CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-605

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 21-605
Drug Name:	Clarinex-D 24 Hour Tablet (Combination of desloratadine 5.0-mg and pseudoephedrine sulfate 240-mg): Formulation1: DL D-24 or Formulation 2: DL D-24 AF), administered QD in the morning
Indication(s):	Clarinex-D is proposed to be indicated for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older.
Applicant:	Schering Corporation
Date(s):	Applicant's letter date: April 30, 2004
Review Priority:	Standard
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Keywords:	NDA review, clinical studies

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EXECUTIVE SUMMARY

Brief Overview of Clinical Studies

Clarinex-D 24-hour tablet is proposed to be indicated for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older.

Desloratadine (DL) is an active metabolite of loratadine (Claritin) which is marketed in the United States for the treatment of SAR. This drug, Clarinex-D, is a combination of DL 5 mg and pseudoephedrine (PSE), administered QD, in two formulations (D-24, D-24 AF). Based on its antihistaminic activity, the DL component of Clarinex-D can be expected to reduce mainly sneezing, nasal discharge, nasal itching, and non-nasal symptoms; and based on its sympathomimetic activity, the PSE component of Clarinex-D can be expected to reduce nasal stuffiness and congestion (page 5, section 8.b., P01875.pdf).

The claims of effectiveness and safety are based on Studies P01875 and P01884. These studies were Phase-III, randomized, parallel-group, multi-center, double-blind, and double-dummy studies. The efficacy claim of Clarinex-D was confirmed by comparing each of the combination formulations with its components. Specifically,

- The antihistamine effect was confirmed by comparing DL D-24 or DL D-24 AF against PSE.
- The decongestant effect was confirmed by comparing DL D-24 or DL D-24 AF against DL.

The sponsor's statistical conclusions were primarily based on the analysis of the pre-specified primary efficacy variables. Because this drug has two main effects, according to the study objectives, two primary efficacy variables were defined as follows:

- The primary efficacy variable for the antihistamine effect was defined as the mean AM/PM PRIOR 12 HOURS' total symptom score, excluding nasal congestion, expressed as a change from Baseline.
- The primary efficacy variable for the decongestant effect was the mean AM/PM PRIOR 12 HOURS' nasal stuffiness/congestion score.

Here, the mean symptom scores (total or nasal alone), above, represent the average score values over the 15-day treatment period.

Secondary efficacy variables include a variety of sums of symptom scores distinguished as reflective or instantaneous measurements of symptoms, depending on the time the symptoms were observed. One of the secondary efficacy variables is particularly worth noting: the mean AM total symptom score, excluding nasal congestion, representing the

drug effect at the end of dosing period, approximate 24 hours after dosing and before taking the next dose. Special attention was paid to the effectiveness of this drug based on this AM total symptom score.

This reviewer's evaluation of the drug's effectiveness is focused on whether the superiority of Clarinex-D 24 to its components (DL and PSE) can be demonstrated, based on the sponsor's data. However, the drug safety was not the focus of this statistical review. This reviewer has left safety evaluation to the medical reviewer.

Statistical Issues and Findings

This reviewer explored, examined, and reanalyzed the sponsor's data for Studies P01875 and P01884. After reanalysis of the data, this reviewer confirmed the sponsor's statistical findings and draws his own conclusions.

The outcome measurements were per-specified nasal and non-nasal symptom score recorded by the participating patients in their diary. The symptom score takes values, 0 to 3, ranging from none to most severe in terms of the symptom. The types of the symptoms are listed in Table 1, below.

Table 1 Symptom types

Nasal Symptoms	Non-Nasal Symptoms
Rhinorrhea (nasal discharge/runny nose and/or postnasal drip) (N1)	Itching/burning eyes (NN1)
Nasal stuffiness/congestion (N4)	Tearing/watering eyes (NN2)
Nasal itching (N2)	Redness of eyes (NN3)
Sneezing (N3)	Itching of ears or palate (NN4)

For convenience, a symptom type in this report is sometimes written as a simple notation, say N4, representing nasal stuffiness/congestion. The total symptom score which consists of eight nasal and non-nasal symptom scores, all together, is simply denoted as TOT. The notation, "TOT7," represents the total symptom score excluding N4, the nasal stuffiness/congestion. The notations, "TOT7" and "N4" also mean the averages over the 15-day treatment period in specific context.

Furthermore, this reviewer simplifies the descriptions of the treatment arms using letters from A to D:

Table 2 Treatments

A	DL D24
B	DL D24 (AF)
C	DL (desloratadine) 5mg
D	PSE (pseudoephedrine) 240mg

In the reviewer's analyses (hypothesis tests), in order to control the Type I error, simultaneous comparisons of A vs. D and B vs. D are adjusted using a 0.025 significance level. The same method is applied to the simultaneous comparisons of A vs. C and B vs. C.

Table 3 summaries the statistical findings on efficacy for the two pivotal studies based on the AM/PM PRIOR 12 HOURS' symptom scores, in other term, the reflective scores.

Table 3 Efficacy findings based on 15-day mean AM/PM PRIOR 12 HOURS symptom scores (Studies P01875 and P01884 compared)

Type of Comparison			P01875	P01884	Findings consistently positive
(A) D-24 vs.	(D) PSE	Antihistamine component (TOT7)	+ P=0.001	+ P=0.015	Yes
	(C) DL	Decongestant component (N4)	+ P=0.001	+ P=0.00004	Yes
(B) D-24 AF vs.	(D) PSE	Antihistamine component (TOT7)	- P=0.033	- P=0.076	No (Consistently Negative)
	(C) DL	Decongestant component (N4)	+ P=0.022	+ P=0.00135	Yes

The comparisons between A and C and that between B and C are based on the nasal stuffiness/congestion symptom score. The comparisons between A and D and that between B and D are based on the total symptom score excluding the nasal stuffiness/congestion symptom score. The p-values in the table link to ANOVA tables in this report.

D-24 was shown (Table 3) to be statistically superior to placebo in reducing the nasal/non-nasal symptoms, based on 15-day mean AM/PM prior 12 hours symptom scores.

However, the formulation, D-24 AF failed to show statistical significance of the relief of the overall nasal/non-nasal symptom, excluding nasal stuffiness/congestion, although statistical significance was shown in relieving nasal stuffiness/congestion. These findings were consistent across the studies. The objective to simultaneously demonstrate the superiority of both antihistamine and decongestant components was not achieved.

Table 4 presents the statistical findings on efficacy for the two pivotal studies based on the AM NOW symptom scores, in other term, the instantaneous scores.

Table 4 Efficacy findings based on 15-day mean AM NOW (instantaneous) symptom scores - (Studies P01875 and P01884 compared)

Type of Comparison			P01875	P01884	Findings consistently positive
(A) D-24 vs.	(D) PSE	Antihistamine component (TOT7)	+ P=0.001	- P=0.0287	No
	(C) DL	Decongestant component (N4)	+ P=0.0009	+ P=0.0015	Yes
(B) D-24 AF vs.	(D) PSE	Antihistamine component (TOT7)	+ P=0.018	- P=0.1278	No
	(C) DL	Decongestant component (N4)	- P=0.0297	+ P=0.0127	No

Note that neither formulation has consistently demonstrated significant effect of relieving nasal/non-nasal symptoms (excluding nasal congestion).

Clarinex-D in D-24 formulation consistently demonstrated a statistically significant decongestant effect across the two studies. However, such consistency was not seen in the D-24 AF formulation.

Overall, **Clarinex-D in formulation D-24** administered QD was shown to be effective in relieving SAR based on prior 12 hours' nasal and non-nasal symptom scores. However, the effectiveness of **Clarinex-D in formulation D-24 AF** administered QD in relieving the overall nasal/non-nasal symptom (excluding nasal congestion) was not demonstrated, though some effect in reducing nasal congestion alone was consistently shown based on the AM/PM PRIOR 12 HOUR data. Such consistency disappeared when analyzing using the instantaneous data (the AM NOW score).

Conclusions and Recommendations

Efficacy Conclusions:

Consistently across Studies P01875 and P01884, Clarinex-D in formulation D-24 was shown to be statistically superior to placebo in the relief of overall nasal/non-nasal symptom.

However, Clarinex-D in formulation D-24 AF failed to demonstrate the statistical significance of antihistamine effect in relieving overall nasal/non-nasal symptom, excluding nasal congestion, though statistical significance was shown in relieving nasal congestion.

These findings were consistent across Studies P01875 and P01884.

Note that, in examining the end-of-dosing effect (the drug effect after 24 hours of taking the first dose) of relieving overall nasal/non-nasal symptom, excluding nasal congestion, neither formulation demonstrated superiority to placebo consistently across the studies. In examining the end-of-dosing effect, Clarinex-D in D-24 formulation consistently demonstrated a statistically significant decongestant effect across the studies. Such statistically significant decongestant effect was seen in Study P01884 alone.

Recommendations:

Clarinex-D 24 QD was shown to be effective in the relief of overall nasal/non-nasal symptom, based on patients' prior-12-hours symptom scores. However, such an effect may not last up to 24 hours.

Clarinex-D 24 AF QD did not show statistical superiority to placebo in the relief of nasal/non-nasal symptoms, excluding nasal congestion. Note that its decongestant effect (in relieving nasal stuffiness/congestion) was shown to be statistically significant.

Overall, Clarinex-D 24 formulation, administrated QD, is recommended for approval.

INTRODUCTION

OVERVIEW

Loratadine (Claritin) is marketed in the United States for the treatment of symptoms of seasonal allergic rhinitis (SAR). Loratadine, as D-12 and D-24 tablets, is also marketed in the United States and internationally containing immediate-release loratadine and sustained-release pseudoephedrine (PSE) also for the treatment of SAR. Here, pseudoephedrine (PSE) is an established sympathomimetic nasal decongestant.

This proposed drug, Clarinex-D 24, is a combination of desloratadine – an active metabolite of loratadine – 5.0-mg, in an immediate-release coating, and pseudoephedrine sulfate 240-mg in a sustained-release matrix formulation designed for once daily dosing (QD). Based on its antihistaminic activity, the DL component can be expected to reduce mainly sneezing, nasal discharge, nasal itching, and non-nasal symptoms. Based on its sympathomimetic activity, PSE can be expected to reduce nasal congestion and stuffiness.

Clarinex-D in two formulations, DL and DL AF, is proposed to be indicated for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older. The purpose of this review is to evaluate the effectiveness of this drug based on evidence submitted by the sponsor, Schering Corporation, in the NDA 21-605 dated April 30, 2004.

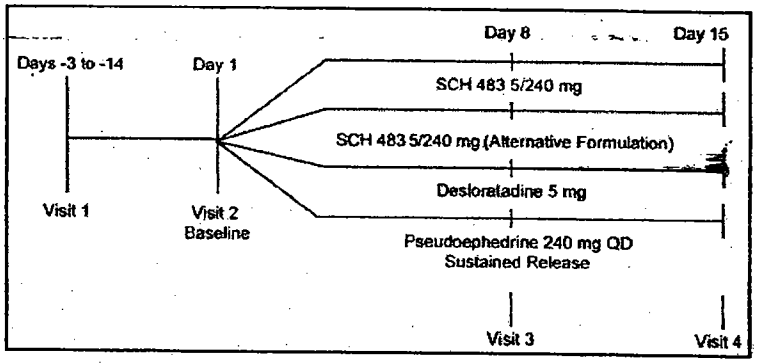
Scope of Statistical Review: Pivotal Efficacy Studies

To demonstrate the effectiveness of the drug, the sponsor submitted two pivotal studies: Studies P01875 and P01884. These studies had the same design.

Studies P01875 and P01884 for Patients Aged 12 and Older

Studies P01875 and P01884 were phase III double-blind, placebo-controlled, parallel-group, multi-center studies. The treatment was administrated QD for 15 days. The time line of the studies is shown in Figure 1.

Figure 1 Study Time Line (Studies P01875 and P01884)



At Visit 2, the patient was randomly assigned to one of the following treatments included in Table 5.

Table 5 Treatments (Studies P01875 and P01884)

Treatment described as…	Treatment denoted using code by reviewer as…
DL D24	A
DL D24 (AF)	B
DL (desloratadine) 5mg	C
PSE (pseudoephedrine) 240mg	D

The statistical conclusions are primarily based on the analysis of the pre-specified primary efficacy variables. Because of the dual major effects of the drug specified in the study protocol,

- The primary efficacy variable for the antihistamine effect was defined as the mean AM/PM PRIOR 12 HOURS' total symptom score, excluding nasal congestion, expressed as a change from Baseline.
- The primary efficacy variable for the decongestant effect was the mean AM/PM PRIOR 12 HOURS' nasal stuffiness/congestion score.

The mean scores, above, represent the average values over the 15-day treatment period. The method of LOCF was NOT used to impute missing observations. If individual-symptom scores were missing, then the total symptom score was calculated only using the non-missing observations.

DATA SOURCES

The sponsor submitted this NDA including the data to the FDA Electronic Document Room (EDR). The submission is recorded in the EDR as indicated in Table 6, below. All the data submitted are in SAS v.5 transport format. The number of data files for the pivotal studies and the number of data files used in the statistical review are shown in Table 7.

Table 6 Data Source

Document: 2385314		
Application: N021605	Letter Date: 30-Apr-2004	Stamp Date: 3-May-2004
Incoming Doc Type: N	Sup Modification Type:	In Doc Type Seq No: 000
Company: SCHERING		
Drug: CLARINEX D24		

Source: EDR of FDA

Table 7 Sponsor's Data Submitted

Path/location	No. data files submitted	No. data files used in statistical review
\\cdsesub1\N21605\N_000\2004-04-30\Clinical Data\P01875\DATA	21	1
\\cdsesub1\N21605\N_000\2004-04-30\Clinical Data\P01884\DATA	21	1

The numbers of data files used in the statistical evaluation are shown in the third column. Given the large amount of data, this reviewer selected the file(s) containing the most relevant evidence for the efficacy of the drug.

STATISTICAL EVALUATION

EVALUATION OF EFFICACY

Study Design and Endpoints

The evaluation of the effectiveness and safety is based on Studies P01875 and P01884. These studies were Phase-III, randomized, parallel-group, multi-center, double-blind, and double-dummy studies. The efficacy claim of Clarinex-D was tested by comparing each of the combination formulations with its components:

- The antihistamine effect was tested by comparing DL D-24 or DL D-24 AF against PSE.
- The decongestant effect was tested by comparing DL D-24 or DL D-24 AF against DL.

The statistical conclusions are primarily based on the analysis of the pre-specified primary efficacy variables. Because there were two major effects of interest, according to the study objectives, two primary efficacy variables are defined:

- The primary efficacy variable for the antihistamine effect was defined as the mean AM/PM PRIOR 12 HOURS' total symptom score, excluding nasal congestion, expressed as a change from Baseline.
- The primary efficacy variable for the decongestant effect was the mean AM/PM PRIOR 12 HOURS' nasal stuffiness/congestion score.

The mean scores, above, represent the average values over the 15-day treatment period.

Patient Disposition, Demographic and Baseline Characteristics

This section focuses on descriptions of patients' dispositions based on status of completion, status of compliance, and reasons for early withdrawal.

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Study P01875

The ITT patient group comprised all randomized patients. The sponsor stated, "All analyses and summaries of safety data were based on all randomized subjects (intent-to-treat principle) (page 64, section 11.1., P01875.pdf)."

Table 8 Patient accountability by validity and treatment (Study P01875)

	Treatment			
	DL D-24 QD	DL D-24 AF QD	DL 5 mg QD	PSE 240 mg QD
#Patients randomized (ITT)	372	374	372	377
#Patients valid for analysis	372	368	369	372
#Patients Invalid for analysis	0	6	3	5

Table 8 shows the number of ITT patients and those determined invalid for analysis. The "invalid" patients comprise those who did not have baseline values and those whose total symptom scores could not be computed because of missing individual symptom scores.

Table 9 Patient accountability by completeness and treatment (Study P01875)

Number (%) of Subjects								
	DL D-24 QD		DL D-24 AF QD		DL 5 mg QD		PSE 240 mg QD	
Number Randomized	372	(100)	374	(100)	372	(100)	377	(100)
Number (%) Completed	351	(94.4)	344	(92.0)	346	(93.0)	350	(92.8)
Number (%) Discontinued	21	(5.6)	30	(8.0)	26	(7.0)	27	(7.2)
Reason for Discontinuation								
Adverse Event	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	(0.5)	2	(0.5)	3	(0.8)
Did Not Wish to Continue	2	(0.5)	1	(0.3)	1	(0.3)	2	(0.5)
Administrative	0		2	(0.5)	0		1	(0.3)

Source: page 63, Table 8, Section 10.1, P01875.pdf

The percentages of discontinued patients account for no more than 8% of the total in the same treatment group, and the percentages are quite balanced across the treatment groups.

The following tables analyze patients' demographic characteristics by race, sex, and age.

Table 10 Number of patients by treatment and race (Study P01875)

	Race						Total
	CAUCASIAN	BLACK	AMERICAN INDIAN	ASIAN	HISPANIC	OTHER	
A	287	42	1	11	29	2	372
B	298	34	0	11	22	3	368
C	296	45	1	3	24	0	369
D	289	38	0	4	35	6	372
Total	1,170	159	2	29	110	11	1,481

Table 11 Number of patients by treatment and sex (Study P01875)

	Sex		Total
	Female	Male	
A	221	151	372
B	250	118	368
C	243	126	369
D	243	129	372
Total	957	524	1,481

Table 12 Patient-age distributions (Study P01875)

	#PATIENT	Lower quartile	Median	Mean	Upper quartile	Min	Max	Range	Std
A	372	22.0	33.0	33.8	44.0	12.0	78.0	66.0	13.5
B	368	23.0	33.0	33.7	43.0	12.0	74.0	62.0	13.2
C	369	25.0	36.0	35.0	44.0	12.0	76.0	64.0	13.3
D	372	25.0	36.0	35.5	45.0	12.0	70.0	58.0	13.0

Table 13 Baseline mean scores (Study P01875)

	Baseline total score	Baseline total score w/o nasal stuffiness/congestion	Baseline nasal stuffiness/congestion
A	17.7	15.1	2.6
B	17.6	15.0	2.6
C	17.4	14.8	2.6
D	17.7	15.2	2.6

The baseline average scores are considered balanced across the treatment groups.

Study P01884

The ITT patient group comprised all randomized patients. The sponsor stated, "All analyses and summaries of safety data were based on all randomized subjects (intent-to-treat principle) (page 63, section 11.1., P01884.pdf)."

Table 14 Patient accountability by validity and treatment (Study P01884)

	Treatment			
	DL D-24 QD	DL D-24 AF QD	DL 5 mg QD	PSE 240 mg QD
#Patients randomized (ITT)	336	338	340	342
#Patients valid for analysis	333	338	337	337
#Patients Invalid for analysis	3	0	3	5

Table 14 shows the number of ITT patients and those determined invalid for analysis. The "invalid" patients comprise those who did not have baseline values and those whose total symptom scores could not be computed because of missing individual symptom scores.

Table 15 Patient accountability by completeness and treatment (Study P01884)

Number (%) of Subjects								
	DL D-24 QD		DL D-24 AF QD		DL 5 mg QD		PSE 240 mg QD	
Number Randomized	336	(100)	339	(100)	340	(100)	342	(100)
Number (%) Completed	314	(93.5)	319	(94.1)	325	(95.6)	316	(92.4)
Number (%) Discontinued	22	(6.5)	20	(5.9)	15	(4.4)	26	(7.6)
Reason for Discontinuation								
Adverse Event	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)
Did Not Wish to Continue	1	(0.3)	0		2	(0.6)	0	
Administrative	0		1	(0.3)a	0		0	

Source: page 61, Table 8, Section 10.1, P01884.pdf

The percentages of discontinued patients account for no more than 6.5% of the total in the same treatment group, and the percentages are quite balanced across the treatment groups.

The following tables analyze patients' demographic characteristics by race, sex, and age.

Table 16 Number of patients by treatment and race (Study P01884)

	Race						Total
	CAUCASIAN	BLACK	AMERICAN INDIAN	ASIAN	HISPANIC	OTHER	
A	261	33	0	8	28	3	333
B	272	26	0	9	27	4	338
C	251	40	1	13	30	2	337
D	287	20	1	7	20	2	337
Total	1,071	119	2	37	105	11	1,345

Table 17 Number of patients by treatment and sex (Study P01884)

	Sex		Total
	Female	Male	
A	211	122	333
B	202	136	338
C	202	135	337
D	218	119	337
Total	833	512	1,345

Table 18 Patient-age distributions (Study P01884)

	#PATIENT	Lower quartile	Median	Mean	Upper quartile	Min	Max	Range	Std
A	333	23.0	35.0	34.1	44.0	12.0	69.0	57.0	13.7
B	338	23.0	33.0	33.0	42.0	12.0	78.0	66.0	13.7
C	337	24.0	35.0	34.7	44.0	11.0	74.0	63.0	13.7
D	337	24.0	33.0	34.3	44.0	12.0	76.0	64.0	13.8

Table 19 Baseline mean scores (Study P01884)

	Baseline total score	Baseline total score w/o nasal stuffiness/congestion	Baseline nasal stuffiness/congestion
A	17.5	14.9	2.6
B	17.6	15.1	2.6
C	17.7	15.1	2.6
D	17.7	15.1	2.6

The baseline average scores are considered balanced across the treatment groups.

Statistical Methodologies

Studies P01875 and P01884

The sponsor applied ANOVA on the primary efficacy variables:

- The primary efficacy variable for the antihistamine effect was defined as the mean AM/PM PRIOR 12 HOURS' total symptom score, excluding nasal congestion, expressed as a change from Baseline.
- The primary efficacy variable for the decongestant effect was the mean AM/PM PRIOR 12 HOURS' nasal stuffiness/congestion score.

The statistical method was described in the following quotes from the application:

> "The primary efficacy variable for the antihistamine effect was defined as the mean AM/PM PRIOR 12 HOURS total symptom score, excluding nasal congestion, expressed as a change from Baseline. The primary efficacy variable for the decongestant effect was the mean AM/PM PRIOR 12 HOURS nasal stuffiness/congestion score. The total symptom score (minus nasal congestion) was the sum of 7 individual symptom scores: 3 nasal and 4 non-nasals. The 3 nasal symptoms were rhinorrhea, nasal itching, and sneezing. The 4 non-nasal symptoms were itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate. The primary efficacy time point was the average over the entire 15-day treatment period.
>
> The primary variables at the above time point were to be analyzed using a two-way analysis of variance (ANOVA), which extracted sources of variation due to treatment and center. For each combination drug, DL D-24 or DL D-24 AF, comparisons of each effect against its components were performed. The primary comparison for the antihistamine component was DL D-24 or DL D-24 AF versus PSE. The primary comparison for the decongestant component was DL D-24 or DL D-24 AF versus DL. These comparisons were to be obtained from the two-way ANOVA model described above.
>
> Each combination, DL D-24 or DL D-24 AF, was to be considered superior to its components independently if, and only if, the comparisons on both the antihistamine and decongestant effects showed a significant improvement over the components as described above (page 51, section 9.7.1.3.2., P01884.pdf)."

Statistical Analyses

The main focus of this reviewer's statistical analysis is to confirm the sponsor's analyses specified in the protocol. This reviewer uses the sponsor's data and analyzes them based on the 15-day mean AM/PM PRIOR 12 HOURS' total and individual nasal and non-nasal symptom scores.

Study P01875

This reviewer verified the sponsor's reported analysis and determined the results to be valid and accurate. The reviewer's analysis results are show in the following tables.

Table 20 Number of patients by treatment (Study P01875)

Time Interval	#Patients in Treatment A	#Patients in Treatment B	#Patients in Treatment C	#Patients in Treatment D
Baseline	372	368	369	372
Day 1	367	361	364	363
Day 2	371	366	367	370
Day 3	370	364	365	368
Day 4	370	362	365	368
Days 1-8	372	368	369	372
Days 9-15	357	353	355	355
Days 1-15	372	368	369	372

Analysis of antihistaminic effect of Clarinex-D 24

Table 21 Unadjusted mean of total symptom score (excluding nasal congestion) (Study P01875)

Time Interval	Mean TOT7 in Treatment A	Mean TOT7 in Treatment B	Mean TOT7 in Treatment C	Mean TOT7 in Treatment D
Baseline	15.12	15.00	14.82	15.17
Day 1	11.75	11.81	12.23	12.33
Day 2	10.39	10.60	11.12	11.37
Day 3	9.67	10.27	10.36	11.14
Day 4	9.45	9.93	10.12	10.59
Days 1-8	9.71	10.05	10.39	10.78
Days 9-15	8.59	8.63	9.33	9.52
Days 1-15	9.22	9.43	9.90	10.25

Table 22 Mean change from baseline of total symptom score (excluding nasal congestion): Unadjusted and LS means compared (Study P01875)

Time Interval	Mean TOT7 chg from baseline in Treatment A	Mean TOT7 chg from baseline in Treatment B	Mean TOT7 chg from baseline in Treatment C	Mean TOT7 chg from baseline in Treatment D	LS Mean of TOT7C for Treatment A	LS Mean of TOT7C for Treatment B	LS Mean of TOT7C for Treatment C	LS Mean of TOT7C for Treatment D
Baseline	.	.	.	.	15.01	14.88	14.71	15.08
Day 1	-3.35	-3.17	-2.58	-2.85	-3.32	-3.14	-2.54	-2.86
Day 2	-4.72	-4.39	-3.71	-3.80	-4.85	-4.53	-3.82	-3.92
Day 3	-5.46	-4.72	-4.45	-4.03	-5.60	-4.84	-4.58	-4.16
Day 4	-5.68	-5.06	-4.69	-4.57	-5.87	-5.24	-4.88	-4.76
Days 1-8	-5.41	-4.94	-4.43	-4.39	-5.57	-5.09	-4.58	-4.54
Days 9-15	-6.61	-6.36	-5.52	-5.60	-6.86	-6.56	-5.72	-5.80
Days 1-15	-5.90	-5.57	-4.92	-4.92	-6.09	-5.74	-5.10	-5.08

Table 23 Mean percent change of total symptom score from baseline (excluding nasal congestion) (Study P01875)

Time Interval	Mean pct chg of TOT7 from baseline in Treatment A	Mean pct chg of TOT7 from baseline in Treatment B	Mean pct chg of TOT7 from baseline in Treatment C	Mean pct chg of TOT7 from baseline in Treatment D
Baseline	.	.	.	.
Day 1	-21.9	-21.1	-17.6	-18.8
Day 2	-31.1	-29.5	-25.2	-25.1
Day 3	-35.9	-31.6	-30.3	-26.6
Day 4	-37.3	-33.8	-31.7	-30.4
Days 1-8	-35.6	-33.0	-30.1	-29.0
Days 9-15	-43.3	-42.5	-37.4	-36.9
Days 1-15	-38.8	-37.2	-33.5	-32.4

Table 24 ANOVA on change of total symptom score (excluding nasal congestion) from baseline (Study P01875)

Time Interval	P-Value: Grope A vs. Grope B	P-Value: Grope A vs. Grope C	P-Value: Grope A vs. Grope D	P-Value: Grope B vs. Grope C	P-Value: Grope B vs. Grope D
Baseline	0.525	0.152	0.739	0.428	0.333
Day 1	0.585	0.016	0.153	0.063	0.379
Day 2	0.303	0.001	0.003	0.028	0.056
Day 3	0.023	0.002	0.000	0.443	0.045
Day 4	0.066	0.004	0.001	0.283	0.160
Days 1-8	0.113	0.001	0.001	0.094	0.072
Days 9-15	0.386	0.001	0.002	0.016	0.031
* Days 1-15	0.250	0.001	**0.001**	0.038	**0.033**

* Table 24 indicates that Clarinex-D in formulation D-24 (A) has statistically significant effect of relieving the overall nasal/non-nasal symptom, excluding nasal stuffiness/congestion (compared with D). Such significance was not demonstrated for the formulation D-24 AF (B) because the p-value 0.033 was greater than the significance level of 0.025.

Analysis of decongestant effect of Clarinex-D 24

Table 25 Unadjusted mean of nasal-stuffiness/congestion symptom score (Study P01875)

Time Interval	Mean CSTUF in Treatment A	Mean CSTUF in Treatment B	Mean CSTUF in Treatment C	Mean CSTUF in Treatment D
Baseline	2.58	2.57	2.56	2.56
Day 1	2.01	2.04	2.16	2.07
Day 2	1.83	1.88	2.04	1.90
Day 3	1.74	1.86	1.91	1.88
Day 4	1.72	1.81	1.86	1.89
Days 1-8	1.76	1.83	1.92	1.88
Days 9-15	1.62	1.64	1.76	1.72
Days 1-15	1.70	1.74	1.84	1.82

Table 26 Mean change from baseline of nasal-stuffiness/congestion symptom score: Unadjusted and LS means compared (Study P01875)

Time Interval	Mean CSTUF chg from baseline in Treatment A	Mean CSTUF chg from baseline in Treatment B	Mean CSTUF chg from baseline in Treatment C	Mean CSTUF chg from baseline in Treatment D	LS Mean of CSTUFC for Treatment A	LS Mean of CSTUFC for Treatment B	LS Mean of CSTUFC for Treatment C	LS Mean of CSTUFC for Treatment D
Baseline	.	.	.	.	2.57	2.57	2.55	2.56
Day 1	-0.57	-0.54	-0.40	-0.50	-0.57	-0.54	-0.40	-0.50
Day 2	-0.74	-0.69	-0.52	-0.67	-0.76	-0.71	-0.54	-0.68
Day 3	-0.84	-0.71	-0.64	-0.69	-0.87	-0.73	-0.67	-0.71
Day 4	-0.86	-0.76	-0.70	-0.67	-0.88	-0.78	-0.72	-0.70
Days 1-8	-0.81	-0.74	-0.64	-0.69	-0.84	-0.76	-0.67	-0.71
Days 9-15	-0.97	-0.94	-0.80	-0.84	-1.01	-0.97	-0.84	-0.87
Days 1-15	-0.87	-0.83	-0.71	-0.75	-0.90	-0.86	-0.74	-0.78

Table 27 Mean percent change of nasal-stuffiness/congestion symptom score from baseline (Study P01875)

Time Interval	Mean pct chg of CSTUF from baseline in Treatment A	Mean pct chg of CSTUF from baseline in Treatment B	Mean pct chg of CSTUF from baseline in Treatment C	Mean pct chg of CSTUF from baseline in Treatment D
Baseline	.	.	.	.
Day 1	-21.4	-20.3	-15.7	-19.4
Day 2	-28.3	-26.5	-20.5	-25.7
Day 3	-32.1	-27.2	-25.2	-26.6
Day 4	-32.8	-29.0	-27.1	-25.8
Days 1-8	-31.0	-28.2	-25.1	-26.4
Days 9-15	-37.2	-35.9	-31.4	-31.9
Days 1-15	-33.4	-31.7	-28.0	-28.6

Table 28 ANOVA on change of nasal-stuffiness/congestion symptom score from baseline (Study P01875)

Time Interval	P-Value: Grope A vs. Grope B	P-Value: Grope A vs. Grope C	P-Value: Grope A vs. Grope D	P-Value: Grope B vs. Grope C	P-Value: Grope B vs. Grope D	P-Value: Grope C vs. Grope D
Baseline	0.831	0.450	0.607	0.589	0.765	0.808
Day 1	0.558	0.003	0.248	0.020	0.571	0.076
Day 2	0.346	0.000	0.154	0.002	0.633	0.009
Day 3	0.024	0.001	0.007	0.247	0.675	0.459
Day 4	0.097	0.005	0.001	0.247	0.125	0.706
Days 1-8	0.133	0.000	0.009	0.048	0.271	0.377
Days 9-15	0.525	0.003	0.015	0.017	0.074	0.551
* Days 1-15	0.353	**0.001**	0.009	**0.022**	0.096	0.527

* Table 28 indicates that Clarinex-D in formulations, D-24 (A) and D-24 AF (B), has statistically significant effect of relieving nasal stuffiness/congestion (compared with C).

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Study P01884

This reviewer verified the sponsor's reported analysis and determined the results to be valid and accurate. The reviewer's analysis results are show in the following tables.

Table 29 Number of patients by treatment (Study P01884)

Time Interval	#Patients in Treatment A	#Patients in Treatment B	#Patients in Treatment C	#Patients in Treatment D
Baseline	333	338	337	337
Day 1	326	329	326	324
Day 2	333	335	337	335
Day 3	332	336	333	333
Day 4	327	334	332	333
Days 1-8	333	338	337	337
Days 9-15	317	323	326	321
Days 1-15	333	338	337	337

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Table 30 Unadjusted mean of total symptom score (excluding nasal congestion) (Study P01884)

Time Interval	Mean TOT7 in Treatment A	Mean TOT7 in Treatment B	Mean TOT7 in Treatment C	Mean TOT7 in Treatment D
Baseline	14.94	15.05	15.15	15.15
Day 1	11.63	12.00	12.71	12.72
Day 2	10.43	10.87	11.42	11.79
Day 3	9.87	10.46	10.98	11.29
Day 4	9.74	9.97	10.60	11.05
Days 1-8	9.85	10.26	10.87	11.01
Days 9-15	8.66	8.91	10.00	9.74
Days 1-15	9.35	9.67	10.47	10.30

Table 31 Mean change from baseline of total symptom score (excluding nasal congestion): Unadjusted and LS means (Study P01884)

Time Interval	Mean TOT7 chg from baseline in Treatment A	Mean TOT7 chg from baseline in Treatment B	Mean TOT7 chg from baseline in Treatment C	Mean TOT7 chg from baseline in Treatment D	LS Mean of TOT7C for Treatment A	LS Mean of TOT7C for Treatment B	LS Mean of TOT7C for Treatment C	LS Mean of TOT7C for Treatment D
Baseline	.	.	.	.	14.84	14.95	15.06	15.03
Day 1	-3.32	-3.03	-2.46	-2.43	-3.26	-2.97	-2.42	-2.38
Day 2	-4.52	-4.16	-3.73	-3.38	-4.57	-4.21	-3.78	-3.42
Day 3	-5.08	-4.57	-4.14	-3.87	-5.20	-4.70	-4.25	-3.97
Day 4	-5.21	-5.07	-4.51	-4.13	-5.33	-5.19	-4.62	-4.23
Days 1-8	-5.10	-4.79	-4.28	-4.14	-5.21	-4.90	-4.37	-4.23
Days 9-15	-6.26	-6.11	-5.15	-5.71	-6.38	-6.25	-5.28	-5.84
Days 1-15	-5.59	-5.38	-4.68	-4.85	-5.71	-5.50	-4.78	-4.95

Table 32 Mean percent change of total symptom score from baseline (excluding nasal congestion) (Study P01884)

Time Interval	Mean pct chg of TOT7 from baseline in Treatment A	Mean pct chg of TOT7 from baseline in Treatment B	Mean pct chg of TOT7 from baseline in Treatment C	Mean pct chg of TOT7 from baseline in Treatment D
Baseline	.	.	.	.
Day 1	-21.7	-19.9	-16.0	-15.8
Day 2	-30.0	-27.9	-24.5	-22.1
Day 3	-33.8	-30.4	-27.2	-25.5
Day 4	-34.8	-33.7	-29.7	-27.2
Days 1-8	-34.0	-31.8	-28.1	-27.3
Days 9-15	-42.2	-40.8	-33.9	-37.7
Days 1-15	-37.4	-35.8	-30.8	-32.0

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Table 33 ANOVA on change of total symptom score (excluding nasal congestion) from baseline (Study P01884)

Time Interval	P-Value: Grope A vs. Grope B	P-Value: Grope A vs. Grope C	P-Value: Grope A vs. Grope D	P-Value: Grope B vs. Grope C	P-Value: Grope B vs. Grope D
Baseline	0.604	0.310	0.370	0.617	0.703
Day 1	0.389	0.014	0.009	0.107	0.080
Day 2	0.275	0.016	0.000	0.188	0.015
Day 3	0.143	0.006	0.000	0.197	0.036
Day 4	0.701	0.042	0.002	0.097	0.006
Days 1-8	0.325	0.007	0.002	0.085	0.028
Days 9-15	0.715	0.002	0.130	0.006	0.247
* Days 1-15	0.498	0.003	0.015	0.021	0.076

* Table 33 indicates that Clarinex-D in formulation D-24 (A) has statistically significant effect of relieving the overall nasal/non-nasal symptom, excluding nasal stuffiness/congestion (compared with D). Such significance was not demonstrated for the formulation D-24 AF (B) because the p-value 0.076 was greater than the significance level of 0.025.

Analysis of decongestant effect of Clarinex-D 24

Table 34 Unadjusted mean of nasal-stuffiness/congestion symptom score (Study P01884)

Time Interval	Mean CSTUF in Treatment A	Mean CSTUF in Treatment B	Mean CSTUF in Treatment C	Mean CSTUF in Treatment D
Baseline	2.57	2.59	2.59	2.56
Day 1	1.97	2.05	2.14	2.08
Day 2	1.85	1.95	2.07	2.02
Day 3	1.81	1.90	2.00	1.94
Day 4	1.79	1.81	1.96	1.94
Days 1-8	1.80	1.87	1.99	1.96
Days 9-15	1.64	1.69	1.88	1.75
Days 1-15	1.73	1.79	1.94	1.86

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Table 35 Mean change from baseline of nasal-stuffiness/congestion symptom score: Unadjusted and LS means compared (Study P01884)

Time Interval	Mean CSTUF chg from baseline in Treatment A	Mean CSTUF chg from baseline in Treatment B	Mean CSTUF chg from baseline in Treatment C	Mean CSTUF chg from baseline in Treatment D	LS Mean of CSTUFC for Treatment A	LS Mean of CSTUFC for Treatment B	LS Mean of CSTUFC for Treatment C	LS Mean of CSTUFC for Treatment D
Baseline	.	.	.	.	2.56	2.58	2.57	2.54
Day 1	-0.60	-0.55	-0.44	-0.48	-0.59	-0.53	-0.43	-0.47
Day 2	-0.72	-0.64	-0.52	-0.54	-0.74	-0.65	-0.53	-0.55
Day 3	-0.77	-0.69	-0.58	-0.62	-0.79	-0.71	-0.60	-0.63
Day 4	-0.79	-0.78	-0.62	-0.62	-0.82	-0.81	-0.65	-0.64
Days 1-8	-0.78	-0.72	-0.59	-0.60	-0.79	-0.74	-0.61	-0.62
Days 9-15	-0.93	-0.90	-0.70	-0.81	-0.94	-0.90	-0.71	-0.81
Days 1-15	-0.84	-0.80	-0.64	-0.70	-0.85	-0.81	-0.65	-0.70

Table 36 Mean percent change of nasal-stuffiness/congestion symptom score from baseline (Study P01884)

Time Interval	Mean pct chg of CSTUF from baseline in Treatment A	Mean pct chg of CSTUF from baseline in Treatment B	Mean pct chg of CSTUF from baseline in Treatment C	Mean pct chg of CSTUF from baseline in Treatment D
Baseline	.	.	.	.
Day 1	-22.9	-21.0	-16.6	-18.5
Day 2	-27.7	-25.0	-19.7	-20.9
Day 3	-29.2	-26.7	-22.3	-24.4
Day 4	-30.0	-30.2	-23.9	-24.3
Days 1-8	-29.5	-27.9	-22.8	-23.5
Days 9-15	-36.0	-34.6	-27.1	-31.3
Days 1-15	-32.3	-30.8	-24.8	-27.1

Table 37 ANOVA on change of nasal-stuffiness/congestion symptom score from baseline (Study P01884)

Time Interval	P-Value: Grope A vs. Grope B	P-Value: Grope A vs. Grope C	P-Value: Grope A vs. Grope D	P-Value: Grope B vs. Grope C	P-Value: Grope B vs. Grope D	P-Value: Grope C vs. Grope D
Baseline	0.59388	0.67727	0.53140	0.90684	0.24532	0.29621
Day 1	0.35381	0.00934	0.05153	0.09359	0.30585	0.51531
Day 2	0.11888	0.00018	0.00068	0.02814	0.06387	0.73653
Day 3	0.20030	0.00102	0.00726	0.04355	0.15589	0.55242
Day 4	0.86245	0.00341	0.00271	0.00552	0.00442	0.93694
Days 1-8	0.24750	0.00016	0.00025	0.00855	0.01152	0.92124
Days 9-15	0.54684	0.00004	0.02977	0.00046	0.11362	0.05543
* Days 1-15	0.34272	0.00004	0.00202	0.00135	0.03130	0.29376

* Table 37 indicates that Clarinex-D in formulations, D-24 (A) and D-24 AF (B), has statistically significant effect of relieving nasal stuffiness/congestion (compared with C).

FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Analysis Based On Instantaneous Symptom Scores:

In the following analyses, this reviewer uses the sponsor's data and analyzes them based on the 15-day mean AM total and individual nasal and non-nasal symptom scores. Using these data, this reviewer can analyze the drug effect at the end of dosing period, approximate 24 hours after dosing, before taking the next dose.

Study P0175

Analysis of antihistaminic effect of Clarinex-D 24

Table 38 Mean percent change of 15-day mean AM NOW (instantaneous) total symptom scores from baseline (excluding nasal congestion) (Study P01875)

Time Interval	Mean TOT7 chg from baseline in Treatment A	Mean TOT7 chg from baseline in Treatment B	Mean TOT7 chg from baseline in Treatment C	Mean TOT7 chg from baseline in Treatment D	LS Mean of TOT7C for Treatment A	LS Mean of TOT7C for Treatment B	LS Mean of TOT7C for Treatment C	LS Mean of TOT7C for Treatment D
Baseline	.	.	.	.	14.65	14.73	14.61	14.79
Day 2	-3.90	-3.80	-2.89	-2.89	-3.98	-3.85	-2.93	-2.97
Day 3	-4.90	-4.20	-3.68	-3.35	-5.01	-4.29	-3.78	-3.44
Day 4	-5.04	-4.38	-3.79	-3.79	-5.16	-4.50	-3.89	-3.93
Days 2-8	-4.99	-4.58	-3.94	-3.86	-5.11	-4.68	-4.04	-3.97
Days 9-15	-6.00	-5.83	-5.08	-5.08	-6.20	-5.97	-5.23	-5.24
Days 2-15	-5.43	-5.19	-4.49	-4.43	-5.57	-5.31	-4.61	-4.56

Table 39 ANOVA on change of 15-day mean AM NOW (instantaneous) total symptom score (excluding nasal congestion) from baseline (Study P01875)

Time Interval	P-Value: Grope A vs. Grope B	P-Value: Grope A vs. Grope C	P-Value: Grope A vs. Grope D	P-Value: Grope B vs. Grope C	P-Value: Grope B vs. Grope D	P-Value: Grope C vs. Grope D
Baseline	0.718	0.871	0.535	0.602	0.796	0.435
Day 2	0.684	0.001	0.002	0.005	0.007	0.892
Day 3	0.042	0.001	0.000	0.157	0.017	0.339

Time Interval	P-Value: Grope A vs. Grope B	P-Value: Grope A vs. Grope C	P-Value: Grope A vs. Grope D	P-Value: Grope B vs. Grope C	P-Value: Grope B vs. Grope D	P-Value: Grope C vs. Grope D
Day 4	0.069	0.000	0.001	0.091	0.111	0.926
Days 2-8	0.180	0.001	0.000	0.045	0.026	0.823
Days 9-15	0.537	0.007	0.008	0.039	0.041	0.987
* Days 2-15	0.409	0.003	**0.001**	0.029	**0.018**	0.863

* Table 39 indicates that Clarinex-D in both formulations D-24 (A) and D-24 AF (B) has statistically significant effect of relieving the overall nasal/non-nasal symptom, excluding nasal stuffiness/congestion (compared with D).

Analysis of decongestant effect of Clarinex-D 24

Table 40 Mean percent change of 15-day mean AM NOW (instantaneous) nasal-stuffiness/congestion symptom score from baseline (Study P01875)

Time Interval	Mean CSTUF chg from baseline in Treatment A	Mean CSTUF chg from baseline in Treatment B	Mean CSTUF chg from baseline in Treatment C	Mean CSTUF chg from baseline in Treatment D	LS Mean of CSTUFC for Treatment A	LS Mean of CSTUFC for Treatment B	LS Mean of CSTUFC for Treatment C	LS Mean of CSTUFC for Treatment D
Baseline	.	.	.	.	2.55	2.57	2.57	2.58
Day 2	-0.61	-0.55	-0.40	-0.50	-0.60	-0.54	-0.39	-0.49
Day 3	-0.71	-0.61	-0.47	-0.57	-0.73	-0.63	-0.49	-0.59
Day 4	-0.77	-0.58	-0.46	-0.58	-0.79	-0.61	-0.49	-0.60
Days 2-8	-0.73	-0.63	-0.52	-0.59	-0.75	-0.65	-0.54	-0.61
Days 9-15	-0.84	-0.81	-0.69	-0.76	-0.88	-0.84	-0.72	-0.79
Days 2-15	-0.77	-0.71	-0.60	-0.67	-0.80	-0.74	-0.63	-0.69

Table 41 ANOVA on change of 15-day mean AM NOW (instantaneous) nasal-stuffiness/congestion symptom score from baseline (Study P01875)

Time Interval	P-Value: Grope A vs. Grope B	P-Value: Grope A vs. Grope C	P-Value: Grope A vs. Grope D	P-Value: Grope B vs. Grope C	P-Value: Grope B vs. Grope D	P-Value: Grope C vs. Grope D
Baseline	0.5067	0.5225	0.3271	0.9810	0.7534	0.7354
Day 2	0.2959	0.0005	0.0617	0.0143	0.4133	0.1010

Day 3	0.1328	0.0002	0.0359	0.0302	0.5558	0.1130
Day 4	0.0055	0.0000	0.0033	0.0528	0.8821	0.0726
Days 2-8	0.0578	0.0001	0.0113	0.0419	0.5264	0.1598
Days 9-15	0.5218	0.0048	0.1258	0.0295	0.3749	0.1965
* Days 2-15	0.2491	0.0009	0.0400	0.0297	0.3692	0.1998

* Table 41 indicates that Clarinex-D in formulation D-24 (A) has statistically significant effect of relieving nasal stuffiness/congestion (compared with C). Such significance was not demonstrated for the formulation D-24 AF (B) because the p-value 0.0297 was greater than the significance level of 0.025.

Study P01884

Analysis of antihistaminic effect of Clarinex-D 24

Table 42 Mean percent change of 15-day mean AM NOW (instantaneous) total symptom scores from baseline (excluding nasal congestion) (Study P01884)

Time Interval	Mean TOT7 chg from baseline in Treatment A	Mean TOT7 chg from baseline in Treatment B	Mean TOT7 chg from baseline in Treatment C	Mean TOT7 chg from baseline in Treatment D	LS Mean of TOT7C for Treatment A	LS Mean of TOT7C for Treatment B	LS Mean of TOT7C for Treatment C	LS Mean of TOT7C for Treatment D
Baseline	.	.	.	.	14.76	14.86	14.93	15.14
Day 2	-3.52	-3.59	-2.99	-2.96	-3.59	-3.66	-3.03	-3.04
Day 3	-4.60	-3.86	-3.43	-3.46	-4.76	-4.05	-3.57	-3.62
Day 4	-4.53	-4.33	-3.74	-3.43	-4.74	-4.56	-3.92	-3.62
Days 2-8	-4.60	-4.30	-3.82	-3.69	-4.79	-4.51	-3.98	-3.87
Days 9-15	-5.71	-5.53	-4.77	-5.24	-5.95	-5.81	-5.01	-5.48
Days 2-15	-5.11	-4.88	-4.28	-4.44	-5.34	-5.12	-4.48	-4.64

Table 43 ANOVA on change of 15-day mean AM NOW (instantaneous) total symptom score (excluding nasal congestion) from baseline (Study P01884)

Time Interval	P-Value: Grope A vs. Grope B	P-Value: Grope A vs. Grope C	P-Value: Grope A vs. Grope D	P-Value: Grope B vs. Grope C	P-Value: Grope B vs. Grope D	P-Value: Grope C vs. Grope D
Baseline	0.6638	0.4758	0.1096	0.7801	0.2416	0.3719
Day 2	0.8352	0.0962	0.1040	0.0614	0.0668	0.9711

Day 3	0.0498	0.0010	0.0018	0.1840	0.2392	0.8854
Day 4	0.6173	0.0244	0.0022	0.0776	0.0098	0.4148
Days 2-8	0.3667	0.0107	0.0036	0.0974	0.0433	0.7116
Days 9-15	0.6990	0.0094	0.1929	0.0264	0.3566	0.1962
* Days 2-15	0.5014	0.0076	**0.0287**	0.0448	**0.1278**	0.6325

* Table 43 indicates that Clarinex-D in **neither** formulation has statistically significant effect of relieving the overall nasal/non-nasal symptom, excluding nasal stuffiness/congestion (compared with D), because the p-values 0.0287 and 0.1278 were greater than the significance level of 0.025.

Analysis of decongestant effect of Clarinex-D 24

Table 44 Mean percent change of 15-day mean AM NOW (instantaneous) nasal-stuffiness/congestion symptom score from baseline (Study P01884)

Time Interval	Mean CSTUF chg from baseline in Treatment A	Mean CSTUF chg from baseline in Treatment B	Mean CSTUF chg from baseline in Treatment C	Mean CSTUF chg from baseline in Treatment D	LS Mean of CSTUFC for Treatment A	LS Mean of CSTUFC for Treatment B	LS Mean of CSTUFC for Treatment C	LS Mean of CSTUFC for Treatment D
Baseline	.	.	.	.	2.56	2.58	2.57	2.58
Day 2	-0.56	-0.55	-0.37	-0.46	-0.57	-0.56	-0.38	-0.47
Day 3	-0.64	-0.51	-0.43	-0.47	-0.66	-0.53	-0.45	-0.49
Day 4	-0.63	-0.62	-0.54	-0.46	-0.67	-0.66	-0.57	-0.50
Days 2-8	-0.65	-0.60	-0.50	-0.48	-0.67	-0.63	-0.52	-0.51
Days 9-15	-0.80	-0.77	-0.63	-0.71	-0.83	-0.81	-0.66	-0.74
Days 2-15	-0.72	-0.68	-0.56	-0.59	-0.75	-0.71	-0.59	-0.61

Table 45 ANOVA on change of 15-day mean AM NOW (instantaneous) nasal-stuffiness/congestion symptom score from baseline (Study P01884)

Time Interval	P-Value: Grope A vs. Grope B	P-Value: Grope A vs. Grope C	P-Value: Grope A vs. Grope D	P-Value: Grope B vs. Grope C	P-Value: Grope B vs. Grope D	P-Value: Grope C vs. Grope D
Baseline	0.5110	0.5868	0.4321	0.9091	0.8958	0.8066
Day 2	0.8553	0.0015	0.0955	0.0027	0.1375	0.1297
Day 3	0.0366	0.0007	0.0069	0.1940	0.5331	0.5016
Day 4	0.9442	0.1159	0.0084	0.1301	0.0096	0.2809
Days 2-8	0.3466	0.0022	0.0009	0.0328	0.0160	0.7782
Days 9-15	0.6260	0.0032	0.0912	0.0133	0.2262	0.2080
* Days 2-15	0.4833	**0.0015**	0.0075	**0.0127**	0.0476	0.6138

* Table 45 indicates that Clarinex-D in both formulations, D-24 (A) and D-24 AF (B) has statistically significant effect of relieving nasal stuffiness/congestion (compared with C).

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Results and Conclusions

Analysis results based on 15-day mean AM/PM PRIOR 12 HOURS (reflective) symptom scores

D-24 was shown (Table 3) to be statistically superior to placebo in reducing the nasal/non-nasal symptoms, based on 15-day mean AM/PM prior 12 hours symptom scores.

However, the formulation, D-24 AF failed to show statistical significance of the relief of the overall nasal/non-nasal symptom, excluding nasal stuffiness/congestion, although statistical significance was shown in relieving nasal stuffiness/congestion. These findings were consistent across the studies. The objective to simultaneously demonstrate the superiority of both antihistamine and decongestant components was not achieved.

Analysis results based on 15-day mean AM NOW (instantaneous) symptom scores

Note that neither formulation has consistently demonstrated significant effect of relieving the overall nasal/non-nasal symptom (excluding nasal congestion).

Clarinex-D in D-24 formulation consistently demonstrated a statistically significant decongestant effect across the two studies. However, such consistency was not seen in the D-24 AF formulation.

SUMMARY AND CONCLUSIONS

Statistical Issues and Collective Evidence

The following table is a summary of the statistical findings of efficacy for the two pivotal studies based on reflective scores.

Table 46 Efficacy findings based on 15-day mean AM/PM PRIOR 12 HOURS symptom scores (Studies P01875 and P01884 compared)

Type of Comparison			P01875	P01884	Findings consistently positive
(A) D-24 vs.	(D) PSE	Antihistamine component (TOT7)	+ P=0.001	+ P=0.015	Yes
	(C) DL	Decongestant component (N4)	+ P=0.001	+ P=0.00004	Yes
(B) D-24 AF vs.	(D) PSE	Antihistamine component (TOT7)	- P=0.033	- P=0.076	No (Consistently Negative)
	(C) DL	Decongestant component (N4)	+ P=0.022	+ P=0.00135	Yes

This table is the same as Table 3.

Clarinex-D formulation, D-24 was shown to be statistically significant in relieving the overall nasal/non-nasal symptom (excluding nasal congestion). However, Clarinex-D formulation, D-24 AF failed to demonstrate a statistically significant effect of relieving the overall nasal/non-nasal symptom (excluding nasal congestion), though statistical significance was found in relieving nasal congestion. These findings were consistent in the two pivotal studies.

Table 47 summaries the statistical findings on efficacy for the two pivotal studies based on instantaneous scores.

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Table 47 Efficacy findings based on 15-day mean AM NOW (instantaneous) symptom scores - (Studies P01875 and P01884 compared)

Type of Comparison			P01875	P01884	Findings consistently positive
(A) D-24 vs.	(D) PSE	Antihistamine component (TOT7)	+ P=0.001	- P=0.0287	No
	(C) DL	Decongestant component (N4)	+ P=0.0009	+ P=0.0015	Yes
(B) D-24 AF vs.	(D) PSE	Antihistamine component (TOT7)	+ P=0.018	- P=0.1278	No
	(C) DL	Decongestant component (N4)	- P=0.0297	+ P=0.0127	No

This table is the same as Table 4.

Note that neither formulation has consistently demonstrated significant effect of relieving nasal/non-nasal symptoms (excluding nasal congestion).

Clarinex-D in D-24 formulation consistently demonstrated a statistically significant decongestant effect across the two studies. However, such consistency was not seen in the D-24 AF formulation.

Overall, **Clarinex-D in formulation D-24** administered QD was shown to be effective in relieving SAR based on prior 12 hours' nasal and non-nasal symptom. However, the effectiveness of **Clarinex-D in formulation D-24 AF** administered QD in relieving the overall nasal/non-nasal symptom (excluding nasal congestion) was not demonstrated, though some effect in reducing nasal congestion alone was consistently shown based on the AM/PM PRIOR 12 HOUR data. Such consistency disappeared when analyzing using the instantaneous data (the AM NOW score).

Conclusions and Recommendations

Efficacy Conclusions:

Consistently across Studies P01875 and P01884, Clarinex-D in formulation D-24 was shown to be statistically superior to placebo in the relief of the overall nasal/non-nasal symptom.

However, Clarinex-D in formulation D-24 AF failed to demonstrate the statistical significance of antihistamine effect in relieving overall nasal/non-nasal symptoms, excluding nasal congestion, though statistical significance was shown in relieving nasal congestion.

These findings were consistent across Studies P01875 and P01884.

Note that, in examining the end-of-dosing effect (the drug effect after 24 hours of taking the first dose) of relieving the overall nasal/non-nasal symptom, excluding nasal congestion, neither formulation demonstrated superiority to placebo consistently across the studies. In examining the end-of-dosing effect, Clarinex-D in D-24 formulation consistently demonstrated a statistically significant decongestant effect across the studies. Such statistically significant decongestant effect was seen in Study P01884 alone.

Recommendations:

Clarinex-D 24 QD was shown to be effective in the relief of the overall nasal/non-nasal symptom, based on patients' prior-12-hours symptom scores. However, such an effect may not last up to 24 hours.

Clarinex-D 24 AF QD did not show statistical superiority to placebo in the relief of nasal/non-nasal symptom, excluding nasal congestion. Note that its decongestant effect (in relieving nasal stuffiness/congestion) was shown to be statistically significant.

Overall, Clarinex-D 24 formulation, administrated QD, is recommended for approval.

DISTRIBUTION LIST

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