

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-978

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Submission Number 21-978
Submission Code 000

Letter Date November 18, 2005
Stamp Date November 28, 2005
PDUFA Goal Date September 21, 2006

Reviewer Name Denise Cook, M.D.
Review Completion Date 8/28/06

Established Name Desonide
(Proposed) Trade Name
Therapeutic Class Topical corticosteroid
Applicant Connectics

Priority Designation S

Formulation Foam, 0.05%
Dosing Regimen bid
Indication For the treatment of mild to moderate atopic dermatitis
Intended Population Age 3 months and above

Table of Contents

1	EXECUTIVE SUMMARY	5
1.1	RECOMMENDATION ON REGULATORY ACTION	5
1.2	RECOMMENDATION ON POSTMARKETING ACTIONS	5
1.2.1	Risk Management Activity	5
1.2.2	Required Phase 4 Commitments	5
1.2.3	Other Phase 4 Requests	5
1.3	SUMMARY OF CLINICAL FINDINGS	5
1.3.1	Brief Overview of Clinical Program	5
1.3.2	Efficacy	6
1.3.3	Safety	7
1.3.4	Dosing Regimen and Administration	7
1.3.5	Drug-Drug Interactions	7
1.3.6	Special Populations	8
2	INTRODUCTION AND BACKGROUND	9
2.1	PRODUCT INFORMATION	9
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS	10
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	11
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	11
2.5	PRESUBMISSION REGULATORY ACTIVITY	11
2.6	OTHER RELEVANT BACKGROUND INFORMATION	12
3	SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	13
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	13
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY	13
4	DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY	14
4.1	SOURCES OF CLINICAL DATA	14
4.2	TABLES OF CLINICAL STUDIES	15
4.3	REVIEW STRATEGY	16
4.4	DATA QUALITY AND INTEGRITY	16
4.5	COMPLIANCE WITH GOOD CLINICAL PRACTICES	17
4.6	FINANCIAL DISCLOSURES	17
5	CLINICAL PHARMACOLOGY	18
5.1	PHARMACOKINETICS	18
5.2	PHARMACODYNAMICS	18
5.3	EXPOSURE-RESPONSE RELATIONSHIPS	18
6	INTEGRATED REVIEW OF EFFICACY	18
6.1	INDICATION	18
6.1.1	Methods	18
6.1.2	General Discussion of Endpoints	19
6.1.3	Study Design	20
6.1.4	Efficacy Findings	21
6.1.5	Clinical Microbiology	26
6.1.6	Efficacy Conclusions	26
7	INTEGRATED REVIEW OF SAFETY	27
7.1	METHODS AND FINDINGS	27
7.1.1	Deaths	27

7.1.2	Other Serious Adverse Events	27
7.1.3	Dropouts and Other Significant Adverse Events	28
7.1.4	Other Search Strategies.....	29
7.1.5	Common Adverse Events	29
7.1.6	Less Common Adverse Events	32
7.1.7	Laboratory Findings.....	32
7.1.8	Vital Signs	34
7.1.9	Electrocardiograms (ECGs).....	37
7.1.10	Immunogenicity	38
7.1.11	Human Carcinogenicity	38
7.1.12	Special Safety Studies	38
7.1.13	Withdrawal Phenomena and/or Abuse Potential.....	50
7.1.14	Human Reproduction and Pregnancy Data	51
7.1.15	Assessment of Effect on Growth.....	51
7.1.16	Overdose Experience	51
7.1.17	Postmarketing Experience.....	51
7.2	ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	52
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	52
7.2.2	Description of Secondary Clinical Data Sources Used to Evaluate Safety	54
7.2.3	Adequacy of Overall Clinical Experience	56
7.2.4	Adequacy of Special Animal and/or In Vitro Testing	56
7.2.5	Adequacy of Routine Clinical Testing.....	56
7.2.6	Adequacy of Metabolic, Clearance, and Interaction Workup.....	57
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.....	57
7.2.8	Assessment of Quality and Completeness of Data	57
7.2.9	Additional Submissions, Including Safety Update	57
7.3	SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	57
7.4	GENERAL METHODOLOGY	57
7.4.1	Pooling Data Across Studies to Estimate and Compare Incidence	57
7.4.2	Explorations for Predictive Factors	60
7.4.3	Causality Determination	62
8	ADDITIONAL CLINICAL ISSUES	63
8.1	DOSING REGIMEN AND ADMINISTRATION	63
8.2	DRUG-DRUG INTERACTIONS	63
8.3	SPECIAL POPULATIONS.....	63
8.4	PEDIATRICS	63
8.5	ADVISORY COMMITTEE MEETING	63
8.6	LITERATURE REVIEW	63
8.7	POSTMARKETING RISK MANAGEMENT PLAN	63
8.8	OTHER RELEVANT MATERIALS	63
9	OVERALL ASSESSMENT.....	64
9.1	CONCLUSIONS	64
9.2	RECOMMENDATION ON REGULATORY ACTION	64
9.3	RECOMMENDATION ON POSTMARKETING ACTIONS	64
9.3.1	Risk Management Activity	64
9.3.2	Required Phase 4 Commitments.....	64
9.3.3	Other Phase 4 Requests.....	64
9.4	LABELING REVIEW	65
9.5	COMMENTS TO APPLICANT.....	65

Clinical Review
Denise Cook, M.D.
NDA 21-978/N-000
Foam, 0.05%/desonide foam, 0.05%

10 APPENDICES	66
10.1 REVIEW OF INDIVIDUAL STUDY REPORTS	66
10.2 LINE-BY-LINE LABELING REVIEW.....	74
REFERENCES	84

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended from a clinical perspective that desonide foam, 0.05% be approved for “treatment of mild to moderate atopic dermatitis in patients ages 3 months and older.”

The sponsor demonstrated in one robust clinical trial through persuasive statistics that desonide foam, 0.05% is efficacious in the treatment of mild to moderate atopic dermatitis ($p < 0.00001$) over a 4 week period. The drug product also demonstrated an adequate safety profile with one caveat. There was HPA axis suppression, albeit reversible, that occurred in 4% of patients. Therefore, it will be recommended that the drug product not be used for more than 4 consecutive weeks.

1.2 Recommendation on Postmarketing Actions

The sponsor should follow all requirements on filing annual reports for any newly marketed drug product.

1.2.1 Risk Management Activity

There is not any special risk management activity necessary with this drug product.

1.2.2 Required Phase 4 Commitments

There are not any required phase 4 commitments from a clinical perspective. However, the sponsor is required to conduct 2 non-clinical studies as phase 4 commitments. These are a dermal carcinogenicity study and a study to determine the photo-carcinogenic potential of desonide foam.

1.2.3 Other Phase 4 Requests

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This NDA was submitted in support of ~~_____~~ (desonide) Foam, 0.05% for the proposed indication of treatment of mild to moderate atopic dermatitis. To support the indication, the sponsor submitted one pivotal, multicentered phase 3 trial for efficacy and safety, one small

phase 2 trial and 1 phase 2 open-label trial to evaluate systemic safety in this topically applied corticosteroid.

Desonide foam, 0.05% was studied in pediatric patients whose ages ranged from 3 months to 17 years. A total of 1014 subjects were evaluated in the clinical program. Of these subjects, 786 were exposed to ~~desonide~~ (desonide) Foam, 0.05% (246 healthy subjects and 540 patients with atopic dermatitis). The phase 3 pivotal trial enrolled 581 patients randomized in a 2:1 ratio into either a desonide foam arm or a vehicle arm, 387 and 194 subjects, respectively. The phase 2 systemic safety study enrolled 81 subjects for a 4 week course of treatment. In the systemic safety study patients had at least 25% of their body surface area affected by atopic dermatitis.

1.3.2 Efficacy

There was one phase 3 trial that was reviewed in support of efficacy of desonide foam, 0.05% in the treatment of mild to moderate atopic dermatitis. The trial, DES.C.301, was multicentered, double-blind, and placebo controlled. The centers were located in the United States. The trial randomization was 2:1, active drug and placebo, respectively. The sponsor conducted the study under the protocol that was agreed upon with the Agency in terms of study design and primary endpoints.

The primary efficacy variables were three, the Investigator's Global Assessment Scale (ISGA), and the signs of erythema and induration/papulation. The ISGA was based on a severity scale from 0-4 (clear, almost clear, mild, moderate, and severe). Subjects had to have at least mild disease to be eligible for enrollment. The erythema and induration/papulation severity scales were also graded from 0-4 with 0 denoting absence of the sign and 4 denoted the most severe.

Secondary efficacy parameters included mean percent reduction in the sum of scores of erythema, induration/papulation, lichenification, and scaling from baseline to week 4 (or end of treatment; the proportion of subjects who have a pruritus score of 0 at week 4 (or end of treatment); and the proportion of subjects who have an ISGA of 0 or 1 at week 4 (or end of treatment) and a minimum improvement in the ISGA score of 2 grades from baseline to week 4 (or end of treatment).

Success in efficacy of desonide foam over placebo in the pivotal trial was determined by the proportion of subjects who at week 4 had an ISGA score of 0 or 1 with a minimum improvement of 2 grades from baseline to week 4 and who had an erythema score of 0 or 1 at week 4 and who had an induration/papulation score of 0 or 1 at week 4. All three of these criteria had to be met and the statistical analysis given this was one trial had to be persuasive.

Analysis of study DES.C.301 demonstrated that desonide foam, 0.05% was statistically significantly superior in treating mild to moderate atopic dermatitis in patients greater than or equal to 3 months of age than its placebo ($p < 0.0001$). The results were robust and consistent across investigational sites and subgroups without any major flaws. Thirty-nine percent of patients treated with desonide foam were a success after 4 weeks of treatment compared to 9% in the placebo group. The per protocol population analysis supported this with 42% of subjects in the desonide foam arm achieving success vs. 13% in the placebo group. The secondary efficacy endpoints supported the primary endpoints ($p < 0.0001$).

1.3.3 Safety

A total of 1014 subjects were evaluated in the clinical program. Of these subjects, 786 were exposed to — (desonide) Foam, 0.05% (246 healthy subjects and 540 patients with atopic dermatitis). In the phase 3 efficacy trial, 354/387 (91%) subjects completed the trial and in the phase 2 systemic safety trial, 78/81 (96%) subjects completed the trial.

There were 5 adverse events that were associated with desonide foam. These were associated with topical application of the drug product and systemic effects on the HPA axis. Four of these adverse events were associated with topical application of the drug product and occurred in 1% or more of subjects. In descending order of frequency, these were application site burning (3%), application site dermatitis (1%), application site reaction (1%), and application site atrophy (1%). The most common adverse event, application site burning occurred at a significantly higher rate in the vehicle subjects (8%) than in those subjects using drug product. This suggests that the adverse event is due to the vehicle and is somewhat mitigated by the anti-inflammatory action of the chemical moiety, desonide. Most of these reactions were mild to moderate in intensity, resulting in 2 interruptions of therapy and no discontinuations.

HPA axis suppression did occur in 4% (3/75) subjects after 4 weeks of bid usage. All of the patients recovered on the following visit (4 weeks following last drug administration). Thus, appropriate caution should be undertaken when using desonide foam and it should not be used for more than 4 consecutive weeks.

Phase 1 dermal safety studies corroborated what was found in the clinical trials. Desonide foam, 0.05% and its vehicle are somewhat irritating but not significantly more irritating than clobetasol vehicle foam (part of an approved drug product) and significantly not as irritating as the positive control, sodium lauryl sulfate, 0.1%. There was no evidence of sensitization from using this drug product in the phase 1 dermal safety studies.

A waiver was given for the dermal phototoxicity and photoallergenicity studies by the Agency on 11/4/05, as the drug product showed minimal absorption in the UVA, UVB, and visible light ranges.

1.3.4 Dosing Regimen and Administration

The dosing regimen for this drug product should be to apply a thin layer of — Foam to the affected area(s) twice daily. Shake the can before use. — Foam should be dispensed by inverting the can (upright actuation will cause loss of the propellant which may affect product delivery). Dispense the smallest amount of foam necessary to adequately cover the affected area(s) with a thin layer. Take care to avoid contact with the eyes. Gently massage the medication in to the affected area(s) until it is absorbed. It should also state that the drug product should not be used for more than 4 consecutive weeks.

1.3.5 Drug-Drug Interactions

There are not any specific drug-drug interactions that were investigated in the conduct of this NDA.

1.3.6 Special Populations

All of the subjects in the safety and efficacy trials were pediatric subjects, ages 3 months to 17 years of age. Subjects were divided into four age cohorts: 3 months to < 3 years; 3 years to < 6 years; 6 years to < 12 years; and 12 years to 17 years. All age cohorts were well represented in the studies, with the second largest cohort being those ages 3 months to < 3 years old. Efficacy across cohorts was similar, as was safety. As the pathogenesis and history of atopic dermatitis is the same in the adult population as it in the pediatric population, efficacy and safety can be extrapolated upward to the adult population, without any added precautions.

Approximately half of the subjects were Caucasian, however, there was good representation of other ethnic groups, African-American and Hispanic. Asian subjects had the least amount of representation. Differences in efficacy and safety were not found across these subgroups.

**APPEARS THIS WAY
ON ORIGINAL**

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.11 Description of the Product

_____™ Foam is a petrolatum-based emulsion aerosol foam containing the active ingredient desonide, a low-potency topical corticosteroid. Desonide is a white powder or crystal that is practically insoluble in water, sparingly soluble in ethanol and in acetone, and soluble in chloroform. Each gram of _____ Foam contains 0.5 mg desonide. The foam also contains anhydrous citric acid, cetyl alcohol, cyclomethicone, isopropyl myristate, light mineral oil, white petrolatum, polyoxyl 20 cetostearyl ether, potassium citrate (monohydrate), propylene glycol, purified water, sorbitan monolaurate, and phenoxyethanol as a preservative.

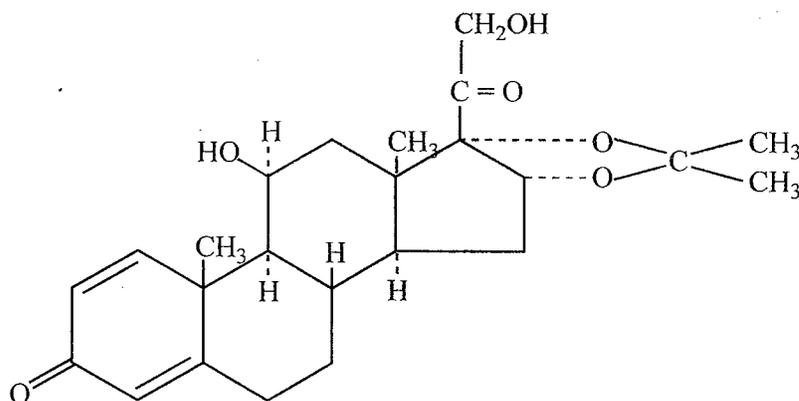
_____ Foam is dispensed from an aluminum can pressurized with a hydrocarbon (propane/butane) propellant.

2.12 Established Name and Proposed Trade Name

The established name of the product is desonide foam. The proposed trade name is _____™ Foam, 0.05%

2.13 Chemical Class

The following is the chemical structure:



Chemically, desonide is (11 β ,16 α)-11,21-dihydroxy-16,1[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione. Desonide has a molecular formula of C₂₄H₃₂O₆ and a molecular weight of 416.51.

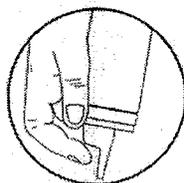
2.14 Pharmacological Class

Topical corticosteroids share anti-inflammatory, antipruritic, and vasoconstrictive actions. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

2.15 Indication, Dosing Regimen, Age Groups

— Foam is indicated for the treatment of mild to moderate atopic dermatitis.

A thin layer of — Foam should be applied to the affected area(s) twice daily. Shake the can before use. — Foam should be dispensed by inverting the can (upright actuation will cause loss of the propellant which may affect product delivery). Dispense the smallest amount of foam necessary to adequately cover the affected areas(s) with a thin layer. Take care to avoid contact with the eyes. Gently massage the medication in the affected area(s) until it is absorbed.



As with other corticosteroids, therapy should be discontinued when control is achieved. Unless directed by a physician, — Foam should not be used with occlusive dressings.

Reviewer's Comment: The above section is taken from the draft labeling of the sponsor. The indication and usage section, section 2.15, is that as it is proposed by the sponsor. Changes may occur depending on the outcome of the review.

2.2 **Currently Available Treatment for Indications**

There are many treatments available for atopic dermatitis. The mainstay of treatment for mild to moderate atopic dermatitis is topical corticosteroids. The potency of these topical corticosteroids range from class VII, the weakest of which hydrocortisone is a classic representative, to class I, the superpotent topical corticosteroids, of which clobetasol is the

classic example. The class I topical corticosteroids are usually reserved, however, for severe disease.

Other treatments available for atopic dermatitis include the topical calcineurin inhibitors, pimecrolimus and tacrolimus; the former for mild to moderate atopic dermatitis and the latter for moderate to severe atopic dermatitis. These drugs, which are topical immunosuppressants, are second line treatment and carry a black box warning about the possible development of cancer.

UVB therapy has been shown to be effective for some patients with atopic dermatitis. Oral cyclosporine has also been used off-label in severe cases of atopic dermatitis.

2.3 Availability of Proposed Active Ingredient in the United States

Desonide in all of its formulations are readily available in the United States.

2.4 Important Issues With Pharmacologically Related Products

Topical corticosteroids can be systemically absorbed and as such, may cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis. In most cases, this has been found to be reversible when the medication is discontinued.

Cutaneous atrophy is the other important issue that occurs with continued use of topical corticosteroids. This adverse event is mitigated by rotational therapy and disease free intervals where the medication is not needed.

2.5 Presubmission Regulatory Activity

PreIND/End of Phase 2 Meeting – March 30, 2004

The sponsor was informed in this meeting that for eventual drug approval one of the following pathways could be followed:

1. Two independent, double-blind, vehicle controlled studies demonstrating superiority to vehicle.
2. One 3-arm (desonide foam, desonide foam vehicle, and comparator desonide active) study demonstrating superiority of desonide foam to its vehicle and non-inferiority to the comparator. A fourth small comparator vehicle-like arm is recommended for blinding purposes.
3. One very persuasive, robust, double-blind, vehicle controlled study demonstrating superiority to vehicle. The study should be highly statistically significant with no major flaws and consistent results across centers and subgroups.

The sponsor was advised that in the HPA axis suppression study, subjects should be grouped into cohorts as follows: 3 months to 3 years old; 3-6 years old; 6-12 years old; and 12-18 years old.

The groups should be studied simultaneously and each subject should have atopic dermatitis with a minimum of 25% BSA involvement.

HPA Axis Suppression Study (DES.C.201) Comments – June 2, 2004

Sponsor was advised that the criterion for HPA axis suppression after cosyntropin stimulation is a serum cortisol value of ≤ 18 $\mu\text{g/dL}$.

Special Protocol Assessment – Letter for DES.C.301 – July 1, 2004

The Agency, with minor changes, to the protocol, from a clinical standpoint, agreed with the protocol design. The sponsor was reminded that since they had chosen option 3 under the protocol design options from the comments made at the preIND/EOP2 meeting, that the efficacy in that trial would have to be persuasive and robust or a second trial might be required.

Pre-NDA Meeting – September 12, 2005

The sponsor was advised to submit comprehensive worldwide safety data of all desonide products. At the end of the review it would be determined if long-term safety studies would be needed. However, the sponsor was advised that if the reported AEs for desonide foam are in keeping with similar AEs reported for the active product, then further long-term studies may not be required.

The sponsor was advised that an electronic submission in the CTD format was acceptable.

2.6 Other Relevant Background Information

Desonide was approved for marketing in the United States in 1972 for the treatment of corticosteroid-responsive dermatoses. It is classified as a Group VI, low potency topical steroid and currently approved at the strength of 0.05% in three dosage forms: lotion, cream, and ointment.

Desonide NDAs:

- 1) NDA 17-010 (Tridesilon {desonide} cream, 0.05%; Corticosteroid responsive dermatoses; HFD-540; approved 1/4/72; Clay Park Labs)
- 2) NDA 17-426 (Tridesilon {desonide} ointment, 0.05%; Corticosteroid responsive dermatoses; HFD-540; approved 11/1/74; Clay Park Labs)
- 3) NDA 19-048 (DesOwen {desonide} cream, 0.05%; Corticosteroid responsive dermatoses; HFD-540; approved 12/14/84; Galderma Labs LP)

Generic desonide ANDAs:

- 1) ANDA 71-425 (DesOwen {desonide} ointment, 0.05%; Corticosteroid responsive dermatoses; HFD-600; approved 5/15/88; Galderma Labs LP)
- 2) ANDA 72-354 (DesOwen {desonide} lotion, 0.05%; Corticosteroid responsive dermatoses; HFD-600; approved 1/24/92; Galderma Labs LP)

- 3) ANDA 73-548 (desonide cream, 0.05%; Corticosteroid responsive dermatoses; HFD- 600; approved 6/30/92; Taro Pharms)
- 4) ANDA 74-027 (desonide cream, 0.05%; Corticosteroid responsive dermatoses; HFD- 600; approved 9/28/92; Copley Pharm)
- 5) ANDA 74-254 (desonide ointment, 0.05%; Corticosteroid responsive dermatoses; HFD- 600; approved 8/3/94; Taro Pharms)
- 6) ANDA 75-751 (desonide ointment, 0.05%; Corticosteroid responsive dermatoses; HFD- 600; approved 3/12/01; Alanta)

Desonide foam is not currently marketed in any other jurisdiction.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The drug substance, desonide, is a low potency anti-inflammatory corticosteroid typically applied topically. The drug product, ~~_____~~™ (desonide) Foam, 0.05%, is a petrolatum-based emulsion aerosol foam. Each gram of the foam contains 0.5 mg desonide. The foam also contains Citric Acid USP, Cetyl Alcohol NF, Cyclomethicone NF, Isopropyl Myristate NF, Light Mineral Oil NF, White Petrolatum USP, Polyoxyl 20 Cetostearyl Ether NF, Potassium Citrate USP, Propylene Glycol USP, Purified Water USP, Sorbitan Monolaurate NF, and Phenoxyethanol NF as a preservative. The product is dispensed from an aluminum can pressurized with a hydrocarbon (propane/butane) propellant.

Dr. Gene W. Holbert and Dr. Brian D. Rogers state in their review that the sponsor “changed the acceptance criterion for propellant pressure at release and stability from not less than _____ to not less than _____ to better reflect manufacturing capability and product used in the clinical trials.” This was discussed with the clinical team and a teleconference was held with the sponsor to reach this agreement.

3.2 Animal Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Dr. Barbara Hill, came to the following conclusion regarding desonide foam:

“Desonide and sorbitan monolaurate were negative in an ICH battery of genotoxicity studies. A nonclinical dermal carcinogenicity study has not been conducted with any topical desonide formulation. In addition, a study to determine the photoco-carcinogenic potential of _____ foam has not been conducted by the sponsor. It was recommended that the sponsor conduct both these studies as phase 4 commitments. The sponsor has agreed to conduct a dermal carcinogenicity study with _____ foam and a study to determine the photocarcinogenic potential of _____ foam as Phase 4 commitments.

The sponsor has provided adequate data to address any potential safety concerns for the _____ that may be contained in the desonide foam. The sponsor has also

provided adequate information to assure that the level of _____ in the propane/butane propellant used for the desonide foam, 0.05% drug product is less than NMT _____ a level previously determined to be low enough to not pose a cancer risk.”

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Data used in the review of this drug product for the indication of the treatment of mild to moderate atopic dermatitis came entirely from the sponsor's NDA submission. This also includes the 120-day safety update. The NDA was entirely electronic and submitted in CTD format.

**APPEARS THIS WAY
ON ORIGINAL**

4.2 Tables of Clinical Studies

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
<u>DES.C.101</u>	Compare the relative vasoconstrictor potency of Desonide Foam, 0.05% (Desonide Foam) to: 1) Elocon [®] cream, 0.1%, 2) hydrocortisone cream 0.5%, 3) Tridesilon [®] cream, 0.05% and 4) Vehicle Foam	Randomized, evaluator-blinded, active comparators; topical application	Desonide Foam, Desonide Cream, Elocon Cream, Desonide Vehicle Foam, EF Clobetasol Propionate Vehicle Foam	36	Healthy Subjects	Single dose
<u>DES.C.102</u>	To evaluate the dose response vasoconstriction profile of Desonide Foam, 0.05%, (Desonide Foam) at different dose durations over a short period of time (15 min–6 hrs).	Staggered application; no control; topical application	Desonide Foam	12	Healthy Subjects	Single dose
<u>DES.C.103</u>	Determine the allergic contact sensitization potential of Desonide Foam, 0.05% (Desonide Foam), Desonide Vehicle Foam, and Ethanol Free Clobetasol Propionate Vehicle Foam (EF Clobetasol Vehicle Foam).	Single-center, evaluator-blinded; occlusive patches.	Desonide Foam, Desonide Vehicle Foam, EF Clobetasol Propionate Vehicle Foam; sodium lauryl sulfate, 0.1% (positive control), and distilled water (negative control).	240	Healthy Subjects	Three times a week for 5 weeks then 1 challenge dose. Re-challenge if needed.

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
<u>DES.C.104</u>	Evaluate the cutaneous irritation potential of Desonide Foam, 0.05% (Desonide Foam), Desonide Vehicle Foam, and Ethanol Free Clobetasol Propionate Vehicle Foam (EF Clobetasol Vehicle Foam)	Single-center, evaluator-blinded	Desonide Foam, Desonide Vehicle Foam, EF Clobetasol Propionate Vehicle Foam; sodium lauryl sulfate, 0.1% (positive control), and distilled water (negative control) daily; topical application	40	Healthy volunteers	Daily for 3 weeks
<u>DES.C.201</u>	Evaluate the safety of Desonide Foam, 0.05% (Desonide Foam) including its effect on the hypothalamic pituitary adrenal (HPA) axis	Open-label, non-controlled	Desonide Foam twice daily; topical application	81	Patients with atopic dermatitis	4 weeks
<u>DES.C.202</u>	Safety and Efficacy; verification of sample size for Phase 3	Randomized, double-blind, vehicle controlled	Desonide Foam or Vehicle Foam twice daily for 4 weeks; topical application	106	Patients with atopic dermatitis	4 weeks
<u>DES.C.301</u>	Safety and Efficacy; superiority to Vehicle Foam	Randomized, double-blind, vehicle controlled	Desonide Foam or Vehicle Foam twice daily for 4 weeks; topical application	581	Patients with atopic dermatitis	4 weeks

4.3 Review Strategy

In this review, all clinical trials were reviewed in detail for efficacy and safety with the exception of the small phase 2 clinical trial. This was reviewed in less detail, as it was not needed to support the efficacy and safety that was demonstrated in the phase 3 pivotal clinical trial.

4.4 Data Quality and Integrity

Before initiating this study, Connetics Corporation held an Investigators' Meeting on 7 August 2004 to review the protocol design, definition of endpoints, statistical considerations, and an overview of key study conduct requirements. Investigators or efficacy assessor designees who were unable to attend the Investigators' Meeting received training on the Investigator's Static

Global Assessment scoring requirements and other efficacy assessments at an initiation visit. Site personnel were trained on data collection procedures either during the Investigators' Meeting or during a study initiation visit. Connetics representatives conducted study site initiation visits.

Connetics representatives conducted appropriate site visits to the investigational facilities to monitor the various aspects of the study. The investigators provided these representatives access to the study drug dispensing and storage areas and to the clinic/hospital files of the subjects for monitoring purposes.

All clinical information requested in the protocol was to be recorded in permanent ink on CRFs provided by the Sponsor. The CRFs were on three-part NCR paper; the white copy was the original, yellow was the working copy for data management, and the pink was the investigator's copy. All response fields on the CRFs were required to be completed; if data were unavailable, unmeasured, or not applicable, this was to be indicated on the CRF. Errors were to be corrected by a single line through the error and the corrected response was to be written near the error in permanent ink and initialed and dated by the person making the correction.

Completed CRFs were to be reviewed by the investigator and made ready for review by Study Monitors within 2 weeks after subject contact unless the forms were incomplete because laboratory data or medical event follow-up was not yet available. A verification of completed forms was to be signed by either the investigator or a physician subinvestigator for each completed set of CRFs.

The Study Monitor(s) reviewed the CRFs against the subject's file (source), evaluating the CRFs for accuracy, consistency, and completeness, and then returned all CRFs with missing data and/or possible errors to the investigator for correction. Data management tasks including data entry, internal and referential data checks, and quality control (QC) were performed by:

4.5 Compliance with Good Clinical Practices

The trials were conducted in accordance with the Helsinki Declaration and in accordance with the CRF. All trials were conducted under an IRB.

4.6 Financial Disclosures

There was one investigator that needed to make a financial disclosure. _____ M.D. has stock with Connetics worth \$67,000. The sponsor states that steps taken to minimize any bias by Dr. _____ included the same as for all investigators, which is that this trial was double-blinded. There were 17 centers in the United States that participated in the study and Dr. Clara Kim, our biostatistician, did not find that the efficacy results were driven by any one center. Therefore, Dr. _____ interest in Connetics did not influence the efficacy outcome of the study.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

A phase 2 HPA Axis Suppression study was performed as a marker for systemic absorption of the drug product. Out of 75 evaluable subjects, with at least 25% BSA involvement with atopic dermatitis, 3 (4%) patients experienced reversible HPA axis suppression (see section 7.1.12, Special Studies for details). The following addition to the pharmacokinetics section of the label was proposed by Dr. Ghosh in his clinical pharmacology review:

5.2 Pharmacodynamics

A human vasoconstrictor assay was performed to determine the relative potency of desonide foam (see clinical pharmacology review for details). The conclusion was that based on the statistical similarity between desonide foam and Tridesilon (desonide) cream, these two formulations should be considered similar in ranking potency. Tridesilon cream, 0.05% is a low potency (Class VI) topical corticosteroid and as such, desonide foam has been found to be the same.

5.3 Exposure-Response Relationships

See HPA axis suppression study under section 7.1.12.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

— Foam is indicated for the treatment of mild to moderate atopic dermatitis.

6.1.1 Methods

The pivotal trial, DES.C.301 was reviewed in detail to support the indication proposed by the sponsor. It was a double-blind, placebo controlled, parallel-group, and multicentered trial (see

Appendix 10.1). A small phase 2 study was performed. The reader is referred to the statistical review page 17, for those results.

6.1.2 General Discussion of Endpoints

The following endpoints were specified in the protocol for efficacy evaluation:

Primary:

Proportion of subjects who have

- ISGA score of clear or almost clear (0 or 1) at Week 4 and a minimum improvement of 2 grades from Baseline to Week 4 (or end of treatment), **and**
- A score of 0 or 1 for erythema at Week 4, **and**
- A score of 0 or 1 for induration/population at week 4.

Patients who met the above criteria were considered a treatment success. The parameters for the primary efficacy variables are denoted in tables 1, 2, and 3.

Table 1
Investigator’s Static Global Assessment

Grade	Score	Description
Clear	0	There may be minor residual discoloration; no erythema or induration/population, no oozing/crusting
Almost clear	1	There may be trace faint pink erythema, with almost no induration/papulaiton, and no oozing/crusting
Mild	2	There may be faint pink erythema, with mild induration/population and no oozing/crusting
Moderate	3	There may be pink-red erythema with moderate induration/population and there may be some oozing/crusting
Severe	4	There may be deep or bright red erythema with severe induration/population and with oozing/crusting

Source: eCTD NDA 21-978, Study report DES.C.301, adapted from table 3, page 25.

Table 2
Erythema

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

Source: eCTD NDA 21-978, Study Report DES.C.301, adapted from table 5, page 26

Table3
Induration/Papulation

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

Source: eCTD NDA 21-978, Study Report DES.C.301, adapted from table 5, page 26

Secondary Efficacy Variables:

- Mean percent reduction in the sum scores of erythema, induration/papulation, lichenification, and scaling from baseline to week 4 (or end of treatment)
- The proportion of subjects who have a pruritus score of 0 at Week 4 (or end of treatment)
- The proportion of subjects who have an ISGA of 0 or 1 at Week 4 (or end of treatment) and a minimum improvement in the ISGA score of 2 grades from baseline to Week4 (or end of treatment).

The sponsor denoted the first secondary endpoint as the principal secondary endpoint and added oozing/crusting to the sum of scores to be evaluated in the submission. This change was partially in response to Agency comments and was done via a protocol amendment dated July 9, 2004, which was before the first subject was enrolled (8/31/04).

The protocol and submission defined the intent-to-treat (ITT) population as all subjects who were randomized and received the study drug. Subjects were excluded from the per-protocol (PP) population if they missed more than a total of 10 applications at any time or six consecutive applications of the study medication, or did not have efficacy evaluations at Baseline and Week 4 visits, or used prohibited medications at any time during the treatment period. The ITT and PP populations were analyzed for efficacy. However, the ITT population was the primary population.

6.1.3 Study Design

Protocol DES.C.301 was a Phase 3, multicenter (17 sites in the United States), randomized, double-blind, vehicle-controlled study comparing desonide foam and its vehicle in the treatment of mild to moderate atopic dermatitis in male and female pediatric and adolescent subjects.

Subjects with atopic dermatitis who had mild or moderate disease, defined as an Investigator's Static Global Assessment (ISGA) score of 2 or 3, a sum of the scores for erythema, induration/papulation, scaling, and oozing/crusting of ≥ 4 , and an involvement of $\geq 5\%$ total body surface area (BSA) were eligible for enrollment.

Approximately 570 subjects were to be randomized to one of two parallel treatment groups in a 2:1 ratio (desonide foam:vehicle foam). Approximately 380 subjects were to be randomly assigned to treatment with desonide foam and approximately 190 subjects to treatment with vehicle foam. Subjects were to be enrolled simultaneously into age cohorts as follows:

- Cohort 1: ≥ 12 years to < 18 years
- Cohort 2: ≥ 6 years to < 12 years
- Cohort 3: ≥ 3 years to < 6 years
- Cohort 4: ≥ 3 months to < 3 years

Investigators, nurse/coordinators, and subjects/primary caregivers were to be blinded to the treatment assignment. Subjects who did not complete the study were not to be replaced. The study was to consist of 4 weeks of treatment with visits at Baseline, Week 2, and Week 4 (or early termination), and a 3-week post-treatment follow-up evaluation. Subjects or their primary caregivers were to be instructed to consistently apply the study drug treatment twice daily in the mornings and evenings throughout the 4-week study.

6.1.4 Efficacy Findings

The 2:1 randomization to desonide foam, 0.05% and vehicle resulted in 387 subjects in the desonide foam arm and 194 subjects in the vehicle arm. The average age of the subjects was approximately 6.9 years and the age range was from 3.6 months to 17.9 years. Table 4 denotes all of the baseline demographic data.

Table 4
Baseline Demographic Data – ITT Population

	Desonide Foam N=387	Vehicle N=194
Age (in years)		
Mean (std)	7.0 (4.8)	6.8 (4.9)
Median	6.2	5.4
Min, max	0.3, 18.0	0.4, 18.0
Gender		
Male	198 (51%)	90 (46%)
Female	189 (49%)	104 (54%)
Race		
Caucasian	191 (49%)	100 (52%)
African-American	94 (24%)	49 (25%)
Hispanic	66 (17%)	32 (16%)
Asian	17 (4%)	6 (3%)
Other	19 (5%)	7 (4%)

Source: Study report 53412-des-c-301.pdf, page 44

Of the 518 subjects enrolled in the study, a total of 87 subjects discontinued, 33 in the desonide foam arm and 54 in the vehicle arm. Table 5 sites the reasons for discontinuation. For the subjects who fall under the category of “other”, 1 subject misunderstood the visit time lines,

1 subject was 4 weeks late for visit 3, and the remaining 16 were lost to follow-up. The adverse events, including the death will be discussed in more detail in section 7, the integrated review of safety.

Table 5
Reason for Study Discontinuation

	Desonide N = 387	Vehicle N = 194
Subjects who discontinued	33 (9%)	54 (28%)
<i>Reason</i>		
Adverse Event	2 (0.5%)	17 (9%)
Non-compliance	6 (2%)	3 (2%)
Disease Progression	3 (1%)	18 (9%)
Subject Request to Withdraw	3 (1%)	12 (6%)
Death	1 (<1%)	0 (0%)
Other	18 (5%)	4 (2%)

Source: Study report 53512-des-c-301.pdf, page 41

Table 6 delineates the baseline severity of disease. The ISGA and %BSA were fairly balanced between the two arms. The desonide arm had a slightly higher proportion of subjects with moderate severity and a marginally higher mean %BSA score than the vehicle arm.

Table 6
Baseline Severity –ITT Population

	Desonide N = 387	Vehicle N = 194
Investigator's Static Global Assessment Score		
2	145 (37%)	74 (38%)
3	242 (63%)	119 (61%)
4	0 (0%)	1 (1%)
Extent of Atopic Dermatitis (%BSA)		
Mean (std)	21 (18.7)	19.8 (17.5)
Median	15	13
Min, max	5, 97	5, 90

Source: Study report 53512-des-c-301.pdf, page 45

Efficacy Analysis – Primary Endpoints

As stated earlier, the protocol defined efficacy success as subjects who had

- ISGA score of 0 or 1 at Week 4, with a minimum improvement of 2 grades from baseline to Week 4; **and**
- Erythema score of 0 or 1 at Week 4; **and**
- Induration/papulation score of 0 or 1 at Week 4.

Table 7 presents the primary efficacy results in the ITT population. At week 4, the primary efficacy time point, 39% of the desonide foam subjects reached success status, versus 9% of those subjects in the vehicle arm. This was highly statistically significant ($p < 0.0001$). Table 8 describes the success rate for each of the three efficacy variables that needed to be met in order to demonstrate efficacy for desonide foam, ISGA, erythema, and induration/papulation. All three were highly statistically significant, $p < 0.0001$, thus establishing the efficacy of desonide foam in the treatment of atopic dermatitis.

Table 7
Primary Efficacy Endpoint Results
ITT Population

	Desonide Foam N = 387	Vehicle N = 194	p-value*
Success	152 (39%)	18 (9%)	<0.0001
*p-values are calculated using CMH statistic stratified by pooled sites Source: Statistical review: Dr. Clara Kim, page 11			

Table 8
Components of Primary Endpoint Results
ITT Population

	Desonide Foam N = 387	Vehicle N = 194	p-value*
ISGA ¹	157 (41%)	18 (9%)	<0.0001
Erythema ²	262 (68%)	69 (36%)	<0.0001
Induration/Papulation ²	268 (69%)	73 (38%)	<0.0001
*p-values are calculated using CMH statistic stratified by pooled sites; ¹ Success is defined as score of 0 or 1 at week 4 with a minimum improvement of 2 grades from baseline to week 4; ² Success is defined as score of 0 or 1 at week 4 Source: Statistical review: Dr. Clara Kim, page 11			

The efficacy results for the per protocol (PP) population were similar to those of the ITT population. A total of 100 patients were excluded from the PP population, 41 subjects (11%) in the desonide foam arm and 59 subjects (30%) in the vehicle foam arm. The most common reason for exclusion in the desonide foam arm was for missing more than a total of 10 applications or no efficacy assessments at baseline or week 4. These occurred with equal frequency in the desonide foam arm. The most common reason for exclusion in the vehicle arm was due to the subject missing more than a total of 10 applications (51 subjects) followed by no efficacy assessment at baseline or week 4 (6 subjects).

Table 9 shows the efficacy results for the PP population for the primary endpoint analysis. The proportion of success was higher in the PP population than in the ITT population for both arms. The p value was highly statistically significant ($p < 0.0001$). The similarity of

results of the PP population to the ITT population further supports the efficacy of desonide foam over vehicle (see statistical review for full analysis of PP population endpoints).

Table 9
Primary Efficacy Endpoint Results
Per Protocol Population

	Desonide Foam N = 346	Vehicle N = 135	p-value*
Success	147 (42%)	17 (13%)	<0.0001
*p-values are calculated using CMH statistic stratified by pooled sites Source: Statistical review: Dr. Clara Kim, page 13			

Efficacy Analysis – Secondary Endpoints

The secondary endpoints defined in the protocol were as follows:

- Mean percent reduction in the sum of scores of erythema, induration/population, lichenification, and scaling from baseline to week 4 (or end of treatment).
- The proportion of subjects who have a pruritus score of 0 at week 4 (or end of treatment)
- The proportion of subjects who have an ISGA of 0 or 1 at week 4 (or end of treatment) and a minimum improvement in the ISGA score of 2 grades from baseline to week 4 (or end of treatment).

The efficacy analysis of the secondary endpoints is summarized in tables 10 and 11. These endpoints support the efficacy of the primary efficacy endpoint (see statistical review for detailed analysis).

Table 10
Mean Percent Reduction in the Sum of Scores for
Clinical Signs from Baseline to Week 4 – ITT Population

	Desonide Foam N = 387	Vehicle N = 194	p-value*
Baseline	9.6 (2.8)^	9.7 (2.7)	<0.0001
Week 4/End of Treatment	4.1 (3.8)	7.8 (4.6)	
Percent Reduction from Baseline	57.2 (37.5)	20.2 (40.5)	
^Numbers in parentheses represent the standard deviation *p-value is derived from a parametric ANOVA model with terms for treatment and pooled sites Source: Biostatistics review, Dr. Clara Kim, page 14			

Table 11
Additional Secondary Endpoints
ITT Population

	Desonide Foam N = 387	Vehicle N = 194	p-value*
Pruritus Score of 0	133 (34%)	19 (10%)	<0.0001
Modified Success [^]	157 (41%)	18 (9%)	<0.0001

*p-values are calculated using CMH statistic stratified by pooled sites;
[^]Modified Success is defined as the proportion of subjects who have an ISGA score of 0 or 1 at week 4 and a minimum improvement in the ISGA score of 2 grades from baseline to week 4.
 Source: Statistical review: Dr. Clara Kim , page 11

During the 3 weeks post follow-up, efficacy of desonide foam decreased. Three weeks post treatment, only 20.7% of patients maintained efficacy, a decrease of 18.6%, from the success achieved after 4 weeks of treatment. There was no evidence of rebound flare in any of the subjects, as no one was worse than baseline (see statistical review for details on efficacy over time, section 3.1.6).

Subgroup Analysis

Subgroup analyses were done for gender, race, and age in the ITT population. Efficacy was not affected by any of these groups. Similar success rates were found for both males and females and across age groups. Hispanic subjects had a slightly higher success rate than other ethnic groups (see table 12).

APPEARS THIS WAY ON ORIGINAL

Table 12
Subgroup Analysis – ITT Population

			Desonide Foam N = 387	Vehicle N = 194
Gender	Male	Total	198	90
		Success (%)	78 (39%)	12 (13%)
	Female	Total	189	104
		Success (%)	74 (39%)	6 (6%)
Race	Caucasian	Total	191	100
		Success (%)	65 (34%)	5 (5%)
	African-American	Total	94	49
		Success (%)	27 (29%)	6 (12%)
	Hispanic	Total	66	32
		Success (%)	(61%)	4 (13%)
	Other	Total	36	13
		Success (%)	20 (56%)	3 (23%)
Age	[12 yrs, 18 yrs)	Total	76	34
		Success (%)	29 (38%)	4 (12%)
	[6 yrs, 12 yrs)	Total	123	53
		Success (%)	48 (39%)	7 (13%)
	[3 yrs, 6 yrs)	Total	86	47
		Success (%)	35 (41%)	3 (6%)
	[3 mos, 3 yrs)	Total	102	60
		Success (%)	40 (39%)	4 (7%)

Source: Study report 53512-des-c-301.pdf, pages 59-61 and Biostatistical Review by Dr. Clara Kim, page 20.

6.1.5 Clinical Microbiology

No clinical micro analysis was done in this NDA.

6.1.6 Efficacy Conclusions

The data demonstrates convincingly, with a highly significant statistical analysis, that desonide cream is efficacious in the treatment of mild to moderate atopic dermatitis. The phase 3 trial undertaken was a robust trial which demonstrated that desonide cream was more efficacious over placebo with a p value <0.0001. The efficacy in the ITT population and in the per protocol population was essentially the same, both with p < 0.0001. The secondary efficacy variables supported the primary efficacy endpoint and the efficacy of the desonide cream across all subgroups, race, gender, and age was comparable.

As atopic dermatitis is primarily a disease of the pediatric population, it was appropriate that the trial was conducted in the pediatric age group. However, it does occur in the adult population and as the pathogenesis of the disease process is the same in both of these populations, the efficacy results can be extrapolated upward to the adult population.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There was one death in the study of a 14 year old female with a history of severe asthma who died of respiratory and cardiac arrest secondary to status asthmaticus on _____
_____ The patient was randomized to study drug on November 4, 2004, which was the date of first application of study drug. At baseline, the patient was assessed as having moderate atopic dermatitis. At the time of enrollment, her medications included Albuterol 2 puffs q day, Singulair 5mg p.o. q day, (both for asthma), and Aleve 2 tabs prn for headaches and menstrual cramps. The patient had been on Albuterol since 1994 and Singulair since February of 2000. The patient met the inclusion criterion in that no systemic steroids had been administered in the previous 4 weeks. The patient did not have a follow-up visit because of the acute event that occurred on day 13 (first follow-up according to the protocol was day 15).

It appears from the CRF that the patient's acute attack may have been precipitated by sleeping with a new puppy. She awakened extremely short of breath. She used albuterol nebulizer for about an hour, and then lost consciousness. Despite intubation, IV epinephrine and atropine, the patient expired.

My review of this case from the CRF concurs with that of the primary investigator. This was not related to study medication. Further, there was not anything in the protocol that would have prohibited the patient from receiving the emergency medical care that was needed.

7.1.2 Other Serious Adverse Events

There were 4 serious adverse events reported in the desonide foam arm and none in the vehicle arm. There was a case of severe cellulitis, a case of severe exacerbation of inflammatory bowel disease, a case of an acute asthma exacerbation, and the case of status asthmaticus that led to death, described in section 7.1.1 above under "Deaths".

The case of cellulitis occurred in a 3 year old female who was admitted to the study with moderate atopic dermatitis involving 97% BSA. The patient received blinded desonide therapy but was admitted into the hospital 11 days after initiation of therapy for a flare of atopic dermatitis and cellulitis. She was discharged 3 days after admission on p.o. Keflex and topical medications to treat her atopic dermatitis.

The case of inflammatory bowel disease occurred in an almost 3 year old male patient who had a history of chronic diarrhea since the age of 6 months. The patient was on blinded study drug from 11/9/04 to 11/14/04. On _____ the patient began having bloody diarrhea and fever. Hospitalization revealed inflammatory bowel disease. One of the drugs that the patient was discharged on was oral prednisone.

The case of asthma exacerbation occurred 6 days after completion of the study. The 10-year-old male subject had to be admitted to the hospital. He was discharged 4 days later, the event completely resolved.

In my opinion, none of these adverse events were directly due to study medication. The case of flare of atopic dermatitis and cellulitis appears due to lack of efficacy of desonide therapy. The other 3 cases are clearly not due to topical desonide therapy.

7.1.3 Dropouts and Other Significant Adverse Events

In the pivotal trial, DES.C.301, there were 33 (9%) discontinuations in the desonide arm and 54 (28%) in the vehicle arm. The reasons for these discontinuations are elicited in the table in section 7.1.3.1 (overall profile of dropouts).

7.1.3.1 Overall profile of dropouts

Table 13 lists the reasons for study discontinuation in the pivotal trial.

Table 13
Reason for Study Discontinuation

	Desonide Foam N=387	Vehicle Foam N=194
Subjects who discontinued	33 (9%)	54 (28%)
Reason for discontinuation		
Adverse Event	2 (5%)	17 (9%)
Non-Compliance	6 (2%)	3(2%)
Disease Progression	3 (1%)	18 (9%)
Subject Request to Withdraw	3 (1%)	12 (6%)
Death	1 (<1%)	0 (0%)
Other	18 (5%)	4 (2%)

Source: Study report 53512-DES.C.301. pdf, pg 41

7.1.3.2 Adverse events associated with dropouts

Adverse events associated with the dropouts in the desonide foam arm included cellulitis, exacerbation of inflammatory bowel disease, and death due to status asthmaticus. The sponsor did not include disease progression as an adverse event but this reviewer would note that that was also a reason for discontinuation in both arms.

Adverse events associated with dropouts in the vehicle arm were primarily application site reactions, specifically, burning at the application site. There was one case each of flare of contact dermatitis and irritant dermatitis. There were 3 cases of hives.

7.1.3.3 Other significant adverse events

There were no other significant adverse events.

7.1.4 Other Search Strategies

7.1.5 Common Adverse Events

The most common adverse events in the safety population were upper respiratory tract infection and application site burning. This was followed by cough, pyrexia, and ear infection. Upper respiratory tract infection and application site burning occurred in more than 5% of subjects in the desonide foam and vehicle groups, therefore the differences between these groups were tested for statistical significance. Statistical significance was not found between the groups for upper respiratory tract infection ($p=0.3491$) but was found for application site burning ($p=0.0038$), with a greater proportion of subjects in the vehicle group experiencing this adverse event.

This suggests that the vehicle is the culprit for the adverse event, and not the chemical moiety. The decrease in incidence in the desonide arm is probably due to the anti-inflammatory properties of the chemical moiety.

7.1.5.1 Eliciting adverse events data in the development program

Subjects were queried at each visit concerning any adverse event experience. These were documented in the CRF. Examination of the skin was to include a documentation of any cutaneous signs of atrophy, striae, telangiectasia, and pigmentation changes at the treated areas.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All reported AEs were coded by MedDRA (Version 7.1) SOC and Preferred Term.

7.1.5.3 Incidence of common adverse events

This section will list the incidence of adverse events as they occurred in the ITT population of the pivotal trial, DES.C.301. The total number of subjects for the safety population was 387 subjects in the desonide foam arm and 194 subjects in the vehicle arm. Again, the most common adverse reaction was upper respiratory tract infection and the second most common adverse event was application site burning. Table 14 lists the incidence of adverse events that occurred in 1% of patients or more of the ITT population.

Table 14
Incidence of Adverse Events in $\geq 1\%$ of Subjects
ITT Population – Study DES.C.301

Preferred Term	Desonide Foam	Vehicle Foam	Total	p-value
Number of Subjects	387	194	581	
Subjects with an adverse experience	143 (37%)	75 (39%)	281 (38%)	
Upper respiratory tract infection	37 (10%)	12 (6%)	49 (8%)	0.1674
Application site burning	11 (3%)	15 (8%)	26 (4%)	0.0072
Cough	14 (4%)	3 (2%)	17 (3%)	
Pyrexia	12 (3%)	4 (2%)	16 (3%)	
Ear infection	8 (2%)	4 (2%)	12 (2%)	
Increased blood pressure	6 (2%)	1 (0%)	7 (1%)	
Nasopharyngitis	6 (2%)	4 (2%)	10 (2%)	
Otitis media	4 (1%)	6 (3%)	10 (2%)	
Vomiting	8 (2%)	1 (1%)	9 (2%)	
Application site reaction	3 (1%)	6 (3%)	9 (2%)	
Headache	7 (2%)	1 (1%)	8 (1%)	
Sinusitis	6 (2%)	2 (1%)	8 (1%)	
Viral infection	6 (2%)	0 (0%)	6 (1%)	
Rhinitis	3 (1%)	3 (2%)	6 (1%)	
Application site atrophy	5 (1%)	0 (0%)	5 (1%)	
Dermatitis contact	3 (1%)	2 (1%)	5 (1%)	
Rhinorrhea	3 (1%)	1 (1%)	4 (1%)	
Gastroenteritis viral	2 (1%)	2 (1%)	4 (1%)	
Application site erythema	1 (0%)	3 (2%)	4 (1%)	
Asthma	3 (1%)	0 (0%)	3 (1%)	
Telangiectasia	3 (1%)	0 (0%)	3 (1%)	
Application site dermatitis	2 (1%)	1 (1%)	3 (1%)	
Diarrhea	2 (1%)	1 (1%)	3 (1%)	
Gastroenteritis	2 (1%)	1 (1%)	3 (1%)	
Hypersensitivity	2 (1%)	1 (1%)	3 (1%)	
Pharyngitis streptococcal	2 (1%)	1 (1%)	3 (1%)	
Pharyngolaryngeal pain	2 (1%)	1 (1%)	3 (1%)	
Application site infection	1 (0%)	2 (1%)	3 (1%)	
Application site pigmentation changes	1 (0%)	2 (1%)	3 (1%)	
Pneumonia	1 (0%)	2 (1%)	3 (1%)	
Irritability	2 (1%)	0 (0%)	2 (0%)	
Pharyngitis	2 (1%)	0 (0%)	2 (0%)	
Sinus congestion	2 (1%)	0 (0%)	2 (0%)	
Teething	2 (1%)	0 (0%)	2 (0%)	
Influenza	1 (0%)	1 (1%)	2 (0%)	
Nasal congestion	1 (0%)	1 (1%)	2 (0%)	
Application site desquamation	0 (0%)	2 (1%)	2 (0%)	
Application site urticaria	0 (0%)	2 (1%)	2 (0%)	
Burns second degree	0 (0%)	2 (1%)	2 (0%)	
Urticaria	0 (0%)	2 (1%)	2 (0%)	

Source: Adapted from NDA 21-978 – Module 5, DES.C.301.pdf table 14.3.3, page 192

There was not a difference in the incidence of adverse events in the above table that could be attributed to desonide cream over vehicle.

7.1.5.4 Common adverse event tables

The following common adverse event table (table 15) is applicable for labeling. It lists the common adverse events found in the pivotal clinical trial.

Table 15
Common Adverse Events Occurring in $\geq 1\%$ of Subjects

Adverse Reaction	— Foam, 0.05% (N=387)	Vehicle Foam (N=194)
System Organ Class		
Cardiac Disorders	7 (2%)	1 (1%)
Increased blood pressure	6 (2%)	1 (1%)
General disorders and administration site conditions	32 (8%)	31 (16%)
Application site burning	11 (3%)	15 (8%)
Application site atrophy	5 (1%)	0 (0%)
Application site dermatitis	2 (1%)	1 (1%)
Application site reaction	3 (1%)	6 (3%)
Infections and infestations	79 (20%)	38 (20%)
Upper respiratory tract infection	37 (10%)	12 (6%)
Ear Infection/ Otitis Media/Otitis Externa	12 (3%)	11 (6%)
Gastroenteritis	2 (1%)	1 (1%)
Gastroenteritis viral	2 (1%)	2 (1%)
Nasopharyngitis	6 (2%)	4 (2%)
Pharyngitis	2 (1%)	0 (0%)
Pharyngitis streptococcal	2 (1%)	1 (1%)
Rhinitis	3 (1%)	3 (2%)
Sinusitis	6 (2%)	2 (1%)
Viral Infection	6 (2%)	0 (0%)
Nervous System Disorder	7 (2%)	1 (1%)
Headache	7 (2%)	1 (1%)
Psychiatric Disorder	3 (1%)	0 (0%)
Irritability	2 (1%)	0 (0%)
Respiratory, Thoracic and Mediastinal Disorders	27 (7%)	7 (4%)
Asthma	3 (1%)	0 (0%)
Cough	14 (4%)	3 (2%)
Pharyngeal pain	2 (1%)	1 (1%)
Rhinorrhea	3 (1%)	1 (1%)
Skin and Subcutaneous Tissue Disorders	10 (3%)	6 (3%)
Dermatitis contact	3 (1%)	2 (1%)
Telangiectasia	3 (1%)	0 (0%)

Source: NDA submission; module 5: Study report DES.C.301, Table 46, pages 94-97

7.1.5.5 Identifying common and drug-related adverse events

The drug related adverse events are listed in table 16. Most of the application site AEs occurred more commonly in the vehicle foam arm and were blunted in the desonide arm with the exception of atrophy. This occurred in 1% of patients and definitely can be attributed to the topical steroid (chemical moiety). This is a known adverse event that can occur with use of topical corticosteroids.

Table 16
Incidence of Treatment-Related Adverse Events
ITT Population – Study DES.C.301

Preferred Term	Desonide Foam	Vehicle Foam	Total
Number of Subjects	387	194	581
Subjects with a treatment related adverse event	25 (6%)	30 (15%)	55 (9%)
General disorders and Administration Site Conditions	22 (6%)	27 (14%)	49 (8%)
Application site atrophy	5 (1%)	0 (0%)	5 (1%)
Application site burning	11 (3%)	15 (8%)	26 (4%)
Application site dermatitis	2 (1%)	1 (1%)	3 (1%)
Application site desquamation	0 (0%)	2 (1%)	2 (0%)
Application site erythema	1 (0%)	3 (2%)	4 (1%)
Application site pigmentation changes	1 (0%)	2 (1%)	3 (1%)
Application site reaction	3 (1%)	6 (3%)	9 (2%)
Application site urticaria	0 (0%)	2 (1%)	2 (0%)
Skin and Subcutaneous Tissue Disorders	1 (0%)	3 (2%)	4 (1%)
Urticaria	0 (0%)	2 (1%)	2 (0%)

Source: Adapted from NDA 21-978, Module 5 Study report DES.C.301, table 48, page 101

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations are needed for evaluation of this topical corticosteroid.

7.1.6 Less Common Adverse Events

The common adverse events in this trial were very small, thus there are no additional adverse events upon which to comment.

7.1.7 Laboratory Findings

Laboratory evaluations were not performed in the pivotal trial for desonide foam. However, the sponsor has cited the desonide cream, 0.05% studies to support the application.

In the Tridesilon (desonide) Cream, 0.05% studies, a subset of subjects in one multicenter, randomized, double-blind study assessed pre- and post-treatment blood chemistries in a total of 204 subjects (84 females and 120 males). These lab tests included all of the following: hemoglobin, hematocrit, fasting blood sugar, alkaline phosphatase, BUN, and SGOT or SGPT, a complete blood count with differential and a complete urinalysis.

There were no appreciable alterations of the laboratory data from baseline with the exception of one subject on desonide cream having a slightly elevated post-treatment blood sugar (112 to 161 mg%), one subject with a history of diabetes who demonstrated an increase in fasting blood sugar from 177 mg% to 294 mg%, and three subjects showing slight elevations in their post-treatment SGOT tests (24 to 55, 59 to 100, and 90 to 121 units). These alterations in lab tests were either equally or more frequently seen in the group treated with the standard reference (fluocinolone acetonide).

Laboratory evaluations of the effect of desonide foam on the HPA axis was evaluated in study DES.C.201. That will be discussed under the special safety studies section (7.1.5).

7.1.7.1 Overview of laboratory testing in the development program

This section is not applicable to this application, as laboratory assessments were drawn from previously approved formulation of desonide, Tridesilon cream, 0.05%.

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

This section is not applicable to this application, as laboratory assessments were drawn from previously approved formulation of desonide, Tridesilon cream, 0.05%.

7.1.7.3 Standard analyses and explorations of laboratory data

This section is not applicable to this application, as laboratory assessments were drawn from previously approved formulation of desonide, Tridesilon cream, 0.05%.

7.1.7.4 Additional analyses and explorations

This section is not applicable to this application, as laboratory assessments were drawn from previously approved formulation of desonide, Tridesilon cream, 0.05%.

7.1.7.5 Special assessments

This section is not applicable to this application, as laboratory assessments were drawn from previously approved formulation of desonide, Tridesilon cream, 0.05%.

7.1.8 Vital Signs

Vital signs (systolic and diastolic blood pressure and pulse) and temperature were measured at the baseline and week 4 (or end of treatment) visits in the pivotal clinical trial. There were no clinically significant differences in the vital sign measurements between the desonide foam and vehicle foam from baseline to week 4 (or end of treatment).

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (systolic and diastolic blood pressure and pulse) and temperature were measured at the Baseline and Week 4 (or end of treatment) visits in the pivotal clinical trial.

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

There was only one pivotal trial, DES.C.301. In this trial, vital signs were taken for all subjects.

7.1.8.3 Standard analyses and explorations of vital signs data

Tables 17-19 provide the summary data of vital signs from the pivotal trial.

**APPEARS THIS WAY
ON ORIGINAL**

Table 17
Summary of Systolic Blood Pressure (mmHg)
ITT Population – DES.C.301

	Desonide Foam	Vehicle Foam
Number of subjects	387	194
Baseline		
n	356	179
mean (std)	97.3 (15.7)	95.9 (14.5)
median	98.0	98.0
min, max	(58, 138)	(60, 130)
Week 4/End of Treatment		
n	334	163
mean (std)	98.3 (14.3)	97.2 (14.8)
median	98.0	98.0
min, max	(60, 145)	(60, 139)

Output: X:\clinical\des301\analysis\statfiles\output\tables\t_time_pt_vit_bpsys_itt.rtf
Source: VIT.SAS7BDAT

Table 18
Summary of Diastolic Blood Pressure (mmHg)
ITT Population – DES.C.301

	Desonide Foam	Vehicle Foam
Number of subjects	387	194
Baseline		
n	354	178
mean (std)	60.9 (12.8)	60.5 (10.8)
median	62.0	60.0
min, max	(0, 86)	(0, 80)
Week 4/End of Treatment		
n	333	163
mean (std)	61.6 (13.0)	62.8 (10.5)
median	62.0	62.0
min, max	(0, 108)	(40, 100)

Output: X:\clinical\des301\analysis\statfiles\output\tables\t_time_pt_vit_bpdia_itt.rtf
Source: VIT.SAS7BDAT

Table 19
Summary of Pulse (bpm)
ITT Population – Study DES.C.301

	Desonide Foam	Vehicle Foam
Number of subjects	387	194
Baseline		
n	364	183
mean (std)	92.5 (18.4)	93.3 (18.9)
median	90.0	91.0
min, max	(30, 152)	(45, 150)
Week 4/End of Treatment		
n	348	168
mean (std)	92.4 (17.6)	93.8 (17.6)
median	90.0	92.0
min, max	(50, 166)	(51, 153)

Output: X:\clinical\des301\analysis\statfiles\output\tables\t_time_pt_vit_pulse_itt.rtf
Source: VIT_SAS7BDAT

7.1.8.4 Additional analyses and explorations

The sponsor was asked to provide more information on the subjects in the trial that had elevated blood pressures, $\geq 140/90$, either systolic or diastolic. The following table was provided:

Subject Demographics, Blood Pressure, and Pulse

Subject	Treatment Group	Age (yr)	Sex	Weight (kg)	Height (cm)	Baseline Systolic	Baseline Diastolic	Baseline Pulse	Week 4/End of Treatment Systolic*	Week 4/End of Treatment Diastolic*	Week 4/End of Treatment Pulse
003-0333	Desonide foam	9	Male	48	140	102	55	85	144	108	86
008-0327	Desonide foam	16	Female	77	168	135	77	86	145	71	79
009-0315	Desonide foam	12	Female	81	140	123	80	72	113	95	74
014-0310	Desonide foam	11	Female	52	127	118	72	71	117	94	93
014-0311	Vehicle foam	11	Male	57	130	129	73	70	122	100	70
014-0321	Desonide foam	12	Female	80	163	129	82	115	134	98	108
015-0310	Desonide foam	11	Female	71	163	109	75	93	109	91	81

* Increases in systolic or diastolic blood pressure relative to Baseline are in bold

Submission dated 7/31/06, page 2.

None of the subjects referenced in the above table had any concomitant medical conditions such as renal disease, thyroid disease, or history of high blood pressure to explain the elevations. All of the subjects were obese for their age and height. Five of the 6 desonide

subjects had a history of asthma or seasonal allergies and 3 were treated with albuterol for asthma during the study. Albuterol can cause elevations in blood pressure. All of the investigators were asked to provide follow-up information for each of these subjects. None of the investigators had reported this as an adverse event, as they did not consider the abnormal blood pressure clinically significant. The following facts were gleaned from each case history:

003-03333 – patient on albuterol and investigator reported problems with blood pressure machine. No follow-up.

008-0327 – patient ran to doctor's office after school.

009-0315 – patient on albuterol and flovent

014-310 – no reason for elevated BP

014-311 – no reason for elevated BP

014-0321 – patient on albuterol

015-0310 – arrived at clinic following gym class where she had been running. Patient was referred to her primary care doctor and at the 3 week post follow-up reported that this slightly elevated diastolic pressure (91 mmHg) was not a concern.

The sponsor performed a Fisher's exact test with a significance level of 0.05 to compare the proportion of subjects with abnormal blood pressure between desonide foam and vehicle treatment groups. They found the p value to be 0.4341, which is not statistically significant.

Reviewer's Comment: After reviewing the case histories, it would be difficult to associate the one time elevation of blood pressure in these pediatric subjects with the use of desonide foam. This is particularly true, given that no statistical significance occurred between the desonide arm and vehicle arm. Unfortunately, none of the blood pressures were repeated during the study by the investigators. Thus, as these values are not normal, in this reviewer's opinion, they would need to be listed as an adverse event.

7.1.9 Electrocardiograms (ECGs)

No ECGs were performed in the pivotal trial.

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

Not applicable as no ECGs were performed in the trials of this NDA.

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

Not applicable as no ECGs were performed in the trials of this NDA.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable as no ECGs were performed in the trials of this NDA.

7.1.9.4 Additional analyses and explorations

Not applicable as no ECGs were performed in the trials of this NDA.

7.1.10 Immunogenicity

See section 7.1.12, "Special Safety Studies" for topical dermal studies performed.

7.1.11 Human Carcinogenicity

There were no formal analyses to explore human carcinogenicity.

7.1.12 Special Safety Studies

Special safety studies were done in this NDA. These included one phase 2 HPA axis suppression study, which is done to ascertain the systemic effect of topical corticosteroids, and 2 phase 1 dermal safety studies, done under exaggerated conditions in an effort to ascertain topical adverse effects of the drug product. These effects include contact irritancy and contact allergy. As this drug product does not absorb in the UV or visible light range, contact photoirritancy and contact photoallergy studies were not conducted.

Phase 2 HPA Axis Suppression Study

DES.C.201

This was a multicenter, open-label study in approximately 60 evaluable adolescent and pediatric subjects with mild to moderate atopic dermatitis to assess the systemic safety of desonide foam via its effect on the HPA axis, as measured by the cosyntropin stimulated change in serum cortisol response. Subjects who met all inclusion and exclusion criteria including a clinical diagnosis of mild to moderate atopic dermatitis based on an Investigator's Static Global Assessment score of 2 or 3, at least 25% treatable body surface area (BSA) involvement and a normal serum cortisol response at screening were eligible to enter the study. The criterion to establish a normal response was a post-injection serum cortisol level greater than 18.0 mcg/dL. Subjects were enrolled into one of the following 4 age cohorts dependent on their age at the Screening Visit: Cohort 1 (≥ 12 years < 18 years); Cohort 2 (≥ 6 years < 12 years); Cohort 3 (≥ 3 years < 6 years) or Cohort 4 (≥ 3 months < 3 years).

Enrollment into each cohort occurred simultaneously and continued until approximately 15 evaluable subjects were enrolled into each cohort at which time enrollment to that cohort was closed. Investigators received written notification when enrollment in a given cohort was closed. The study consisted of 4 weeks of treatment with visits at screening, baseline, weeks 1, 2, 4 (or end of treatment) and a conditional visit scheduled 4 weeks post-treatment as needed for laboratory testing or adverse experience evaluations. The maximum time a subject could be in

the study was 8 weeks if they were required to return for a conditional visit. All treatments were administered twice daily (morning and evening) for 4 weeks to a minimum 25% BSA of disease involved skin. All areas affected with atopic dermatitis were treated with the study drug, including the face, scalp, and intertriginous areas. In the event of improving or clearing of disease, the subject was to continue to apply study drug to at least 25% BSA.

The cosyntropin stimulation test was performed at approximately 8:00 am on the day of screening, visit 4, and the conditional visit (if required). Patients could receive either an IM dose or IV dose of cosyntropin. Those subjects aged 3 years and older received 0.25 mg of cosyntropin and those 2 years old or less received 0.125 mg of cosyntropin. Instructions for administration were to follow those in the package insert for cosyntropin.

Results

The study enrolled 81 subjects by age cohort: in Cohort 1 nineteen subjects were enrolled; in Cohort 2 sixteen subjects were enrolled; in Cohort 3 twenty-two subjects were enrolled; and in Cohort 4 twenty-four patients were enrolled. Additional subjects were enrolled to ensure 15 evaluable subjects in each cohort. Table 20 shows the baseline demographics for each cohort.

Table 20
Baseline Demographics – Study DES.C.201

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
Number of subjects	19	16	22	24	81
Age (years)					
N	19	16	22	24	81
Mean (std)	14.3 (1.6)	8.8 (1.8)	4.4 (0.9)	1.5 (0.6)	6.7 (5.1)
Median	13.8	8.7	4.4	1.5	5.1
Min, max	(12.1, 16.9)	(6.5, 11.4)	(3.0, 5.6)	(0.6, 2.8)	(0.6, 16.9)
Sex					
Male	9 (47%)	5 (31%)	6 (27%)	10 (42%)	30 (37%)
Female	10 (53%)	11 (69%)	16 (73%)	14 (58%)	51 (63%)
Race					
Asian	1 (5%)	3 (19%)	0 (0%)	1 (4%)	5 (6%)
African American	4 (21%)	4 (25%)	9 (41%)	12 (50%)	29 (36%)
Caucasian	10 (53%)	6 (38%)	10 (45%)	9 (38%)	35 (43%)
Hispanic	2 (11%)	3 (19%)	3 (14%)	2 (8%)	10 (12%)
Other	2 (11%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)

Source: NDA submission; Module 5; adapted from table 7, page 29; study DES.C.201

Table 21 displays the ISGA and extent of atopic dermatitis for subjects enrolled in the study. The majority of patients in each cohort had a severity score of 3 (moderate) atopic dermatitis at screening and all subjects had a BSA of at least 25% with the highest extent of involvement being 96% in cohort 1 (ages 12-17 years).

Table 21
ISGA and Extent of Atopic Dermatitis (BSA%)
Study DES.C.201

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	TOTAL
Number of Subjects	19	16	22	24	81
Investigator's Static Assessment Score (ISGA) at Screening					
2	8 (42%)	3 (19%)	4 (18%)	6 (25%)	21 (26%)
3	11 (58%)	13 (81%)	18 (82%)	18 (75%)	60 (74%)
Extent of Atopic Dermatitis (%BSA) at Screening					
n	19	16	22	24	81
mean(std)	33.7(16.4)	34.3(14.1)	31.4(6.8)	46.3(19.6)	36.9(16.1)
median	27.0	28.5	28.0	40.0	30.0
min, max	(25.0,96.0)	(25.0,75.0)	(25.0,46.0)	(25.0,80.0)	(25.0,96.0)
Extent of Atopic Dermatitis (%BSA) at Baseline					
n	19	16	22	24	81
mean(std)	33.8(16.5)	35.5(15.5)	34.0(8.2)	48.2(21.7)	38.5(17.3)
median	28.0	28.5	33.5	38.5	30.0
min, max	(25.0,96.0)	(25.0,75.0)	(25.0,60.0)	(25.0,81.0)	(25.0,96.0)

Source: NDA Submission: Module 5, table 8, page 30

In this trial, there were 75 evaluable patients, defined as those who completed the study. Table 22 denotes the reasons for those subjects who discontinued. The most common reason for discontinuation was "other" and these subjects were lost to follow-up.

**APPEARS THIS WAY
ON ORIGINAL**

Table 22
Reason for Study Drug Discontinuation
Study DES.C.201

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
Number of Subjects	19 (100%)	16 (100%)	22 (100%)	24 (100%)	81 (100%)
Subjects who Completed Study	18 (95%)	16 (100%)	20 (91%)	22 (92%)	76 (94%)
Subjects who Early Discontinued	1 (5%)	0 (0%)	2 (9%)	2 (8%)	5 (6%)
Reasons for Early Discontinuation					
Adverse Experience	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Subject Non-Compliance	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Disease Progression	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (1%)
Subject Request to Withdraw	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subject Died	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other Reason	0 (0%)	0 (0%)	2 (9%)	1 (4%)	3 (4%)

Source: NDA submission: Module 5, table 5, page 27.

HPA Axis Stimulation Results

The proportion of subjects determined to have demonstrated HPA axis suppression was 4% (3/75) of subjects overall: 5% (1/18) of subjects in Cohort 1 ($\geq 12 < 18$ years), 5% (1/20) of subjects in Cohort 3 ($\geq 3 < 6$ years), and 5% (1/22) of subjects in Cohort 4 (≥ 3 months < 3 years). No subjects in Cohort 2 ($>6 < 12$ years) demonstrated any evidence of HPA axis suppression (see table 23).

Table 23
Incidence of (Reversible) HPA Axis Suppression* by Cohort

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
Number of subjects	19	16	22	24	81
Week 4/End of Treatment					
N	19	16	20	20	75
HPA Axis Suppression	1 (5%)	0	1 (5%)	1 (5%)	3 (4%)
Conditional Visit					
N	1	0	1	1	3
HPA Axis Suppression	0	N/A	0	0	0

*HPA axis suppression defined as a post-injection serum cortisol level of less than or equal to 18µg/dl.

Source: Table 2, biopharmaceutics review, page 16

In Cohort 1, subject 155-0013 was determined to have demonstrated HPA axis suppression at Week 4 which was reversed at the conditional visit. The post-stimulation result at week 4 for subject 155-0013 was 18.0 µg/dL. At the Conditional Visit, the pre-stimulation level was 14.6 µg/dL and the post-stimulation level was 20.3 µg/dL. The subject was an otherwise healthy, 16-year-old female who weighed 122.8 lbs. Her initial % BSA was 28%.

In Cohort 3, subject 176-0009 was determined to have demonstrated HPA axis suppression at Week 4 which was reversed at the conditional visit. The subject was an otherwise healthy, 4-year-old male who weighed 40.0 lbs. The post-stimulation value at week 4 for subject 176-0009 was 16.2 µg/dL and the post-reading was 16.1 µg/dL. At the Conditional Visit, the pre-stimulation level was 24.4 µg/dL and the post-stimulation level was 40.6 µg/dL. His initial BSA was 34%.

In Cohort 4, subject 176-0010 was determined to have demonstrated HPA axis suppression at Week 4 which was reversed at the conditional visit. The subject was an otherwise healthy, 2 year old male who weighed 31.0 lbs. The post-stimulation result at week 4 for subject 176-0010 was 17.5 µg/dL. At the Conditional Visit, the pre-stimulation level was 8.9 µg/dL and the post-stimulation level was 30.8 µg/dL. The subject suffered from occasional fevers during the study which might have been a secondary cause of the mild suppression. His initial BSA was 30%.

***Reviewer's Comment:** This study demonstrated that desonide foam, 0.05% does have the ability to induce HPA axis suppression in a small percentage of susceptible patients. The majority of subjects (72/75) or 96% of subjects did not experience HPA axis suppression, even with a BSA involvement of at least 25%. In this reviewer's opinion, one can only report that reversible HPA axis suppression can occur after 4 weeks of use of desonide foam and therefore, treatment should not exceed 4 consecutive weeks.*

Phase 1 Dermal Safety Studies

DES.C.103 – A Repeat Insult Patch Test Study to Determine the Potential of Desonide Foam, 0.05%, Desonide Vehicle Foam, and Ethanol Free Clobetasol Propionate Vehicle Foam to Induce Allergic Contact Sensitization

This was a single-center, within subject, randomized, evaluator blind trial to determine the safety in terms of contact allergy potential of the intended to-be-marketed formulation of desonide foam, 0.05% in healthy volunteers. The test products included desonide foam, 0.05%, its vehicle spray and EF clobetasol vehicle foam. The study initiation date was April 11, 2005 and the study completion date was June 18, 2005.

A total of 240 healthy adult volunteer subjects were enrolled into the study so that 200 evaluable subjects completed the study. There were three phases to the study: Induction, Rest, and Challenge. At the baseline visit, subjects provided written informed consent prior to any study procedures and signed a Health Information Portability and Accountability Act (HIPAA) form. Inclusion and exclusion criteria were reviewed; demographics, medical history, and

concomitant medications were recorded; and a urine pregnancy test was performed; patch sites were identified and marked on a subject's back and patches prepared with the test articles were applied.

During the Induction Phase test articles were applied under separate occlusive patches on the backs of subjects 3 times per week for 3 weeks. Each application was observed 48 hours (72 hours if scheduled reading is on a weekend day) later for signs of irritation or inflammation. All skin evaluations during the Induction Phase were conducted using the Grading Scale for Irritation (see table 24). On Visit 10 (Day 22) patches were removed and the skin was evaluated for skin reaction.

Table 24
Grading Scale for Irritation

Score		Definition
0	=	No visible reaction
1	=	Minimal erythema; no sign of edema or papular response
2	=	Definite erythema with no significant edema; and/or minimal papular response
3	=	Moderate erythema with no significant edema or epidermal damage; and/or definite papular response (covering less than 50% of the site)
4	=	Moderate erythema with edema; and/or papular response covering more than 50% of the site; and/or epidermal damage
5	=	Severe erythema, edema, epidermal damage, and/or papulovesicular response

Notation		Definition
X	=	Subject absent
PD	=	Patch dislodged
NA	=	Patch not applied
NP	=	No patch due to limiting irritation
NOG	=	No ninth grade in induction (i.e., missing 1 reading in the induction period)

Source: NDA 21-978, Module 5, table 3, page 21

Following the Induction Phase there was a rest period of approximately 2 weeks during which time no patches were applied. After the rest period, separate occlusive patches were applied to sites on previously unpatched areas of the backs of subjects for 48 hours. The Challenge Phase began on Visit 11 (Day 36) with the application of patches treated with test articles on previously unpatched areas of the subjects' backs. Forty-eight hours later, Visit 12 (Day 38) the patches were removed. The test sites were then evaluated for any signs of skin sensitization using the Grading Scale for Contact Sensitization immediately following patch removal and at 24, 48, and 72 hours following patch removal. A subject would be re-challenged

if any signs suggestive of contact sensitization (erythema and/or papulation) in the opinion of the investigator was observed at any of the evaluations following the removal of the challenge patch within 30 minutes of removal, and at 24, 48, and 72 hours following patch removal. Re-challenge was conducted at naïve test sites at least 2 weeks after the initial challenge phase. Patches applied at re-challenge were applied under both occlusive and semi-occlusive conditions. Table 25 denotes the grading scale for contact sensitization.

Table 25
Grading Scale for Contact Sensitization

Response	Symbol
No reaction	-
Minimal or doubtful response, slightly different from surrounding normal skin	?
Definite erythema: no edema	+
Definite erythema and edema	++
Definite erythema, edema, and vesiculation	+++

Response/Comment	Notation
Marked/severe erythema	E
Spreading of reaction beyond patch study site (ie, reaction where study material was not in contact with the skin).	S
Burning or stinging sensation	B
Papular response > 50%	P
Papulovesicular response > 50%	PV
Damage to epidermis: oozing, crusting and/or superficial erosions	D
Itching	I
Subject absent	X

Source: NDA 21-978, Module 5, table 4, page 22

A urine pregnancy test was conducted for all females of child bearing potential at the end of the study. Subjects were queried for concomitant medication use, adverse experiences and compliance with study requirements at all visits.

Results

A total of 240 subjects were enrolled and 206 subjects completed all phases of the study. See table 26 for disposition of subjects.

Table 26
Disposition of Subjects
Study DES.C.103

Number of subjects enrolled	240
Number of subjects treated	240
Number of subjects discontinued	34
Adverse event	2
Non-compliance	14
Voluntarily withdrew	16
Other (Lost to follow-up 1) (not enough rest 1)	2
Number of subjects completed	206

Source: Section 14.1, Table 1

Subject demographics are depicted in table 27

Table 27
Subject Demographics – Study DES.C.301

Age	Mean (SD)	48.2 (14.8)
	Median	48.2
	Range	18.1–75.1
Sex N (%)	Male	45 (18.8)
	Female	195 (81.3)
Race N (%)	Asian	5 (2.1)
	Black	12 (5.0)
	Caucasian	178 (74.2)
	Hispanic	45 (18.8)

Source: Section 14.1, Table 2

Dermal Irritation

There were 5 test articles for the cumulative irritancy portion of the trial. These included desonide foam, desonide foam vehicle, EF clobetasol vehicle foam, 0.1 sodium lauryl sulfate (positive control), and distilled water (negative control). The cumulative irritancy index (CII) ranged from 0.02 to 1.31 for the test articles as depicted in table 28.

**Table 28
Summary of Mean Irritation Scores**

Product tested	Mean CII score (±SD)
Desonide Foam	0.16 (0.36)
Desonide Vehicle Foam	0.33 (0.57)
EF Clobetasol Vehicle Foam	0.26 (0.45)
0.1% SLS (positive control)	1.31 (0.73)
Distilled water (negative control)	0.02 (0.22)
P-values	
Desonide Foam vs. 0.1% SLS	<.001
Desonide Foam vs distilled water	0.002
Desonide Vehicle Foam vs. 0.1% SLS	<.001
Desonide Vehicle Foam vs. distilled water	<.001
EF Clobetasol Vehicle Foam vs. 0.1% SLS	<.001
EF Clobetasol Vehicle Foam vs. distilled water	<.001
0.1% SLS vs. distilled water	<.001

Source: Section 14.3.1, Table 3.3

The test products were significantly less irritating than the positive control (p<0.001) and more irritating than the negative control (p=0.002).

Reviewer's Comment: Desonide vehicle foam has a mean CII that is more irritating than desonide foam, (0.33 vs. 0.33) which explains the clinical safety results where patients experienced more application site reactions with the foam vehicle than with the drug product.

Dermal Sensitization

Challenge Phase

Two subjects (Subject No. 069 and Subject 140) had reactions to desonide vehicle foam and EF clobetasol vehicle foam during the Challenge Phase that required a re-challenge. Subject 069 experienced a decrease in reaction scores for the desonide vehicle foam and EF clobetasol vehicle foam from ++ (definite erythema and edema) at the 30-minute challenge

evaluation to a score of + (definite erythema; no edema) over the 24- and 48-hour evaluations, with a final score of “?” (minimal or doubtful response) by the time of the 72-hour evaluation for both products.

Subject 140 had a reaction score of + in response to each of the 2 vehicle products at the 30- minute challenge observation, which increased to ++ by the time of the 24-hour evaluation and then returned and remained at + for the 48- and 72-hour evaluations.

Re-challenge Phase

Both subjects were re-challenged to desonide vehicle foam and EF clobetasol vehicle foam under occlusive and semi-occlusive patch conditions. Subject 069, by the time of the 72-hour evaluation, regardless of the patch condition, exhibited a response to each of the 2 treatments of “?” suggesting a minimal or doubtful response. The rechallenge response for this subject was not indicative of sensitization. Subject 140 responded to both treatments under occlusive and semi-occlusive conditions with an initial response score of ++ (definite erythema and edema), which rapidly declined over time. By the time of the 72-hour evaluation, the response to each of the 2 treatments under occlusive conditions had decreased to + (definite erythema, no edema). The responses under semiocclusive conditions at 72 hours were “?” (minimal or doubtful) for the Desonide Vehicle Foam and + (erythema, no edema) for the EF Clobetasol Vehicle.

Although the two subjects exhibited early responses that were suggestive of a sensitization reaction, the rapid decrease in the degree of response over time is considered to be suggestive of irritant contact dermatitis rather than sensitization.

Reviewer’s Comment: Agree with the above analysis. Desonide foam and its vehicle do not appear to be sensitizing agents.

Six subjects experienced a total of 7 AEs during the trial. These were dizziness and nausea, mild sinus infection, cyst removal, mild headache, moderate headache, and a mild stroke. None of these AEs were related to study medication.

DES.C.104 – A single-center, evaluator-blinded study to evaluate the potential for Desonide Foam, 0.05% (Desonide Foam), Desonide Vehicle Foam, and Ethanol Free Clobetasol Propionate Vehicle Foam, (EF Clobetasol Vehicle Foam) to induce cutaneous irritation using a cumulative irritation assay in healthy volunteers.

This was a single-center, within subject, randomized, positive and vehicle controlled, evaluator blind trial to test the cumulative irritancy potential of desonide foam, 0.05% in healthy volunteers. The test products included desonide foam, 0.05%, its vehicle foam, EF clobetasol vehicle foam, a positive control, sodium lauryl sulfate, 0.5% and distilled water (negative control). The study testing began on May 2, 2005 and ended May 23, 2005.

A total of 40 healthy adult volunteer subjects were enrolled into the study in order that at least 30 evaluable subjects would complete the study. Approximately 0.2 mL of the test article was applied to each patch. Patches were prepared at least 5 minutes and no longer than 60

minutes before application to study subjects. After 23 hours \pm 1 hour, the patches were removed, and the test sites evaluated based on a 6-point integer scale (range: 0 = no visible reaction to 5 = severe erythema, edema, epidermal damage, and/or papulovesicular response). This process was repeated daily over a 3 week period for a total of 21 applications. Each application was observed daily for signs of irritation or inflammation. If a score of 4 or 5 was noted by the assessor for a test site, the patch at that site was discontinued permanently. Safety was assessed from subject reported and investigator observed adverse experiences.

The following grading system was used for irritation:

- 0 = No visible reaction
- 1 = Minimal erythema; no sign of edema or popular response
- 2 = Definite erythema with no significant edema; and/or minimal popular response
- 3 = Moderate erythema with no significant edema or epidermal damage; and/or definite popular response (covering less than 50% of the site)
- 4 = Moderate erythema with edema and/or popular response covering more than 50% of the site; and/or epidermal damage
- 5 = Severe erythema, edema, epidermal damage, and/or papulovesicular response

Results

A total of 40 subjects enrolled and 34 completed the study. Table 29 describes the subject disposition.

Table 29
Subject Enrollment and Disposition

Number of subjects enrolled	40
Number of subjects treated	40
Number of subjects discontinued	6
Adverse event	1
Non-compliance	3
Voluntarily withdrew	2
Number of subjects completed	34

Source: Section 14.1, Data Listing 1

The study population was comprised of 31 females (78%) and 9 (23%) males who ranged in aged from 19 -71 years old. The patient demographics are presented in table 30.

Table 30
Subject Demographics

Age	Mean (SD)	41.9 (13.9)
	Median	40.8
	Range	19.0–71.2
Sex N (%)	Male	9 (22.5)
	Female	31 (77.5)
Race N (%)	Caucasian	26 (65.0)
	Hispanic	14 (35.0)

Source: Section 14.1, Table 2

Results

The statistical analysis showed that the mean cumulative irritation scores ranged from 0.03 to 1.92 for the 5 test articles. The lowest mean score was in sites treated with the negative control (distilled water) and the highest score was in sites treated SLS (positive control).

Desonide foam, desonide vehicle foam, and EF clobetasol vehicle foam were similarly irritating with mean scores of 0.08, 0.18, and 0.21, respectively. Irritation scores for each of the three test articles were also not significantly different from the score for the negative control, and they were significantly less irritating than the score for the positive control ($p < 0.001$). Table 31 shows those results.

Table 31
Mean Cumulative Irritation Scores – DES.C.104

Product Tested (n = 34)	Mean Score (\pm SD)*	p Value vs			
		B	C	D	E
Desonide Foam (A)	0.08 (0.18)	0.534	0.202	<.001	0.667
Desonide Vehicle Foam (B)	0.18 (0.25)		0.754	<.001	0.163
EF Clobetasol Vehicle (C)	0.21 (0.28)			<.001	0.089
SLS 0.1% (D)	1.92 (0.98)				.001
Distilled Water (E)	0.03 (0.09)				

Source: Section 14.3.1, Table 3.2

The results based on the total cumulative scores for desonide foam, desonide vehicle foam, and EF clobetasol vehicle foam were similar with mean scores of 1.48, 2.93, and 3.25, respectively (see table 32). Total cumulative irritation scores for each of the 3 test articles were also not significantly different from the score for the negative control (distilled water) and they were significantly less irritating than the score for the positive control SLS ($p < 0.001$).

Table 32
Cumulative Irritation Scores

Product Tested	Mean Score (\pm SD)*	p Value vs			
		B	C	D	E
Desonide Foam (A)	1.48 (3.68)	0.503	0.412	< .001	0.694
Desonide Vehicle Foam (B)	2.93 (3.85)		0.880	< .001	0.288
EF Clobetasol Vehicle (C)	3.25 (3.33)			< .001	0.226
SLS 0.1% (D)	39.7 (21.1)				< .001
Distilled Water (E)	0.63 (1.90)				

Source: Section 14.3.1, Table 3.3.

Reviewer's Comment: *This trial corroborates the fact that the vehicle foam of desonide is more irritating than the drug product itself; thus, the results of the clinical trial. However, this has little clinical significance, as the active chemical moiety is an anti-inflammatory agent, and mitigates this effect of the foam. This is clearly demonstrated in the clinical trials where application site reaction in the desonide foam arm is minimal.*

One subject experienced a single AE during the study. The subject experienced a mild tape reaction, which was considered as probably not related to treatment. The subject discontinued treatment on Day 11 and was withdrawn from study on Day 17.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No instances of drug abuse were reported in subjects treated in any of the Connetics studies or in the studies conducted by _____ . None of the topical drugs applied in the studies have any known potential for drug abuse.

No instances of withdrawal or rebound were reported in subjects treated in any of the Connetics studies or in the studies conducted by _____ . None of the topical drugs applied in the studies have any known potential for withdrawal or rebound.

7.1.14 Human Reproduction and Pregnancy Data

Because desonide foam carries a Pregnancy Category C rating, pregnant or breastfeeding females were excluded from participating in the Connetics-sponsored studies. Females of childbearing potential were required to use medically acceptable methods of birth control throughout their participation in the studies. Urine pregnancy tests were conducted at baseline and week 4 (end of treatment) for female participants of childbearing potential. One healthy volunteer became pregnant at the end of the skin sensitization study, DES.C.103. Multiple attempts were made to contact this subject to determine the outcome of the pregnancy, but were not successful.

7.1.15 Assessment of Effect on Growth

There were no studies done to assess the effect of desonide foam on growth.

7.1.16 Overdose Experience

There are not any reports of overdose with desonide foam.

7.1.17 Postmarketing Experience

Desonide foam has not been marketed; therefore there are no post-marketing pharmacovigilance data available.

Limited post-marketing information is available from [redacted]. Annual updates to the NDA for Tridesilon Cream (NDA 17-010) were made available to Connetics for 1973, 1975–1978, and 2003 and for Tridesilon Ointment (NDA 17-426) for 1977–1980, 1982, and 2003. Based on reports from physicians and pharmacists, the package insert for both the Cream and the Ointment has been updated to include the following AEs in decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria. All of these AEs have been reported infrequently. This list of AEs is complete as of the package inserts included in the 11/2002–10/2003 annual report.

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 768 subjects were evaluated in the clinical program. These subjects were derived from studies DES.C.201 (HPA Axis Suppression Study), DES.C.202, a phase 2 study, and DES.C.301 (pivotal phase 3 study). The phase 2 and 3 studies were randomized double-blind studies with desonide or vehicle foam administered twice daily for 4 weeks. The HPA axis study was open-label and used desonide foam twice daily for 4 weeks in all subjects. Treatment was applied to all areas of disease even if lesions had cleared. See sections 4.1 and 4.2.

7.2.1.2 Demographics

A total of 768 subjects were included in the summary of clinical safety. A total of 540 subjects were randomized to receive desonide foam and 228 subjects to receive vehicle foam.

Subjects in the safety population were grouped into 4 age cohorts: 161 (21%) were enrolled in the 12 to < 18 year old age cohort, 219 (29%) were enrolled in the 6 to < 12 years cohort, 179 (23%) were enrolled in the 3 to < 6 years cohort and 209 (27%) were enrolled in the 3 months to < 3 years cohort. Approximately 48% of these subjects were males (370/768) and 52% were female (398/768). Fifty percent (380/768) of the subjects were Caucasian, 26% (203/768) were African-American, 15% (118/768) were Hispanic, and 9% (67/768) were reported as being "Other." The demographic characteristics are presented by treatment group in table 33.

Subjects who were enrolled in the HPA Axis suppression study had, by design, a larger percent body surface area involved with atopic dermatitis (average % BSA was 38.5%) than the Phase 3 (mean of 21.3% and 19.8% in the desonide foam and vehicle foam groups, respectively) or the Phase 2 (mean of 18.0% and 13.6% in the desonide foam and vehicle foam groups, respectively) studies. Otherwise, there were no remarkable differences between studies in the baseline disease characteristics.

Table 33
Demographics – Desonide Foam Studies

	Desonide Foam	Vehicle Foam
Number of Subjects	540	228
Age		
mean(std)	6.6(4.9)	6.5(4.9)
median	6.0	5.0
min, max	(0.3,17.0)	(0.4,17.0)
Age Category		
12 < 18 Years	117 (22%)	44 (19%)
6 < 12 Years	155 (29%)	64 (28%)
3 < 6 Years	126 (23%)	53 (23%)
3 Months < 3 Years	142 (26%)	67 (29%)
Sex		
Male	263 (49%)	107 (47%)
Female	277 (51%)	121 (53%)
Race		
Caucasian	263 (49%)	117 (51%)
African-American	143 (26%)	60 (26%)
Hispanic	83 (15%)	35 (15%)
Other	51 (9%)	16 (7%)

Source: NDA Submission – Module 2, Clinical Summary, section 2.7.4, page 12, table 2.7.4-C.

7.2.1.3 Extent of exposure (dose/duration)

In the studies using desonide foam, a total of 540 subjects received at least one dose of desonide foam. Table 34 summarizes the extent of exposure to each of the study drugs for the subjects in the safety population for these studies. Study drug usage was determined by weighing the containers prior to dispensing and upon return to the study site.

Table 34
Study Drug Exposure – Desonide Foam Studies
(DES.C.201, DES.C.202, DES.C.301)

	Desonide Foam	Vehicle Foam
Number of Subjects	540	228
Days on Study Drug		
n	525	225
mean(std)	29.1(4.2)	25.0(8.9)
median	29.0	29.0
min, max	(2,55)	(2,55)
Total Study Drug Usage(g)		
n	523	221
mean(std)	142.08(93.77)	121.74(95.94)
median	120.83	97.60
min, max	(3.3,495.6)	(0.5,529.3)
Daily Drug Usage (g/day)		
n	523	221
mean(std)	4.92(3.21)	4.99(3.57)
median	4.20	4.00
min, max	(0.2,17.1)	(0.3,19.2)

Note: Study drug usage is defined as total container weight dispensed minus total container weight returned.
Mean drug usage is defined as the average amount of drug subjects used per study day.

Source: NDA Submission: Clinical Summary of Safety, module 2, section 2.7.4, page 10 table 2.7.4-B.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Secondary clinical data sources were summaries provided by the sponsor of the desonide cream and ointment studies. At the time that these studies were done, only “side effects” of the drug were recorded on the CRFs. These “side effects” were assumed to be treatment related AEs. Overall, approximately 3% (27/1074) of the subjects treated with desonide cream or ointment had side effects (AEs) reported. Application site reaction was the only significant “side effect” recorded for these formulations of desonide, occurring in 1% of subjects.

7.2.2.1 Other studies

See section 7.2.2.

7.2.2.2 Postmarketing experience

This drug product has not been approved in any jurisdiction; therefore there are no post-marketing pharmacovigilance data available.

Limited post-marketing information is available from [redacted]. Annual updates to the NDA for Tridesilon Cream (NDA 17-010) were made available to Connetics for 1973, 1975– 1978, and 2003 and for Tridesilon Ointment (NDA 17-426) for 1977–1980, 1982, and 2003. Based on reports from physicians and pharmacists, the package insert for both the Cream and the ointment has been updated to include the following AEs in decreasing order of occurrence: burning, [redacted], irritation, [redacted], folliculitis, [redacted], acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, [redacted], secondary infection, [redacted] striae, miliaria. All of these AEs have been reported infrequently. This list of AEs is complete as of the package inserts included in the 11/2002–10/2003 annual report.

7.2.2.3 Literature

Connetics conducted a thorough review of publicly available literature on the use of desonide 0.05% to meet the FDA's request for worldwide post-marketing safety data on all desonide products at the Pre-NDA meeting held on September 12, 2005. The focus of this review was on articles that contained information on the safety of the use of desonide (cream, ointment, or lotion).

The seminal article on the post-marketing safety for desonide was prepared Vicky Kwan Wong et al. and provided information on the safety record of desonide cream, lotion, and ointment as determined from AE reports and published literature. Adverse event information was collected via a global post-marketing surveillance program that was initiated by Galderma in 1992 and collected information for over 9 years. The program, in accordance with the International Conference on Harmonization E2 guidelines, collected safety-related information using a database which enabled any safety concerns to be reported. The two most important sources for this database were direct reporting by consumers and health care professionals. In addition, published reports of randomized controlled trials of desonide in comparison with hydrocortisone were reviewed. Sixty-two reports were collected; most were from consumers and not medically substantiated.

There were no serious reactions that were reported as being directly attributable to desonide treatment. One SAE was reported by a 41-year-old patient who had applied desonide ointment onto streaked skin with open, bleeding lesions, inflammation and pruritus that followed use of a "chemical peel." She developed a rash under her jaw line and experienced itching and burning sensation on her face for several days. The event was considered unlikely to be related to desonide ointment. The second event concerned a 6-month-old child who was hospitalized with bulging fontanel and a mild fever; she had been prescribed desonide ointment, 0.05% for atopic dermatitis 10 weeks previously and was also receiving the antihistamine hydroxyzine. Desonide therapy was temporarily interrupted and the hydroxyzine was discontinued. The patient made an uneventful recovery and the AE was considered unlikely to be related to the use of desonide.

The majority (66%) of the 62 AEs that were reported were local reactions of a type expected with corticosteroid topical treatment and consisted of skin irritation, local allergic reaction, and eye irritation; medical confirmation was available for 40% of these. Other AEs

reported included hypochromia and cataracts. There was no statement regarding relationship to desonide therapy for these AEs. The frequency of AEs by formulation type is listed in table 35.

Table 35
Number of Patients (N=62) Reporting Adverse Events
By Formulation and Type of Reaction

Adverse Event	Formulation			Total
	Cream	Ointment	Lotion	
Expected local reactions				
Skin irritation	10	8	11	29
Allergic reaction (local)	6	2	1	9
Eye irritation	2	0	1	3
Exacerbation of disease or lack of effect				
Worsening of disease	1	0	4	5
Lack of effect	1	2	5	8
Unexpected or other	4	1	3	8
Total number of Events	24	13	25	62

Source: NDA submission 21-978; Module 2, Summary of Clinical Safety, table 2.7.4-N, page 38

7.2.3 Adequacy of Overall Clinical Experience

A total of 540 patients were exposed to desonide foam in the clinical trials who had mild to moderate atopic dermatitis. Given that there is a wealth of safety data from decades of use of desonide in various formulations, it was felt that these numbers would be adequate to ascertain any safety issues that may be unique to the vehicle in this new formulation.

The dose and duration of exposure was adequate to assess the safety for intended use and the design of the trials was adequate to answer critical safety questions.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Preclinical animal studies were adequate.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was not performed in this NDA, as laboratory assessments were drawn from a previously approved formulation of desonide, Tridesilon cream, 0.05% (see section 7.1.7).

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See clinical pharmacology review.

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

There are no recommendations for further study for this drug product.

7.2.8 Assessment of Quality and Completeness of Data

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

7.2.9 Additional Submissions, Including Safety Update

The 120 day safety update was submitted on March 15, 2006. There was no new safety information to report concerning any subjects in the clinical trials or new post-marketing data of the other formulations of topical desonide.

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

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

The incidence of all AEs in the desonide foam trials are listed in descending order of frequency for the safety population in table 36.

Table 36
Adverse Experience Reported in $\geq 2\%$ of Subjects
In Descending Order of Frequency – ITT Population

Preferred Term	Desonide Foam	Vehicle Foam	Total	p-value ^a
Number of Subjects	540	228	768	
Subjects with an adverse experience	208(39%)	84(37%)	292(38%)	
Upper respiratory tract infection	41(8%)	13(6%)	54(7%)	0.3491
Application site burning	14(3%)	16(7%)	30(4%)	0.0038
Cough	21(4%)	4(2%)	25(3%)	
Pyrexia	18(3%)	4(2%)	22(3%)	
Ear infection	16(3%)	5(2%)	21(3%)	
Nasopharyngitis	12(2%)	4(2%)	16(2%)	
Headache	11(2%)	1(0%)	12(2%)	

^a P-values are based on comparing Desonide Foam versus Vehicle Foam based on the Chi-Square test ($\alpha = 0.10$) and are calculated when the incidence is at least five percent in any one treatment group.

Source: Sponsor's NDA submission – Module 2, Clinical Summary of Safety, section 2.7.4, table 2.7.4-E, page 15

Reviewer's Comment: Table 36 should also have the addition of increased blood pressure which occurred in 6 (2%) of subjects in the desonide foam arm and 1 (0%) of subjects in the vehicle foam arm.

The pooled data from all the studies does not reveal any additional adverse events from the data in the pivotal trial alone. Furthermore, the order of frequency and statistical significance do not change for these events (see section 7.1.5.3).

The incidence of treatment related AEs for all of the desonide foam trials are listed in table 37 below.

Table 37
Incidence of Treatment-Related Adverse Experiences
Desonide Foam Studies – ITT Population

SYSTEM ORGAN CLASS Preferred Term	Desonide Foam	Vehicle Foam	Total	p-value ^a
Number of Subjects	540	228	768	
Subjects with an Treatment-Related adverse experience	33(6%)	33(14%)	66(9%)	0.0002
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	30(6%)	30(13%)	60(8%)	0.0003
Application site atrophy	5(1%)	0(0%)	5(1%)	
Application site burning	14(3%)	16(7%)	30(4%)	0.0038
Application site dermatitis	2(0%)	1(0%)	3(0%)	
Application site desquamation	0(0%)	2(1%)	2(0%)	
Application site dryness	3(1%)	0(0%)	3(0%)	
Application site erythema	4(1%)	4(2%)	8(1%)	
Application site pigmentation changes	1(0%)	2(1%)	3(0%)	
Application site pruritus	2(0%)	0(0%)	2(0%)	
Application site reaction	3(1%)	7(3%)	10(1%)	
Application site urticaria	0(0%)	2(1%)	2(0%)	
INFECTIONS AND INFESTATIONS	1(0%)	1(0%)	2(0%)	
Application site infection	0(0%)	1(0%)	1(0%)	
Cellulitis	1(0%)	0(0%)	1(0%)	
PSYCHIATRIC DISORDERS	1(0%)	0(0%)	1(0%)	
Irritability	1(0%)	0(0%)	1(0%)	
Sleep disorder	1(0%)	0(0%)	1(0%)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1(0%)	3(1%)	4(1%)	
Dermatitis atopic	0(0%)	1(0%)	1(0%)	
Dry skin	1(0%)	0(0%)	1(0%)	
Urticaria	0(0%)	2(1%)	2(0%)	

^a P-values are based on comparing Desonide Foam versus Vehicle Foam based on the Chi-Square test ($\alpha = 0.10$) and are calculated when the incidence is at least five percent in any treatment group.

Source: NDA Submission, Module 2, Clinical Summary of Safety, section 2.7.4, table 2.7.4-F

Reviewer's Comment: *The treatment related adverse events do not differ significantly from the treatment related adverse events in the pivotal trial (see section 7.1.5.4). The most common were application site burning (3%) and atrophy (1%).*

7.4.1.2 Combining data

Pooling the safety data was done simply by summation of subjects in each study and summation of adverse events divided by the total number of subjects.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Application site burning, the most common treatment related adverse event in the pivotal trial, is an adverse event that by nature is not dose dependent. It is well known that cutaneous atrophy with topical corticosteroids can be a combination of dose and time dependency.

7.4.2.2 Explorations for time dependency for adverse findings

Even low potency topical corticosteroids can cause cutaneous atrophy over time. This adverse event was seen in 5 (1%) of patients in the desonide foam arm of the pivotal trial.

7.4.2.3 Explorations for drug-demographic interactions

Subgroup Analysis by Gender

Females constituted 52% (398/768) of the safety population, and males, 48% (370/768). AEs were reported by 42% (116/277) of female subjects in the desonide foam treatment group and 40% (48/121) in the vehicle foam group. AEs were reported by 35% (92/263) of male subjects in the desonide foam treatment group and 34% (36/107) in the vehicle foam group. There was no statistically significant difference in AE reporting between treatment groups for females or males ($p = 0.6806$ and $p = 0.8065$, respectively). In addition, the incidence of AEs by treatment group was consistent across the male and female subgroups.

Males and females overall reported AEs in the SOC of Infections and Infestations most frequently (18% (67/370) for males and 22% (86/398) for females). In the SOC of Infections and Infestations, the proportion of subjects with AEs in the desonide foam and vehicle foam groups were not significantly different from each other for either males or females.

For both males and females, the AE most frequently reported in the SOC of Infections and Infestations was upper respiratory tract infection (7% females, 7% for males). The differences in reporting across the treatment groups were not statistically significant. The most frequently reported AE in the SOC of General Disorders and Administration Site Conditions was application site burning for females (5%, 21/398) and pyrexia for males (3%, 10/370). A significantly greater proportion of females in the vehicle foam group reported application site burning as compared to the desonide foam group ($p = 0.0062$). The differences in reporting across the treatment groups for males in the SOC of General Disorders and Administration Site Conditions were not analyzed for statistical significance since they were rare (< 5%).

Neither male nor female subjects reported a significantly greater number of AEs in the desonide foam group as compared to the vehicle foam group.

Subgroup Analysis by Age Cohort

Subjects in Cohort 1 constituted 21% (161/768) of the safety population, subjects in Cohort 2 were 28.5% (219/768), subjects in Cohort 3 were 23.3% (179/768), and subjects in Cohort 4 were 27% (209/768).

The incidence of AEs reported by subjects in the desonide foam group of Cohort 1 was 32% (37/117) and 18% (8/44) in the Vehicle Foam group. The incidence of AEs reported by subjects in the desonide foam group of Cohort 2 was 32% (50/155) and 31% (20/64) in the Vehicle Foam group. The incidence of AEs reported by subjects in the desonide foam group of Cohort 3 was 41% (52/126) and 38% (20/53) in the Vehicle Foam group. Within Cohort 4, 49% (69/142) of subjects in the desonide foam group reported AEs and 54% (36/67) of subjects in the vehicle foam group reported AEs. Overall AEs were reported in a statistically significantly higher proportion of subjects in the desonide foam treatment group than the vehicle foam group for Cohort 1 ($p = 0.0903$) although there were no statistically significant differences noted in this cohort for any of the SOCs or for specific AEs. Therefore, this difference is believed not to represent a clinically meaningful difference. The proportion of subjects who reported an AE was consistent between treatment groups for Cohorts 2, 3, and 4.

No individual AEs were reported in a significantly greater proportion of the desonide foam group than the vehicle foam group in 3 of the 4 age cohorts. However, in Cohort 4 (ages 3 months to <3 years), the desonide foam group reported a statistically significantly higher proportion of subjects who had pyrexia than those in the vehicle foam group (9% (13/142) compared to 1% (1/67), $p = 0.0386$). This does not appear to be clinically meaningful as there are no significant differences in the other AEs that might explain why this difference occurred (e.g., AEs in the Infections and Infestations SOC).

Individual AEs were reported in a significantly greater proportion of the vehicle foam group than the desonide foam group in Cohort 2: application site reaction ($p = 0.0116$) and Cohort 4: application site burning ($p = 0.0232$) and application site erythema ($p = 0.0033$).

Subgroup Analysis by Race

Caucasians constituted 49% (380/768) of the safety population. African Americans comprised 26% (203/768). Hispanics were 15% (118/768). Subjects categorized as Asian and Other were 9% (67/768) of the safety population.

In the Caucasian group, 37% (97/263) of subjects in the desonide foam treatment group and 33% (39/117) in the vehicle foam group reported an AE. In the African American group, 34% (49/143) of subjects in the desonide foam treatment group and 42% (25/60) in the vehicle foam group reported an AE. In the Hispanic group, 41% (34/83) of subjects in the desonide foam treatment group and 34% (12/35) in the vehicle foam group reported an AE. Among the Asian/Other group, 55% (28/51) of subjects in the desonide foam treatment group and 50% (8/16) in the vehicle foam group reported an AE. Across all racial groups, there was no statistically significant difference between the proportion of subjects in each treatment group who reported AEs.

AEs were reported most frequently in the Infections and Infestations SOC by all racial groups overall: Hispanics (25%, 29/118), Asian/Other (22%, 15/67), Caucasians (19% 71/380),

and African Americans (19%, 38/203). The incidence of AEs by treatment group was consistent across all of the racial subgroups. In the Infections and Infestations SOC, there were no statistically significant differences across treatment groups for the African American and Caucasian groups. However, in the Asian/Other group and in the Hispanic group there were statistically significant differences between the treatment groups for several AEs (e.g., gastroenteritis, otitis media). These differences are not viewed as clinically meaningful due to the rarity of the events and the small number of subjects in this subgroup (e.g., 1% (1/16) subjects treated with vehicle foam and 0% in the desonide foam group in the Asian/Other group). In the General Disorders and Administration Site Conditions SOC, Caucasians in the vehicle foam group had significantly more AEs (16%, 19/117) than those in the desonide foam group (8%, 21/263) ($p = 0.0155$) and African American in the vehicle foam treatment group had significantly more AEs (15%, 9/60) than African American in the desonide foam treatment group (7%, 10/143) ($p = 0.0739$). There were no significant differences in the proportion of AEs across treatment groups in this SOC for Hispanics ($p = 0.7689$), or those reported as Other/Asian, ($p = 0.9002$).

For the Caucasian, African American, and Other/Asian groups, the most frequently reported AE in the General Disorders and Administration Site Conditions SOC was application site burning: Caucasian 4% (17/380), African American 4% (8/203), Other 7% (5/67). Pyrexia was the most frequently reported AE in this SOC for Hispanics, 3% (4/118).

A significantly greater proportion of subjects in the African American and Caucasian groups reported application site burning in the vehicle foam group than in the desonide foam group ($p = 0.0041$ and $p = 0.0104$, respectively). Application site erythema and otitis media were reported by Hispanics in significantly greater proportions in the vehicle foam group than in the desonide foam group ($p = 0.0281$ and $p = 0.0069$, respectively). These statistically significant differences were not seen in any of the other three racial groups.

Reviewer's Comments: There were not any safety issues revealed by the subgroup analyses by gender, age, or ethnicity.

7.4.2.4 Explorations for drug-disease interactions

No formal explorations for drug-disease interactions were performed for this topical drug product. However, it is generally accepted that topical anti-inflammatory agents, such as topical corticosteroids, should not be applied to infected skin.

7.4.2.5 Explorations for drug-drug interactions

No explorations were performed for drug-drug interaction for this topical drug product.

7.4.3 Causality Determination

The data from the clinical trial supports that desonide foam vehicle is the culprit for the application site burning. This effect is somewhat blunted in the drug product by the presence of the chemical moiety, desonide, a low potency topical corticosteroid, which has anti-

inflammatory effects. The occurrence of atrophy in a small percentage of patients is not surprising, as all topical corticosteroids are capable of inducing this cutaneous adverse event.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There are not any special concerns with the dosing regimen or administration of the drug product.

8.2 Drug-Drug Interactions

There are not any concerns with drug-drug interactions with this topical drug product.

8.3 Special Populations

There are not any concerns or modifications that need to be made with the use of this topical drug product for the indication and duration of use as it relates to special populations.

8.4 Pediatrics

As atopic dermatitis is primarily a disease of childhood, the pivotal trial was performed in the pediatric population, ages 3 months – 17 years. No special concerns arose in the evaluation of the safety data from this trial.

8.5 Advisory Committee Meeting

No advisory committee meeting was held concerning this drug product.

8.6 Literature Review

There are no additional concerns from the review of the literature submitted by the sponsor concerning the chemical moiety, desonide, 0.05%.

8.7 Postmarketing Risk Management Plan

Given that this is a topical low potency corticosteroid, with minimal adverse events, and with only a small percentage of patients experiencing reversible HPA axis suppression, no postmarketing risk management plan is necessary.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor demonstrated in one robust clinical trial through persuasive statistics that desonide foam, 0.05% is efficacious in the treatment of mild to moderate atopic dermatitis ($p < 0.00001$) over a 4 week period. The drug product also demonstrated an adequate safety profile. The cutaneous events that occurred are not uncommon for a topically applied drug product that contains an irritant. Since the application site burning did not result in any patients discontinuing from the trial, it is likely that this will not be a significant problem post-marketing. Five subjects (1%) did experience cutaneous atrophy. This is also a known possible adverse event of topical corticosteroids. It will be recommended that continuous use should not exceed 4 consecutive weeks and that the medication should be discontinued when an adequate response has been achieved. Finally, there was HPA axis suppression, albeit reversible, that occurred in 4% of patients. Therefore, it will be recommended that the drug product not be used for more than 4 consecutive weeks. And again, the medication should be discontinued when an adequate response has been achieved.

9.2 Recommendation on Regulatory Action

It is recommended from a clinical perspective that desonide foam, 0.05% be approved for "treatment of mild to moderate atopic dermatitis in patients ages 3 months and older."

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The sponsor should submit annual reports as required for a marketed drug product in the United States that should include any reports of adverse events with desonide foam, 0.05%.

9.3.2 Required Phase 4 Commitments

There are not any required phase 4 commitments from a clinical perspective. However, the sponsor is required to conduct 2 non-clinical studies as phase 4 commitments. These are a dermal carcinogenicity study and a study to determine the photo-carcinogenic potential of desonide foam.

9.3.3 Other Phase 4 Requests

There are none from clinical.

9.4 Labeling Review

Many of the clinical sections of the proposed label submitted by the sponsor were inadequate. General additions to the label include the following:

- Limitation to 4 consecutive weeks of use
- Age group for indication
- Description of HPA axis suppression study in several sections: pharmacology, general precautions, and pediatric use
- Expansion of "Information for Patient's" Section
- Expansion of "Adverse Events" Section
- Rewording of "Clinical Studies" Section

See line-by-line labeling review for details (Appendix 10.2).

9.5 Comments to Applicant

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

**APPEARS THIS WAY
ON ORIGINAL**

10 APPENDICES

10.1 Review of Individual Study Reports

Reviewer's Comment: The summary of the protocol for the phase 3 pivotal trial is described below. It is taken from section 9 of the final study report as submitted to the NDA. The entire protocol and protocol amendments can be found in section 16 of the final study report submitted to the NDA.

Trial DES.C.301 – “A Phase 3, Multicenter, Randomized, Double-Blind Vehicle-Controlled Study of the Safety and Efficacy of Desonide Foam, 0.05%, in the Treatment of Adolescent and Pediatric Subjects with Mild to Moderate Atopic Dermatitis”

List of Investigators

┌

└

Overall Study Design and Plan – Description

Protocol DES.C.301 was a Phase 3, multicenter (17 sites in the United States), randomized, double-blind, vehicle-controlled study comparing Desonide Foam and its vehicle in the treatment of mild to moderate atopic dermatitis in male and female pediatric and adolescent subjects.

Subjects with atopic dermatitis as defined by the Hanifin and Rajka criteria who had mild or moderate disease, defined as an Investigator's Static Global Assessment (ISGA) score of 2 or 3, a sum of the scores for erythema, induration/papulation, scaling, and oozing/crusting of ≥ 4 , and an involvement of $\geq 5\%$ total body surface area (BSA) were eligible for enrollment.

Approximately 570 subjects were to be randomized to one of two parallel treatment groups in a 2:1 ratio (Desonide Foam:Vehicle Foam). Approximately 380 subjects were to be randomly assigned to treatment with Desonide Foam and approximately 190 subjects to treatment with Vehicle Foam. Subjects were to be enrolled simultaneously into age cohorts as follows:

- Cohort 1: ≥ 12 years to < 18 years
- Cohort 2: ≥ 6 years to < 12 years
- Cohort 3: ≥ 3 years to < 6 years
- Cohort 4: ≥ 3 months to < 3 years

Investigators, nurse/coordinators, and subjects/primary caregivers were to be blinded to the treatment assignment. Subjects who did not complete the study were not to be replaced.

The study was to consist of 4 weeks of treatment with visits at Baseline, Week 2, and Week 4 (or early termination), and a 3-week post-treatment follow-up evaluation. Subjects or their primary caregivers were to be instructed to consistently apply the study drug treatment twice daily in the mornings and evenings throughout the 4-week study.

At the first visit (Baseline, Day 1), written informed consent was to be obtained; a medical history/review of systems conducted; vital signs (blood pressure, pulse, temperature), weight, and height measured; a urine pregnancy test performed on all females of childbearing potential; subjects/primary caregivers were to complete the Dermatology Life Quality Index (DLQI) or the Children's Dermatology Life Quality Index (CDLQI) questionnaire; and, at four investigational sites, clinical photography was to be performed.

Efficacy evaluations were to be conducted at all study visits, (Baseline, Week 2, and Week 4 (or end of treatment), and the 3-week post-treatment follow-up evaluation), and were to include an

ISGA, a subject/primary caregiver evaluation of pruritus, a complete examination of the skin and an evaluation of the clinical signs of atopic dermatitis (erythema, induration/papulation, lichenification, scaling, and oozing/crusting), and a Subject's Global Assessment (SGA) of treated areas. Subjects were to be queried for compliance with the study drug regimen.

Safety evaluations were to be conducted at all study visits. Subjects were to be queried for adverse experiences (beginning with the Week 2 visit) and their use of concomitant medications. Study drug application sites were to be assessed for changes in skin atrophy, striae, telangiectasia, and pigmentation.

At the Week 4 (or end of treatment) visit, vital signs were to be measured, subjects/primary caregivers were to complete the DLQI or CDLQI questionnaire, a urine pregnancy test was to be performed on all females of childbearing potential, and, at four investigational sites, clinical photography was to be performed. Additionally, subjects/primary caregivers were to complete a post-study questionnaire at this visit.

Study drug containers were to be weighed and dispensed at the Baseline and Week 2 visits; previously dispensed study drug containers were to be collected and weighed at the Week 2 and Week 4 (or end of treatment) visits.

Inclusion Criteria

Subjects must have fulfilled all of the following criteria to be eligible for study admission:

1. Male or female subjects age 3 months to 17 years in good general health.
2. Atopic dermatitis of the face, groin/perineal area, trunk, or extremities as defined by the criteria of Hanifin and Rajka. The atopic dermatitis must be of mild to moderate intensity (score 2 or 3) as determined by the Investigator's Static Global Assessment, with a sum of the scores for erythema, induration/papulation, and oozing/crusting of ≥ 4 and involvement of $\geq 5\%$ total BSA.
3. The ability and willingness to follow all study procedures, attend all scheduled visits, and successfully complete the study.
4. The ability to understand and sign a written informed consent form, which must be obtained prior to treatment. Because subjects are under the age of 18, a parent or guardian must sign the informed consent form, and the subject must provide written assent (age 7 and older), in accordance with local IRB guidance and state governance.
5. The ability to understand and sign a HIPAA authorization form, which shall permit the use and disclosure of subject's individually identifiable health information. As subjects are under the age of 18, a parent or guardian must sign the HIPAA authorization form and the signed form must be obtained prior to treatment.

Exclusion Criteria

1. Known allergy to desonide or other topical corticosteroids; or to any component of the investigational formulations.
2. Clinically infected atopic dermatitis.

3. Other serious skin disorder or any chronic condition that is not well controlled.
4. Use of topical corticosteroid therapy for atopic dermatitis within the past 1 week or other topical therapy for atopic dermatitis (e.g., topical antibiotics, topical immunomodulators [tacrolimus or pimecrolimus]) within the past 2 weeks and during the conduct of the study. Use of inhaled/intranasal steroids is permitted prior to and during the course of the study.
5. Use of harsh cleansing agents such as soaps or washes. Use of mild cleansing agents such as Basis Bar or Dove are allowed. Use of bland moisturizers such as Eucerin Cream is allowed in between applications of study medication but should not be applied within 4 hours prior to any study visit.
6. Use of systemic or phototherapy that affects atopic dermatitis (e.g., corticosteroids, psoralen and ultraviolet A [PUVA], ultraviolet B [UVB], cyclosporine, azathioprine, tacrolimus, methotrexate) within the past 4 weeks and during the conduct of the study. Subjects being treated with systemic or topical antihistamines at Baseline are allowed to enroll as long as they have not changed dose or drug within the past 2 weeks and do not expect to discontinue use during the study.
7. Use of any investigational therapy within the past 4 weeks.
8. Pregnant females, females who are breast feeding, or females of childbearing potential who are not practicing an acceptable method of birth control (abstinence, birth control pill, patch, or implant, barrier with spermicidal jelly, intrauterine device, etc.) as determined by the investigator. Acceptable contraception must be used during the entire study.
9. Current drug or alcohol abuse (drug screening not required).
10. Any other condition which, in the judgment of the investigator, would put the subject at unacceptable risk for participation in the study.

Removal of Subjects From Therapy or Assessment

Subjects could withdraw or be removed from the study in the following instances:

1. Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree, require discontinuation of drug, or both
2. Unacceptable toxicity
3. Subject noncompliance
4. Subject's request to withdraw

If a subject withdrew prior to study completion, the evaluations for the Week 4 visit were to be performed at an Early Termination visit. The subject was also urged to return for the 3-week post-treatment follow-up evaluations if possible.

Treatments Administered

All treatments were to be administered twice daily (morning and evening) for a maximum of 4 weeks. Subjects were to self-administer the treatments if possible. If the subject was not able to self-administer the study drug due to age or other reason, the primary caregiver was to administer the study drug. At the Baseline visit, subjects/caregivers were to be instructed to dispense a small amount of foam and gently massage the medication into the affected areas until the foam was absorbed. Study drug was to be applied during the Baseline visit at the study site, but could be applied later that day or evening. No modifications of the dosing regimen were permitted.

All areas affected with atopic dermatitis were to be treated with the study drug, including the face, scalp, and intertriginous areas. In the event of clearing, subjects/primary caregivers were to continue to apply study drug to areas originally affected by atopic dermatitis for the entire 4-week treatment period if this was considered to be safe by the investigator. Prior to the Week 4 visit, any newly affected areas were to be treated at the first sign of flaring.

Efficacy Assessments

ISGA evaluations were to be performed at each study visit by an efficacy assessor (principal investigator or designee). If possible, the same efficacy assessor was to perform all efficacy assessments on the same subject at all visits. The definitions of the scores for the ISGA are provided in table 1.

Table 1: Investigator’s Static Global Assessment

Score	Definition
0	Clear; there may be minor residual discoloration; no erythema or induration/papulation, no oozing/crusting
1	Almost Clear; there may be trace faint pink erythema, with almost no induration/ papulation and no oozing/crusting
2	Mild; there may be faint pink erythema, with mild induration/papulation and no oozing/crusting
3	Moderate; there may be pink-red erythema with moderate induration/papulation and there may be some oozing/crusting
4	Severe; there may be deep or bright red erythema with severe induration/papulation and with oozing/crusting

Pruritus was to be assessed by subjects/primary caregivers over the 24 hours prior to each study visit. Subjects not able to read and/or understand this table were to have their pruritus scored by direct interview of the subject/primary caregiver by the investigator/designee. The definitions of the scores for pruritus are provided in table 2.

Table 2: Pruritus Score

Score	Definition
0	Absent; no itching
1	Minimal; very rarely aware of localized itching; only present when relaxing and lasts for very short time
2	Mild; only aware of itching at times; only present when relaxing; not present when focused on other activities
3	Moderate; often aware of itching; annoying; sometimes disturbs sleep and daytime activities
4	Severe; constant itching; distressing; frequent sleep disturbance; interferes with activities

The clinical signs of atopic dermatitis (erythema, induration/papulation, lichenification, scaling, and oozing/crusting) were to be assessed at each study visit as a visual “average” integrating all treated areas. Following the Baseline assessment, assessments were to be made without reference to the Baseline state. The definitions of the scores for clinical signs are provided in table 3.

Table 3: Erythema, Induration/Papulation, Lichenification, Scaling, and Oozing/Crusting Scoring

Erythema	Definition
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
Induration/Papulation	
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
Lichenification	
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
Scaling	
0	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
Oozing/Crusting	
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

Safety Assessments

A complete examination of the skin was to be conducted by the investigator at each study visit. The extent of atopic dermatitis body surface involvement and application site reactions (atrophy, striae, telangiectasia, and pigmentation changes) were to be noted.

Vital signs (systolic and diastolic blood pressure and pulse) and temperature were to be measured at the Baseline and the Week 4 (or end of treatment) visit.

Adverse experiences were to be recorded from the first application of study medication until the last study visit. Any adverse experiences not resolved by the last study visit and considered to be potentially related to study drug were to be followed as clinically indicated until resolution or, if non-resolving, until considered stable.

An adverse experience was defined as any unfavorable, harmful, or pathological change in a research subject as indicated by physical signs, symptoms, and/or clinically significant laboratory abnormalities that occur in association with the use of a product or vehicle, whether or not considered product-related. This definition includes: intercurrent illness; injuries; exacerbation of pre-existing conditions; adverse experiences occurring as a result of product withdrawal, abuse, or overdose; or a change in a laboratory variable if considered by the attending physician to be clinically significant or if it caused (or should have caused) the clinician to reduce or discontinue the use of the study drug or institute therapy. This definition does not include inpatient or outpatient elective surgery for a condition that was present prior to the start of the trial and which has not worsened unexpectedly during the trial.

The investigator was to monitor the occurrence of adverse experiences during the course of the study. The investigator was to provide to the Sponsor appropriate information concerning any findings that suggest significant hazards, contraindications, side effects or precautions pertinent to the safety of the study medication. Prior to the initiation of study drug administration, the investigator was to instruct the subjects/primary caregivers to report any physical changes or new symptoms noticed during the course of the study.

All adverse experiences occurring after the Baseline Visit were to be recorded on the Adverse Experience Case Report Form (CRF) page.

Primary Efficacy Variables

The primary efficacy variables assessed in this study were based on ISGA scores and erythema and induration/papulation scores. All efficacy assessments were collected at all study visits: Baseline, Week 2, Week 4 (or end of treatment), and 3 weeks post-treatment.

The primary endpoint for this study was to determine the proportion of subjects who had an ISGA score of clear (0) or almost clear (1) and a score of 0 or 1 for both erythema and induration/papulation at Week 4 (or end of treatment), and a minimum improvement of two

grades in the ISGA score from Baseline to Week 4 (or end of treatment). Satisfaction of all components of this endpoint for a given subject was defined as treatment success.

Secondary Efficacy Endpoints

The secondary efficacy endpoints of the study were:

Mean percent reduction in the sum of the scores of erythema, induration/papulation, lichenification, scaling, and oozing/crusting from Baseline to Week 4 (or end of treatment)

The proportion of subjects who have a pruritus score of 0 at Week 4 (or end of treatment)

The proportion of subjects who have an ISGA of 0 or 1 at Week 4 (or end of treatment) and a minimum improvement in the ISGA score of two grades from Baseline to Week 4

Demographic and Baseline Comparability

The following demographic and baseline characteristics were summarized and/or listed for each treatment group and each population:

Age, sex, and race

Weight, height, temperature, medical history, physical examination, and vital signs

Investigator's Static Global Assessment score, subject's evaluation of pruritus, and extent of body surface area (%BSA) involvement

Efficacy Analysis

Efficacy analyses were performed for the intent-to-treat (ITT) population on primary, secondary, and additional endpoints. The ITT analysis was the primary analysis. The Per-Protocol population was analyzed for the primary and secondary endpoints only and was used to provide supporting evidence and to ensure that the results were not driven by the method of dealing with missing responses. Sensitivity analyses were performed for the ITT population on the primary endpoint.

Sites were combined based on geographical and climate similarities if enrollment was less than 10 subjects per treatment group per site.

Subgroup analyses were performed only on the primary endpoint in the ITT and the Per-Protocol populations, and were grouped into the following demographic categories:

Gender: Male, female

Cohort: ≥ 12 years to < 18 years; ≥ 6 years to < 12 years; ≥ 3 years to < 6 years;

≥ 3 months to < 3 years

Race: Caucasian, African-American, Hispanic, and Other (including Asian)

Safety Analysis

Safety analyses were only performed on the ITT population. Safety was assessed based on adverse experiences, extent of atopic dermatitis, vital signs, and changes in skin atrophy, striae, telangiectasia, and pigmentation at the application sites.

11 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Denise Cook
9/6/2006 12:00:04 PM
MEDICAL OFFICER

Markham Luke
9/7/2006 01:03:22 PM
MEDICAL OFFICER
Concur with Dr. Cook regarding action recommendation.

Stanka Kukich
9/8/2006 07:53:47 PM
MEDICAL OFFICER