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**APPLICATION NUMBER
21-363**

Statistical Review(s)

Statistical Review and Evaluation
Clinical Studies

NDA #: 21-363
Applicant: Schering Corporation
Name of Drug: Clarinex (Desloratadine) 5 mg Tablets
Indication: Allergic Rhinitis in Adults and Adolescents
Documents Reviewed: Volumes 1.1, 1.52-1.72 and data dated April 9, 2001. Data dated May 22, 2001.

This review pertains to the evaluation of two Phase 3 studies in patients with perennial allergic rhinitis and two Phase 3 studies in patients with asthma who also have seasonal allergic rhinitis. The asthma/seasonal allergic rhinitis studies will only be briefly discussed because desloratadine failed to show efficacy in the primary efficacy variable assessing its effect in asthma. Its effect in seasonal allergic rhinitis has already been demonstrated in other populations. The fact that it shows efficacy for seasonal allergic rhinitis in an asthmatic population is not surprising. Other studies in seasonal allergic rhinitis have already been reviewed and will not be discussed here.

The medical officer for this submission is R. Nicklas, M.D. (HFD-570), with whom this review was discussed.

I. Background

Desloratadine is the major active metabolite of loratadine, marketed in the U.S. as Claritin. Desloratadine will be denoted as DL throughout this review. Desloratadine is currently under review for the SAR indication. Since it was not approved at the time of this submission, it was submitted as a new NDA, rather than as a supplement. This reviewer noticed that some datafiles were not provided with the original submission. These data files were requested and supplied by the sponsor in their May 22, 2001 submission.

II. Perennial Allergic Rhinitis Studies

A. Study Description and Method of Analysis

These were multicenter, parallel group, randomized, double-blind studies with a 4 to 14 day run-in period and a four-week treatment period comparing DL 5 mg and placebo both given QD in the AM, in adult and adolescent patients with perennial allergic rhinitis. Patients with seasonal allergic rhinitis to allergen pollinating at the time the participant would be participating in the study were excluded.

Keywords: Clinical Studies, NDA review

The patients kept a daily diary in which they rated their symptoms (rhinorrhea, post nasal drip/drainage, nasal itching, sneezing, itching/burning eyes, tearing/watering eyes, itching of ears or palate, and nasal stuffiness/congestion) using a 4 point scale: (0=none, 1=mild, 2=moderate, 3=severe). The first 7 symptom scores were summed to create a Total Symptom Score (excluding nasal congestion). The patient at arising in the AM, before taking his treatment tablet, recorded the severity of the symptoms both as a reflective rating of the last 12 hours and as a instantaneous (NOW) rating. Similar ratings were taken in the evening (PM ratings) at bedtime.

To enter the study, the patient had to have, at the baseline visit, the following reflective (prior 12 hours) sign/symptom scores:

1. Three complete days of diary entries prior to the Baseline visit (called Day 1 if patient is randomized).
2. For these three days, the Total Symptom Score including nasal stuffiness/congestion calculated from the 6 reflective assessments had to have a value of at least 60.
3. For these three days, a stuffiness/congestion total from the 6 reflective assessments had to be ≤ 12 .
4. A score ≥ 2 (moderate) in an overall assessment (4-point scale) of perennial allergic rhinitis.

Since the AM score on the day of randomization was assessed before taking treatment, it represents a run-in score. If we denote the day of randomization as Day 1, then the following values were used to calculate baseline averages: AM averages were Days -2, -1, 0, and Day 1. PM averages were Days -2, -1, and 0. AM/ PM combined were averages of AM Days -2, -1, 0 and 1, and PM Days -2, -1, and 0.

The primary efficacy variable is change from baseline in Total Symptom Score (excluding nasal stuffiness/congestion) combined AM/PM NOW score averaged over Days 1-29. This was analyzed by an analysis of variance with factors: treatments and centers.

This reviewer will, also, focus on the AM NOW Total Symptom Score excluding nasal stuffiness/congestion averaged over Days 2-29 because it is the end of dosing interval assessment.

The protocol stated that prior to database lock, study sites from Protocol P00217 (with a similar study protocol) would be ranked sequentially based on number of subjects enrolled. The study sites would be then distributed on an alternative basis into Protocols P00218 and P00219 in order to meet sample size requirements. An increase in sample size was needed because of a change in primary efficacy variable after discussion with the agency (change from AM/PM reflective to AM/PM instantaneous).

B. Results

Study P00218 randomized 676 subjects (337 to DL 5 mg QD and 339 to placebo) at 33 centers

(9 centers from Protocol P00217). A total of 42 subjects in Study P00218 failed to complete the study (20 on DL and 22 on placebo). Study P00219 randomized 698 subjects (348 to DL 5 mg QD and 350 to placebo) at 30 centers (8 centers from Protocol P00217). A total of 44 subjects in Study P00219 failed to complete the study (22 in each group).

Demographic and other baseline characteristics were similar across the treatment groups in each study.

Tables 1 and 3 give the results for the analysis of changes from baseline in Total Symptom Score (excluding nasal stuffiness/congestion) AM/PM NOW. DL showed efficacy for the primary analysis average for Days 1-29 in Study P00218 ($P=0.005$) but not in Study P00219 ($P=0.493$).

Tables 2 and 4 give the results for the analysis of changes from baseline in Total Symptom Score (excluding nasal stuffiness/congestion) AM NOW. DL showed efficacy for the primary analysis average for Days 2-29 in Study P00218 ($P=0.022$) but not in Study P00219 ($P=0.337$).

C. Reviewer's Comments

This reviewer verified the sponsor's analyses from programs and data supplied with the submission.

The sponsor's partitioning of centers in Study P00217 to Studies P00218 and P00219 is reasonable, given that the sample size had to be increased, and it was pre-specified before the blind was broken. Although the protocol did not specify whether sites would be ordered from largest to smallest or from smallest to largest or how ties would be handled, almost identical assignments would be made. The sponsor ordered sites from smallest to largest before assigning. The sponsor handled ties in site sample sizes by ordering by site number.

DL showed efficacy in Study P00218 but not in Study P00219. The results in Study P00219 actually numerically slightly favored placebo rather than DL.

III. Seasonal Allergic Rhinitis/Asthma Studies

A. Study Description and Method of Analysis

These were randomized, placebo-controlled, parallel group studies comparing DL 5 mg QD AM versus Montelukast 10 mg QD AM in asthma patients who also had seasonal allergic rhinitis.

The patients kept a daily diary in which they rated their SAR signs/symptoms (rhinorrhea, nasal itching, sneezing, itching/burning eyes, tearing/watering eyes, itching of ears or palate, redness of the eyes, and nasal stuffiness/congestion) using a 4 point scale: (0=none, 1=mild, 2=moderate, 3=severe). The first 7 symptom scores were summed to create a Total SAR Symptom Score (excluding nasal stuffiness/congestion). The patient arising in the AM, before taking his treatment tablet, recorded the severity of the symptoms both as a reflective rating of the last 12

hours and as a instantaneous (NOW) rating. Similar ratings were taken in the evening (PM ratings) at bedtime. The sponsor also rated similarly the asthma signs/symptoms (cough, wheeze, difficulty breathing) using the same 4-point scale.

To enter the study, the scores (reflective) for the 3 calendar days prior to baseline and the AM score on the Baseline day had to total the following:

1. Total Nasal Symptom Score of at least 42.
2. Total Non-nasal Symptom Score of at least 35.
3. Subjects were to have an $FEV_1 \geq 70\%$ of the predicted value at screening and have demonstrated reversibility after administration of an inhaled bronchodilator at time of screening or in the past 2 years.

Since the AM score on the day of randomization was assessed before taking treatment, it represents a run-in score. If we denote the day of randomization as Day 1, then the following values were used to calculate baseline averages: AM averages were Days -2, -1, 0, and Day 1. PM averages were Days -2, -1, and 0. AM/ PM combined were averages of AM Days -2, -1, 0 and 1, and PM Days -2, -1, and 0.

The primary efficacy variables were change from baseline in Total Symptom Score (excluding nasal stuffiness/congestion) combined AM/PM (reflective) averaged over Days 1-15 and change from baseline FEV_1 averaged over the 4 weekly assessments. These were analyzed by an analysis of variance with factors: treatments and centers. The primary comparison was DL 5.0 mg versus placebo and, as such, no adjustment was made for multiple comparisons.

The sponsor had to increase the sample sizes in these studies because of a change in the primary efficacy variable (to changes from baseline in FEV_1 averaged over the 4 visits from changes from baseline in Total Asthma Symptom Score). The sponsor amended the protocol to increase sample size as follows:

- 1) Arranging all study centers of Study P00216 in random order using a random number generator.
- 2) Starting at the top of the list of centers obtained above, begin assigning centers to the larger enrollment of the two Studies P00214 and P00215.
- 3) Stop the assignment when the resulting enrollment in the study identified in 2 reaches 500, or one half of the total number of subjects enrolled in the three studies, whichever is greater.
- 4) Assign the remaining centers to the smaller of the two studies P00214 and P00215.

B. Results

Study P00214 randomized 501 subjects (168 to DL 5 mg QD, 170 to montelukast 10 mg QD and 163 to placebo) at 37 centers (13 centers from Protocol P00216). A total of 63 subjects in Study P00214 failed to complete the study (15 on DL, 16 on montelukast and 32 on placebo).

Study P00215 randomized 423 subjects (143 to DL 5 mg QD, 141 to montelukast 10 mg QD and 139 to placebo) at 32 centers (10 centers from Protocol P00216). A total of 43 subjects in Study P00215 failed to complete the study (12 on DL, 7 on montelukast and 24 on placebo).

Demographic and other baseline characteristics were similar across the treatment groups in each study.

In Study P00214 neither DL nor montelukast were significantly better than placebo (P=0.908 and 0.388, respectively) for change from baseline in FEV₁ averaged over weeks 1 through 4. In Study P00215 DL was not significantly better than placebo (P=0.196) for change from baseline in FEV₁ averaged over weeks 1 through 4. Montelukast, however, was significantly better than both placebo (P<0.001) and DL (P=0.042) for this primary efficacy asthma variable.

Tables 5 and 6 gives the results for the analysis of changes from baseline in Total SAR Symptom Score AM/PM average over the prior 12 hours. DL showed efficacy for the primary analysis for Days 1-15 in both studies (P<0.001 and P=0.021, respectively). Montelukast showed efficacy for in Study P00214 (P<0.001) for the primary efficacy analysis for SAR symptoms.

C. Reviewer's Comments

This reviewer verified the sponsor's analyses from programs and data supplied with the submission.

The sponsor's partitioning of centers in Study P00216 to Studies P00214 and P00215 is reasonable, given that the sample size had to be increased, and it was pre-specified before the blind was broken.

DL showed efficacy for SAR symptoms in Studies P00214 and P00215. Montelukast also showed efficacy for SAR symptoms in Study P00214. In Study P00214 DL showed efficacy in asthma symptoms (a secondary variable). It is impossible to assess whether this is caused by some contamination from the improvement in SAR symptoms. It would be interesting to see how montelukast would work in patients with SAR but not with asthma. Failure would support cross contamination of the asthma and SAR symptom assessments.

IV. Overall Comments

Clarinet showed efficacy for changes from baseline in Total Symptom Score AM/PM (NOW) averaged over Days 1-29, which was the primary efficacy variable for perennial allergic rhinitis, in Study P00218 but not in Study P00219. Clarinet, also, showed efficacy for changes from baseline in Total Symptom Score AM (NOW) averaged over Days 1-29 in Study P00218, which supports QD dosing. In Study P00219, the data for these variables numerically slightly favored placebo.

In Studies P00214 and P00215, clarinet showed efficacy for changes from baseline in Total Symptom Score AM/PM (reflective) averaged over Days 1-15, which was the primary efficacy variable for SAR symptoms, but not for changes in FEV₁ averaged over the four visits, which was the primary efficacy variable for asthma.

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Concur: Dr. Nevius

This review contains 6 pages of text and 6 pages of tables.

cc:

Archival NDA 21-363

HFD-570

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**Table 1 - Total Symptom Score (Excluding Nasal Congestion) Analysis Results
(All Randomized Subjects) Subject Evaluated Mean of AM/PM Now**

(Study No. P00218)

Interval	DL 5.0 mg QD (A)			Placebo (B)			Analysis		
	N	LS Mean ^b	(Mean % Change) ^c	N	LS Mean	(Mean % Change)	Pstd ^b	Trt	Site
Baseline	337	10.70		337	10.64		3.11	0.789	<.001
Change from Baseline									
Day 1 ^a	325	-2.58	(-22.0%)	324	-2.02	(-18.0%)	3.72	0.057	0.117
Day 2	335	-3.07	(-25.2%)	331	-2.16	(-17.7%)	3.58	0.001	0.618
Day 3	335	-3.30	(-28.2%)	334	-2.40	(-20.3%)	3.73	0.002	0.683
Day 4	334	-3.40	(-30.8%)	333	-2.32	(-20.7%)	3.78	<.001	0.780
Days 1-8	336	-3.26	(-29.1%)	336	-2.41	(-21.3%)	3.34	<.001	0.593
Days 9-15	327	-3.73	(-35.0%)	332	-2.94	(-28.0%)	3.75	0.008	0.054
Days 16-22	323	-4.14	(-39.1%)	324	-3.31	(-31.3%)	4.04	0.010	0.068
Days 23-29	319	-4.23	(-39.8%)	319	-3.58	(-32.9%)	4.18	0.050	0.064
Days 1-15	337	-3.45	(-31.7%)	337	-2.64	(-24.4%)	3.34	0.002	0.380
Days 1-29	337	-3.73	(-35.0%)	337	-2.95	(-27.4%)	3.55	0.005	0.269

a: Day 1 includes PM scores only.

b: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with treatment and site effects.

c: Mean percent changes are raw means.

Sites 07, 02, 06, 04, 16, 15, 10, 11, and 09 of P00217 have been assigned to P00218 as indicated in the protocol.

Run Date (Time) : 06/18/01 (9:14 AM)

Table 2 - Total Symptom Score (Excluding Nasal Congestion) Analysis Results
(All Randomized Subjects) Subject Evaluated AM Now

(Study No. P00218)

Interval	DL 5.0 mg QD (A)			Placebo (B)			Analysis		
	N	LS Mean ^a	(Mean % Change) ^b	N	LS Mean	(Mean % Change)	Pstd ^a	Trt	Site
Baseline	337	10.73		337	10.82		3.24	0.726	<.001
Change from Baseline									
Day 2	330	-2.57	(-21.8%)	326	-1.81	(-14.3%)	3.76	0.010	0.507
Day 3	332	-2.92	(-25.6%)	334	-2.10	(-16.9%)	3.94	0.007	0.773
Day 4	328	-2.86	(-27.0%)	332	-2.10	(-18.3%)	4.05	0.016	0.864
Days 2-8	336	-2.97	(-26.9%)	336	-2.24	(-19.4%)	3.46	0.007	0.640
Days 9-15	326	-3.44	(-32.5%)	332	-2.76	(-25.1%)	3.88	0.025	0.051
Days 16-22	323	-3.78	(-36.2%)	324	-3.11	(-29.1%)	4.11	0.041	0.040
Days 23-29	319	-4.02	(-37.9%)	319	-3.46	(-30.7%)	4.23	0.098	0.057
Days 2-15	337	-3.16	(-29.4%)	337	-2.48	(-22.1%)	3.45	0.011	0.342
Days 2-29	337	-3.45	(-32.7%)	337	-2.81	(-25.3%)	3.63	0.022	0.224

a: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with treatment and site effects.

b: Mean percent changes are raw means.

Sites 07, 02, 06, 04, 16, 15, 10, 11, and 09 of P00217 have been assigned to P00218 as indicated in the protocol.

Run Date (Time): 06/18/01 (9:29 AM)

Table 3- Total Symptom Score (Excluding Nasal Congestion) Analysis Results
(All Randomized Subjects) Subject Evaluated Mean of AM/PM Now

(Study No. P00219)

Interval	DL 5.0 mg QD (A)			Placebo (B)			Analysis		
	N	LS Mean ^b	(Mean % Change) ^c	N	LS Mean	(Mean % Change)	Pstd ^b	Trt	Site
Baseline	346	10.28		349	11.00		3.01	0.002	<.001
Change from Baseline									
Day 1 ^a	333	-2.09	(-20.2%)	332	-1.71	(-15.6%)	3.50	0.153	0.308
Day 2	345	-2.26	(-22.0%)	347	-1.86	(-16.4%)	3.28	0.109	0.077
Day 3	346	-2.75	(-25.2%)	347	-2.42	(-20.8%)	3.56	0.235	0.019
Day 4	345	-2.78	(-26.0%)	348	-2.50	(-21.6%)	3.57	0.303	0.034
Days 1-8	346	-2.73	(-25.6%)	349	-2.52	(-22.2%)	3.11	0.383	0.002
Days 9-15	340	-3.45	(-32.0%)	343	-3.55	(-31.0%)	3.52	0.701	<.001
Days 16-22	333	-3.75	(-35.2%)	338	-4.02	(-35.5%)	3.80	0.353	<.001
Days 23-29	329	-3.90	(-36.5%)	328	-4.20	(-38.1%)	3.92	0.319	<.001
Days 1-15	346	-3.04	(-28.4%)	349	-2.99	(-26.3%)	3.15	0.855	<.001
Days 1-29	346	-3.32	(-31.1%)	349	-3.49	(-30.9%)	3.31	0.493	<.001

a: Day 1 includes PM scores only.

b: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with treatment and site effects.

c: Mean percent changes are raw means.

Sites 01, 03, 05, 08, 12, 13, 14, and 17 of P00217 have been assigned to P00219 as indicated in the protocol.

Run Date (Time): 06/18/01 (10:54 AM)

Table 4 - Total Symptom Score (Excluding Nasal Congestion) Analysis Results
(All Randomized Subjects) Subject Evaluated AM Now

(Study No. P00219)

Interval	DL 5.0 mg QD (A)			Placebo (B)			Analysis		
	N	LS Mean ^a	(Mean % Change) ^b	N	LS Mean	(Mean % Change)	Pstd ^c	Model P-values	
							Trt	Site	
Baseline	346	10.32		349	11.05		3.03	0.002	<.001
Change from Baseline									
Day 2	341	-1.89	(-19.0%)	341	-1.46	(-12.9%)	3.37	0.100	0.029
Day 3	345	-2.44	(-22.3%)	343	-2.12	(-18.1%)	3.84	0.277	0.037
Day 4	342	-2.53	(-23.2%)	343	-2.31	(-19.8%)	3.84	0.453	0.103
Days 2-8	346	-2.51	(-23.4%)	349	-2.36	(-20.5%)	3.16	0.533	<.001
Days 9-15	340	-3.23	(-29.1%)	343	-3.43	(-29.8%)	3.61	0.467	<.001
Days 16-22	333	-3.56	(-32.9%)	338	-3.88	(-34.0%)	3.82	0.271	<.001
Days 23-29	329	-3.71	(-34.2%)	328	-4.05	(-36.7%)	3.93	0.260	<.001
Days 2-15	346	-2.83	(-26.0%)	349	-2.86	(-25.0%)	3.21	0.881	<.001
Days 2-29	346	-3.13	(-28.8%)	349	-3.37	(-29.7%)	3.35	0.337	<.001

a: LS means and Pstd (pooled standard deviations) are obtained from two-way Anova model with treatment and site effects.

b: Mean percent changes are raw means.

Sites 01, 03, 05, 08, 12, 13, 14, and 17 of P00217 have been assigned to P00219 as indicated in the protocol.

Run Date (Time): 06/18/01 (10:35 AM)

Table 5 Total SAR Symptom Score (Including Congestion) Analysis Results (All Randomized Subjects) Subject Evaluated Mean of AM/PM Prior 12 Hrs

(Study No. P00214)

	DL 5 mg QD			Montelukast 10 mg QD			Placebo		
	(A)			(B)			(C)		
	N	LS Mean ^a	(Mean % Change) ^b	N	LS Mean	(Mean % Change)	N	LS Mean	(Mean % Change)
Baseline	166	15.45		168	15.37		160	15.43	
<u>Change from Baseline</u>									
Day 1	161	-3.13	(-20.6%)	163	-2.52	(-17.2%)	156	-1.06	(-7.2%)
Day 2	164	-3.72	(-24.7%)	166	-3.21	(-22.9%)	160	-1.51	(-10.8%)
Day 3	164	-4.12	(-27.1%)	166	-3.83	(-26.8%)	159	-1.93	(-13.1%)
Day 4	164	-4.59	(-30.0%)	166	-4.17	(-29.0%)	158	-2.13	(-14.2%)
Days 1-8	166	-4.37	(-28.4%)	168	-3.98	(-27.4%)	160	-2.35	(-16.1%)
Days 9-15	160	-5.51	(-34.6%)	162	-5.42	(-35.9%)	148	-3.81	(-25.7%)
Days 16-22	158	-6.10	(-38.9%)	158	-6.11	(-40.6%)	140	-4.70	(-31.0%)
Days 23-29	151	-6.41	(-40.1%)	156	-6.66	(-44.0%)	134	-5.41	(-36.0%)
Days 1-15	166	-4.90	(-31.3%)	168	-4.62	(-30.9%)	160	-2.98	(-20.1%)
Days 1-29	166	-5.47	(-34.9%)	168	-5.37	(-35.7%)	160	-3.73	(-25.0%)
Days 16-29	158	-6.19	(-39.6%)	158	-6.35	(-42.2%)	140	-5.02	(-33.6%)

Analysis Results (Change from Baseline)

	Pooled SD ^a	Model P-values		Pairwise Comparisons P-values		
		Treatment	Site	A-C	A-B	B-C
Day 1	4.35	<.001	0.002	<.001	0.212	0.003
Day 2	4.19	<.001	<.001	<.001	0.281	<.001
Day 3	4.52	<.001	0.029	<.001	0.562	<.001
Day 4	4.64	<.001	0.005	<.001	0.423	<.001
Days 1-8	3.86	<.001	0.004	<.001	0.364	<.001
Days 9-15	4.63	0.002	0.109	0.002	0.853	0.003
Days 16-22	5.20	0.032	0.582	0.022	0.993	0.021
Days 23-29	5.30	0.118	0.212	0.115	0.690	0.049
Days 1-15	4.00	<.001	0.022	<.001	0.519	<.001
Days 1-29	4.33	<.001	0.116	<.001	0.834	<.001
Days 16-29	5.10	0.057	0.306	0.052	0.777	0.027

a: LS Means and pooled SD (pooled standard deviations) are obtained from the two-way ANOVA model

With treatment and site effects.

b: Mean percent changes are raw means.

Run Date (Time) : 06/19/01 (10:10 AM)

Table 6 Total Symptom Score (Including Congestion) Analysis Results (All Randomized Subjects) Subject Evaluated Mean of AM/PM Prior 12 Hrs

(Study No. P00215)

	DL 5 mg QD			Montelukast 10 mg QD			Placebo		
	(A)			(B)			(C)		
	N	LS Mean ^a	(Mean % Change) ^b	N	LS Mean	(Mean % Change)	N	LS Mean	(Mean % Change)
Baseline	140	16.13		141	16.03		138	16.09	
Change from Baseline									
Day 1	137	-2.16	(-12.8%)	140	-1.66	(-9.3%)	131	-0.99	(-6.9%)
Day 2	140	-3.20	(-20.6%)	141	-2.47	(-16.4%)	138	-1.98	(-13.6%)
Day 3	140	-3.85	(-23.8%)	139	-2.82	(-17.5%)	137	-2.85	(-17.7%)
Day 4	139	-3.96	(-23.1%)	139	-3.04	(-17.9%)	137	-2.94	(-17.2%)
Days 1-8	140	-3.79	(-22.9%)	141	-2.88	(-17.2%)	138	-2.86	(-17.5%)
Days 9-15	135	-4.96	(-30.9%)	138	-4.56	(-28.2%)	125	-3.74	(-22.7%)
Days 16-22	132	-5.63	(-34.8%)	137	-5.27	(-32.7%)	119	-4.99	(-31.3%)
Days 23-29	129	-5.85	(-37.1%)	136	-5.89	(-36.7%)	116	-5.76	(-35.9%)
Days 1-15	140	-4.33	(-26.5%)	141	-3.69	(-22.4%)	138	-3.22	(-19.7%)
Days 1-29	140	-4.97	(-30.4%)	141	-4.58	(-28.1%)	138	-4.03	(-24.7%)
Days 16-29	132	-5.78	(-35.9%)	137	-5.59	(-34.8%)	119	-5.30	(-33.2%)

Analysis Results (Change from Baseline)

	Pooled SD ^a	Model P-values		Pairwise Comparisons P-values		
		Treatment	Site	A-C	A-B	B-C
Day 1	4.47	0.108	0.915	0.036	0.364	0.221
Day 2	4.17	0.056	0.503	0.017	0.150	0.334
Day 3	4.50	0.099	0.683	0.067	0.058	0.960
Day 4	4.64	0.137	0.476	0.070	0.103	0.849
Days 1-8	4.00	0.092	0.386	0.056	0.060	0.966
Days 9-15	4.54	0.095	0.067	0.033	0.478	0.145
Days 16-22	4.74	0.572	0.035	0.293	0.542	0.639
Days 23-29	4.77	0.979	0.043	0.896	0.943	0.840
Days 1-15	3.98	0.069	0.105	0.021	0.183	0.322
Days 1-29	4.10	0.163	0.046	0.058	0.425	0.267
Days 16-29	4.65	0.721	0.040	0.421	0.749	0.616

a: LS Means and pooled SD (pooled standard deviations) are obtained from the two-way ANOVA model with treatment and site effects.

b: Mean percent changes are raw means.

Run Date (Time): 06/19/01 (9:14 AM)

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/s/

James Gebert
9/26/01 01:49:23 PM
BIOMETRICS

S. Edward Nevius
9/26/01 04:35:39 PM
BIOMETRICS
Concur with review.