on or before treatment start date; Endpoint value is first value after treatment stop date.

b: Baseline Evaluation: Males, 430 to 450 for Borderline; >450 for Prolonged; Females, 450 to 470 for Borderline; >470 for Prolonged.

c: DL D-24 and DL D-24 AF=5 mg DL/240 mg PSE QD.

d: Due to an error in recording the final visit QT for Subject P01884-13/7180, which was discovered post database lock, the above change from Baseline in Fridericia QTc was recalculated and reflect the correct value for that subject. Additional details are provided in Section 14.3.7.1.1. of the CSR for P01884.

Source: ISS, 8.H.6.3.2, Table 24, p70, iss.pdf

Five of the 2852 enrolled patients had prolonged QTc (Fridericia) interval values at Endpoint (defined as QTc >450 msec for males and >470 msec for females): 1 of 708 in the DL D-24 group; 2 of 713 in the DL D-24 AF group, and 2 of 719 in the PSE group, as described below. None were in the DL-alone group. The narratives (below) for these five patients are taken directly from the Applicant's ISS. [ISS, 8.H.6.3.2, p68-9, iss.pdf]

- "Subject P01884-17/6346 (DL D-24), a 56-year-old female, had a QTc (Fridericia) value of 445 msec at Visit 1. The subject had a QTc interval of 475 msec at the Final visit, which was reported as abnormal but not clinically significant. This subject had sinus bradycardia at Visit 1 and the Final visit. The subject reported no adverse events, and had a medical history of irregular heartbeat (stable).

- P01884-34/7283 (DL D-24 AF), a 43-year-old male with a history of hypertension, had an ECG at Visit 1 showing sinus bradycardia, left bundle branch block, and a Fridericia QTc interval of 457 msec. The Final visit ECG was performed on the site's ECG machine due to an inability to transmit the ECG trans-telephonically to Cardiac Alert. The Final visit ECG showed a normal sinus rhythm, left bundle branch block,

and a QTc interval of 444 msec. The ECG was re-read by Cardiac Alert, who reported normal sinus rhythm, left bundle branch block, and a QTc interval of 474 msec. The subject reported no adverse events.

- Subject P01875-18/7082 (DL D-24 AF), a 44-year-old female, who had a QTc interval (Fridericia) of 396 msec at Screening, had a QTc interval of 483 msec at the Final visit (Visit 4), which was reported by the investigator as abnormal but not clinically significant. The subject had no adverse events, and the Final visit ECG showed normal sinus rhythm. No other information is available.

- Subject P01875-03/5640 (PSE), a 22-year-old female, had a prolonged QTc interval of 495 msec at Visit 1, which was considered by the investigator to be clinically significant. The subject had sinus bradycardia, sinus arrhythmia, and right bundle branch block. At the Final visit, the QTc interval was 446 msec, and was considered to be normal by the investigator. The subject had normal sinus rhythm at the Final visit.

- Subject P01875-18/6779 (PSE), a 44-year-old female, had a prolonged QTc interval of 476 msec at Visit 1. The subject had normal sinus rhythm. The subject had a normal ECG at the Final visit; the QTc interval was 427 msec."

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Outliers are discussed above. Not surprisingly (because ECG was only performed at baseline and at the end of treatment), there were no dropouts for ECG abnormalities.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.10 Immunogenicity

An assessment of immunogenicity was not applicable to this clinical development program.

7.1.11 Human Carcinogenicity

Under NDA 21-165, and as a phase-4commitment, the sponsor performed a 2-yr carcinogenicity study of desloratadine in mice (Study #97255). The study was submitted on November 13, 2003, and the review team completed the review of the study during this NDA review cycle. According to the statistical review of the study, the evaluation of Study SN97255 for carcinogenic potential on mice found no statistically significant dose-tumor positive linear trends for all tumor types reported.

7.1.12 Special Safety Studies

No special safety studies were conducted for this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The applicant states that there is no known potential for drug abuse with Clarinex-D® 24 Hour Tablets, and this is likely to be correct with this long-acting fixed-combination prescription-only formulation. Information regarding the individual component drugs follows.

There is no information to suggest that desloratadine or the parent loratadine is associated with any dependency or abuse.

However, pseudoephedrine, like other central nervous system stimulants, has been associated with abuse and abuse potential. Higher doses are commonly associated with "elevations of mood, a sense of increased energy and alertness, and decreased appetite. Some individuals become anxious, irritable, and loquacious. In addition to the marked euphoria, the user experiences a sense of markedly enhanced physical strength and mental capacity. With continued use, tolerance develops, the user increases the dose, and toxic signs and symptoms appear. Depression may follow rapid withdrawal." [Clinical, 8.I, p3, 8i.pdf]

7.1.14 Human Reproduction and Pregnancy Data

Desloratadine is labeled as Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. A published article in 2003 concerned the Swedish Medical Birth Registry (SMBR), which contained 15 cases of hypospadias with loratadine administered to pregnant women in the first trimester. After further review of the literature concerning loratadine and DL containing products, the applicant revised the label for loratadine to state that the use of the product is not recommended during pregnancy.[2]

Desloratadine does pass into breast milk; therefore a clinical decision should be made regarding a mother who wishes to nurse as to whether to breast feed or avoid use of loratadine.

7.1.15 Assessment of Effect on Growth

An assessment of the effects of Clarinex-D® 24 Hour Tablets on growth was not performed in the clinical development program. Such an assessment was not requested or considered necessary by the Division.

7.1.16 Overdose Experience

The NDA application for this drug product contains an overdosage discussion section, but unfortunately the discussion simply lists the supportive measures to be taken in the event of an overdose [Clinical, 8.I, pp 3-4, 8i.pdf]. What was missing was a discussion of reports of adverse events associated with overdose in clinical practice, either with desloratadine or with pseudoephedrine. While a safety update was sent in December 2004, overdose was not listed as an adverse event associated with a reported AE or SAE for either desloratadine or

pseudoephedrine in patients over age 12 years of age. This deficiency was note noted during the review process until too late in the review cycle to address. However, the safety update does contain an Overdose section (5.6.4) for desloratadine. Therefore, it is not clear if any overdoses were reported to the applicant's database for patients ≥12 years of age.

There were 14 cases of overdose (as much as 18 times the recommended dose) reported in children with DL syrup and/or tablet/RediTabs. Two cases of overdose were reported in children less than 2 years old; seven cases in children 2 to <6 years old, and five cases in children 6 to <12 years old. All recovered. In 8 of the 14 cases, no adverse occurrences were reported, and in none of the cases did the adverse event appear to be serious in nature. The safety update for pseudoephedrine did not mention overdose.

One patient in Study P01875 took an overdose of study medication during the study. Subject P01875-24/7054 took three doses of DL D-24 AF on Day 14 of the study because of increasing allergy symptoms. The patient did not discontinue. The investigator stated that the actual overdose of study medication was considered not to be a serious adverse event. [ISS, 8.H.6.1.6 p40, iss.pdf]

7.1.17 Postmarketing Experience

There is no post-marketing experience with this formulation.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Please refer to Section 4.1 for a discussion of the clinical data sources.

7.2.1.1 Study type and design/patient enumeration

Safety data were polled from the two 2-week pivotal clinical studies, the study designs for which are described in Section 0. The five clinical pharmacology studies were of such short duration and had such small numbers of patients, that no meaningful safety data could be derived from their evaluation. Indeed, there were no serious or unexpected adverse events reported in any of the clinical pharmacology studies, and no discontinuations due to an adverse event. Therefore, they are not discussed further in this Safety Summary.

The applicant states that a total of 2852 patients were randomized and received at least one dose of study drug in the two Phase 3 studies. All 2852 were included in the safety evaluations: 708 received DL D-24, 713 received DL D-24 AF, 712 received DL, and 719 received PSE, as presented in Figure 1. However, this figure does not include six patients who were inadvertently randomized and received DL D-24 6/240 mg QD (2) or placebo (4), who were not included in the safety or efficacy evaluations. This randomization error

occurred primarily because of last-minute protocol amendments eliminating two arms of the studies that were not communicated to some of the study centers.

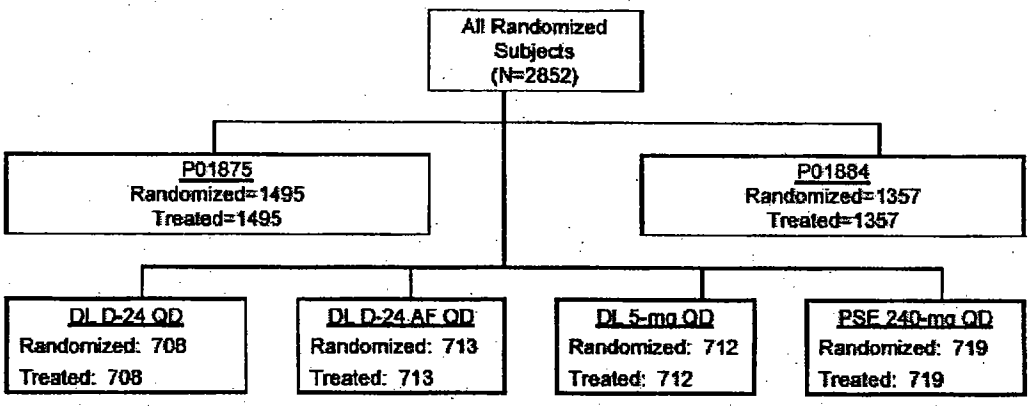


Figure 1. ISS: Distribution of Patients in Pivotal Clinical Trials*

* Numbers do not include six patients who were inadvertently randomized and received the following treatments: two (P01875-07/6865 and P01875-07/6872) received DL D-24 6/240 mg QD and four (P01875-07/6863, P01875-07/6871, P01875-41/7319, and P01884-10/7366) received placebo.
Source: Section 3H6, Figure 1, p 181, summary.pdf

7.2.1.2 Demographics

Demographics for the pooled clinical studies are shown in Table 13. All treatment groups were comparable for demographic characteristics. The majority of patients were female and Caucasian. Only 8 patients ≥65 years of age were exposed to the to-be-marketed formulation in the clinical studies.

Table 13. ISS: Summary of Demographic Data at Baseline, Pooled Studies P01875 and P01884, MITT

Pooled Data from Protocol Nos. P01875 and P01884

Demographic Characteristics	DL D-24 QD (N=708)	DL D-24 AF QD (N=713)	DL 5-mg QD (N=712)	PSE 240-mg QD (N=719)
Age (years)				
Mean	34.0	33.4	34.9	34.9
Median	34	33	35	34
Range (Min-Max)	12 – 78	12 – 78	11[a] - 76	12 - 76
Age Subgroup, n (%)				
< 12 years	0	0	1 (< 1)[a]	0
12 to < 18 years	117 (17)	108 (15)	96 (13)	81 (11)
18 to < 65 years	583 (82)	596 (84)	602 (85)	623 (87)
≥ 65 years	8 (1)	9 (1)	13 (2)	15 (2)
Sex, n (%)				
Female	435 (61)	458 (64)	448 (63)	468 (65)
Male	273 (39)	255 (36)	264 (37)	251 (35)
Race, n (%)				
Caucasian	550 (78)	576 (81)	551 (77)	583 (81)
Black	75 (11)	61 (9)	85 (12)	60 (8)
American Indian	1 (< 1)	0	2 (< 1)	1 (< 1)
Asian	19 (3)	20 (3)	16 (2)	11 (2)
Hispanic	58 (8)	49 (7)	58 (8)	56 (8)
Other	5 (< 1)	7 (< 1)	2 (< 1)	8 (1)
Weight (lb)				
Mean	168.3	166.6	167.5	168.7
Median	162	160	162	160
Range (Min-Max)	67 - 382	71 - 380	70 – 430	75 – 380
Missing	0	4	3	0
Height (in)				
Mean	66.2	66.3	66.0	66.2
Median	66	66	66	66
Range (Min-Max)	56 - 82	55 - 78	55 - 81	53 - 78
Missing	0	3	2	0
Duration of SAR (years)				
Mean	17.0	17.4	18.1	17.8
Median	14	15	15	15
Range (Min-Max)	2 - 55	2 - 66	2 – 62	2 – 69

a: One subject (Subject P01884-24/5541) was 11 years, 9 months of age at study entry.

Source: Section 3H6, Table 8, p 183, summary.pdf

7.2.1.3 Extent of exposure (dose/duration)

In the two clinical studies, the extent of exposure was considered adequate to evaluate treatment outcomes. The extent of exposure to study drugs was similar in all treatment groups, as shown in Table 14. The majority of patients (92.7%) received treatment for 13 to

15 days, although the mean duration of treatment was more than 16 days for 10% of patients due to variations in scheduling of the final study visit. The quantity of study drugs dispensed to any patient was sufficient to last 20 days.

Table 14. ISS: Extent of Exposure by Treatment Group, Pooled Studies P01875 and P01884, MITT

Pooled Data from Protocol Nos. P01875 and P01884

	Number (%) of Subjects			
Day Interval	DL D-24 QD (N=708)	DL D-24 AF QD (N=713)	DL 5-mg QD (N=712)	PSE 240-mg QD (N=719)
1 to 3 days	705 (99.6)	707 (99.2)	707 (99.3)	713 (99.2)
4 to 6 days	695 (98.2)	695 (97.5)	694 (97.5)	698 (97.1)
7 to 9 days	689 (97.3)	683 (95.8)	689 (96.8)	693 (96.4)
10 to 12 days	670 (94.6)	673 (94.4)	676 (94.9)	679 (94.4)
13 to 15 days	661 (93.4)	661 (92.7)	668 (93.8)	669 (93.0)
16 to 18 days	162 (22.9)	136 (19.1)	150 (21.1)	146 (20.3)
19 to 21 days	16 (2.3)	16 (2.2)	12 (1.7)	24 (3.3)
22 to 24 days[a]	0	0	2 (0.3)	2 (0.3)
Missing[b]	3 (0.4)	6 (0.8)	5 (0.7)	6 (0.8)
n	705	707	707	713
Mean	14.8	14.7	14.8	14.7
Median	15	15	15	15
Range (min - max)	1 - 20	1 - 21	1 - 23	1 - 22

a: Four subjects had a duration of exposure of 22 to 24 days based on first dose and last dose dates. Subject P01875-07/6527 (PSE), Subject P01884-24/5536 (DL), and Subject P01884-27/6945 (PSE) each had a duration of exposure of 22 days. Subject P01884-32/6460 (DL) had a duration of exposure of 24 days. Tablet counts confirmed that none of these subjects received more than 40 tablets.

b: All subjects received at least one dose of study drug; start date or end date was not available for subjects with missing length of exposure.

Source: Section 3H6, Table 9, p 184, summary.pdf

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The five clinical pharmacology studies were of such short duration and had such small numbers of patients, that no meaningful safety data could be derived from their evaluation and were not reviewed for further evidence of safety, since there were no serious or unexpected adverse events reported and no discontinuations due to an adverse event.

7.2.2.2 Postmarketing experience

A safety update for desloratadine from post-marketing adverse events for the period from December 21, 2001 to September 30, 2004 was submitted by the applicant for patients 12 years of age and older. Summary results may be found in Section 7.2.9.

The applicant also conducted a search of the AERS database and published literature for adverse events reported for pseudoephedrine from December 21, 2001 to December 31, 2003. Important events are described in Sections 7.1.1, 7.1.2, and 7.1.16.

7.2.2.3 Literature

The applicant conducted a literature search including Bios Previews, Embase and Ovid Medline(R) which yielded 17 references relevant to the safety of PSE. Results of a literature search for any safety-related data for the combined product, desloratadine and pseudoephedrine yielded one reference (Schenkel et al.)[3], which concerned the results of Study P01884 submitted for this NDA.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience in the submitted studies was considered adequate to evaluate pertinent adverse events and risk factors, given that the two drugs and drug classes are well known and have been adequately studied previously.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Exploration for special animal and/or in vitro testing was not necessary or applicable for two short studies employing two well-known drugs and drug classes.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was considered adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic pathways, clearance, and drug interactions of both desloratadine and pseudoephedrine are well characterized. Such an evaluation was not part of drug development for this drug product.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Neither of the two constituent drugs are new molecular entities, and both have been evaluated previously for safety and efficacy independently. The only potential deficiency for this drug development program was the lack of a placebo group in the clinical trials so that an estimation of adverse events for the combination drug product might be compared to placebo. However, since both drugs have been evaluated previously individually with a comparison to placebo, this is not a significant issue.

7.2.8 Assessment of Quality and Completeness of Data

During the review, there were no issues with the quality of completeness of the data in this application.

7.2.9 Additional Submissions, Including Safety Update

On December 2, 2004, the applicant submitted a safety update including information for desloratadine from published literature and post-marketing adverse events for the period between December 21, 2001 and September 30, 2004 for patients 12 years of age and older. The estimated total DL exposure in this reporting period was 2,095,679,500 patient-days, or 5,737,658 patient-years, broken down by 1,941,933,500 patient-days for the tablets, 146,504,000 patient-days for the syrup, and 7,242,000 patient-days for the RediTabs. [12/2/2004, Section 5.3, safety update.pdf]

Having limited information about pseudoephedrine in their database, the applicant conducted a literature search and a search of the FDA-AERS database for adverse events reported for pseudoephedrine from December 21, 2001 to December 31, 2003. The most common disproportionately reported AEs with pseudoephedrine-only or pseudoephedrine combination products were insomnia, nervousness, palpitations, and tachycardia. These AEs are consistent with the pharmacological properties of pseudoephedrine, and should be represented in the package insert. The searches did not reveal any adverse events of special concern or adverse events that have not previously been reported with pseudoephedrine.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety database was considered adequate for review, and there were no significant safety findings noted in the review of the submitted studies.

7.4 General Methodology

All safety data was considered for both baseline and changes from baseline values.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Data was pooled for the two clinical studies, Studies P01875 and P01884.

7.4.1.2 Combining data

Since the clinical studies had virtually identical study designs and protocols, there were no issues with regard to combining or pooling of data.

7.4.2 Explorations for Predictive Factors

Exploration for predictive factors was not necessary or applicable for two short studies employing two well-known drugs and drug classes.

7.4.2.1 Explorations for dose dependency for adverse findings

Exploration for dose dependency for adverse findings was not necessary or applicable for two short studies employing two well-known drugs and drug classes.

7.4.2.2 Explorations for time dependency for adverse findings

Exploration for time dependency for adverse findings was not necessary or applicable for two short studies employing two well-known drugs and drug classes.

7.4.2.3 Explorations for drug-demographic interactions

Safety subgroup comparisons based on age (12 to <18, 18 to <65, ≥65 years), race (Caucasian, Black, Asian, Hispanic, American Indian, and "Other"), and sex were performed for adverse events, laboratory tests, vital signs, and ECGs. Review revealed no specific safety concerns in any subgroup.

7.4.2.4 Explorations for drug-disease interactions

Exploration for drug-disease interactions was not necessary or applicable for two short studies employing two well-known drugs and drug classes.

7.4.2.5 Explorations for drug-drug interactions

Exploration for drug-drug interactions was not necessary or applicable for two short studies employing two well-known drugs and drug classes.

7.4.3 Causality Determination

During this review, there were no specific safety concerns for which a causality determination was an issue.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The applicant's proposed dosing regimen for Clarinex-D 24 Hour tablets is one tablet once daily. The results of the applicant's data support the efficacy claim for once daily dosing for a SAR indication. Once daily AM dosing was studied in both clinical trials. For the PSE component, Clarinex-D 24 Hour Tablets was shown to have a statistical significant effect in both studies on the instantaneous end-of-dosing interval over the primary treatment period. However, for the antihistamine component, a statistically significant effect was found in only one of the two studies, with a borderline effect in the second. This borderline effect may be related to the lower systemic exposure to desloratadine from this drug product than from

desloratadine 5 mg that was found in the clinical pharmacology studies. Nevertheless, the results of the applicant's data are felt to be clinically adequate to support the proposed dosing interval for a SAR indication.

Clinical pharmacology Study P00441 supports the statement in the DOSAGE AND ADMINISTRATION section that Clarinex-D 24 Hour extended-release tablets can be administered with or without a meal.

8.2 Drug-Drug Interactions

Drug interactions with Clarinex-D 24 Hour tablets were not studied in the development program. Based on previous experience with the individual ingredients DL and PSE, significant drug interactions with Clarinex-D 24 Hour tablets is not anticipated.

8.3 Special Populations

In the two clinical studies, P01875 and P01884, response to treatment was examined by age, sex, and race and similar results were seen among age and race subgroups. Having made this statement, it should be noted that only 8 patients ≥65 years of age were exposed to the to-be-marketed formulation in the clinical studies, and no geriatric patients were exposed to the combination during the clinical pharmacology studies.

Previous experience with the individual components indicated that special dosing considerations are not recommended for desloratadine based on race, gender, and older age (>65 years of age). The product label for Clarinex has recommended doses for populations <12 years of age at doses less than the combination product.[4] Dose adjustment is recommended in patients with hepatic or renal impairment at a starting dose of Clarinex 5 mg every other day. Dosing in this manner is not practicable for Clarinex-D 24 Hour tablets, which contain a fixed-dose combination of desloratadine and pseudoephedrine in which the dosage of pseudoephedrine is not appropriate for every other day dosing. Therefore, Clarinex-D 24 Hour tablets should be contraindicated in patients with renal or hepatic impairment.

Desloratadine is designated as a Pregnancy Category C drug product. No adequate and well-controlled studies have been conducted in pregnant women.

The product label for pseudoephedrine states that patients currently using prescription monoamine oxidase inhibitors (MAOI) or for 2 weeks after stopping the MAOI, should not used PSE. Patients are advised to ask a doctor before using PSE for certain conditions, thyroid disease, diabetes, prostate conditions, and pregnancy.[5]

8.4 Pediatrics

During a Type C meeting for the NDA on November 7, 2000, the sponsor requested a waiver of the requirements of 21 CFR 314.55 (a) "Pediatric use information" for the pediatric age groups below the age of 12. The applicant stated that the drug product does not represent a meaningful therapeutic benefit over existing treatments for children below the age of 12 years. The Agency agreed with the applicant's rationale for a pediatric waiver request and informed the applicant that the formal waiver process would be handled at the time of the NDA action. In this NDA, the applicant has now requested a waiver for pediatric studies in patients <12 years of age. Desloratadine syrup (NDA 21-300 and NDA 21-563) was recently approved (September 9, 2004) for patients >6 months of age for PAR and >2 months of age for SAR. A suitable pediatric dosage form currently exists for pseudoephedrine and is available as an OTC product. There are alternative antihistamine formulations available that are more appropriate for pediatric patients less than 12 years of age. Therefore, a waiver of pediatric studies is recommended for patients below the age of 12 years since the dose of pseudoephedrine in Clarinex-D® 24 HOUR extended-relief tablets and is not appropriate for use in children less than 12 years of age.

8.5 Advisory Committee Meeting

There was no advisory committee meeting for this NDA application as none was indicated based upon the review of the data.

8.6 Literature Review

The applicant conducted a literature search for any safety-related data for desloratadine, pseudoephedrine, and the combined product. Of 41 references concerning DL, two[1,2] were found to be relevant to the safety of DL and are discussed in Section 7.1.3.3. and 7.1.14 [safety update.pdf, pages 44-46]. A worldwide medical literature search of pseudoephedrine, including Bios Previews, Embase, and Ovid Medline (R) yielded 69 references of which 17 were found to be relevant to the safety of PSE [safety update.pdf, pages 53-56]. Results of a literature search for any safety-related data for the combined product, desloratadine and pseudoephedrine yielded one reference (Schenkel et al.), which concerned the results of Study P01884 submitted for this NDA. Discussion of all findings may be found in Section 7 of this review.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan was submitted by the applicant.

8.8 Other Relevant Materials

There were no other relevant materials that would impact upon the evaluation of the drug product. The Division of Drug Marketing, Advertising, and Communication (DDMAC) will be consulted during the labeling review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The proposed indications for Clarinex-D 24 Hour extended-relief tablets are treatment of nasal and non-nasal symptoms of SAR [redacted]. This review found adequate data to support the efficacy claim for this combination drug product using once daily dosing for a SAR indication. [redacted] There were no safety issues found in the review of this application.

9.2 Recommendation on Regulatory Action

The clinical recommendation is for an Approval action for the indication of treatment of symptoms of seasonal allergic rhinitis. [redacted]

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No specific risk management activities are warranted for this product.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

No Phase 4 requests are recommended.

9.4 Labeling Review

A brief review of proposed labeling was performed, with detailed review to be performed after finalization of this review. Specifically, the labeling will be reviewed in comparison to previous Claritin D24 Hour extended-release tablet prescription labeling and the last revised Clarinex labeling. Several preliminary labeling concerns are noted below.

- In the "INDICATIONS AND USAGE" section, the proposed label states that "Clarinex-D® 24 HOUR Extended Release Tablets is indicated for the relief of nasal and non-nasal symptoms of allergic rhinitis (seasonal [redacted], including nasal congestion, in patients 12 years of age and older. Clarinex-D® 24 HOUR Extended

Release Tablets can be administered when the antihistaminic properties of desloratadine and the nasal decongestant activity of pseudoephedrine are desired."
The two clinical studies only support an indication for SAR [redacted]

- The labeling should note in the CLINICAL PHARMACOLOGY section that the combination drug product (5/240 mg) failed to show bioequivalence to the individual desloratadine 5 mg mono-product (i.e. the approved Clarinex 5 mg) in two bioequivalence studies and that systemic exposure to desloratadine with this combination is lower than with Clarinex 5 mg mono-product. It may be appropriate to include the AUC and C_{max} values from these studies.

- The labeling should note in the CLINICAL STUDIES section that the clinical program was performed because the combination drug product failed to show bioequivalence to the individual desloratadine 5 mg mono-product (i.e. the approved Clarinex 5 mg). This section includes studies performed with Clarinex 5 mg for SAR [redacted]. Since a clinical program was required due to a lack of bioequivalence, and since systemic exposure is lower with this product than with the Clarinex 5 mg mono-product, all Clarinex mono-product studies should be deleted from the labeling.

- Since systemic exposure to desloratadine with this combination is lower than with Clarinex 5 mg mono-product, consideration should be given to including a statement in the labeling that some patients who are switched from the mono-product to the combination product in order to add treatment with a decongestant may suffer from the loss of antihistamine exposure and not be adequately treated. For those patients, it would be preferable to continue use of the Clarinex 5 mg mono-product and add an oral decongestant mono-product as needed.

- A major, previously identified, safety concern with desloratadine has been the issue of bioavailability of desloratadine in slow metabolizers or in patients with liver or kidney impairment who may have desloratadine levels up to nine times that seen in normal metabolizers. For Clarinex 5 mg, the result is a labeling recommendation that patients with liver or kidney impairment be treated with every-other-day dosing. Dosing in this manner is not practicable for Clarinex-D 24 Hour tablets, which contain a fixed-dose combination of desloratadine and pseudoephedrine in which the dosage of pseudoephedrine is not appropriate for every-other-day dosing. Therefore, Clarinex-D 24 Hour tablets should be contraindicated in patients with renal or hepatic impairment.

- While somnolence and dizziness are two of the AEs reported at ≥2% in the two clinical trials, and therefore will be in the adverse event table in the label, headache was not. This reviewer suggests that all three be included in the section of the PI entitled 'Adverse Events Observed in Clinical Practice.'

9.5 Comments to Applicant

The comment below may be considered a labeling comment during labeling negotiations, or considered for inclusion in the Approval letter

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study P01875

10.1.1.1 Final Protocol

Title: Efficacy and Safety of Two Formulations of SCH 483 5/240 mg Compared to Desloratadine 5 mg and Pseudoephedrine 240 mg Sustained release in the Treatment of Patients with Seasonal Allergic Rhinitis

Protocol amendments:	July 17, 2000
Study initiated:	August 17, 2000
Study completed:	December 15, 2000
Study report:	November 4, 2001
Study centers:	47 centers in the United States (32 patients per center)
IRB:	[clinstat\p01875.pdf, pages 1661]

The Applicant states that the study was conducted according to FDA regulations and in compliance with good clinical practice guidelines and that written informed consent was obtained from each subject prior to participation in the study. Study investigators were qualified to conduct the study and [redacted] monitored the study sites [clinstat\p01875.pdf, page 21].

10.1.1.2 Protocol Amendment [clinstat\p01875.pdf, page 1479-91]

The protocol was amended once, on July 17, 2000. The amendment replaced one of the four treatment groups in the study. The study protocol initially included a combination product containing DL D-24 6/240 mg QD. The sponsor believed that this combination was required in order to achieve desloratadine plasma concentrations matching those obtained from a plain 5 mg desloratadine tablet. However, due to a failed bioequivalence study, this treatment group was eliminated and replaced by an alternate formulation of a combination product containing DL D-24 5/240 mg (called 'DL D-24 AF' for alternate formulation) QD as the fourth treatment group. The two DL D-24 5/240 mg formulations only differ by a slight modification in the quantity of excipients in the film coat, although the qualitative formula remains the same.

The final protocol, therefore, did not include the DL D-24 6/240 mg treatment group and patients were randomized 1:1:1:1 to the remaining 4 groups containing DL D-24, DL D-24

Alternate Formulation (AF), DL 5 mg, and sustained-release PSE (identical to the sustained-release PSE in both DL D-24 formulations).

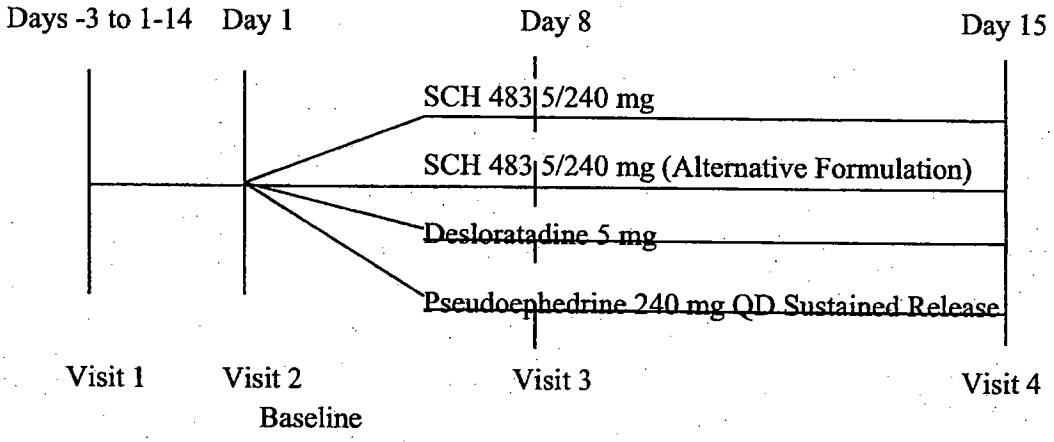
10.1.1.3 Objective/Rationale [clinstat\p01875.pdf, pages 24, 1399]

The primary objective of the study was to assess the efficacy of two formulations of SCH 483 5/240 mg QD (DL D-24 and DL D-24 AF) sustained release compared to 5 mg desloratadine QD tablets and to pseudoephedrine 240 mg QD sustained release tablets.

The secondary objective of the study was to evaluate the safety profiles of the two SCH 483 5/240 mg QD formulations using the following parameters: subject-reported adverse events, ECG, vital sign evaluations, and laboratory results.

10.1.1.4 Study Design [clinstat\p01875.pdf, pages 24, 1400]

This was a Phase 3, 15-day, multi-center, randomized, double-blind, double-dummy, active-controlled, parallel-group, multiple-dose, efficacy and safety study of 2 formulations of DL D-24 versus its components in 1495 patients, ages 12 to 78 years of age, with SAR.



10.1.1.5 Study Population [clinstat\p01875.pdf, pages 27, 1401]

The study will recruit 32 patients at approximately 48 centers in the U.S. to ensure at least 1400 evaluable patients.

10.1.1.5.1 Inclusion Criteria [clinstat\p01875.pdf, page 27, 1401]

- Patients are 12 years of age and older, of either sex and of any race.
- Patients will have at least a two-year documented history of fall SAR.
- Patients will have a positive skin test (prick or intradermal) response to an appropriate fall seasonal allergen within the 12 months prior to Visit 1. IgE-mediated hypersensitivity to an appropriate fall seasonal allergen will be documented by either a

positive response to skin prick test with a wheal diameter at least 3 mm larger than skin prick diluent control or a positive response to intradermal testing with a wheal diameter at least 7 mm larger than intradermal diluent control.

- Patients will be clinically symptomatic at the Screening visit, based upon reflective (PRIOR 12 hours) sign/symptom scores. As evaluated jointly by the subject and investigator, nasal rhinorrhea (anterior or posterior) will be graded at least moderate (score of at least 2); nasal stuffiness will be at least moderate; total nasal symptom score will be at least 6, and total non-nasal symptom score will be at least 5.
- In order for the subject to qualify at Baseline, the 7 Screening diary reflective scores (PRIOR 12 hours) for the 3 days prior to Baseline and the AM of the Baseline visit will be a total a minimum of 42 for the total nasal symptom score, a minimum of 35 for the total non-nasal symptom score and a minimum of 14 for each of the nasal stuffiness/congestion and rhinorrhea scores.
- Patients will be in general good health as confirmed by routine clinical and laboratory testing. Clinical laboratory tests (CBC, blood chemistries, and urinalysis) must be within normal limits or clinically acceptable to the investigator/sponsor.
- Patients will be free of any clinically significant disease, other than SAR, which would interfere with the study evaluations.
- Patients and/or parents or guardians must be willing to provide written informed consent, and be able to adhere to dosing and visit schedules and meet study requirements.
- For females of childbearing potential, the serum pregnancy test (HCG) must be negative at Screening.
- All nonsterile or premenopausal female patients must use a medically accepted method of birth control, i.e. double barrier method (e.g., condom with spermicide), oral contraceptive, hormonal implant or depot injectable (e.g., Depo-Provera® or Norplant®), prior to Screening and during the entire study. Female patients who were not currently sexually active were to agree and consent to use one of the above-mentioned methods, if they became sexually active while participating in the study. Female patients who are not of childbearing potential must have had a medical record of being surgically sterile (e.g., hysterectomy, tubal ligation), or had been at least one year postmenopausal. Documented absence of menses for at least 1 year would indicate that a female was postmenopausal. Female patients whose sexual partner was vasectomized are considered protected by a single barrier. All female patients of childbearing potential were to be strongly counseled in the appropriate use of birth control while in this study, and were cautioned against becoming pregnant while a subject in a clinical research study.

10.1.1.5.2 Exclusion Criteria [clinstat\p01875.pdf, page 28-29, 1402-1404]

- Patients with asthma who require chronic use of inhaled or systemic corticosteroids.
- Patients with current or history of frequent, clinically significant sinusitis or chronic purulent postnasal drip.
- Patients with rhinitis medicamentosa.
- Patients with a history of allergies to more than 2 classes of medication or who are allergic to or cannot tolerate antihistamines or pseudoephedrine.

- Patients who had an upper respiratory tract or sinus infection that required antibiotic therapy, and had not had at least a 14 day washout period prior to Screening, or who had a viral upper respiratory infection within 7 days prior to Screening.
- Patients who have nasal structural abnormalities, including large nasal polyps or marked septal deviation, that significantly interfere with nasal air flow.
- Patients who, in the opinion of the investigator, were dependent upon nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids.
- Patients who used any drug in an investigational protocol in the last 30 days prior to Screening.
- Patients on immunotherapy (desensitization therapy), unless on a stable dose prior to the Screening visit and stayed on this dose for the remainder of the study. Patients were not to receive desensitization treatment within 24 hours prior to any visit.
- Pregnant or nursing females.
- Patients with a history of hypersensitivity to the study drugs or their excipients.
- Investigational study staff or family members.
- Patients previously randomized into this study.
- Patients with current evidence of clinically significant hematopoietic, cardiovascular, hepatic, renal, neurologic, psychiatric, autoimmune disease, or other disease that precluded the patient's participation in the study. Particular attention was to be given to patients with conditions that would currently interfere with the absorption, distribution, metabolism, or excretion of the study medication or interfere with the subject's ability to reliably complete the diary card.
- Patients were not to have any significant medical condition(s) which, in the judgment of the investigator, might interfere with the study or require treatment (e.g., narrow-angle glaucoma, urinary obstruction or retention, severe hypertension, severe coronary artery disease, hyperthyroidism, stenosing peptic ulcer, pyloroduodenal obstruction, ischemic heart disease, diabetes mellitus, monoamine oxidase inhibitor, digitalis, or anticoagulant treatment).
- Patients whose ability to provide informed consent was compromised.
- Patients with a history of noncompliance with medications or treatment protocols.

10.1.1.5.3 Prior or Concomitant Therapy [clinstat\p01875.pdf, pages 35, 1406-1407]

All medications and other treatments taken by the subject during the study, including those treatments initiated prior to the start of the study, were to be recorded on the case report form. Recent use (within the past month) of all medications (and all depot preparations of intramuscular or intra-articular corticosteroids, or astemizole, during the past 3 months) were also to be recorded.

Patients were allowed to take any medication that was not restricted by the protocol and that would not be expected to interfere with the conduct of the study. Chronic medication was to be dosed on a stable regimen. In the case of medications restricted by the protocol, adequate washout times were to be observed. Acetaminophen was allowed as needed for appropriate indications. All concomitant medications were to be appropriately documented on the CRF.

10.1.1.5.4 Prohibited Medications [clinstat\p01875.pdf, pages 36, 1407]

Table 15. Prohibited medications

Medication	Washout Period
Corticosteroids	
nasal, ocular, oral, inhaled, intravenous or rectal, short-acting intramuscular	1 month
intramuscular or intra-articular depot preparations	3 months
high-potency dermatological corticosteroids[1]	1 week
Nasal or inhaled cromolyn sodium or nedocromil	2 weeks
Antihistamines	
short acting (eg, chlorpheniramine)	12 hours
Clemastine, long-acting OTC forms of chlorpheniramine	48 hours
long-acting antihistamines (eg, cetirizine, terfenadine, fexofenadine, hydroxyzine)	10 days
loratadine	10 days
azelastine and other topical antihistamines	10 days
astemizole	3 months
MAO inhibitors	14 days
Decongestants (nasal, oral, or ocular)	3 days
Topical anti-inflammatory drugs (other than corticosteroids)	3 days
Nasal atropine or ipratropium bromide	1 week
Systemic antibiotics (unless on a stable dose for prophylactic therapy)[2]	2 weeks
Nasal saline	12 hours
Ocular saline	12 hours
Ocular levocabastine	3 days
Accolate®, Singulair®, Zileuton®	10 days

[1] Classification of mid-strength, potent, or superpotent by Stoughton-Cornell Scale (Appendix 2 of the protocol, Section 16.1.1 of this report).
[2] The washout refers to antibiotics used to treat lower or upper respiratory tract infections and sinusitis.

10.1.1.5.5 Removal of Patients from Therapy or Assessment [clinstat\p01875.pdf, page 30, 1404]

Patients will be withdrawn from the study if they experience intolerable symptoms, are noncompliant, or the investigator believes the patients will be placed at risk for continuing in the study. If a subject discontinues prior to completion of the study, the reason, date of discontinuation, and date of the last study dose will be recorded. Patients will have all procedures and evaluations originally scheduled for the final visit. Patients will not be replaced.

10.1.1.6 Study Procedures [clinstat\p01875.pdf, pages 30-49, 1409-1418]

Each study was conducted at 47 investigational sites throughout the United States during the fall 2000 allergen season. Patients signed written informed consents at the start of any protocol-specified procedures and attended a total of four clinic visits that included a screening visit (Day -14 to 3), Baseline visit (Day 1 of treatment), and visits on Days 8 and 15. Each study center recorded pollen counts (counts per m^3) daily or at least several times

weekly for at least the time period beginning with first subject screened to last subject completed.

On Visit 1 (Days -14 to 3), after informed written consent was obtained, patients had a complete medical history and physical examination, 12-lead EKG, and clinical laboratory evaluations (chemistry, hematology, serum pregnancy test). Patients had a skin prick or intradermal tests (if not done within the last 12 months) to confirm hypersensitivity to an appropriate fall seasonal allergen extract at Visit 1. Patients entered a screening period and were instructed to complete diary cards with AM and PM scoring for at least three calendar days prior to the Baseline visit. The daily number of hours the subject was exposed to outside air was also recorded on the diary card. Patients were also instructed to record dosing information, concomitant medication use, and adverse events on a separate diary card.

Following a 3- to 14-day Screening period, qualifying patients at Screening and Baseline were randomized 1:1:1:1 to 15 days of treatment with one of four study drugs designated DL D-24, DL D-24 Alternate Formulation (AF), DL 5 mg, and sustained-release PSE (identical to the sustained-release PSE in both DL D-24 formulations. Patients received the first dose of study drug in the clinic on the morning of the Baseline visit (Visit 2). Patients received two bottles, labeled "A" or "B" and were instructed to take one tablet from each bottle daily at approximately the same time each morning without regard for the timing of meals or other daily activities, according to their assigned treatment group as shown in Table 16. Patients received enough medication for 20 days. Each day's daily dose consisted of 2 tablets (1 active and 1 placebo). Study drugs and matching placebo were identical in appearance and were dispensed at Visits 2 and 3 and collected at Visits 3 and 4 (Final Visit). The composition of the study drugs is shown in Table 17.

Table 16. Treatment Groups

Treatment	AM Regimen	
	Bottle A	Bottle B
1	Placebo DL tablets	SCH 483 5/240 mg sustained-release tablets
2	Placebo DL tablets	SCH 483 5/240 mg AF sustained-release tablets
3	DL 5 mg tablets	Placebo PSE tablets
4	Placebo DL tablets	Pseudoephedrine 240 mg sustained-release tablets

SCH 483 5/240 mg sustained-release, SCH 483 5/240 mg sustained-release AF, and PSE 240 mg sustained release were all identical in appearance.

Table 17. Study Drug Treatments

Treatment	Formulation	Batch Number
DL D-24 sustained-release tablet	Film-coated tablet with sustained-release PSE 240 mg in the core layer and DL 5 mg in the immediate-release layer	75882-056
DL D-24 AF sustained-release tablet	Film-coated tablet with sustained-release PSE 240 mg in the core layer and DL 5 mg in the immediate-release layer	75466-073
DL 5-mg tablet		0700032
DL placebo tablet		07000-30
PSE tablet	Tablet containing 240 mg of sustained-release PSE	75882-061

Treatment	Formulation	Batch Number
	in the matrix layer that is identical in appearance to both sustained-release formulations of DL D-24	
PSE placebo tablet		76466-079

Treatment compliance was evaluated by questioning patients, diary entry of study drug administration, and tablet counts at Visit 3 and 4. All concomitant medications were recorded in the CRF with the start and stop dates and reasons for use. Adverse events were evaluated by the Investigator and recorded on source documents and case report forms. Adverse events were graded as mild, moderate, severe, and life-threatening using standard criteria.

A final-visit ECG was to be obtained approximately 2 to 6 hours after the last dose of study medication.

Each subject had the right to withdraw consent to participate in the study at any time. The investigator had the option to discontinue any subject's participation for any reason.

Table 18. Schedule of Study Procedures and Evaluations

	Screening	Baseline	Treatment	
	Visit 1	Visit 2	Visit 3 ± 2 Days	Visit 4 ± 2 Days
	Day -14 to 3	Day 1	Day 8	Day 15
General Procedures				
Informed consent	X			
Inclusion/Exclusion Criteria	X	X		
Physical Examination/Medical history	X			
Concomitant medications review	X	X	X	X
Vital signs	X	X	X	X
Body Height and Weight	X			
Skin Test[a]	X			
12-Lead Electrocardiogram	X			X
Serum pregnancy test (all females)	X			X
Clinical laboratory tests	X			X
Assessment of Rhinitis Signs and Symptoms (Joint)	X			
Assessment of Rhinitis Signs and Symptoms and Severity form Diary		X		
Overall Condition of Seasonal Allergic Rhinitis	X	X	X	X
Evaluation of Therapeutic Response			X	X
Dispense Diaries	X	X	X	
Provide Instruction on Symptom Diary	X	X	X	
Collect/Review Symptom Diary		X	X	X
Dispense/Re-dispense Study Drug		X	X	
Collect/Count Study Drug			X	X
Adverse Events Evaluation		X	X	X

[a] If not done within previous 12 months

Source: clinstat\p01875.pdf, Table 2, pages 26

10.1.1.7 Assessment of Signs and Symptoms

10.1.1.7.1 Rhinitis Signs and Symptoms: Visit 1-4, Run-In, and Treatment Diary Data [clinstat\p01875.pdf, pages 38-40, 1413-1415]

During the screening period and throughout the 15-day treatment period, patients recorded the severity and signs and symptoms of fall seasonal allergic rhinitis twice daily on the diary. The reflective or PRIOR (over the previous 12 hours) and instantaneous or NOW scores for nasal and non-nasal symptoms were recorded twice daily, upon arising (before dosing) and approximately 12 hours later in the evening. The total symptom score was the sum of the eight individual symptom scores (four nasal and four non-nasal symptoms):

Table 19. Individual Symptom Scores

Nasal Signs/Symptoms	Non-Nasal Signs/Symptoms
Rhinorrhea (nasal discharge/runny nose and/or postnasal drip)	Itching/burning eyes
Nasal stuffiness/congestion	Tearing/watering eyes
Nasal itching	Redness of eyes
Sneezing	Itching of ears or palate
Source: [clinstat\p01875.pdf, Table 7, pages 39]	

Severity of each nasal and non-nasal sign/symptom was graded as follows:

0 = None: No sign/symptom evident.
1 = Mild: Sign/symptom was clearly present but minimal awareness; easily tolerated, and was not bothersome to daily living and/or sleeping.
2 = Moderate: Definite awareness of sign/symptom, which was bothersome to daily living and/or sleeping but tolerable.
3 = Severe: Sign/symptom was hard to tolerate; may have caused interference with activities of daily living and/or sleeping.

To qualify for screening, patients had to be clinically symptomatic based on upon reflective (PRIOR 12 hours) sign/symptom scores and have the following reflective sign/symptom scores as assessed jointly by the investigator and the subject:

1. Nasal rhinorrhea score of at least 2 (moderate)
2. Nasal congestion score of at least 2 (moderate)
3. Total nasal symptom score of at least 6
4. Total non-nasal symptom score of at least 5

To quality for randomization (Baseline visit), patients had to have a minimum score of each of the following 7 twice-daily (AM and PM) run-in diary "reflective" scores over the 3 calendar days prior to Baseline and the AM score of the Baseline day as shown below:

1. Total nasal rhinorrhea score of at least 14
2. Total nasal stuffiness/congestion score of at least 14
3. Total nasal symptom score of at least 42
4. Total non-nasal symptom score of at least 35

The combination of 4 AM and 3 PM reflective "PRIOR" scores was used as the Baseline PRIOR score. A similar set of 7 instantaneous or "NOW" scores was used as the Baseline NOW score.

10.1.1.7.2 Overall Condition of Seasonal Allergic Rhinitis: All Visits [clinstat\p01875.pdf, pages 40-41, 1415-1416]

The overall condition of SAR was evaluated jointly by the investigator or designee and the subject (with assistance from the parent or guardian, if required) at Screening and all subsequent visits. These evaluations were conducted after the diaries had been reviewed except during Visit 1. The score, based on the entire period since the last visit, up to and including the current time (reflective or PRIOR) was graded according to the following criteria 4 point scale as for rhinitis symptoms in section 10.1.1.7.1 above:

10.1.1.7.3 Evaluation of Therapeutic Response: Visit 3 and 4 [clinstat\p01875.pdf, pages 41, 1416]

Therapeutic response was evaluated at Visits 3 and 4 on a scale from 1 (complete relief) to 5 (treatment failure). The score was based on the entire time interval since the last visit, up to and including the current time (reflective or PRIOR), compared with the condition at Baseline. However, on the Case Report Form, therapeutic response was reported on a scale of 11 (complete relief) to 15 (treatment failure) as is denoted in the square brackets below.

1 [11] = Complete Relief:	Virtually no symptoms present;
2 [12] = Marked Relief:	Signs/symptoms were greatly improved and although present, were scarcely troublesome;
3 [13] = Moderate Relief:	Signs/symptoms were present and may have been troublesome, but were noticeably improved;
4 [14] = Slight Relief:	Signs/symptoms were present and only minimal improvement had been obtained;
5 [15] = Treatment Failure:	No relief; symptoms were unchanged or worse than Baseline.

10.1.1.8 Pharmacokinetic Parameters [clinstat\p01875.pdf, page 49]

Pharmacokinetic parameters such as measurement of drug concentrations were not conducted.

10.1.1.9 Efficacy Variables, Endpoints, and Analysis [clinstat\p01875.pdf, page 37, 48-49, 1424-1426]

10.1.1.9.1 Primary efficacy variable, endpoint, and analysis [clinstat\p01875.pdf, pages 48-49, 1424-1426]

The primary efficacy variable for the antihistamine component of the 2 DL D-24 formulations was the average AM/PM PRIOR (12 hour reflective) total symptom score excluding nasal stuffiness/congestion (from the subject diary). The primary endpoint was the

average over the entire 15-day treatment period. The primary comparisons for this variable were each of the 2 DL D-24 formulations versus PSE.

The primary efficacy variable for the decongestant component of the 2 DL D-24 formulations was the average AM/PM PRIOR (12 hour reflective) nasal stuffiness/congestion score (from the subject diary). The primary endpoint was the average over the entire 15-day treatment period. The primary comparisons for this variable were each of the 2 DL D-24 formulations versus DL.

The baseline period was defined as the interval of time that began 3 days prior to the Baseline visit (Day 1 of treatment) and ended on the day of the Baseline visit (Day 1 before the first dose of study drug was given). The baseline visit was Day 1, before the fist dose of treatment was given.

The primary efficacy analysis was based on a comparison of DL D-24 or DL D-24 AF versus PSE for the change from baseline in mean AM/PM PRIOR total symptom score (excluding nasal congestion) for the antihistamine effect, and DL D-24 or DL D-24 AF versus DL 5 mg for the mean of AM/PM PRIOR congestion for the decongestant effect. Since both primary comparisons had to be statistically significant as stated in the protocol in order to control the overall alpha level at 0.025, no adjustment of the significance level was necessary for each of these individual comparisons.

Efficacy variables were analyzed using general descriptive statistics and two-way analyses of variance (ANOVA), which extracted sources of variation due to treatment and center. Because there were two independent sets of comparisons (DL D-24 versus its components and DL D-24 AF versus its components), the alpha level was set to 0.025 for each pair of comparisons based on Bonferroni criteria to control the overall alpha level of 0.05.

Summary statistics for the primary variables were provided for the following subgroups: sex (male, female), age (12 to <18, 18 to <65, ≥65 years), and race (Caucasian, non-Caucasian).

10.1.1.9.2 Secondary efficacy variable, endpoint, and analysis [clinstat\p01875.pdf, page 49, 1424-1426]

For the antihistamine component and the decongestant component, the main comparisons were based on the change from Baseline in mean instantaneous (AM NOW) total symptom score excluding nasal congestion, and nasal stuffiness/congestion score, respectively, over the 15-day treatment period.

Secondary efficacy variables included total symptom score (sum of the 8 individual symptoms including nasal congestion), total nasal symptom score (sum of the 4 individual nasal symptom scores: rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing), total non-nasal symptom score (sum of the 4 individual non-nasal symptom scores: itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate), and each of the 8 individual symptom scores. Total nasal symptom scores were also computed without the symptom of nasal congestion.

Other secondary efficacy variables included:
1) other subject-evaluated PRIOR and NOW total symptom scores;
2) other subject-evaluated PRIOR and NOW nasal congestion scores;
3) individual symptom scores other than nasal stuffiness/congestion;
4) joint subject-investigator evaluation of overall condition of SAR;
5) joint subject-investigator evaluation of therapeutic response.

Secondary variables, expressed as mean change from Baseline, were analyzed using a two-way ANOVA model that extracted sources of variation due to treatment and center. Frequency tabulations and summary statistics were provided for the incidence of treatment-emergent adverse events, discontinuations due to adverse events, and changes from Baseline in vital signs, laboratory test results, and ECGs. In addition to the primary time point (the average over the entire 15-day treatment period), all variables were analyzed for each of the first 4 days of treatment, and the average over each of Week 1 (Days 1-8) and Week 2 (Days 9-15). Separate analyses were performed on the AM, PM, and mean AM/PM scores for both reflective (PRIOR) and instantaneous (NOW) evaluations. The overall condition of SAR and the response to therapy also were evaluated.

10.1.1.9.3 Safety variables [clinstat\p01875.pdf, pages 43-48, 60, 1418-1422, 1426]

Safety variables were summarized and tabulated for incidence of treatment-emergent adverse events, discontinuations due to adverse events, and changes from Baseline in laboratory test results, vital signs, and ECG intervals. Safety measurements included adverse event assessments captured in the daily patient log, and clinical assessment of AEs at each visit. ECG parameters included QT, PR, QRS, ventricular rate, and QTc interval calculated by both Bazett and Fridericia formulas.

10.1.1.10Statistical Plan [clinstat\p01875.pdf, pages 50-60, 1422-1426]

10.1.1.10.1 Sample Size [clinstat\p01875.pdf, pages 54, 1423]

With a sample size of 350 evaluable patients per treatment group, a two-tailed alpha-level of 0.025 and a pooled standard deviation of 4.25 points on the change from Baseline, differences of 1.2 points or more between treatment groups would be detectable with power of at least 90%.

The primary statistical comparison of the decongestant effect of the DL D-24 or DL D-24 AF groups was based on a comparison to the DL group in the change from Baseline in the individual average AM/PM PRIOR 12 hours symptom of nasal stuffiness/congestion. With a sample size of 350 evaluable patients per treatment group, a two-tailed alpha-level of 0.025 and a pooled standard deviation of 0.6 points on the change from Baseline, differences of 0.16 points or more between treatment groups would be detectable with power of at least 90%. With 350 patients in each treatment group, the overall power for both comparisons being statistically significant is at least 84%.

10.1.1.10.2 Statistical Analysis [clinstat\p01875.pdf, pages 51, 1424-1426]

The efficacy variables were analyzed by a two-way analysis of variance (ANOVA) that extracted sources of variation due to treatment, center, and treatment by center interaction. The analyses prospectively identified in the protocol were carried out as planned.

10.1.1.10.3 Data Sets analyzed [clinstat\p01875.pdf, pages 51, 1424-1426]

The following data sets were used for evaluations and analyses in this study:

10.1.1.10.3.1 'All Randomized Subjects' or Modified Intent-to-Treat (MITT) population

All analyses and summaries of safety data were based on all randomized subjects (intent-to-treat principle) who had at least one dose of study drug. All analyses and summaries of primary and secondary efficacy data were based on all randomized subjects who had Baseline plus some post-baseline efficacy data for the variable analyzed (MITT population).

10.1.1.10.3.2 'Efficacy-evaluable population'

This data set included all randomized subjects who met the key eligibility and evaluability criteria defined above. Confirmatory efficacy analyses were based on the efficacy-evaluable patients. Evaluability criteria were established at a meeting held prior to unblinding the treatment assignment and were based on (1) inclusion/exclusion criteria, (2) compliance, and (3) concomitant medication use.

Efficacy analyses were based on the 'all randomized subjects' or MITT population. Subjects who did not have post-baseline efficacy data for a particular variable were not included in the analysis for that variable. The significance level for all comparisons was 0.025 since there were two sets of primary variables/comparisons [p01875.pdf, page 67].

10.1.1.11Results

10.1.1.11.1 Subject Disposition [clinstat\p01875.pdf, page 61-62]

A total of 1495 patients (527 [35%] male, 968 [65%] female) with SAR, ages 12 to 78 years of age were randomized to treatment at 47 centers in the United States and received at least one dose of study drug. The majority of patients in all 4 treatment groups was female (range, 59% to 68%) and Caucasian (range, 77% to 81%) and between 18 to <65 years of age (range, 82% to 89%). The groups were comparable. The mean ages were 33.8 years for the DL D-24 group, 33.6 years for the DL D-24 AF group, 35.0 years for the DL group, and 35.5 years for the PSE group. The mean duration of SAR ranged from 16.5 years to 18.0 years across treatment groups.

A total of 1391 (93.0%) patients completed the study. A total of 107 patients failed to complete the study: 62 (58%) were due to adverse events; 6(5.6%) due to treatment failures, and the remainder for other reasons unrelated to study treatment. No patients were replaced.

Table 20. Study 01875: Demographics and Baseline Characteristics, MITT

Characteristic	DL D-24 QD N = 372	DL D-24 AF N=374	DL N = 372	PSE N=377
Gender	n (%)	n (%)	n (%)	n (%)
Male	151 (41)	119 (32)	127 (34)	130 (34)
Female	221 (59)	255 (68)	245 (66)	247 (66)
Age, years				
Mean age	33.8	33.6	35.0	35.5
Range	12-78	12-74	12-76	12-70
Race	n (%)	n (%)	n (%)	n (%)
Caucasian	287 (77)	303 (81)	297 (80)	293 (78)
Black	42 (11)	35 (9)	45 (12)	39 (10)
Hispanic	29 (8)	22(6)	26 (7)	35 (9)
Asian	11 (3)	11 (3)	3 (<1)	4 (1)
American Indian	1 (<1)	0	1 (<1)	0
SAR duration (yr): mean (range)	16.5 (2-51)	17.2 (2-50)	18.0 (2-55)	17.9 (2-50)
Source: clinstat\p01875.pdf, Table 11, page 66				

Table 21. Study 01875: Number (%) of randomized patients who completed treatment, number (%) who discontinued, and reasons for discontinuation

	DL D-24	DL D-24 AF	DL	PSE
Number randomized	372	374	372	377
Number completed	351 (94.4%)	344 (92%)	346 (93%)	350 (92.8%)
Number discontinued	21 (5.6)	30 (8.0)	26 (7.0)	27 (7.2)
Reasons for discontinuation				
AE	13 (3.5)	17 (4.5)	17 (4.6)	14 (3.7)
Treatment Failure	1 (0.3)	2 (0.5)	1 (0.3)	2 (0.5)
Lost to Follow-up	0	2 (0.5)	4 (1.1)	2 (0.5)
Noncompliance	2 (0.5)	4 (1.1)	1 (0.3)	3 (0.8)
Did not meet protocol eligibility	3 (0.8)	2 (0.05) *	2 (0.5)	3 (0.8)
Voluntary withdrawal	2 (0.5)	1 (0.3)	1 (0.3)	2 (0.5)
Administrative	0	2 (0.5)	0	1 (0.3)
* One subject (P001875-35/5895) in the DL D-24 AF group was specified by the investigator on the final-status module of the CRF as having discontinued because she did not meet protocol eligibility. The same subject was specified as having discontinued due to adverse events (autonomic system disorder [heat & cold intolerance], mouth dry, fatigue, dizziness, tachycardia, nervousness) in the adverse-event module of the CRF. In the FDA analyses, this patient is counted as an adverse event.				
Source: clinstat\p01875.pdf, Table 8, page 62				

10.1.1.11.2 Protocol Deviations [clinstat\p01875.pdf , page 62-64]

A total of 85 patients had protocol deviations that excluded them from the efficacy-evaluable subset. The protocol deviations were minor and do not impact the results of the study. These are shown in Table 22 and Table 23. Note that the efficacy evaluable subset was not the primary analysis population.

Table 22. Study 01875: Distribution of Patients by Analysis Subset and Treatment Group

	DL D-24	DL D-24 AF	DL	PSE
Number randomized (ITT)	372	374	372	377
Number completed	351 (94.4%)	344 (92%)	346 (93%)	350 (92.8%)
Efficacy-Evaluable subset	348 (93.5)	350 (93.6)	358 (96.2)	354 (93.9)
Patients excluded from Efficacy-Evaluable subset	24 (6.5)	24 (6.4)	14 (3.8)	23 (6.1)
Source: clinstat\p01875.pdf, Table 10, page 65				

Table 23. Study 01875: Number (%) of Patients Excluded from the Efficacy-Evaluable Subset Due to Protocol Deviations

	DL D-24	DL D-24 AF	DL	PSE
Insufficient Medication	7 (1.9)	9 (2.4)	7 (1.9)	8 (2.1)
Noncompliance with dosing regimen[a]	4 (1.1)	2 (0.5)	4 (1.1)	0
Insufficient washout	8 (2.2)	5 (1.3)	0	3 (0.8)
Unacceptable concomitant medication	6 (1.6)	2 (0.5)	2 (0.5)	6 (1.6)
Insufficient efficacy data[b]	0	6 (1.6)	3 (0.8)	5 (1.3)
Did not meet entrance criteria	4 (1.1)	4 (1.1)	3 (0.8)	6 (1.6)
Total number of patients excluded[c]	24 (6.5)	24 (6.4)	14 (3.8)	23 (6.1)
[a] Patients received <75% or >125% of their scheduled doses [b] Patients had no post-Baseline diary data [c] Patients may have had more than 1 protocol deviation				
Source: clinstat\p01875.pdf, Table 9, page 63				

Subject Unit 5874 (DL D-24) at Center P01875-17 was mistakenly dispensed to a patient who was undergoing screening procedures for another investigational study [redacted] The subject [redacted] took one dose of study drug at the study center and immediately discontinued treatment. No adverse experiences were reported. Data for this subject were not included in the clinical database for either Study P01875 or [redacted]. Randomization No.5874 was never used in Study P01875 and the Subject Unit 5874 was returned to the sponsor for destruction. Blinding of the study treatment was preserved using a double-dummy technique.

According to the applicant, the study was originally designed to include (at least) one different treatment arm. The originally planned DL D-24 6/240 mg treatment arm was replaced by a DL D-24 5/240 mg treatment arm in the final 'amended' protocol. Six patients were inadvertently randomized and received the following treatments: two patients (P01875-07/6865 and P01875-07/6872) received DL D-24 6/240 mg QD for a total of 18 days and 14 days, respectively, and three patients (P01875-07/6863, P01875-07/6871, and P01875-41/7319) received placebo for a total of 14 days, 14 days, and 1 day, respectively. In addition, one patient with SAR who was undergoing screening at Center P01875-17 for another investigational drug for SAR mistakenly received one dose of study medication (DL D-24) before discontinuing treatment. The most frequent adverse events these patients experienced were headache, dry mouth, and upset stomach.

Four of the six improperly randomized patients were from Study site 07 [redacted] 4.

This site enrolled a total of 24 patients. Of interest, neither the original nor the final protocol contained a treatment arm with a placebo group, so how patients were treated with placebo only was never adequately explained. As an explanation, in the Protocol Deviation section of the study report the applicant states the original protocol had six arms, including a placebo arm, the 6/240 arm that was replaced, and the replacement 5/240 AF arm [Section 8, P01875, pp 63-4, P01875.pdf]. However, this does not jibe with the actual protocols themselves. In any event, these patients were excluded from all analyses as presented; however, safety data was submitted.

10.1.1.11.3 Efficacy Endpoint Outcomes [clinstat\p01875.pdf, page 64-65]

Analyses of the efficacy variables are shown in Table 24 through Table 27. Results support the efficacy of DL D-24 once daily for the relief of nasal and non-nasal symptoms of SAR in patients 12 years of age and above. For patient evaluated nasal and non-nasal symptoms of allergic rhinitis, DL D-24 was statistically better than each individual component, DL or PSE at Day 15. Likewise, DL D-24 was significantly better than DL (p=0.02) and PSE (p=0.096) in reducing nasal stuffiness and congestion.

10.1.1.11.3.1 Primary Efficacy [clinstat\p01875.pdf, page 67-73]

Table 24. Study 01875: Primary Efficacy Analyses: Mean AM/PM PRIOR 12 Hours, Days 1-15, MITT

		Baseline		Change from Baseline			Δ*	Pairwise Comparisons vs. DL D-24 and DL D-24 AF (P-value)	
	N	N[a]	LS Mean [b]	N[a]	LS Mean [b]	%c	Δ	DL D-24	DL D-24 AF
Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR									
DL D-24	372	372	15.01	372	-6.09	-38.8			0.250
DL D-24 AF	374	368	14.88	368	-5.74	-37.2		0.250	
DL	372	369	14.71	369	-5.10	-33.5	-0.99	0.001	0.038
PSE	377	372	15.08	372	-5.08	-32.4	-1.01	0.001	0.033
Nasal Stuffiness/Congestion AM/PM PRIOR									
DL D-24	372	372	2.57		-0.90	-33.4			0.353
DL D-24 AF	374	368	2.57		-0.86	-31.7		0.353	
DL	372	369	2.55		-0.74	-28.0	-0.16	0.001	0.022
PSE	377	372	2.56		-0.78	-28.6	-0.12	0.009	0.096

[a] Calculation of mean Baseline values included all patients with Baseline and Endpoint data; calculation of mean post Baseline values included all patients with both Baseline and post Baseline data at the specified time point(s).
[b] LS Means are obtained from the two-way ANOVA model with treatment and site effects
[c] Mean percent changes are raw means
* Difference between DI D-24 and listed group

Source: p01875.pdf, Table 1, page 226 ; Table 5, page 26

10.1.1.11.3.2 Secondary Efficacy [clinstat\p01875.pdf, page 74- 91]

Table 25. Study P01875: Total Scores, AM/PM Prior 12 Hours, MITT

Treatment	Baseline		Change from Baseline			Pairwise Comparisons vs. DL D-24	
	N[a]	LS Mean[b]	N[a]	LS Mean[b]	%[c]	Δ	p-value
Total Symptom Score (excluding nasal congestion)							
DL D-24	372	15.01	372	-6.09	-38.8		
DL	369	14.71	369	-5.10	-33.5	0.99	0.001
PSE	372	15.08	372	-5.08	-32.4	-1.01	0.001
Total Symptom Score (including nasal congestion)							
DL D-24	372	17.58	372	-6.99	-38.0		
DL	369	17.26	369	-5.84	-32.7	-1.15	<0.001
PSE	372	17.64	372	-5.86	-31.9	-1.13	0.001
Total Nasal Symptom Score (excluding nasal congestion)							
DL D-24	372	6.81	372	-2.69	-37.8		
DL	369	6.68	369	-2.24	-32.1	-0.45	0.001
PSE	372	6.83	372	-2.17	-3.01	-0.52	<0.001
Total Nasal Symptom Score (including nasal congestion)							
DL D-24	372	9.39	372	-3.60	-36.6		
DL	369	9.23	369	-2.99	-31.1	-0.61	<0.001
PSE	372	9.39	372	-2.94	-29.8	-0.66	<0.001
Total Non Nasal Symptom Score							
DL D-24	372	8.20	372	-3.40	-39.6		
DL	369	8.03	369	-2.85	-34.3	-0.55	0.003
PSE	372	8.24	372	-2.91	-34.1	-0.49	0.008

[a] Calculation of mean Baseline values included all patients with Baseline and Endpoint data; calculation of mean post Baseline values included all patients with both Baseline and post Baseline data at the specified time point(s).
[b] LS Means are obtained from the two-way ANOVA model with treatment and site effects
[c] Mean percent changes are raw means

Source: clinstat\p01875.pdf, Table 1, page 226 ; Table 1, page 286 ; Table 1, page 290 ; Table 1, page 288 ; Table 1, page 292

Table 26. Study P01875: Mean AM or PM NOW, Day 2-15, MITT

Treatment	Baseline		Change from Baseline		Pairwise Comparisons vs. DL D-24	
	N[a]	LS Mean[b]	LS Mean[b]	%[c]	Δ	p-value
Total Symptom Score (excluding nasal congestion) AM NOW						
DL D-24	372	14.65	-5.57	-36.6		
DL	369	14.61	-4.61	-30.2	-0.96	0.003
PSE	372	14.79	-4.56	-29.2	-1.01	0.001
Total Symptom Score (excluding nasal congestion) PM NOW						
DL D-24	372	14.88	-6.39	-40.7		
DL	369	14.51	-5.12	-33.7	-7.0	<0.001
PSE	372	14.89	-5.18	-33.2	-7.5	<0.001
Nasal Congestion Score AM NOW						
DL D-24	372	2.55	-0.80	-30.0		
DL	367	2.57	-0.63	-22.6	-0.17	<0.001
PSE	371	2.58	-0.69	-25.0	-0.11	0.040

Treatment	Baseline		Change from Baseline		Pairwise Comparisons vs. DL D-24	
	N[a]	LS Mean[b]	LS Mean[b]	%[c]	Δ	p-value
Nasal Congestion Score PM NOW						
DL D-24	372	2.52	-0.93	-34.7		
DL	369	2.52	-0.74	-27.3	-7.4	<0.001
PSE	372	2.53	-0.82	-30.4	-4.3	0.041

[a] Calculation of mean Baseline values included all patients with Baseline and Endpoint data; calculation of mean post Baseline values included all patients with both Baseline and post Baseline data at the specified time point(s).
[b] LS Means are obtained from the two-way ANOVA model with treatment and site effects
[c] Mean percent changes are raw means
Source: summary.pdf, Section 3.H, Table 6, page 29, 410; Table 16, page 83

Table 27. Study P01875: Individual Symptom Scores, AM/PM Prior 12 Hours, MITT

Treatment	Baseline		Change from Baseline			Pairwise Comparisons vs. DL D-24	
	N[a]	LS Mean[b]	N[a]	LS Mean[b]	%[c]	Δ	P-value
Rhinorrhea							
DL D-24	372	2.53	372	-0.85	-31.9		
DL	369	2.51	369	-0.74	-28.5	-0.11	0.030
PSE	372	2.53	372	-0.70	-26.2	-0.15	0.002
Nasal Congestion							
DL D-24	372	2.57	372	-0.90	-33.4		
DL	369	2.55	369	-0.74	-28.0	-0.16	0.001
PSE	372	2.56	372	-0.78	-28.6	-0.12	0.009
Nasal Itching							
DL D-24	372	8.20	372	-2.24	-38.5		
DL	369	8.03	369	-2.21	-31.7	-0.03	0.003
PSE	372	8.24	372	-2.27	-30.2	0.03	0.002
Sneezing							
DL D-24	372	2.05	372	-0.94	-43.7		
DL	369	1.96	369	-0.76	-36.8	-0.18	<0.001
PSE	372	2.04	372	-0.73	-33.1	-0.21	<0.001
Itching/Burning Eyes							
DL D-24	372	2.24	372	-0.93	-39.0		
DL	369	2.20	369	-0.76	-33.0	-0.17	0.002
PSE	372	2.22	372	-0.79	-33.0	-0.14	0.006
Tearing/Watering Eyes							
DL D-24	372	2.08	372	-0.88	-39.6		
DL	369	2.03	369	-0.76	-35.5	-0.12	0.031
PSE	372	2.09	372	-0.77	-33.8	-0.11	0.038
Redness of Eyes							
DL D-24	372	1.96	372	-0.80	-38.8		
DL	369	1.92	369	-0.66	-33.3	-0.14	0.006
PSE	372	1.95	372	-0.70	-34.4	-0.10	0.053
Itching of Ears/or Palate							
DL D-24	372	1.92	372	-0.79	-40.0		
DL	369	1.88	369	-0.66	-33.4	-0.13	0.014
PSE	372	1.99	372	-0.66	-31.9	-0.13	0.011

Source: clinstat\p01875.pdf, pages 293-301, Tables 1-8

Analyses of joint patient-investigator evaluations for overall condition of seasonal allergic rhinitis and the evaluation of therapeutic response in all randomized subjects demonstrated similarities at all times points. The overall condition for either component was not significantly affected by either component and the evaluation of therapeutic response achieved statistical significance (p=0.005) for the comparison to PSE.

10.1.1.11.3.3 Response by Age, Sex, and Race [p01875.pdf, page 71]

Response to treatment was examined by age, sex, and race. Overall, DL D-24 was numerically more effective than PSE in reducing mean AM/PM PRIOR 12 hours total symptom scores excluding nasal congestion in both sexes. Similar results were seen among age and race subgroups.

10.1.1.11.4 Safety Outcomes

10.1.1.11.4.1 Total Drug Exposure [clinstat\p01875.pdf, page 95]

Treatment duration was similar among the groups with the majority of patients (≥ 92.7%) receiving treatment for 13 to 15 days. The median duration of treatment was 15 days for all treatment groups; providing sufficient duration of exposure to characterize safety over the protocol-specified length of treatment. Ten percent of the subject population was dosed for more than 16 days; this was attributed to the scheduling of the final visit. Only two patients did not receive all treatments.

10.1.1.11.4.2 Adverse Events [clinstat\p01875.pdf, page 96-117]

According to the Applicant, both formulations of DL D-24 were well tolerated. Treatment-emergent adverse events were reported for 35.8%, 39.8%, 28.8%, and 38.7% of patients treated with DL D-24, DL D-24 AF, DL, and PSE, respectively. The most frequently reported adverse events (reported for ≥ 5% of patients in any treatment group) were dry mouth, headache, and insomnia, and these AEs were more prevalent in the DL D-24, DL D-24, and PSE treatment group indicating the known sympathomimetic side effects of PSE. According to the investigators, the overall incidence of treatment-related adverse events was greater among patients treated with DL D-24 (23.4%), DL D-24 AF (27.0%), and PSE (27.9%) than among patients treated with DL (15.3%). Four patients experienced a serious adverse event (SAE), none of which were attributed to study drug. One patient 7244 was hospitalized due to a general feeling of malaise, swollen ankles, and swollen legs, and diagnosed with congestive health failure (CHF) 5 days after the Final visit. Four patients became pregnant during the study.

Table 28 Study P01875: Treatment-Emergent Adverse Events Reported by ≥2% of Patients in Any Treatment Group, MITT

	Number (%) of Patients[a]			
	DL D-24	DL D-24 AF	DL	PSE
N	372	374	372	377
TOTAL ADVERSE EVENTS[b]	133 (35.8)	149 (39.8)	107 (28.8)	146 (38.7)
Autonomic Nervous System Disorders	31 (8.3)	48 (12.8)	14 (3.8)	56 (14.9)
Mouth Dry	31 (8.3)	44 (11.8)	11 (3.0)	51 (13.5)
Body as a whole	29 (7.8)	34 (9.1)	39 (10.5)	39 (10.3)
Fatigue	7 (1.9)	7 (1.9)	12 (3.2)	9 (2.4)
Headache	19 (5.1)	16 (4.3)	22 (5.9)	24 (6.4)
Central and Peripheral Nervous System Disorders	13 (3.5)	24 (6.4)	9 (2.4)	19 (5.0)
Dizziness	6 (1.6)	12 (3.2)	5 (1.3)	8 (2.1)
Psychomotor Hyperactivity	7 (1.9)	10 (2.7)	1 (0.3)	10 (2.7)
Gastrointestinal system Disorders	33 (8.9)	20 (5.3)	13 (3.5)	32 (8.5)
Dyspepsia	8 (2.2)	3 (0.8)	4 (1.1)	4 (1.1)
Nausea	6 (1.6)	7 (1.9)	3 (0.8)	10 (2.7)
Cardiovascular system	5 (1.3)	8 (2.1)	4 (1.1)	11 (2.9)
Tachycardia	3 (0.8)	7 (1.9)	1 (0.3)	10 (2.7)
Musculoskeletal Disorders	7 (1.9)	11 (2.9)	13 (3.5)	10 (2.7)
Myalgia	1 (0.3)	5 (1.3)	9 (2.4)	6 (1.6)
Psychiatric Disorders	37 (9.9)	41 (11.0)	12 (3.2)	45 (11.9)
Insomnia	17 (4.6)	22 (5.9)	3 (0.8)	27 (7.2)
Somnolence	14 (3.8)	11 (2.9)	5 (1.3)	10 (2.7)
Respiratory System Disorders	33 (8.9)	22 (5.9)	22 (5.9)	30 (8.0)
Pharyngitis	14 (3.8)	4 (1.1)	5 (1.3)	12 (3.2)

a Number of patients reporting adverse events at least once during the study. Some patients may have reported more than 1 adverse event
b Without regard to relationship to treatment
Sources: p01875.pdf, Table 22, p 99; pp 464-473

10.1.1.11.4.3 Discontinuation or treatment interruption due to adverse events [clinstat\p01875.pdf, page 97, 108, 112]

A total of 62 (4.2%) patients discontinued study treatment because of adverse events. There were 13 (3.5%), 18 (4.8%), 17(4.6%), and 14(3.7%) patients in the DL D-24, DL D-24 AF, DL, and PSE groups, respectively. Most of these were associated with the sympathomimetic effects of PSE such as insomnia, nausea, psychomotor activity, and dizziness. One of the patients in the DL D-24 AF group was discontinued because she did not meet protocol eligibility in the final-status module of the CRF. The same subject was specified as having discontinued due to adverse events in the adverse-event module of the CRF and is counted in the FDA analyses as an AE. Four patients (1 DL D-24 AF, 1 PSE) became pregnant unintentionally during the study and were discontinued.

10.1.1.11.4.4 Severe Adverse Events [clinstat\p01875.pdf, page 104-107]

The overall proportion of patients reporting severe adverse events was slightly higher in the DL D-24, DL D-24 AF, and PSE treatment groups than in the DL treatment group (7.3%, 6.1%, and 5.8% versus 4.3%, respectively). The most frequently occurring severe

adverse event (reported by >2 patients in any treatment group) among patients treated with DL D-24, DL D-24 AF, and PSE was dry mouth, reported for 5 (1.3%), 9 (2.4%), and 8 (2.1%) patients, respectively; dry mouth was reported for 2 (0.5%) of patients treated with DL. Severe headache was reported for 5 (1.3%) patients treated with DL D-24 compared with 2 (0.5%) in the DL D-24 AF group and 3 (0.8%) in the PSE group; no patients in the DL group reported severe headache. Severe psychomotor hyperactivity (hyperactivity/felt wired; jitteriness; jittery) was reported for 3 (0.8%) patients in the DL D-24 group. No other individual severe adverse event was reported for more than 2 patients in any treatment group.

10.1.1.11.4.5 Serious adverse events and death [clinstat\p01875.pdf, page 107-112]

No subject died or experienced a life-threatening adverse event necessitating withdrawal from the study.

Serious AEs were reported by an investigator for four patients (1 in the DL D-24 AF group, and 2 in the PSE group). In the DL D-24 AF group, one subject was discontinued due to hyperpyrexia and cholelithiasis, and in the PSE group, one subject each was discontinued due to asthma and pneumonia. One serious adverse event was inadvertently not captured in the database, but is discussed in detail in the study report. Patient P01875-02/7244 (DL) was hospitalized with malaise, swollen ankles, and swollen legs, and was diagnosed with congestive heart failure 5 days after completing the study (Final visit). All events were considered to be unrelated to treatment with study medication. The Applicant's narratives of each of the SAEs are presented below. [ISS, pp37-9]

DL D-24 AF group:

- P01875-29/6095. F/19/C. Hospitalization for Hyperpyrexia/Suspected Meningitis. "A 19-year-old female was randomized into the study and took the first dose of study medication on 30-AUG-2000. The day before, the subject started to complain about fever, sore throat, headache and neck stiffness. This increased in severity with new symptoms of chills and night sweats, and on the evening of [redacted] she went to the Emergency Room. The study medication was discontinued on that date. Total duration of treatment with the study medication was one day. The medical history was positive for migraine headaches. The subject was admitted with possible meningitis, persistent temperature elevation (up to 101.3°F), persistent sore throat and painful swallowing. HEENT revealed an injected erythematous pharynx and tonsils and enlarged cervical nodes. The neck was tender. Clinical impression: hyperpyrexia, most likely secondary to tonsillitis and pharyngitis with the stiff neck secondary to discomfort from pain. The CT scan of the brain was unremarkable; the spinal tap was negative. Treatment with IV fluids and IV antibiotics was given, together with pain medication. The subject was discharged from the hospital on [redacted] with only a few remaining symptoms. The discharge medication consisted of Keflex® 250 mg QD (cephalexin) for 1 week and Flonase® BID (flucanase). The investigator considered the event unlikely related to the study medication since the first signs and symptoms occurred prior to randomization. The blind was not broken.

After closure of the database, the study blind was broken and the patient was found to have received ~~DL D-24 AF.~~"

DL 5 mg group:

- P01875-02/7244. M/69/C. Hospitalization for Congestive Heart Failure. "A 69-year-old male was randomized into the study and took the first dose of study medication on 17-OCT-2000. Shortly after initiation of treatment, on 21-OCT-2000, the subject reported ankle edema as an adverse event. No other adverse events were reported. The subject completed the study as per protocol on 31-OCT-2000. The ECG obtained at the final visit also showed some abnormalities (Quadrigeminy). The medical history was positive for hypertension. On [redacted] the subject was hospitalized due to a general feeling of malaise, swollen ankles, and swollen legs, and the diagnosis of Congestive Heart Failure was made. Initially, the investigator considered the event possibly related to the study medication. This resulted in a 15-day alert report to the FDA and the study blind was broken. The subject was found to have received DL 5.0 mg. The subject was discharged from the hospital on [redacted]
  A second hospitalization occurred on [redacted] since the subject was not feeling well. Discharge occurred on [redacted] (no diagnostic work- up was performed). A third hospitalization took place on [redacted] and the subject informed the site that he was diagnosed with a pericarditis (unconfirmed). Hospital discharge was on [redacted]. A repeat ECG done at the site on [redacted] was slightly abnormal (not clinically significant); the subject gave permission to contact the cardiologist but refused to sign papers in order to obtain copies of the hospital records. Subsequently, after re-evaluation and consultation with the treating cardiologist, the relationship was changed to unlikely related. The subject was diagnosed with congestive heart failure due to a cardiomyopathy with an unknown etiology."

PSE 240 group:

- P01875-15/7544. F/39/B. Hospitalization for Pneumonia. A 39-year-old female was randomized into the study and took the first dose of study medication on 06-NOV-2000. On 17-NOV-2000, the subject was discontinued from the study because of gross non-compliance with the dosing regimen. Around 22-NOV-2000, the subject started to complain of a mild fever and a non-productive cough, followed by chills a couple of days later. Shortly before the admission, the subject developed some shortness of breath and right-sided chest pain. The cough became productive with yellowish phlegm. Subsequently, the subject was taken to the emergency room on [redacted] and was hospitalized with a diagnosis of bilateral pneumonia requiring treatment with IV antibiotics and oxygen (moderate hypoxia was present). The event resolved and the subject was discharged from the hospital on [redacted] The investigator considered the event unlikely related to the study. The blind was not broken. After closure of the database, the study blind was broken and the patient was found to have received PSE.

- P01875-24/6947. F/47/B. Hospitalization for Asthma Exacerbation. A 47-year-old female was randomized into the study and took the first dose of study medication on 30-SEP-2000. On [redacted], the subject started to complain about wheezing and shortness of breath. Subsequently, the subject was hospitalized for the treatment of the asthma exacerbation/bronchitis. The study medication was discontinued on 07-OCT-2000. The treatment consisted of the following: oxygen, nebulizers, Proventil, Atrovent, solumedrol and antibiotics. The subject was discharged from the hospital on [redacted] with Flovent, albuterol and prednisone therapy (tapering schedule). The medical history was positive for asthma. At the time of entry into the study, no asthma medication was used at all. The investigator considered the event unlikely related to the study. The blind was not broken. After closure of the database, the study blind was broken and the patient was found to have received PSE.

Four patients (1 DL D-24 AF, 1 PSE) became pregnant unintentionally during the study and were discontinued. Patient 6763 (DL D-24 AF) had planned to abort the pregnancy, but was lost to follow-up. Patient 5700 (PSE) elected to terminate the pregnancy. One additional unintended pregnancy was inadvertently not captured in the database, but is discussed in detail in the study report. Subject P01875-41/5435 (PSE) had a positive pregnancy test at the Final visit and delivered a healthy baby at term. Subject P01875-24/7054 took 3 doses of DL D-24 AF on Day 14 of the study because of increasing allergy symptoms. The subject completed the study per protocol. The only abnormality reported for this subject was mild sinus tachycardia at the Final visit which resolved without treatment.

10.1.1.11.4.6 Physical examination, ECG, and laboratory measure [clinstat\p01875.pdf, page 118-

Slight increases in mean heart rate were observed in patients in the DL D-24, DL D-24 AF, and PSE groups (2.8, 2.8, and 2.4 bpm, respectively) compared to the DL group (0.4 bpm) and are likely attributable to the effects from PSE. There were no significant changes in vital signs, median laboratory parameters, or ECG intervals, including QTc intervals. There were no significant differences in these parameters across the four treatment groups. Analyses of these variables by age, gender, and race did not indicate any differential response to treatment.

10.1.T.12 Discussion and Conclusions

Study P10875 compared the efficacy and safety of two formulations of SCH 483 5/240 mg to desloratadine 5 mg and pseudoephedrine 240 mg sustained release in the treatment of 1495 patients, ages 12 to 78 years, with seasonal allergic rhinitis. Patients were randomized 1:1:1:1 to 15 days of treatment with one of four treatment groups designated DL D-24, DL D-24 AF, DL 5 gm, and sustained-release PSE. Each morning, patients took 2 tablets (one active, one placebo). A total of 1391 patients completed the study with the majority of discontinuations due to adverse events or reasons unrelated to study treatment. Treatment groups were comparable at baseline with respect to demographics and disease characteristics and there was adequate representation of age groups. Based on the lack of statistical significance of the antihistamine component of the DL D-24 AF formulation, the sponsor

elected to pursue the DL D-24 formulation as the to-be-marketed drug product due to its superiority compared to the DL D-24 AF formulation. Results support the efficacy of once daily DL D-24 for the treatment of nasal and non-nasal symptoms of allergic rhinitis in patients with SAR. DL D-24 was statistically significantly better compared to DL and PSE for patient evaluated total symptom scores and nasal congestion at Day 15 (primary endpoint) and at other time points as well as for individual symptom scores. Analyses of joint patient-investigator evaluations for overall condition of seasonal allergic rhinitis and the evaluation of therapeutic response in all randomized subjects demonstrated similarities at all times points. At endpoint, DL D-24 was numerically more effective than DL or PSE for the improvement in overall condition of SAR. The evaluation of therapeutic response achieved statistical significance (p=0.005) for the comparison to PSE at endpoint.

Review of the safety data indicate that DL D-24 was well tolerated during the study. The adverse event profiles for the two formulations of DL D-24 were quite similar. Many of the adverse events associated with the DL D-24 and DL D-24 AF formulations such as insomnia, nausea, psychomotor activity, and dizziness can be attributed to the sympathomimetic effects of PSE. No clinically relevant changes in laboratory test results were observed in any treatment groups.

The sponsor's proposed indication for CLARINEX-D 24 HOUR Extended Release Tablets is for the relief of the nasal and non-nasal symptoms of allergic rhinitis (seasonal , including nasal congestion, in patients 12 year of age and older. The data, however, only support the indication for seasonal allergic rhinitis

Thus, this study only supports the efficacy and safety of DL D-24 in patients 12 years and older with SAR.

Appears This Way
On Original

10.1.2 Study P01884

10.1.2.1 Final Protocol [clinstat\p01884.pdf, page 1358-1448]

Title: Efficacy and Safety of Two Formulations of SCH 483 5/240 mg Compared to Desloratadine 5 mg and Pseudoephedrine 240 mg Sustained Release in the Treatment of Patients with Seasonal Allergic Rhinitis

Protocol amendments:	July 17, 2000
Study initiated:	August 19, 2000
Study completed:	December 18, 2000
Study report:	November 15, 2001
Study centers:	47 centers in the United States (32 patients per center)
IRB:	[clinstat\p01884.pdf, pages 1616]

The Applicant states that the study was conducted according to FDA regulations and in compliance with good clinical practice guidelines and that written informed consent was obtained from each subject prior to participation in the study.

10.1.2.2 Protocol Amendment [clinstat\p01884.pdf, page 1450-1461]

The protocol was amended once, on July 17, 2000. The amendment changed one of the treatment groups in the study. The study protocol initially had 4 treatment groups including a combination product containing DL D-24 6/240 mg QD. The sponsor believed that this combination was required in order to achieve desloratadine plasma concentrations matching those obtained from a plain 5 mg desloratadine tablet. However, due to a failed bioequivalence study, this treatment group was eliminated and instead the sponsor included an alternate formulation of a combination product containing DL D-24 5/240 mg QD as the fourth treatment group. The two DL D-24 5/240 mg formulations only differ by a slight modification in the quantity of excipients in the film coat, although the qualitative formula remains the same.

The final protocol, therefore, did not include the DL D-24 6/240 mg treatment group and patients were randomized 1:1:1:1 to the remaining 4 groups containing DL D-24, DL D-24 Alternate Formulation (AF), DL 5 mg, and sustained-release PSE (identical to the sustained-release PSE in both DL D-24 formulations).

10.1.2.3 Study Design [clinstat\p01884.pdf, page 23-26]

Study 01884 was identical in design to Study P01875 with the same primary objective to assess the efficacy of two formulations of SCH 483 5/240 mg QD (DL D-24 and DL D-24 AF) sustained release compared to 5 mg desloratadine QD tablets and to pseudoephedrine 240 mg QD sustained release tablets. Inclusion and exclusion criteria, withdrawal criteria,

study procedures, and efficacy and safety assessments were identical. The two formulations of DL D-24 differ only by a s light modification in the quantity of some of the excipients in the film coat, although the qualitative formula remains the same, thereby causing modest differences between the two formulations in the Cmax and AUC of desloratadine following oral ingestion.

10.1.2.4 Study Population [clinstat\p01884.pdf, page 26-30]

The study will recruit 32 patients at approximately 48 centers in the U.S. to ensure at least 1400 evaluable patients.

10.1.2.5 Results

10.1.2.5.1 Subject Disposition [clinstat\p01884.pdf, page 59-61]

A total of 1357 patients with SAR (516 males and 841 females) between the ages of 11 to 78 were randomized to treatment; 336 received DL D- 24, 339 received the AF formulation of DL D-24, 340 received DL, and 342 received PSE. There were 1274 (93.9%) completers and 83 (6.1%) patients failed to complete the study with most discontinuations (40) due to adverse events (25 from the DL D-24 groups, 11 from the PSE group, and 4 from the DL group). Treatment failure was higher in the PSE group (2.0%) than in the DL group (0.3%); no treatment failures occurred with either formulation of DL D-24.

10.1.2.5.2 Patient Demographics and Baseline Disease Characteristics [clinstat\p01884.pdf, page 64-65]

Demographics and disease characteristics of patients enrolled in the study are shown below. Treatment groups were comparable with the majority of patients in the groups being female (range, 60% to 65%) and Caucasian (range, 75% to 85%) and between 18 to <65 years of age (range, 82% to 85%). One patient was 11 years, 9 months of age on entry into the study.

Table 29. Study P01884: Demographics and Baseline Characteristics, MITT

Characteristic	DL D-24 QD N = 336	DL D-24 AF N=339	DL N = 340	PSE N=342
Gender	n (%)	n (%)	n (%)	n (%)
Male	122 (36)	136(40)	137 (40)	121 (35)
Female	214 (64)	203 (60)	203 (60)	221 (65)
Age, years				
Mean age	34.2	33.1	34.8	34.2
Range	12-69	12-78	11-74	12-76
Race	n (%)	n (%)	n (%)	n (%)
Caucasian	263 (78)	273 (81)	254 (75)	290 (86)
Black	33 (10)	26 (8)	40 (12)	21 (6)
Hispanic	29 (9)	27(8)	30 (9)	21 (6)
Asian	8 (2)	9 (3)	13 (4)	7 (2)
American Indian	0	0	1 (<1)	1 (<1)
SAR duration (yr): mean (range)	17.5 (2-55)	17.5 (2-66)	18.3 (2-62)	17.6 (2-69)
Source: clinstat\p01875.pdf, Table 11, page 65				

Table 30. Study P01884: Number (%) of randomized patients who completed treatment, number (%) who discontinued, and reasons for discontinuation

	DL D-24	DL D-24 AF	DL	PSE
Number randomized	336	339	340	342
Number discontinued	22 (6.5)	20 (5.9)	15 (4.4)	26 (7.6)
Number completed	314 (93.5 %)	319 (94.1%)	325 (95.6%)	316 (92.4%)
Reasons for discontinuation				
AE	11 (3.3)	14 (4.1)	4 (1.2)	11 (3.2)
Treatment Failure	0	0	1 (0.3)	7 (2.0)
Lost to Follow-up	2 (0.6)	1 (0.3)	5 (1.5)	5 (1.5)
Noncompliance	4 (1.2)	3 (0.9)	2 (0.6)	2 (0.6)
Did not meet protocol eligibility	4 (1.2)	1 (0.3)	1 (0.3)	1 (0.3)
Voluntary withdrawal	1 (0.3)	0	2 (0.6)	0
Administrative	0	1 (0.3)	0	0
Source: clinstat\p01884.pdf,Table 8, page 61				

10.1.2.5.3 Protocol Deviations [clinstat\p01884.pdf, pages 61]

A total of 87 patients including 23 (6.8%) in the DL D-24 group, 21 (6.2%) in the DL D-24 AF group, 23 (6.8%) in the DL group, and 20 (5.7%) in the PSE group had protocol deviations that excluded them from the efficacy-evaluable subset. These deviations included insufficient medication, noncompliance with the dosing regimen, insufficient washout, use of unacceptable concomitant medications, insufficient efficacy data, and failure to meet the entrance criteria. Analysis subsets and protocol deviations are shown in Table 31 and Table 32.

Table 31. Study P01884: Distribution of Patients by Analysis Subset and Treatment Group

	DL D-24	DL D-24 AF	DL	PSE
Number randomized	336	339	340	342
Number completed	314 (93.5 %)	319 (94.1%)	325 (95.6%)	316 (92.4%)
Efficacy-Evaluable subset	313 (93.2%)	318 (93.8%)	346 (93%)	317 (94.2%)
Patients excluded from Efficacy-Evaluable subset	23 (6.8)	21 (6.2)	23 (6.8)	20 (5.8)
Source: clinstat\p01884.pdf, page 64				

Table 32. Study P01884: Number (%) of Patients Excluded from the Efficacy-Evaluable Subset Due to Protocol Deviations

	DL D-24	DL D-24 AF	DL	PSE
Insufficient Medication	9 (2.7)	7 (2.1)	10 (2.9)	6 (1.8)
Noncompliance with dosing regimen[a]	4 (1.2)	3 (0.9)	3 (0.9)	5 (1.5)
Insufficient washout	7 (2.1)	6 (1.8)	2 (0.6)	1 (0.3)
Unacceptable concomitant medication	1 (0.3)	2 (0.6)	4 (1.2)	1 (0.3)
Insufficient efficacy data[b]	3 (0.9)	0	3 (0.9)	5 (1.5)
Did not meet entrance criteria	3 (0.9)	4 (1.2)	6 (1.8)	6 (1.8)
Total number of patients excluded[c]	23 (6.8)	21 (6.2)	23 (6.8)	20 (5.8)
a Patients received <75% or >125% of their scheduled doses b Patients had no post Baseline diary data c Patients may have had more than 1 protocol deviation				
Source: clinstat\p01884.pdf, Table 9, page 62				

One randomized subject, P01884-30/5739 was undergoing screening procedures for another investigational study sponsored by the sponsor [redacted] when she mistakenly took one dose of study medication (DL D-24 AF) and was immediately discontinued for "administrative" reasons. No adverse experiences were reported. No data for this subject were included in the clinical database for [redacted]

10.1.2.5.4 Efficacy Endpoint Outcomes [clinstat\p01884.pdf, page 66-88]

Analyses of the efficacy variables are shown in Table 33 through Table 36. Results support the efficacy of DL D-24 once daily for the relief of nasal and non-nasal symptoms of SAR in patients ≥12 years of age and above. For patient evaluated nasal and non-nasal symptoms of allergic rhinitis, DL D-24 was statistically better than DL and PSE in reducing AM/PM PRIOR 12 hour total symptom scores excluding nasal congestion at the primary time point. The improvement with DL D-24 AF over PSE was not significant (p= 0.076) except for at Day 2(p=0.015) and Day 4 (p=0.006) at Day 15. DL D-24 and DL D-24 AF were significantly better than DL and PSE in reducing nasal stuffiness and congestion. Based on the efficacy results of this study, the sponsor has decided to pursue DL D-24 as the to-be-marketed formulation.

The significance level for all comparisons was 0.025 since there were two sets of primary variables/comparisons.

10.1.2.5.4.1 Primary Efficacy Variable [clinstat\p01884.pdf, page 66-73]

Table 33. Study P01884: Primary Efficacy Analyses, Mean AM/PM PRIOR 12 Hours, Days 1-15, MITT

		Baseline		Change from Baseline			Δ*	Pairwise Comparisons vs. DL D-24 and DL D-24 AF (P-value)	
	N	N[a]	LS Mean[b]	N[a]	LS Mean[b]	%c	Δ	DL D-24	DL D-24 AF
Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR									
DL D-24	333	333	14.84	333	-5.71	-37.4			0.498
DL D-24 AF	338	338	14.95	338	-5.50	-35.8		0.498	
DL	337	337	15.06	337	-4.78	-30.8	-0.93	0.003	0.021
PSE	337	337	15.03	337	-4.95	-32.0	-0.76	0.015	0.076
Nasal Stuffiness/Congestion AM/PM PRIOR									
DL D-24	333	333	2.56	333	-0.85	-32.3			0.343
DL D-24 AF	338	338	2.58	338	-0.81	-30.8		0.343	
DL	337	337	2.57	337	-0.65	-24.8	-0.20	<0.001	0.001
PSE	337	337	2.54	337	-0.70	-27.1	-0.15	0.002	0.031

[a] LS Means are obtained from the two-way ANOVA model with treatment and site effects
[b] Mean percent changes are raw means
* Difference between DL D-24 and listed group

Source: clinstat\p01884.pdf, Table 12, page 68 ; Table 13, page 71

10.1.2.5.4.2. Secondary Efficacy Variable [clinstat\p01884.pdf, page 72-88]

Table 34. Study P01884: Total Scores, Mean AM/PM Prior 12 Hours, MITT

Treatment	Baseline		Change from Baseline			Pairwise Comparisons vs. DL D-24	
	N[a]	LS Mean [b]	N[a]	LS Mean [b]	%[c]	Δ	p-value
Total Symptom Score (excluding nasal congestion)							
DL D-24	333	14.84	333	-5.71	-37.4		
DL	337	15.06	337	-4.78	-30.8	-0.93	0.003
PSE	337	15.03	337	-4.95	-32.0	-0.76	0.015
Total Symptom Score (including nasal congestion)							
DL D-24	333	17.40	333	-6.57	-36.7		
DL	337	17.63	337	-5.44	-29.9	-1.13	0.001
PSE	337	17.58	337	-5.65	-31.3	-0.92	0.010
Total Nasal Symptom Score (excluding nasal congestion)							
DL D-24	333	6.73	333	-2.56	-36.8		
DL	337	6.79	337	-2.09	-30.0	-0.47	<0.001
PSE	337	6.81	337	-2.16	-30.9	-0.40	0.003
Total Nasal Symptom Score (including nasal congestion)							
DL D-24	333	9.29	333	-3.41	-35.7		
DL	337	9.36	337	-2.74	-28.6	-0.67	<0.001
PSE	337	9.35	337	-2.87	-30.0	-0.54	0.002
Total Non Nasal Symptom Score							
DL D-24	333	8.11	333	-3.15	-37.9		
DL	337	8.27	337	-2.69	-31.3	-0.46	0.015
PSE	337	8.23	337	-2.79	-32.8	-0.36	0.053

[a] LS Means are obtained from the two-way ANOVA model with treatment and site effects
[b] Mean percent changes are raw means

Source: clinstat\p01884.pdf, Table 12, page 68 ; Table 1, page 217 ; Table 1, page 279 ; Table 1, page 281 ; Table 1, page 283

Table 35. Study P01884: Mean AM or PM NOW, Days 2-15, MITT

Treatment	Baseline		Change from Baseline		Pairwise Comparisons vs. DL D-24	
	N[a]	LS Mean [b]	LS Mean [b]	%[c]	Δ	p-value
Total Symptom Score (excluding nasal congestion) AM NOW						
DL D-24	333	14.76	-5.34	-34.4		
DL	337	14.93	-4.48	-27.8	-0.86	0.008
PSE	335	15.14	-4.64	-29.1	-0.70	0.029
Total Symptom Score (excluding nasal congestion) PM NOW						
DL D-24	333	14.81	-5.80	-37.4		
DL	337	15.01	-5.02	-31.8	-0.78	0.019
PSE	336	15.01	-5.06	-32.3	-0.74	0.027
Nasal Congestion Score AM NOW						
DL D-24	333	2.56	-0.75	-27.6		
DL	337	2.57	-0.59	-21.1	-0.16	0.001
PSE	335	2.58	-0.61	-22.3	-0.14	0.008
Nasal Congestion Score PM NOW						
DL D-24	333	2.55	-0.89	-33.0		

DL	337	2.55	-0.68	-24.6	-0.21	<0.001
PSE	336	2.51	-0.72	-26.8	-0.17	0.001

[a] Calculation of mean Baseline values included all patients with Baseline and Endpoint data
[b] LS Means are obtained from the two-way ANOVA model with treatment and site effects
[c] Mean percent changes are raw means
Source: clinstat\p01884.pdf, Table 14, page 75 ; Table 15, page 77 ; Table 16, page 80 ; Table 17, page 8

Table 36. Study P01884: Individual Symptom Scores (excluding nasal congestion), AM/PM Prior 12 Hours, MITT

Treatment	Baseline		Change from Baseline			Pairwise Comparisons vs. DL D-24	
	N[a]	LS Mean [b]	N[a]	LS Mean [b]	%[c]	Δ	P-value
Rhinorrhea							
DL D-24	333	2.50	333	-0.79	-30.4		
DL	337	2.48	337	-0.67	-26.4	-0.12	0.017
PSE	337	2.51	337	-0.66	-25.3	-0.13	0.009
Nasal Congestion							
DL D-24	333	2.56	333	-0.85	-32.3		
DL	337	2.57	337	-0.65	-24.8	-0.20	<0.001
PSE	337	2.54	337	-0.70	-27.1	-0.15	0.002
Nasal Itching							
DL D-24	333	2.26	333	-0.90	-38.9		
DL	337	2.24	337	-0.70	-29.7	-0.20	<0.001
PSE	337	2.25	337	-0.74	-31.7	0.16	0.002
Sneezing							
DL D-24	333	1.97	333	-0.87	-43.4		
DL	337	2.06	337	-0.71	-33.1	-0.16	0.002
PSE	337	2.05	337	-0.76	-38.5	-0.11	0.032
Itching/Burning Eyes							
DL D-24	333	2.20	333	-0.86	-37.5		
DL	337	2.26	337	-0.74	-30.4	-0.12	0.025
PSE	337	2.23	337	-0.75	-31.9	-0.11	0.033
Tearing/Watering Eyes							
DL D-24	333	2.20	333	-0.86	-37.5		
DL	337	2.26	337	-0.74	-30.4	-0.12	-0.25
PSE	337	2.23	337	-0.75	-31.9	-0.11	-0.33
Redness of Eyes							
DL D-24	333	1.94	333	-0.73	-35.8		
DL	337	1.99	337	-0.63	-30.2	-0.10	0.049
PSE	337	1.96	337	-0.67	-33.7	-0.06	0.0242
Itching of Ears/or Palate							
DL D-24	333	1.96	333	-0.77	-39.5		
DL	337	1.93	337	-0.62	-32.0	-0.15	0.005
PSE	337	1.99	337	-0.65	-30.7	-0.12	0.028

Source: clinstat\p01884.pdf,Table13, page 71 ; Table 18, pages 83-84

Analyses of joint patient-investigator evaluations for overall condition of seasonal allergic rhinitis were not statistically significant at any time points. The evaluation of therapeutic response of DL D-24 compared to PSE in all randomized subjects demonstrated statistical significance at the primary endpoint. However, the comparison to DL was only statistically significant at Day 15 (p=0.027).

10.1.2.5.4.3 Response by Age, Sex, and Race [p01884.pdf, page 69]

Response to treatment was examined by age, sex, and race. Overall, DL D-24 was numerically more effective than PSE in reducing mean AM/PM PRIOR 12 hours total symptom scores excluding nasal congestion in both sexes. Similar results were seen among age and race subgroups.

10.1.2.5.5 Safety Outcomes

10.1.2.5.5.1 Total Drug Exposure [clinstat\p01884.pdf, page 92]

Treatment duration was similar among the groups with the majority of patients (≥ 92%) receiving treatment for 13 to 15 days. The median duration of treatment was 15 days for all treatment groups; providing sufficient duration of exposure to characterize safety over the protocol-specified length of treatment. Three subjects had a duration of exposure of 22 to 24 days: Subject 24/5536 (DL), 22 days; Subject 32/6460 (DL), 24 days; and Subject 27/6945 (PSE), 22 days.

10.1.2.5.5.2 Adverse Events [clinstat\p01884.pdf, page 93-127]

According to the Applicant, both formulations of DL D-24 were well tolerated. Treatment-emergent adverse events were reported for 38.7%, 44.2%, 26.2%, and 35.7% of patients treated with DL D-24, DL D-24 AF, DL, and PSE, respectively. The most frequently reported adverse events (reported for ≥ 5% of patients in any treatment group) were dry mouth, headache, and insomnia, and these AEs were more prevalent in the DL D-24, DL D-24, and PSE treatment group indicating the known sympathomimetic side effects of PSE. According to the investigators, the overall incidence of treatment-related adverse events was greater among patients treated with DL D-24 (25.3%), DL D-24 AF (28.3%), and PSE (22.8%) than among patients treated with DL (10.6%).

All but three cardiovascular AEs (2 severe palpitations and 1 severe migraine) were mild or moderate in severity. None were considered to be serious. One subject treated with DL D-24 (P01884-24/5529) had QTc/QT prolongation at the Final visit (September 19, 2000) and a follow up ECG 2 weeks later was normal. Twenty-two patients (8 each treated with DL D-24 and DL D-24 AF, 2 treated with DL, and 4 treated with PSE) experienced heart rate and rhythm disorders with all but one report of AV block (DL D-24) considered by the investigator to be possibly related to treatment. Palpitation was reported by 10 patients (5 in DL D-24 and 4 in DL D-24 AF, 1 DL).

Adverse events were stratified according to age, sex, and race. There was a lower incidence of AEs among patients aged 12 to <18 years compared to patients aged 18 to <65 years with a greater incidence of AEs in those patients treated with Dl D-24, DL D-24 AF, or PSE.

Females had a higher percentage of AEs compared to males in all treatment groups; however, the difference in the DL D-24 was minimal. There were too few subjects to make a formal assessment of a differential treatment response in terms of race.

Table 37. Study P01884: Treatment-Emergent Adverse Events Reported by ≥2% of Patients in Any Treatment Group, MITT

	Number (%) of Patients[a]			
	DL D-24	DL D-24 AF	DL	PSE
N	336	339	340	342
TOTAL ADVERSE EVENTS[b]	130 (38.7)	150 (44.2)	89 (26.2)	122 (35.7)
Autonomic Nervous System Disorders	32 (9.5)	38 (11.2)	7 (2.1)	28 (8.2)
Mouth Dry	28 (8.3)	37 (10.9)	6 (1.8)	26 (7.6)
Body as a Whole	42 (12.5)	34 (10.0)	29 (8.5)	35 (10.2)
Fatigue	11 (3.3)	9 (2.7)	7(2.1)	5(1.5)
Headache	26 (7.7)	21 (6.2)	15 (4.4)	23 (6.7)
Central and Peripheral Nervous System Disorders	21 (6.3)	22 (6.5)	7 (2.1)	12 (3.5)
Dizziness	8 (2.4)	10 (2.9)	1 (0.3)	5 (1.5)
Psychomotor Hyperactivity	10 (3.0)	9 (2.7)	1 (0.3)	6 (1.8)
Gastrointestinal system Disorders	33 (9.8)	35 (10.3)	19 (5.6)	30 (8.8)
Abdominal Pain	7 (2.1)	5 (1.5)	7 (2.1)	2 (0.6)
Anorexia	9 (2.7)	12 (3.5)	1 (0.3)	7 (2.0)
Constipation	7 (2.1)	4 (1.2)	0	5 (1.5)
Nausea	6 (1.8)	10 (2.9)	4 (1.2)	8 (2.3)
Cardiovascular system	12 (3.6)	9 (2.7)	7 (2.1)	7 (2.0)
Musculoskeletal Disorders	9 (2.7)	11 (3.2)	5 (1.5)	7 (2.0)
Myalgia	7 (2.1)	7 (2.1)	4 (1.2)	6 (1.8)
Psychiatric Disorders	42 (12.5)	39 (11.5)	16 (4.7)	41 (12.0)
Insomnia	18 (5.4)	18 (5.3)	2 (0.6)	27 (7.9)
Nervousness	10 (3.0)	5 (1.5)	3 (0.9)	3 (0.9)
Somnolence	10 (3.0)	16 (4.7)	7 (2.1)	8 (2.3)
Respiratory System Disorders	17 (5.1)	23 (6.8)	21 (6.2)	24 (7.0)
Pharyngitis	4 (1.2)	5 (1.5)	6 (1.8)	8 (2.3)
Upper Respiratory Tract Infection	3 (0.9)	6 (1.8)	7 (2.1)	7 (2.0)

a Number of patients reporting adverse events at least once during the study. Some patients may have reported more than 1 adverse event
b Without regard to relationship to treatment
Source: p01884.pdf, Table 22, page 96

10.1.2.5.5.3 Discontinuation or treatment interruption due to adverse events [clinstat\p01884.pdf, page 94-99, 107-114]

Forty (2.9%) patients discontinued treatment because of AEs with the majority of AEs being attributed to those effects observed with PSE treatment. There were 11 (3.3%), 14 (4.1%), 4 (1.2%), and 11 (3.2%) patients in the DL D-24, DL D-24 AF, DL, and PSE groups, respectively. Most of the adverse events that occurred during treatment with either formulation of DL D-24 were similar in type and frequency to those observed with PSE such as headache, insomnia, nausea, psychomotor activity, and dizziness. Six patients reported hypertension: 2(0.6%) patients each treated with DL D-24 and DL; 1 (0.3%) patient each treated with DL D-24 AF and PSE. Three patients from the DL D-24 AF and DL group were

discontinued. Two patients out of eight who reported palpitations were discontinued from the study due to AEs that included palpitation, tremor, and nausea.

Eleven patients (2 DL D-24, 3 DL D-24 AF, 6 PSE) interrupted treatment due to AEs with six patients discontinuing from the study.

10.1.2.5.5.4 Severe Adverse Events [clinstat\p01884.pdf, page 94, 102]

The overall proportion of patients reporting severe adverse events was slightly higher in the DL D-24, DL D-24 AF, and PSE treatment groups than in the DL treatment group (6.8%, 10.9%, and 8.2% versus 3.8%, respectively). The most frequently occurring severe adverse event (reported by ≥3 patients in any treatment group) among patients treated with DL D-24, DL D-24 AF, and PSE was dry mouth, reported for 6 (1.8%), 8 (2.4%), and 7 (2.0%) patients, respectively, and headache, reported by 5 (1.5%) patients treated with DL D-24, 5 (1.5%) in the DL D-24 AF group and 6 (1.8%) in the PSE group. No patients in the DL group reported severe dry mouth, headache, or insomnia.

10.1.2.5.5.5 Serious adverse events and death [clinstat\p01884.pdf, page 95, 106-109]

No life-threatening adverse events or deaths were reported. Three pregnancies were reported during screening.

Two patients (1 DL D-24 AF, 1 PSE) had SAEs. These events were considered by the investigator to be unrelated to study medication and both patients were discontinued from the study. The Applicant's narratives of each of the SAEs are presented below. [ISS, pp37-9]

DL D-24 AF group:

- P01884-46/7154. F/30/C. Hospitalization for Cholecystitis and Cholelithiasis Requiring Cholecystectomy. "A 30-year-old female was randomized and received the first dose of the study medication on 02-OCT-2000. Gastrointestinal symptoms consisting of abdominal pain started on 07-OCT-2000. On the morning of [redacted] the subject visited the Emergency Room with complaints of severe abdominal pain, nausea and vomiting and was subsequently hospitalized. The diagnosis of cholecystitis was made and the subject underwent a cholecystectomy on [redacted]. The study medication was discontinued on 07-OCT-2000. The investigator considered the event unlikely related to the used study medication. The blind was not broken. After closure of the database, the study blind was broken and the patient was found to have received DL D-24 AF."

PSE 240 mg group:

- P01884-48/5925. F/28/C. Hospitalization for Diarrhea/Nausea/Vomiting with Subsequent Diagnosis of Lower Respiratory Infection/Sinusitis. "A 28-year-old female was randomized and received the first dose of the study medication on 31-AUG-2000. Gastrointestinal symptoms consisting of nausea, vomiting and diarrhea started on 12-SEP-2000 and increased in severity over time. The subject was

hospitalized on [redacted] and IV replacement therapy was initiated. The subject was also diagnosed as having an acute sinusitis and a lower respiratory tract infection. After initiation of the appropriate therapy, the clinical condition improved and discharge from the hospital occurred on [redacted] after a complete resolution of the symptoms on 23-SEP-2000. The study medication was discontinued on 12-SEP-2000. The investigator considered the event unlikely related to the used study medication. The blind was not broken. After closure of the database, the study blind was broken and the patient was found to have received PSE."

10.1.2.5.5.6 Physical examination, ECG, and laboratory measure [clinstat\p01884.pdf, page 115-127]

There were no clinically relevant changes in median laboratory test values observed across the four treatment groups. Laboratory results were stratified by age, sex, and race. Analyses of these variables by age, gender, and race did not indicate any differential response to treatment between sexes, ages, and between Caucasians, Blacks, and Hispanics. There were too few patients of Asian, American Indian, or "Other" ethnic groups to adequately assess the differential response to treatment for these subgroups.

Shifts from normal ECGs at Baseline to abnormal, clinically significant ECGs at endpoint were observed in 14 (1%) patients: 5 (2%) patients treated with DL D-24; and 3 (<1%) patients each treated with DL D-24 AF, DL, and PSE. Three of these were reported as AEs (first degree AV block; incomplete right bundle branch block; AV block/left posterior hemiblock and late R-wave transition; atrial fibrillation and prolonged QT interval). The last two patients had follow-up ECGs that were still abnormal and clinically significant and had no additional follow-up information. None of the subjects had a previous history of cardiovascular disease.

10.1.2.6 Discussion and Conclusions

Study P01884 compared the efficacy and safety of two formulations of SCH 483 5/240 mg to desloratadine 5 mg and pseudoephedrine 240 mg sustained release in the treatment of 1357 patients, ages 11 to 78, with SAR (516 males and 841 females). Patients were randomized 1:1:1:1 to 15 days of treatment with one of four treatment groups designated DL D-24, DL D-24 AF, DL 5gm, and sustained-release PSE 240 mg. Each morning, patients took 2 tablets (one active, one placebo). A total of 1274 patients completed the study with the majority of discontinuations due to adverse events or reasons unrelated to study treatment. Treatment groups were comparable at baseline with respect to demographics and disease characteristics and there was adequate representation of age groups.

Both the antihistaminic efficacy and the decongestant efficacy of DL D-24 were significantly greater than those of either of its components alone thereby justifying the combination product in the treatment of patients with SAR. Mean AM/PM PRIOR 12 hours total symptom scores excluding nasal congestion for DL D-24 were significantly (p=0.015) greater than for PSE over the 15-day treatment interval. Although DL D-24 AF was numerically superior to PSE at all time points and intervals during the study, no statistically

significant difference was observed over the 15-day treatment and based on the lack of significance for the antihistamine component of the DL D-24 formulation at the primary time point, there is insufficient evidence to justify the contribution of the DL component of the DL D-24 AF formulation. Therefore, the sponsor did not pursue the DL D-24 formulation as the final to-be-marketed drug product.

The applicant states that the antihistaminic efficacy of DL D-24 versus PSE approached significance ($p=0.015$) at the primary time point. The applicant states that the decongestant efficacy of DL D-24 as measured by the AM nasal stuffiness/congestion symptom scores was significantly ($p<0.001$) greater than DL.

Review of the safety data indicate that DL D-24 was well tolerated during the study. The adverse event profiles for the two formulations of DL D-24 were quite similar. The overall incidence of AEs was low, with a higher frequency among patients treated with DL D-24 (6.8%), DL D-24 AF (10.9%), and PSE (8.2%) than among patients treated with DL (3.8%). Many of the adverse events associated with the DL D-24 and DL D-24 AF formulations such as insomnia, nausea, psychomotor activity, and dizziness can be attributed to the sympathomimetic effects of PSE. No clinically relevant changes in laboratory test results were observed in any treatment groups.

Safety data revealed no indications of any significant cardiovascular safety concerns for either formulation of DL D-24. Patient treated with DL D-24, DL D-24 AF, and PSE had slight increases in mean heart rate and ventricular rate, and these findings are typical for patients treated with PSE. No clinically relevant changes in median laboratory parameters, vital signs, or ECG intervals, including QTc intervals, were observed other than what might be expected from an established effect of PSE treatment. All but 3 cardiovascular AEs (2 severe palpitations, 1 severe migraine) were mild or moderate in intensity.

The sponsor's proposed indication for CLARINEX-D 24 HOUR Extended Release Tablets is for the relief of the nasal and non-nasal symptoms of allergic rhinitis (seasonal [redacted], including nasal congestion, in patients 12 year of age and older. As in Study P01875, the data for Study P01884, only support the indication for seasonal allergic rhinitis

[redacted]

Thus, this study only supports the efficacy and safety of DL D-24 in patients 12 years and older with SAR.

10.2 Line-by-Line Labeling Review

A line-by-line labeling review was not performed prior to finalization of this review.

11 REFERENCES

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