

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-313

STATISTICAL REVIEW(S)

**STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES**

Date	September 1, 2001
NDA #	21-313
Applicant	Schering Corporation
Name of Drug	Clarinet-D™ 12 Hour Extended Release Tablets
Indication	Extended release for Seasonal Allergic Rhinitis (SAR) in adults and children ≥ 12 years of age.
Documents Reviewed	• Vol. 1 - Sponsor's cover letter dated December 12, 2000 • Clinical studies: • Vol. 1 (Clinical Data Summary and Results of Statistical Analysis) • Vol. 34 (16.1.1.1 Study P00355 protocol) • Vol. 32 (Study P00355 Clinical Trial Report 6/19/00) • Vol. 39 (16.1.1.1 Study P00362 protocol) • Vol. 36 (Study P00362 Clinical Trial Report 6/19/00) • Vol. 40 (8G-Integrated Summary of Efficacy) • Vol. 41 (8H-Integrated Summary of Safety) EDR Data: \N000\2000-12-08\SAS DATA
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Summary

Clarinet-D™ 12 Hour extended release tablet has been developed as a combination product of desloratadine 2.5 mg and pseudoephedrine 120 mg. The new product, Clarinet-D™ 12 Hour is indicated for the relief of symptoms of seasonal allergic rhinitis in adults and children 12 years of age and older. The proposed dosage of Clarinet-D™ 12 Hour for adults and adolescents aged 12 years and older is 2.5mg/120mg twice daily.

Based on a statistical evaluation of studies P00355 and P00362, this reviewer concludes that the sponsor has presented adequate evidence to demonstrate that Clarinet-D™ 12 Hour is effective in adults and adolescent patients ages 12 years and older.

More specifically, this reviewer has concluded that:

1. The antihistaminic efficacy of DL D-12, as measured by mean AM/PM PRIOR 12 hours total symptom score excluding nasal congestion, was statistically ($p < 0.0013$) superior to PSE over the 15-day treatment period and was observed as early as Day 2 of treatment and afterward.
2. The decongestant efficacy of DL D-12, as measured by mean AM/PM PRIOR 12 hours nasal congestion scores, was statistically ($p < 0.0025$) superior to DL over the 15-day treatment period and was observed as early as Day 2 and afterward.
3. The antihistaminic and decongestant efficacy of DL D-12 at the end of the dosing interval were significantly greater than PSE and DL, respectively, over the 15-day treatment period ($p < 0.015$).

In summary, the sponsor has provided sufficient statistical evidence to demonstrate that Clarinet-D™ 12 Hour is superior to both components for the treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older.

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Introduction

Desloratadine D-12 (DL D-12, or Clarinet-D 12 Hour) is a bilayer combination of immediate-release desloratadine (2.5mg) and pseudoephedrine (120mg) in a sustained release matrix formulation designed for twice-daily dosing. The proposed indication is seasonal allergic rhinitis (SAR) in adults and children 12 years of age and older. Symptoms of SAR are generally classified as nasal (rhinorrhea, nasal congestion, nasal itching, and sneezing) and non-nasal (eye itching, eye tearing, eye redness, and itching of ears and/or palate). Desloratadine, which is an active metabolite of loratadine (Claritin®), is an oral H1-antagonist. Based on this activity, the desloratadine (DL) component is intended to reduce sneezing, rhinorrhea, nasal itching, and non-nasal symptoms associated with SAR. Pseudoephedrine (PSE) is an established oral sympathomimetic nasal decongestant, which reduces nasal congestion associated with SAR. The sponsor, Schering Corporation, asserts that the effects of DL and PSE will be complementary in the treatment of SAR such that the combination tablet will provide greater benefit than either component alone.

Loratadine, the parent compound of DL, is marketed alone and as a combination product with PSE (loratadine D-12 and D-24) for the treatment of SAR. Loratadine D-12, which is comprised of loratadine 5mg and PSE 120mg, is dosed BID. The sponsor states that pharmacokinetic studies have demonstrated that administration of 5mg DL gives the same systemic exposure (plasma AUC) as administration of the marketed dose of 10mg loratadine. Therefore, the sponsor expects that the DL D-12 formulation (DL 2.5mg/ PSE 120mg) for twice-daily administration will be as effective as the loratadine 5mg/PSE 120 mg currently marketed product.

The sponsor intends to demonstrate that desloratadine 2.5mg BID is effective for allergic rhinitis by comparing the effects of DL D-12 versus PSE on the histamine-related symptoms of allergic rhinitis (sneezing, itching, and rhinorrhea).

The sponsor proposes that Clarinet-D™ 12 Hour be approved for the relief of symptoms of seasonal allergic rhinitis in adults and children 12 years of age and older. The proposed dosage of Clarinet-D™ 12 Hour for adults and adolescents aged 12 years and older is 2.5mg/120mg twice daily.

This review evaluates the sponsor's claims that the effects of the DL and the PSE will be complementary in the treatment of SAR such that the combination tablet will provide greater benefit than either component alone.

Overview of the Studies

The sponsor submitted evidence from five phase-II and two phase-III studies to support efficacy and safety claims. **Table 1** summarizes these studies.

Table 1. List of Studies Submitted (p5, vol.1)

Study Number	Location	Phase	Date	Type
P00355	U.S.	III	8/19/99 – 12/11/99	Double-blind active-controlled
P00362	U.S.	III	8/21/98 – 11/29/99	Double-blind active-controlled
P01352	U.S.	II		Open-label 4-way crossover
P00230	U.S.	II		Open-label 4-way crossover
P00446	U.S.	II		Open-label 3-way crossover
P00440	U.S.	II		Open-label 2-way crossover
P00883	U.S.	II		Open-label

Based on a discussion with the medical reviewer, Dr. Eugene J. Sullivan of the Division of Pulmonary and Allergy Drug Products (HFD-570), this reviewer evaluated the statistical evidence presented in the two phase-III studies: P00355 and P00362.

These two-week, randomized, double-blind, double-dummy, active-controlled, parallel group, phase-III studies were conducted in 20 US centers. The primary objective of these studies was to assess the efficacy of DL D-12 BID, a twice-daily bilayer tablet antihistamine/decongestant containing 2.5mg of immediate-release desloratadine (DL 5.0-mg QD) and 120 mg of sustained-release pseudoephedrine (PSE 120-mg BID), compared with its components in patients with seasonal allergic rhinitis (SAR). The secondary objective was to evaluate the safety profile of DL D-12 using the following parameters: patient reported adverse events, electrocardiograms, vital signs evaluations, and laboratory results.

Table 2 highlights the characteristics of these studies.

Table 2. Characteristics of Studies (Studies P00355 & P00362)

Study Dates # Of Center	# Of Patients Age Range (y) Gender	Treatment Arms (# Of Patients)	Design	Duration Of Treatment
Protocol P00355 (pp. 892, vol. 33) Aug. – Dec. 1999 20 centers in US	598 12-76 224M, 374F	DL D-12 BID (200) DL 5.0-mg QD (198) PSE 120-mg BID (200)	Multiple-center Randomized Double-blind Active-controlled Parallel-group	2 weeks
Protocol P00362 (p. 903, vol. 39) Aug. – Nov. 1999 20 centers in US	650 12-78 221M, 429F	DL D-12 BID (214) DL 5.0-mg QD (214) PSE 120-mg BID (222)	Multiple-center Randomized Double-blind Active-controlled Parallel-group	2 weeks

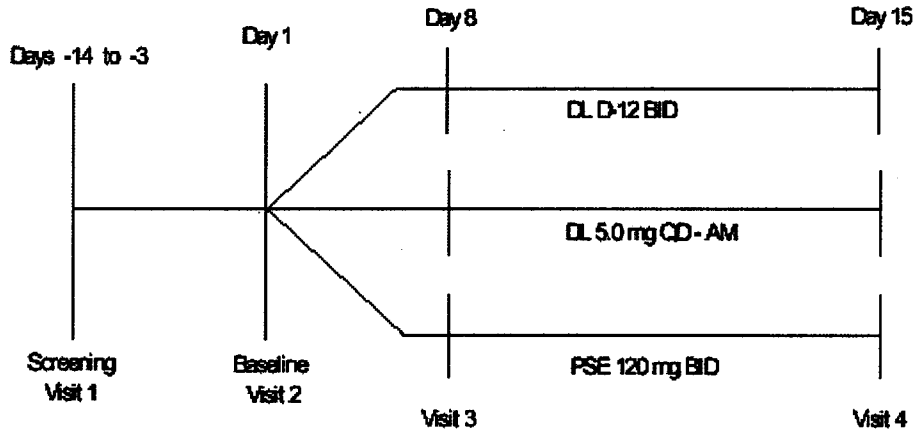
In both of these two studies, the qualified patients for the study were randomly assigned at baseline to one of the following three treatments:

- DL D-12 BID
- DL 5.0-mg QD
- PSE 120-mg BID

The randomization followed a 1:1:1 ratio.

Figure 1 describes the plan of two studies (P.22, Vol.32). During the 3 to 14 day “diary run-in period” (between screening and baseline), patients completed diary cards addressing SAR symptoms, adverse events, and the use of concomitant medications. Both instantaneous and reflective (previous 12 hours) signs and symptoms were recorded in the diary. Symptom severity was scored using a 0-3 scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, and 3=severe symptoms). Diary cards were completed upon arising (before dosing) and approximately 12 hours later (before dosing). Patients who qualified at screening and baseline were randomized and treated with study medication for two weeks.

Figure 1. Design Diagram (Studies P00355 & P00362)



Follow-up visits on Days 8 and 15 (Visits 3 and 4).

To preserve the blinding of the study treatments, a double-dummy technique was used in both studies. Study drugs and matching placebo were identical in appearance. Assigned study drug was to be administered orally twice daily, in the morning and the evening, at approximately the same time each day, without regard for the timing of meals or other daily activities. As shown in **Table 3**, each day's AM dose consisted of two tablets, and each day's PM dose consisted of one tablet.

Table 3. Study Treatment (Studies P00355 & P00362)

Study Treatments	AM Dose	PM Dose
DL D-12 BID*	DL D-12 + DL placebo	DL D-12
DL 5.0 mg QD	DL 5.0 mg + DL D-12 placebo	DL D-12 placebo
PSE 120 mg BID*	PSE 120 mg +DL placebo	PSE 120 mg

* DL D-12 and PSE 120 were identical in appearance.

Each individual symptom score was evaluated each morning and evening. Patients recorded how they felt at the time before taking the next dose (NOW) and over the previous 12 hours (PRIOR 12 hrs.). These evaluations were recorded in daily diaries (AM or PM, as appropriate). For the derived intervals, the corresponding values were averaged over all non-missing days in the interval.

The Sponsor's Analysis of Efficacy

Statistical Methods

The statistical methods for both studies are identical and can be found on page 12 of vol. 1. The primary efficacy variables were analyzed using an analysis of variance (ANOVA) model with factors for TREATMENT and CENTER. The primary comparison for the antihistamine effect [total nasal symptom score (excluding nasal congestion)] was DL D-12 versus PSE and for the decongestant effect [stiffness/nasal congestion] was DL D-12 versus DL. These comparisons were to be obtained from the least square means from the above two-way ANOVA model.

According to the final study report, the sponsor performed separate ANOVAs as listed in **Table 4**

Table 4. List of Statistical Reports (Studies P00355 & P00362)

Efficacy Variables	Comparison	Statistical Model	By Day	By Timepoint
Total Nasal symptom Score (Excluding Nasal Congestion)	DL D-12 vs. PSE	ANOVA Center Treatment	Day 2	AM/PM PRIOR 12 hrs.
			Day 3 Day 4	AM NOW
Stiffness/Congestion Score	DL D-12 vs. DL		Days 1-8	
			Days 9-15 Days 1-15	
Total Nasal symptom Score (Excluding Nasal Congestion)	DL D-12 vs. PSE	ANOVA Center Treatment	Days 1-15	AM/PM NOW
				AM PRIOR PM PRIOR PM NOW
Stiffness/Congestion Score	DL D-12 vs. DL			PM NOW
Individual Symptom Scores	DL D-12 vs. PSE	ANOVA Center Treatment	Baseline	AM/PM NOW
			Days 1-15	AM PRIOR PM PRIOR
	DL D-12 vs. DL			PM NOW

The following points highlight the sponsor's statistical method and analysis setup: (p47-84, vol. 32 & 36)

- **The patient population** used for the sponsor's statistical analyses for efficacy claim was based on the ITT patients. The ITT population was defined as all randomized patients who had baseline plus some post-baseline efficacy data for each variable. As a subgroup, the efficacy-evaluable patients were those randomized patients who met key prespecified eligibility and evaluability criteria. This group of patients was analyzed to confirm and support the efficacy analyses.
- **Comparability of treatment groups at baseline** was to be assessed by comparing the three treatment groups with respect to demographic (sex, age, and race) and disease characteristics (baseline symptom scores) using descriptive statistics.
- **Consistency of results across centers** was to be assessed by examining the center-specific results and the significance of the treatment-by-center interaction for the primary efficacy variable from a two-way analysis of variance (ANOVA) model extracting sources of variation due to treatment, center, and treatment-by-center interaction.
- **The primary efficacy variable** for the antihistamine effect was the change from baseline in mean AM/PM PRIOR 12 hours total symptom score excluding nasal congestion and the primary efficacy variable for the decongestant effect was change from baseline in mean AM/PM PRIOR

Clarinet-D™ 12 Hour Extended Release Tablets, Schering Corporation

12 hours nasal congestion score. The primary efficacy time point was the average over the 2-week treatment period.

- **The secondary efficacy variables** included the total (with nasal congestion), total nasal (with and without nasal congestion), total non-nasal, and individual mean AM/PM PRIOR 12 hours symptom scores expressed as a change from baseline. Additional variables included the overall condition of SAR and evaluation of therapeutic response. At each visit, the investigator and patient evaluated jointly the overall condition of SAR, which was recorded on a scale of 0 (none) to 3 (severe). **The investigator and patient jointly evaluated the patient's response to therapy at Days 8 and 15** by comparing his/her current severity of symptoms with baseline, which was recorded on a scale from 1 (complete relief) to 5 (treatment failure).
- **The sample size** for the primary statistical comparison for the antihistaminic efficacy, DL D-12 with PSE, was 200 evaluable patients per treatment group, a two-tailed alpha-level of 0.05, and a pooled standard deviation of 4.25 points on the change from baseline, differences of 1.6 points or more between treatment groups would be detectable with power of at least 90%. The sample size for the primary statistical comparison of the decongestant efficacy, DL D-12 with DL, was 200 evaluable patients per treatment group. With a two-tailed alpha-level of 0.05, and a pooled standard deviation of 0.6 points on the change from baseline, differences of 0.2 points or more between treatment groups would be detectable with power of at least 90%. With two hundred subjects in each treatment group, the overall power for both comparisons being statistically significant will be at least 88%.
- **Missing data** was handled as following: the total symptom score was defined as the sum of all individual symptom scores. Whenever any of the individual symptom scores was missing, the total score was considered missing. Similarly, the total nasal score was the sum of the 4 nasal symptom scores (rhinorrhea, nasal congestion, nasal itching, and sneezing) and the total non-nasal score was the sum of all non-nasal symptom scores (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate). Each individual symptom score was evaluated each morning and evening. For the derived intervals, the corresponding values were averaged over all non-missing days in the interval.
- **Subgroup analyses** were provided by summary statistics for the primary variables in the following patient subgroups: gender, race (Caucasian, non-Caucasian), and age categories (12 to <18 years, 18 to < 65 years, ≥ 65 years).

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Statistical Results

The following tables present the sponsor's statistical results for the primary variables. (Vol.1, p20 and p21)

Table 4 Total Symptom Score Excluding Nasal Congestion Analysis Results for Primary Endpoint (Days 1-15): Subject-Evaluated Mean AM/PM PRIOR 12 Hours (All Randomized Subjects) (Studies P00355 and P00362)

Treatment Group	Baseline		Change from Baseline (Days 1-15)			DL D-12 Comparison
	N ^a	LS Mean ^b	N	LS Mean	% ^c	p-value
P00355						
DL D-12 BID (DL 2.5 / PSE 120 mg)	199	14.18	199	-6.54	-46.0	—
DL QD (5.0 mg)	197	14.82	197	-5.09	-33.5	<.001
PSE BID (120 mg)	197	14.06	197	-5.07	-35.9	<.001
P00362						
DL D-12 BID (DL 2.5 / PSE 120 mg)	213	15.19	213	-6.65	-43.0	—
DL QD (5.0 mg)	212	14.66	212	-5.35	-36.1	0.001
PSE BID (120 mg)	221	14.86	221	-5.28	-35.4	<.001

- a: Calculation of mean Baseline values included all subjects with Baseline and Endpoint data; calculation of mean postbaseline values included all subjects with both Baseline and postbaseline 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.

Table 5 Nasal Stuffiness/Congestion Analysis Results for Primary Endpoint (Days 1-15): Subject Evaluated Mean AM/PM PRIOR 12 Hours (All Randomized Subjects) (Studies P00355 and P00362)

Treatment Group	Baseline		Change from Baseline (Days 1-15)			DL D-12 Comparison
	N ^a	LS Mean ^b	N	LS Mean	% ^c	p-value
P00355						
DL D-12 BID (2.5 DL/120 PSE mg)	199	2.47	199	-0.93	-37.4	—
DL QD (5.0 mg)	197	2.50	197	-0.66	-26.7	<.001
PSE BID (120 mg)	197	2.46	197	-0.75	-31.2	0.006
P00362						
DL D-12 BID (2.5 DL/120 PSE mg)	214	2.55	214	-0.92	-36.0	—
DL QD (5.0 mg)	213	2.56	213	-0.73	-28.9	0.005
PSE BID (120 mg)	221	2.56	221	-0.83	-31.8	0.167

- a: Calculation of mean Baseline values included all subjects with Baseline and Endpoint data; calculation of mean postbaseline values included all subjects with both Baseline and postbaseline 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.

Conclusions

The sponsor's conclusions can be found on page 84 of vol.32 & 36. The sponsor concluded that:

- The antihistaminic efficacy of DL D-12, as measured by mean AM/PM PRIOR 12 hours total symptom scores excluding nasal congestion, was significantly greater than PSE over the 15-day treatment period and was observed as early as Day 2 of treatment.
- The decongestant efficacy of DL D-12, as measured by mean AM/PM PRIOR 12 hours nasal congestion scores, was significantly greater than DL over the 15-day treatment period and was observed as early as Day 2 of treatment.
- The antihistaminic and decongestant efficacy of DL D-12 at the end of the dosing interval were significantly greater than PSE and DL, respectively, over the 15-day treatment period and was observed as early as Day 1 of treatment (12 hours post dose).
- DL D-12 was shown to be more effective than either component alone, justifying the need for the combination product in the treatment of patients with SAR.

More details can be found in the sponsor's report in TABLE 12 – TABLE 20 on page 63 - 80, vol. 32 & 36, or Electronic submission `\N_000\2001-04-02\p00355.pdf`
`\N_000\2001-04-02\p00362.pdf`

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Reviewer's Evaluation of Study P00355

Description of Patients

Accountability of Patients

In this study, 598 patients at 20 centers were randomized to the following treatment groups:

- DL D-12 BID
- DL 5.0-mg QD
- PSE 120-mg BID

The randomization followed a 1:1:1 ratio.

In the protocol, the sponsor defined the patient population as follow:

“ All analyses and summaries of efficacy and safety data will be based on all randomized subjects who received at least one dose of study medication (intent-to-treat principle). In addition, an evaluable subject subset will be defined as randomized subjects who meet key eligibility and evaluability criteria. Confirmatory efficacy analyses will be based on this subset.”¹

The specific “key eligibility and evaluability criteria” were not defined in the protocol.

The definition of the ITT population was slightly different in the study report. The ITT group was defined as “All randomized subjects who had baseline plus some post-baseline efficacy data for each variable”. (P.58, vol. 32) The specific “key eligibility” criteria was not defined and “evaluability criteria” were defined as (1) inclusion/exclusion criteria, (2) compliance, and (3) concomitant medication use.

Table 5 shows patient disposition by treatment. A total of 598 patients were randomized and received at least one dose of study medication. Among the 598 patients, 44 were considered non-evaluable prior to unblinding by the sponsor and 37 didn't complete the study. These two groups of patients were not mutually exclusive and **Table 6** shows the relationship of these two populations.

The reviewer considered that the sponsor's definition of intent-to-treat (ITT) population was not clear and was not consistent between the protocol and study report. This evaluation of efficacy was based on the 598 all randomized patients (ITT population). The five patients (16/265, 15/304, 08/379, 04/445, and 01/477), who were lost to follow-up, only had baseline values. This reviewer imputed the endpoint value for these five patients using the LOCF method. The imputation of these five patients (out of 598) did not affect the outcome of the study.

¹ Page 924, Vol. 34, NDA 21- 313

Table 5. Patient Disposition by Final Status, Study P00355

Final Status	DL D-12	DL	PSE	Total
	2.5 DL/120 PSE mg BID N (%)	5.0 mg QD N (%)	120 mg BID N (%)	
All Randomized Patients (ITT)	200	198	200	598
Evaluable Subset	186 (93.0)	186 (93.9)	182 (91.0)	554 (92.6)
Not Evaluable Subset	14 (7.0)	12 (6.1)	18 (9.0)	44 (7.4)
Didn't Meet Entry Criteria	11 (5.5)	9 (4.5)	11 (5.5)	31 (5.2)
Insufficient Efficacy Data	0	0	2 (1.0)	2 (<1)
No Valid Visits	1 (<1)	1 (<1)	2 (1.0)	4 (<1)
Unacceptable Concomitant Medication	2 (1.0)	2 (1.0)	3 (1.5)	7 (1.2)
Completed	189 (94.5)	191 (96.5)	181 (90.5)	561 (86.3)
Not Completed	11 (5.5)	7 (3.5)	19 (9.5)	37 (5.7)
Adverse Event	7 (3.5)	4 (2.0)	9 (4.5)	20 (3.1)
Treatment Failure	1 (<1)	0	4 (2.0)	5 (<1)
Lost to Follow-up	2 (1.0)	0	0	2 (<1)
Non-Compliance	0	2 (1.0)	2 (1.0)	4 (<1)
Protocol Violation	1 (<1)	0	1 (<1)	2 (<1)
Did Not Wish to Continue	0	1 (<1)	3 (1.5)	4 (<1)

Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Dem.xpt
 Source Code: Check_ITT.sas

Table 6. Patient Disposition by Final Status, Study P00355

Final Status	DL D-12	DL	PSE	Total
	2.5 DL/120 PSE mg BID N (%)	5.0 mg QD N (%)	120 mg BID N (%)	
All Randomized Patients	200 (33.4)	198 (33.1)	200 (33.4)	598
ITT	200	198	200	598
Evaluable Subset	186 (93.0)	186 (93.9)	182 (91.0)	554 (92.6)
Completed	117 (95.1)	181 (97.3)	169 (92.9)	527
Not Completed	9 (4.8)	5 (2.7)	13 (7.1)	27
Not Evaluable Subset	14 (7.0)	12 (6.1)	18 (9.0)	44 (7.4)
Completed	12 (85.7)	10 (83.3)	12 (66.7)	34 (77.3)
Not Completed	2 (14.3)	2 (16.7)	6 (33.3)	10 (22.7)

Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Dem.xpt
 Source Code: Check_ITT.sas

Patient Demographics

Demographic data are summarized in **Table 7**. The treatment groups appear to be fairly balanced and comparable. The majority of patients in the treatment groups were female (62%), and Caucasian (80%). Very few patients at either end of the age spectrum (<18 and ≥ 65 years) were studied.

Table 7. Summary of Demographic Data, Study P00355

Demographic	Characteristic	DL D-12 2.5 DL/120 PSE mg BID	DL 5.0 mg QD	PSE 120 mg BID	Total
Age, (years)					
	Mean	34.9	36.4	34.5	35.3
	Median	33.5	37	35	36
	Range (Min - Max)	12 – 74	12 – 76	12 – 68	12 – 76
Age Subgroup, n (%)					
	12 - < 18	18 (9.0)	23 (11.6)	25 (12.5)	66 (11.0)
	18 - < 65	177 (88.5)	173 (87.4)	172 (86.0)	522 (87.3)
	≥ 65	5 (2.5)	2 (1.0)	3 (1.5)	10 (1.7)
Gender, n (%)					
	Male	79 (39.5)	69 (34.9)	76 (38.0)	224 (37.5)
	Female	121 (60.5)	129 (65.1)	124 (62.0)	374 (62.5)
Race, n (%)					
	Caucasian	161 (80.5)	152 (76.8)	163 (81.5)	476 (79.6)
	Non – Caucasian	39 (19.5)	46 (23.2)	37 (18.5)	122 (20.4)
	Black	24 (12.0)	26 (13.1)	19 (9.5)	69 (11.5)
	Asian	4 (2.0)	4 (2.0)	6 (3.0)	14 (2.3)
	Hispanic	8 (4.0)	13 (6.6)	7 (3.5)	28 (4.7)
	American Indian	0	0	1 (0.5)	1 (0.2)
	Other	3 (1.5)	3 (1.5)	4 (2.0)	10 (1.7)
Weight, (lbs)					
	Mean	168.4	163.2	167.0	166.2
	Median	165	155	160	160
	Range (Min - Max)	75 – 303	58 – 340	68 – 312	58 – 340
	Missing	2	0	1	3
Height, (in)					
	Mean	66.3	65.9	66.3	66.2
	Median	66	66	66	66
	Range (Min - Max)	52 – 78	54 – 75	54 – 77	52 – 78
	Missing	0	0	2	2
Duration of SAR, (years)					
	Mean	19.8	17.9	18.1	18.6
	Median	17	14	15	15
	Range (Min - Max)	2 – 69	2 – 56	2 – 54	2 – 69
All		200	198	200	598

Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Dem.xpt, Vitals.xpt, and Dishx.xpt
 Source Code: Demo_SUM.sas

Evaluation of Consistency of Results Across Centers

Twenty centers participated in this study. All centers contributed between 6 and 72 completed patients. The preliminary test for treatment-by-center interaction was not statistically significant for the primary efficacy variables (for nasal stuffiness/congestion symptom score, p=0.6955; and for total nasal symptom score excluding nasal congestion, p=0.6729). Therefore, the results are generally consistent across centers.

Evaluation of Missing Observations

The primary efficacy variables defined in the protocols were:

- Change from baseline in mean AM/PM PRIOR 12-hour total symptom score excluding nasal congestion (from the diary) for the antihistamine component, and
- Change from baseline in mean AM/PM PRIOR 12 –hour nasal Stuffiness/congestion score (from the diary) for the decongestant component.

The total symptom score was defined as the sum of all individual symptom scores. Whenever any one of the individual symptom scores was missing, the total score was considered missing. Similarly, the total nasal score was the sum of the 4 nasal symptom scores (rhinorrhea, nasal congestion, nasal itching, and sneezing) and the total non-nasal score was the sum of all non-nasal symptom scores (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate). Each individual symptom score was evaluated each morning and evening. For the derived intervals, the corresponding values were averaged over all non-missing days in the interval.

Table 8 describes the count of ITT patients (out of 598), who were not included in the primary efficacy variable, categorized by treatment and visit. Since there was a very small percentage of missing data, no separate analysis is necessary.

Table 8. Missing Observations of Primary Efficacy Variables, Study P00355

Variable	Treatment	<u>Visit</u>							
		Day 0 (baseline)	Day 1	Day 2	Day 3	Day 4	Days 1-8	Days 9-15	Days 1-15 (endpoint)
Total	DL D-12	0	4	1	3	3	1	7	0
Symptom	DL	0	7	3	1	2	1	7	0
Score (7 Sympts.)	PSE	0	5	3	3	6	3	15	0
Nasal	DL D-12	0	2	1	3	3	1	7	0
Stuffiness/	DL	0	3	2	1	3	1	6	0
Congestion	PSE	0	5	3	3	5	3	15	0

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 Source Code: Check_ITT.sas

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Analysis of Efficacy

This reviewer evaluated the sponsor’s statistical analyses by reanalyzing the sponsor’s data. The purpose for this reviewer’s analyses was to verify that the sponsor’s analyses, prospectively identified in the protocol, were carried out as planned. The following text details the reviewer’s analyses.

Primary Efficacy Variable

The primary efficacy variables defined in the protocols were:

- Change from baseline in mean AM/PM PRIOR 12-hour total symptom score excluding nasal congestion (from the diary) for the antihistamine component, and
- Change from baseline in mean AM/PM PRIOR 12 –hour nasal Stuffiness/congestion score (from the diary) for the decongestant component.

The primary time point for both variables was the average over the 15-day treatment period. The primary comparison for the antihistamine component was DL D-12 versus PSE. The primary comparison for the decongestant component was DL D-12 versus DL.

This reviewer evaluated the efficacy variables by two components: Antihistamine component and Decongestant component.

Antihistamine Component

Table 9 shows the raw mean changes and percent changes from baseline across the three treatments for mean total symptom score, excluding nasal congestion, for AM/PM PRIOR 12 hours.

Table 9. Raw Mean Changes of Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours, by Treatment and Interval, Study P00355

Interval	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	Mean ^a	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Baseline	200	14.43		198	15.10		200	14.36	
Change from Baseline									
Day 1	196	-3.43	(-23.3)	191	-2.41	(-15.1)	195	-2.83	(-18.8)
Day 2	199	-5.42	(-37.8)	195	-3.87	(-25.2)	197	-3.98	(-27.9)
Day 3	197	-6.25	(-43.6)	197	-4.32	(-28.0)	197	-4.26	(-29.5)
Day 4	197	-6.43	(-44.7)	196	-4.59	(-29.5)	194	-4.71	(-32.8)
Days 1-8	199	-6.16	(-42.8)	197	-4.57	(-29.5)	197	-4.50	(-31.4)
Days 9-15	193	-7.23	(-50.4)	191	-5.95	(-38.6)	185	-6.13	(-42.5)
Days 1-15	200	-6.58	(-45.8)	198	-5.15	(-33.4)	200	-5.09	(-35.4)

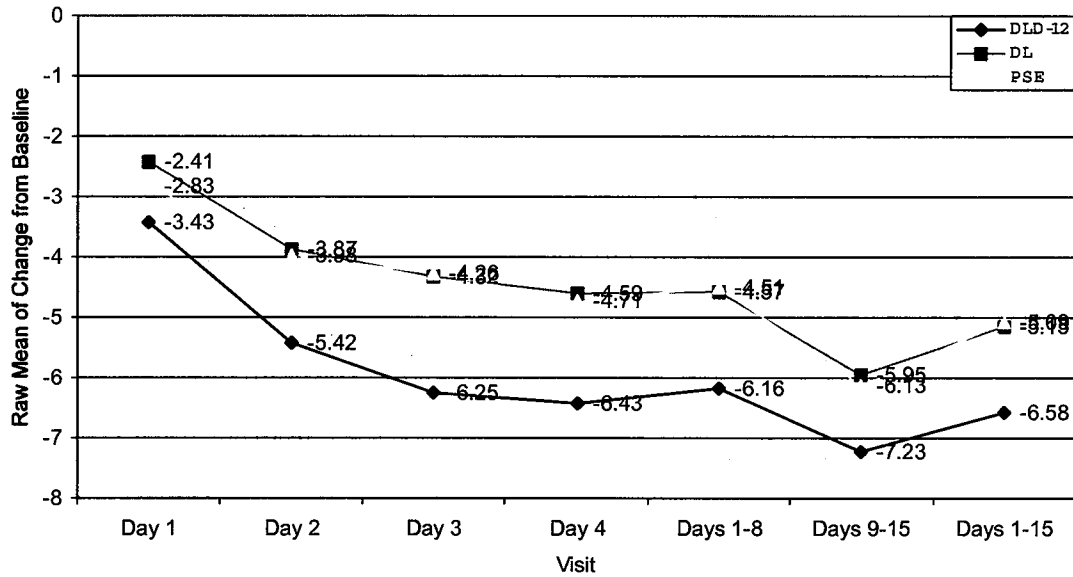
a: Mean and mean percent change are raw means.

Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt

Source Code: Diary.sas

Figure 2 shows the treatment effect by showing the raw mean changes from baseline across the three treatments for mean total symptom score, excluding nasal congestion, for AM/PM PRIOR 12 hours.

Figure 2. Raw Mean Changes of Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours, by Interval, Study P00355



Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt
 Source Code: Diary355.xls

Raw mean total symptom scores excluding nasal congestion at baseline were similar in the DL D-12 and PSE groups. Mean percent reductions from baseline in AM/PM PRIOR 12 hours total symptom scores excluding nasal congestion averaged over Days 1-15 were 45.8% and 35.4% for DL D-12 and PSE, respectively. The graphic shows the difference between DL D-12 and PSE was seen as early as Day 2.

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Table 10 shows the Least Square Mean and 95% Confidence Interval of mean change from baseline with pairwise comparisons across the three treatments for mean total symptom scores (excluding nasal congestion) for AM/PM PRIOR 12 hours.

DL D-12 was significantly more effective than PSE at the primary endpoint on this variable ($p=0.0003$). Statistically significant improvement ($p\leq 0.0172$) compared with PSE was observed on Day 2 and afterward. However, the difference between DL D-12 and PSE was smaller (1.46) than the difference between groups of 1.6, which was the estimated effect size. The power calculation assumed a pooled standard deviation of 4.25. The actual pooled standard deviation was 3.99. With a sample size of 200 subjects per treatment group, a two-tailed alpha-level of 0.05, and a pooled standard deviation of 3.99 points on the change from baseline, differences of 1.46 between treatment groups would be detectable with power of 95%.

Table 10. Statistical Results of Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours, Study P00355

Interval	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	LS Mean	95% CI	N	LS Mean	95% CI	N	LS Mean	95% CI
Baseline	200	14.20	(13.8, 14.6)	198	14.84	(14.4, 15.3)	200	14.08	(13.6, 14.5)
Change from Baseline									
Day 1	196	-3.77	(-4.4, -3.1)	191	-2.50	(-3.2, -1.8)	195	-3.20	(-3.9, -2.5)
Day 2	199	-5.59	(-6.2, -4.9)	195	-3.83	(-4.5, -3.1)	197	-4.17	(-4.8, -3.5)
Day 3	197	-6.30	(-7.0, -5.6)	197	-4.11	(-4.8, -3.5)	197	-4.36	(-5.0, -3.7)
Day 4	197	-6.46	(-7.1, -5.8)	196	-4.35	(-5.0, -3.7)	194	-4.78	(-5.5, -4.1)
Days 1-8	199	-6.26	(-6.9, -5.7)	197	-4.39	(-5.0, -3.8)	197	-4.63	(-5.2, -4.0)
Days 9-15	193	-7.37	(-8.0, -6.7)	191	-5.72	(-6.4, -5.1)	185	-6.30	(-7.0, -5.6)
Days 1-15	200	-6.69	(-7.3, -6.1)	198	-4.96	(-5.6, -4.4)	200	-5.23	(-5.8, -4.6)

Interval	Pstd	Model p-value		Pairwise Comparison p-value		
		Treatment	Center	DL D-12 vs. DL	DL D-12 vs. PSE	DL vs. PSE
Baseline	2.92	0.0209	<.0001	0.0295	0.6750	0.0095
Change from Baseline						
Day 1	4.44	0.0195	0.5702	0.0051	0.2067	0.1208
Day 2	4.36	0.0001	0.3600	<.0001	0.0013	0.4510
Day 3	4.40	<.0001	0.3964	<.0001	<.0001	0.5838
Day 4	4.56	<.0001	0.6033	<.0001	0.0003	0.3598
Days 1-8	4.04	<.0001	0.3278	<.0001	<.0001	0.5580
Days 9-15	4.33	0.0009	0.0689	0.0002	0.0172	0.1998
Days 1-15	3.99	<.0001	0.1355	<.0001	0.0003	0.5037

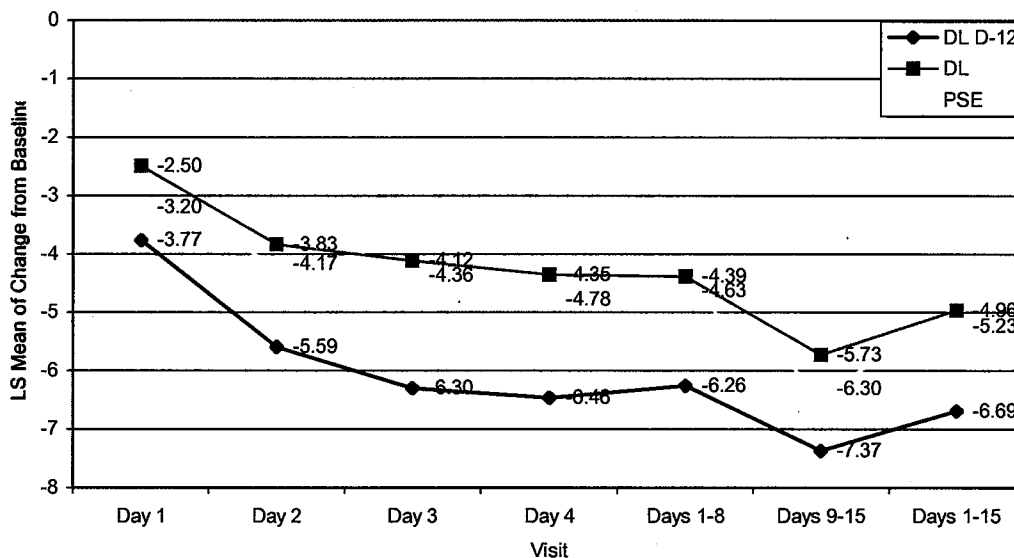
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Source Code: Diary.sas

Figure 3 shows the treatment effect by showing the least square mean changes from baseline across the three treatments for mean total symptom score, excluding nasal congestion, for AM/PM PRIOR 12 hours.

The DL D-12 group demonstrated a decline in symptom severity by Day 2 and was significantly more effective than PSE for this variable.

Figure 3. LS Mean Changes of Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours by Visit, Study P00355

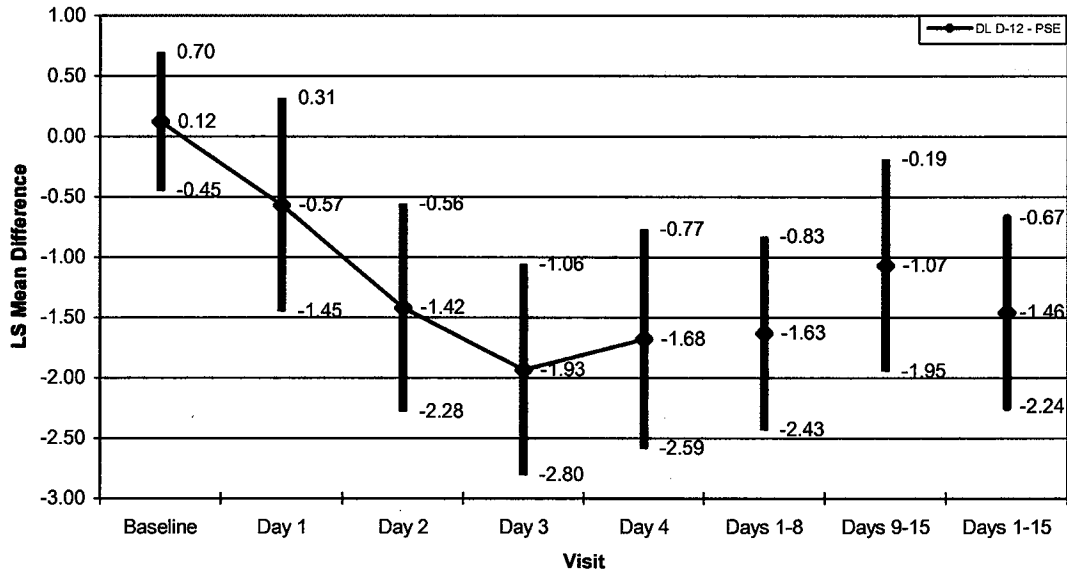


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 Source Code: LSmean.xls

Figure 4 and **Figure 5** show the confidence intervals of difference in LS means between treatment groups for each visit and endpoint for this primary efficacy variable.

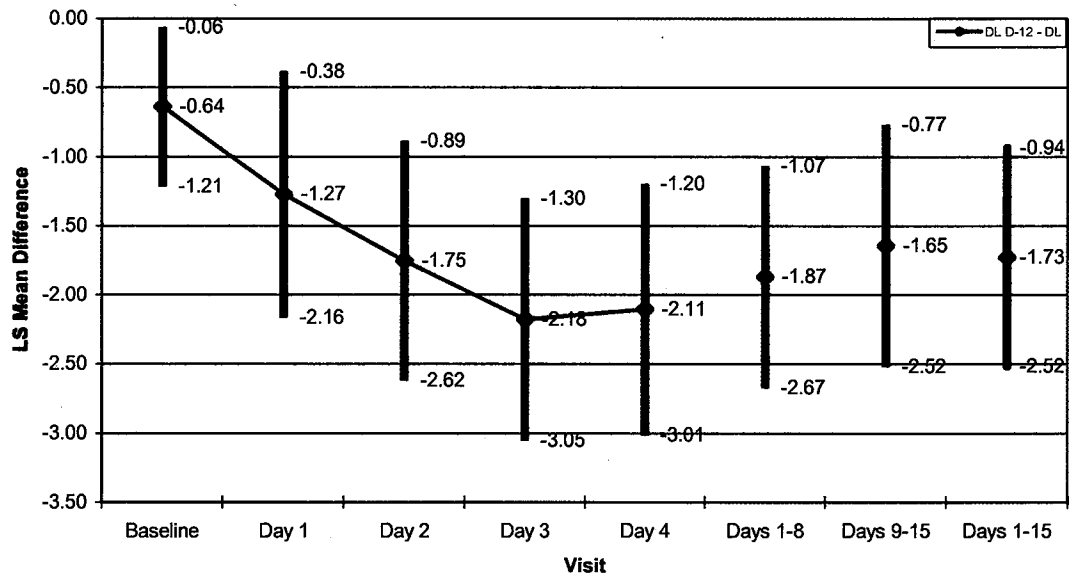
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Figure 4. Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours
LS Mean Difference between DL D-12 and PSE, Study P00355



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Figure 5. Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours
LS Mean Difference between DL D-12 and DL, Study P00355



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 Source Code: Mean-diff355.xls

Decongestant Component

Table 11 shows the raw mean changes and percent changes from baseline across the three treatments for mean nasal stuffiness/congestion score, for AM/PM PRIOR 12 hours.

Raw means of nasal stuffiness/congestion at baseline were similar in the DL D-12 and DL groups. Mean percent reductions from baseline in AM/PM PRIOR 12 hours nasal congestion symptom scores averaged over Days 1-15 were 37.2% and 26.5% for DL D-12 and DL, respectively.

Table 11. Raw Mean Changes of Nasal Stuffiness/Congestion Symptom Score AM/PM PRIOR 12 Hours, by Treatment and Interval, Study P00355

Interval	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	Mean ^a	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Baseline	200	2.49		198	2.52		200	2.48	
Change from Baseline									
Day 1	200	-0.56	(-22.0)	198	-0.41	(-16.1)	200	-0.52	(-21.0)
Day 2	199	-0.86	(-34.3)	191	-0.52	(-20.8)	195	-0.69	(-28.1)
Day 3	198	-0.91	(-36.3)	197	-0.58	(-23.0)	198	-0.71	(-29.0)
Day 4	198	-0.95	(-37.5)	196	-0.61	(-23.6)	197	-0.74	(-30.1)
Days 1-8	200	-0.94	(-35.7)	198	-0.60	(-23.5)	200	-0.70	(-28.5)
Days 9-15	193	-1.00	(-39.8)	192	-0.79	(-31.1)	185	-0.85	(-34.8)
Days 1-15	200	-0.95	(-37.2)	198	-0.67	(-26.5)	200	-0.75	(-30.8)

a: Mean and mean percent change are raw means.

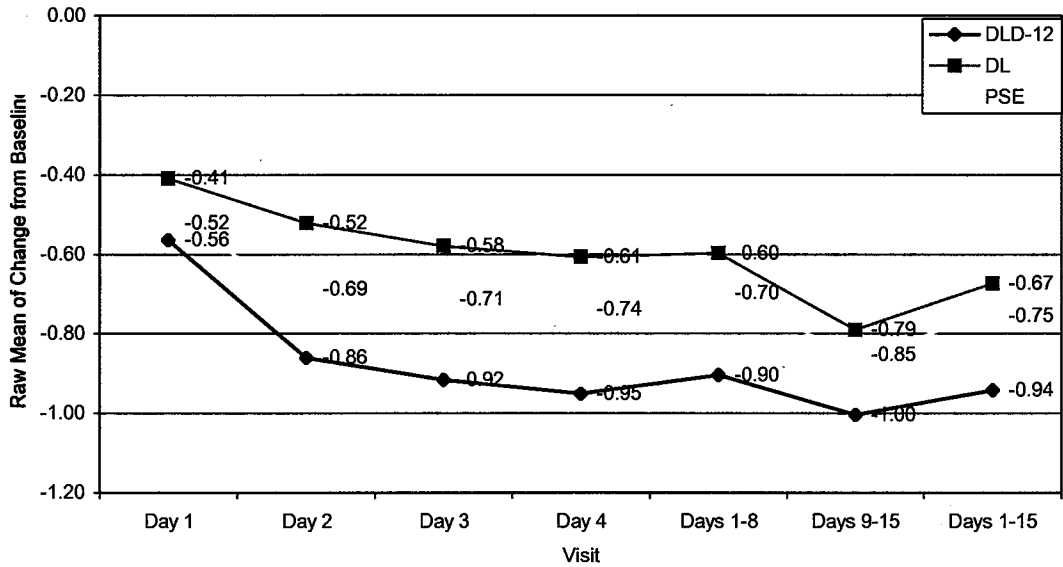
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Figure 6 shows the treatment effect by showing the raw mean changes from baseline across the three treatments for mean nasal stuffiness/congestion symptom score for AM/PM PRIOR 12 hours.

Figure 6. Raw Mean Changes of Nasal Stuffiness/Congestion Symptom Score AM/PM PRIOR 12 Hours, by Interval, Study P00355



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Table 12 shows the Least Square Mean and 95% Confidence Interval of mean change from baseline with pairwise comparisons across the 3 treatments for mean nasal stuffiness/congestion symptom scores for AM/PM PRIOR 12 hours.

DL D-12 was significantly more effective than DL at the primary endpoint (Days 1-15) on this variable ($p < .0001$). Statistically significant improvement ($p < 0.0026$) compared with DL was observed on Day 2 and afterwards. The difference between DL D-12 and DL was larger (0.27) than the difference between groups of 0.2, which was the assumed effect size. The power calculation assumed a pooled standard deviation of 0.6 points. The actual pooled standard deviation was 0.64.

Table 12. Statistical Results of Nasal Stuffiness/Congestion Symptom Score AM/PM PRIOR 12 Hours, Study P00355

Interval	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	LS Mean	95% CI	N	LS Mean	95% CI	N	LS Mean	95% CI
Baseline	200	2.48	(2.42, 2.53)	198	2.50	(2.44, 2.56)	200	2.46	(2.40, 2.52)
Change from Baseline									
Day 1	200	-0.61	(-.73, -.49)	198	-0.45	(-.57, -.33)	200	-0.58	(-.70, -.46)
Day 2	199	-0.85	(-.95, -.74)	191	-0.50	(-.61, -.40)	195	-0.68	(-.78, -.57)
Day 3	198	-0.90	(-1.0, -.79)	197	-0.56	(-.67, -.44)	198	-0.70	(-.82, -.59)
Day 4	198	-0.93	(-1.1, -.81)	196	-0.57	(-.69, -.46)	197	-0.73	(-.84, -.61)
Days 1-8	200	-0.89	(-1.0, -.80)	198	-0.58	(-.67, -.48)	200	-0.69	(-.79, -.59)
Days 9-15	193	-1.00	(-1.1, -.88)	192	-0.77	(-.88, -.66)	185	-0.86	(-.97, -.74)
Days 1-15	200	-0.93	(-1.0, -.83)	198	-0.66	(-.75, -.56)	200	-0.75	(-.85, -.66)

Interval	Pstd	Model p-value		Pairwise Comparison p-value		
		Treatment	Center	DL D-12 vs. DL	DL D-12 vs. PSE	DL vs. PSE
Baseline	0.38	0.5221	0.0003	0.4897	0.6587	0.2581
Change from Baseline						
Day 1	0.81	0.1208	0.1257	0.0525	0.7130	0.1177
Day 2	0.70	<.0001	0.1865	<.0001	0.0164	0.0131
Day 3	0.76	<.0001	0.2596	<.0001	0.0108	0.0546
Day 4	0.78	<.0001	0.0930	<.0001	0.0098	0.0576
Days 1-8	0.64	<.0001	0.0786	<.0001	0.0019	0.0782
Days 9-15	0.72	0.0098	0.0486	0.0026	0.01619	0.2622
Days 1-15	0.64	<.0001	0.0433	<.0001	0.0050	0.1236

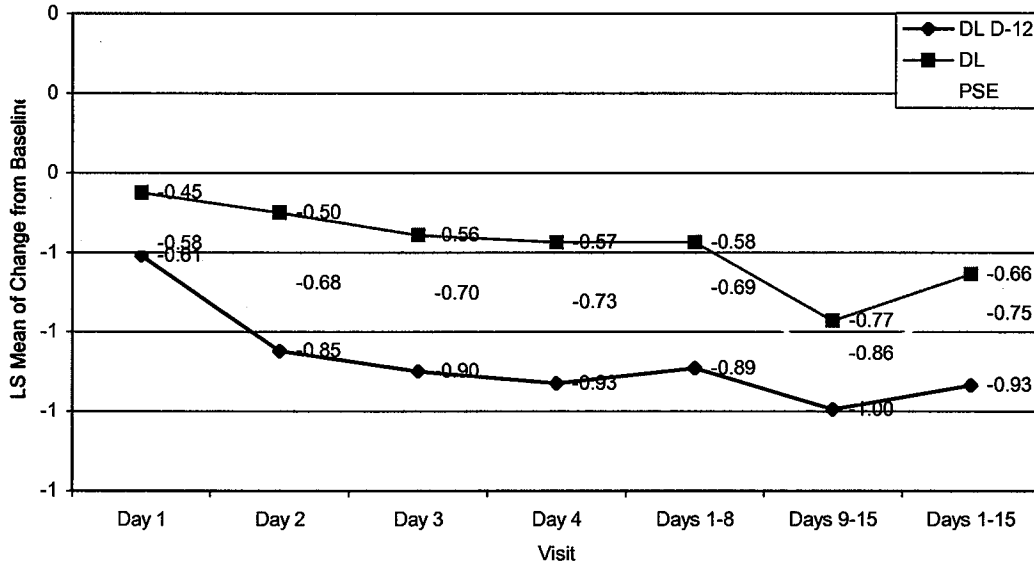
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Figure 7 shows the least square mean changes from baseline across the three treatments for mean nasal stuffiness/congestion symptom score, for AM/PM PRIOR 12 hours.

The DL D-12 group demonstrated a decline in symptom severity starting at Day 2 and was significantly more effective than DL for this variable.

Figure 7. LS Mean Changes of Nasal Stuffiness/Congestion Symptom Score AM/PM PRIOR 12 Hours, by Visit, Study P00355

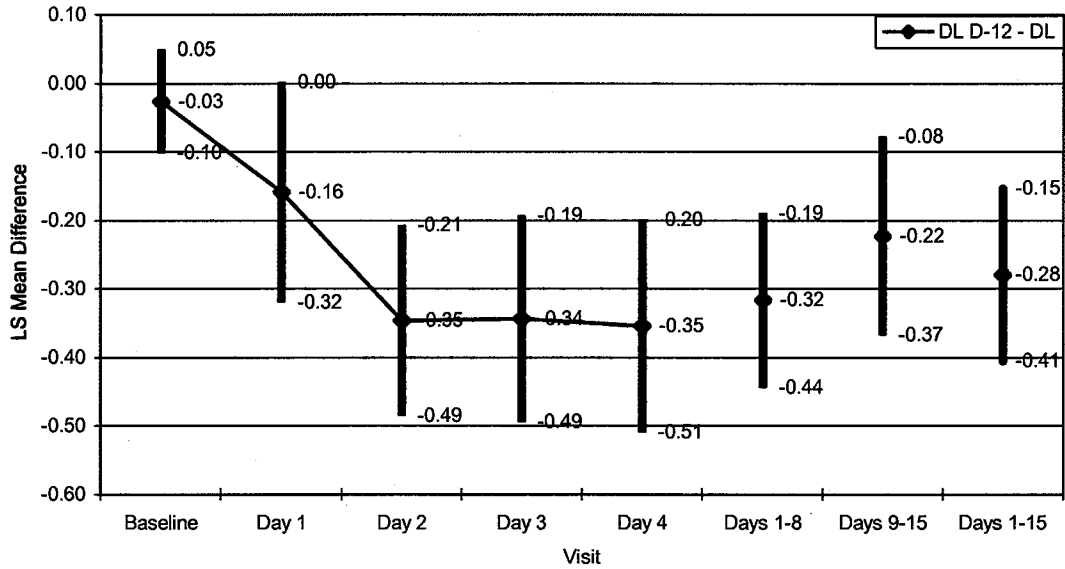


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Figure 8 and Figure 9 show the confidence intervals of difference in LS means between treatment groups for each visit and endpoint for this variable.

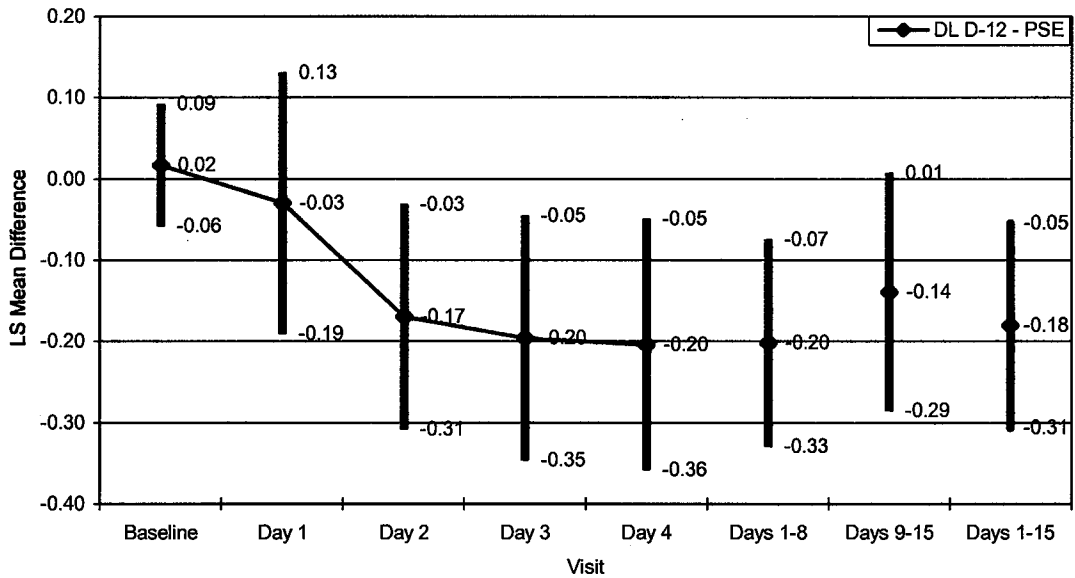
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Figure 8. Nasal Stuffiness/Congestion Symptom Score AM/PM PRIOR 12 Hours
LS Mean Difference between DL D-12 and DL, Study P00355



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 Source Code: Mean-diff355.xls

Figure 9. Nasal Stuffiness/Congestion Symptom Score AM/PM PRIOR 12 Hours
LS Mean Difference between DL D-12 and PSE, Study P00355



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 Source Code: Mean-diff355.xls

Interim Analyses and Data Monitoring

No interim analyses were planned in the protocol and none was performed. There was no Data Monitoring Committee for this protocol.

Multiple Comparisons/Multiplicity

No adjustment for multiple comparisons was planned in the protocol. This reviewer considers that no adjustment for multiple comparisons is needed because the DL D-12 must beat both components (DL and PSE) for the efficacy variables.

Evaluation of Subgroups

Summary statistics for the primary efficacy variables, total symptom score excluding nasal congestion and nasal stuffiness/congestion symptom score, averaged over 2 weeks, were evaluated for the following subject subgroups: age (12 - < 18 years, 18 - < 65 years, ≥ 65 years), gender, and race (Caucasian, non-Caucasian). **Table 13**, **Table 14**, and **Table 15** show the results comparing the three treatment groups for these demographic variables. Overall, DL D-12 showed a statistically significant decline in symptom severity for both primary efficacy variables in both male and female patients. There were too few subjects age 12 to <18 years or ≥ 65 years, or who were non-Caucasian to provide a formal assessment of differential treatment response by age or race. However, no appreciable differences between the treatments were noted for age and race subgroups.

Table 13. Primary Efficacy Variables AM/PM PRIOR 12 Hours 2-week Average, by Age Group (Study P00355)

Demographic Characteristic	Total Symptom Score Excluding Nasal Congestion						Nasal Stuffiness/Congestion Symptom Score					
	Change from Baseline											
	DL D-12		DL		PSE		DL D-12		DL		PSE	
	N	Mean ¹	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Age												
12 - < 18	18	-5.97	23	-5.74	25	-4.83	18	-0.84	23	-0.78	25	-0.63
18 - < 65	177	-6.64	173	-5.11	172	-5.10	177	-0.96	173	-0.66	172	-0.77
≥ 65	5	-6.69	2	-1.55	3	-6.52	5	-0.81	2	-0.42	3	-0.79
All	200	-6.58	198	-5.15	200	-5.09	200	-0.95	198	-0.67	200	-0.75
	Pairwise Comparisons p-value ²											
	DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE		DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE	
Age												
12 - < 18	0.1331		0.0546		0.6949		0.1554		0.0674		0.7051	
18 - < 65	<.0001		0.0006		0.3801		<.0001		0.0097		0.0487	
≥ 65	NA ³		NA		NA		NA		NA		NA	
All	<.0001		0.0003		0.5037		<.0001		0.0050		0.1236	

1: Mean was raw mean.

2: p-value were obtained from the two-way ANOVA model with baseline, treatment, and site effects.

3: There were too few subjects age year ≥ 65 to calculate the statistics.

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Source Code: Subg_ANA.sas

Table 14. Primary Efficacy Variables AM/PM PRIOR 12 Hours 2-week Average, by Gender Group (Study P00355)

Demographic Characteristic	Total Symptom Score Excluding Nasal Congestion						Nasal Stiffness/Congestion Symptom Score					
	Change from Baseline											
	DL D-12		DL		PSE		DL D-12		DL		PSE	
	N,	Mean ¹	N,	Mean	N,	Mean	N,	Mean	N,	Mean	N,	Mean
Gender												
Female	121	-6.17	129	-5.10	124	-5.29	121	-0.86	129	-0.65	124	-0.79
Male	79	-7.21	69	-5.25	76	-4.75	79	-1.10	69	-0.73	76	-0.70
All	200	-6.58	198	-5.15	200	-5.09	200	-0.95	198	-0.67	200	-0.75
	Pairwise Comparisons p-value ²											
	DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE		DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE	
Gender												
Female	0.0034		0.0482		0.3410		0.0007		0.1497		0.0521	
Male	0.0005		0.0011		0.7756		0.0031		0.0132		0.5915	
All	<.0001		0.0003		0.5037		<.0001		0.0050		0.1236	

1: Mean was raw mean.

2: p-value were obtained from the two-way ANOVA model with baseline, treatment, and site effects.

Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt and Dem.xpt

Source Code: Subg_ANA.sas

Table 15. Primary Efficacy Variables AM/PM PRIOR 12 Hours 2-week Average, by Race Group (Study P00355)

Demographic Characteristic	Total Symptom Score Excluding Nasal Congestion						Nasal Stiffness/Congestion Symptom Score					
	Change from Baseline											
	DL D-12		DL		PSE		DL D-12		DL		PSE	
	N,	Mean ¹	N,	Mean	N,	Mean	N,	Mean	N,	Mean	N,	Mean
Race												
Caucasian	161	-6.49	152	-5.26	163	-5.16	161	-0.93	152	-0.71	163	-0.75
Non-Caucasian	39	-6.94	46	-4.78	37	-4.75	39	-0.98	46	-0.56	37	-0.77
All	200	-6.58	198	-5.15	200	-5.09	200	-0.95	198	-0.67	200	-0.75
	Pairwise Comparisons p-value ²											
	DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE		DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE	
Race												
Caucasian	<.0001		0.0017		0.3905		0.0007		0.0122		0.3391	
Non-Caucasian	0.1502		0.0502		0.5892		0.0566		0.2076		0.5156	
All	<.0001		0.0003		0.5037		<.0001		0.0050		0.1236	

1: Mean was raw mean.

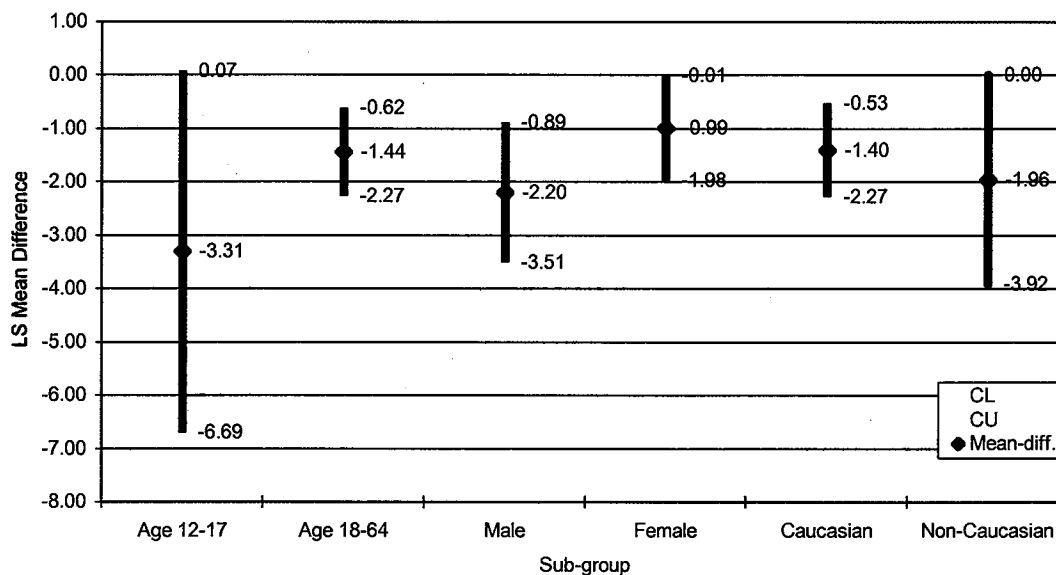
2: p-value were obtained from the two-way ANOVA model with baseline, treatment, and site effects.

Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt and Dem.xpt

Source Code: Subg_ANA.sas

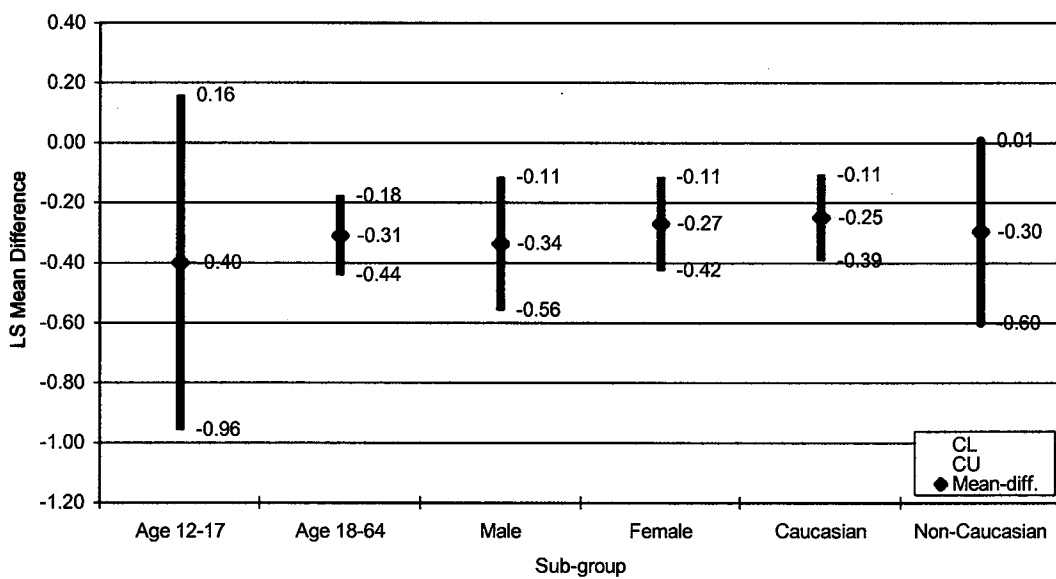
Figure 10 and Figure 11 show the confidence intervals of LS mean difference for each sub-group.

Figure 10. Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours
LS Mean Difference between DL D-12 and PSE, by Sub-group, Study P00355



Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt
 Source Code: Mean-diff355.xls

Figure 11. Nasal Stiffness/Congestion Symptom Score AM/PM PRIOR 12 Hours
LS Mean Difference between DL D-12 and DL, by Sub-group, Study P00355



Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt
 Source Code: Mean-diff355.xls

Secondary Efficacy Variable

The secondary efficacy variables defined in the protocols were:

- End of Dosing Interval
 - Change from baseline in mean AM/PM NOW total symptom score excluding nasal congestion (from the diary) for the antihistamine component, and
 - Change from baseline in mean AM/PM NOW nasal stuffiness/congestion score (from the diary) for the decongestant component.
- Change from baseline in the total (with nasal congestion), total nasal (with and without nasal congestion), total non-nasal, and individual mean AM/PM PRIOR 12 hours symptom scores expressed as a change from baseline. Additional variables included the overall condition of SAR expressed as the change from baseline, and the evaluation of therapeutic response expressed as a raw score.

For the antihistamine component, the main comparison was DL D-12 versus PSE over the 15-day treatment period, based on the change from baseline in mean AM/PM NOW total symptom score excluding nasal congestion. For Day 1-15, DL D-12 was numerically superior to PSE at all the time assessments and reached the statistical significance ($p < 0.0026$), as shown in the **Table 16**.

Table 16. Total Symptom Score (Excluding Nasal Congestion), by Time Point, Study P00355

Time Point	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	Mean ^a	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Change from Baseline to Days 1-15									
AM P-12 hrs	199	-6.40	(-45.3)	197	-5.00	(-32.8)	198	-5.02	(-35.1)
AM Now	199	-6.18	(43.5)	197	-5.24	(-34.2)	198	-5.00	(-34.8)
PM P-12 hrs	200	-6.83	(-46.2)	197	-5.34	(-33.7)	200	-5.30	(-36.2)
PM Now	200	-6.62	(-45.9)	197	-5.43	(-35.7)	200	-5.18	(-36.1)
AM/PM P-12 hrs	199	-6.61	(-46.0)	198	-5.17	(-33.5)	200	-5.16	(-35.9)
AM/PM Now	200	-6.42	(-45.1)	198	-5.34	(-35.2)	200	-5.09	(-35.6)

	DL D-12 vs. DL			DL D-12 vs. PSE		
	LS Mean Difference	95% CI	p-value	LS Mean Difference	95% CI	p-value
Change from Baseline to Days 1-15						
AM P-12 hrs	-1.738	(-2.55, -0.93)	<.0001	-1.344	(-2.15, -0.54)	0.0011
AM Now	-1.424	(-2.24, -0.61)	0.0006	-1.240	(-2.05, -0.44)	0.0026
PM P-12 hrs	-1.798	(-2.59, -1.01)	<.0001	-1.485	(-2.27, -0.70)	0.0002
PM Now	-1.494	(-2.29, -0.69)	0.0003	-1.392	(-2.19, -0.60)	0.0006
AM/PM P-12 hrs	-1.743	(-2.53, -0.96)	<.0001	-1.418	(-2.20, -0.64)	0.0004
AM/PM Now	-1.444	(-2.24, -0.65)	0.0004	-1.334	(-2.12, -0.55)	0.0009

a: Mean and Mean percent change are raw means.

Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt

Source Code: Second.sas

For the decongestant component, the main comparison was DL D-12 versus DL over the 15-day treatment period, based on the change from baseline in mean AM NOW nasal congestion score. The AM time point was chosen as the end of dosing interval based on the once daily dosing regimen for DL. The AM NOW score represents symptoms present at the end of the dosing interval (approximately 24 hours after DL dosing, prior to taking the next DL dose). For Days 1-15, DL D-12 was numerically superior to DL at all the time assessments and reached the statistical significance ($p < 0.0009$), as shown in the **Table 17**.

Table 17. Nasal Stuffiness/Congestion Score, by Time Point, Study P00355

Time Point	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	Mean ^a	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Change from Baseline to Days 1-15									
AM P-12 hrs	199	-0.91	(-36.1)	197	-0.68	(-26.3)	198	-0.72	(-29.0)
AM Now	199	-0.84	(33.0)	197	-0.62	(-22.8)	198	-0.69	(-27.7)
PM P-12 hrs	200	-0.98	(-38.0)	197	-0.68	(-26.1)	200	-0.81	(-32.8)
PM Now	200	-0.87	(-33.7)	197	-0.68	(-24.9)	200	-0.76	(-30.5)
AM/PM P-12 hrs	199	-0.95	(-37.4)	198	-0.68	(-26.7)	200	-0.77	(-31.2)
AM/PM Now	200	-0.85	(-34.2)	198	-0.65	(-24.5)	200	-0.72	(-29.6)

	DL D-12 vs. DL			DL D-12 vs. PSE		
	LS Mean Difference	95% CI	p-value	LS Mean Difference	95% CI	p-value
Change from Baseline to Days 1-15						
AM P-12 hrs	-0.257	(-0.39, -0.12)	0.0002	-0.180	(-0.31, -0.05)	0.0077
AM Now	-0.246	(-0.38, -0.11)	0.0003	-0.160	(-0.29, -0.03)	0.0177
PM P-12 hrs	-0.310	(-0.44, -0.18)	<.0001	-0.167	(-0.30, -0.04)	0.0108
PM Now	-0.228	(-0.36, -0.09)	0.0009	-0.133	(-0.27, -0.00)	0.0519
AM/PM P-12hrs	-0.281	(-0.41, -0.15)	<.0001	-0.175	(-0.30, -0.05)	0.0067
AM/PM Now	-0.228	(-0.36, -0.10)	0.0005	-0.143	(-0.27, -0.01)	0.0289

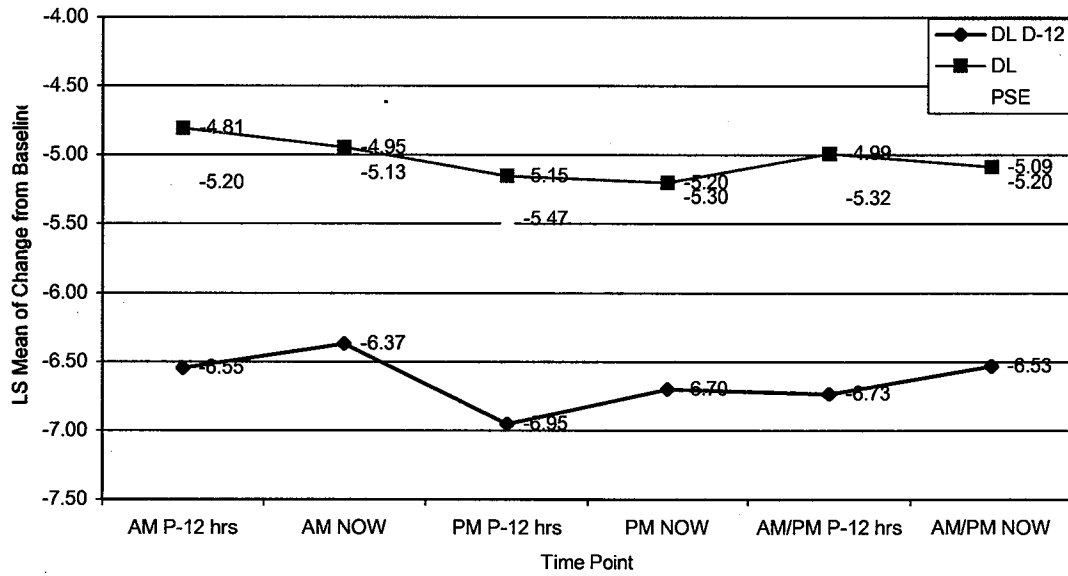
a: Mean and Mean percent change are raw means.

Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt

Source Code: Second.sas

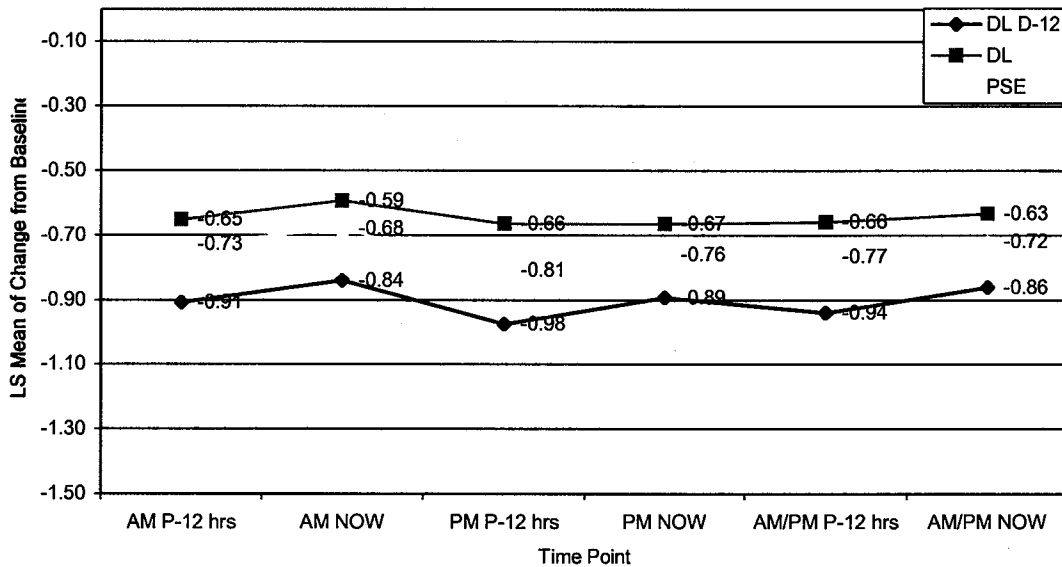
Figure 12 and **Figure 13** show the LS mean changes of total symptom score (excluding nasal congestion) and nasal stuffiness/congestion symptom score, by time assessment.

Figure 12. LS Mean Changes of Total Symptom Score (Excluding Nasal Congestion), by Time Point, Study P00355



Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt
 Source Code: LSmean.xls

Figure 13. LS Mean Changes of Nasal Stuffiness/Congestion Symptom Score, by Time Point, Study P00355



Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt
 Source Code: LSmean.xls

Clarinet-D™ 12 Hour Extended Release Tablets, Schering Corporation

The statistical analysis of the individual symptom scores other than nasal congestion did show that for Day 1-15, DL D-12 was numerically superior to both DL and PSE and reached statistical significance ($p < 0.025$). Please reference to p76, vol.32.

The overall condition of SAR was evaluated jointly by the subject and investigator and recorded on a scale of 0-3. For Days 1-15, DL D-12 was numerically slightly superior to both DL and PSE, but was not statistical significant, as shown in the **Table 18**.

Table 18. Overall Condition of SAR Analysis Results, Study P00355

Time Point	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	Mean ^a	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Baseline	199	2.578		196	2.602		195	2.549	
Change from Baseline									
Day 1-15	199	-1.05	(-40.0)	196	-0.93	(-33.8)	195	-0.90	(-33.6)
DL D-12 vs. DL									
		LS Mean Difference	95% CI	p-value		LS Mean Difference	95% CI	p-value	
Baseline		-0.025	(-0.12, 0.07)	0.6218		0.036	(-0.06, 0.13)	0.4695	
Change from Baseline									
Day 1-15		-0.130	(-0.27, 0.011)	0.0698		-0.124	(-0.26, 0.02)	0.0847	

a: Mean and Mean percent change are raw means.

Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt

Source Code: Second.sas

For the evaluation of the therapeutic response, which was evaluated jointly by the subject and investigator and recorded on a scale of 1 (complete relief) to 5 (treatment failure), for Day 1-15, DL D-12 was numerically slightly superior to both DL and PSE, but was not statistical significant, as shown in the **Table 19**.

Table 19. Evaluation of Therapeutic Response Analysis Results, Study P00355

Time Point	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD		PSE 120 mg BID		
	N	Mean ^a		N	Mean	N	Mean	
Change from Baseline								
Days 1-15	197	2.964		195	3.169	195	3.108	
DL D-12 vs. DL								
		LS Mean Difference	95% CI	p-value		LS Mean Difference	95% CI	p-value
Change from Baseline								
Days 1-15		-0.204	(-0.41, 0.003)	0.0541		-0.131	(-0.34, 0.08)	0.2173

a: Mean and Mean percent change are raw means.

Source: \N_000\2000-12-08\CD of Clinical Data\P00355\DATA\Diaryn.xpt

Source Code: Second.sas

Summary of Efficacy

This randomized, double-blind, double-dummy study was designed to demonstrate that DL D-12 has superior antihistamine effects as compared with PSE, and that DL D-12 has superior decongestant effects, as compared with DL.

The pre-specified primary endpoint evaluating the antihistamine effect was the change from baseline in the AM/PM PRIOR 12 HOURS total symptom score, excluding nasal congestion, averaged over Days 1-15. The primary comparison for this variable was DL D-12 versus PSE. The results of the study demonstrated that DL D-12 was statistically superior to PSE on this variable ($p=0.0003$). Statistically significant improvement ($p\leq 0.0172$) compared with PSE was observed on Day 2 and afterward.

The pre-specified primary endpoint concerning the decongestant effect was the change from baseline in the reflective AM/PM PRIOR 12 HOURS nasal congestion score averaged over Days 1-15. The primary comparison on this variable was DL D-12 versus DL. The results of the study demonstrated that DL D-12 was statistically superior to DL on this variable ($p<0.0001$). Statistically significant improvement ($p<0.0026$) compared with DL was observed on Day 2 and afterward.

The various secondary analyses of symptom scores supported the conclusions drawn from the primary endpoints. Instantaneous symptom scores demonstrated that the efficacy of DL D-12 is maintained at the end of the dosing interval ($p\leq 0.0009$). Evaluations of the overall condition of SAR and the therapeutic response, which were performed jointly by the patients and investigator, favored DL D-12 but failed to reach statistical significance.

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Reviewer's Evaluation of Study P00362

Description of Patients

Accountability of Patients

In this study, 650 patients at 20 centers were randomized to the following treatment groups:

- DL D-12 BID
- DL 5.0-mg QD
- PSE 120-mg BID

The randomization followed a 1:1:1 ratio.

In the protocol, the sponsor defined the patient population as follow:

“ All analyses and summaries of efficacy and safety data will be based on all randomized subjects who received at least one dose of study medication (intent-to-treat principle). In addition, an evaluable subject subset will be defined as randomized subjects who meet key eligibility and evaluability criteria. Confirmatory efficacy analyses will be based on this subset.”²

The specific “key eligibility and evaluability criteria” were not defined in the protocol.

The definition of the ITT population was slightly different in the study report. The ITT group was defined as “All randomized subjects who had baseline plus some post-baseline efficacy data for each variable”. (P.58, vol. 32) The specific “key eligibility” was not defined and “evaluability criteria” were defined as (1) inclusion/exclusion criteria, (2) compliance, and (3) concomitant medication use.

Table 20 shows patient disposition by treatment. A total of 650 patients were randomized and received at least one dose of study medication. Among the 650 patients, 37 were considered non-evaluable prior to unblinding and 46 didn't complete the study. These two groups of patients were not mutually exclusive and **Table 21** shows the relationship between these two populations.

The reviewer's evaluation of efficacy was based on the 650 ITT patients. The two patients (09/324 and 10/352 were lost to follow-up) only had the baseline values and two patients (08/700 – did not meet the entrance criteria and 08/712 – no reason given) did not have valid baseline values. This reviewer imputed the endpoint value for these four patients using the LOCF method. The imputation of these four patients (out of 650) did not affect the outcome of the study.

² Page 935, Vol. 39, NDA 21- 313

Table 20. Patient Disposition by Final Status, Study P00362

Final Status	DL D-12	DL	PSE	Total
	2.5 DL/120 PSE mg BID	5.0 mg QD	120 mg BID	
	N (%)	N (%)	N (%)	N (%)
All Randomized Patients (ITT)	214	214	222	650
Efficacy Evaluable Subset	204 (95.3)	199 (93.0)	210 (94.6)	613 (94.3)
Not Evaluable Subset	10 (4.7)	15 (7.0)	12 (5.4)	37 (5.7)
Did Not Meet Entry Criteria	6 (2.8)	13 (6.1)	9 (4.1)	28 (4.3)
Insufficient Efficacy Data	0	0	1 (1.0)	1 (<1)
No Valid Visits	0	1 (<1)	1 (<1)	2 (<1)
compliance with Protocol	1 (<1)	0	0	1 (<1)
Unacceptable Concomitant Medication	3 (1.4)	1 (<1)	1 (<1)	5 (<1)
Completed	200 (93.5)	200 (93.5)	204 (91.9)	604 (92.9)
Not completed	14 (6.5)	14 (6.5)	18 (8.1)	46 (7.1)
Adverse Event	7 (3.3)	5 (2.3)	12 (5.4)	24 (3.7)
Treatment Failure	2 (1.0)	5 (2.3)	5 (2.3)	12 (1.9)
Lost to Follow-up	1 (<1)	2 (1)	0	3 (<1)
Non-Compliance	3 (1.4)	2 (1.0)	1 (<1)	6 (<1)
Protocol Violation	0	0	0	0
Did Not Wish to Continue	1 (<1)	0	0	1 (<1)

Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Dem.xpt
 Source Code: Check_ITT.sas

Table 21. Patient Disposition by Final Status, Study P00362

Final Status	DL D-12	DL	PSE	Total
	2.5 DL/120 PSE mg BID	5.0 mg QD	120 mg BID	
	N (%)	N (%)	N (%)	N (%)
All Randomized Patients	214 (32.9)	214 (32.9)	222 (34.2)	650
ITT	214	214	222	650
Evaluable Subset	204 (95.3)	199 (93.0)	210 (94.6)	613 (94.3)
Completed	192 (94.1)	187 (94.0)	195 (92.9)	574 (93.6)
Not Completed	12 (5.9)	12 (6.0)	15 (7.1)	39 (6.4)
Not Evaluable Subset	10 (4.7)	15 (7.0)	12 (5.4)	37 (5.7)
Completed	8 (80)	13 (86.7)	9 (75)	30 (81.1)
Not Completed	2 (20)	2 (13.3)	3 (25.0)	7 (18.9)

Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Dem.xpt
 Sourced Code: Check_ITT.sas

Patient Demographics

Demographic data are summarized in **Table 22**. The treatment groups appear to be fairly balanced and comparable. The majority of patients in the treatment groups were female (66%) and Caucasian (84%). Very few patients at either end of the age spectrum (<18 and ≥ 65 years) were studied.

Table 22. Summary of Demographic Data, Study P00362

Demographic	Characteristic	DL D-12 2.5 DL/120 PSE mg BID	DL 5.0 mg QD	PSE 120 mg BID	Total
Age, (Year)	Mean	35.8	36.8	36.4	36.3
	Median	36	37	36	36
	Range (Min - Max)	12 – 76	12 – 78	12 – 78	12 – 78
Age, N (%)	12 - < 18	17 (7.9)	25 (11.7)	13 (5.9)	55 (8.5)
	18 - < 65	192 (89.7)	182 (85.1)	206 (92.8)	580 (89.2)
	≥ 65	5 (2.3)	7 (3.3)	3 (1.4)	15 (2.3)
Gender, N (%)	Male	77 (36.0)	66 (30.8)	78 (35.1)	221 (34.0)
	Female	137 (64.0)	148 (69.2)	144 (64.9)	429 (66.0)
Race, N (%)	Caucasian	177 (82.7)	178 (83.2)	191 (86.0)	546 (84.0)
	Non – Caucasian	37 (17.3)	36 (16.8)	31 (14.0)	104 (16.0)
	Black	19 (8.9)	12 (5.6)	14 (6.3)	45 (6.9)
	Asian	2 (0.9)	2 (0.9)	0	4 (0.6)
	Hispanic	13 (6.1)	19 (8.9)	17 (7.7)	49 (7.5)
	American Indian	0	1 (0.5)	0	1 (0.2)
	Other	3 (1.4)	2 (0.9)	0	5 (0.8)
Weight, (lbs)	Mean	170.2	167.1	165.1	167.4
	Median	165	160	160	161
	Range (Min - Max)	100 – 367	90 – 305	85 – 350	85 – 367
	Missing	1	0	0	1
Height, (in)	Mean	66.2	65.9	66.0	66.0
	Median	66	66	66	66
	Range (Min - Max)	56 – 76	57 – 80	56 – 78	56 – 80
	Missing	0	0	0	0
Duration of SAR, (years)	Mean	18.1	19.4	19.2	18.9
	Median	15	17	16	16
	Range (Min - Max)	2 – 65	2 – 59	2 – 59	2 – 65
All		214	214	222	650

Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Dem.xpt, Vitals.xpt, and Dishx.xpt
 Source Code: Demo_SUM.sas

Evaluation of Consistency of Results Across Centers

Twenty centers participated in this study. All centers contributed between 7 and 53 completed patients. The preliminary test for treatment-by-center interaction was not statistically significant for the primary efficacy variables (for nasal stuffiness/congestion symptom score, p=0.1266; and for total nasal symptom score excluding nasal congestion, p=0.1504). Therefore, the results are generally consistent across centers.

Evaluation of Missing Observations

The primary efficacy variables defined in the protocols were:

- Change from baseline in mean AM/PM PRIOR 12-hour total symptom score excluding nasal congestion (from the diary) for the antihistamine component, and
- Change from baseline in mean AM/PM PRIOR 12 –hour nasal Stuffiness/congestion score (from the diary) for the decongestant component.

The total symptom score was defined as the sum of all individual symptom scores. Whenever any one of the individual symptom scores was missing, the total score was considered missing. Similarly, the total nasal score was the sum of the 4 nasal symptom scores (rhinorrhea, nasal congestion, nasal itching, and sneezing) and the total non-nasal score was the sum of all non-nasal symptom scores (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate). Each individual symptom score was evaluated each morning and evening. For the derived intervals, the corresponding values were averaged over all non-missing days in the interval.

Table 23 describes the count of ITT patients (out of 650), who were not included in the primary efficacy variable, categorized by treatment and visit. Since there was a very small percentage of missing data, no separate analysis is necessary.

Table 23. Missing Observations of Primary Efficacy Variables, Study P00362

Variable	Treatment	<u>Visit</u>							
		Day 0 (baseline)	Day 1	Day 2	Day 3	Day 4	Days 1-8	Days 9-15	Days 1-15 (endpoint)
Total Symptom Score (7 Sympts)	DL D-12	0	0	0	2	2	0	9	0
	DL	0	0	2	1	2	0	8	0
	PSE	0	0	2	3	5	0	13	0
Nasal Stuffiness/ Congestion	DL D-12	0	0	0	2	2	1	9	0
	DL	0	0	2	1	2	1	8	0
	PSE	0	0	2	3	5	3	13	0

Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diaryn.xpt
 Sourced Code: Check_ITT.sas

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Analysis of Efficacy

This reviewer evaluated the sponsor’s statistical analyses by reanalyzing the sponsor’s data. The purpose for this reviewer’s analyses was to verify that the sponsor’s analyses, prospectively identified in the protocol, were carried out as planned. The following text details the reviewer’s analyses.

Primary Efficacy Variable

The primary efficacy variables defined in the protocols were:

- Change from baseline in mean AM/PM PRIOR 12-hour total symptom score excluding nasal congestion (from the diary) for the antihistamine component, and
- Change from baseline in mean AM/PM PRIOR 12 –hour nasal Stuffiness/congestion score (from the diary) for the decongestant component.

The primary time point for both variables was the average over the 15-day treatment period. The primary comparison for the antihistamine component was DL D-12 versus PSE. The primary comparison for the decongestant component was DL D-12 versus DL.

This reviewer evaluated the efficacy variables by two components: Antihistamine component and Decongestant component.

Antihistamine Component

Table 24 shows the raw mean changes and percent changes from baseline across the three treatments for mean total symptom score, excluding nasal congestion, for AM/PM PRIOR 12 hours.

Table 24. Raw Mean Changes of Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours, by Treatment and Interval, Study P00362

Interval	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	Mean ^a	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Baseline	214	15.2		214	14.7		222	14.8	
Change from Baseline									
Day 1	214	-3.41	(-22.4)	214	-2.44	(-16.8)	222	-2.25	(-15.2)
Day 2	214	-5.46	(-35.6)	212	-3.70	(-25.6)	220	-4.21	(-28.7)
Day 3	212	-6.10	(-40.2)	213	-4.46	(-30.4)	219	-4.58	(-31.1)
Day 4	212	-6.30	(-41.7)	212	-5.28	(-36.0)	217	-5.07	(-34.3)
Days 1-8	214	-6.13	(-40.2)	214	-4.78	(-32.6)	222	-4.80	(-32.6)
Days 9-15	205	-7.21	(-47.2)	206	-6.03	(-40.8)	209	-5.93	(-39.7)
Days 1-15	214	-6.56	(-43.0)	214	-5.29	(-35.9)	222	-5.22	(-35.3)

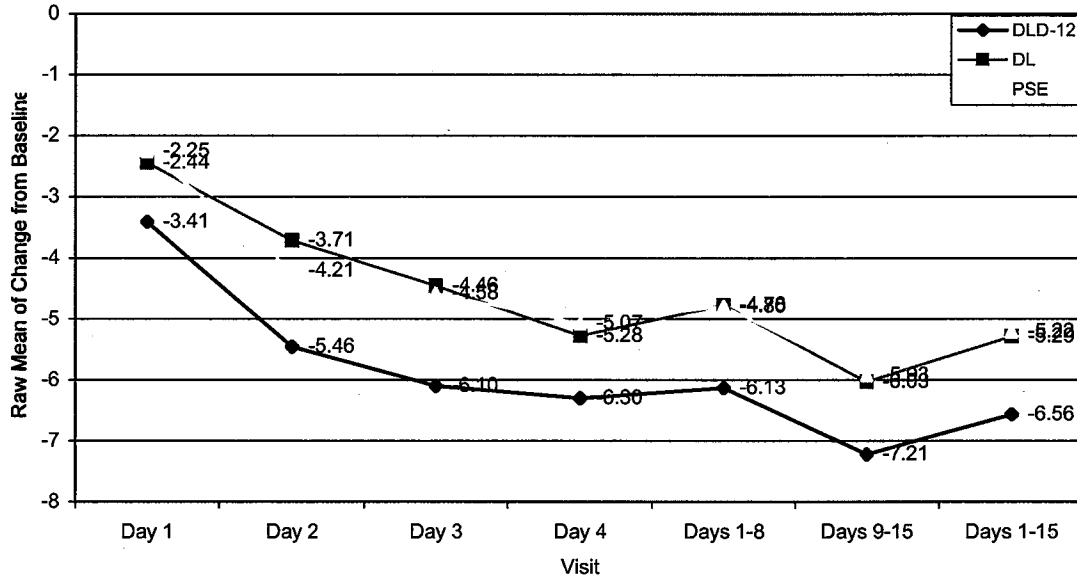
a: Mean and mean percent change are raw means.

Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diaryn.xpt

Source Code: Diary.sas

Figure 14 shows the treatment effect by showing the raw mean changes from baseline across the three treatments for mean total symptom score, excluding nasal congestion, for AM/PM PRIOR 12 hours.

Figure 14. Raw Mean Changes of Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours, by Interval, Study P00362



Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diaryn.xpt
Source Code: Diary362.xls

Raw mean total symptom scores excluding nasal congestion at baseline were similar in the DL D-12 and PSE groups. Mean percent reductions from baseline in AM/PM PRIOR 12 hours total symptom scores excluding nasal congestion averaged over Days 1-15 were 43.0% and 35.9% for DL D-12 and PSE, respectively. The graphic shows the difference between DL D-12 and PSE was seen as early as Day 2.

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Table 25 shows the Least Square Mean and 95% Confidence Interval of mean change from baseline with pairwise comparisons across the three treatments for mean total symptom score (excluding nasal congestion) for AM/PM PRIOR 12 hours.

DL D-12 was significantly more effective than PSE at the primary endpoint on this variable (p=0.0013). Statistically significant improvement (p≤0.0089) compared with PSE was observed on Day 1 and afterward. However, the difference between DL D-12 and PSE was smaller (1.46) than the difference between groups of 1.6, which was the estimated effect size. The power calculation assumed a pooled standard deviation of 4.25. The actual pooled standard deviation was 3.90. With a sample size of 200 subjects per treatment group, a two-tailed alpha-level of 0.05, and a pooled standard deviation of 3.90 points on the change from baseline, differences of 1.46 between treatment groups would be detectable with power of 95%.

Table 25. Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours

Study P00362									
Interval	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	LS Mean	95% CI	N	LS Mean	95% CI	N	LS Mean	95% CI
Baseline	214	15.15	(14.8, 15.5)	214	14.70	(14.3, 15.1)	222	14.81	(14.4, 15.2)
Change from Baseline									
Day 1	214	-3.28	(-3.9, -2.7)	214	-2.39	(-3.0, -1.8)	222	-2.19	(-2.8, -1.6)
Day 2	214	-5.38	(-6.0, -4.8)	212	-3.76	(-4.4, -3.2)	220	-4.22	(-4.8, -3.6)
Day 3	212	-6.02	(-6.6, -5.4)	213	-4.53	(-5.1, -3.9)	219	-4.58	(-5.2, -4.0)
Day 4	212	-6.25	(-6.9, -5.6)	212	-5.38	(-6.0, -4.7)	217	-5.09	(-5.7, -4.5)
Days 1-8	214	-6.07	(-6.6, -5.5)	214	-4.87	(-5.4, -4.3)	222	-4.83	(-5.4, -4.3)
Days 9-15	205	-7.13	(-7.8, -6.5)	206	-6.20	(-6.8, -5.6)	209	-5.99	(-6.6, -5.4)
Days 1-15	214	-6.52	(-7.1, -6.0)	214	-5.41	(-6.0, -4.9)	222	-5.30	(-5.8, -4.8)

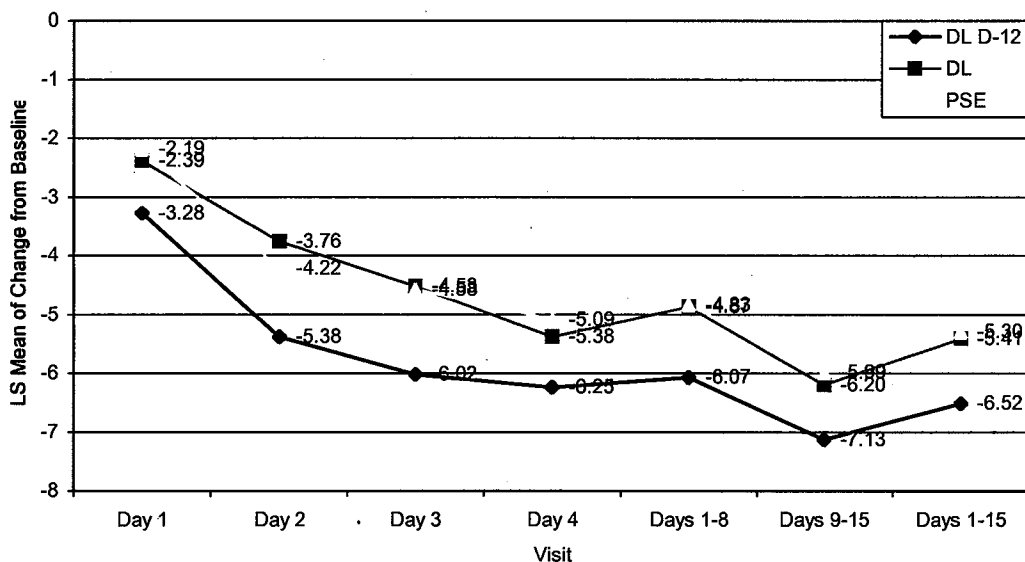
Interval	Pstd	Model p-value		Pairwise Comparison p-value		
		Treatment	Center	DL D-12 vs. DL	DL D-12 vs. PSE	DL vs. PSE
Baseline	2.79	0.2141	<.0001	0.0926	0.1995	0.6775
Change from Baseline						
Day 1	4.30	0.0211	0.0023	0.0345	0.0088	0.6249
Day 2	4.24	0.0003	0.0266	<.0001	0.0046	0.2649
Day 3	4.36	<.0004	0.0371	<.0005	<.0007	0.9061
Day 4	4.54	0.0254	0.0115	0.0524	0.0089	0.5052
Days 1-8	3.94	0.0012	0.0015	0.0018	0.0011	0.9157
Days 9-15	4.35	0.0183	0.0280	0.0304	0.0077	0.6266
Days 1-15	3.90	0.0019	0.0035	0.0036	0.0013	0.7732

Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diaryn.xpt
 Source Code: Diary.sas

Figure 15 shows the treatment effect by showing the least square mean changes from baseline across the three treatments for mean total symptom score, excluding nasal congestion, for AM/PM PRIOR 12 hours.

The DL D-12 group demonstrated a decline in symptom severity by Day 1 and was significantly more effective than PSE for this variable.

Figure 15. LS Mean Changes of Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours, by Visit, Study P00362

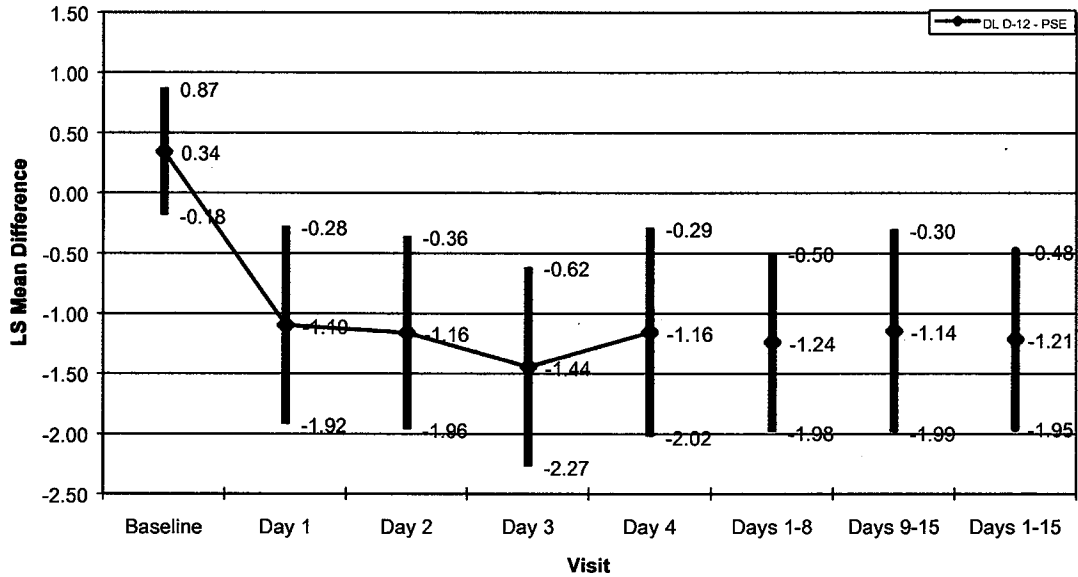


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 Source: Lsmean.xls

Figure 16 and Figure 17 show the confidence intervals of difference in LS means between treatment groups for each visit and endpoint for this primary efficacy variable.

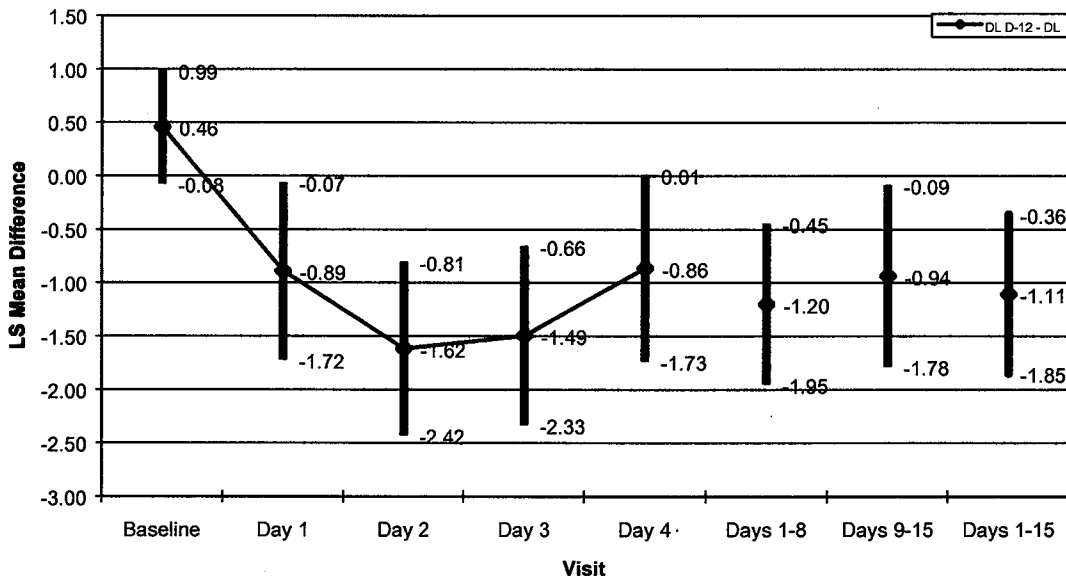
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**Figure 16. Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours
 LS Mean Difference between DL D-12 and PSE, Study P00362**



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 Source Code: Mean-diff362.xls

**Figure 17. Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours
 LS Mean Difference between DL D-12 and DL, Study P00362**



Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diary.n.xpt
 Source Code: Mean-diff362.xls

Decongestant Component

Table 26 shows the raw mean changes and percent changes from baseline across the three treatments for mean nasal stuffiness/congestion score, for AM/PM PRIOR 12 hours.

Raw means of nasal stuffiness/congestion at baseline were similar in the DL D-12 and DL groups. Mean percent reductions from baseline in AM/PM PRIOR 12 hours nasal congestion symptom scores averaged over Days 1-15 were 36.0% and 28.8% for DL D-12 and DL, respectively.

Table 26. Raw Mean Changes of Nasal Stuffiness/Congestion Symptom Score AM/PM PRIOR 12 Hours, by Treatment and Interval, Study P00362

Interval	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	Mean ^a	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Baseline	214	2.55		214	2.56		222	2.56	
Change from Baseline									
Day 1	214	-0.60	(-23.1)	214	-0.39	(-15.0)	222	-0.50	(-18.9)
Day 2	214	-0.84	(-32.8)	212	-0.53	(-20.7)	220	-0.68	(-26.2)
Day 3	212	-0.90	(-35.5)	213	-0.62	(-23.9)	219	-0.69	(-26.1)
Day 4	212	-0.89	(-35.2)	212	-0.72	(-28.1)	217	-0.81	(-30.9)
Days 1-8	214	-0.87	(-34.1)	214	-0.66	(-25.8)	222	-0.75	(-28.9)
Days 9-15	205	-0.99	(-38.6)	206	-0.84	(-32.9)	209	-0.94	(-35.8)
Days 1-15	214	-0.92	(-36.0)	214	-0.73	(-28.8)	222	-0.83	(-31.6)

a: Mean and mean percent change are raw means.

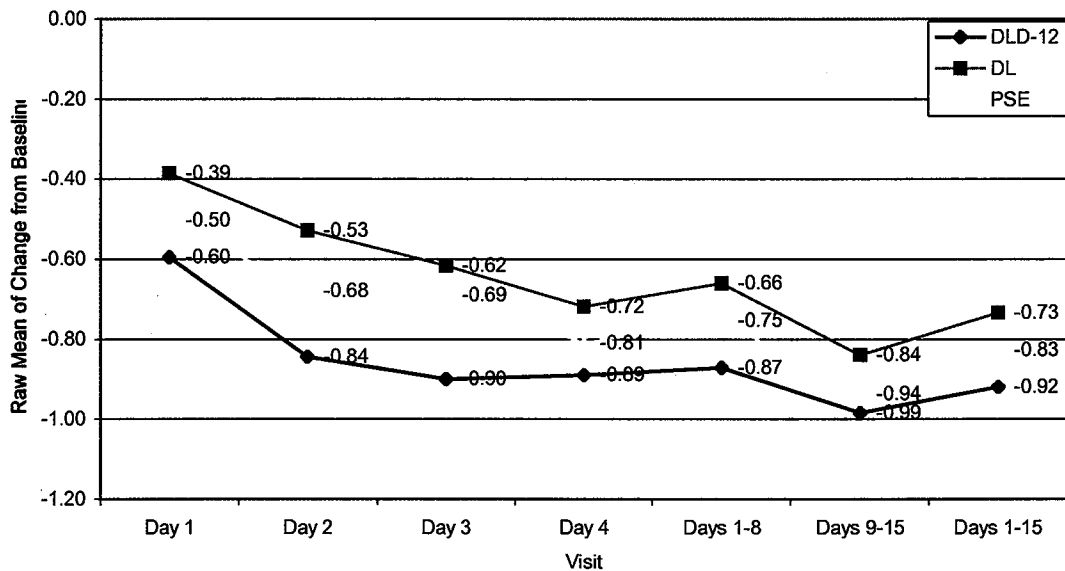
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Figure 18 shows the treatment effect by showing the raw mean changes from baseline across the three treatments for mean nasal stuffiness/congestion symptom score for AM/PM PRIOR 12 hours.

Figure 18. Nasal Stuffiness/Congestion Symptom Score AM/PM PRIOR 12 Hours
by Interval, Study P00362



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Table 27 shows the Least Square Means and 95% Confidence Interval of mean changes from baseline with pairwise comparisons across the 3 treatments for mean nasal stuffiness/congestion symptom scores for AM/PM PRIOR 12 hours.

DL D-12 was significantly more effective than DL at the primary endpoint (Days 1-15) on this variable ($p=0.0025$). Statistically significant improvement ($p<0.0438$) compared with DL was observed on Day 1 and afterward. The difference between DL D-12 and DL was slightly smaller (0.19) than the difference between groups of 0.2, which was the assumed effect size. The power calculation assumed a pooled standard deviation of 0.6 points. The actual pooled standard deviation was 0.65.

Table 27. Statistical Results of Nasal Stuffiness/Congestion Symptom Score AM/PM PRIOR 12 Hours, Study P00362

Interval	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	LS Mean	95% CI	N	LS Mean	95% CI	N	LS Mean	95% CI
Baseline	214	2.55	(2.50, 2.60)	214	2.56	(2.51, 2.61)	222	2.55	(2.51, 2.61)
Change from Baseline									
Day 1	214	-0.58	(-.69, -.48)	214	-0.37	(-.48, -.26)	222	-0.49	(-.60, -.38)
Day 2	214	-0.85	(-.95, -.74)	214	-0.53	(-.63, -.42)	222	-0.68	(-.78, -.57)
Day 3	212	-0.89	(-1.0, -.79)	213	-0.60	(-.71, -.50)	219	-0.67	(-.78, -.57)
Day 4	212	-0.89	(-1.0, -.78)	212	-0.72	(-.83, -.61)	217	-0.81	(-.92, -.70)
Days 1-8	214	-0.87	(-.96, -.78)	214	-0.65	(-.75, -.56)	222	-0.75	(-.84, -.66)
Days 9-15	205	-0.98	(-1.1, -.88)	206	-0.83	(-.94, -.73)	209	-0.93	(-1.0, -.83)
Days 1-15	214	-0.92	(-1.0, -.83)	214	-0.73	(-.82, -.64)	222	-0.82	(-.91, -.74)

Interval	Pstd	Model p-value		Pairwise Comparison p-value		
		Treatment	Center	DL D-12 vs. DL	DL D-12 vs. PSE	DL vs. PSE
Baseline	0.36	0.9604	<.0001	0.7814	0.8473	0.9303
Change from Baseline						
Day 1	0.78	0.0208	0.5571	0.0055	0.2180	0.1147
Day 2	0.75	<.0001	0.0817	<.0001	0.0179	0.0363
Day 3	0.75	0.0002	0.0896	<.0001	0.0030	0.3151
Day 4	0.80	0.0889	0.2705	0.0279	0.2682	0.2664
Days 1-8	0.66	0.0033	0.0458	0.0008	0.0517	0.1440
Days 9-15	0.73	0.1215	0.1126	0.0438	0.4975	0.1769
Days 1-15	0.65	0.0104	0.0540	0.0025	0.1261	0.1262

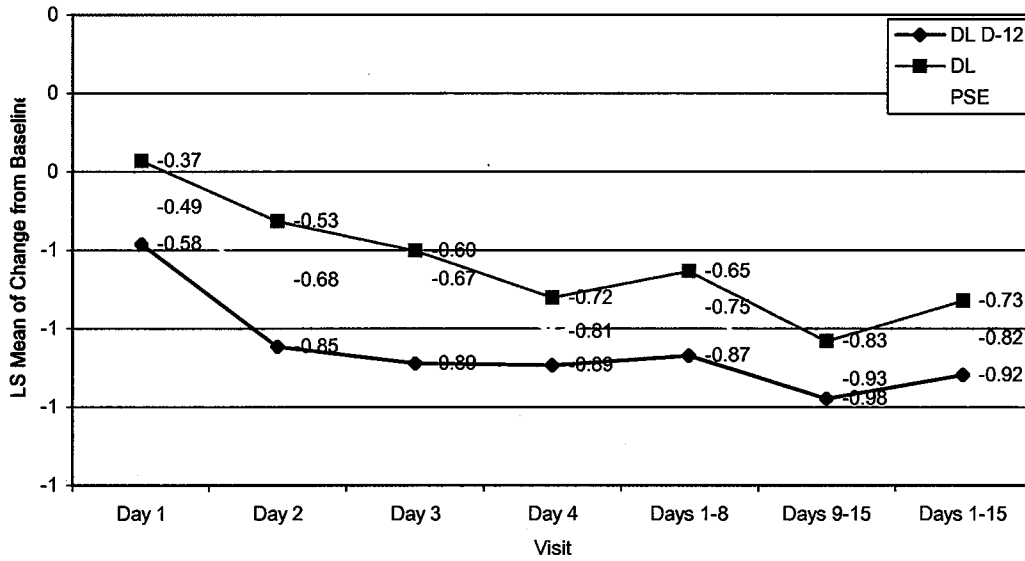
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Figure 19 shows the least square mean changes from baseline across the three treatments for mean nasal stuffiness/congestion symptom score, for AM/PM PRIOR 12 hours.

The DL D-12 group demonstrated a decline in symptom severity starting at Day 1 and was significantly more effective than DL for this variable.

Figure 19. LS Mean Changes of Nasal Stuffiness/Congestion Symptom Score AM/PM PRIOR 12 Hours, by Visit, Study P00362

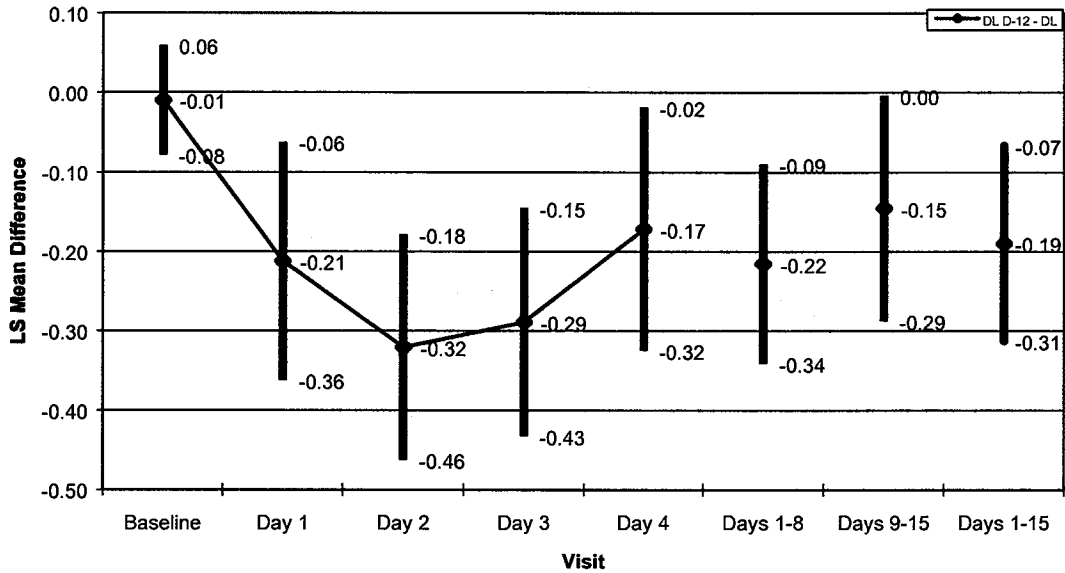


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 Source Code: Lsmean.xls

Figure 20 and **Figure 21** show the confidence intervals of difference in LS means between treatment groups for each visit and endpoint for this variable.

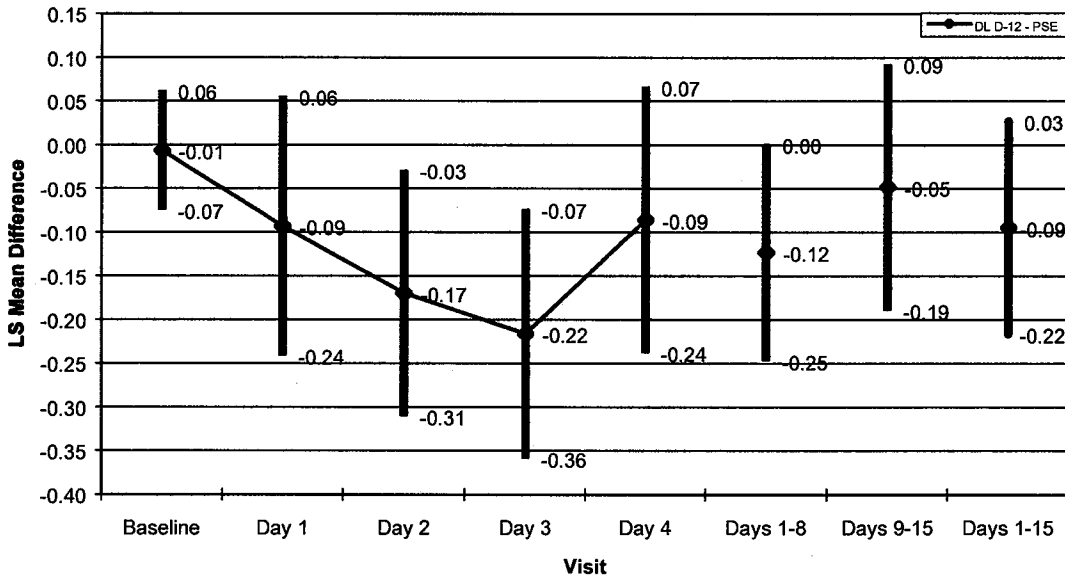
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Figure 20. Nasal Stiffness/Congestion Symptom Score AM/PM PRIOR 12 Hours
LS Mean Difference between DL D-12 and DL, Study P00362



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 Source Code: Mean-diff362.xls

Figure 21. Nasal Stiffness/Congestion Symptom Score AM/PM PRIOR 12 Hours
LS Mean Difference between DL D-12 and PSE, Study P00362



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 Source Code: Mean-diff362.xls

Interim Analyses and Data Monitoring

No interim analyses were planned in the protocol and none was performed. There was no Data Monitoring Committee for this protocol.

Multiple Comparisons/Multiplicity

No adjustment for multiple comparisons was planned in the protocol. This reviewer considers that no adjustment for multiple comparisons is needed because the DL D-12 must beat both components (DL and PSE) for the efficacy variables.

Evaluation of Subgroups

Summary statistics for the primary efficacy variables, total symptom score excluding nasal congestion and nasal stuffiness/congestion symptom score, averaged over 2 weeks, were evaluated for the following subject subgroups: age (12 - < 18 years, 18 - < 65 years, ≥ 65 years), gender, and race (Caucasian, non-Caucasian). **Table 28**, **Table 29**, and **Table 30** show the results comparing the three treatment groups for these demographic variables. Overall, DL D-12 showed a statistically significant decline comparing to PSE in symptom severity for mean AM/PM PRIOR total symptom scores (excluding nasal congestion) in both male and female patients. DL D-12 was numerically more effective than DL in reducing mean AM/PM PRIOR nasal stuffiness/congestion symptom score in both male and female patients. There were too few subjects age 12 to <18 years or ≥ 65 years, or who were non-Caucasian to provide a formal assessment of differential treatment response by age or race. However, no appreciable differences between the treatments were noted for sex, age, and race subgroups.

Table 28. Primary Efficacy Variables AM/PM PRIOR 12 Hours 2-week Average, by Age Group (Study P00362)

Demographic Characteristic	Total Symptom Score Excluding Nasal Congestion						Nasal Stuffiness/Congestion Symptom Score					
	Change from Baseline											
	DL D-12		DL		PSE		DL D-12		DL		PSE	
	N	Mean ¹	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Age												
12 - < 18	17	-4.03	25	-4.85	13	-3.65	17	-0.43	25	-0.77	13	-0.63
18 - < 65	192	-6.79	182	-5.39	206	-5.30	192	-0.96	182	-0.73	206	-0.83
≥ 65	5	-6.46	7	-4.15	3	-6.29	5	-1.27	7	-0.63	3	-1.23
All	214	-6.56	214	-5.29	222	-5.22	214	-0.92	214	-0.73	222	-0.83
	Pairwise Comparisons p-value ²											
	DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE		DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE	
Age												
12 - < 18	0.5788		0.8216		0.7921		0.3125		0.3371		0.9345	
18 - < 65	0.0036		0.0006		0.6698		0.0014		0.0628		0.1558	
≥ 65	0.5945		0.2697		0.1914		0.2242		0.3831		0.1466	
All	0.0036		0.0013		0.7732		0.0025		0.1261		0.1262	

1: Mean was raw mean.

2: p-value were obtained from the two-way ANOVA model with baseline, treatment, and site effects.

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Table 29. Primary Efficacy Variables AM/PM PRIOR 12 Hours 2-week Average, by Gender Group (Study P00362)

Demographic Characteristic	Total Symptom Score Excluding Nasal Congestion						Nasal Stuffiness/Congestion Symptom Score					
	Change from Baseline											
	DL D-12		DL		PSE		DL D-12		DL		PSE	
	N,	Mean ¹	N,	Mean	N,	Mean	N,	Mean	N,	Mean	N,	Mean
Gender												
Female	137	-6.73	148	-5.70	144	-5.69	137	-0.86	148	-0.64	144	-0.75
Male	77	-6.26	66	-4.37	78	-4.34	77	-0.96	66	-0.78	78	-0.87
All	214	-6.56	214	-5.29	222	-5.22	214	-0.92	214	-0.73	222	-0.83
Pairwise Comparisons p-value²												
	DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE		DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE	
Gender												
Female	0.0711		0.0212		0.6001		0.0232		0.1534		0.3988	
Male	0.0094		0.0260		0.6615		0.0553		0.6586		0.1435	
All	0.0036		0.0013		0.7732		0.0025		0.1261		0.1262	

1: Mean was raw mean.

2: p-value were obtained from the two-way ANOVA model with baseline, treatment, and site effects.

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Table 30. Primary Efficacy Variables AM/PM PRIOR 12 Hours 2-week Average By Race Group (Study P00362)

Demographic Characteristic	Total Symptom Score Excluding Nasal Congestion						Nasal Stuffiness/Congestion Symptom Score					
	Change from Baseline											
	DL D-12		DL		PSE		DL D-12		DL		PSE	
	N,	Mean ¹	N,	Mean	N,	Mean	N,	Mean	N,	Mean	N,	Mean
Race												
Caucasian	177	-6.48	178	-5.10	191	-5.20	177	-0.92	178	-0.72	191	-0.83
Non-Caucasian	37	-6.97	36	-6.20	31	-5.31	37	-0.93	36	-0.82	31	-0.78
All	214	-6.56	214	-5.29	222	-5.22	214	-0.92	214	-0.73	222	-0.83
Pairwise Comparisons p-value²												
	DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE		DL D-12 vs. DL		DL D-12 vs. PSE		DL vs. PSE	
Race												
Caucasian	0.0034		0.0059		0.8270		0.0028		0.1667		0.0947	
Non-Caucasian	0.5157		0.0129		0.0543		0.3424		0.1391		0.5439	
All	0.0036		0.0013		0.7732		0.0025		0.1261		0.1262	

1: Mean was raw mean.

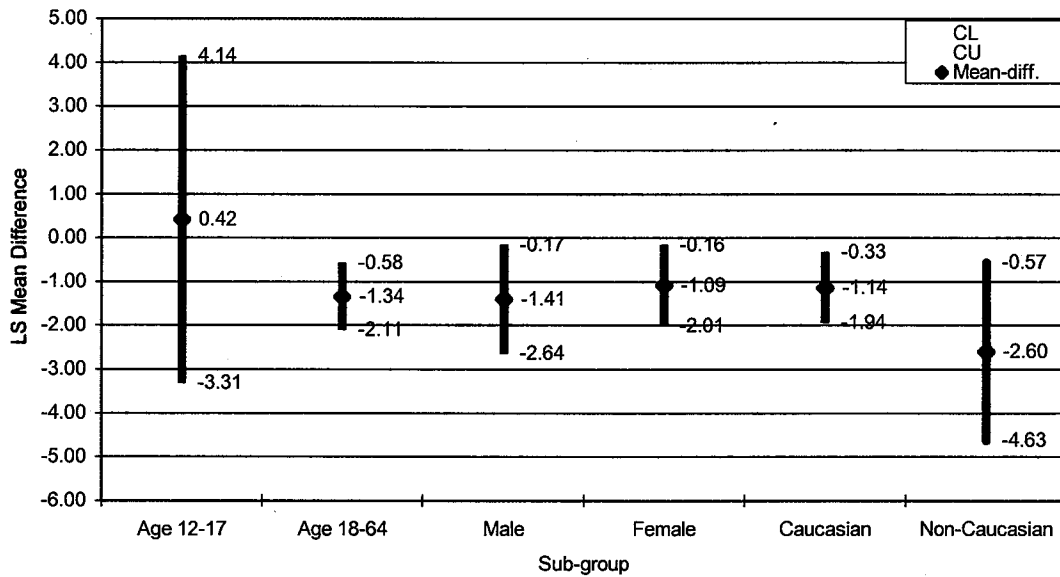
2: p-value were obtained from the two-way ANOVA model with baseline, treatment, and site effects.

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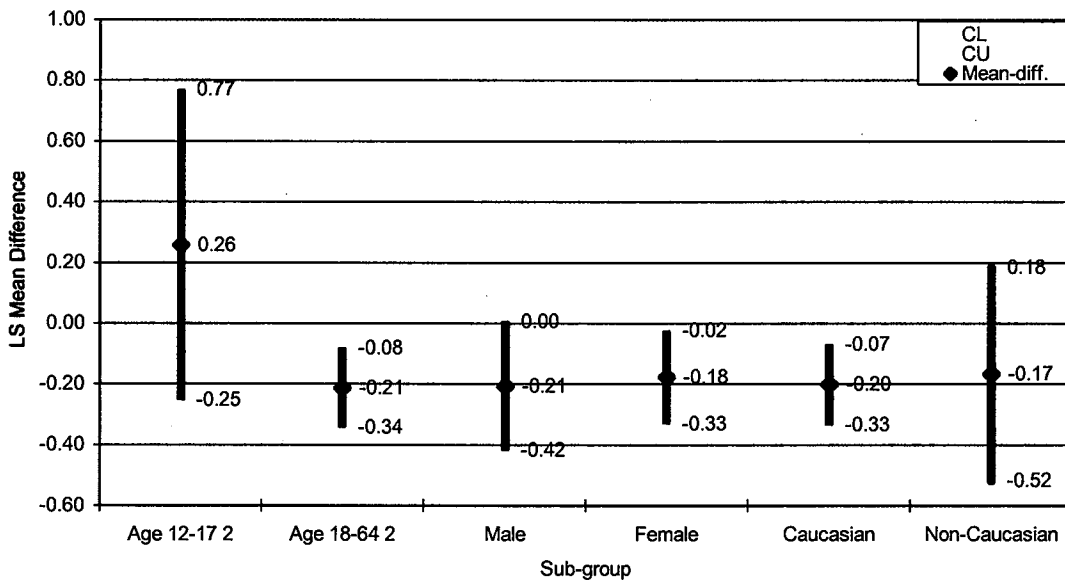
Figure 22 and Figure 23 show the confidence intervals of LS mean difference for each sub-group.

Figure 22. Total Symptom Score (Excluding Nasal Congestion) AM/PM PRIOR 12 Hours
LS Mean Difference between DL D-12 and PSE, Study P00362



Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diaryn.xpt
 Source Code: Mean-diff362.xls

Figure 23. Nasal Stiffness/Congestion Symptom Score AM/PM PRIOR 12 Hours
LS Mean Difference between DL D-12 and DL, Study P00362



Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diaryn.xpt
 Source Code: Mean-diff362.xls

Secondary Efficacy Variable

The secondary efficacy variables defined in the protocols were:

- End of Dosing Interval
 - Change from baseline in mean AM/PM NOW total symptom score excluding nasal congestion (from the diary) for the antihistamine component, and
 - Change from baseline in mean AM/PM NOW nasal stuffiness/congestion score (from the diary) for the decongestant component.
- Change from baseline in the total (with nasal congestion), total nasal (with and without nasal congestion), total non-nasal, and individual mean AM/PM PRIOR 12 hours symptom scores expressed as a change from baseline. Additional variables included the overall condition of SAR expressed as the change from baseline, and the evaluation of therapeutic response expressed as a raw score.

For the antihistamine component, the main comparison was DL D-12 versus PSE over the 15-day treatment period, based on the change from baseline in mean AM/PM NOW total symptom score excluding nasal congestion. For Day 1-15, DL D-12 was numerically superior to PSE at all the time assessments and reached the statistical significance ($p < 0.0209$), as shown in the **Table 31**.

Table 31. Total Symptom Score (Excluding Nasal Congestion), by Time point, Study P00362

Time Point	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	Mean ^a	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Change from Baseline to Days 1-15									
AM P-12 hrs	214	-6.42	(-42.4)	213	-5.30	(-36.3)	220	-5.01	(-34.6)
AM Now	214	-6.03	(40.4)	213	-5.08	(-34.2)	220	-5.10	(-34.7)
PM P-12 hrs	214	-6.75	(-43.3)	214	-5.31	(-35.3)	222	-5.46	(-35.8)
PM Now	214	-6.47	(-43.3)	214	-5.21	(-35.5)	214	-5.40	(-36.3)
AM/PM P-12 hrs	214	-6.59	(-43.0)	214	-5.30	(-36.1)	222	-5.24	(-35.5)
AM/PM Now	214	-6.25	(-42.1)	214	-5.15	(-35.2)	222	-5.25	(-35.7)

	DL D-12 vs. DL			DL D-12 vs. PSE		
	LS Mean Difference	95% CI	p-value	LS Mean Difference	95% CI	p-value
Change from Baseline to Days 1-15						
AM P-12 hrs	-0.9330	(-1.69, -0.17)	0.0160	-1.2271	(-1.98, -0.48)	0.0014
AM Now	-0.8603	(-1.61, -0.11)	0.0245	-0.8752	(-1.62, -0.13)	0.0209
PM P-12 hrs	-1.1639	(-1.92, -0.40)	0.0028	-1.2121	(-1.96, -0.46)	0.0016
PM Now	-0.9320	(-1.70, -0.17)	0.0170	-1.0329	(-1.79, -0.28)	0.0073
AM/PM P-12 hrs	-1.0718	(-1.82, -0.33)	0.0049	-1.2244	(-1.96, -0.49)	0.0012
AM/PM Now	-0.9175	(-1.66, -0.18)	0.0102	-0.9622	(-1.70, -0.23)	0.0155

a: Mean and Mean percent change are raw means.

Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diaryn.xpt

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For the decongestant component, the main comparison was DL D-12 versus DL over the 15-day treatment period, based on the change from baseline in mean AM NOW nasal congestion score. The AM time point was chosen as the end of dosing interval based on the once daily dosing regimen for DL. The AM NOW score represents symptoms present at the end of the dosing interval (approximately 24 hours after DL dosing, prior to taking the next DL dose). For Days 1-15, DL D-12 was numerically superior to DL at all the time assessments and reached the statistical significance ($p < 0.0317$), as shown in the **Table 32**.

Table 32. Nasal Stuffiness/Congestion Score, by Time point, Study P00362

Time Point	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID		
	N	Mean ^a	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Change from Baseline to Days 1-15									
AM P-12 hrs	214	-0.89	(-34.5)	213	-0.72	(-28.1)	220	-0.80	(-30.2)
AM Now	214	-0.83	(31.4)	213	-0.67	(-25.5)	220	-0.77	(-28.6)
PM P-12 hrs	214	-0.95	(-37.0)	214	-0.76	(-29.1)	222	-0.86	(-32.6)
PM Now	214	-0.89	(-35.2)	214	-0.74	(-28.8)	222	-0.82	(-30.9)
AM/PM P-12 hrs	214	-0.92	(-36.0)	214	-0.74	(-28.9)	222	-0.83	(-31.8)
AM/PM Now	214	-0.86	(-33.6)	214	-0.70	(-27.8)	222	-0.80	(-30.2)

Time Point	DL D-12 vs. DL			DL D-12 vs. PSE		
	LS Mean Difference	95% CI	p-value	LS Mean Difference	95% CI	p-value
Change from Baseline to Days 1-15						
AM P-12 hrs	-0.1702	(-0.30, -0.04)	0.0087	-0.0906	(-0.22, -0.04)	0.1590
AM Now	-0.1760	(-0.31, -0.05)	0.0075	-0.0507	(-0.18, -0.08)	0.4366
PM P-12 hrs	-0.2011	(-0.33, -0.07)	0.0019	-0.167	(-0.30, -0.04)	0.1125
PM Now	-0.1407	(-0.27, -0.01)	0.0317	-0.0713	(-0.20, -0.06)	0.2710
AM/PM P-12hrs	-0.1850	(-0.31, -0.06)	0.0032	-0.0927	(-0.21, -0.03)	0.1347
AM/PM Now	-0.1575	(-0.28, -0.03)	0.0133	-0.0607	(-0.18, -0.06)	0.3346

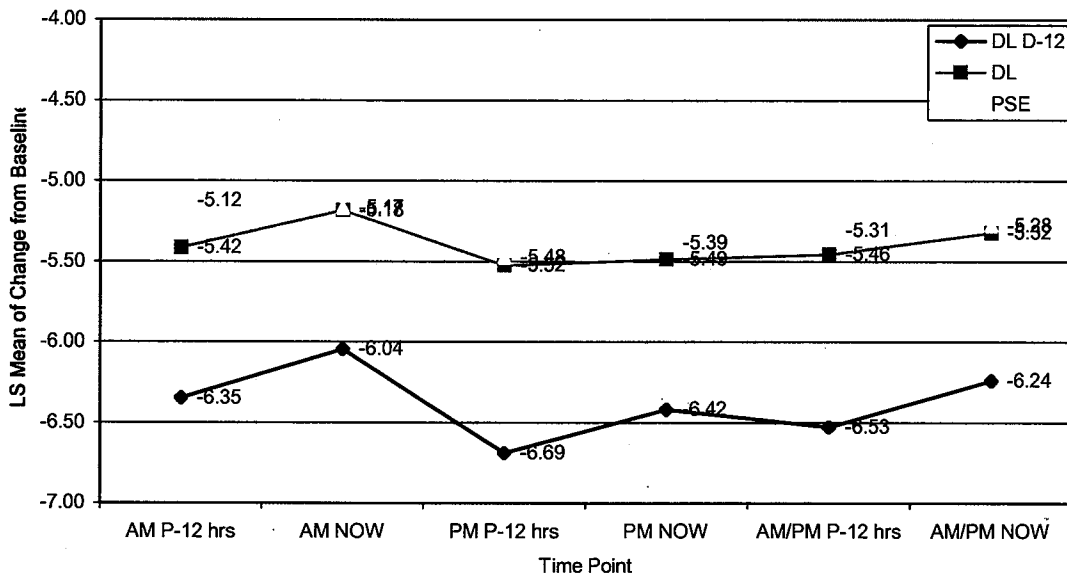
a: Mean and Mean percent change are raw means.

Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diaryn.xpt

Source Code: Second.sas

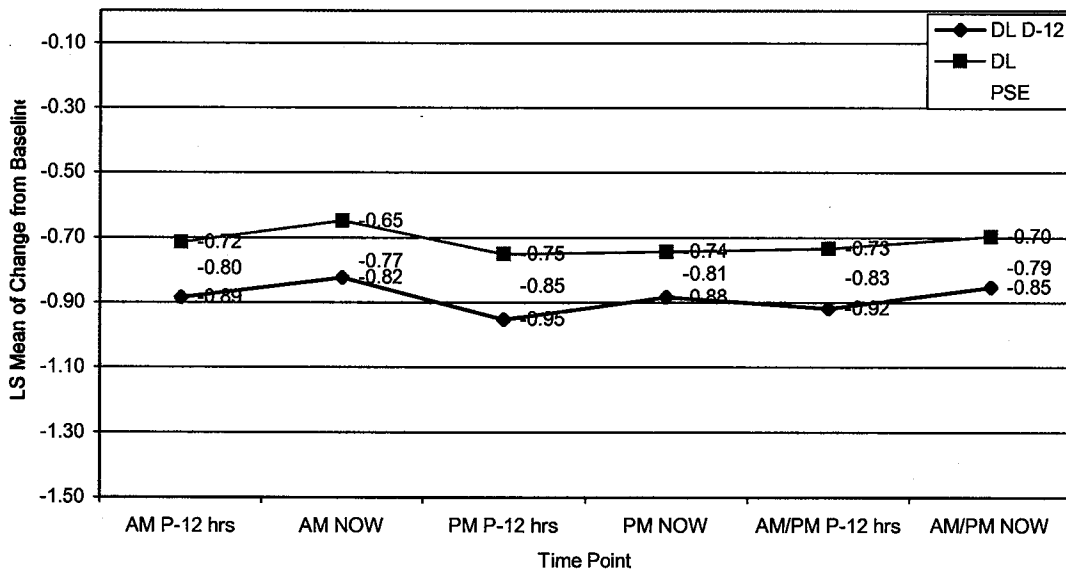
Figure 24 and **Figure 25** show the LS means of total symptom score (excluding nasal congestion) and nasal stuffiness/congestion symptom score, by time assessment.

Figure 24. LS Mean Changes of Total Symptom Score (Excluding Nasal Congestion), by Time Point, Study P00362



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Figure 25. LS Mean Changes of Nasal Stuffiness/Congestion Symptom Score, by Time Point, Study P00362



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 Source Code: LSmean.xls

The statistical analysis of the individual symptom scores other than nasal congestion did show that for Day 1-15, DL D-12 was numerically superior to both DL and PSE. For Nasal Itching, Sneezing Itching/Burning

Eyes, and Tearing/Watering Eyes, DL D-12 reached statistical significance ($p < 0.017$). For Day 1-15, DL D-12 did not show the statistically significant better than DL in Rhinorrhea ($p = 0.065$) and Itching of Ears or Palate ($p = 0.056$). Please reference to p76, vol.36.

The overall condition of SAR was evaluated jointly by the subject and investigator and recorded on a scale of 0-3. For Days 1-15, DL D-12 was numerically slightly superior to both DL and PSE, but was not statistical significant, as shown in the **Table 33**.

Table 33. Overall Condition of SAR Analysis Results, Study P00362

Time Point	DL D-12 2.5 DL/120 PSE mg BID			DL 5.0 mg QD			PSE 120 mg BID			
	N	Mean ^a	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change	
Baseline	213	2.667		211	2.583		219	2.607		
Change from Baseline										
Day 1-15	213	-1.05	(-36.8)	211	-0.83	(-31.0)	219	-0.89	(-31.9)	
DL D-12 vs. DL										
		LS Mean Difference	95% CI	p-value				LS Mean Difference	95% CI	p-value
Baseline		-0.085	(-0.01, 0.17)	0.0635		0.062		(-0.03, 0.15)	0.1710	
Change from Baseline										
Day 1-15		-0.145	(-0.28, 0.01)	0.0341		-0.106		(-0.24, 0.03)	0.1170	

a: Mean and Mean percent change are raw means.

Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diaryn.xpt

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For the evaluation of the therapeutic response, which was evaluated jointly by the subject and investigator and recorded on a scale of 1 (complete relief) to 5 (treatment failure), for Day 1-15, DL D-12 was numerically superior to both DL and PSE and reached statistical significance ($p < 0.0007$), as shown in the **Table 34**.

Table 34. Evaluation of Therapeutic Response Analysis Results, Study P00362

Time Point	DL D-12 2.5 DL/120 PSE mg BID		DL 5.0 mg QD		PSE 120 mg BID			
	N	Mean ^a	N	Mean	N	Mean		
Change from Baseline								
Days 1-15	213	2.882	211	3.213	219	3.205		
DL D-12 vs. DL								
		LS Mean Difference	95% CI	p-value		LS Mean Difference	95% CI	p-value
Change from Baseline								
Days 1-15		-0.327	(-0.51, 0.14)	0.0006		-0.321	(-0.51, 0.14)	0.0007

a: Mean and Mean percent change are raw means.

Source: \N_000\2000-12-08\CD of Clinical Data\P00362\DATA\Diaryn.xpt

Source Code: Second.sas

Summary of Efficacy

This randomized, double-blind, double-dummy study was designed to demonstrate that DL D-12 has superior antihistamine effects as compared with PSE, and that DL D-12 has superior decongestant effects, as compared with DL.

The pre-specified primary endpoint evaluating the antihistamine effect was the change from baseline in the AM/PM PRIOR 12 HOURS total symptom score, excluding nasal congestion, averaged over Days 1-15. The primary comparison for this variable was DL D-12 versus PSE. The results of the study demonstrated that DL D-12 was statistically superior to PSE on this variable ($p=0.0013$). Statistically significant improvement ($p\leq 0.0089$) compared with PSE was observed on Day 1 and afterward.

The pre-specified primary endpoint concerning the decongestant effect was the change from baseline in the reflective AM/PM PRIOR 12 HOURS nasal congestion score averaged over Days 1-15. The primary comparison on this variable was DL D-12 versus DL. The results of the study demonstrated that DL D-12 was statistically superior to DL on this variable ($p=0.0025$). Statistically significant improvement ($p\leq 0.0438$) compared with DL was observed on Day 1 and afterward.

The various secondary analyses of symptom scores supported the conclusions drawn from the primary endpoints. Instantaneous symptom scores demonstrated that the efficacy of DL D-12 is maintained at the end of the dosing interval ($p\leq 0.0155$). Evaluations of the overall condition of SAR, which were performed jointly by the patients and investigator, favored DL D-12 but failed to reach statistical significance. Evaluations of the therapeutic response, which were performed jointly by the patients and investigator, favored DL D-12 and reached statistical significance ($p<0.0007$).

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Reviewer's Evaluation of Safety

Evaluation of Adverse Events

Safety variables included adverse events (AEs), discontinuations due to AEs, changes in baseline in vital signs, nasal examination, hematology, clinical chemistry, urinalysis, ophthalmic, and ECGs. Because studies P00355 and P00362 were performed under identical protocols, this review concentrated on evaluating the adverse event data from both studies collectively.

Table 35 shows the most common adverse events (those reported in $\geq 1\%$ of patients in any treatment group) in both studies. The overall incidence of adverse events was similar in the DL D-12 and PSE treatment groups (48% and 50%), but was lower in the DL group (43%). The most frequently reported adverse events (those occurring in at least 5% of patients in any treatment group) were headache, insomnia, and dry mouth. Insomnia and dry mouth occurred with greater frequency among patients treated with DL D-12 (9.7% and 7.5%, respectively) or PSE (12.8% and 7.8%, respectively) than in patients treated with DL (2.7% and 2.4%, respectively). Headache occurred frequently in all treatment groups with rates 12.1% for DL D-12, 10.7% for DL, and 12.3% for PSE.

Table 35. Adverse Events Occurring More Commonly in Studies at a Rate $\geq 1\%$

Adverse Event	Number (%) of Patients ¹			Total (1248)
	DL D-12 2.5 DL/120 PSE mg BID (414)	DL 5.0 mg QD (412)	PSE 120 mg BID (422)	
Patients with AEs	197 (47.58)	176 (42.72)	213 (50.47)	586 (46.96)
Headache	50 (12.08)	44 (10.68)	52 (12.32)	146 (11.70)
Insomnia	40 (9.66)	11 (2.67)	54 (12.80)	105 (12.80)
Dry Mouth	31 (7.49)	10 (2.43)	33 (7.82)	74 (5.93)
Fatigue	17 (4.11)	11 (2.67)	11 (2.61)	39 (3.13)
Dizziness	14 (3.38)	10 (2.43)	9 (2.13)	33 (2.64)
Somnolence	13 (3.14)	16 (3.88)	7 (1.66)	36 (2.88)
Pharyngitis	14 (3.38)	12 (2.91)	13 (3.08)	39 (3.13)
Myalgia	9 (2.17)	11 (2.67)	9 (2.13)	29 (2.32)
Nausea	9 (2.17)	7 (1.70)	13 (3.08)	29 (2.32)
Infection Viral	9 (2.17)	9 (2.18)	12 (2.84)	30 (2.4)
Dyspepsia	7 (1.69)	9 (2.18)	8 (1.90)	24 (1.92)
Nervousness	6 (1.45)	1 (0.24)	11 (2.61)	18 (1.44)
Sinusitis	3 (0.72)	4 (0.97)	11 (2.61)	18 (1.44)
Upper Resp. Tract Infection	1 (0.24)	7 (1.70)	9 (2.13)	17 (1.36)
Anorexia	8 (1.93)	0	9 (2.13)	17 (1.36)
Back Pain	6 (1.45)	4 (0.97)	7 (1.66)	17 (1.36)
Abdominal Pain	3 (0.72)	6 (1.46)	7 (1.66)	16 (1.28)
Arthralgia	7 (1.69)	3 (0.73)	4 (0.95)	14 (1.12)
Sleep Disorder	6 (1.45)	0	7 (1.66)	13 (1.04)
Epistaxis	2 (0.48)	5 (1.21)	5 (1.18)	12 (0.96)
Diarrhea	1 (0.24)	7 (1.70)	3 (0.71)	11 (0.88)
Palpitation	2 (0.48)	1 (0.24)	7 (1.66)	10 (0.80)

1: Percentages were based on patient population of each treatment group.

Table 36 shows the numbers and percentages of adverse events reported by $\geq 5\%$ of patients by treatment and subgroup in studies.

Subgroup analysis of AEs did not reveal meaningful differences in the subgroup, but reveal the same pattern, which was the frequencies of AEs were similar between DL D-12 and PSE treatment groups and smaller in DL treatment group. In age groups, the frequencies of AEs were smaller in younger patients (34.7%) and slightly larger in age 18+ patients (48.0%). The frequencies of AEs were higher in females than males (50.6% and 40.5%, respectively). Headache was reported more frequently in females (10.8%-14.0%) than in males (9.0%-10.4%). The frequency and types of AEs were similar for DL D-12 and PSE treatment groups in Caucasian (49.7% and 52.3%, respectively) and the small number of non-Caucasian patients (38.2%, 41.2%, respectively). Insomnia was reported more frequently in age 65+ patients for DL and PSE treatment groups (22.2% and 33.3%, respectively). Dry mouth was reported more frequently in age 65+ patients for DL D-12 (40%) compared to 0% for DL and PSE.

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Table 36. Adverse Events Reported by ≥ 5% of Patients by Treatments and Subgroup

Adverse Event	Number (%) of Patients ¹			Total (1248)
	DL D-12 2.5 DL/120 PSE mg BID (414)	DL 5.0 mg QD (412)	PSE 120 mg BID (422)	
Patients with AEs	197 (47.58)	176 (42.72)	213 (50.47)	586 (46.96)
Male	66 (42.3)	50 (37.0)	64 (41.6)	180 (40.5)
Female	131 (50.8)	126 (45.5)	149 (55.6)	406 (50.6)
Age 12 – 17	13 (37.1)	13 (27.1)	16 (42.1)	42 (34.7)
Age 18 – 64	179 (48.5)	159 (44.8)	194 (51.3)	532 (48.3)
Age 65+	5 (50.0)	4 (44.4)	3 (50.0)	12 (48.0)
Caucasian	168 (49.7)	141 (42.7)	185 (52.3)	494 (48.3)
Non-Caucasian	29 (38.2)	35 (42.7)	28 (41.2)	92 (40.7)
Headache	50 (12.08)	44 (10.68)	52 (12.32)	146 (11.70)
Male	14 (9.0)	14 (10.4)	16 (10.4)	44 (9.9)
Female	36 (14.0)	30 (10.8)	36 (13.4)	102 (12.7)
Age 12 – 17	2 (5.7)	6 (12.5)	2 (5.3)	10 (8.3)
Age 18 – 64	48 (13.0)	38 (10.7)	50 (13.2)	136 (12.3)
Age 65+	0	0	0	0
Caucasian	44 (13.0)	34 (10.3)	44 (12.4)	122 (11.9)
Non-Caucasian	6 (7.9)	10 (12.2)	8 (11.8)	24 (10.6)
Insomnia	40 (9.66)	11 (2.67)	54 (12.80)	105 (12.80)
Male	11 (7.1)	3 (2.2)	16 (10.4)	30 (6.7)
Female	29 (11.2)	8 (2.9)	38 (14.2)	75 (9.3)
Age 12 – 17	2 (5.7)	2 (4.2)	3 (7.9)	7 (5.8)
Age 18 – 64	37 (10.0)	7 (2.0)	49 (13.0)	93 (8.4)
Age 65+	1 (10.0)	2 (22.2)	2 (33.3)	5 (20.0)
Caucasian	37 (11.0)	10 (3.0)	49 (13.8)	96 (9.4)
Non-Caucasian	3 (4.0)	1 (1.2)	5 (7.4)	9 (4.0)
Dry Mouth	31 (7.49)	10 (2.43)	33 (7.82)	74 (5.93)
Male	13 (8.3)	3 (2.2)	5 (3.3)	21 (4.7)
Female	18 (7.0)	7 (2.5)	28 (10.5)	53 (6.6)
Age 12 – 17	2 (5.7)	1 (2.1)	1 (2.6)	4 (3.3)
Age 18 – 64	25 (6.8)	9 (2.5)	32 (8.5)	66 (6.0)
Age 65+	4 (40.0)	0	0	4 (16.0)
Caucasian	24 (7.1)	8 (2.4)	27 (7.6)	59 (5.8)
Non-Caucasian	7 (9.2)	2 (2.4)	6 (8.8)	15 (6.6)

* Percentages were based on patient population of each treatment by each subgroup.

Summary of Safety Evaluation

This reviewer only evaluated the AEs in two studies P00355 and P00362 and concluded as following:

- The majority of adverse events that occurred following treatment with DL D-12 were similar in type and frequency to those observed with PSE.
- The overall incidence of adverse events was greater in the DL D-12 and PSE groups compared with the DL group.
- Headache was the most frequently reported adverse event in the three treatment groups.
- Insomnia and dry mouth were frequently reported adverse events in the DL D-12 and PSE treatment group.

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Conclusions

Clarinet-D™ 12 Hour extended release tablet has been developed as a combination product of desloratadine 2.5 mg and pseudoephedrine 120 mg. The new product, Clarinet-D™ 12 Hour is indicated for the relief of symptoms of seasonal allergic rhinitis in adults and children 12 years of age and older. The proposed dosage of Clarinet-D™ 12 Hour for adults and adolescents aged 12 years and older is 2.5mg/120mg twice daily.

Based on a statistical evaluation of studies P00355 and P00362, this reviewer concludes that the sponsor has presented adequate evidence to demonstrate that Clarinet-D™ 12 Hour is effective in adults and adolescent patients ages 12 years and older.

More specifically, this reviewer has concluded that:

1. The antihistaminic efficacy of DL D-12, as measured by mean AM/PM PRIOR 12 hours total symptom score excluding nasal congestion, was statistically ($p < 0.0013$) superior to PSE over the 15-day treatment period and was observed as early as Day 2 of treatment and afterward.
2. The decongestant efficacy of DL D-12, as measured by mean AM/PM PRIOR 12 hours nasal congestion scores, was statistically ($p < 0.0025$) superior to DL over the 15-day treatment period and was observed as early as Day 2 and afterward.
3. The antihistaminic and decongestant efficacy of DL D-12 at the end of the dosing interval were significantly greater than PSE and DL, respectively, over the 15-day treatment period ($p < 0.015$).

In summary, the sponsor has provided sufficient statistical evidence to demonstrate that Clarinet-D™ 12 Hour is superior to the both components for the treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older.

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Signoff Page

Reviewer: Feng Zhou

Concur: James Gebert, Ph.D.

CC:
Archival NDA 21-313

HFD-570/Division file
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/s/

Feng Zhou
9/27/01 02:55:41 PM
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James Gebert
9/27/01 03:17:54 PM
BIOMETRICS
I concur.