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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name Desonide
(Proposed) Trade Name Desonide gel, 0.05%
Therapeutic Class Topical Corticosteroid
Applicant Dow Pharmaceuticals

Priority Designation S

Formulation gel
Dosing Regimen twice daily topical application
Indication mild to moderate atopic dermatitis
Intended Population pediatric and adult

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends approval with revisions to proposed labeling.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No specific risk management activity is needed for this NDA.

1.2.2 Required Phase 4 Commitments

No nonclinical dermal carcinogenicity or photo-carcinogenicity studies have been conducted with any of the topical formulations of desonide. A dermal carcinogenicity study conducted with Desonide Gel 0.05% and a study to determine the photoco-carcinogenic potential of Desonide Gel are recommended as Phase 4 commitments. See Pharmacology/Toxicology review by Dr. Barbara Hill.

1.2.3 Other Phase 4 Requests

No other phase 4 requests were deemed necessary.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical development program included two phase 3 clinical studies in pediatric patients with mild to moderate atopic dermatitis (AD). One of the phase 3 studies, Study 403, was a three-arm study that compared Desonide Gel 0.05% (Desonide gel) to Desonide Gel Vehicle (Vehicle gel) and also to the reference listed drug, DesOwen® Lotion (DesOwen lotion). The second phase 3 study, Study 105, compared Desonide gel to Vehicle gel.

Special safety studies consisted of an HPA axis suppression study in pediatric patients with moderate to severe AD, a cumulative irritation and contact sensitization study in healthy adults, and a vasoconstrictive study to compare with vasoconstrictive properties of DesOwen lotion compared with Desonide gel.

1.3.2 Efficacy

Desonide gel showed clinically and statistically significant efficacy when compared with vehicle gel in two randomized, double-blind controlled phase 3 clinical trials in pediatric patients with mild to moderate AD (Study 403 and Study 105). The duration of each of these trials was 4 weeks and the primary efficacy endpoint measured at week 4 was clear or almost clear and at least a two-grade reduction in severity on the Investigator's Global Severity Score (IGSS).

1.3.3 Safety

Desonide gel was evaluated in 3 phase 1 safety studies including an hypothalamic-pituitary-adrenal (HPA) axis suppression study in 40 children (37 evaluable) with moderate to severe AD ages 3 months to 12 years. One of the patients, a 6 month-old infant, showed laboratory findings of HPA axis suppression after 4 weeks of twice daily application.

Desonide gel was also evaluated in two phase 3, randomized, placebo controlled clinical studies in pediatric patients 3 months and older with mild to moderate AD. The adverse events observed did not raise safety concerns with four weeks of twice daily use treatment of affected areas. Patients were not to treat the intertriginous skin in these studies and the safety of application to these sites has not been studied. A waiver was granted for photoirritancy and photosensitization studies, because information was submitted to the IND that showed no significant absorption by the drug product in the range of **290** nm to **700** nm.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen is twice daily topical use for the minimum duration needed to achieve control of the disease and for no more than 4-consecutive weeks. Product labeling will also include statements concerning avoiding use under occlusion and in intertriginous areas.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were studied as part of this clinical development program and none were needed.

1.3.6 Special Populations

An important consideration for safety is systemic absorption of this topical corticosteroid product in infants and young children. Children have a larger skin surface to body mass ratio and may be more susceptible to systemic toxicity from equivalent doses of topical steroids than adults. The phase 3 clinical trial study population enrolled children as young as age 0.26 years. In the HPA axis suppression study one 6 month-old infant (the youngest subject enrolled) had laboratory findings of HPA axis suppression after 4 weeks of treatment. Labeling for this topical corticosteroid will include precautions regarding the risks of systemic absorption of topical corticosteroids in:

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Labeling will also include advice about using the product for the minimum duration needed to achieve desired results and discontinuing use after 4-consecutive weeks.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Desonide TM (desonide gel) 0.05%, contains desonide, a low-to-medium potency topical steroid, at a concentration of 0.5 mg per gram in an aqueous gel base of purified water, glycerin, propylene glycol, edetate disodium dihydrate, methylparaben, propylparaben, sodium hydroxide, and Carbopol® 981. None of these components are new in pharmaceuticals and cosmetic applications. The drug product will be packaged in 15-g, 30-g, and 60-g tubes. See product review by Dr. Ernest Pappas for more details.

2.2 Currently Available Treatment for Indications

Currently available topical medications for the treatment of AD include other FDA-approved topical corticosteroids as well as topical calcineurin inhibitors, pimecrolimus and tacrolimus. Pimecrolimus is approved for mild to moderate AD and the tacrolimus for moderate to severe AD. The topical calcineurin inhibitors are topical immunosuppressants and are approved as second-line treatment. Both carry a black box warning about the possible development of cancer.

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient is available in the United States. The reference listed drug for this NDA is Desowen® Lotion.

2.4 Important Issues With Pharmacologically Related Products

Safety concerns with topical corticosteroids include local reactions such as atrophy, striae, and telangiectasia with longer term use. Allergic reactions can occur with topical steroids. The signs and symptoms may be lessened by the anti-inflammatory properties of the steroids, leading to the assessment of failure to respond rather than allergic reaction.

Systemic absorption can result in HPA axis suppression in certain situations. Children are at higher risk than adults due to their larger body surface area to body mass.

2.5 Presubmission Regulatory Activity

A guidance meeting with the Agency took place on February 10, 2005. The purpose was to provide general guidance on the content and format of the NDA application under 21 CFR 312.

The following were among the discussion items at this meeting:

- The FDA stated that the sponsor needs to address the systemic exposure of desonide and its metabolites with maximum use conditions.
- **The sponsor's bridging study did not meet the** pre-specified non-inferiority analysis and the sponsor agreed after discussion with the FDA that an additional 4-week vehicle-controlled study would be conducted.

Additional clinical information requested by the Agency included the following:

- The results of the topical safety studies should be reported as line listings and the number of patients with a positive response rather than the cumulative index.
- HPA suppression study should be done with the final formulation. Systemic levels should also be determined as part of this study.
- The sponsor was advised to address ICH E1a guidelines for chronic use. The sponsor was advised that they could extend the new phase 3 study beyond 4 weeks. They could also supply data from the published literature for FDA review.

2.6 Other Relevant Background Information

No other background information was reviewed.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

Please see CMC review by Dr. Ernest Pappas. The CMC reviewer recommended approval of this application because the information submitted **ensures the Agency's Quality Standards; i.e.,** identity, strength, quality and purity.

3.2 Animal Pharmacology/Toxicology

Please see animal pharmacology/ toxicology review by Dr. Barbara Hill. Dr. Hill found this NDA is approvable from a pharmacological/toxicological perspective and recommended the following nonclinical studies as Phase 4 commitments:

- A dermal carcinogenicity study conducted with Desonide gel; and
- A study to determine the photoco-carcinogenic potential of Desonide gel.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The only sources of clinical data reviewed were those submitted as part of the NDA application.

4.2 Tables of Clinical Studies

Study No./phase	Objectives	Design/ Control Type/Duration	Population	Number entered/completed	Endpoint
103/ Phase 1	Safety/ Irritation and sensitization	Desonide Gel; DesOwen lotion and Vehicle gel	Healthy adult volunteers	230 enrolled; 227 evaluable for irritation analysis; 212 evaluable for sensitization analysis	Assessment of irritation (scale 0 to 4);
203/ Phase 1	Safety and Biologic activity/ Vasoconstriction	Single application: Desonide Gel; DesOwen lotion; Cyclocort Cream 0.1% And hydrocortisone cream 0.5% and Vehicle gel	Healthy adult volunteers	36/36	Visual assessment of vasoconstriction of the test sites using a 4-point scale.
303/ phase 2	Safety/ adrenal suppression	Open label/ Desonide gel twice daily/ 4 weeks	Moderate to severe AD; Group 1 Group 2	Group 1: 20/20 Group 2: 20/17	Cosynotropin stimulation test
403/ Phase 3	Safety and clinical efficacy	3 arm randomized, controlled trial; Desonide gel; DesOwen lotion and vehicle gel.	Mild to moderate AD in children ages 3 months to 18 years.	Desonide gel (289 enrolled) DesOwen lotion (285 enrolled) Vehicle gel (92 enrolled)	Clear or almost clear and 2-grade improvement on IGSS
105	Safety and clinical efficacy	Randomized, controlled trial; Desonide gel vs. Vehicle gel	Mild to moderate AD in children ages 3 months to 18 years.	Desonide gel (136 enrolled) Vehicle gel (65 enrolled)	Clear or almost clear and 2-grade improvement on IGSS

4.3 Review Strategy

All clinical studies submitted in the NDA application are reviewed here for safety and both phase 3 studies were reviewed for efficacy as well as safety.

4.4 Data Quality and Integrity

No issues were identified as part of the NDA review with the data quality and integrity.

4.5 Compliance with Good Clinical Practices

The studies were conducted in compliance with good clinical practices.

4.6 Financial Disclosures

Financial disclosure was complete and did not raise any concerns.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Not measured as part of the clinical development program. Please see review by Dr. Ghosh.

5.2 Pharmacodynamics

The vasoconstrictive properties of Desonide gel were evaluated in a 36-patient single application, evaluator-blind study (Study 203). Overall, the data demonstrate that the vasoconstrictive properties of Desonide gel are comparable to DesOwen lotion, a group VI corticosteroid. See review by Dr. Tapash Ghosh.

A 4-week study to evaluate the potential for HPA axis suppression in pediatric patients with moderate to severe AD was done which showed laboratory findings of HPA axis suppression at week 4 by cosyntropin stimulation test in one of the subjects tested. See review by Dr. Tapash Ghosh.

5.3 Exposure-Response Relationships

Not done as part of this application.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Mild to Moderate Atopic Dermatitis

6.1.1 Methods

Clinical efficacy and safety data from two phase 3 studies, Study 403 and Study 105, were used to support the proposed indication.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint, measured by the IGSS, a categorical scale, has been previously accepted by FDA in the study of AD and was agreed upon during the end-of-phase 2 meeting with the applicant. Almost clear or clear with a two-grade improvement is considered a clinically meaningful response.

6.1.3 Study Design

Study 403 was a randomized, evaluator-blind, three-arm study of Desonide gel vs. Vehicle gel and DesOwen lotion in the treatment of AD. Subjects age 3 months to 18 years with mild to moderate AD were enrolled in a 3:3:1 ratio to desonide gel, DesOwen lotion, and Vehicle gel. The study enrolled 666 subjects (289 desonide gel, 285 DesOwen lotion, and 92 Vehicle gel) at 31 centers. Subjects applied study medication to affected areas twice daily for four weeks and were evaluated at baseline, Week 2, and Week 4. The severity of AD was assessed using the IGSS, erythema, induration, oozing/crusting and body surface area (BSA) involvement.

Study 105 has a similar design to Study 403 except that it has only two arms, Desonide gel and Vehicle gel. The efficacy evaluations were also slightly different. The study enrolled 201 subjects (136 Desonide gel and 65 Vehicle gel) at 15 centers. Subjects applied study medication to affected areas twice daily for four weeks and were evaluated at baseline, Week 2, and Week 4. The IGSS differed from that used in Study 403. The IGSS in Study 105 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. See also statistical review by Dr. Kathleen Fitsch.

6.1.4 Efficacy Findings (from Statistical review by Dr. Fritsch)

The primary efficacy analysis for Study 403 is shown below.

Table 1 –Study 403: Treatment Success at Week 4, ITT

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

^a Protocol-specified primary analysis

^b 97.5% lower confidence bound for (Desonide gel - DesOwen lotion)

^c p-value for Desonide gel vs. Vehicle gel

This study failed to meet the pre-specified criteria for demonstrating non-inferiority to DesOwen lotion. Therefore, the sponsor conducted another phase 3 trial, study 105, comparing Desonide gel to Vehicle gel. The results of the primary efficacy analysis for Study 105 are shown below.

Table 2 – Study 105: Treatment Success at Week 4, ITT

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

^a Protocol-specified primary analysis

^b p-value for Desonide gel vs. Vehicle gel

This study, like Study 403, demonstrated effectiveness of Desonide gel compared with Vehicle gel. The treatment effect was 21.7% (active- vehicle) for the protocol specified primary analysis, which included clear or almost clear as well as at least a two grade reduction on the IGSS as the definition of responder.

A summary of treatment effect in subgroups defined by gender, age, ethnicity is shown in Table 3.

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Table 3 Subgroup Analyses by Gender, Age and Ethnicity (from Sponsor's table 2.7.3.2.1.1.12)

	Desonide (N=425)		Desonide Vehicle (N=157)	
	Male	Female	Male	Female
Gender				
Success	80 (41%)	86 (37%)	6 (9%)	11 (13%)
Failure	114 (59%)	145 (63%)	64 (91%)	76 (87%)
Age				
Success	<u>3 mths to <3 yrs</u> 55 (45%)	<u>3 yrs to <6 yrs</u> 42 (41%)	<u>3 mths to <3 yrs</u> 5 (10%)	<u>3 yrs to <6 yrs</u> 3 (9%)
Failure	68 (55%)	61 (59%)	44 (90%)	29 (91%)
Success	<u>6 yrs to <12 yrs</u> 39 (31%)	<u>12 yrs to 18 yrs</u> 30 (41%)	<u>6 yrs to <12 yrs</u> 6 (12%)	<u>12 yrs to 18 yrs</u> 3 (11%)
Failure	87 (69%)	43 (59%)	43 (88%)	24 (89%)
Ethnicity				
Success	<u>Hispanic/Latino</u> 19 (38%)	<u>Not Hispanic/Latino</u> 147 (39%)	<u>Hispanic/Latino</u> 2 (11%)	<u>Not Hispanic/Latino</u> 15 (11%)
Failure	31 (62%)	228 (61%)	17 (89%)	123 (89%)

These data show treatment effect in subgroups defined by gender, age and ethnicity.

Treatment effect by race and baseline disease severity is shown in Table 4 .

Table 4 Subgroup Analyses by Race and Baseline Disease Severity (Source: Sponsor's table 2.7.3.2.1.1.12)

	Desonide (N=425)			Desonide Vehicle (N=157)		
	White	Black/African American	American Indian/Alaskan Native	White	Black/African American	American Indian/Alaskan Native
Race						
Success	88 (41%)	42 (34%)	2 (50%)	12 (13%)	3 (8%)	0 (0%)
Failure	128 (59%)	82 (66%)	2 (50%)	81 (87%)	34 (92%)	1 (100%)
Success	<u>Asian</u> 9 (53%)	<u>Native Hawaiian/Other Pacific Islander</u> 0 (0%)	<u>Other</u> 26 (40%)	<u>Asian</u> 0 (0%)	<u>Native Hawaiian/Other Pacific Islander</u> 0 (0%)	<u>Other</u> 2 (10%)
Failure	8 (47%)	1 (100%)	39 (60%)	6 (100%)	0 (0%)	18 (90%)
Baseline Investigator's Global Severity						
Success	<u>2 (Mild)</u> 60 (31%)	<u>3 (Moderate)</u> 106 (46%)	<u>2 (Mild)</u> 8 (11%)	<u>3 (Moderate)</u> 9 (11%)		
Failure	134 (69%)	125 (54%)	65 (89%)	75 (89%)		

These data show treatment effect in subgroups defined by race and baseline IGSS score.

Treatment effect was also observed in each of the signs of AD, which include erythema, crusting/oozing and induration as shown in the following table.

Table 5 Effect on Individual Signs of Atopic Dermatitis (from Sponsor's Table 2.7.3.3.2.2)

Intent-to-Treat Subjects						
	7001-G3HP-04-03			7001-G3HP-01-05		
Week 4	Desonide Gel LSMEAN	Vehicle LSMEAN	P-Value*	Desonide Gel LSMEAN	Vehicle LSMEAN	P-Value*
Erythema	61.2%	29.7%	<0.001	48.4%	14.6%	<0.001
Induration	57.4%	27.8%	<0.001	47.4%	17.5%	<0.001
Oozing/Crusting	76.4%	43.5%	<0.001	69.2%	31.6%	<0.001

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Statistically and clinically significant improvement in AD has been demonstrated in two randomized-controlled clinical trials of four weeks duration in pediatric patients with mild to moderate AD. In each study a dichotomized IGSS was used as the major criteria for treatment success, in which patients were categorized as success if they demonstrated a two-grade improvement from baseline. Although, Study 403 did not succeed in demonstrating non-inferiority to DesOwen lotion, both pivotal studies succeeded in showing a statistically and clinically significant difference was between Desonide gel and Vehicle gel in favor of Desonide gel. Treatment effect was observed in subgroups defined by age, gender and race. Improvement was noted in each of the investigator observed signs of AD, which included erythema, induration and crusting/oozing.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths were reported.

7.1.2 Other Serious Adverse Events

Serious adverse events were reported for three patients. One patient, an 8-year-old girl randomized to active treatment in Study 403, was seen in the emergency department for Streptococcal pharyngitis. The patient continued study treatment and completed the study. The investigator considered the event unlikely related to study medication. The event was initially classified as serious but later, it was determined that the patient never was admitted to the hospital and therefore no longer met criteria for classification as a serious adverse event.

A 3-year-old girl had two events-mycoplasma pneumonia and partial seizures with secondary generalization. The seizures took place the day after the onset of study medication and following the cosyntropin stimulation test. The patient had a history of seizures and left hemiparesis and mild CP. The patient was hospitalized and diagnosed with mycoplasma pneumonia. The subject continued on study medication and completed the study.

Reviewer's comment: The recurrence of seizures took place in a patient with history of seizures after the cosyntropin stimulation test. This reviewer agrees that the seizures are not likely to be related to study drug.

A 59-year-old man had a serious adverse event of gall stones requiring surgical treatment. The event was considered severe and unrelated to study drug by the investigator. The patient completed the study.

Reviewer's comment: This reviewer agrees with the investigator's assessment of relationship to study drug.

In the Phase 1 study, Study 103, two subjects (#105, 213) had positive pregnancy tests at the **final visit**. **Subject 105's pregnancy** was confirmed with a second test by the site and by her primary care physician. The subject delivered a normal baby boy without any complications. Subject 213 had informed the site one day prior to the final visit that a recent change in her hormonal birth control method could result in a positive pregnancy test. After several unsuccessful attempts to contact the subject, the investigational site reported that the pregnancy outcome information was lost to follow up.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The overall profile of dropouts is shown below for each of the pivotal studies is shown below. In both of the pivotal trials a higher proportion of patients in the vehicle arm discontinued early compared to the active arm(s). Overall, the principle reasons for early discontinuation in the **vehicle arm in each of the studies were "lack of efficacy" and "patient request"**. The principle reason for patient discontinuation in the active arms was **"lost to follow-up"**. In both pivotal

studies, < 1% of patients in the desonide gel arm discontinued for lack of efficacy or for adverse events.

Study 403 took place from March 10, 2004 to October 19, 2004.

Table 6 Overall Profile of Dropouts for Study 403.

	Desonide Gel	DesOwen Lotion	Vehicle Gel
Subjects Enrolled	289	285	92
Completed the Study	272	268	82
Discontinued the Study	17	17	10
Number of patients discontinued by reason			
Lack of Efficacy/Worsening of Condition	2	1	5
Adverse Event	2	4	0
Subject Request	4	2	2
Protocol Violation	0	0	0
Lost to Follow-Up	9	8	3
Pregnancy	0	0	0
Other*	0	2	0

A smaller proportion of patients in each of the active treatment groups discontinued compared with vehicle. In the vehicle arm 11% of patients (10/92) discontinued early compared with 6% of patients in the DesOwen lotion group and 6% of patients in the Desonide gel group.

Study 105 took place from May 9, 2005 to September 13, 2005.

Table 7 Overall profile of dropouts for Study 105

	Desonide	Vehicle
Subjects Enrolled	136	65
Completed the Study	132	55
Discontinued Study	4	10
Number discontinued by reason for discontinuation		
Lack of Efficacy/Worsening of Condition	0	3
Adverse Event	1	1
Subject Request	1	5
Protocol Violation	0	0
Lost to Follow-Up	2	1
Pregnancy	0	0
Other*	0	0

A high proportion of patients in the vehicle arm (10/65, 15%) discontinued the study early compared with patients in the active arm (4/136, 3.0%). Five patients in the Vehicle gel arm requested to be removed from the study and 3 were discontinued for lack of efficacy, including worsening from baseline. In contrast, none of the patients in the Desonide gel arm discontinued for lack of efficacy.

7.1.3.2 Adverse events associated with dropouts

A total of 11 subjects prematurely discontinued from the phase 3 studies due to an adverse event: three among Desonide gel-treated subjects (N= 425), four among Vehicle gel-treated subjects (N=157) and four among DesOwen-treated subjects (N=285).

The following is a summary of the three subjects assigned to Desonide gel who discontinued due to adverse events. For details, please see appended reviews of study reports.

- *Subject 13-60 in Study 403, a 1-year-old girl, was discontinued for an adverse event of telangiectasia on the upper arms, trunks, and legs.*
- *Subject 28-427 in Study 403, a 1-year-old male was discontinued for a flare of AD.*
- *Subject 08-017 in Study 105, a 4.75 year old male was discontinued for a rash on the face and arms and fever. Both events resolved and were considered unrelated to study drug by the investigator.*

Of the four subjects assigned to Vehicle gel that discontinued due to an adverse event, three discontinued for worsening or flare of AD and one also discontinued for burning and stinging on application of study drug. See appended review of Study 105. There were no discontinuations in the Vehicle gel group in Study 403.

The four DesOwen lotion- treated patients who discontinued for adverse events reported the following: skin infection and urticaria in one subject each as well two events of contact dermatitis in two subjects. See appended review of Study 403.

7.1.3.3 Other significant adverse events

Two percent of subjects in the Desonide gel group and 8% of subjects in the Vehicle gel group reported at least one treatment-related adverse event, defined as at least possibly related to study medication, during the study. See review of appended review of individual study reports for a comprehensive listing of adverse events.

7.1.4 Other Search Strategies

The reviewer sought to identify all application site AE's that were spontaneously reported regardless in Desonide gel group and the Vehicle gel group in the combined phase 3 studies. These were summarized regardless of investigator attribution.

Methods:

The AE datasets for studies 403 and 105 were summarized by body system using terms "General Disorders and Administration site conditions" and "Skin and subcutaneous tissue disorders". Cases of pyrexia and injection site reaction were excluded from consideration. The results are summarized below for Vehicle and for Desonide gel. The subject numbers are in parentheses.

Vehicle-treated subjects:

Study 403: 7 events in 7 subjects (107, 159, 214, 301, 431, 475, 850)

Study 105: 9 events in 8 subjects (46, 65, 69, 80, 85, 117, 127, 130)
The total number of events was 16 in 15 subjects for the combined vehicle group.

Desonide Gel-treated subjects:

Study 403: 11 events in 10 subjects (33, 60, 292, 318, 319, 427, 603, 624, 771, 856)

Study 105: 1 event in 1 subject (#17) (excluded subject 68 because it stated that this was not in application site)

Total Events 12 in 11 subjects

The total number of events was 12 in 11 subjects for the combined Desonide gel group.

Incidence rate of AEs that were Application related and Skin-related was 16/157 (10%) in the vehicle group and 12/425 (3%) in the Desonide gel group. These 12 events in the Desonide gel group included burning (4 events), rash (3), pruritus (2), worse atopic dermatitis (2) and telangiectasia (1).

Reviewer's comment: These data should be summarized in the Adverse Reaction section in labeling.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were elicited using a non-directive approach at each office visit. The treatment period in the phase 3 program was four weeks. Patients had physical examination and history at baseline. At week 2 and week 4 patients had safety evaluations which included recording of adverse events as well as local adverse reactions.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse event categorization and preferred terms were appropriate. MedRA classification system was used.

In addition to adverse events assessments, study 403 included active assessments of local adverse events, dryness, scaling, and burning/stinging, on a 0 (none) to 3 (severe) point scale. These are reviewed in the following section.

7.1.5.3 Incidence of common adverse events

The incidence of active assessments for dryness, scaling and burning/stinging in study 403 are discussed here. Study 403 was chosen because it contains a standard of care arm to which both

active study drug and its vehicle can be compared. This allows an assessment of the safety of the study drug vehicle.

The severity of dryness at baseline was similar across treatment groups with 46%, 45%, and 47% of subjects with moderate to severe dryness in the Desonide gel, DesOwen lotion, and Vehicle gel groups, respectively. At the end of the 4-week treatment period, approximately 8% of subjects in the Desonide gel group, approximately 4% of subjects in the DesOwen lotion group, and 19% of subjects in the Vehicle gel group had moderate to severe dryness. Severity scores averaged 1.4 in all three treatment groups at baseline, which reduced to 0.6, 0.5, and 0.9 at the Week 4 evaluation for the Desonide gel, DesOwen lotion, and Vehicle gel groups, respectively.

Reviewer's comment: Desonide gel was intermediate in proportions of patients experiencing dryness at week 4 and fell between DesOwen lotion, which had the lowest proportion of patients with dryness and vehicle gel, with the highest. In all three treatment groups, proportion of patients with moderate to severe dryness at Week 4 were less than at baseline. These data do not raise any safety concerns.

The severity of scaling at baseline was similar across treatment groups with approximately 29%, 29%, and 25% of subjects with moderate to severe scaling in the Desonide gel, DesOwen lotion, and Vehicle gel groups, respectively. At the end of the 4-week treatment period, 2% of subjects in the Desonide gel group, approximately 5% of subjects in the DesOwen lotion group, and 14% of subjects in the Vehicle gel group had moderate to severe scaling. Severity scores averaged 1.0 in all three treatment groups at baseline and reduced to 0.3, 0.3, and 0.6 at the Week 4 evaluation for the Desonide gel, DesOwen lotion, and Vehicle gel groups, respectively.

Reviewer's comment: The proportions of patients with moderate to severe scaling decreased from baseline in all three treatment groups. These data do not raise any safety concerns.

The severity of burning/stinging at baseline was similar across treatment groups with 11%, 12%, and 16% of subjects with moderate to severe burning/stinging in the Desonide gel, DesOwen lotion, and Vehicle gel groups, respectively. At the end of the 4-week treatment period, 1% of subjects in the Desonide gel and DesOwen lotion groups and 12% of subjects in the Vehicle gel group had moderate to severe burning/stinging. Severity scores averaged 0.5 in the Desonide gel and DesOwen lotion groups and 0.6 in the Vehicle gel group, which reduced to 0.1 at the Week 4 evaluation for the Desonide gel and DesOwen lotion groups and 0.4 in the Vehicle gel group.

Reviewer's comment: The proportions of patients with moderate to severe stinging/burning decreased from baseline in all three treatment groups. These data do not raise any safety concerns.

7.1.5.4 Common adverse event tables

The following table shows adverse events observed in $\geq 5\%$ of patients in the phase 3 studies. The counts reflect the number of patients in each treatment group reporting one or more adverse events.

Table 8 Adverse Events Occurring at a Frequency of $\geq 5\%$ (of Subjects) (Source: Table 2.7.4.2.1.1.4)

	Desonide Gel	Desonide Vehicle
Number of Subjects	425	157
Number of Subjects Reporting		
One or More Events	85 (20%)	46 (29%)
System Organ Class		
General disorders and administration site conditions	19 (4%)	12 (8%)
Infections and infestations	36 (8%)	18 (11%)
Skin and subcutaneous tissue disorders	6 (1%)	9 (6%)
Dermatitis atopic	2 (<1%)	8 (5%)

Of all the common adverse events, defined as those occurring in $\geq 5\%$ of the AD study population in either the desonide gel or desonide vehicle treatment group, all were higher in Vehicle gel compared with Desonide gel. The common adverse events included infections and infestations, skin and subcutaneous tissue disorders, AD and general disorders and administration site conditions.

Reviewer's comment: Some level of background occurrence of these adverse events is expected given the study population. Patients with AD are susceptible to skin infections, especially with S Aureus, requiring antimicrobial treatment. The data suggest that with active treatment of the AD with desonate, subjects are less likely to suffer adverse events related to AD compared with vehicle treatment.

The incidence rates of common adverse events occurring in $\geq 1\%$ in the combined phase 3 studies are shown in the following table.

Table 9 Incidence Rates of Adverse Events for Studies 403 and 105 (From sponsor's Table 2.7.4.2.1.1.5)

	Desonide Gel N=425	Vehicle Gel N=157
Number of Subjects Reporting One or More Events	85 (20%)	46 (29%)
System Organ Class		
Eye disorders	5 (1%)	1 (1%)
Conjunctivitis	4 (1%)	1 (1%)
Gastrointestinal disorders	4 (1%)	4 (3%)

	Desonide Gel N=425	Vehicle Gel N=157
Abdominal pain upper	1 (<1%)	1 (1%)
Diarrhea	1 (<1%)	1 (1%)
Stomach discomfort	1 (<1%)	1 (1%)
Toothache	0 (0%)	1 (1%)
Vomiting	0 (0%)	1 (1%)
General disorders and administration site conditions	19 (4%)	12 (8%)
Application site burning	4 (1%)	4 (3%)
Application site pruritus	2 (<1%)	3 (2%)
Pyrexia	10 (2%)	6 (4%)
Immune system disorders	1 (<1%)	1 (1%)
Hypersensitivity	0 (0%)	1 (1%)
Infections and infestations	36 (8%)	18 (11%)
Ear infection	4 (1%)	1 (1%)
Eye infection	0 (0%)	1 (1%)
Gastroenteritis	0 (0%)	1 (1%)
Gastroenteritis viral	2 (<1%)	2 (1%)
Impetigo	0 (0%)	1 (1%)
Infection	1 (<1%)	1 (1%)
Influenza	1 (<1%)	2 (1%)
Nasopharyngitis	7 (2%)	5 (3%)
Otitis media	0 (0%)	1 (1%)
Pneumonia	0 (0%)	1 (1%)
Staphylococcal bacteremia	1 (<1%)	1 (1%)
Staphylococcal infection	0 (0%)	1 (1%)
Upper respiratory tract infection	6 (1%)	1 (1%)
Injury, poisoning and procedural complications	19 (4%)	5 (3%)
Arthropod bite	4 (1%)	2 (1%)
Blood blister	0 (0%)	1 (1%)
Excoriation	3 (1%)	1 (1%)
Sunburn	3 (1%)	2 (1%)
Musculoskeletal and connective tissue disorders	5 (1%)	1 (1%)
Muscle cramp	0 (0%)	1 (1%)
Nervous system disorders	8 (2%)	2 (1%)
Headache	8 (2%)	2 (1%)
Respiratory, thoracic and mediastinal disorders	4 (1%)	5 (3%)
Asthma	1 (<1%)	1 (1%)
Nasal congestion	1 (<1%)	1 (1%)
Pharyngolaryngeal pain	0 (0%)	1 (1%)
Rhinorrhea	1 (<1%)	2 (1%)
Skin and subcutaneous tissue disorders	6 (1%)	9 (6%)
Dermatitis atopic	2 (<1%)	8 (5%)
Skin atrophy	0 (0%)	1 (1%)

The incidence rates of headache were numerically higher, albeit similar, in the Desonide gel group (2%) compared with Vehicle gel (1%). All of the adverse events of headache in both treatment groups were rated *mild* in severity and all were assessed as either definitely unrelated or unlikely related to study drug by the investigator. This reviewer identified no other differences in incidence rates of adverse events that suggested attribution to Desonide gel over Vehicle gel.

7.1.5.5 Identifying common and drug-related adverse events

Adverse events listed as definitely, probably, or possibly related to study drug by the investigator are summarized in the following table.

Table 10 Adverse Events -At Least Possibly Related- Occurring at a Frequency of \geq 1% of Subjects (Sponsor's Table 2.7.4.2.1.1.6)

	Desonide Gel N=425	Vehicle Gel N=157
Number of Subjects Reporting One or More Events	9 (2%)	13 (8%)
System Organ Class		
General disorders and administration site conditions	6 (1%)	6 (4%)
Application site burning	4 (1%)	4 (3%)
Application site pruritus	2 (<1%)	2 (1%)
Infections and infestations	0 (0%)	1 (1%)
Impetigo	0 (0%)	1 (1%)
Injury, poisoning and procedural complications	0 (0%)	1 (1%)
Sunburn	0 (0%)	1 (1%)
Skin and subcutaneous tissue disorders	3 (1%)	7 (4%)
Dermatitis atopic	1 (<1%)	6 (4%)
Skin atrophy	0 (0%)	1 (1%)

Application site burning occurred in 1% of subjects treated with Desonide gel compared with 3% of subjects treated with Vehicle gel. It appears that the active moiety is mitigating these effects in the Desonide gel group. As would be expected, a higher proportion of subjects in the Vehicle gel group had AD-related adverse events compared with those assigned to Desonide gel.

Reviewer's comment: This corresponds to the table that the sponsor has proposed in draft labeling. This table may be misinterpreted, because it seems that application of Desonide gel is protective from adverse events such as stinging and burning. However, this may be misleading if, as it appears, the vehicle component is causing these adverse events. The table does not include a control arm that would establish the effects of vehicle itself.

7.1.5.6 Additional analyses and explorations

No additional analyses and explorations were done in this review.

7.1.6 Less Common Adverse Events

Not shown in Table 10 because they accounted for \leq 1% of study subjects in the Desonide gel group were the adverse events heat rash (mild), telangiectasia (mild) and application site erythema (severe) in one subject each. These events were assessed as at least possibly related to study drug by the investigator.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing was not done as part of the phase 3 development program. Laboratory testing was done as part of the safety study evaluating for HPA axis suppression, Study 303. None of the subjects in that study showed HPA axis suppression. See appended review.

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

Not applicable.

7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable.

7.1.7.4 Additional analyses and explorations

Not applicable.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were not collected in the clinical development program.

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

Not applicable.

7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable.

7.1.8.4 Additional analyses and explorations:

Not applicable.

7.1.9 Electrocardiograms (ECGs)

ECGs were not collected in the clinical development program.

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

Not applicable.

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

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

Immunogenicity was not assessed as part of the clinical development program and was not needed.

7.1.11 Human Carcinogenicity

Human carcinogenicity was not assessed as part of the clinical development program and was not needed based on the drug class.

7.1.12 Special Safety Studies

Special safety studies included the following:

7001-G3HP-01-03(Study 103): A Single Center, Evaluator-Blind Evaluation of the Cumulative Irritation and Contact Sensitization Potential of Desonide Gel, DesOwen® Lotion 0.05%, Desonide Gel Vehicle, and Control Following Repeated Topical Application to Healthy Subjects

7001-G3HP-02-03(Study 203): A vasoconstrictive study. The primary visual scoring efficacy data demonstrate vasoconstrictive properties of Desonide Gel similar to DesOwen Lotion.

7001-G3HP-03-03 (Study 303): HPA axis suppression: Phase 2 Multicenter, Open-Label Evaluation of the Adrenal Suppression Potential of Topically Applied Desonide Gel in Pediatric Subjects with Moderate to Severe Atopic Dermatitis.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No instances of abuse have been reported in any of the studies in this development program and none of the topical drugs in these studies have known potential for abuse.

No instances of withdrawal or rebound were reported in the safety database.

7.1.14 Human Reproduction and Pregnancy Data

No studies in pregnant women were performed as part of this clinical development program. The product will be pregnancy class C, if approved.

7.1.15 Assessment of Effect on Growth

Assessment of effect on growth was not done as part of the clinical development program. The phase 3 studies were of 4-weeks duration.

7.1.16 Overdose Experience

No overdose experience occurred during clinical development.

7.1.17 Postmarketing Experience

The drug is not marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

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

7.2.1.1 Study type and design/patient enumeration

A total of 425 patients were exposed to desonate gel in the phase 3 clinical program. Another 157 patients were treated with vehicle, and 285 were treated with Desowen lotion. A listing of studies by type and patient enumeration is shown below.

Special Safety Studies:

303: HPA axis suppression in patients with moderate to severe AD

Cohort 1 (≥ 3 years, < 5 years): 20 subjects entered/ 20 completed.

Cohort 2 (≥ 3 months, < 3 years): 20 subjects entered/ 17 completed.

103: Dermal safety and repeat insult patch test

230 entered/ 227 evaluable for irritation analysis, 212 evaluable for sensitization.

203: **Vasoconstrictive assay:** 36 entered/36 completed.

Phase 3 Studies:

403: Safety and efficacy in pediatric patients with mild to moderate AD, 4 week study

Desonide gel: 289 entered/ 272 completed

Vehicle gel: 92 entered / 82 completed

DesOwen lotion: 285 entered / 268 completed

105: Safety and efficacy in pediatric patients (3 months to 18 years) with mild to moderate AD

Desonide Gel: 136 enrolled

Vehicle gel: 65 enrolled

7.2.1.2 Demographics

For the combined phase 3 studies, the mean age ranged from 0.3 to 18.9 years, the gender distribution ranged from 45-46% male and 54-55% female, and the most common race was Caucasian which ranged from 51% to 59%.

7.2.1.3 Extent of exposure (dose/duration)

The planned extent of exposure in the phase 3 studies was twice daily topical application for 4 weeks.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Not applicable.

7.2.2.2 Postmarketing experience

Not applicable.

7.2.2.3 Literature

Not applicable.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience was deemed adequate to assess safety and effectiveness of short term treatment e.g., 4 weeks. The safety and effectiveness for longer than 4 weeks is not established and product labeling will reflect this.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal and in vitro testing was deemed adequate. See pharmacology/toxicology review by Dr. Barbara Hill.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was deemed adequate to assess the safety and efficacy of short term use.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable.

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

Not applicable.

7.2.8 Assessment of Quality and Completeness of Data

The data provided for the safety review was complete and of adequate quality.

7.2.9 Additional Submissions, Including Safety Update

The 120 day safety update was submitted on April 19, 2006. There was no new clinical information to report.

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

The clinical trial data support the safety of the use of Desonide gel in subjects with mild to moderate AD as young as age 3 months. The most common treatment-related adverse events in

the phase 3 trials were application site burning and itching. An important limitation of the data is that the duration of treatment in the clinical studies was four weeks whereas, AD is a chronic disease. It will be emphasized in product labeling that the safety of Desonide gel treatment beyond four weeks is not established. Although no instances of HPA suppression were noted in the special safety study (Study 303), it is important to note that while this study meets FDA requirements, it is limited in sample size and duration of treatment. Therefore, class labeling will be included for describing risks of HPA axis suppression. Class labeling will also describe cutaneous risks of topical corticosteroids.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

This reviewer reviewed both individual study data from the two pivotal efficacy studies as well as the pooled data from the sponsor's integrated summary of safety, in which the sponsor pooled for the safety data for Desonide gel and Vehicle gel from Study 403 and Study 105. A total of 425 subjects treated with Desonide gel and 157 subjects were treated with Vehicle gel in the two phase 3 studies combined.

7.4.1.2 Combining data

Data were combined for Desonide gel and Vehicle gel in the sponsor's ISS report. DesOwen lotion was not included in the combined data tables.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Only one drug concentration was tested in the clinical development program, 0.05%.

7.4.2.2 Explorations for time dependency for adverse findings

The treatment period for all clinical studies was four weeks or shorter in duration. No explorations were performed for greater than four weeks. Labeling will reflect that the safety and efficacy of use beyond four weeks has not been evaluated.

Several adverse effects including cutaneous atrophy and HPA axis suppression with topical corticosteroids can be dose and time dependent. The package insert will include "class labeling" with cautions regarding such adverse events.

7.4.2.3 Explorations for drug-demographic interactions

This reviewer described adverse events by gender and age using SOC terms. After reviewing the safety database of Study 403 for adverse events classified as either General and Administration Related or Skin and Subcutaneous, this reviewer noted a higher number of flares (or worsening) of AD in children less than the median age of 5.4 years (N=334) compared to those older than the median age (N=332). The highest number occurred in the Vehicle gel group.

Among patients less than age 5.4 years, there were four children Vehicle gel group (N=50) and two children in Desonide gel treatment group (N=146), all under age 2, who had worsening or flare of AD in Study 403. One subject assigned to DesOwen lotion (N=138) had worsening of AD. In contrast, among those who were older than the median age, only one subject (an 11-year-old child assigned to the Vehicle gel group) in any treatment group had worsening of AD.

Reviewer's comment: These data suggest that the younger children treated with Vehicle gel (especially under age 2 years) are more likely to have worsening of AD compared with older children as the incidence rate was 8% among children less than the median age in the Vehicle group. The incidence was smaller in the active arms and it is not clear from these small numbers what relationship these events might have to active study drug. Among children less than the median age, the proportions in the two active arms were similar to each other (each ~1%), both lower than Vehicle gel.

By Gender:

In Study 105, rates of infections and infestations were no higher in active compared with vehicle for either gender. Rates in the active groups were 12% in both males and females compared with 19% in males treated with vehicle and 12% for females treated with vehicle. In Study 403, rates of infections and infestations in the Desonide gel group were no higher than vehicle for either gender, though they were numerically higher than DesOwen lotion in females. The rates in the Desonide gel, DesOwen lotion and Vehicle gel group were: 10%, 7% and 16% in males and 5%, 4%, and 5% in females, respectively.

Table 11 Rates (%) of Adverse Events by Gender: Study 403

		Desonide Gel	DesOwen lotion	Vehicle gel
Infections/Infestations	males	9 (12/127)	7 (10/136)	16 (6/38)
	females	5 (9/162)	4 (6/149)	5 (3/54)
Skin and subcutaneous d/o	males	2 (2/127)	5 (7/136)	8 (3/38)
	females	1.2 (2/162)	4 (6/149)	3.7 (2/54)
General and administration	males	4 (5/127)	4 (6/136)	8 (3/38)
	females	4 (7/162)	2 (3/149)	1.8 (1/54)

In this table, the only adverse event class that showed a higher rate in the Desonide gel group compared with vehicle gel was in general and administration conditions for females. Of the seven females with general and administration site conditions in the Desonide gel group, two had

pyrexia, one had fatigue, one had an injection reaction from another product. This leaves three subjects in the Desonide gel group with application site reactions: (#771) had erythema and pruritus of her face, # 603 reported stinging, #292 reported burning and stinging at the application site. One female subject in the DesOwen lotion group reported application site pruritus. None of the subjects assigned to vehicle gel experienced application site reactions.

Among male subjects, two experienced application site burning and one male subject reported application site pruritus in the Desonide gel group. One male patient experienced application site burning and one experienced application site pigmentary changes in the DesOwen lotion group. Two male patients assigned to vehicle gel reported application site pruritus. In both males and females combined, application site burning and stinging have been reported in about 2% (6/289) of subjects treated with Desonide gel. This should be described in labeling. Overall, these safety data do not suggest any meaningful differences by gender when comparing Desonide gel treated patients to either control group.

7.4.2.4 Explorations for drug-disease interactions

Not applicable.

7.4.2.5 Explorations for drug-drug interactions

Not applicable.

7.4.3 Causality Determination

The data from the clinical trials support that desonide gel vehicle may cause application site symptoms such as burning based on the close temporal relationship of to study drug application. This effect may be reduced in the drug product by the presence of the active ingredient, desonide, which has anti inflammatory effects. One patient in Study 403 had new onset atrophy which may have been caused by the study drug, given that atrophy is a well-described potential side-effect of topical steroids. The label should adequately address these concerns.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There are not any concerns with the dosing regimen and the topical administration of this drug product. The dosing and administration is similar to marketed topical formulations of desonide.

In the clinical trials, patients were to apply the gel topically twice daily to the affected areas and avoid application to the face and inguinal area.

8.2 Drug-Drug Interactions

No drug-drug interactions were studied in the clinical development program.

8.3 Special Populations

8.4 Pediatrics

AD is predominantly a disease of children. The safety and effectiveness of desonate gel was studied in pediatric patients as part of this drug development program, including special safety studies of HPA axis suppression in children down to age 3 months.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

No literature was reviewed for this NDA.

8.7 Postmarketing Risk Management Plan

No special post-marketing risk management plan is deemed necessary.

8.8 Other Relevant Materials:

No other materials were reviewed for this NDA.

9 OVERALL ASSESSMENT

9.1 Conclusions

The data support the safety and efficacy of Desonide gel in the treatment of patients ages 3 months and older with mild to moderate AD. Desonide gel was superior (clinically and statistically) to vehicle gel in two well controlled phase 3 clinical trials in pediatric patients with mild to moderate AD. The active assessments for local reactions did not raise concerns when compared to DesOwen lotion or Vehicle gel. The drug product was also studied in an HPA axis suppression study in pediatric patients ages 3 months and older with moderate to severe AD and none of the patients were found to have adrenal suppression with 4 weeks of use.

9.2 Recommendation on Regulatory Action

This reviewer recommends approval with revised labeling and phase 4 commitments.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Postmarketing risk management is to include the submission of annual reports, including adverse event reports, as required for a marketed drug product in the United States.

9.3.2 Required Phase 4 Commitments

No nonclinical dermal carcinogenicity or photo-carcinogenicity studies have been conducted with any of the topical formulations of desonide. A dermal carcinogenicity study conducted with Desonide Gel and a study to determine the photoco-carcinogenic potential of Desonide Gel are recommended as Phase 4 commitments. See Pharmacology/Toxicology review by Dr. Barbara Hill.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are needed.

9.4 Labeling Review

Please see the appended line-by-line labeling review for details.

9.5 Comments to Applicant

There are no additional comments to be conveyed to the sponsor other than the phase 4 commitments needed for pharmacology/toxicology and the changes to the proposed label.

APPEARS THIS WAY ON ORIGINAL

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 7001-G3HP-04-03 (Study 403): A Randomized, Evaluator-Blind, 3-Arm, Multi-Center Study to Evaluate the Safety and Efficacy of Topically Applied Desonide Gel vs. Desonide Gel Vehicle and DesOwen® Lotion for the Treatment of Pediatric Subjects with Mild to Moderate Atopic Dermatitis

Trial Design Study 403:

Study Sites: 31, US

Number of Patients: 666

Study period: March –October 2004

Objectives:

The objective of this study was to determine the safety and efficacy of Desonide gel compared to its Vehicle gel and DesOwen lotion in the treatment of mild to moderate AD in pediatric subjects ages three (3) months to 18 years.

The trial was to be evaluator blind, therefore, it was the investigator's designee who observed the first application of study drug rather than the investigator. There are visible differences in packaging between the Desonide gel and DesOwen lotion as well as the appearance of the drug product.

Study Design: multi-center, randomized, evaluator-blind, vehicle- and active-controlled, parallel comparison involving pediatric subjects with mild to moderate AD.

No. Patients: 666 subjects were enrolled (Desonide gel: 289 subjects, DesOwen lotion: 285 subjects, Vehicle gel: 92 subjects).

Diagnosis and Main Criteria for Inclusion:

Male or female subjects in generally good health of any race, 3 months to 18 years of age with visible flexural dermatitis.

Subjects had a diagnosis of AD as defined by the United Kingdom refinement of the Hanifin and Rajka diagnostic criteria for AD. The subject must have had:

- a) An itchy skin condition in the last 12 months (children under the age of 12 months must have had a "history" of itchy skin) plus three (3) or more of the following:
- b) Onset of AD below two (2) years of age.

- c) History of flexural involvement.
- d) History of generally dry skin.
- e) Personal history of other atopic disease (in children under four years, history of atopic disease in a first-degree relative could be included).
- f) Visible flexural dermatitis.

Subjects were required to have AD that involved a minimum of 10% of body surface area (BSA) and a baseline Investigator's Global Severity Score, erythema score, and induration score rated as mild or moderate and an oozing/crusting score rated as moderate or less.

Test product, reference product, batch number:

Desonide gel, batch numbers: 878, 879, 880

Vehicle gel, batch number: 881

Duration of Treatment: Twice daily for 4 weeks

Criteria for Evaluation:

Primary Efficacy:

- **Dichotomized Investigator's Global Severity Score (IGSS) at Week 4**

Secondary Efficacy:

- Percent change from baseline in Signs and Symptoms of AD scores at Week 4

Other Efficacy:

- Dichotomized IGSS Score at Week 2
- Percent change from baseline in Signs and Symptoms of AD scores at Week 2
- Pruritus severity
- Percent change from baseline in BSA of areas treated with study drug

How Measured:

IGSS:

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

Signs and Symptoms of AD

The following guidelines were used for grading erythema, induration, and oozing and crusting in each of the five areas of the body (face, scalp, trunk, arms and legs). The signs and symptoms were evaluated and summed over the body regions and the percent change from baseline was analyzed.

Reviewer's comment: Analyzing the percent change in data obtained from an ordinal scale such as those used to evaluate the signs and symptoms does not appear to be a very meaningful analysis.

1. Erythema Severity:

Erythema was defined as abnormal redness of the skin. It was scored on a scale of 0 to 3 as follows:

Score	Grade	Guideline
0	None	No redness present
1	Mild	Faintly detectable erythema; very light pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/ dark red

2. Induration Severity:

Induration was scored on a scale of 0 to 3 as follows:

Score	Grade	Guideline
0	None	No elevation
1	Mild	Barely perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation

3. Oozing and Crusting Severity:

Oozing and Crusting was scored on a scale of 0 to 3 as follows:

Score	Grade	Guideline
0	Absent	None
1	Mild	Faint signs of oozing
2	Moderate	Definite oozing or crust but with 5 or fewer sites per area
3	Severe	Marked and extensive

Pruritus Severity Score

The pruritus score was determined by the investigator for pediatric subjects by using his/her clinical judgment and input from the subject and parent/guardian. The following scores were used to describe the severity grade:

Score	Grade	Guideline
0	None	No pruritus
1	Mild	Occasional, slight itching/scratching

- | | | |
|---|----------|---|
| 2 | Moderate | Constant or intermittent itching/scratching which is not disturbing sleep |
| 3 | Severe | Bothersome itching/scratching which is disturbing sleep |

Safety Evaluation:

All non-solicited adverse events were recorded.

Local Adverse Events

The evaluator also assessed local irritation by rating the following symptoms: dryness, scaling, stinging/burning, striae, telangiectasia, skin atrophy, secondary infection, hypertrichosis, miliaria, and ecchymoses. The evaluator determined the score for each of these variables by direct evaluation (dryness and scaling) or through interviewing the subject (stinging/burning) when possible. The following definitions of terms were applied to these evaluations.

1. Dryness

Score	Grade	Guideline
0	None	No dryness
1	Mild	Slight but definite roughness
2	Moderate	Moderate roughness
3	Severe	Marked roughness

2. Scaling

Score	Grade	Guideline
0	None	No scaling
1	Mild	Barely perceptible shedding, noticeable only on light scratching or rubbing
2	Moderate	Obvious but not profuse scaling
3	Severe	Heavy scale production

3. Stinging/Burning

Score	Grade	Guideline
0	None	No stinging/burning
1	Mild	Slight warm, tingling sensation; not really bothersome
2	Moderate	Definite warm; tingling/stinging sensation that is somewhat bothersome
3	Severe	Hot, tingling/stinging sensation that has caused definite discomfort

4. **Striae**: Striae was recorded as either present or absent.

5. **Telangiectasia**: Telangiectasia was recorded as either present or absent.

6. **Skin Atrophy**: Skin atrophy was recorded as either present or absent.

7. **Secondary Infection**: Secondary infection was recorded as either present or absent.

Statistical Methods:

The primary analyses included non-inferiority and superiority testing of the IGSS conducted on the intent-to-treat population.

Non-inferiority testing used the one-sided 97.5% confidence interval approach with a non-inferiority margin of 10% for dichotomized IGSS and a noninferiority margin of 15% for the percent change from baseline in Signs and Symptoms of AD scores at Week 4. Two-sided hypothesis testing was conducted for the superiority analyses of the dichotomized IGSS and for the percent change from baseline in Signs and Symptoms of AD scores at Week 4 using a significance level of 0.05.

The last observation carried forward method was used to extrapolate missing efficacy data. No imputations were made for safety data (localized adverse events) that were missing.

Additional Analyses

A March 10, 2004 communication from the FDA Clinical reviewer recommended that the dichotomized IGSS be modified so that the definition of success required a two-point minimum improvement from baseline.

Subject demographics and baseline characteristics are shown in the following two tables.

Table 12 Subject Demographics

	Desonide Gel	DesOwen Lotion	Vehicle Gel
Number of Subjects	289	285	92
Age (Years)			
Mean	6.55	6.87	6.39
STD	4.68	4.75	4.91
Range	0.26-18.50	0.28-18.97	0.55-18.54
Gender			
Male	127 (44%)	136 (48%)	38 (41%)
Female	162 (56%)	149 (52%)	54 (59%)
Race			
White	158 (55%)	178 (62%)	65 (71%)
Non-White	131 (45%)	107 (38%)	27 (29%)
Black	67 (23%)	50 (18%)	12 (13%)
Asian/Pacific Islander	9 (3%)	7 (2%)	0 (0%)
Hispanic/Latino	36 (12%)	32 (11%)	12 (13%)
American/Alaskan Native	4 (1%)	2 (1%)	0 (0%)
Other	15 (5%)	16 (6%)	3 (3%)

The mean age in this study was 6 years across treatment groups. Patients ranged in age from approximately 3 months to 18 years. More than half of the study subjects were female (52%-59%). The majority of subjects were Caucasian. There was an imbalance in the racial

distribution among treatment groups with a Caucasian patients making up a larger proportion of the patients assigned to vehicle gel compared with the other treatment groups.

Table 13 Baseline Characteristics:

	Desonide Gel (N=289)	DesOwen Lotion (N=285)	Vehicle Gel (N=92)
Investigator's Global Severity			
Clear	0 (0%)	0 (0%)	0 (0%)
Almost Clear	0 (0%)	0 (0%)	0 (0%)
Mild	123 (43%)	134 (47%)	46 (50%)
Moderate	166 (57%)	151 (53%)	46 (50%)
Severe	0 (0%)	0 (0%)	0 (0%)
Very Severe	0 (0%)	0 (0%)	0 (0%)

All of the patients enrolled were classified as mild or moderate on the IGSS. A higher proportion of patients were classified as moderate in the Desonide gel group (57%) compared with either DesOwen lotion (53%) or Vehicle gel (50%).

EFFICACY RESULTS:

Primary Analysis: Dichotomized Investigator's Global Evaluation at Weeks 2 and 4. Subjects were considered a success if the global evaluation was a 0 (Clear) or 1 (Almost Clear).

Table 14 (ITT) From Sponsor's report

	Desonide Gel Success Rate	DesOwen Lotion Success Rate	Difference in Success Rates	97.5% Lower Confidence Limit	Non- Inferior
Week 4	59.9%	68.4%	-8.6%	-16.72%	No
Week 2	41.5%	47.4%	-5.8%	-14.31%	No

The results of the primary analysis failed to demonstrate non-inferiority of Desonide gel to DesOwen lotion. The observed lower confidence bound for the difference between Desonide gel and Desowen lotion exceeded the protocol pre-specified limit by 5% for the primary variable.

In the following analysis, subjects were considered a success if the Week 2 or Week 4 global evaluation was a 0 (Clear) or 1 (Almost Clear) for subjects with a baseline global severity of 3 (Moderate). Subjects with a baseline global severity of 2 (Mild) were considered a success if the Week 2 or Week 4 investigator's global was a 0 (Clear).

Table 15 Response at Week 4 (ITT) Study 403 (FDA statistician's analysis)

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

a: Protocol-specified primary analysis

b: 97.5% lower confidence interval bound for (Desonide gel-DesOwen Lotion) Margin=10%

c: p-value for Desonide gel vs. Vehicle gel

The FDA statistician's results for the primary efficacy endpoint agreed with that of the sponsor. The difference in response rate for either definition of treatment success failed to demonstrate non-inferiority. The treatment effect was 20% for Desonide gel - Vehicle gel and 27% for DesOwen lotion – Vehicle gel using the two-grade improvement criteria for treatment success.

Secondary Efficacy Endpoint:

A description of changes on the signs and symptoms evaluation is as follows. These tables are from the sponsor's study report (Source page 179-181; Tables 14.3.3.1). Although, the percentage change is not a meaningful analysis, these data demonstrate the general trend toward a larger decrease in all three signs, erythema, induration and oozing/crusting over time in both active arms compared with Vehicle gel.

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Table 16 Summary of Mean Erythema, Induration and Oozing/Crusting

Desonide Gel (N= 289)

	Baseline	Week 4
Erythema	4.6	1.8
Induration	4.4	1.9
Oozing/Crusting	1.3	0.4

DesOwen lotion (N=285)

	Baseline	Week 4
Erythema	4.7	1.7
Induration	4.4	1.7
Oozing/Crusting	1.3	0.4

Vehicle gel (N=92)

	Baseline	Week 4
Erythema	4.4	3.1
Induration	4.2	3.1
Oozing/Crusting	1.2	1.1

Pruritus:

The mean pruritus score in the three treatment groups is as follows.

Table 17 Mean pruritus scores over time (Adapted from sponsor's table 14.3.5)

	N	Baseline	Week 4
Desonide Gel	289	2.1	0.6
DesOwen lotion	288	2.0	0.6
Vehicle gel	92	1.9	1.4

The magnitude of the decreases in mean pruritus in both active arms were similar and both showed a greater change compared with vehicle.

SAFETY:

There were no deaths reported in this study.

One significant adverse event was reported during the study. An 8-year-old girl (14-743) randomized to the Desonide gel group experienced sore throat and a high fever and was diagnosed with strep pharyngitis. The subject was treated with antibiotics and antipyretics and resolved. The event was initially reported as a serious adverse event. However, the event was later reclassified as a non-serious adverse event, because it was noted that the patient was seen in the Emergency Department, but was never admitted to the hospital. The event was considered unlikely related to the study medication.

The percentages of subjects in each treatment group who experienced adverse events during the Study were: 19% Desonide gel, 0.05%, 19% Desowen lotion and 29% Vehicle gel.

There were 6 subjects who prematurely discontinued from the study due to an adverse event, 2 subjects in the Desonide gel group, 4 subjects in the DesOwen lotion group, and no subjects in the Vehicle gel group. More subjects reporting the adverse events of AD in the Vehicle gel group than in the groups assigned to Desonide gel and DesOwen lotion.

Telangiectasia (Desonide gel):

In the Desonide gel group, subject 13-60, a 1-year-old girl was enrolled in the study on March 23, 2004 and reported an adverse event on April 1, 2004 of telangiectasia on the upper arms, trunks, and legs. The subject withdrew from the study on April 9, 2004. The adverse event was considered probably related to study medication. The subject applied 28 applications of study medication while enrolled in the study. No concomitant medications were prescribed for this subject.

Reviewer's comment: This adverse event is notable in that the telangiectasia occurred with relatively short-term use and no other concomitant medications had been prescribed for the patient. It is possible that the patient's young age made her vulnerable to this adverse event.

Atopic dermatitis flare (Desonide gel):

Subject 28-427, a 1-year-old boy was enrolled into the study on August 24, 2004. On September 6, 2004, he was reported to have had an AD flare and was prescribed 1% hydrocortisone. The investigator considered the event unrelated to study medication and resolved on September 8, 2004. The subject discontinued from the study on September 14, 2004 after having received 31 applications of study medication.

Skin infection (DesOwen lotion):

In the DesOwen lotion group, subject 11-784, a 6-year-old girl was enrolled in the study on September 7, 2004. The subject reported an adverse event of skin infection on September 13, 2004 and was prescribed Bactroban cream and Clindamycin. The subject discontinued from the study on September 13, 2004 after having applied 13 applications of study medication. The adverse event was considered unrelated to study medication and was resolved on September 20, 2004.

Urticaria (DesOwen Lotion):

Subject 13-174, a 7-year-old girl enrolled in the study on April 14, 2004. On April 30, 2004 she experienced urticaria and was prescribed Diphedryl allergy. The subject withdrew from the study on May 4, 2004 after having received 33 applications of study medication. The adverse events considered probably related to study medication by the investigator and resolved on May 1, 2004.

Contact dermatitis (DesOwen Lotion):

Subject 23-438, a 0.5-year-old girl was enrolled in the study on July 1, 2004 and reported an adverse event of contact dermatitis on July 7, 2004. The subject withdrew from the study on July 9, 2004 after having received 17 applications of study medication. No concomitant medications were prescribed for this subject. The adverse event was considered unlikely related to study medication and was noted as "continuing" at the time the subject withdrew from the study.

Reviewer's comment: Although the investigator deemed the contact dermatitis to be unlikely related to study medication, an alternative etiology was not provided.

Contact dermatitis (DesOwen Lotion):

Subject 28-345, an 11.84-year-old boy was enrolled in the study on May 13, 2004 and reported an adverse event of contact dermatitis on May 20, 2004. Benadryl was prescribed for this subject for the indication of itching. The subject withdrew from the study on May 21, 2004 after having received 17 applications of study medication. The event was considered possibly related to study medication by the investigator and was resolved on May 25, 2004.

Reviewer's comment: Two patients assigned to DesOwen lotion experienced contact dermatitis. This is a difficult diagnosis to make, since the steroid would tend to mask the signs of dermatitis.

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10.1.2 7001-G3HP-01-05 (Study 105): A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Topically Applied Desonide Gel vs. Desonide Gel Vehicle for the Treatment of Pediatric Subjects with Mild to Moderate Atopic Dermatitis

Trial Design:

Study Sites: 15, U.S.

Number of patients: 201 (136 in active, 65 in vehicle)

Study Period: May 9, 2005 to September 13, 2005

Objectives: The objective of this study was to determine the safety and efficacy of Desonide gel compared to Vehicle gel in the treatment of mild to moderate AD in pediatric subjects ages three (3) months to 18 years.

Study Design: multi-center, randomized, double-blind, placebo-controlled comparison involving pediatric subjects with mild to moderate AD.

Diagnosis and Main Criteria for Inclusion:

Male or female subjects in generally good health of any race, 3 months to 18 years of age.

Subjects had a diagnosis of AD as defined by the United Kingdom refinement of the Hanifin and Rajka diagnostic criteria for AD.

Subjects were required to have AD that

- involved a minimum of 10% body surface area (BSA),
- a baseline IGSS of mild to moderate; and
- an erythema and induration score of at least mild.

Reviewer's comment: These criteria (bulleted) differed somewhat from that in Study 403.

Test product and reference product, batch number:

Desonide gel, batch number: 880

Desonide gel Vehicle, batch number: 881

Method of Application and Treatment Schedule:

The study drug should be applied in a thin film (approximately 1-2 mg/cm²) and gently rubbed into the skin over affected areas. The first application of study drug will be made under supervision of the investigator's designee. Areas selected for treatment at the Day 0 Visit were to be treated for the duration of the study unless signs of localized adverse events exist.

Primary and secondary efficacy endpoints were identical to Study 403.

How Measured:

Table 18 Erythema Severity

Score	Grade	Guideline
0	Absent	No erythema present (may be minor discoloration)
1	Minimal	Faint pink, barely apparent
2	Mild	Light pink, noticeable
3	Moderate	Pink-red, easily noticeable
4	Severe	Deep or bright red, may feel warm to the touch

Table 19 Induration/Papulation Severity:

Score	Grade	Guideline
0	Absent	No evidence of elevation
1	Minimal	Barely perceptible elevation
2	Mild	Perceptible but not extensive elevation
3	Moderate	Marked and somewhat extensive elevation
4	Severe	Marked and extensive elevation

Table 20 Lichenification:

Score	Grade	Guideline
0	Absent	No lichenification present
1	Minimal	Slightly accentuated superficial skin lines
2	Mild	Minor epidermal thickening in one or two areas
3	Moderate	Moderate epidermal thickening in few areas, moderately accentuated skin lines
4	Severe	Prominent epidermal thickening with deep skin lines, 4 or more areas involved

Table 21 Scaling

Score	Grade	Guideline
0	Absent	Absent, no evidence of scaling
1	Minimal	Occasional fine scale
2	Mild	Fine, flaky scale predominates
3	Moderate	Coarse scale predominates
4	Severe	Thick, coarse, crusted scale predominates

Table 22 Oozing and Crusting

Score	Grade	Guideline
0	Absent	No evidence of oozing or crusting
1	Minimal	Rare oozing/crusting
2	Mild	Occasional oozing/crusting
3	Moderate	Diffuse oozing/crusting
4	Severe	Marked oozing/crusting

Table 23 Pruritus

Score	Grade	Guideline
0	Absent	No pruritus
1	Mild	Occasional, slight itching/scratching
2	Moderate	Constant or intermittent itching/scratching which is not disturbing sleep
3	Severe	Bothersome itching/scratching which is disturbing sleep

Safety evaluation was also similar to Study 403.

Table 24 Safety Assessments:

Parameter	Screening	Visit 2 Day 0	Visit 3 Week 2	Visit 4 Week 4
Adverse Events			X	X
Local Adverse Events Evaluations		X	X	X

Direct evaluation by the evaluator was performed for dryness and scaling. Stinging and burning were assessed through interview of the subject.

1. Dryness

0	None	No dryness
1	Mild	Slight but definite roughness
2	Moderate	Moderate roughness
3	Severe	Marked roughness

2. Scaling

0	None	No scaling
1	Mild	Barely perceptible shedding, noticeable only on light scratching or rubbing
2	Moderate	Obvious but not profuse scaling
3	Severe	Heavy scale production

3. Stinging/Burning

0	None	No stinging/burning
1	Mild	Slight warm, tingling sensation; not really bothersome
2	Moderate	Definite warmth; tingling/stinging sensation that is somewhat bothersome
3	Severe	Hot, tingling/stinging sensation that has caused definite discomfort

- 4. Striae**
Striae will be recorded as either present or absent.
 - 5. Telangiectasia**
Telangiectasia will be recorded as either present or absent.
 - 6. Skin Atrophy**
Skin atrophy will be recorded as either present or absent.
 - 7. Secondary Infection**
Secondary infection will be recorded as either present or absent.
 - 8. Hypertrichosis**
Hypertrichosis will be recorded as either present or absent.
 - 9. Miliaria**
Miliaria will be recorded as either present or absent.
 - 10. Ecchymoses**
Ecchymoses will be recorded as either present or absent.
 - 11. Thin, Shiny Skin**
Thin, shiny skin will be recorded as either present or absent.
-

Open ended query was used to assess whether any adverse events were experienced since the last visit.

Method of Treatment Assignment:

Subjects were to be randomized to Desonide gel, or Vehicle gel on a 2:1 basis. Drug supplies were to be numbered and dispensed sequentially to the subjects entering the study within an investigational site. The sequentially numbered drug supplies were to be randomly selected from the Desonide gel, and Vehicle gel supplies in blocks having a ratio of 2:1.

Complete blocks of drug supplies were to be distributed to the investigational sites to maintain the randomization ratio of 2:1 within an investigational site.

Statistical Methods:

Statistical significance was based on two-sided hypothesis testing resulting in p-values of 0.05 or less. No adjustments of p-values for multiple comparisons were made. Primary and secondary tests of superiority of Desonide gel over Vehicle gel were conducted primarily on the intent-to-treat population and the last observation carried forward method was used to extrapolate efficacy data which were missing.

Primary Efficacy Analyses

The primary variable dichotomized IGSS at Week 4 was analyzed with a Cochran-Mantel-Haenszel test, stratified by site.

Secondary Efficacy Analyses

The percent change from baseline in signs of AD including erythema, induration/papulation, lichenification, scaling, and oozing/crusting scores were analyzed with an analysis of variance with factors of treatment and site.

Other Efficacy Analyses

The following were also summarized using descriptive statistics by treatment group and visit:

- IGSS;
- The dichotomized IGSS at week 2;
- Signs of Atopic Dermatitis including erythema, induration/papulation, lichenification, scaling, and oozing/crusting;
- Percent change from baseline in signs of AD scores;
- Pruritus; and
- Percentage of BSA affected.

Sensitivity Analyses: Sensitivity analyses to assess the potential effects of missing data included both a **non-responder imputation** and a **responder imputation** for missing data.

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ON ORIGINAL**

Patient Disposition:

Table 25 Summary of Subject Enrollment, Evaluability, and Completion/Discontinuation

	Desonide	Vehicle
Subjects Enrolled (all ITT)	136	65
Study Completion/Discontinuation Reason		
Completed the Study	132	55
Lack of Efficacy/Worsening of Condition	0	3
Adverse Event	1	1
Subject Request	1	5
Protocol Violation	0	0
Lost to Follow-Up	2	1
Pregnancy	0	0

A higher number of patients discontinued study treatment in the vehicle arm compared with desonide ointment. Most of the patients withdrew for “patient request” followed by lack of “efficacy, worsening.” Overall, about 10/65 (15%) vehicle patients discontinued early compared to 4/136 (3%) patients assigned to active treatment.

Study Conduct:

Table 26 Protocol Deviations

	Desonide Gel	Vehicle Gel	Total
Number of Subjects	136	65	201
Number of Subjects with Deviations	14	13	27
Deviation*			
Missed Week 4 Visit	4	5	9
Week 4 Visit Outside the Visit Window of ±3 Days	5	5	10
Not Compliant with Dosing Regimen			8
Prohibited Concomitant Medication	0	0	0
Total	14	13	27

* Subjects may have had more than one exclusionary violation.

Reviewer’s comment: These protocol deviations are unlikely to have influenced the overall trial outcome.

EFFICACY RESULTS:

Table 27 Analysis of the Primary Endpoint: Dichotomized IGSS at Week 4 (ITT) (from sponsor's report)

Dichotomized Global Severity	Desonide (N=136)	Desonide Vehicle (N=65)	
Success	38 (27.9%)	4 (6.2%)	P-Value <0.001
Failure	98 (72.1%)	61 (93.8%)	

LOCF was implemented prior to dichotomization

Table 28 Primary analysis of IGSS (source FDA statistical reviewer)

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

a: Protocol-specified primary analysis

b: p-value for Desonide gel vs. vehicle gel

**APPEARS THIS WAY
ON ORIGINAL**

Table 29 Analysis of the Secondary Endpoints (ITT)

	Desonide (N=136)		Vehicle (N=65)		P-Value
	N	MEAN	N	MEAN	
Erythema	136	48.4	65	14.6	<0.001
Induration/Papulation	136	47.4	65	17.5	<0.001
Lichenification	118	43.2	53	9.9	<0.001
Scaling	121	55.3	60	19.4	<0.001
Oozing/Crusting	62	69.2	38	31.6	0.006

Table 30 Sensitivity Analyses (ITT) (Source: Sponsor's study report)

Dichotomized IGSS at Week 4			
Missing Evaluation = "Failure"			
	Desonide Gel (N=136)	Desonide Vehicle (N=65)	P-Value
Dichotomized Global Severity			
Success	38 (27.9%)	4 (6.2%)	<0.001
Failure	98 (72.1%)	61 (93.8%)	
Missing Evaluation = "Success"			
	Desonide Gel (N=136)	Desonide Vehicle (N=65)	P-Value
Dichotomized Global Severity			
Success	42 (30.9%)	12 (18.5%)	0.047
Failure	94 (69.1%)	53 (81.5%)	

Each of the sensitivity analyses assessing the potential impact of missing data supports the primary analysis.

Subgroup Analyses:

Table 31 Subgroup Analyses of Dichotomized IGSS at Week 4 by Gender, Age, and Ethnicity

	Desonide (N=136)		Desonide Vehicle (N=65)	
	Male	Female	Male	Female
Gender				
Success	23 (34%)	15 (22%)	3 (9%)	1 (3%)
Failure	44 (66%)	54 (78%)	29 (91%)	32 (97%)
Age				
	<u>3 mths to <3 yrs</u>	<u>3 yrs to <6 yrs</u>	<u>3 mths to <3 yrs</u>	<u>3 yrs to <6 yrs</u>
Success	14 (37%)	4 (14%)	1 (6%)	1 (8%)
Failure	24 (63%)	24 (86%)	17 (94%)	11 (92%)
	<u>6 yrs to <12 yrs</u>	<u>12 yrs to 18 yrs</u>	<u>6 yrs to <12 yrs</u>	<u>12 yrs to 18 yrs</u>
Success	9 (21%)	11 (39%)	0 (0%)	2 (17%)
Failure	33 (79%)	17 (61%)	23 (100%)	10 (83%)
Ethnicity				
	<u>Hispanic/Latino</u>	<u>Not Hispanic/Latino</u>	<u>Hispanic/Latino</u>	<u>Not Hispanic/Latino</u>
Success	2 (14%)	36 (30%)	0 (0%)	4 (7%)
Failure	12 (86%)	86 (70%)	7 (100%)	54 (93%)

Gender

In the Desonide Gel group, 34% of male subjects (23/67 subjects) and 22% of female subjects (15/69 subjects) were considered a treatment success compared 9% of male subjects (3/32 subjects) and 3% of female subjects (1/33 subjects) in the Desonide Gel Vehicle group.

Age

In the Desonide Gel group, 37% of subjects age 3 months to less than 3 years (14/38 subjects), 14% of subjects age 3 years to less than 6 years (4/28 subjects), 21% of subjects age 6 years to less than 12 years (9/42 subjects), and 39% of subjects age 12 to 18 years (11/28 subjects) were considered a treatment success. In the Desonide Gel Vehicle group, 6% of subjects age 3 months to less than 3 years (1/18 subjects), 8% of subjects age 3 years to less than 6 years (1/12 subjects), 0% of subjects age 6 years to less than 12 years (0/23 subjects), and 17% of subjects age 12 to 18 years (2/12 subjects) were considered a treatment success.

Ethnicity

In the Desonide Gel group, 14% of Hispanic/Latino subjects (2/14 subjects) and 30% of non Hispanic/Latino subjects (36/122 subjects) were considered a treatment success compared 0% of Hispanic/Latino subjects (0/7 subjects) and 7% of non Hispanic/Latino subjects (4/58 subjects) in the Desonide Gel Vehicle group.

Table 32 Subgroup Analyses of Dichotomized IGSS at Week 4 by Race and Baseline Disease Severity

Race	Desonide (N=136)			Desonide Vehicle (N=65)		
	White	Black/African American	American Indian/ Alaskan Native	White	Black/African American	American Indian/ Alaskan Native
Success	15 (26%)	16 (28%)	0 (0%)	2 (7%)	2 (8%)	0 (0%)
Failure	43 (74%)	41 (72%)	0 (0%)	26 (93%)	23 (92%)	1 (100%)
	Asian	Native Hawaiian/ Other Pacific Islander	Other	Asian	Native Hawaiian/ Other Pacific Islander	Other
Success	4 (50%)	0 (0%)	4 (29%)	0 (0%)	0 (0%)	0 (0%)
Failure	4 (50%)	1 (100%)	10 (71%)	6 (100%)	0 (0%)	5 (100%)
Baseline Investigator's Global Severity	2 (Mild)	3 (Moderate)		2 (Mild)	3 (Moderate)	
Success	16 (23%)	22 (34%)		3 (11%)	1 (3%)	
Failure	55 (77%)	43 (66%)		24 (89%)	37 (97%)	

Race

In the Desonide gel group, 26% of White subjects (15/58 subjects), 28% of Black/African American subjects (16/57 subjects), 50% of Asian subjects (4/8 subjects), 0% of Native Hawaiian/Other Pacific Islander subjects (0/1 subjects), and 29% of subjects of “other” races (4/14 subjects) were considered a treatment success. In the Desonide Gel Vehicle group, 7% of White subjects (2/28 subjects), 8% of Black/African American subjects (2/25 subjects), 0% of American Indian/Alaskan Native subjects (0/1 subjects), 0% of Asian subjects (0/6 subjects), and no subjects of “other” races (0/5 subjects) were considered a treatment success.

Baseline Investigator's Global Severity

In the Desonide gel group, 23% of subjects with mild baseline severity (16/71 subjects) and 34% of subjects with moderate baseline severity (22/65 subjects) were considered a treatment success compared 11% of subjects with mild baseline severity (3/27 subjects) and 3% of subjects with moderate baseline severity (1/38 subjects) in the Desonide Gel Vehicle group. Results of the subgroup analyses for the per-protocol can be found in Table 14.4.2 and closely resemble the results of the intent-to-treat population.

Reviewer's comment: In conclusion, subgroup analyses showed treatment effect in subgroups defined by age, gender, race, ethnicity and baseline severity.

Safety:

There were no deaths in this study and no serious adverse events were reported.

Two percent and 33% of adverse events reported in the Desonide gel and Vehicle gel groups, respectively were considered certainly, probably, or possibly related to study medication.

There were 5 subjects that prematurely discontinued from the study due to an adverse event. One subject in the Desonide gel group discontinued prematurely and 4 subjects in the Vehicle gel group discontinued prematurely. Subject 08-017 was assigned to the Desonide gel group. Subjects 12-085, 10-046, 04-080, and 03-130 were assigned to the Vehicle gel group.

Desonide Gel group:

- Subject 08-017, a 4.75 year old male was enrolled on June 01, 2005 and assigned to active study drug. A rash on the face and arms was reported to have occurred on June 07, 2005 (resolution date June 19, 2005) and fever on June 11, 2005 (resolution date June 17). He was prescribed Ibuprofen as needed for fever. The subject withdrew from the study on June 20, 2005 after having received 12 applications of study medication. Both events were considered to be unlikely related to study medication by the investigator.

Reviewer's comment: These symptoms (fever and rash) could be explained by a viral infection. This reviewer agrees with the investigator's assessment that the adverse events are unlikely related to study medication.

Vehicle gel group:

- Subject 12-085, a 7.33 year old male was enrolled in the study on May 31, 2005. On June 03, 2005, he experienced worsening from baseline in his condition and started Cutivate. The subject withdrew from the study on June 14, 2005. The event was considered related to study medication by the investigator and was considered resolved on June 14, 2005.
- Subject 10-046, an 11.34 year old male was enrolled in the study on May 25, 2005. On June 13, 2005, he experienced of worsening from baseline in his condition and was prescribed Keflex as well as Topicort 0.05% cream. The subject withdrew from the study on June 14, 2005. The event was considered unlikely related to study medication by the investigator and was considered resolved on July 12, 2005.
- Subject 04-080, a 5.92 year old male was enrolled in the study on June 21, 2005. On June 24, 2005, he experienced burning and stinging and was prescribed Cutivate. The subject withdrew from the study on July 05, 2005. The event was considered related to study medication by the investigator and was considered resolved on June 30, 2005.
- Subject 03-130, a 1.66 year old female was enrolled in the study on June 29, 2005. On July 05, 2005, she was reported to have flaring of AD and was prescribed Bactroban ointment. She withdrew from the study on July 20, 2005. The event was considered to be probably related to study medication by the investigator and the outcome was "resolved".

Reviewer's comment: These reports raise the question of whether the vehicle used is irritating and exacerbating the disease vs. whether these adverse events would have occurred as part of the natural course of the disease. It is very difficult to make any conclusions in this regard.

Table 33 Summary of Adverse Events (ITT) (From Sponsor's table 14.6.3.1)

<u>System Organ Class^a</u>	<u>Desonide</u>	<u>Desonide Vehicle</u>
Ear and labyrinth disorders	1 (1%)	0 (0%)
Ear pain	1 (1%)	0 (0%)
Eye disorders	5 (4%)	1 (2%)
Conjunctivitis	4 (3%)	1 (2%)
Eye swelling	1 (1%)	0 (0%)
Gastrointestinal disorders	1 (1%)	1 (2%)
Diarrhoea	1 (1%)	0 (0%)
Toothache	0 (0%)	1 (2%)
General disorders and administration site conditions	7 (5%)	8 (12%)
Application site burning	0 (0%)	4 (6%)
Application site pruritus	0 (0%)	1 (2%)
Injection site pain	1 (1%)	0 (0%)
Pyrexia	6 (4%)	3 (5%)
Infections and infestations	16 (12%)	10 (15%)
Application site infection	1 (1%)	0 (0%)
Ear infection	3 (2%)	1 (2%)
Gastroenteritis viral	1 (1%)	2 (3%)
Impetigo	0 (0%)	1 (2%)
Influenza	0 (0%)	1 (2%)
Nasopharyngitis	5 (4%)	3 (5%)
Pneumonia	0 (0%)	1 (2%)
Pneumonia viral	1 (1%)	0 (0%)
Staphylococcal bacteraemia	1 (1%)	1 (2%)
Tinea infection	1 (1%)	0 (0%)
Upper respiratory tract infection	2 (1%)	0 (0%)
Urinary tract infection	1 (1%)	0 (0%)

<u>System Organ Class^a</u>	<u>Desonide</u>	<u>Desonide Vehicle</u>
Injury, poisoning and procedural complications	5 (4%)	0 (0%)
Arthropod sting	1 (1%)	0 (0%)
Excoriation	1 (1%)	0 (0%)
Fall	1 (1%)	0 (0%)
Foot fracture	1 (1%)	0 (0%)
Joint sprain	1 (1%)	0 (0%)
Musculoskeletal and connective tissue disorders	0 (0%)	1 (2%)
Muscle cramp	0 (0%)	1 (2%)
Nervous system disorders	1 (1%)	1 (2%)
Headache	1 (1%)	1 (2%)
Respiratory, thoracic and mediastinal disorders	2 (1%)	0 (0%)
Cough	1 (1%)	0 (0%)
Nasal congestion	1 (1%)	0 (0%)
Skin and subcutaneous tissue disorders	2 (1%)	4 (6%)
Dermatitis atopic	0 (0%)	3 (5%)
Heat rash	1 (1%)	0 (0%)
Rash	1 (1%)	0 (0%)
Skin atrophy	0 (0%)	1 (2%)
Vascular disorders	1 (1%)	0 (0%)
Vein pain	1 (1%)	0 (0%)

All of these were either mild or moderate, with the exception of one case of severe diarrhea and two cases of severe AD (both in vehicle arm). As would be expected, a higher incidence rate of AD-related adverse events were observed in the Vehicle gel group (5%) compared with Desonide gel (0%). A numerically higher incidence rate of conjunctivitis was observed in the Desonide gel group (3%) compared with Vehicle gel (2%).

Table 34 Adverse Events Occurring at a Frequency of $\geq 5\%$

	<u>Desonide</u>	<u>Desonide Vehicle</u>
Number of Subjects	136	65
Number of Subjects Reporting One or More Events	29 (21%)	19 (29%)
System Organ Class^a		
General disorders and administration site conditions	7 (5%)	8 (12%)
Application site burning	0 (0%)	4 (6%)
Pyrexia	6 (4%)	3 (5%)
Infections and infestations	16 (12%)	10 (15%)
Nasopharyngitis	5 (4%)	3 (5%)
Skin and subcutaneous tissue disorders	2 (1%)	4 (6%)
Dermatitis atopic	0 (0%)	3 (5%)

Table 35 Adverse Events At Least Possibly Related Occurring at a Frequency of $\geq 1\%$

	<u>Desonide</u>	<u>Desonide Vehicle</u>	<u>P-Value</u>
Number of Subjects	136	65	
Number of Subjects Reporting One or More Events	1 (1%)	7 (11%)	0.002
System Organ Class^a			
General disorders and administration site conditions	0 (0%)	5 (8%)	0.003
Application site burning	0 (0%)	4 (6%)	0.010
Application site pruritus	0 (0%)	1 (2%)	0.323
Infections and infestations	0 (0%)	1 (2%)	0.323
Impetigo	0 (0%)	1 (2%)	0.323
Skin and subcutaneous tissue disorders	1 (1%)	3 (5%)	0.100
Dermatitis atopic	0 (0%)	2 (3%)	0.103
Heat rash	1 (1%)	0 (0%)	1.000
Skin atrophy	0 (0%)	1 (2%)	0.323

Overall, vehicle alone appears to be associated with local symptoms of burning and pruritus. As stated previously, two patients had adverse events related to worsening of AD in the vehicle arm. Adverse events related to AD were not observed in active arm.

Results of the active assessments for atrophy, telangiectasia and striae are described below. The source for these data is the sponsor's Figure 14.6.2.

Table 36 Atrophy

	Desonide Gel			Vehicle Gel		
	Baseline	Week 2	Week 4	Baseline	Week 2	Week 4
N	136	129	132	65	63	57
Absent	131 (96%)	124 (96%)	128 (97%)	63 (97%)	61 (97%)	56 (98%)
Present	5 (4%)	5 (4%)	4 (3%)	2 (3%)	2 (3%)	1 (2%)

Table 37 Telangiectasia

	Desonide			Vehicle		
	Baseline	Week 2	Week 4	Baseline	Week 2	Week 4
N	136	129	132	65	63	57
Absent	135 (99%)	128 (99%)	132 (100%)	65 (100%)	63 (100%)	57 (100%)
Present	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 38 Striae

	Desonide			Vehicle		
	Baseline	Week 2	Week 4	Baseline	Week 2	Week 4
N	136	129	132	65	63	57
Absent	130 (96%)	122 (95%)	126 (95%)	61 (94%)	59 (94%)	53 (93%)
Present	6 (4%)	7 (5%)	6 (5%)	4 (6%)	4 (6%)	4 (7%)

APPEARS THIS WAY ON ORIGINAL

Table 39 Summary of Adverse Events Including Severity and Relationship (source Table 14.6.3.1)

	Desonide	Vehicle
Number of Subjects	136	65
Number of Events	41	27
Number of Subjects Reporting One or More Events	29 (21%)	19 (29%)
Serious		
No	41 (100%)	27 (100%)
Yes	0 (0%)	0 (0%)
Severity		
Mild	22 (54%)	17 (63%)
Moderate	18 (44%)	8 (30%)
Severe	1 (2%)	2 (7%)
Relationship to Study Medication		
Definitely Unrelated	36 (88%)	16 (59%)
Unlikely	4 (10%)	2 (7%)
Possible	1 (2%)	2 (7%)
Probable	0 (0%)	3 (11%)
Related	0 (0%)	4 (15%)

Two patients in the vehicle arm had worsening of AD. One of these was (003-130), a one year old girl with 70% BSA involvement at baseline.

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10.1.3 Dermal Safety Studies

Study 7001-G3HP-03-03: A Multi-Center, Open-Label Evaluation of the Adrenal Suppression Potential of Topically Applied Desonide Gel in Pediatric Subjects with Moderate to Severe Atopic Dermatitis

Study Period: March 9, 2004 – September 16, 2004

Phase of Development: 2

Objectives: To determine the safety and systemic tolerance of Desonide Gel in the treatment of pediatric subjects with moderate to severe AD

Number of subjects planned: ~20 subjects were to be enrolled into each cohort-3 months to 2 years 11 months and 3 years to 5 years 11 months. Forty subjects were enrolled, 20 in each group.

Forty subjects were enrolled (3 months to 2 years 11 months: 20 subjects, 3 years to 5 years 11 months: 20 subjects). All 40 subjects enrolled in the study were included in the intent-to-treat population.

Diagnosis and Main Criteria for Inclusion:

Male or female subjects of any race between the ages of 3 months and 5 years 11 months weighing a minimum of 8 pounds with visible flexural dermatitis. Subjects had a diagnosis of AD as defined by the UK refinement of the Hanifin and Rajka diagnostic criteria for AD. The subject must have had an itchy skin condition in the last 12 months, plus 3 or more of the following:

- a) Onset of AD below two (2) years of age.
- b) History of flexural involvement.
- c) History of generally dry skin.
- d) Personal history of other atopic disease (in children under four (4) years, history of atopic disease in a first-degree relative could be included).
- e) Visible flexural dermatitis.

Subjects were required to have AD that involved a minimum of 35% body surface area (BSA) and a baseline Physician's Global Severity Score and baseline erythema score rated as moderate or severe.

Test product, dose and mode of administration, batch number:

Desonide Gel, topical application to the affected areas twice daily for 4 weeks, batch number: 878.

Study Assessments: Included assessment of AD by **Physician's Global Severity Score (0-5, clear to very severe)**; percentage BSA affected; skin irritation evaluation at baseline, week 2 and week 4.

AM cortisol adrenal function tests (pre and post cosyntropin administration) were done at baseline and at week 4. Any subject with abnormal test results was to return for follow-up. If the Visit 3 laboratory results show a Subject has an abnormal adrenal function, this was to be reported as an AE and the adrenal function test repeated monthly until the cortisol levels return to normal.

Reviewer's comment: Of note, no blood pressure measurements were taken.

All endpoints were evaluated using descriptive statistics. The intent-to-treat population consisted of all subjects who used at least one dose of study medication. The modified intent-to-treat population was the primary population for evaluating end of treatment HPA suppression and it consisted of subjects who completed 4 weeks of the study and had complete cosyntropin stimulation test data at baseline and at Week 4.

Study Results:

The study enrolled 40 pediatric subjects ages 6 months to 5.6 years. Of these 37 had complete cosyntropin stimulation test data at baseline and week 4.

One 6-month old subject (3 %) showed abnormal adrenal response following 4 weeks of twice daily application of study medication. The remaining evaluable subjects had no laboratory findings of adrenal suppression after 4 weeks of twice daily application of study medication.

Local Adverse Events:

No subjects reported striae, skin atrophy, secondary infection, ecchymoses, sensitization, or thin, shiny skin, at any evaluation. Localized burning/stinging was present in 2/38 subjects (5%) at only the Week 2 visit.

Adverse Events:

Ten of 40 subjects (25%) enrolled reported a total of 13 adverse events during the study. Two of the events were serious. The two serious AEs were mycoplasma pneumonia and partial seizures with secondary generalization and both occurred in the same subject.

Adrenal suppression is defined as a post-stimulation cortisol peak value \leq 18.0 $\mu\text{g/dL}$ at Week 4.

Subject 30 of clinical site 1 had a history of seizure disorder.

Protocol violation: Subject 50 of site 3 was withdrawn for a low cortisol level on visit 1.

The patient listings of cortisol levels are shown in the following table.

Table 40 Adrenal Function Test Results - Cortisol Levels (Source: Listing 16.2.10.1.2)

Site	Subject	Age/Sex	Visit	Pre Cortisol Level	Post Cortisol Level	Diff Pre to Post	Fold Increase	Week 4 Pre Diff	Week 4 Post Diff	Adrenal suppression
1	17	4.7/F	1	10.0	29.0	19.0	1.9	-2.3	-3.0	Normal
			3	7.7	26.0	18.3	2.3			
	18	5.6/M	1	9.2	30.0	20.8	2.2	2.8	-7.0	Normal
			3	12.0	23.0	11.0	0.9			
	19	5.5/M	1	12.0	29.0	17.0	1.4	0.0	-1.0	Normal
			3	12.0	28.0	16.0	1.3			
	20	5.2/F	1	6.9	22.0	15.1	2.1	2.7	2.0	Normal
			3	9.6	24.0	14.4	1.5			
	29	4.7/F	1	13.0	29.0	16.0	1.2	0.0	-1.0	Normal
			3	13.0	28.0	15.0	1.1			
	30	3.2/F	1	6.5	28.0	21.5	3.3	2.2	2.0	Normal
			3	8.7	30.0	21.3	2.4			
31	1.5/M	1	14.0	28.0	14.0	1.0	-2.0	-2.0	Normal	
		3	12.0	26.0	14.0	1.1				
32	2.2/M	1	7.9	22.0	14.1	1.7	-1.4	-2.0	Normal	
		3	6.5	20.0	13.5	2.0				
3	1	3.8/M	1	12.0	22.0	10.0	0.8	-2.0	6.0	Normal
			3	10.0	28.0	18.0	1.8			
	2	3.8/M	1	14.0	22.0	8.0	0.5	2.0	2.0	Normal
			3	16.0	24.0	8.0	0.5			
	3	4.4/F	1	8.2	28.0	19.8	2.4	3.8	4.0	Normal
			3	12.0	32.0	20.0	1.6			
	4	1.9/F	1	41.0	45.0	4.0	0.0	-25.0	-14.0	Normal
			3	16.0	31.0	15.0	0.9			
	49	2.7/F	1	19.0	26.0	7.0	0.3	-4.0	-3.0	Normal
			3	15.0	23.0	8.0	0.5			
50	2.0/M	1	3.9	20.0	16.1	4.1			Not evaluable (abnormal baseline cortisol levels)	
		3								
4	13	3.1/F	1	17.0	22.0	5.0	0.2	-8.0	8.0	Normal
			3	9.0	30.0	21.0	2.3			

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	14	0.5/F	1 3	3.3 5.3	25.0 8.1	21.7 2.8	6.5 0.5	2.0	-16.9	Abnormal
	15	1.3/M	1 3	11.0	ND					Not evaluable (missing baseline post-stimulation cortisol levels)
	16	2.9/F	1 3	7.9 9.2	27.0 29.0	19.1 19.8	2.4 2.1	1.3	2.0	Normal
	53	0.8/F	1 3	4.6	19.0	14.4	3.1			Not evaluable (abnormal baseline cortisol levels)
	54	2.0/M	1 3	9.0 12.0	21.0 19.0	12.0 7.0	1.3 0.5	3.0	-2.0	Normal
5	9	4.9/F	1 3	10.0 9.5	21.0 22.0	11.0 12.5	1.1 1.3	-0.5	1.0	Normal
	10	3.8/F	1 3	5.1 6.4	22.0 22.0	16.9 15.6	3.3 2.4	1.3	0.0	Normal
	11	3.4/M	1 3	7.0 6.4	20.0 19.0	13.0 12.6	1.8 1.9	-0.6	-1.0	Normal
	12	4.1/F	1 3	11.0 7.5	21.0 18.1	10.0 10.6	0.9 1.4	-3.5	-2.9	Normal
	21	4.7/F	1 3	7.2 6.1	23.0 24.0	15.8 17.9	2.1 2.9	-1.1	1	Normal
	22	3.0/F	1 3	9.6 8.6	22.0 22.0	12.4 13.4	1.2 1.5	-1	0	Normal
	23	3.4/M	1 3	9.0 5.4	28.0 23.0	19.0 17.6	2.1 3.2	-3.6	-5	Normal
	24	3.3/F	1 3	14.0 11.0	35.0 26.0	21.0 15.0	1.5 1.3	-3	-9	Normal
	25	5.0/F	1 3	8.2 8.9	24.0 26.0	15.8 17.1	1.9 1.9	0.7	2	Normal
	26	2.9/M	1 3	7.1 9.2	21.0 23.0	13.9 13.8	1.9 1.5	2.1	2	Normal
	27	2.7/F	1 3	13.0 13.0	20.0 23.0	7.0 10.0	0.5 0.7	0	3	Normal
	28	3.8/F	1 3	11.0 18.0	24.0 30.0	13.0 12.0	1.1 0.6	7	6	Normal
	37	2.2/M	1 3	9.7 18.0	22.0 26.0	12.3 8.0	1.2 0.4	8.3	4	Normal
	38	2.6/M	1 3	12.0 9.8	26.0 24.0	14.0 14.2	1.1 1.4	-2.2	-2	Normal
	39	1.3/F	1 3	19.0 9.7	28.0 28.0	9.0 18.3	0.4 1.8	-9.3	0	Normal
	40	2.9/F	1 3	10.0 8.5	20.0 25.0	10.0 16.5	1.0 1.9	-1.5	5	Normal

8	41	2.6/M	1	9.0	19.0	10.0	1.1	1	1	Normal
			3	10.0	20.0	10.0	1.0			
	42	2.4/M	1	19.0	33.0	14.0	0.7	3	-7	Normal
			3	22.0	26.0	4.0	0.1			
	43	1.4/M	1	12.0	27.0	15.0	1.2	0	-6	Normal
			3	12.0	21.0	9.0	0.7			
	44	1.5/F	1	15.0	36.0	21.0	1.4	8	-6	Normal
			3	23.0	30.0	7.0	0.3			

Narratives of selected patients with abnormal cortisol values follow:

Subject 4-14, a 6-month girl, had a pre-stimulation cortisol value of 3 mcg/dL at baseline. The subject was allowed to continue in the study based on normal post-stimulation results of 25 mcg/dL. At Week 4, the subject had a pre-stimulation value in the normal range per the CST package insert (5 mcg/dL) and a post-stimulation value of 8 mcg/dL. As stated earlier, adrenal suppression was defined as a post-stimulation cortisol peak value \leq 18.0 μ g/dL at Week 4. Therefore, this subject met this criterion for adrenal suppression.

Reviewer's comment: The sponsor removed this subject from the MITT population because of delayed collection of the poststimulation blood sample. However, the FDA has included this subject as an evaluable subject since she had laboratory data at baseline as well after 4 weeks of Desonide gel use. The case report form has been carefully reviewed by the Agency and supports inclusion of this subject. This subject did not have repeat Cosyntropin stimulation testing to evaluate reversibility of suppression, and the abnormal result was not reported as an AE; both are protocol violations.

Subject 3-4, a 4 year old girl, displayed considerable signs of anxiety over the blood draws and lost consciousness after the baseline CST was completed. The pre-stimulation plasma cortisol value was 40 mcg/dL and the post-stimulation value was 45 mcg/dL. The study endocrinologist deemed the elevated prestimulation value was likely due to the emotional state of the child. At Week 4, the pre and post-stimulation cortisol levels were 16 and 31 mcg/dL, respectively. This subject was included in the MITT population.

Subjects 3-50 and 4-53 were administered the baseline CST. However, these subjects were **withdrawn from the study at sponsor's request** for safety due to the $<$ 5 mcg/dL prestimulation level and were not included in the MITT population.

Conclusions:

This study was done in a limited sample of children with moderate to severe AD who were administered topical Desonide gel twice daily for four weeks. Some of the children were not evaluable due to abnormal cortisol levels at baseline or delays and/or difficulty with drawing blood or administering the cosyntropin. One of the subjects included in the evaluable population (3%) had abnormal cosyntropin stimulation tests.

Study 103:

Title: A Single Center, Evaluator-Blind Evaluation of the Cumulative Irritation and Contact Sensitization Potential of Desonide Gel, DesOwen® Lotion 0.05%, Desonide Gel Vehicle, and Control Following Repeated Topical Application to Healthy Subjects

Trial Design:

This was a single-center, investigator blind, phase I study.

There were 3 phases of this study: induction/irritation, rest and challenge.

Induction/irritation: Desonide gel, DesOwen lotion, Vehicle gel, and 0.3% sodium lauryl sulfate were to be applied under separate occlusive patches on the back of subjects 3 times per week for 3 weeks. Each application was to be observed 48 hours (72 hours on weekends) later for signs of irritation or inflammation.

Rest Period: After the induction/irritation phase, there was to be a rest period of approximately 1-2 weeks (7-18 days) during which no patches were to be applied.

Challenge Phase: After the rest period, 3 patches (Desonide Gel, Desonide Gel Vehicle and DesOwen lotion) was applied to previously untreated sites on the back for 48 hours. Sites were evaluated at the time of patch removal (48 hours post patching) and 72 hours post-patching. The rater evaluated the skin signs using the following scale:

- 0 = No sign of irritation
- 0.5 = Barely perceptible erythema
- 1 = Slight erythema
- 2 = Noticeable erythema with slight infiltration
- 3 = Erythema with marked edema
- 4 = Erythema with edema and blistering

Any subject showing a potential for delayed contact sensitization was to be re-challenged 14 to 18 days later to confirm the reaction. Other symptoms of skin reactions (i.e. pruritus, stinging, burning) to the test products was noted as an adverse event.

Eligibility:

Men and women 18-70 years of age were eligible for the study.

Study Results:

Two hundred thirty (230) subjects were enrolled and treated with test articles. Seventeen (17) subjects terminated the study early. Of the 17 who discontinued early, five discontinued due to noncompliance by missing two or more of the scheduled visits. Five (5) subjects withdrew consent. One (1) subject discontinued due to prohibited concurrent medication. Six (6) subjects discontinued due to adverse events, four of which were probably related to the test articles, one that was possibly related and one that was unrelated to the test articles. One subject (# 138) was patched once but never evaluated and was not included in the cumulative irritation.

There were 10 instances of burning and seven instances of stinging at the sodium lauryl sulfate site. The DesOwen lotion site had 19 cases of burning and 5 cases of stinging. Burning occurred at the Vehicle gel site four times but stinging did not occur at this site. There was 1 instance of burning and 2 instances of stinging at the Desonide gel site.

There was one serious adverse event (gallstones, Subject # 009) during the study that was determined to be not related to the study drug. Two subjects (#105, 213) had positive pregnancy tests at the final visit. Subject 105's pregnancy was confirmed with a second test by the site and by the subject's primary care physician. The site will follow up with this subject until the conclusion of her pregnancy.

Summary of Cumulative Irritation

The cumulative irritation score for each test article was obtained by summing subjects' scores from all irritation/induction phase evaluation days. The test article cumulative irritation scores noted were as follows:

Table 41 Irritancy Scores

Test Article	Cumulative Skin Evaluation Score vs. Theoretical Maximum	Classification
Vehicle Gel	454/7924	No significant irritation
Desonide Gel	602/7928	No significant irritation
DesOwen Lotion	4424/7928	Moderately irritating
0.3% Sodium Lauryl Sulfate	3061/7928	Slightly irritating

The theoretical maximum was less for Vehicle gel than the other test articles as there was one less evaluation for subject #031 due to a patching error on the last induction/irritation visit for Vehicle gel.

On April 16, 2004, a memo was written to establish an analysis plan that would support and give greater detail than Section 19 of the amended protocol. This was done prior to data base lock and breaking of the blind.

For data analysis, the initial Grade 4 reaction score was carried forward until Study Visit 11 (end of irritation/induction) or until the subject discontinued, if prior to Visit 11.

A total (cumulative) irritation score for each product was calculated by summing subjects' scores from all irritation/induction evaluation days. The cumulative irritation score was dependent upon the actual number of enrolled subjects and the actual number of completed visits, with a maximum possible cumulative score of 8280 (230 subjects x 9 evaluations x 4 [maximum daily irritation score]). The test articles were classified as shown below and with an example assuming 230 subjects completing all induction/irritation phase visits.

Table 42 Irritancy Classification

CLASSIFICATION	ALGORITHM FOR RANGE CALCULATION	CUMULATIVE IRRITATION SCORE FOR 230 SUBJECTS
No significant irritation	0 to 0.5*X	0-1035
Slightly irritating	(0.5*X)+1 to (1.5*X)	1036-3105
Moderately irritating	(1.5*X)+1 to 3*X	3106-6210
Highly irritating	(3*X)+1 to 4*X	6211-8280

X = total number of irritation/induction visits completed by all subjects

Summary of Study Results:

Sodium lauryl sulfate (0.3%), a known irritant at this concentration, was included in the study as a positive control for the irritation/induction phase of the study. The cumulative irritation score for this product indicates that the study may not have been very sensitive in detecting irritation since the results of the positive control was rated as only slightly irritating and less so than DesOwen lotion. Desonide Gel 0.05% and Desonide Gel Vehicle were both shown to be not significantly irritating while DesOwen lotion was found to be a moderate irritant.

Of the 212 subjects who were evaluable for sensitization, 1 subject and 2 subjects (0.5% and 0.9%) had confirmed sensitization reactions to the Desonide Gel Vehicle and DesOwen lotion, 0.05% groups, respectively. Four (4) and 5 subjects (1.9% and 2.4%) in the Desonide Gel and DesOwen lotion groups, respectively had challenge reactions consistent with sensitization but these reactions were not confirmed as the subjects did not consent to a re-challenge.

7 Page(s) Withheld

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