

CLINICAL REVIEW

Application Type NDA
Application Number(s) 21-152/ S-004
Priority or Standard Standard

Submit Date(s) April 22, 2010
Received Date(s) April 22, 2010
PDUFA Goal Date February 22, 2011
Division / Office DDDP/ODE3/OND

Reviewer Name(s) Amy S. Voitach, D.O., M.S.
Review Completion Date October 21, 2010

Established Name Fluticasone Propionate, 0.05%
(Proposed) Trade Name Cutivate Lotion, 0.05%
Therapeutic Class Topical Corticosteroid
Applicant Nycomed US Inc.

Formulation(s) Lotion
Dosing Regimen Once daily topical application
Indication(s) Relief of the inflammatory and pruritic manifestations of atopic dermatitis
Intended Population(s) 3 months of age to 12 months

(b) (4)

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Reviewer comment: Line listings assessing compliance show that the sponsor’s numbers are slightly off. This reviewer determined that all 56 subjects applied some study medication and 54 subjects applied medication for at least 19 days. Also, 46 and not 48 subjects actually applied study drug at least 22 days. Regardless, subject compliance was high and the extent of exposure appears adequate for evaluation of safety.	27
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Figure 1: Schedule of Events 17

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)

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(b) (4)

1.2 Risk Benefit Assessment

Cutivate lotion was approved on 3/31/2005 and is currently indicated for atopic dermatitis in ages 1 year and above. (b) (4)

(b) (4)

This open-labeled study was not designed to statistically assess efficacy. Efficacy has been previously demonstrated in this patient population in the randomized, controlled phase 3 trials conducted for the original 2005 approval. Efficacy was assessed based on percent Body Surface Area (%BSA) affected and treated and the signs and

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symptoms of AD at each evaluation. The percent BSA affected decreased from an average of 56.9% at Baseline to an average of 6.7 % at Day 29. All signs and symptoms showed marked progressive improvement beginning with Day 8 through the Day 29 evaluation. These efficacy findings are consistent with prior studies evaluating Cutivate Lotion and the data is supportive for efficacy in this patient population.

The trial is adequate to inform safety

(b) (4)

Of 49 evaluable subjects with BSA of $\geq 35\%$ who were treated twice daily for three to four weeks, one subject showed laboratory evidence of adrenal suppression at the End of Treatment. Adrenal suppression resolved in this subject within one week as documented by normal cortrosyn stimulation testing.

No cutaneous signs of atrophy (telangiectasia, loss of elasticity, purpura, dusky erythema, striae) were seen in this trial although these are known adverse events associated with the use of topical corticosteroids, particularly with higher potency steroids and with prolonged use. This assessment is limited due to the short duration of treatment, which is consistent with existing approved labeling. Treatment-related assessments of hyper/ hypopigmentation were indeterminate in this open-labeled study.

No deaths occurred in this trial and all but one of the 37 reported adverse events were non-serious. The serious AE (hospitalization for pyrexia) is unlikely to be due to study medication. The significant findings related to the study medication included bacterial and viral skin infections. These findings are not unexpected in this population with use of topical corticosteroids for atopic dermatitis.

No other risk management is recommended by this reviewer other than the revised information in product labeling which describes the safety outcomes of this study.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

None recommended.

2 Introduction and Regulatory Background

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2.1 Product Information

Fluticasone propionate is available for topical application as cream, lotion, and ointment formulations. The lotion was approved in 2005 and is indicated for atopic dermatitis in ages 1 year and above.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Drug Treatments Indicated for Atopic Dermatitis

Treatment Class	Drug Products
Topical corticosteroids	Products are available in an array of vehicles and potencies.
Topical calcineurin inhibitors	<p>Pimecrolimus is approved for mild to moderate AD as second line therapy.</p> <p>Tacrolimus for second line therapy of moderate to severe AD.</p> <p>Both topical calcineurin inhibitors are immunosuppressants and carry a boxed warning about the possible development of cancer.</p>

Mild cases of AD can be treated with non-drug treatments such as emollients.

2.3 Availability of Proposed Active Ingredient in the United States

Cutivate (fluticasone propionate) is also currently marketed as Cutivate 0.005% Ointment (NDA 19-957, approved December 14th, 1990) and, Cutivate 0.05 % Cream (NDA-19-958, approved December 18th, 1990). Both the cream and ointment are currently indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults. The cream and ointment are labeled to be applied to adults twice daily. In addition, Cutivate Cream is also approved for the treatment of atopic dermatitis in children as young as three months, to be applied once or twice daily (NDA 19-958, approved June 17th, 1999).

Fluticasone propionate is available for inhalation as a powder and aerosol in multiple strengths (powder range 0.05 -0.5 mg/ inhalation and aerosol range (0.044- 0.22 mg/ inhalation) and as a nasal spray 0.05 mg/ spray for the treatment of asthma and allergic rhinitis.

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2.4 Important Safety Issues With Consideration to Related Drugs

Safety concerns with topical corticosteroids include both local and systemic adverse events. Systemic adverse effects of topical corticosteroids are rarely seen but can include Cushing's syndrome, hyperglycemia, osteopathy, adrenocortical suppression, decreased growth rate, edema, hypocalcemia, hypertension, posterior subcapsular cataracts, and glaucoma. Children are at higher risk than adults for HPA axis suppression due to their larger body surface area to body mass. Common local adverse effects include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura, and less frequent adverse effects include hypertrichosis, pigmentary alterations, delayed wound healing, exacerbation of skin infections, and contact sensitization reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

March 31, 2005: NDA 21152 for Cutivate (fluticasone propionate) Lotion 0.05% was approved. The approval letter included a postmarketing commitment to conduct a deferred pediatric study under PREA in subjects aged 3 months to 1 year. The wording for PMC #1 in the approval letter was as follows:

Deferred pediatric studies under PREA for the treatment of atopic dermatitis in pediatric patients aged 3 months to 1 year. These studies will evaluate the safety (both local and systemic, to include laboratory tests) and systemic exposure of this product.

November 30th, 2005: The sponsor submitted the protocol (ALT 0434-01-01) (b) (4)

May 16th, 2006: The sponsor sent a revised protocol the study protocol incorporating changes suggested by the Agency. The clinical reviewer deemed the revised protocol acceptable.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

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3.1 Submission Quality and Integrity

No study site investigations by the Division of Scientific Integrity were requested by the division upon preliminary review of the study data.

3.2 Compliance with Good Clinical Practices

The studies were conducted in compliance with good clinical practices.

3.3 Financial Disclosures

Financial disclosure was complete and did not raise any concerns.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no new CMC data for this previously approved product (b) (4)

[Redacted]

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

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4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

There is no new Pharmacology/ Toxicology data for this previously approved product

(b) (4)
A separate supplement S-005 provides data for a photo-carcinogenicity study. This data has been reviewed by Dr. Barbara Hill and recommendations for labeling based on this study have been proposed for the label associated with this efficacy supplement.

(b) (4)

4.4 Clinical Pharmacology

The clinical pharmacology review team's discussion regarding this HPA study has been incorporated into Section 7, Review of Safety, in this clinical review.

(b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Table of Clinical Trials

Study	Objective
ALT 0434-01-01	Evaluate the safety systemic and local safety of Cutivate Lotion in subjects 3 mo- < 12 mo of age. Safety evaluation to include the effect on the HPA axis, hematology and blood chemistries, and dermal safety.

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5.2 Review Strategy

One open-labeled study for Cutivate Lotion was reviewed for local and systemic safety in a patient population younger (3 months to < 12 months) [REDACTED] (b) (4)

Efficacy in this patient population was evaluated in blinded phase 3 trials which were reviewed at the time of the original NDA submission. Efficacy assessment in this trial was viewed as supportive of the review conclusions related to the original application which led to the 2005 approval action for the population down to one year of age.

5.3 Discussion of Individual Studies/Clinical Trials

Protocol # ALT 0434-01-01

Title: A Multicenter, Open-label Study to Evaluate the Effect of Cutivate (Fluticasone Propionate) Lotion 0.05% on the Hypothalamic Pituitary Adrenal Axis in the Treatment of Atopic Dermatitis in a Pediatric Population

Development Phase: 4

Objective:

To evaluate the safety of a 3- or 4- week course of twice-daily applications of Cutivate (Fluticasone Propionate) Lotion 0.05% in pediatric subjects aged 3 months to 12 months with moderate to severe atopic dermatitis (AD) covering $\geq 35\%$ Body Surface Area (BSA). Safety was assessed by the following:

1. Effect on the HPA axis as determined by the response to cosyntropin stimulation tests (CST) (pre-and post stimulation cortisol levels)
2. Hematology and blood chemistries
3. Signs of skin atrophy and pigmentation changes at application site (i.e. cutaneous effects)
4. Other adverse events

Study design:

A multi-center, open-label study that evaluated the effect of Cutivate® Lotion 0.05 % on the Hypothalamic Pituitary Adrenal (HPA) Axis in pediatric patients aged 3 months to 11 months with moderate to severe atopic dermatitis covering $\geq 35\%$ Body Surface Area (BSA). Cutivate® Lotion was applied twice daily for 3- or 4-weeks.

Study population:

Investigators and Study Centers: 10 sites in the US

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Study Site #	Investigator	Study Site
1	Elizabeth Connelly, M.D.	University of Miami, Department of Dermatology, Cedars South Building, 1295 NW 14 Street, Suite K, Miami, FL 33125
2	Lawrence Eichenfield, M.D.	Rady Children's Hospital, San Diego, Division of Pediatric and Adolescent Dermatology, 8010 Frost Street, Suite 602, San Diego, CA 92123
3	Alan B. Fleischer, Jr., M.D.	Department of Dermatology, Wake Forest University Health Sciences, Medical Center Boulevard, Winston-Salem, NC 27157
4	Adelaide Hebert, M.D.	The University of Texas Health Science Center at Houston, 6655 Travis, Suite 600, Houston, TX 77030
5	Kenneth Bloom, M.D.	Dermatology Center for Children & Young Adults, P.A., 2795 Pilot Knob Road, Suite 300, Eagan, MN 55121
6	Craig L. Leonardi, M.D.	Central Dermatology, P.C., 1034 S. Brentwood Boulevard, Suite 600, St. Louis, MO 63117
7	Sharon S. Raimer, M.D.	University of Texas Medical Branch, 301 University Boulevard, Department of Dermatology, 4.112 McCullough Building, Galveston, TX 77555-0783
8	Lawrence C. Parish, M.D.	Paddington Testing Company, Inc., 1760 Market Street, Suite 301, Philadelphia, PA 19103
9	David L. Kaplan, M.D.	Adult and Pediatric Dermatology, P.A., 4601 West 109th Street, Suite 116, Overland Park, KS 66211
10	Stephen W. Shewmake, M.D.	Centre for Health Care Medical Associates, 15611 Pomerado Road, Suite 400, Poway, CA 92064

Study Dates: July 25th, 2007 (first subject enrollment) to September 25th, 2008 (last subject completed).

Number of Subjects:

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Fifty six (56) male and female pediatric subjects aged 3-11 months with moderate to severe atopic dermatitis were enrolled in the study. Of the 56 subjects enrolled, 52 subjects completed the study.

Inclusion Criteria:

1. Subjects who were male or female, at least 3 months of age, and not greater than 12 months of age on the date of Baseline Visit.
2. Subjects who had atopic dermatitis covering >35% Body Surface Area (BSA) excluding the eyelids, perioral area, around the nostrils, and in the diaper area of those subjects who wore diapers or plastic pants.
3. Subjects who had AD with a total severity score of at least 6.0 for any three of eight potential signs and symptoms, where each sign/symptom was rated on a scale of 0 (absent) to 3 (severe).
4. Subject's parent or legal guardian signed a current IRB approved written informed consent.
5. Subject's consenting parent/guardian was willing and able to understand and comply with the requirements of the study, applied the study medication as instructed, returned for the required visits, complied with therapy prohibitions, and was able to complete the study.
6. Subjects who were in good health, as confirmed by medical history and physical exam, and free from any clinically significant disease/condition, other than atopic dermatitis, that could have interfered with the study evaluations.

Exclusion Criteria:

1. Subjects who had signs of skin atrophy in the areas to be treated with study drug.
2. Subjects who had acute self-limiting AD (e.g., allergic contact eczema, etc.), which was likely to improve spontaneously during the study.
3. Subjects who had a known or suspected history of any condition that could have been exacerbated by treatment with Cutivate® (FP) Lotion 0.05% or that could have impaired the examination of the treatment area (i.e., psoriasis).
4. Subjects who had any disease affecting the HPA-axis (e.g., Addison's Disease, Cushing's Syndrome).
5. Subjects who had a known or suspected history of a clinically significant systemic disease (e.g., immunological deficiencies), unstable medical disorders (e.g., unstable diabetes), life-threatening disease, or current malignancies.

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6. Subjects who had a known or suspected hypersensitivity to any of the following (in any dosage form): lidocaine/prilocaine, heparin, fluticasone propionate, any component of the study medications, or to any of the components of the cosyntropin.

7. Subjects who were treated with any of the following chronic therapies (more than 4 weeks continuously): cyclosporine, methotrexate and PUVA for skin lesions within 4 weeks prior to the start of study drug (Day 1) or had an anticipated need for any such systemic therapy during the study.

8. Subjects who required treatment with systemic retinoids (e.g., Tegison®, Accutane®, Acitretin®) or topical retinoids (e.g., Tazorac®) during the course of the study.

9. Subjects who received any topical corticosteroid therapies within 1 week prior to the start of study drug or anticipated need for use during the study. (Bland emollients could be used during the screening phase and post-treatment phase, if applicable, and on untreated areas during the treatment phase.)

10. Subjects who received inhaled or intranasal corticosteroid therapies within 1 week prior to the start of study drug (Day 1) or anticipated need for use during the study.

11. Subjects who received systemic corticosteroids within one month prior to the start of the study drug (Day 1).

12. Subjects who required treatment with any other topical or systemic therapy for the study disease other than bland emollients in untreated areas of disease, with the exception of those approved by the Sponsor and known to have no effect on cortisol levels and HPA axis function.

13. Subjects who required use of tanning booths, sunbathing, or ultraviolet light treatment during the course of the study.

14. Subjects who required the use of any medication known to affect cortisol levels of HPA axis integrity.

15. Subjects who had any condition that would compromise compliance, in the investigator's opinion, with this protocol.

16. Subjects who were treated with an investigational drug or investigational device within a period of 30 days prior to study entry.

17. Subjects who were previously enrolled in this study.

Study Plan:

This is an open-label, multicenter study of a 3- or 4- week course of twice-daily (approximately 12 hours apart, once in the morning and once in the evening) applications of Cutivate (Fluticasone Propionate) Lotion 0.05%. Up to six clinic visits

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(screening, Days 1, 8, 15, 22, 29) were scheduled with a conditional seventh visit 1 or 2 weeks post-treatment if needed for repeat laboratory tests or adverse event assessments. Thus the maximum total time a subject could be in the study, after screening, was 6 weeks.

Figure 1: Schedule of Events

Visit Number	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5/ Final Visit ¹	Visit 6/ Conditional Follow-up ²	Unscheduled Visit
Visit Day	Day -30 to Day 1	Day 1 (Baseline)	Day 8 (± 1)	Day 15 (± 1)	Day 22 (± 1)	Day 22 or 29 (± 1)	Day 29, 36, or 43 (± 1)	
Screening/Consent	X							
Demographics	X							
Medical History	X							
Physical Exam (including vital signs)	X							
I/E Criteria Review	X	X						
Diagnosis of AD (including BSA evaluation)	X	X						
AD Signs and Symptoms		X	X	X	X	X	X	X
Local signs of skin atrophy and pigmentation changes		X	X	X	X	X	X	X
30 minute CST		X				X	X	
Blood Chemistry and Hematology		X				X		
RAST (optional)		X				X		
AE Reporting			X	X	X	X	X	X
Concomitant Medication Review		X	X	X	X	X	X	X
Drug Dispensing, weigh bottles (if applicable)		X	X	X	X			X
Subject Instruction/Compliance Review		X	X	X	X	X	X	X
Drug Return, weigh bottles, Accountability			X	X	X	X	X	If applicable

¹ Procedures were performed at the Final Visit (Day 22 or 29, depending on whether clearing occurred at Day 15 or Day 22, for those subjects whose lesions cleared) or Discontinuation Visit, if different from the Final Visit.

² Conditional Follow-Up (1 or 2 weeks after Final Visit, at the investigator's discretion) was to be scheduled for all subjects at conclusion of Final Visit or Discontinuation Visit. If CST was not abnormal at last visit and there was no further need to follow up on any laboratory tests or adverse events, then Follow-Up Visit was canceled by the study site.

6 Review of Efficacy

Efficacy Summary

This study was conducted at 10 study sites in the United States. All data were pooled and no statistical tests were conducted to examine possible study site differences because no formal hypothesis testing was conducted. No imputations were made for missing data.

Efficacy summaries included the signs and symptoms of AD at each evaluation and BSA affected and treated at each evaluation.

From an efficacy standpoint, all signs and symptoms showed marked progressive improvement beginning with Day 8 through the Day 29 evaluation. The percent BSA

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affected decreased from an average of 56.9 % at Baseline to an average of 6.7 % at Day 29. These efficacy findings are consistent with prior studies evaluating Cutivate Lotion.

Since the study was not designed to afford statistical conclusions related to efficacy, no labeling changes for the efficacy of Cutivate Lotion are recommended as part of the current labeling revisions.

6.1 Indication

Cutivate Lotion is an approved topical corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 12 months of age and older. (b) (4)

6.1.1 Methods

Although efficacy assessment was not the primary objective of this study, disease severity was relevant for assessing safety. Each subject was required to have at least 35% body surface area (BSA) affected to be enrolled. Subjects were to have atopic dermatitis with a total severity score of at least 6.0 for any three of eight potential signs and symptoms (Erythema, Papulation, Induration, Scaling, Oozing/Crusting, Excoriation, Lichenification, and Pruritus), where each sign/ symptom is rated on a scale of 0 (absent) to 3 (severe)].

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 Demographics

Table 3: Summary of Subject Demographic Criteria (ITT)

	Cutivate Lotion 0.05% (N=56)
Age (months)	
Mean	7.2
Median	7.2
STD	2.6
STDERR	0.3
Range	3.2-12.0
95% CI	6.5 to 7.9
Gender	
Male	38 (67.9%)
Female	18 (32.1%)
Ethnicity	
Hispanic/Latino	9 (16.1%)
Not Hispanic/Not Latino	47 (83.9%)
Race	
White	19 (33.9%)
Black or African American	31 (55.4%)
Asian	7 (12.5%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)
American Indian or Alaska Native	1 (1.8%)
Other	3 (5.4%)

Source: Sponsor's Table 11.2.1

Reviewer comment: Although the table above presents the age range for subjects from 3- 12 months. No subjects were 12 months of age. See table below for the number of subjects in each age cohort.



Also noted in this table is that under the race category some subjects were counted twice. It appears that subjects who reported more than one race were entered in both cohorts. White subjects are underrepresented in his study as compared to U.S. demographics. Although this could impact local safety evaluation, it is this reviewer's opinion that since the safety is supportive of previously conducted trials, the 19 white subjects assessed is sufficient.

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Table 4: Number of Subjects per Age Cohort

Age in months	Number of subjects in cohort
3	5
4	10
5	8
6	4
7	8
8	5
9	5
10	5
11	6
Total number of subjects	56

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Table 5: Baseline Characteristics (ITT)

Cutivate Lotion 0.05% (N=56)

Body Surface Area	<u>BSA Affected</u>	<u>BSA Treated</u>	
Mean	56.9	54.4	
Median	51.5	50.0	
STD	18.0	18.3	
STDERR	2.4	2.4	
Range	36.0-100.0	35.0-94.0	
95% CI	52.1 to 61.8	49.5 to 59.3	
Signs and Symptoms of Atopic Dermatitis	<u>Erythema</u>	<u>Papulation</u>	<u>Induration</u>
Absent	3 (5.4%)	2 (3.6%)	13 (23.2%)
Mild	10 (17.9%)	26 (46.4%)	23 (41.1%)
Moderate	34 (60.7%)	27 (48.2%)	20 (35.7%)
Severe	9 (16.1%)	1 (1.8%)	0 (0.0%)
	<u>Scaling</u>	<u>Oozing/Crusting</u>	<u>Excoriation</u>
Absent	1 (1.8%)	23 (41.1%)	8 (14.3%)
Mild	24 (42.9%)	24 (42.9%)	25 (44.6%)
Moderate	28 (50.0%)	8 (14.3%)	20 (35.7%)
Severe	3 (5.4%)	1 (1.8%)	3 (5.4%)
	<u>Lichenification</u>	<u>Pruritus</u>	
Absent	13 (23.2%)	0 (0.0%)	
Mild	31 (55.4%)	3 (5.4%)	
Moderate	9 (16.1%)	35 (62.5%)	
Severe	3 (5.4%)	18 (32.1%)	
Total Signs and Symptoms Severity Score			
Mean	11.5		
Median	11.0		
STD	2.7		
STDERR	0.4		
Range	7.0-19.0		
95% CI	10.7 to 12.2		

Source: Sponsor's Table 11.2.2 (part 1 of 3)

Reviewer comment: Enrolled subjects had ≥35% BSA per protocol. Baseline disease characteristics are consistent with moderate to severe atopic dermatitis.

6.1.3 Subject Disposition

Of the 56 subjects enrolled, 52 subjects completed the study. Of the four subjects that did not complete the study; one (1) was related to an adverse event of a Herpes Simplex Virus infected skin lesion (Subject 5-95), one (1) was lost to follow-up after completing all visits prior to the Final Visit (Subject 8-82) and 2 were related to abnormal CST testing at Baseline (Subjects 3-101 and 5-166).

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 6.1.4 *Analysis of Primary Endpoint(s)*

Not applicable

6.1.5 *Analysis of Secondary Endpoints(s)*

Not applicable

Other Endpoints

Efficacy summaries included BSA affected and treated and the signs and symptoms of AD at each evaluation. The percent BSA affected decreased from an average of 56.9% at Baseline to an average of 6.7 % at Day 29. All signs and symptoms showed marked progressive improvement beginning with Day 8 through the Day 29 evaluation. Result summaries are in tables 6 and 7 below:

Table 6: Summary of BSA affected (ITT)

	<u>Baseline</u>	<u>Day 8</u>	<u>Day 15</u>	<u>Day 22</u>	<u>Final Visit Day 22 or 29</u>	<u>Conditional Follow-Up</u>
Body Surface Area Affected						
N	56	54	54	54	54	3
Mean	56.9	33.8	20.7	10.8	6.7	24.0
Median	51.5	34.5	20.0	5.0	1.5	22.0
STD	18.0	19.7	18.7	14.3	11.1	15.1
STDERR	2.4	2.7	2.5	1.9	1.5	8.7
Range	36.0-100.0	2.0-90.0	0.0-80.0	0.0-63.0	0.0-52.0	10.0-40.0
Body Surface Area Treated						
N	56	54	54	54	54	
Mean	54.4	40.6	37.1	28.3	0.7	
Median	50.0	36.0	35.0	35.0	0.0	
STD	18.3	17.7	15.1	20.4	5.4	
STDERR	2.4	2.4	2.0	2.8	0.7	
Range	35.0-94.0	0.0-90.0	5.0-80.0	0.0-79.0	0.0-40.0	

Source: Sponsor's Table 14.2.2

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Table 7: Summary of signs and symptoms (ITT)

	<u>Baseline</u>	<u>Day 8</u>	<u>Day 15</u>	<u>Day 22</u>	<u>Final Visit Day 22 or 29</u>	<u>Conditional Follow-Up</u>
Erythema						
N	56	54	54	54	54	3
Absent	3 (5.4%)	4 (7.4%)	14 (25.9%)	24 (44.4%)	31 (57.4%)	0 (0.0%)
Mild	10 (17.9%)	33 (61.1%)	37 (68.5%)	26 (48.1%)	22 (40.7%)	3 (100.0%)
Moderate	34 (60.7%)	17 (31.5%)	3 (5.6%)	4 (7.4%)	1 (1.9%)	0 (0.0%)
Severe	9 (16.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Papulation						
N	56	54	54	54	54	3
Absent	2 (3.6%)	8 (14.8%)	19 (35.2%)	34 (63.0%)	35 (64.8%)	0 (0.0%)
Mild	26 (46.4%)	37 (68.5%)	30 (55.6%)	15 (27.8%)	17 (31.5%)	3 (100.0%)
Moderate	27 (48.2%)	9 (16.7%)	5 (9.3%)	5 (9.3%)	2 (3.7%)	0 (0.0%)
Severe	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Induration						
N	56	54	54	54	54	3
Absent	13 (23.2%)	24 (44.4%)	30 (55.6%)	43 (79.6%)	46 (85.2%)	0 (0.0%)
Mild	23 (41.1%)	25 (46.3%)	21 (38.9%)	8 (14.8%)	6 (11.1%)	3 (100.0%)
Moderate	20 (35.7%)	5 (9.3%)	3 (5.6%)	3 (5.6%)	2 (3.7%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Scaling						
N	56	54	54	54	54	3
Absent	1 (1.8%)	9 (16.7%)	22 (40.7%)	33 (61.1%)	32 (59.3%)	0 (0.0%)
Mild	24 (42.9%)	34 (63.0%)	30 (55.6%)	20 (37.0%)	20 (37.0%)	3 (100.0%)
Moderate	28 (50.0%)	11 (20.4%)	2 (3.7%)	1 (1.9%)	2 (3.7%)	0 (0.0%)
Severe	3 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oozing/Crusting						
N	56	54	54	54	54	3
Absent	23 (41.1%)	41 (75.9%)	48 (88.9%)	48 (88.9%)	53 (98.1%)	3 (100.0%)
Mild	24 (42.9%)	12 (22.2%)	6 (11.1%)	6 (11.1%)	1 (1.9%)	0 (0.0%)
Moderate	8 (14.3%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Excoriation						
N	56	54	54	54	54	3
Absent	8 (14.3%)	21 (38.9%)	34 (63.0%)	39 (72.2%)	43 (79.6%)	0 (0.0%)
Mild	25 (44.6%)	28 (51.9%)	19 (35.2%)	12 (22.2%)	9 (16.7%)	3 (100.0%)
Moderate	20 (35.7%)	5 (9.3%)	1 (1.9%)	3 (5.6%)	2 (3.7%)	0 (0.0%)
Severe	3 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lichenification						
N	56	54	54	54	54	3
Absent	13 (23.2%)	20 (37.0%)	41 (75.9%)	43 (79.6%)	44 (81.5%)	1 (33.3%)
Mild	31 (55.4%)	26 (48.1%)	8 (14.8%)	8 (14.8%)	7 (13.0%)	2 (66.7%)
Moderate	9 (16.1%)	7 (13.0%)	5 (9.3%)	2 (3.7%)	2 (3.7%)	0 (0.0%)
Severe	3 (5.4%)	1 (1.9%)	0 (0.0%)	1 (1.9%)	1 (1.9%)	0 (0.0%)
Pruritus						
N	56	54	54	54	54	3
Absent	0 (0.0%)	6 (11.1%)	20 (37.0%)	27 (50.0%)	33 (61.1%)	0 (0.0%)
Mild	3 (5.4%)	38 (70.4%)	29 (53.7%)	23 (42.6%)	18 (33.3%)	3 (100.0%)
Moderate	35 (62.5%)	9 (16.7%)	5 (9.3%)	2 (3.7%)	3 (5.6%)	0 (0.0%)
Severe	18 (32.1%)	1 (1.9%)	0 (0.0%)	2 (3.7%)	0 (0.0%)	0 (0.0%)

Source: Sponsor's Table 14.2.1

Reviewer comment: The provided data is a summary of efficacy and no imputations were made for missing data. Interpretation is limited; (b) (4)

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(b) (4)

6.1.7 Subpopulations

No formal statistical analyses of the data was proposed or conducted. No formal biostatistical Agency review was conducted for the submitted efficacy data.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing was not evaluated in this trial. Subjects received an exaggerated dose of twice daily as compared to the labeled dose of once daily to obtain the objectives of the HPA suppression test.

(b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence and Tolerance were not assessed in this trial.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

Results of this HPA axis suppression trial support the safety of Cutivate Lotion 0.05% with respect to adrenal suppressive effects in children 3 to 12 months of age with atopic dermatitis. Of 49 evaluable subjects with BSA of $\geq 35\%$ who were treated twice daily for three to four weeks, one subject showed laboratory evidence of adrenal suppression at the End of Treatment. Adrenal suppression resolved in this subject within one week as documented by normal cortrosyn stimulation testing.

No cutaneous signs of atrophy (telangiectasia, loss of elasticity, purpura, dusky erythema, striae) were seen in this trial although these are known adverse events associated with the use of topical corticosteroids. This assessment is limited due to the short duration of treatment. The risk of atrophy and telangiectasia would be expected to increase with longer duration of treatment. Treatment-related assessments of hyper/hypopigmentation were indeterminate in this open-labeled study.

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No deaths occurred in this trial and all but one of the 37 reported adverse events were non-serious. The serious AE (hospitalization for pyrexia) is unlikely to be due to study medication. The significant findings related to the study medication included bacterial and viral skin infections. These findings are not unexpected with use of topical corticosteroids for atopic dermatitis.

No Agency Biostatistics review of the safety data was conducted for this application. Review of the clinical data related to this submission by this reviewer did not identify any issues or irregularities. (b) (4)

(b) (4)

(b) (4)

7.1 Methods

Safety assessment in this open-labeled trial includes evaluation of the effect of Cutivate Lotion on the HPA axis, dermal safety, adverse event (AE) reporting, and hematology and blood chemistries.

Studies/Clinical Trials Used to Evaluate Safety

The objective of this study is to evaluate the systemic and local safety of Cutivate Lotion in subjects 3 mo- < 12 mo of age. Safety evaluation includes Cosyntropin Stimulation Testing, dermal evaluation by the investigator, adverse event (AE) reporting at each evaluation, and laboratory testing. HPA axis suppression and local skin changes (atrophy, telangiectasia, striae, hyper/ hypopigmentation) are all potential AE for the topical corticosteroid drug class and results are discussed in section 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.

No deaths and only 1 serious AE occurred in the study. The majority of discussion regarding AE is contained in section 7.4.1 Common Adverse Events.

Laboratory assessments were conducted at baseline and final visit (either week 22 or 29) and the results are discussed in section 7.4.2 Laboratory Findings.

7.1.2 Categorization of Adverse Events

MedDRA preferred terms (version 10.1) were used for classification of AEs. Terms are appropriate to evaluate for safety signals.

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7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

(b) (4)

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Subjects received a 3- or 4- week course of twice-daily applications of Cutivate Lotion. A thin film of lotion was to be applied to the areas affected by atopic dermatitis (AD) covering >35% Body Surface Area (BSA) excluding the eyelids, perioral area, around the nostrils, and in the diaper area of those subjects who wore diapers and plastic pants. Subjects should not have bathed within 2 hours after study medication applications. Occlusive dressings were not to be used. The first application of study medication was applied in the office under the supervision of the study medication dispenser. After at least 15 days of study treatment, therapy was to be continued for one more week after complete clearance was achieved (absence of all signs and symptoms, including residual erythema).

At the end of 2 weeks of treatment (Day 15):

- If lesions were cleared (absence of all signs and symptoms, including residual erythema) such that the BSA affected falls to < 35%, the parent was to continue to treat at least 35%BSA (treating cleared skin in addition to any remaining lesional skin) for 1 more week and return for the Final visit (Day 22) at that time.
- For subjects who were < 100% cleared after 2 weeks of treatment, the parent/guardian was to continue to treat at least 35% BSA for 2 more weeks and return for the Final visit (Day 29) at that time.

Reviewer comment: The twice daily dosing regimen applied in this study is consistent with the dosing regimen that was used in the previous HPA axis suppression study conducted in patients aged 4 months to < 6 years old for Cutivate Lotion. This dosing regimen was found acceptable by the Agency after review of the protocol prior to the initiation of the study.

The number of applications during the study ranged from 6 to 62 and averaged 50.8 ± 10.2 . The majority of subjects missed less than 10 % of the study medication application (50 subjects) and continued treatment to at least 22 days (46 subjects). The table below generally summaries extent of exposure:

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Table 8: Extent of Exposure (ITT)

	<u>Overall</u>	<u>1-7 Days</u>	<u>8-14 Days</u>	<u>15-21 Days</u>	<u>22-28 Days</u>	<u>29+ Days</u>
Number of Subjects	55	55	53	53	48	16
Number of Applications						
Mean	50.8	13.3	13.5	13.7	12.0	2.6
STD	10.2	1.6	1.0	0.7	3.6	1.5
Range	6.0 to 62.0	6.0 to 14.0	8.0 to 14.0	10.0 to 14.0	2.0 to 14.0	1.0 to 6.0
Number of Missed Applications						
0%	26 (47.3%)	39 (70.9%)	37 (69.8%)	43 (81.1%)	38 (79.2%)	13 (81.3%)
>0% to < 10%	24 (43.6%)	12 (21.8%)	12 (22.6%)	7 (13.2%)	6 (12.5%)	0 (0.0%)
10% to < 20%	5 (9.1%)	1 (1.8%)	1 (1.9%)	3 (5.7%)	1 (2.1%)	0 (0.0%)
20% to < 30%	0 (0.0%)	2 (3.6%)	2 (3.8%)	0 (0.0%)	2 (4.2%)	1 (6.3%)
≥ 30%	0 (0.0%)	1 (1.8%)	1 (1.9%)	0 (0.0%)	1 (2.1%)	2 (12.5%)
Mean	1.5	0.5	0.5	0.2	0.3	0.2
STD	2.1	1.2	1.0	0.6	0.7	0.4
Range	0.0 to 8.0	0.0 to 7.0	0.0 to 6.0	0.0 to 2.0	0.0 to 3.0	0.0 to 1.0

Source: Sponsor's table 14.3.0

Reviewer comment: Line listings assessing compliance show that the sponsor's numbers are slightly off. This reviewer determined that all 56 subjects applied some study medication and 54 subjects applied medication for at least 19 days. Also, 46 and not 48 subjects actually applied study drug at least 22 days. Regardless, subject compliance was high and the extent of exposure appears adequate for evaluation of safety.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Animal and in vitro testing was deemed adequate for approval in patients 12 months of age and older. There is no new Pharmacology/ Toxicology data with this submission. A separate supplement S-005 provides data for a photo-carcinogenicity study which is currently under review by Dr. Barbara Hill. Recommendations for labeling based on this study have been proposed for the label associated with this efficacy supplement.

7.2.4 Routine Clinical Testing

No routine clinical testing was performed. Laboratory assessment was performed and results are discussed in section 7.4.2 Laboratory Findings.

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7.2.5 Metabolic, Clearance, and Interaction Workup

The applicant did not measure Plasma Fluticasone blood levels in this study and the Agency did not request measurement. In a previous HPA axis suppression study (FPL 10005) conducted with Cutivate Lotion in patients aged 3 months to 5 years, plasma fluticasone levels were not measured in children less than 2 years of age. Based on experience from an HPA axis study for fluticasone cream the sponsor cited states that "some IRBs [Institutional Review Boards] were not comfortable with a large volume of blood being drawn from infants and some of the investigational sites did not have the technical proficiency to collect this volume of blood from small peripheral veins(Sponsor's NDA submission, Volume14, p.18)".

Reviewer comment: Plasma fluticasone levels were not determined in children less than 2 years of age in the development of Cutivate Cream, 0.05% which is approved down to 3 months of age. It is this reviewer's opinion that the sponsor's rationale is reasonable. The protocol was assessed by the Agency biopharmaceutics and clinical reviewers and was deemed acceptable to establish the safety of the lotion for the infant age group. The study was conducted in accordance with Agency recommendations.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

HPA Axis Suppression

The primary systemic safety assessment for this study was the response to the Cosyntropin Stimulation Testing (CST) at end-off treatment. CST was performed to evaluate HPA axis suppression and was administered at baseline and final visit (either week 22 or 29). An abnormal HPA response was defined as a 30-minute post-stimulation serum cortisol level < 18 micrograms/dL at the end of treatment. Subjects with an abnormal an CST result at baseline were discontinued from the study. 49 subjects completed testing. CST is described below. The reader is also referred to the clinical pharmacology and biopharmaceutics review of Dr. Abimbola Adebowale (9/29/10) for analysis of the study.

The dose of Cortrosyn® administered was 0.125 mg. The preferred route for administration was intravenous. However, if this was unachievable, intramuscular administration was permitted. The applicant cited a study (Hawkins, JG and Warner, MB, North Carolina Medical Journal 1989; 50 (6): 306-308) that has shown that administration of Cortrosyn by either the intravenous or intramuscular route produced similar results. At approximately 8:00 AM on Day 1 (Screening/Baseline Visit), pre-stimulation and 30 minutes post-stimulation blood samples (3-5mL) were taken. The End of Treatment CST was also performed in the morning within one hour of the time the Baseline CST was performed.

Reviewer's Comments: Cosyntropin was administered at both baseline and end of treatment to 15 subjects (IV route) and 24 subjects (IM route). All the other subjects had

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either IV or IM administration before and after treatment. Subject 2-134 who demonstrated HPA axis suppression had IV administration only. This reviewer concurs with Dr. Adebowale's conclusion that there does not appear to be a correlation between post-stimulation cortisol levels and the route of administration (IV or IM) of cosyntropin.

Baseline response:

3 subjects had an abnormal adrenal response (i.e. < 18 micrograms/dL) at baseline. Only 2 of the 3 subjects (3-101 and 5-166) were excluded from the study. Subject (2-135) had a baseline CST of 17.4 micrograms/dL, which on re-analysis yielded 20.3 micrograms/dL and the subject was permitted to remain in the study. This subject completed the study and was found to have normal adrenal axis function with a post-stimulation cortisol level of 20.9µg/dL.

Reviewer comment: This reviewer agrees with Dr. Adebowale that it is reasonable to consider this subject evaluable despite the initial low cortisol level at baseline.

Evaluable subjects:

Of the 56 subjects enrolled 7 subjects were considered not evaluable for HPA axis suppression assessment. 2 subjects (3-101, 5-166) had abnormal Baseline cortisol levels (described above); 3 subjects (6-117, 8-19, 8-76) had venous access difficulties/insufficient samples; 1 subject (08-82) withdrew consent; 1 subject's sample (08-83) was invalid due to a lab error. The table below represents the non-evaluative subjects:

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Table 9: Evaluable Subjects in HPA Axis Suppression Assessment

Subject #	Reason Non-Evaluable	Post-Treatment CST
3-101	Baseline HPA Axis Results Demonstrate Suppression; Post-CST cortisol: 11.3 µg/dL.	Not applicable – subject discontinued
5-166	Baseline HPA Axis Results Demonstrate Suppression; Post-CST cortisol: 16.9 µg/dL.	Not applicable – subject discontinued
6-117	EOT CST not done – specimen could not be obtained	Not Done
8-019	EOT CST - inadequate specimen. Lab could not perform analysis.	No EOT CST lab result; parent would not allow redraw
8-076	EOT CST - inadequate specimen. Lab could not perform analysis.	No EOT CST lab result. Subject had repeat normal CST test (Post-CST cortisol: 37.1 µg/dL at follow-up visit) done one week past the Final Visit window but subject was off study medication
8-082	EOT CST not done, subject lost to follow-up, subject's parent refused to return for evaluation	Not Done
8-083	EOT CST was performed but results invalid due to lab handling error.	Subject had repeat normal CST test (Post-CST cortisol: 28.8 µg/dL at follow-up visit) done 13 days past the Final Visit but subject was off study medication

Source: Sponsor's table 12.1.2.1

Subject 5-95 discontinued the study after completing 24 days of dosing due to Herpes Simplex Virus skin infection. The subject had sufficient exposure to study medication, completed CST without evidence of suppression, and is considered by the applicant to be an evaluable subject.

Reviewer comment: There is limited information on the case report form regarding this subject's HSV-1 infection (see 7.4.1 Common Adverse Events). It is unclear whether this subject's Herpes Simplex skin infection could affect cortisol levels. Since the HPA axis is a highly stress-sensitive system, stress-related factors have been shown to affect cortisol levels. This reviewer has been unable to find evidence that HSV infection would increase a cortisol response. In fact infections such as HIV and sepsis have demonstrated a blunting in cortisol response to CST. It is this reviewer's opinion that the HSV infection is unlikely to impact CST anymore than other stressors/ minor infections which have not been controlled for in this trial. It is recommended that this subject be considered evaluable.

Post-treatment response:

One subject out of 49 (2%) evaluable subjects, subject 2-134 (4 month old male) demonstrated adrenal suppression at the End of Treatment evaluation as documented by a post-stimulation cortisol level of 15 micrograms/dL. This subject had a BSA of 94%

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treated at baseline and a post-stimulation cortisol level of 31 micrograms/dL at baseline.

The adrenal suppression observed in this subject resolved within one week as

documented by a normal post-stimulation cortisol level at follow-up (22.1

micrograms/dL). The table below summarizes all CST results:

Table 10: Summary of Cosyntropin Stimulation Test Results

Cosyntropin Stimulation Test	Baseline	End of Treatment ^a	Change from Baseline ^b	Follow-Up	Change from Baseline ^b
Post-Stimulation Cortisol Level (µg/dL)					
N	56	49	49	3	3
Mean	27.6	26.5	-1.8	29.3	2.1
STD	5.0	4.8	4.9	7.5	10.4
Range	11.3 to 38.3	15.0 to 36.7	-16.0 to 7.7	22.1 to 37.1	-8.9 to 11.9
Adrenal Response ^c					
Normal	53 (94.6%)	48 (98.0%)		3 (100.0%)	
Abnormal	3 (5.4%)	1 (2.0%)		0 (0.0%)	
Subjects with Baseline and End of Treatment CST Results					
Cosyntropin Stimulation Test	Baseline	End of Treatment ^a	Change from Baseline ^b	Follow-Up	Change from Baseline ^b
Post-Stimulation Cortisol Level (µg/dL)					
N	49	49	49	1	1
Mean	28.2	26.5	-1.8	22.1	-8.9
STD	4.5	4.8	4.9	NA	NA
Range	17.4 to 38.3	15.0 to 36.7	-16.0 to 7.7	22.1 to 22.1	-8.9 to -8.9
Adrenal Response ^c					
Normal	48 (98.0%)	48 (98.0%)		1 (100.0%)	
Abnormal	1 (2.0%)	1 (2.0%)		0 (0.0%)	

^a CST performed for subjects suppressed at baseline and discontinued at Day 8 are not included in the end of treatment results.

^b Change from baseline computed as end of treatment minus baseline and follow-up minus baseline, respectively.

^c Abnormal adrenal suppression is indicated by a post-stimulation cortisol level ≤ 18 µg/dL.

Source: Sponsor's table 14.3.4.1

Signs of Skin Atrophy

Local signs of skin atrophy were assessed at baseline, day 8, 15, 22, 29, and follow-up.

Signs of skin atrophy were evaluated for intensity by the same investigator, to the extent possible, at each visit. Atrophy was considered an AE. Assessments included:

- Telangiectasia: chronic dilation of groups of superficial capillaries
- Loss of elasticity: the loss of flexibility of the skin, not able to return to an initial form or state following deformation
- Purpura: hemorrhages of the skin resulting in purplish spots or patches
- Dusky erythema: a deep redness
- Striae: a thin line, band, stripe, or streak distinguished from the other skin tissue
- Any other signs of atrophy

The investigator evaluated the severity of each clinical sign of skin atrophy using the following scale. 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe.

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 Results are summarized in the table below:

Table 11: Summary of Signs and Symptoms of Atrophy

	<u>Baseline</u>	<u>Day 8</u>	<u>Day 15</u>	<u>Day 22</u>	<u>Final Visit Day 22 or 29</u>	<u>Conditional Follow-Up</u>
Telangiectasia						
N	56	54	54	54	54	3
Absent	56 (100.0%)	53 (98.1%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	3 (100.0%)
Mild	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Loss of Elasticity						
N	56	54	54	54	54	3
Absent	56 (100.0%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	3 (100.0%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Purpura						
N	56	54	54	54	54	3
Absent	56 (100.0%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	3 (100.0%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dusky Erythema						
N	56	54	54	54	54	3
Absent	56 (100.0%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	3 (100.0%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: No imputations were made for missing data.

	<u>Baseline</u>	<u>Day 8</u>	<u>Day 15</u>	<u>Day 22</u>	<u>Final Visit Day 22 or 29</u>	<u>Conditional Follow-Up</u>
Striae						
N	56	54	54	54	54	3
Absent	56 (100.0%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	3 (100.0%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Sponsor's table 14.3.1.1

Reviewer Comment: Cutaneous atrophy, striae and telangiectasia are known adverse events associated with the use of topical corticosteroids. Clinical signs of atrophy were not observed in subjects in these studies. Treatment in this study was from 3 – 4 weeks; the risk of atrophy and telangiectasia would be expected to increase with longer duration of treatment.

Skin Pigmentation Evaluation

Lesion site hypopigmentation or hyperpigmentation was assessed at baseline, day 8, 15, 22, 29, and follow-up. To the greatest extent possible, the same investigator assessed the subject throughout the course of the study. Resolution of preexisting pigmented areas was not considered an AE. Any pigmentation changes not considered part of the healing process could be considered an AE. The table below summarizes evaluation of pigmentation:

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Table 12: Summary of Lesion Site Pigmentation

	Baseline	Day 8	Day 15	Day 22	Final Visit Day 22 or 29	Conditional Follow-Up
Evidence of Cutaneous Atrophy						
N	56	54	54	54	54	3
No	56 (100.0%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	54 (100.0%)	3 (100.0%)
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperpigmentation						
N	56	54	54	54	54	3
No	44 (78.6%)	44 (81.5%)	48 (88.9%)	47 (87.0%)	48 (88.9%)	3 (100.0%)
Yes	12 (21.4%)	10 (18.5%)	6 (11.1%)	7 (13.0%)	6 (11.1%)	0 (0.0%)
Hypopigmentation						
N	56	54	54	54	54	3
No	53 (94.6%)	51 (94.4%)	50 (92.6%)	47 (87.0%)	48 (88.9%)	3 (100.0%)
Yes	3 (5.4%)	3 (5.6%)	4 (7.4%)	7 (13.0%)	6 (11.1%)	0 (0.0%)

Note: No imputations were made for missing data.
 Source: Sponsor's table 14.3.1.2

The changes seen in pigmentation were all considered by investigators to be due to a post-inflammatory process. (b) (4)

Reviewer Comment: Pigmentary change is a known adverse event associated with the use of topical corticosteroids. However, post-inflammatory hyper- or hypopigmentation may also occur secondary to inflammation from atopic dermatitis. It is possible that treatment with Cutivate Lotion played a role in the formation of pigmentation changes in certain patients. Without a control group, causality cannot be determined. (b) (4)

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths associated with this study.

7.3.2 Nonfatal Serious Adverse Events

There was one (1) SAE reported which resulted in hospitalization. Subject 1-88 (11-month-old male) presented with a fever of unknown origin after the site had referred the child to the ER for evaluation. The subject was admitted to the hospital on (b) (6) for work-up and monitoring and was discharged on (b) (6). The work-up was negative including negative cultures although the child was treated with fluids and

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antibiotics. The subject remained on study medication during the event and the event was determined to be unrelated to study drug.

Reviewer comment: This reviewer has noted that this child at baseline had mildly abnormal (less than 2 fold increase) ALT of 70 (reference range 13-45) and AST of 78 (reference range 16-52) which remained elevated at end of study (ALT 68/ AST86). Pyrexia was the only AE reported for this subject and the reported outcome was resolved. Diagnosis and causality is difficult to determine from the limited information provided from this open-labeled trial.

7.3.3 Dropouts and/or Discontinuations

Of the 56 subjects enrolled, 52 subjects completed the study. Of the four subjects that did not complete the study; one (1) was related to an adverse event of a Herpes Simplex Virus infected skin lesion (Subject 5-95), one (1) was lost to follow-up after completing all visits prior to the Final Visit (Subject 8-82) and 2 were related to abnormal CST testing at Baseline (Subjects 3-101 and 5-166).

7.3.4 Significant Adverse Events

AE reporting was collected at day 8, 15, 22, 29, and follow-up. Safety analysis of AE includes the intention to treat population (ITT). Twenty-five of 56 subjects (44.6%) reported a total of 37 adverse events. The majority of the AEs (27/37 or 73%) were mild in severity. No AE was considered severe. Most (34/37 or 91.9%) were considered not related to study medication. Three of the 37 (8.1%) adverse events (herpes simplex (5-165), folliculitis (5-163), and impetigo (5-163) were considered possibly related to study medication. A summary of the AE characteristics are shown in the table below. Since the AE in this study do not demonstrate major safety concerns, reported AE are discussed in section 7.4.1 Common Adverse Events.

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Table 13: Summary of AE Characteristics

	Cutivate Lotion 0.05% (N=56)
Number of Events Reported	37
Number of Subjects who Reported One or More Adverse Events ^a	25 (44.6%)
Serious ^b	
No	36 (97.3%)
Yes	1 (2.7%)
Severity ^b	
Mild	27 (73.0%)
Moderate	10 (27.0%)
Severe	0 (0.0%)
Relationship to Study Medication ^b	
Not Related	34 (91.9%)
Possible	3 (8.1%)
Probable	0 (0.0%)
Definite	0 (0.0%)

Source: Sponsor's table 14.3.1.4.1

7.3.5 Submission Specific Primary Safety Concerns

HPA axis suppression is a submission specific safety concern and has already been address in section 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events reported during the study were infections and infestations (15/37 events, 40.5%), general disorders such as pyrexia and irritability (5/37 events, 13.5%), respiratory, thoracic and mediastinal disorders (5/37 events, 13.5%), and gastrointestinal disorders (4/37 events, 10.8%).

Table 14: Summary of AE (ITT)

Adverse Event	Number of Subjects ^a (N=56)	Number of Events (N=37)
Infections and infestations	11 (19.6%)	15 (40.5%)
Gastroenteritis	2 (3.6%)	2 (5.4%)
Herpes simplex	2 (3.6%)	2 (5.4%)
Nasopharyngitis	2 (3.6%)	3 (8.1%)
Upper respiratory tract infection	2 (3.6%)	3 (8.1%)
Folliculitis	1 (1.8%)	1 (2.7%)
Impetigo	1 (1.8%)	1 (2.7%)
Oral candidiasis	1 (1.8%)	1 (2.7%)
Otitis media	1 (1.8%)	1 (2.7%)
Staphylococcal infection	1 (1.8%)	1 (2.7%)
Gastrointestinal disorders	4 (7.1%)	4 (10.8%)
Constipation	1 (1.8%)	1 (2.7%)
Diarrhoea	1 (1.8%)	1 (2.7%)
Gastrooesophageal reflux disease	1 (1.8%)	1 (2.7%)
Teething	1 (1.8%)	1 (2.7%)
General disorders and administration site conditions	4 (7.1%)	5 (13.5%)
Pyrexia	3 (5.4%)	3 (8.1%)
Irritability	2 (3.6%)	2 (5.4%)
Respiratory, thoracic and mediastinal disorders	4 (7.1%)	5 (13.5%)
Cough	2 (3.6%)	2 (5.4%)
Nasal congestion	1 (1.8%)	1 (2.7%)

Adverse Event	Number of Subjects ^a (N=56)	Number of Events (N=37)
Respiratory, thoracic and mediastinal disorders (continued)		
Rhinorrhoea	1 (1.8%)	1 (2.7%)
Wheezing	1 (1.8%)	1 (2.7%)
Immune system disorders	2 (3.6%)	3 (8.1%)
Hypersensitivity	2 (3.6%)	3 (8.1%)
Congenital, familial and genetic disorders	1 (1.8%)	1 (2.7%)
Ichthyosis	1 (1.8%)	1 (2.7%)
Eye disorders	1 (1.8%)	1 (2.7%)
Conjunctivitis	1 (1.8%)	1 (2.7%)
Reproductive system and breast disorders	1 (1.8%)	1 (2.7%)
Genital rash	1 (1.8%)	1 (2.7%)
Skin and subcutaneous tissue disorders	1 (1.8%)	2 (5.4%)
Dermatitis diaper	1 (1.8%)	1 (2.7%)
Skin fissures	1 (1.8%)	1 (2.7%)

Source: Sponsor's table 14.3.1.4.4

Reviewer comment: Three of the 37 (8.1%) adverse events herpes simplex (5-165), folliculitis (5-163), and impetigo (5-163) were considered possibly related to study medication. It is this reviewer's opinion that another herpes simplex at application site (5-95), and application site staph infection (4-156) are likely related to study medication.

The extent of HSV disease in both subjects is not described in full detail in the case report forms. Subject 5-165 had documented HSV clusters on two areas of the chest wall and one on the posterior thigh. There is no description of the extent on subject's 5-95 lesions. Both subjects were treated with oral acyclovir. Neither case resolved by the

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end of study. Subject 5-165 completed the study; subject 5-95 discontinued the study after completing 24 days of dosing.

7.4.2 Laboratory Findings

The post-marketing commitment letter requested laboratory assessment be included in the trial due to abnormalities in serum chemistries seen in pediatric subjects in the open-labeled HPA axis trial conducted for the original approval. The most notable abnormality was a one 4- month-old male subject with marked elevations of both AST and ALT. His baseline values were elevated, with an AST of 113 U/L (normal range 11-36 U/L) and an ALT of 110 U/L (normal range 6-43 U/L). The end-of-treatment AST for this patient was 366 U/L, and the ALT was 523 U/L. Information regarding this subject is included in the current labeling.

Reviewer comment: No marked ALT or AST elevations were observed in this trial.

Table 15: Summary of Chemistry, Hematology and Transaminase Tests

	<u>Baseline</u>	<u>End of Treatment</u>
Chemistry Test Results		
Normal	2 (3.6%)	3 (6.0%)
Abnormal	54 (96.4%)	47 (94.0%)
Not Reported	0	6
Hematology Test Results		
Normal	0 (0.0%)	0 (0.0%)
Abnormal	53 (100.0%)	47 (100.0%)
Not Reported	3	9
ALT (AGPT)		
N	55	50
Mean	25.7	24.0
STD	11.2	11.1
Range	10.0 to 70.0	10.0 to 68.0
AST (AGOT)		
N	55	50
Mean	38.9	39.0
STD	11.3	12.5
Range	20.0 to 82.0	24.0 to 86.0

Source: Sponsor's table 14.3.1.4.4

Chemistry assessments showed abnormal values for lactate dehydrogenase (LDH) and alkaline phosphatase (AP). 3 subjects (2-132, 3-100, 4-115) had normal LDH at baseline, but elevated at end of treatment. 2 subjects 3-100 (10 month old female) and

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4-115 (7 month old male) had mild elevations of LDH of 366 and 374 respectively (upper limit of reference range varies from 327-367). One subject 2-132 (11 month old male) had a greater elevation of 559 (reference range 155-345). The only subject reporting an AE was subject 3-100 and that AE was diaper rash.

Reviewer comment: LDH is a non-specific laboratory measurement and is an indicator of cell turnover. It is this reviewer's opinion that the 2 subjects with mild elevations are not clinically significant. The significance of 1 subject with the nearly 2-fold increase of LDH in this trial is difficult to interpret in this open-labeled study.

3 subjects had elevated levels of alkaline phosphatase at end of treatment. Subject 8-81 (10 month old female) showed a marked elevation of 4849 (reference range 101-431), subjects 8-78 (11 month old female) and 1-87 (11 month old male) had less elevated levels of 419 and 369 respectively (reference range 121-291). None of the subjects reported AEs.

Reviewer comment: Mild elevations in AP could be of bone origin and attributed to growth spurts. The 10 fold increase in AP in one subject is of concern. However, it is difficult to interpret in the context of this open-labeled trial.

The majority of abnormal hematology parameters were mildly elevated platelets and eosinophils. The majority of subjects demonstrated elevations at baseline as well as at end of treatment.

Reviewer comment: Elevated platelets may signal non-specific inflammation and were also seen in a number of subjects only at baseline. An elevation of eosinophils is not unexpected in subjects with atopy. It is this reviewer's opinion that these abnormal laboratory tests have no clinical significance in this patient population.

A number of subjects also demonstrated elevated white blood cells (WBC) either at baseline, end of study or both. 3 subjects with normal WBC at baseline demonstrated significantly elevated WBC at the end of study: subject 5-97 (WBC 18.1), subject 4-151 (WBC 22.3), and subject 4-111 (WBC 19.7).

Reviewer comment: Elevated leukocytes could represent infection which is likely the case for subject 5-97(4 month old male). This subject showed a predominance of neutrophils and reported pyrexia 3 days prior to laboratory analysis. Elevated WBC could also be due to demarginalization of leukocytes which can be caused by systemic steroids. It is possible that the WBC elevations in subjects 4-151 (9 month old male with BSA of 58%) and 4-111 (4 month old male with BSA of 61%) could represent systemic absorption. However, no AEs or HPA axis suppression were reported for these subjects. The significance of elevated WBC as a potential indicator for treatment-related infection or systemic exposure is difficult to interpret in this open-labeled study.

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7.4.3 *Vital Signs*

Vital signs were assessed at screening. No additional data was collected regarding the affect of Cutivate on vital signs.

7.4.4 *Electrocardiograms (ECGs)*

ECGs were not performed during this trial.

7.4.5 *Special Safety Studies/Clinical Trials*

Not applicable.

7.4.6 *Immunogenicity*

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

7.5 Other Safety Explorations

7.5.1 *Dose Dependency for Adverse Events*

Only one concentration, 0.05%, was studied.

7.5.2 *Time Dependency for Adverse Events*

The treatment period for this clinical trial was four weeks or less. No explorations were performed for time-dependency within this narrow window of time. (b) (4)

Reviewer comment: Some adverse effects of topical steroids (e.g., HPA axis suppression, telangiectasia, striae, atrophy, effects on growth) may be dose and time dependent, (b) (4)

7.5.3 *Drug-Demographic Interactions*

With only one case of HPA axis suppression, frequency by age cohort could not be determined.

Reviewer comment: Although subject 2-134 demonstrated suppression and had a BSA of 94 % at baseline, this does not definitively indicate a correlation between %BSA

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treated and adrenal suppression. There were 4 other subjects who had a % BSA value between 90 and 92% and none of them were suppressed.

7.5.4 Drug-Disease Interactions

With only one case of HPA axis suppression frequency by percentage of BSA could not be determined.

7.5.5 Drug-Drug Interactions

No drug-drug interactions were studied in this trial.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity was not assessed in this trial.

7.6.2 Human Reproduction and Pregnancy Data

No studies in pregnant women were performed (b) (4)
(b) (4). Cutivate Lotion is categorized as pregnancy class C.

7.6.3 Pediatrics and Assessment of Effects on Growth

(b) (4)

(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

Cutivate Lotion contains the excipient imidurea (b) (4). Imidurea is a water soluble antimicrobial preservative which releases formaldehyde as a breakdown product. Prior to this NDA submission, the sponsor had submitted a labeling supplement, SLR-002, to address significant levels of formaldehyde in Cutivate Lotion which was

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identified post-marketing. Labeling modifications have been made to address the presence of formaldehyde and these will be included the PLR format.

Reviewer comment: Although there is a theoretical risk for carcinogenicity in pediatric patients given the potential for a larger cumulative exposure to formaldehyde than adults, there is no data at this time to support topical exposure to low levels of formaldehyde poses and increased risk. Current labeling, which includes additional information regarding formaldehyde risks, was approved in September, 2010 and includes warnings regarding the presence of formaldehyde and states that safety has not been established beyond 4 weeks of use.

(b) (4)

8 Postmarket Experience

The sponsor has yet to submit the 120 day safety update and the Agency has requested submission of the safety information as required by the 21 CFR 314.50(d)(5)(vi)(b).

Reviewer comment:

(b) (4)

Review of Periodic Safety Reports and Distribution Data

(b) (4)

They have provided 5 adverse experience reports which consist of 6 reported AEs (2 serious and 4 non-serious):

Mfr Report # 436893- this is a case of drug induced myopathy associated with inhaled fluticasone propionate

Mfr Report # O8C428- this is a case of rectal bleeding and diarrhea in a patient on Cutivate and concomitant Plavix

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Mfr Report # 571974-this is a case of right-sided facial swelling associated with Cutivate reported by the patient

Mfr Report # 512737-this is a case of an “allergic reaction” with “redness and irritation” associated with Cutivate reported by a pharmacist

Mfr Report # 607424-this is a case of “white/ red colored marks” associated with Cutivate reported by patient

Reviewer comment: The information contained in these MedWatch reports is limited and this reviewer cannot determine a diagnosis or draw a conclusion about the causality regarding these reports. These reported AEs are included in the most recent labeling:

Post Marketing Experience:

The following localized adverse reactions have been reported during post approval use of CUTIVATE® Lotion: erythema, edema/swelling, bleeding, and a reported lack of efficacy.

Reviewer comment:

(b) (4)

9 Appendices

9.1 Literature Review/References

Hawkins, JG and Warner, MB. (1989) North Carolina Medical Journal 50 (6): 306-308

Fries, E., Dettenborn, L., & Kirschbaum, C. (2009) International Journal of Psychophysiology; 72: 67–73.

9.2

(b) (4)

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(b) (4)

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(b) (4)

9.3 Advisory Committee Meeting

An Advisory Committee meeting was deemed to be unnecessary for this application.

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

/s/

AMY S WOITACH
10/25/2010

DAVID L KETTL
10/26/2010

(b) (4)