CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
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STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

NDA/Serial Number:	21-844 / N-000
Drug Name:	Desonate (desonide) Gel, 0.05%
Indication(s):	Atopic dermatitis
Applicant:	Dow Pharmaceutical Sciences/Skin Medica
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Keywords: 505(b)2, atopic dermatitis

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1 Executive Summary

1.1 Conclusions and Recommendations

The efficacy of Desonate (desonide) gel 0.05% was demonstrated to be statistically superior to vehicle gel in two studies in the treatment of atopic dermatitis. The original development plan for this 505(b)2 application was to conduct a single study (04-03) demonstrating that desonide gel was superior to vehicle gel and non-inferior to DesOwen (desonide) lotion 0.05% and thus bridge to the Agency's findings of safety and efficacy for DesOwen lotion. However, Study 04-03 failed to demonstrate that desonide gel was non-inferior to DesOwen lotion for the primary endpoint. Thus the sponsor was unable to establish an efficacy bridge to the Agency's findings of efficacy for DesOwen lotion. Subsequently the sponsor conducted a second study comparing desonide gel to vehicle (01-05).

The primary efficacy endpoint was based on the Investigator's Global Severity Score (IGSS). Treatment success in Study 04-03 was defined as achieving a score of clear (0) or almost clear (1) at Week 4. In Study 01-05 treatment success was defined slightly differently as achieving a score of clear (0) or almost clear (1) *with at least 2 grades reduction* at Week 4. Efficacy results using the stricter definition of treatment success are presented in Table 1. Results from the other definition are also significant.

Table 1 – Treatment Success[1] at Week 4, ITT

	Desonide Gel	DesOwen Lotion	Vehicle Gel
Study 04-03	128/289 (44.3%)	147/285 (51.6%) -15.8%[2]	13/92 (14.1%) <0.001[3]
Study 01-05	38/136 (27.9%)	--	4/65 (6.2%) <0.001[3]

[1] Clear or Almost Clear with at least 2 grades reduction
[2] 97.5% lower confidence bound for (Desonide gel - DesOwen Lotion)
[3] p-value for Desonide gel vs. vehicle gel

1.2 Brief Overview of Clinical Studies

The sponsor conducted two studies (7001-G3HP-04-03 and 7001-G3HP-01-05) evaluating the safety and efficacy of desonide gel in the treatment of atopic dermatitis. Study 04-03 had 3 arms: desonide gel, DesOwen lotion, and vehicle gel. The original goal was to demonstrate the superiority of desonide gel to vehicle gel and the non-inferiority of desonide gel to DesOwen lotion; however, the sponsor was only able to demonstrate the superiority of desonide gel to its vehicle. Consequently the sponsor conducted a second 2-arm study to demonstrate the superiority of desonide gel to its vehicle.

Efficacy in both studies was evaluated based on a global evaluation and individual signs and symptoms scales; however, the scales and criteria for success were slightly different in the two studies. In brief, the Investigators' Global Severity Score (IGSS) was a 6-

point scale in Study 04-03 and a 5-point scale in Study 01-05. Treatment success in Study 04-03 was defined as achieving a score of clear or almost clear, while in Study 01-05 it was defined as a score of clear or almost clear with at least 2 grades reduction. In addition, the individual sign scores were evaluated over 5 separate body regions (scalp, face, trunk, arms, and legs) and the 5 scores were summed in Study 04-03, while the subject was evaluated globally for each sign in Study 01-05.

The treatment duration in both studies was 4 weeks. Both studies enrolled pediatric patients aged 3 months to 18 years with mild to moderate atopic dermatitis. Independent investigators were used for the two studies. All study centers were located in the United States.

1.3 Statistical Issues and Findings

The sponsor is addressing the efficacy and safety informational needs for this 505(b)2 application by establishing efficacy through two studies demonstrating superiority of desonide gel to vehicle gel and bridging to the Agency's previous findings of safety for DesOwen lotion through Study 04-03 which evaluated both desonide gel and DesOwen lotion. The second study comparing desonide gel to vehicle was initiated when the original study failed to establish an efficacy bridge to DesOwen lotion.

The secondary analyses on the signs of atopic dermatitis (erythema, induration, and oozing/crusting) were statistically significant in both studies, though the pre-specified analysis is difficult to interpret. The pre-specified analyses for the signs of atopic dermatitis was based on the percent reduction on the sign scores (ordinal scales with range 0 to 15 in Study 04-03 and of 0 to 4 in Study 01-05). It is difficult to interpret percent reductions on ordinal scales with few categories as the categories do not represent categories of equal length. Although the analysis based on the percent change may not be meaningful, the results do indicate that the sign scores trended in the appropriate direction with more favorable results on the desonide arms than the vehicle arm. In addition, efficacy results for the primary endpoint were generally consistent across centers and subgroups.

2 Introduction

2.1 Overview

Topical formulations of desonide for the treatment of corticosteroid responsive dermatoses have been marketed since the early 1970's. Desonide is a mid-potent (Class 6) corticosteroid. In this application the sponsor is seeking the narrower indication of atopic dermatitis. The sponsor conducted two efficacy and safety studies for desonide gel in the treatment of mild to moderate atopic dermatitis. The studies enrolled exclusively pediatric subjects aged 3 months to 18 years. All study centers were located in the United States. Features of these studies are presented in Table 2.

Table 2 – Clinical Study Program for Desonide Gel

Study	Treatment Arms	No. of Subjects	Study Dates
7001-G3HP-04-03	Desonide gel	289	March 2004-
	DesOwen Lotion	285	October 2004
	Vehicle gel	92	
7001-G3HP-01-05	Desonide gel	136	May 2005-
	Vehicle gel	65	September 2005

2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. The datasets used in this review are archived at \\Cdsesub1\evsprod \n021844\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopic-dermatitis\5351-stud-rep-contr\study-report-7001-g3hp-04-03\datasets and ...\study-report-7001-g3hp-01-05\datasets.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

Desonate (desonide) gel for atopic dermatitis is a 505(b)2 application with reference drug DesOwen lotion. The sponsor's original development plan was to establish efficacy by conducting one three-arm study (Study 04-03) demonstrating that desonide gel was superior to vehicle gel and non-inferior to DesOwen lotion. Although the study demonstrated that desonide gel was superior to its vehicle, it failed to demonstrate that desonide gel was non-inferior to DesOwen lotion. Consequently, the sponsor conducted a second study (Study 01-05) to demonstrate the superiority of desonide gel to its vehicle. Thus, the sponsor is relying on comparisons to vehicle from two studies to establish the efficacy of desonide gel in the treatment of atopic dermatitis.

3.1.1 Study Design

3.1.1.1 Study 04-03

Study 04-03 is a randomized, evaluator-blind, three-arm study of desonide gel versus vehicle gel and DesOwen (desonide) lotion in the treatment of atopic dermatitis. Subjects age 3 months to 18 years with mild to moderate atopic dermatitis were enrolled in a 3:3:1 ratio to desonide gel, desonide lotion, and vehicle gel. The study enrolled 666 subjects (289 desonide gel, 285 desonide lotion, and 92 vehicle gel) in 31 centers. Subjects treated affected areas twice daily for four weeks and were evaluated at baseline, Week 2, and Week 4.

Subjects were evaluated based on the Investigator's Global Severity Score (IGSS), erythema, induration, oozing/crusting and body surface area (BSA) involvement. See Table 3 and Table 4 for the definitions of the scales. Erythema and induration were

evaluated separately over five body regions (face, scalp, trunk, arms, legs). At baseline subjects were to have an IGSS of 2 or 3 (mild or moderate), erythema and induration scores of 1 or 2 (mild or moderate) in at least one of the five body areas, and BSA of at least 10%.

Table 3 – Investigator's Global Severity Score (Study 04-03)

Score	Grade	Definition
0	Clear	No inflammatory signs of AD
1	Almost Clear	Just perceptible erythema, and Just perceptible papulation/induration
2	Mild	Mild erythema, and Mild papulation/induration
3	Moderate	Moderate erythema, and Moderate papulation/induration
4	Severe	Severe erythema, and Severe papulation/induration
5	Very Severe	Severe erythema, and Severe papulation/induration with oozing/crusting

Table 4 – Signs of Atopic Dermatitis (04-03)

Score	Grade	Erythema	Induration	Oozing/Crusting
0	None	No redness present	No elevation	None
1	Mild	Faintly detectable erythema; very light pink	Barely perceptible elevation	Faint signs of oozing
2	Moderate	Dull red, clearly distinguishable	Clearly perceptible elevation but not extensive	Definite oozing or crust but with 5 or fewer sites per area
3	Severe	Deep/ dark red	Marked and extensive elevation	Marked and extensive

The primary efficacy endpoint, treatment success, was defined as achieving a score of 0 or 1 (clear or almost clear) at Week 4. The secondary endpoints were the percent change in erythema, induration, and oozing/crusting scores (each summed over the 5 body regions) from baseline to Week 4.

The study had two goals, to demonstrate the superiority of desonide gel to vehicle gel and to demonstrate the non-inferiority of desonide gel to desonide lotion. The superiority of desonide gel to vehicle gel for treatment success was analyzed with a Cochran-Mantel-Haenszel test stratified on center. The non-inferiority of desonide gel to desonide lotion was evaluated with a 10% non-inferiority margin and a 97.5% one-sided confidence interval based on the following formula (Wald's formula with Yates continuity correction, where *T*=test and *R*=reference):

$$p_T - p_R - z_{\alpha/2}\sqrt{p_T(1-p_T)/n_T + p_R(1-p_R)/n_R} - (1/n_T + 1/n_R)/2$$

The secondary endpoints of the percent change in signs and symptoms for the superiority comparison were analyzed with ANOVA with factors for treatment and analysis site. For

the non-inferiority comparison, the secondary endpoints were analyzed with one-sided 97.5% confidence intervals based on least squares means and mean square for error from an ANOVA with factors for treatment and analysis site. The non-inferiority margin for the secondary endpoints was 15%.

The ITT population was defined as all subjects randomized and dispensed medication. The per protocol population was defined as all subjects who met the inclusion criteria and had at least 8% BSA (note that this is slightly relaxed from the specified inclusion criterion of at least 10% BSA), did not take interfering concomitant medication, attended the Week 4 visit within ± 3 days and did not miss more than one other visit, and applied at least 75% of expected doses.

3.1.1.2 Study 01-05

Study 01-05 has a similar design to Study 04-03 except that it has only two arms (desonide gel and vehicle) and the efficacy evaluations were slightly different. The study enrolled 201 subjects (136 desonide gel and 65 vehicle) at 15 centers. Like in the earlier study, subjects treated affected areas twice daily for four weeks and were evaluated at baseline, Week 2, and Week 4. The scales for the IGSS and the signs of atopic dermatitis were slightly different than in Study 04-03. In particular, the IGSS in Study 01-05 was a 5-point scale rather than a 6-point scale (it did not have a 'very severe' category) and it included oozing and crusting as part of the descriptions of the levels. The scales for the signs of atopic dermatitis were global scales rather than evaluated on separate body regions and included an additional level, 'almost clear' (five levels versus four). Study 01-05 also evaluated scaling and lichenification in addition to erythema, induration, and oozing/crusting. The scales for the endpoints are presented in Table 5 and Table 6. At baseline subjects were to have a score on the IGSS of 2-3 (mild to moderate), and erythema and induration scores of at least 2 (mild), and a BSA of at least 10%.

Table 5 – Investigator's Global Severity Score (Study 01-05)

Score	Grade	Definition
0	Clear	No inflammatory signs of AD
1	Almost Clear	Just perceptible erythema, and Just perceptible papulation/induration
2	Mild	Mild erythema, and Mild papulation/induration. No oozing or crusting
3	Moderate	Moderate erythema, and Moderate papulation/induration. Oozing and crusting may be present
4	Severe	Severe erythema, and Severe papulation/induration. Oozing and Crusting is present

Table 6 – Signs of Atopic Dermatitis (01-05)

Score	Grade	Erythema	Induration	Oozing/Crusting
0	Absent	No erythema present (may be minor discoloration)	No evidence of elevation	No evidence of oozing or crusting
1	Minimal	Faint pink, barely apparent	Barely perceptible elevation	Rare oozing/crusting
2	Mild	Light pink, noticeable	Perceptible but not extensive elevation	Occasional oozing/crusting
3	Moderate	Pink-red, easily noticeable	Marked and somewhat extensive elevation	Diffuse oozing/crusting
4	Severe	Deep or bright red, may feel warm to the touch	Marked and extensive elevation	Marked oozing/crusting

Score	Grade	Lichenification	Scaling
0	Absent	No lichenification present	Absent, no evidence of scaling
1	Minimal	Slightly accentuated superficial skin lines	Occasional fine scale
2	Mild	Minor epidermal thickening in one or two areas	Fine, flaky scale predominates
3	Moderate	Moderate epidermal thickening in few areas, moderately accentuated skin lines	Coarse scale predominates
4	Severe	Prominent epidermal thickening with deep skin lines, 4 or more areas involved	Thick, coarse, crusted scale predominates

The primary efficacy endpoint, treatment success, was defined as achieving a score of 0 or 1 (clear or almost clear) with at least 2 grades reduction at Week 4. The need for at least a 2 grade reduction was additional requirement not included in the definition of treatment success in the previous study, 04-03. The secondary endpoints were the percent change in erythema, induration, oozing/crusting, lichenification, and scaling scores from baseline to Week 4.

Treatment success was analyzed with a Cochran-Mantel-Haenszel test stratified on center. The percent reduction in sign scores were analyzed with ANOVA with factors for treatment and analysis site.

In this study the ITT population was also defined as all subjects randomized and dispensed medication. The definition for the per protocol population was similar to Study 04-03, except subjects had to meet the 10% BSA inclusion criterion rather than an 8% criterion, and they had to apply between 80% and 120% of study doses rather than at least 75% of doses.

3.1.2 Disposition of Subjects

3.1.2.1 Study 04-03

Study 04-03 enrolled 666 subjects (289 desonide gel, 285 desonide lotion, and 92 vehicle gel) at 31 centers. Study 04-03 was conducted from March to October 2004. Discontinuation rates were similar for desonide gel and lotion (about 6%) and were slightly higher on the vehicle arm (11%). Reasons for study discontinuations are presented in Table 7. The most common reason for discontinuation on the desonide gel and lotion arms was loss to follow-up (3%). The most common reason for discontinuation on the vehicle gel arm was lack of efficacy (5%).

Table 7 – Reason for Study Discontinuation (Study 04-03)

	Desonide Gel N=289	DesOwen Lotion N=285	Vehicle Gel N=92
Discontinued Subjects	17 (5.9%)	17 (6.0%)	10 (10.9%)
Lack of Efficacy	2 (0.7%)	1 (0.4%)	5 (5.4%)
Adverse Event	2 (0.7%)	4 (1.4%)	0 (0%)
Subject Request[1]	4 (1.4%)	2 (0.7%)	2 (2.2%)
Lost to Follow-up	9 (3.1%)	8 (2.8%)	3 (3.3%)
Other[2]	0 (0%)	2 (0.7%)	0 (0%)

[1] Includes withdrawal of consent, scheduling difficulties, lack of improvement

[2] Includes subject did not return and medical monitor decision

3.1.2.2 Study 01-05

Study 01-05 enrolled 201 subjects (136 desonide gel and 65 vehicle gel) at 15 centers. The study was conducted from May to September 2005. All investigators in Study 01-05 were distinct from the investigators in Study 04-03. The discontinuation rate for vehicle subjects (15%) was higher than for desonide gel subjects (3%). The reasons for discontinuation are presented in Table 8. The vehicle discontinuations were primarily due to subject request (withdrawal of consent) and lack of efficacy. The most common reason for discontinuation on the desonide gel arm was lost to follow-up.

Table 8 – Reason for Study Discontinuation (Study 01-05)

	Desonide Gel N=136	Vehicle Gel N=65
Discontinued Subjects	4 (2.9%)	10 (15.4%)
Lack of Efficacy	0 (0%)	3 (4.6%)
Adverse Event	1 (0.7%)	1 (1.5%)
Subject Request[1]	1 (0.7%)	5 (7.7%)
Lost to Follow-up	2 (1.5%)	1 (1.5%)

[1] Includes withdrawal of consent, scheduling difficulties, and lack of improvement.

3.1.3 Baseline and Demographic Data

Both studies were fairly evenly balanced across treatment arms for the baseline demographic data, though there were some slight imbalances with regards to gender and race in Study 04-03, with the vehicle enrolling slightly more females and white subjects than the desonide arms. The studies enrolled slightly more females than males. Study 01-05 enrolled nearly equal numbers of white and black subjects. All subjects were between 3 months and 18 years old. The average age was 6 in Study 04-03 and 7 in 01-05. Approximately 28% of the subjects were less than 3 years old in both studies. The baseline demographic data for the two studies is presented in Table 9 and Table 10.

Table 9 – Baseline Demographic Data (Study 04-03)

		Desonide Gel N=289	DesOwen Lotion N=285	Vehicle Gel N=92
Gender	Male	127 (44%)	136 (48%)	38 (41%)
	Female	162 (56%)	149 (52%)	54 (59%)
Race	White	158 (55%)	178 (62%)	65 (71%)
	Black	67 (23%)	50 (18%)	12 (13%)
	Hispanic	36 (12%)	32 (11%)	12 (13%)
	Asian/Pac Isld	9 (3%)	7 (2%)	0 (0%)
	Other	19 (7%)	18 (6%)	3 (3%)
Age (Years)	Mean (SD)	6.6 (4.7)	6.9 (4.8)	6.4 (4.9)
	Range	0.26-18.50	0.28-18.97	0.55-18.54
	3 mos-<3 yrs	85 (29%)	72 (25%)	31 (34%)
	3 yrs-<6 yrs	75 (26%)	76 (27%)	20 (22%)
	6 yrs-<12 yrs	84 (29%)	87 (31%)	26 (28%)
	12 yrs-18 yrs	45 (16%)	50 (18%)	15 (16%)

Table 10 – Baseline Demographic Data (Study 01-05)

		Desonide Gel N=136	Vehicle Gel N=65
Gender	Male	67 (49%)	32 (49%)
	Female	69 (51%)	33 (51%)
Ethnicity	Hispanic/Latino	14 (10%)	7 (11%)
	Not Hisp/Latino	122 (90%)	58 (89%)
Race	White	58 (43%)*	28 (43%)
	Black	57 (42%)*	25 (38%)
	Asian	8 (6%)	6 (9%)
	Other	15 (11%)*	6 (9%)
Age (Years)	Mean (SD)	7.2 (4.9)	7.2 (5.0)
	Range	0.28-18.92	0.34-18.01
	3 mos-<3 yrs	38 (28%)	18 (28%)
	3 yrs-<6 yrs	28 (21%)	12 (18%)
	6 yrs-<12 yrs	42 (31%)	23 (35%)
	12 yrs-18 yrs	28 (21%)	12 (18%)

* Subjects could mark more than one race. Two subjects are included twice in the totals. One subject is included under white and black, and one subject is included under black and other.

At baseline, the subjects were fairly evenly divided between mild and moderate scores on the IGSS. One difference between the study evaluations for the two studies was that in Study 04-03 individual signs were evaluated separately for the different body regions (scalp, face, trunk, arms, legs) while in Study 01-05 they were evaluated globally. Table 11 and Table 12 present the baseline severity scores for Studies 04-03 and 01-05.

Table 11 – Baseline Severity (Study 04-03)

	Desonide Gel N=289	DesOwen Lotion N=285	Vehicle Gel N=92
Investigator's Global Severity			
Clear (0)	--	--	--
Almost Clear (1)	--	--	--
Mild (2)	123 (43%)	134 (47%)	46 (50%)
Moderate (3)	166 (57%)	151 (53%)	46 (50%)
Severe (4)	--	--	--
Very Severe (5)	--	--	--
Maximum Erythema[1]			
None (0)	--	--	--
Mild (1)	79 (27%)	72 (25%)	28 (30%)
Moderate (2)	210 (73%)	212 (74%)	63 (68%)
Severe (3)	--	1 (0.4%)	1 (1%)
Erythema Sum[2]			
Mean	4.6	4.7	4.4
Range	1 – 10	1 – 10	1 – 8
Maximum Induration[1]			
None (0)	1 (0.4%)	--	--
Mild (1)	84 (29%)	93 (33%)	23 (25%)
Moderate (2)	204 (71%)	192 (67%)	69 (75%)
Severe (3)	--	--	--
Induration Sum[2]			
Mean	4.4	4.4	4.2
Range	0 – 10	1 – 10	1 – 8

[1] Maximum score over scalp, face, trunk, arms, and legs.
[2] Sum score over scalp, face, trunk, arms, and legs.

Table 12 – Baseline Severity (Study 01-05)

	Desonide Gel N=136	Vehicle Gel N=65
Investigator's Global Severity		
Clear (0)	--	--
Almost Clear (1)	--	--
Mild (2)	71 (52%)	27 (42%)
Moderate (3)	65 (48%)	38 (58%)
Severe (4)	--	--
Erythema[1]		
Absent (0)	--	--
Minimal (1)	--	--
Mild (2)	83 (61%)	37 (57%)
Moderate (3)	53 (39%)	28 (43%)
Severe (4)	--	--
Induration[1]		
Absent (0)	--	--
Minimal (1)	--	--
Mild (2)	82 (60%)	32 (49%)
Moderate (3)	54 (40%)	33 (51%)
Severe (4)	--	--

[1] Global evaluation

3.1.4 Primary Efficacy Analyses

3.1.4.1 Study 04-03

The sponsor's original development plan was to conduct one study demonstrating the superiority of desonide gel to vehicle gel and the non-inferiority of desonide gel to DesOwen lotion. The primary efficacy analysis was the proportion of subjects clear or almost clear on the IGSS at Week 4. For the ITT population, desonide gel was superior to vehicle gel (59.9% vs. 32.6%, $p < 0.001$), but was not non-inferior to DesOwen lotion (59.9% vs. 68.4%, 97.5% lower confidence bound -16.7%) using the prespecified non-inferiority margin of 10%. The results for the per protocol analysis are similar. The ITT results are presented in Table 13 and the per protocol results are presented in Table 14.

Table 13 – Treatment Success at Week 4, ITT (Study 04-03)

	Desonide Gel N=289	DesOwen Lotion N=285	Vehicle Gel N=92
Clear (0) or Almost Clear (1)[1]	173 (59.9%)	195 (68.4%) -16.7%[2]	30 (32.6%) <0.001[3]
Clear (0) or Almost Clear (1) with at least 2 grades reduction	128 (44.3%)	147 (51.6%) -15.8%[2]	13 (14.1%) <0.001[3]

[1] Protocol-specified primary analysis
[2] 97.5% lower confidence bound for (Desonide gel - DesOwen Lotion)
[3] p-value for Desonide gel vs. vehicle gel

Table 14 – Treatment Success at Week 4, PP (Study 04-03)

	Desonide Gel N=243	DesOwen Lotion N=243	Vehicle Gel N=75
Clear (0) or Almost Clear (1)[1]	155 (63.8%)	176 (72.4%) -17.3%[2]	25 (33.3%) <0.001[3]
Clear (0) or Almost Clear (1) with at least 2 grades reduction	119 (49.0%)	135 (55.6%) -15.9%[2]	11 (14.7%) <0.001[3]

[1] Protocol-specified primary analysis
[b] 97.5% lower confidence bound for (Desonide gel - DesOwen Lotion)
[c] p-value for Desonide gel vs. vehicle gel

Because the sponsor was unable to demonstrate the non-inferiority of desonide gel to DesOwen lotion and bridge to the Agency's findings of efficacy for DesOwen lotion, the sponsor subsequently needed to conduct a second trial to establish the superiority of desonide gel to vehicle gel (Study 01-05). The agreed upon endpoint for Study 01-05 differed slightly from the endpoint in Study 04-03 in that in addition to achieving a score of 0 or 1 on the IGSS at Week 4 the subject must also have at least a 2-grade reduction. To harmonize with the results of Study 01-05, the results for clear or almost clear with 2-grades reduction are also presented in Table 13 (ITT) and Table 14 (PP). Under this endpoint, the success rates for all arms are lower, however, the treatment difference between arms remains essentially the same.

3.1.4.2 Study 01-05

Study 01-05 also demonstrated that desonide gel was superior to vehicle gel with regards to treatment success on the IGSS. The prespecified definition of success for Study 01-05 was achieving clear or almost clear at Week 4 with at least 2 grades reduction. The results for this definition of success and the results for clear almost clear (the primary definition of success in Study 04-03) are presented in Table 15 (ITT) and Table 16 (PP). The results for these two definitions of success are consistent and both support the superiority of desonide gel.

Table 15 – Treatment Success at Week 4, ITT (Study 01-05)

	Desonide Gel N=136	Vehicle Gel N=65
Clear (0) or Almost Clear (1)	74 (54.4%)	9 (13.8%) <0.001[2]
Clear (0) or Almost Clear (1) with at least 2 grades reduction[1]	38 (27.9%)	4 (6.2%) <0.001[2]

[1] Protocol-specified primary analysis
[2] p-value for Desonide gel vs. vehicle gel

Table 16 – Treatment Success at Week 4, PP (Study 01-05)

	Desonide Gel N=122	Vehicle Gel N=52
Clear (0) or Almost Clear (1)	65 (53.3%)	6 (11.5%) <0.001[2]
Clear (0) or Almost Clear (1) with at least 2 grades reduction [1]	32 (26.2%)	3 (5.8%) 0.002[2]

[1] Protocol-specified primary analysis
[2] p-value for Desonide gel vs. vehicle gel

3.1.5 Week 2 Analyses

During treatment, subjects were also evaluated at Week 2. The Week 2 results are consistent with the Week 4 results, although as would be expected, the overall success rates are lower. The Week 2 treatment success rates, where success is defined as clear or almost clear with at least 2 grades reduction, are presented in Table 17. The treatment success rates at Week 2 are approximately half of the success rates at Week 4 in both studies.

Table 17 – Treatment Success[1] at Week 2, ITT

	Desonide Gel	DesOwen Lotion	Vehicle Gel
Study 04-03	63/289 (21.8%)	71/285 (24.9%) -10.4%[2]	3/92 (3.3%) 0.0045[3]
Study 01-05	17/136 (12.5%)	--	1/65 (1.5%) 0.0075[3]

[1] Clear or Almost Clear with at least 2 grades reduction
[2] 97.5% lower confidence bound for (Desonide gel - DesOwen Lotion)
[3] p-value for Desonide gel vs. vehicle gel

3.1.6 Secondary Efficacy Analyses

3.1.6.1 Study 04-03

The secondary endpoints in Study 04-03 were the percent change in erythema, induration, and oozing/crusting from baseline to Week 4. Each sign was evaluated on a 0-3 scale (see Table 4) on 5 body regions (scalp, face, trunk, arms, legs) and summed over the 5 body regions. At baseline, subjects were to have scores of 1 or 2 for erythema and induration, but there was no inclusion requirement regarding oozing/crusting.

The choice of secondary endpoints was not critiqued by the Agency during the protocol review stage. However, computing the percent change for an ordinal scale with relatively few categories may not be meaningful and could imply a greater precision than is warranted by an ordinal scale. When the baseline score is small, relatively small changes can lead to large percent reductions. In addition, the sizes of the categories are not necessarily equal. Another concern, which is particularly relevant to oozing since just over half of the subjects did not have any oozing at baseline, is that it is not possible to calculate the percent reduction when the baseline score is 0. In fact, 22 subjects in Study 04-03 had oozing sum scores of 0 at baseline but had scores greater than 0 at Week 4.

These subjects are not included in the calculations since the percent reduction is not calculable. Therefore, in addition to the percent reductions for the sign endpoints, the mean sum scores at baseline and Week 4 are presented in Table 18. The mean scores include all subjects, including those with scores of 0 at baseline. Although not formally tested, the mean change in absolute score trends in the direction favoring desonide gel over desonide vehicle. The p-values for the analysis specified in the protocol (percent reduction) for desonide gel versus vehicle gel are statistically significant, however this endpoint is difficult to interpret as previously noted. For the desonide gel versus DesOwen lotion comparison, the 97.5% lower confidence limits are with the 15% non-inferiority margin specified in the protocol. However, since non-inferiority was not established for the primary endpoint, the non-inferiority comparison for the secondary endpoint is not very useful.

Table 18 – Mean and Mean Percent Change in Sign Sum Scores[1] from Baseline to Week 4 (Study 04-03) (ITT)

	Desonide Gel N=289	DesOwen Lotion N=285	Vehicle Gel N=92
Erythema			
Evaluable[2] (N)	289	285	92
Baseline Sum Score	4.6	4.7	4.4
Week 4 Sum Score	1.8	1.7	3.1
Percent Change	61.5%	65.2%	30.1%
LCL/P-value[3]		-10.3%	<0.0001
Induration			
Evaluable[2] (N)	288	285	92
Baseline Sum Score	4.4	4.4	4.2
Week 4 Sum Score	1.9	1.7	3.1
Percent Change	57.5%	62.7%	28.1%
LCL/P-value[3]		-12.2%	<0.0001
Oozing			
Evaluable[2] (N)	137	134	44
Baseline Sum Score	1.3	1.3	1.2
Week 4 Sum Score	0.4	0.4	1.1
Percent Change	73.4%	72.5%	39.8%
LCL/P-value[3]		-11.5%	0.0001

[1] Scores for scalp, face, trunk, arms, and legs were evaluated separately on 0-3 scales and summed. Thus the sum score has a range from 0 to 15.

[2] The number of subjects with non-zero scores at baseline.

[3] LCL = 97.5% Lower Confidence Limit. Confidence limits and p-values computed using least squares means and mean square for error from an ANOVA with terms for treatment and pooled center. The sponsor's analyses use estimates from an ANOVA using only the pairs of treatment used in the comparison (i.e. desonide gel and desonide lotion, or desonide gel and vehicle gel). The specified non-inferiority margin was 15%.

3.1.6.2 Study 01-05

Sign scores in Study 01-05 were evaluated using a 5-point global evaluation (see Table 6) rather than as a sum of five 4-point global evaluations. In addition to erythema, induration, and oozing, the sponsor also evaluated lichenification and scaling. As in Study 04-03, the pre-specified secondary endpoints were the percent change in sign scores from baseline to Week 4. The baseline and Week 4 means and the mean percent reduction are presented in Table 19. The difficulties of interpreting the percent reduction from a 5-point scale are the same as for the scales in Study 04-03. However, the protocol specified analyses of the percent change in sign scores are statistically significant. Although not formally analyzed, the mean absolute changes in sign scores favor desonide gel over vehicle.

Table 19 – Mean and Mean Percent Change in Sign Scores[1] from Baseline to Week 4 (Study 01-05) (ITT)

	Desonide Gel N=136	Vehicle Gel N=65	P-value[3]
Erythema			
Evaluable (N)[2]	136	65	
Baseline Score	2.4	2.4	
Week 4 Score	1.3	2.1	
Percent Change	47.5%	14.6%	<0.0001
Induration			
Evaluable (N)[2]	136	65	
Baseline Score	2.4	2.5	
Week 4 Score	1.3	2.1	
Percent Change	46.4%	17.4%	<0.0001
Oozing			
Evaluable (N)[2]	62	38	
Baseline Score	0.7	0.9	
Week 4 Score	0.3	0.7	
Percent Change	66.1%	28.9%	0.0056
Lichenification			
Evaluable (N)[2]	118	53	
Baseline Score	2.0	1.9	
Week 4 Score	1.1	1.7	
Percent Change	44.1%	10.5%	<0.0001
Scaling			
Evaluable (N)[2]	121	60	
Baseline Score	1.6	1.7	
Week 4 Score	0.8	1.4	
Percent Change	52.9%	19.2%	<0.0001

[1] Scores were evaluated globally. Each score has a range from 0 to 4.
[2] The number of subjects with non-zero scores at baseline.
[3] P-values based on an ANOVA model with terms for treatment and pooled center.

3.1.7 By-Center Results

Study 04-03 involved 31 investigators. The centers with fewer than 15:15:5 subjects in the desonide gel:desonide lotion:vehicle gel arms were pooled into 16 analysis centers by pooling the smallest center with the largest center not meeting the 15:15:5 criterion and so forth. The protocol for Study 04-03 originally stated that centers with fewer than 10 subjects per treatment arm would be subject to pooling, but this was modified before the analysis due to the unequal randomization. Study 01-05 involved 15 investigators. The centers with fewer than 8:8 subjects in the desonide gel:vehicle gel arms were pooled into 7 analysis centers using the same procedure.

The desonide arms generally had higher success rates than vehicle at each pooled center. Only one pooled site in Study 04-03 had a higher success rate on vehicle gel than desonide gel. The treatment success rates (clear or almost clear with at least 2 grades reduction) by pooled investigator are presented in Figure 1 and Figure 2 for the two studies. The results from the Breslow-Day test for the homogeneity across pooled centers were non-significant for desonide gel versus vehicle gel ($p = 0.2838$ in Study 04-03 and $p = 0.5536$ in Study 01-05).

Figure 1 – Success Rate by Grouped Investigator (Study 04-03)

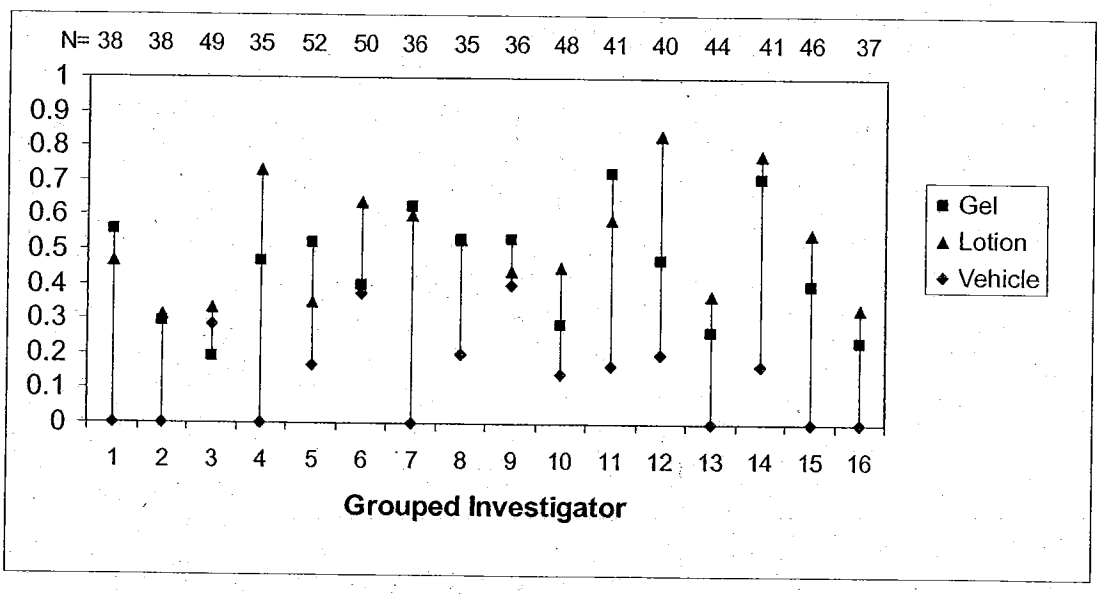
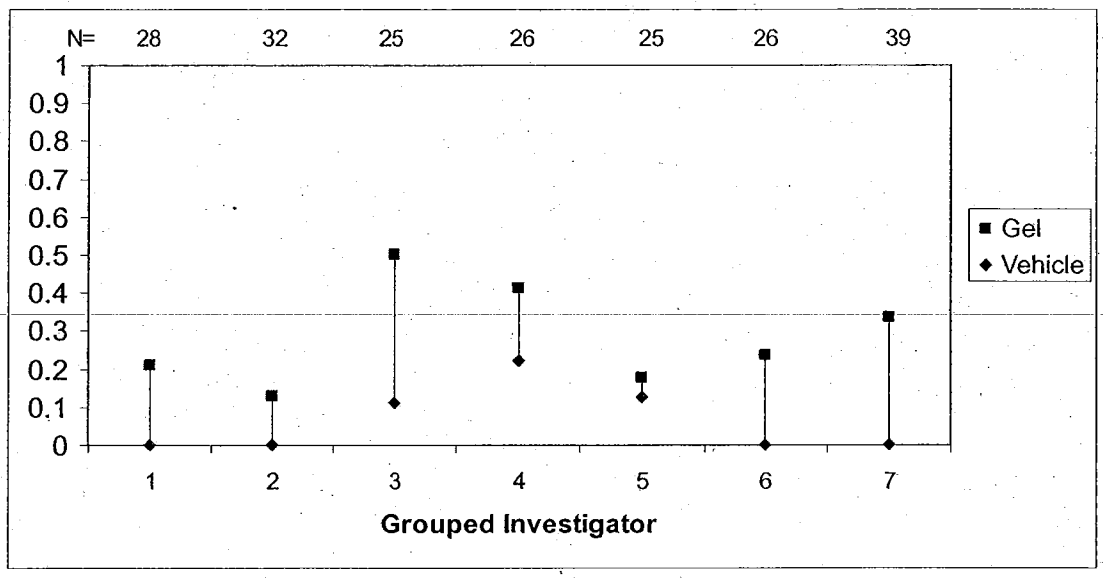


Figure 2 – Success Rate by Grouped Investigator (Study 01-05)



3.2 Evaluation of Safety

3.2.1 Extent of Exposure

The amount of medication used on the various treatment arms was similar, with slightly higher use on the active arms than the vehicle. In Study 04-03 subjects on the desonide gel used treatment an average of 56.6 times versus 55.4 times for the desonide lotion and 53.9 times for vehicle gel. The expected number of applications was 56 (twice daily for 4 weeks). The results in Study 01-05 were similar, with slightly lower use on the vehicle arm. Subjects on the desonide gel arm using treatment an average of 56.7 times versus 51.8 times on vehicle.

3.2.2 Local Tolerance

Scores for burning, scaling, and dryness were evaluated at each visit. The results of the two studies were similar with scores for burning, scaling, and dryness decreasing throughout the treatment period with lower mean scores on the desonide arms than vehicle. In Study 04-03 the scores for desonide gel and lotion were very similar. The mean local tolerance scores are presented in Figure 3 and Figure 4.

Figure 3 – Mean Local Tolerance Scores by Week (Study 04-03)

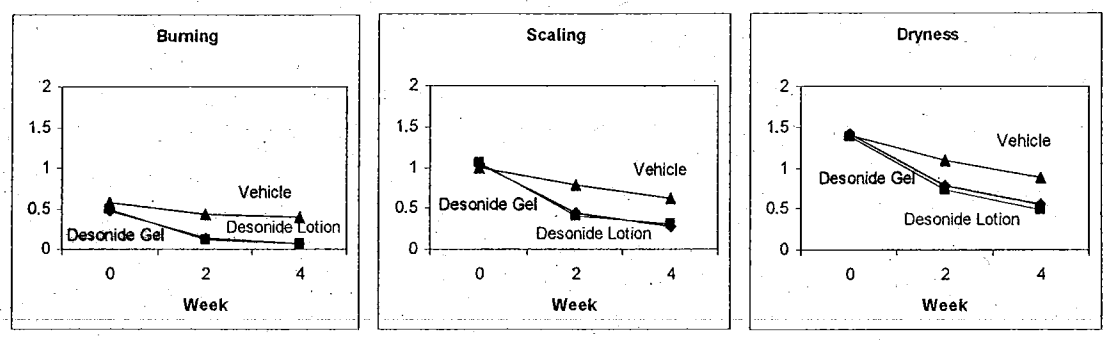
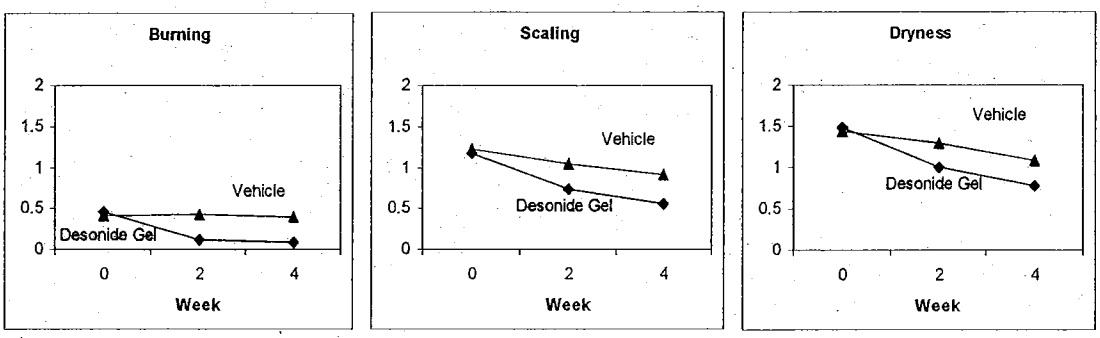


Figure 4 – Mean Local Tolerance Scores by Week (Study 01-05)



3.2.3 Adverse Events

Approximately 20% of desonide and 29% of vehicle subjects experienced adverse events in each of the studies. Application site and skin adverse events occurred in a relatively small number of subjects. The most common application site adverse event on the desonide gel arm was application site burning. The application site and skin adverse events in Studies 04-03 and 01-05 are presented in Table 20.

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Table 20 – Application Site and Skin Adverse Events

	Study 04-03			Study 01-05	
	Desonide Gel N=289	DesOwen Lotion N=285	Vehicle Gel N=92	Desonide Gel N=136	Vehicle Gel N=65
All Adverse Events	56 (19%)	53 (19%)	27 (29%)	29 (21%)	19 (29%)
Application Site Reactions					
Application site burning	12 (4%)	9 (3%)	4 (4%)	0 (0%)	4 (6%)
Application site erythema	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
App. site pigment. changes	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Application site pruritus	2 (1%)	1 (<1%)	2 (2%)	0 (0%)	1 (2%)
Application site infection	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Skin and Subcutaneous tissue disorders					
Dermatitis allergic	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Dermatitis atopic	2 (1%)	1 (<1%)	5 (5%)	0 (0%)	3 (5%)
Dermatitis contact	0 (0%)	5 (2%)	0 (0%)	0 (0%)	0 (0%)
Heat rash	0 (0%)	1 (<1%)	0 (0%)	1 (1%)	0 (0%)
Rash macular	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rash papular	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Rash	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Skin irritation	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Skin atrophy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Telangiectasia	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Urticaria	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

The response rates across gender, race, and age subgroups were very similar in Study 04-03. There is slightly more variability in response rates across subgroups in Study 01-05, but the sample sizes are smaller. Treatment success rates by gender, race and age are presented in Table 21 and Table 22.

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Table 21 – Treatment Success[1] at Week 4 (Study 04-03)

		Desonide Gel	DesOwen Lotion	Vehicle Gel
Gender	Male	57/127 (44.9%)	73/136 (53.7%)	3/38 (7.9%)
	Female	71/172 (43.8%)	74/149 (49.7%)	10/54 (18.5%)
Race	White	73/158 (46.2%)	98/178 (55.1%)	10/65 (15.4%)
	Black	26/67 (38.8%)	22/50 (44.0%)	1/12 (8.3%)
	Hispanic	17/36 (47.2%)	15/32 (46.9%)	2/12 (16.7%)
	Other	12/28 (42.9%)	12/25 (48.0%)	0/3 (0%)
Age	3 mos-<3 yrs	41/85 (48.2%)	37/72 (51.4%)	4/31 (12.9%)
	3 yrs-<6 yrs	38/75 (50.7%)	40/76 (52.6%)	2/20 (10.0%)
	6 yrs-<12 yrs	30/84 (35.7%)	45/87 (51.7%)	6/26 (23.1%)
	12 yrs-18 yrs	19/45 (42.2%)	25/50 (50.0%)	1/15 (6.7%)

[1] Clear or Almost Clear with at least 2 grades reduction

Table 22 – Treatment Success[1] at Week 4 (Study 01-05)

		Desonide Gel	Vehicle Gel
Gender	Male	23/67 (34.3%)	3/32 (9.4%)
	Female	15/69 (21.7 %)	1/33 (3.0%)
Ethnicity	Hispanic/Latino	2/14 (14.3%)	0/7 (0%)
	Not Hisp/Latino	36/122 (29.5%)	4/58 (6.9%)
Race[2]	White	15/58 (25.9%)	2/28 (7.1%)
	Black	16/57 (28.1%)	2/25 (8.0%)
	Other	8/23 (34.8%)	0/12 (0%)
Age	3 mos-<3 yrs	14/38 (36.8%)	1/18 (5.6%)
	3 yrs-<6 yrs	4/28 (14.3%)	1/12 (8.3%)
	6 yrs-<12 yrs	9/42 (21.4%)	0/23 (0%)
	12 yrs-18 yrs	11/28 (39.3%)	2/12 (16.7%)

[1] Clear or Almost Clear with at least 2 grades reduction

[2] Subjects could mark more than one race. Two desonide subjects are included twice in the totals. One subject is included under white and black, and one subject is included under black and other.

4.2 Other Special/Subgroup Populations

Subjects with moderate disease at baseline were more likely to achieve treatment success (defined as clear or almost clear with at least 2 grades reduction) than subjects with mild disease at baseline. This may be due to the fact that moderate subjects needed to reach 'almost clear' to be declared a success while mild subjects needed to reach 'clear'. The treatment success rates are presented in Table 23 and Table 24.

Table 23 – Treatment Success[1] at Week 4 by Baseline Severity (Study 04-03)

	Desonide Gel	DesOwen Lotion	Vehicle Gel
Investigator's Global Severity			
Mild (2)	44/123 (35.8%)	53/134 (39.6%)	5/46 (10.9%)
Moderate (3)	84/166 (50.6%)	94/151 (62.3%)	8/46 (17.4%)

[1] Clear or Almost Clear with at least 2 grades reduction

Table 24 – Treatment Success[1] at Week 4 by Baseline Severity (Study 01-05)

	Desonide Gel	Vehicle Gel
Investigator's Global Severity		
Mild (2)	16/71 (22.5%)	3/27 (11.1%)
Moderate (3)	22/65 (33.9%)	1/38 (2.6%)

[1] Clear or Almost Clear with at least 2 grades reduction

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The sponsor has submitted two efficacy and safety studies to support a 505(b)2 application. The sponsor has established the superiority of desonide gel versus vehicle gel in the treatment of mild to moderate atopic dermatitis in two studies. The primary efficacy endpoint was treatment success at Week 4 (Study 04-03: achieving clear or almost clear, Study 01-05: achieving clear or almost clear with at least 2 grades reduction). Study 04-03 also allows for a comparative safety assessment of desonide gel and DesOwen lotion based on 289 desonide gel and 285 DesOwen lotion subjects. The sponsor was not able to demonstrate that desonide gel is non-inferior to DesOwen lotion with regard to treatment success using a pre-specified non-inferiority margin of 10%. The secondary analyses were based on the signs of atopic dermatitis (erythema, induration, and oozing/crusting). The pre-specified analyses for the signs of atopic dermatitis was to calculate the percent reduction on the sign score (ordinal scales with range 0 to 15 in Study 04-03 and of 0 to 4 in Study 01-05). Although the percent reduction on a narrow ordinal scale is difficult to interpret, the sign scores trended in the appropriate direction. In addition, efficacy results were generally consistent across centers and subgroups.

Local tolerance scores of burning, scaling, and dryness were very similar for desonide gel and DesOwen lotion. On treatment, the local tolerance scores on desonide improved more rapidly than on vehicle. Other adverse event rates were similar across treatment arms.

5.2 Conclusions and Recommendations

Although the sponsor was unable to establish an efficacy bridge between desonide gel and DesOwen lotion, the sponsor was able to establish the efficacy of desonide gel via comparisons with vehicle gel in two studies. The primary efficacy endpoint was based on the Investigator's Global Severity Score (IGSS). Treatment success in Study 04-03 was defined as achieving a score of clear (0) or almost clear (1) at Week 4. Treatment success in Study 01-05 was defined as achieving a score of clear (0) or almost clear (1) with at least 2 grades reduction at Week 4. The efficacy results for treatment success defined as achieving a score of clear or almost clear with at least 2 grades reduction are presented in Table 25.

Table 25 – Treatment Success[1] at Week 4, ITT

	Desonide Gel	DesOwen Lotion	Vehicle Gel
Study 04-03	128/289 (44.3%)	147/285 (51.6%) -15.8%[2]	13/92 (14.1%) <0.001[3]
Study 01-05	38/136 (27.9%)	--	4/65 (6.2%) <0.001[3]

[1] Clear or Almost Clear with at least 2 grades reduction
[2] 97.5% lower confidence bound for (Desonide gel - DesOwen Lotion)
[3] p-value for Desonide gel vs. vehicle gel

Signatures/Distribution List

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Date: 10/2/2006

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