CLINICAL REVIEW of NDA 19-452

Application Type	505(b)(1)
Submission Number	S-024
Submission Code	SE5
Letter Date	February 12, 2007
Stamp Date	February 12, 2007
PDUFA Goal Date	December 15, 2007
Reviewer Name	Brenda Carr, M.D.
Review Completion Date	July 19, 2007
Established Name	fluocinolone acetonide, 0.1%
Trade Name	Derma-Smoothe/FS
Therapeutic Class	corticosteroid
Applicant	Hill Dermaceuticals, Inc
Priority Designation	S
Formulation	solution
Dosing Regimen	twice daily for up to 4 weeks
Indication	atopic dermatitis
Intended Population	3 months and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The sponsor's fluocinolone acetonide product, Derma-Smoothe/FS, a low to mid-potency topical corticosteroid, was approved on February 3, 1988 for the indication of atopic eczema in adults. On February 16, 1995, the product was approved for psoriasis of the scalp in adults. On August 18, 1999, the product received approval for atopic dermatitis in pediatric patients ≥ 6 years of age. On October 10, 2001, approval of the product was extended to atopic dermatitis in pediatric patients ≥ 2 years of age. The sponsor intends that the clinical data submitted in this efficacy supplement will support labeling changes for use of their product for treatment of atopic dermatitis in patients 3 months and older.

From a clinical perspective, it is recommended that the application be approved.

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The submission provided for the final report for a study entitled, "An Open-Label Safety Study of Derma-Smoothe/FS® Topical Oil in Pediatric Patients, 3 months to 2 years, with Atopic Dermatitis. The study was conducted to assess the HPA axis by Cosyntropin stimulation testing following treatment twice daily for 4 weeks with the sponsor's product. The study was conducted in subjects 3 months to 2 years in age with moderate to severe atopic dermatitis with disease involvement on 20% or greater total body surface area.

Study product was applied to all affected areas (as identified at baseline by the investigator). Additionally, caregivers were instructed to treat new areas that arose during the treatment period. Cosyntropin stimulation testing was done at baseline and at Week 4. Final evaluation was one week post-treatment. The reviewer applied the criterion of a post-stimulation cortisol level of > 18 mcg as being reflective of normal adrenal function.

A total of 30 subjects received study drug and had at least one visit; these subjects constituted the intent-to-treat population. A total of 29 subjects completed the study. A total of 14 of the 29 subjects (48%) were under one year of age, 7 (24%) of whom were between the ages of 3 to < 6 months, and 7 of whom (50%) were between the ages of 6 to 12 months. A total of 3 subjects (10%) were between the ages of 3 to 4 months. A total of 12 subjects (41%) were < 7 months of age.

All three subjects between the ages of 3 to 4 months had extensive disease with > 75% body surface area involvement. Two of these subjects missed ≤ 2 doses (one of these missed no doses), and the third missed 2 to 4 doses. Thus, the equivalent of two days of treatment was the most that any of these three subjects missed. All three subjects were considered to have "moderate" disease at baseline. At Week 4, two of the three had "none", and the third had "mild" disease.

1.3.3 Safety

No subjects showed evidence of adrenal suppression at Week 4 (end of treatment).

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen is twice daily for no longer than 4 weeks and is the approved regimen for patients ≥ 2 years of age.

1.3.5 Drug-Drug Interactions

Not applicable

1.3.6 Special Populations

See Sections 1.3.2 and 1.3.3.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor's fluocinolone acetonide product (Derma-Smoothe/FS), a low to mid-potency topical corticosteroid, was approved on February 3, 1988 for the indication of atopic eczema in adults. On February 16, 1995, the product was approved for psoriasis of the scalp in adults. On August 18, 1999, the product received approval for atopic dermatitis in pediatric patients ≥ 6 years of age. On October 10, 2001, approval of the product was extended to atopic dermatitis in pediatric patients ≥ 2 years of age.

For atopic eczema in adults, the dosing is 3 times daily. For treatment of scalp psoriasis in adults, Derma-Smoothe/FS is left on overnight or for a minimum of 4 hours, under shower cap occlusion then washed off. For treatment of atopic dermatitis in pediatric patients, the dosing is twice daily for no longer than 4 weeks.

The submission provides for the final report for a study entitled, "An Open-Label Safety Study of Derma-Smoothe/FS® Topical Oil in Pediatric Patients, 3 months to 2 years, with Atopic Dermatitis (initiation date: April 13, 2005; completion date November 29, 2006). The report provides for safety data from an HPA axis study conducted in subjects 3 months to 2 years in age with moderate to severe atopic dermatitis with disease involvement on 20% or greater total body surface area. The sponsor intends that the submitted clinical data will support labeling changes for use of their product for treatment of atopic dermatitis in patients 3 months and older.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is for the treatment of moderate to severe atopic dermatitis in pediatric patients, 3 months and older with moderate to severe atopic dermatitis for no longer than 4 weeks.

6.1.1 Methods

See Section 7.1.

6.1.2 General Discussion of Endpoints

See Section 7.1.

6.1.3 Study Design

See Section 7.1

6.1.4 Efficacy Findings

Although this was primarily a safety study, efficacy was assessed. Results are presented in the following table.

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Listing 1 Investigator Global Severity and Global Improvement Scores

Inv	PtId	Baseline	Day 14		Day 29	
		Global Severity	Global Severity	Global Improvement	Global Severity	Global Improvement
1	1	Moderate	Mild	Marked	None	Clear
1	2	Moderate	Mild	Marked	Mild	Marked
1	3	Moderate	Mild	Marked	None	Clear
1	4	Moderate	Mild	Almost Clear	None	Clear
1	5	Moderate	Mild	Almost Clear	None	Clear
1	6	Moderate	Mild	Almost Clear	Mild	Marked
1	7	Moderate	None	Clear	None	Clear
1	8	Moderate	Moderate	No Change	Mild	Almost Clear
1	9	Moderate	Moderate	Moderate	Moderate	Marked
1	10	Moderate	Mild	Almost Clear	Mild	Almost Clear
1	11	Moderate	Mild	Almost Clear	Mild	Almost Clear
1	12	Moderate	Mild	Marked	Mild	Almost Clear
1	13	Moderate	Mild	Marked	None	Clear
1	14	Moderate	Mild	Marked	Mild	Almost Clear
1	15	Moderate	Mild	Almost Clear	None	Clear
1	16	Moderate			None	Clear
1	18	Moderate	Mild	Marked	Mild	Marked
1	19	Moderate	Mild	Marked	None	Clear
1	20	Moderate	Mild	Marked	Mild	Marked
1	21	Moderate	Mild	Almost Clear	Mild	Almost Clear
1	22	Moderate	Mild	Almost Clear	None	Clear
1	25	Severe	Mild	Marked	Mild	Almost Clear
2	201	Moderate	Mild	Almost Clear	Mild	Marked
2	202	Severe	Moderate	Marked	Moderate	Moderate
2	203	Moderate	Mild	Marked	None	Clear
2	205	Moderate	Mild	Moderate	Mild	Marked
2	207	Moderate	Mild	Almost Clear	None	Clear
2	208	Severe	Moderate	Slight	Mild	Marked
2	209	Moderate	Moderate	Slight	Mild	Marked
2	210	Moderate	Mild	Marked	Mild	Marked

6.1.6 Efficacy Conclusions

Efficacy of the product for treatment of atopic dermatitis has already been established.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Principal Investigators: Margaret Dohil, M.D. (Children's Hospital, San Diego, CA) and Elizabeth Connelly, M.D. (University of Miami, Miami, FL).

Number of subjects: 32 subjects at 2 investigational sites.

Objectives:
1. To evaluate the potential of Derma-Smoothe/FS® Topical Oil to suppress the HPA axis in pediatric subjects with atopic dermatitis (ages 3 months to 2 years)
2. To evaluate the effectiveness of Derma-Smoothe/FS® Topical Oil in pediatric subjects with atopic dermatitis (ages 3 months to 2 years)

Study design: controlled, open-label

Criteria for evaluation:
Serum cortisol levels before and 30 minutes after Cosyntropin Stimulation test at baseline
Serum cortisol levels before and 30 minutes after Cosyntropin Stimulation test at Week 4 (end of treatment)

Main Inclusion Criteria

- male or females subject 3 months to 2 yeas of age with atopic dermatitis
- moderate to severe atopic dermatitis covering at least 20% of body surface area and the following features:

must have 3 or more basic features:
1. pruritus
2. typical morphologic varieties of skin lesions
3. chronic or chronically-relapsing dermatitis
4. personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

must have 3 or more minor features:
1. xerosis
2. immediate (type I) skin test reactivity
3. Elevated serum IgE
4. Early age of onset

5. Tendency toward non-specific hand or foot dermatitis
6. nipple eczema
7. cheilitis
8. Dennie-Morgan infraorbital fold
9. orbital darkening
10. pityriasis alba
11. itch when sweating
12. intolerance to wool and lipid solvents
    - normally functioning HA axis as defined by an 8:00 AM (drawn no later than 10:AM) plasma cortisol level exceeding 5 mcg/mL, and demonstrated a response to Cosyntropin injection exceeding 18 mcg/mL (after 30 minutes)

Main Exclusion Criteria

- subjects who had used the following within 14 days of the specified washout period(s): topical corticosteriods or immunomodulators ; systemic medication known to affect cortisol levels or HPA axis integrity, systemic corticosteroids
- concomitant disorders that would interfere with study objectives and/or evaluations
- immunocompromised or immuosuppressive treatment
- significant endocrinological disorder that may have required contraindicated treatment with potent corticosteroids

Subjects were dispensed a total of four 4-ounce bottles of study product for the 4-week treatment period (two at Baseline and two at Day 14). Study product was applied to all affected areas (as identified at baseline by the investigator) twice daily for four weeks. Additionally caregivers were instructed to treat new areas that arose during the treatment period. Vehicle was applied as often as needed.

Subjects were assessed at each visit (baseline, and Days 14, 29 and 35) on a static global scale from none (0) to severe (3) (however, the levels on the scale were not defined) and on a dynamic scale from 1 (complete clearing; 100%) to 6 ("exacerbation of condition as compared to baseline") on Days 14 and 29. Al efficacy parameters were secondary. Signs and symptoms (pruritus, prurigo, eczematous lesions and lichenification) were evaluated on Days 14 and 29 on scales from 0 (none) to 3 (severe). Cosyntropin stimulation testing (0.125 mg) was done at baseline and at Week 4 (see Section 7.1). Final evaluation was one week post-treatment.

Serum cortisol levels were evaluated pretreatment and at end of treatment (Week 4). All cortisol levels were obtained between 8:00 AM and 10:00 Am prior to application of study product. Cortisol levels below 5 mcg/100 mL were considered subnormal. Additionally, the 30-minute level exceeded 18 mcg/mL and showed an increment of at least 7 mcg/mL above the basal level. Subjects with subnormal pre-stimulation serum cortisol levels below 5 mcg/100 mL and post-stimulation levels below 18 mcg/mL at the end of treatment were to be re-tested 14 days after the final dose. The subject was to be referred to an endocrinologist if the re-test cortisol level were still subnormal.

7.1.1 Deaths

There were no deaths in the study.

7.1.2 Other Serious Adverse Events

There were no serious adverse events in the study.

7.1.3 Dropouts and Other Significant Adverse Events

A total of 32 subjects were enrolled in the study. Subject 204 was withdrawn prior to receiving study drug because his baseline cortisol level was < 5 mcg. Subject 206 did not return for a baseline blood draw and did not receive study drug; this subject was considered lost to follow-up. Both subjects were excluded from the ITT database.

A total of 30 subjects received study drug and had at least one visit; these subjects constituted the ITT population. Subject 205 did not return for final evaluation (Day 35) and was considered lost to follow-up; however, this subject did have end of treatment cortrosyn testing done. Subject 210 withdrew at Day 14 because of an adverse event (abscess on the right antecubital area), but had cortrosyn testing done at that time point. Subjects 205 and 210 were included in the ITT database.

Reasons for Withdrawal from Study (From Sponsor Table 2)

	N
Number enrolled	32
Number who did not complete the study	4
Reason for discontinuation:	
Baseline cortisol level was < 5 mcg	1
Did not return for baseline cortisol	1
Did not return for final follow-up visit	1
Withdrew due to adverse event	1

7.1.5 Common Adverse Events

7.1.5.3 Incidence of common adverse events

In the ITT, 17 of 30 subjects (57%) experienced an adverse event.

7.1.5.4 Common adverse event tables

The following table is a presentation of all adverse events that occurred in the study:

Sponsor Table 7: Incidence of Adverse Events by Body System and Preferred Term

Body System	**Medra Preferred Term**	**Incidence (N = 30)**
Number of subjects with at least one AE		**17 (56.7%)**
Gastrointestinal disorder		**2 (6.7%)**
	Diarrhea	1 (3.3%)
	Vomiting	1 (3.3%)
General disorder and administration site conditions		**3 (10.0%)**
	Pyrexia	3 (10.0%)
Infections and infestations		**7 (23.3%)**
	Abscess	1 (3.3%)
	Bite, insect	1 (3.3%)
	Molluscum	1 (3.3%)
	Nasopharyngitis	2 (6.7%)
	URI	1 (3.3%)
	Otitis media	1 (3.3%)
Respiratory, thoracic and mediastinal disorder		**8 (26.6%)**
	Cough	6 (20%)
	Rhinorrhea	4 (13.3)
Skin and subcutaneous tissue disorder		**5 (16.7%)**
	Atopic dermatitis	1 (3.3%)
	Eczema	1 (3.3%)
	Hyperpigmentation	1 (3.3%)
	Hypopigmentation	2 (6.7%)
	Rash	1 (3.3%)

7.1.5.5 Identifying common and drug-related adverse events

All adverse events are presented in Section 7.1.5.4.

7.1.6 Less Common Adverse Events

All adverse events are presented in Section 7.1.5.4.

7.1.7.1 Overview of laboratory testing in the development program

Assessment of HPA Axis Function

The reviewer applied the sole criterion of a post-stimulation cortisol level of > 18 mcg as being reflective of normal adrenal function. By this criterion, no subjects showed evidence of adrenal suppression on post-stimulation Cortrosyn testing at Week 4. The review will primarily consider three groups:

- all subjects
- subjects who had Week 4 cortisol levels drawn at ≤ 35 Minutes post-stimulation
- subjects who had baseline and Week 4 cortisol levels drawn at ≤ 35 Minutes post-stimulation

Baseline extent of disease is presented in the following table.

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Listing 2 Baseline Disease Attributes

Inv	PtID	Date	BSA	Duration (days)	Severity	Enrolled
1	1	6/3/2005	20%	30	Moderate	Yes
1	2	6/7/2005	20%	21	Moderate	Yes
1	3	6/13/2005	50-75%	21	Moderate	Yes
1	4	6/27/2005	20%	15	Moderate	Yes
1	5	6/29/2005	20%	28	Moderate	Yes
1	6	7/6/2005	20%	60	Moderate	Yes
1	7	8/2/2005	20%	15	Moderate	Yes
1	8	8/19/2005	>75%	21	Moderate	Yes
1	9	10/6/2005	20%	28	Moderate	Yes
1	10	10/17/2005	20%	2	Moderate	Yes
1	11	10/20/2005	20%	100	Moderate	Yes
1	12	11/3/2005	50-75%	25	Moderate	Yes
1	13	11/16/2005	50-75%	90	Moderate	Yes
1	14	11/30/2005	50-75%	120	Moderate	Yes
1	15	12/1/2005	50-75%	365	Moderate	Yes
1	16	12/12/2005	20%	80	Moderate	Yes
1	18	2/28/2006	>75%	60	Moderate	Yes
1	19	2/24/2006	>75%	90	Moderate	Yes
1	20	4/5/2006	>75%	60	Moderate	Yes
1	21	5/15/2006	>75%	90	Moderate	Yes
1	22	6/2/2006	>75%	120	Moderate	Yes
1	25	8/16/2006	>75%	150	Severe	Yes
2	201	8/19/2005	50-75%	45	Moderate	Yes
2	202	8/16/2005	>75%	30	Severe	Yes
2	203	10/11/2005	50-75%	90	Moderate	Yes
2	205	11/1/2005	50-75%	90	Moderate	Yes
2	207	11/22/2005	50-75%	90	Moderate	Yes
2	208	12/8/2005	50-75%	60	Severe	Yes
2	209	12/20/2005	50-75%	60	Moderate	Yes
2	210	2/7/2006	50-75%	90	Moderate	Yes

RESULTS

All Subjects

The following table presents baseline and Week 4 post-stimulation cortisol results (for all subjects who had such testing) and the times of blood draw:

Week 4 Cortisol Test Results for All Subjects (Source: Listing 6)

Subject # (n=29)	Baseline Cortisol Levels				End of Treatment Cortisol (Day 29) Levels			
	Time	Pre-Stim	Time	Post-Stim	Time	Pre-Stim	Time	Post-Stim
1	10:30 AM	15.5	11:00 AM	20.5	9:15 AM	14.5	9;45AM	39.7
2	9:05 AM	9.9	9:40 AM	32.4	9:25 AM	14.6	9:55 AM	30.2
3	9:10 AM	6.9	9:50 AM	35.9	9:30AM	3.9	10:20 AM	27.5
4	8:55 AM	20.6	9:27AM	31.3	8:46 AM	17.7	9:16 AM	32.2
5	8:55 AM	14.2	9:45AM	38.5	8:55AM	10.6	9:26 AM	26.4
6	8:42 AM	8.6	9:15 AM	29.8	9:05AM	6.0	9:38 AM	36.3
7	9:10 AM	5.1	9:44AM	33.7	9:29AM	5.4	10:00 AM	27.3
8	9:40 AM	13.4	10:20 AM	47.0	9:44 AM	17.8	10:15 AM	32.7
9	9:20 AM	16.6	10:00 AM	38.9	8:55 AM	10.9	9:35 AM	30.6
10	9:05 AM	6.8	9:45 AM	32.1	9:42 AM	14.6	10:25AM	41.9
11	9:19 AM	11.3	9:56 AM	29.2	9:15 AM	11.5	9:45AM	35.3
12	9:45 AM	18.5	10:30 AM	34.4	9:00 AM	11.1	9:30 AM	26.6
13	10:00 AM	18.4	10:40 AM	46.9	10:15 AM	4.3	10:45 AM	29.0
14	9:55 AM	5.5	10:33 AM	27.2	9:50 AM	6.6	11:05AM	30.4
15	9:50 AM	6.3	10:30 AM	24.5	8:30 AM	22.8	9:00AM	40.1
16	9:05 AM	9.7	9:50 AM	29.8	9:40 AM	13.0	10:13 AM	26.0
18	9:55 AM	8.5	11:10 AM	66.0	9:25 AM	6.9	10:00 AM	36.8
19	9:43 AM	17.6	10:30 AM	42.1	9:45 AM	9.4	10:15 AM	23.9
20	8:40 AM	5.5	9:20 AM	31.8	8:20 AM	10.3	9:00 AM	38.4
21	9:30 AM	5.4	10:18 AM	24.4	8:50 AM	8.4	9:30 AM	35.1
22	9:30 AM	7.4	10:10 AM	34.4	8:50 AM	8.4	9:30 AM	35.1
25	9:20 AM	10.6	9:52 AM	31.3	9:35 AM	6.7	10:05AM	30.8
201	9:08 AM	4.9	9:38 AM	20.7	8:25 AM	8.2	8:55 AM	18.1
202	9:25 AM	19.1	9:55 AM	33.5	9:05 AM	10.6	9:35 AM	21.8
203	8:20 AM	12.7	8:50 AM	32.5	8:05 AM	7.1	8:35 AM	26.4
205	8:20 AM	6.4	8:50 AM	27.3	8:10 AM	4.6	8:40 AM	23.7
207	8:30 AM	8.1	9:00 AM	32.9	8:15 AM	12.0	8:45 AM	23.8
208	8:20 AM	9.0	8:50 AM	27.9	8:10 AM	7.3	8:40 AM	22.0
209	8:15 AM	16.6	8:45 AM	26.5	8:15 AM	25.3	8:45 AM	30.6

Baseline Post-Stimulation Cortisol Obtained > 30 Minutes Post-Stimulation

Of the 29 subjects who had Week 4 Cortrosyn testing done, 21 (72%) had cortisol levels obtained > 30 minutes post-stimulation at baseline, as shown in the following table (all from investigative site 1):

Subjects with Baseline Post-Stimulation Cortisol Obtained > 30 Minutes Post-Stimulation (Source: Listing 6)

Subject # (n=21)	Pre-Stim	Post-Stim	Time Elapsed(minutes)
2	9:05 AM	9:40 AM	35
3	9:10 AM	9:50 AM	40
4	8:55 AM	9:27AM	32
5	8:55 AM	9:45AM	49
6	8:42 AM	9:15 AM	33
7	9:10 AM	9:44AM	34
8	9:40 AM	10:20 AM	47
9	9:20 AM	10:00 AM	40
10	9:05 AM	9:45 AM	40
11	9:19 AM	9:56 AM	37
12	9:45 AM	10:30 AM	45
13	10:00 AM	10:40 AM	40
14	9:55 AM	10:33 AM	38
15	9:50 AM	10:30 AM	40
16	9:05 AM	9:50 AM	45
18	9:55 AM	11:10 AM	75
19	9:43 AM	10:30 AM	47
20	8:40 AM	9:20 AM	40
21	9:30 AM	10:18 AM	48
22	9:30 AM	10:10 AM	40
25	9:20 AM	9:52 AM	32

Week 4 Post-Stimulation Cortisol Obtained > 30 Minutes Post-Stimulation

Of the 29 subjects who had Week 4 Cortrosyn testing done, 13 (45%) had cortisol levels obtained > 30 minutes post-stimulation at Week 4 as shown in the following table:

Subjects with Week 4 Cortisol Obtained > 30 Minutes Post-Stimulation (Source: Listing 6)

Subject # (n=13)	Pre-Stim	Post-Stim	Time Elapsed(minutes)
3	9:30AM	10:20 AM	50
5	8:55AM	9:26 AM	31
6	9:05AM	9:38 AM	33
7	9:29AM	10:00 AM	31
8	9:44 AM	10:15 AM	31
9	8:55 AM	9:35 AM	40
10	9:42 AM	10:25AM	43
14	9:50 AM	11:05AM	75
16	9:40 AM	10:13 AM	33
18	9:25 AM	10:00 AM	35
20	8:20 AM	9:00 AM	40
21	8:50 AM	9:30 AM	35
22	8:50 AM	9:30 AM	40

Of the 13 subjects in this category who had Week 4 Cortrosyn testing done, 7 had cortisol levels obtained within what the reviewer considers to be an acceptable window, i.e. ≤ 35 minutes. Thus, 23 subjects in this category will be further considered in the review.

Subjects Who Had Week 4 Cortisol Levels Drawn at ≤ 35 Minutes (Source: Listing 6)

Subject # n=23	Age (months)	Week 4 Post-Stimulation Cortisol Level
1	12.4	39.7
2	19.9	30.2
4	30.6	32.2
5	28.0	26.4
6	17.1	36.3
7	4.2	27.3
8	3.7	32.7
11	16.3	35.3
12	32.3	26.6
13	5.0	29.0
15	19.9	40.1
16	7.7	26.0
18	5.4	36.8
19	3.7	23.9
21	6.4	35.1
25	6.2	30.8
201	27.8	18.1
202	6.6	21.8
203	14.3	26.4
205	9.3	23.7
207	17.4	23.8
208	18.5	22.0
209	12.5	30.6

Subjects Who Had Baseline and Week 4 Cortisol Levels Drawn at ≤ 35 Minutes

Of the 29 subjects who had Week 4 Cortrosyn testing done, 13 (45%) had both baseline and Week 4 testing done within what the reviewer considers to be an acceptable window, i.e. ≤ 35 minutes. Those subjects and their Week 4 post-stimulation cortisol levels are presented in the following table (next page):

Subjects Who Had Baseline and Week 4 Cortisol Levels Drawn at ≤ 35 Minutes (Source: Listing 6)

Subject # n=13	Age (months)	Week 4 Post-Stimulation Cortisol Level
1	12.4	39.7
2	19.9	30.2
4	30.6	32.2
6	17.2	36.3
7	4.2	27.3
25	6.2	30.8
201	27.8	18.1
202	6.6	21.8
203	14.3	26.4
205	9.3	23.7
207	17.4	23.8
208	18.5	22.0
209	12.5	30.6

Outcomes: Presented by Compliance (≤ 2 doses Missed)

The reviewer conducted analyses based on compliance data provided in the submision (Listing 11 "Dose Compliance"). The reviewer defined compliance as missing ≤ 2 doses, i.e. the equivalent of one day of treatment. Compliance was defined thusly in an attempt to capture close to maximum exposure. By this definition, a total of 21 of all 29 subjects (72%) missed ≤ 2 doses over the treatment period, 17 of whom (59%) missed no doses. Of the remaining 4 subjects who missed ≤ 2 doses, Subject 21 missed one dose, and Subjects 12, 14 and 19 missed 2 doses (non-consecutively for Subject 19). The study report did not provide for the volume of study product subjects used over the treatment period. An Information Request for such was forwarded to the sponsor during the review cycle, and this information will be added should it become available prior to closing of the review. Compliance is also supported by the efficacy outcomes at Day 29 (see Section 6.1.4).

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All Subjects

The following table presents the Week 4 outcomes for subjects who were compliant (again, defined by the reviewer as missed ≤ 2 doses). Additionally, the table includes the % body surface area of involvement.

End-of-Treatment Post-Stimulation Cortisol Levels for Who Missed ≤ 2 doses (Sources: Listings 3,6,&11)

Subject # (n=21)	Age (months)	%BSA+ involved at baseline	Week 4 Post-Stimulation Cortisol Level
1	12.4	20	39.7
2	19.9	20	30.2
3	6.2	50-75	27.5
4	30.6	20	32.2
7	4.2	20	27.3
9	13.9	20	30.6
12*	32.3	50-75	26.6
14*	8.4	50-75	30.4
15	19.9	50-75	40.1
18	5.4	>75	36.8
19*	3.7	>75	23.9
20	6.4	>75	38.4
21*	4.2	>75	21.6
22	3.7	>75	35.1
25	6.2	>75	30.8
201	27.8	50-75	18.1
202	6.6	50-75	21.8
203	14.3	50-75	26.4
205	9.3	50-75	23.7
207	17.4	50-75	23.8
209	12.5	50-75	30.6

+BSA=body surface area
* Subjects 12, 14 and 19 missed 2 doses (not consecutive for Subject 19). Subject 21 missed one dose

Subjects Who Had Week 4 Cortisol Levels Drawn at ≤ 35 Minutes

A total of 16 of 23 subjects (70%) who had Week 4 cortisol levels drawn at ≤ 35 Minutes missed ≤ 2 doses over the treatment period, 13 of whom missed no doses. Of the remaining 3 subjects who missed ≤ 2 doses, Subject 21 missed one dose, and Subjects 12 and 19 missed 2 doses (non-consecutively for Subject 19). The following table presents the Week 4 outcomes for this category of subjects. Additionally, the table includes the % body surface area of involvement.

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End-of-Treatment Post-Stimulation Cortisol Levels (at ≤ 35 Minutes) for Subjects Who Missed ≤ 2 doses (Sources: Listings 3,6,&11)

Subject # n=16	Age (months)	%BSA+ involved at baseline	Week 4 Post-Stimulation Cortisol Level
1	12.4	20	39.7
2	19.9	20	30.2
4	30.6	20	32.2
7	4.2	20	27.3
12*	32.3	50-75	26.6
15	19.9	50-75	40.1
18	5.4	>75	36.8
19*	3.7	>75	23.9
21*	4.2	>75	21.6
25	6.2	>75	30.8
201	27.8	50-75	18.1
202	6.6	50-75	21.8
203	14.3	50-75	26.4
205	9.3	50-75	23.7
207	17.4	50-75	23.8
209	12.5	50-75	30.6

+BSA=body surface area
* Subjects 12 and 19 missed 2 doses (not consecutively for Subject 19). Subject 21 missed one dose

Outcomes for Subjects Who Had Baseline & Week 4 Cortisol Levels Drawn at ≤ 35 Minutes

Of the 29 subjects who had Week 4 Cortrosyn testing done, 13 (45%) had testing done within what the reviewer considers to be an acceptable window, i.e. ≤ 35 minutes. Outcomes for this group are presented in the table below:

Subjects Who Had Baseline & Week 4 Testing Done at ≤ 35 minutes (Sources: Listings 1,3,6 & 11)

Subject # n=13	Age (Months)	%BSA+ involved at baseline	Number of Doses Missed	Week 4 Post-Stimulation Cortisol Level
1	12.4	20	None	39.7
2	19.9	20	None	30.2
4	30.6	20	None	32.2
6	17.1	20	2-4 consecutive	36.3
7	4.2	20	None	27.3
25	6.2	>75	None	30.8
201	27.8	50-75	None	18.1
202	6.6	>75	None	21.8
203	14.3	50-75	None	26.4
205	9.3	50-75	None	23.7
207	17.4	50-75	None	23.8
208	18.5	50-75	> 4 consecutive	22.0
209	12.5	50-75	None	30.6

++BSA=body surface area

Outcomes for Subjects < One Year of Age

The following table presents the end-of-treatment post-stimulation cortisol levels for all 14 subjects who were < one year of age:

All Subjects: End-of-Treatment Post-Stimulation Cortisol Levels for Subjects < One Year (Sources: Listings 1, 6 & 11)

Subject # n=14	Age (mos)	%BSA involved at baseline	Number of Doses Missed	Week 4 Post-Stimulation Cortisol Level
3	6.2	50-75	None	27.5
7	4.2	20	None	27.3
8	3.7	>75%	2-4	30.6
13	5.0	50-75	4-8 (not consecutive)	32.7
14	8.4	50-75	2	30.4
16	7.7	20	2-4 (not consecutive)	26.0
18	5.4	>75	None	36.8
19	3.7	>75	2 (not consecutive)	23.9
20	6.4	>75	None	38.4
21	4.2	>75	1	21.6
22	3.7	>75	None	35.1
25	6.2	>75	None	30.8
202	6.6	50-75	None	21.8
205	9.2	50-75	None	23.7

The following table presents the end-of-treatment post-stimulation cortisol levels for subjects < one year of age who had the cortisol levels obtained within what the reviewer considers to be an acceptable window, i.e. ≤ 35 minutes:

End-of-Treatment Post-Stimulation Cortisol Levels for Subjects < One Year; done ≤ 35 minutes (Sources: Sponsor Listing 1, 6 & 11)

Subject # n=10	Age (mos)	%BSA involved at baseline	Number of Doses Missed	Cortisol level at end of treatment
7	4.2	20	None	27.3
8	3.7	>75%	2-4	30.6
13	5.0	50-75	4-8 (not consecutive)	32.7
16	7.7	20	2-4 (not consecutive)	26.0
18	5.4	>75	None	36.8
19	3.7	>75	2 (not consecutive)	23.9
21	4.2	>75	1	21.6
25	6.2	>75	None	30.8
202	6.6	50-75	None	21.8
205	9.2	50-75	None	23.7

Sponsor's Analyses

Per Section 3.8.1of the protocol, the sponsor applied the three criteria listed in the Cortrosyn® label in their interpretation of the test results. The criteria applied by the sponsor follow (next page:

- >5 micrograms/100mL for the control plasma level,
- at least a 7 mcg incremental increase over the basal level for the 30-minute level and
- >18 micrograms/100mL for the 30-minute level.

By those criteria, the sponsor considered 24 subjects to have been evaluable at Week 4. Table 4 from their study report is presented below:

Sponsor Table 4 Patients Who Did Not Meet the Criteria for the HPA Axis Evaluation

Visit	Baseline Value < 5 µg/dL	Post-Stimulation Value < 18 µg/dL	No Day 29 Blood Draws	Post-Stimulation Inc < 7 µg/dL
Baseline	1	0	0	0
Day 29	3	0	1	1

The following table is the sponsor's presentation of the test results at Week 4 (Day 29) for subjects considered evaluable by the sponsor's definition, i.e. the Cortrosyn criteria:

Sponsor Table 5: Cortisol Levels Pre- and Post-Stimulation at Baseline and Day 29

(Evaluable Subjects)

Study Visit	Cortisol Concentration (µg/dL)		Increase in Cortisol Concentration (µg/dL) (N = 24)
	Pre-Stim (N = 24)	Post Stim (N = 24)	
Baseline (BL)	11.1 ± 4.8	34.2 ± 8.5	23.1 ± 8.8 (208.1%)
Day 29	10.9 ± 4.4	30.7 ± 6.2	19.8 ± 6.0 (181.6%)
p-value (BL vs. Day 29) Paired t-test	0.87	0.09	0.06

The following table is the sponsor's presentation of the test results at Week 4 (Day 29) for the ITT population defined by the sponsor as "patients who received at least one dose of study drug and had baseline values":

Sponsor Table 6: Cortisol Levels Pre- and Post-Stimulation at Baseline and Day 29

(ITT Population)

Study Visit	**Cortisol Concentration (µg/dL)**		**Increase in Cortisol Concentration (µg/dL) (N = 29)**
	Pre-Stim (N = 29)	**Post Stim (N = 29)**	
Baseline (BL)	11.0 ± 5.0	33.8 ± 8.7	22.8 ± 8.6
Day 29	10.6 ± 5.3	29.8 ± 6.2	19.2 ± 6.5
p-value (BL vs Day 29) Paired t-test	0.73	0.03	0.02

The sponsor concluded that, "this study has shown that treatment of atopic dermatitis in children, between 3 months and 2 years old, have no deleterious effect on the HPA axis when used twice daily for 4 weeks. All of the cortisol response *(sic)* were above 20 µg/dL, which is the normal cortisol response. Cortisol values higher than 20 µg/dL reflects *(sic)* a normal adrenal response. Acute psychological stresses raises cortisol levels which most likely explains the higher levels of cortisol for patient # 209 age 1, most likely from the injection of cortisol and drawing of blood as anticipation to pain. This study also confirmed a previous study, which showed Derma-Smoothe/FS® to be safe for the treatment of atopic dermatitis in a pediatric population, ages between 2 and 13 years of age. This study provides support with this submission for the approval of Derma-Smoothe/FS® Topical Oil for the treatment of Atopic Dermatitis for pediatric patients 3 months to 2 years old."

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

The source for the data was the sponsor's clinical study report for the study conducted under protocol 38.

7.2.1.1 Study type and design/patient enumeration

See Section 7.1

7.2.1.2 Demographics

There were 32 subjects enrolled in the study. Thirty subjects received study drug, and 29 subjects completed the study.

Demographics of the ITT Population (Source: Table 3)

Gender	Male Female	15 (50%) 15 (50%)
Race	Caucasian Black Asian Other	7 (23.3%) 10 (33.3%) 6 (20.0%) 7 (23.3%)
Age (years)	Mean SD Min-Max	1.1 0.7 0.3-2.7
Temperature (◦F)	Mean SD Min-Max	98.0 0.9 96.0-99.6
Height (inches)	Mean SD Min-Max	29.1 4.0 22.4-36.0
Weight (lbs)	Mean SD Min-Max	20.9 6.3 11.7-34.0

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Baseline Demographsics: All Subjects (Sources: Listings 1 & 3)

Subject #	Age (yrs)	Race/Sex	% BSA Involvement	Height (in)	Weight (lbs)
1	1.03	Other/M	20%	33.0	22.8
2	1.66	W/F	20%	33.0	24.0
3	0.52	A/M	50 to 75%	26.5	16.6
4	2.55	Other/M	20%	36.0	32.0
5	2.33	W/M	20%	35.0	33.0
6	1.43	W/M	20%	32.5	24.0
7	0.35	B/M	20%	26.0	16.0
8	0.31	B/M	>75%	23.5	12.3
9	1.16	B/M	20%	32.5	28.5
10	1.29	Other/M	20%	30.0	22.5
11	1.36	Other/F	20%	30.0	23.0
12	2.69	A/F	50 to 75%	33.0	24.0
13	0.42	W/F	50 to 75%	25.0	16.0
14	0.70	A/M	50 to 75%	26.5	17.3
15	1.66	Other/F	50 to 75%	33.0	26.0
16	0.64	A/M	20%	29.0	18.4
18	0.45	A/F	>75%	23.6	12.8
19	0.31	W/F	>75%	22.4	11.7
20	0.53	A/M	>75%	27.0	20.0
21	0.35	Other/F	>75%	24.0	15.5
22	0.31	W/F	>75%	24.0	12.1
25	0.52	W/F	>75%	24.5	13.8
201	1.69	B/F	50 to 75%	33.5	27.0
202	0.55	B/M	>75%	26.0	17.0
203	1.19	Other/F	50 to 75%	31.5	25.5
205	0.77	B/M	50 to 75%	28.0	18.1
207	1.45	B/F	50 to 75%	33.0	22.0
208	1.54	B/M	50 to 75%	32.7	34.0
209	1.04	B/F	50 to 75%	31.0	24.3
210	0.58	B/F	50 to 75%	27.0	18.0

Number of Subjects < 1 year (Source: Listing 3)

3-4 months (n=3)		> 4-5 months (n=3)		> 5-7 months (n=6)		> 7 < 1 2 months	
Subject #	Age (mos)	Subject #	Age (mos)	Subject #	Age (mos)	Subject #	Age (mos)
8	3.7	7	4.2	3	6.2	14	8.4
19	3.7	13	5.0	18	5.4	16	7.7
22	3.7	21	4.2	20	6.6	205	9.2
-	-	-	-	25	6.2	-	-
-	-	-	-	202	6.6	-	-
-	-	-	-	210	6.7	-	-
-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-

7.2.1.3 Extent of exposure (dose/duration)

The duration of treatment was 4 weeks, and study product was applied twice daily.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

None

7.2.3 Adequacy of Overall Clinical Experience

See Section 7.2.3

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

The reviewer applied the sole criterion of a post-stimulation cotisol level of > 18 mcg as being reflective of normal adrenal function. Using this approach, no subjects showed evidence of adrenal suppression on post-stimulation Cortrosyn testing at the end of treatment (Week 4). While all 30 subjects in the ITT had post-treatment Cortrosyn testing done, one subject had testing done at Day 14 (subject discontinued due to an adverse event); this subject showed no evidence of adrenal suppression at Day 14.

Of the 29 subjects who had Cortrosyn testing done at Week 4, 13 (45%) had post-stimulation cortisol levels drawn outside of the 30-minute window. However, the reviewer considered the 7 subjects who had their cortisol levels drawn ≤ 35 minutes post-stimulation to be evaluable. Thus, 23 subjects were considered in analysis of this group.

Of the 29 subjects who had Cortrosyn testing done at Week 4, 13 (45%) had both baseline and Week 4 testing done within what the reviewer considers to be an acceptable window, i.e. ≤ 35 minutes. All 13 subjects were considered in the analysis of this group.

<u>All Subjects with Post-Stimulation Testing at 4 Weeks (n=29)</u>

A total of 14 subjects (48%) were under one year of age, 7 (24%) of whom were between the ages of 3 to < 6 months, and 7 of whom (50%) were between the ages of 6 to 12 months. A total of 3 subjects (10%) were between the ages of 3 to 4 months. A total of 12 subjects (41%) were < 7 months of age.

Of the 3 subjects between the ages of 3 to 4 months, all had > 75% body surface area (BSA) involvement by disease. One of these subjects missed no applications of study product, one missed 2 applications (not consecutively), and the third subject missed "2 to 4" applications.

Of the 5 subjects < 5 months of age, 4 (80%) had > 75% BSA involvement by disease (the fifth had 20% BSA involvement). Of these 5 subjects, 4 (80%), missed ≤ 2 applications of study drug (the fifth subject missed "2-4" applications).

Of the 12 subjects < 7 months of age, 11 (92%) had at least 50% BSA involvement by disease. Of the 12 subjects in this age group, 8 (67%) were reported to have missed no applications of study medication. An additional subject in this age group missed one application of study product during the treatment period.

Subjects Who Had Week 4 Post-Stimulation Cortisol Levels Drawn at ≤ 35 Minutes (n=23)

A total of 9 subjects (40%) were under one year of age: 2 subjects (7%) were between the ages of 3 to 4 months, 4 subjects (18%) were < 5 months, and 8 subjects (35%) were < 7 months of age.

Both subjects between the ages of 3 to 4 months, had > 75% BSA involvement by disease. One of these subjects missed 2 applications of study product (not consecutively), and the third subject missed "2 to 4" applications.

Of the 4 subjects < 5 months, 3 (75%) had > 75% BSA involvement by disease (the fourth subject had 20% BSA involvement), and 3 of the 4 subjects (75%) missed ≤ 2 doses of study product (the remaining subject missed "2-4 doses").

Of the 8 subjects < 7 months of age, 7 (88%) had at least 50% BSA involvement by disease [6 (75%) had >75% BSA involved]. Of the 7 subjects in this age group, 4 (57%) were reported to have missed no applications of study medication.

Subjects Who Had Baseline & Week 4 Post-Stimulation Cortisol Levels Drawn at ≤ 35 Minutes (n=13)

A total of subjects (23%) in this group were under one year of age, and all were < 7 months of age. One of these subjects (8%) was between the ages of 4 to 5 months. Two of these subjects (6.2 and 6.6 months) had > 75% body surface area disease involvement. None of these 3 subjects missed any application of study product.

Important Limitations of Data and Conclusions

No subjects showed evidence of adrenal suppression at Week 4 testing under any analysis. In the reviewer's opinion, the study results convincingly demonstrate that pediatric subjects younger than the lower limit for which the product is currently approved, i.e. down to 2 years, could safely tolerate the product for use twice daily for up to 4 weeks. There were some problems with the conduct of the study in regard to timing of drawing of the post-stimulation cortisol levels. The reviewer therefore conducted analyses (discussed above) that considered

- subjects who had Week 4 cortisol levels drawn ≤ 35 minutes post-stimulation
- subjects who had baseline and Week 4 cortisol levels drawn ≤ 35 minutes post-stimulation.

The reviewer's recommendations will be based primarily on results for subjects who had Week 4 cortisol levels drawn ≤ 35 minutes post-stimulation (n=23), since results at this time point would reflect post-treatment adrenal status.

In the reviewer's opinion, the sponsor has adequately demonstrated that subjects down to 3 months can safely tolerate the product for use twice daily for up to 4 weeks. There were three subjects between the ages of 3 and 4 months in the study, all of whom had Cortrosyn testing done at Week 4, and two of whom had cortisol levels drawn ≤ 35 minutes post-stimulation; the third subject was tested 40 minutes post-stimulation. All three of these subjects (each 3.7 months of age) had extensive disease with > 75% body surface area involvement. Two of these subjects missed ≤ 2 doses (one of these missed no doses), and the third missed 2 to 4 doses. Thus, the equivalent of two days of treatment was the most that any of these three subjects missed. All three subjects were considered to have "moderate" disease at baseline. At Week 4, two of the three had "none", and the third had "mild" disease. None of these three subjects showed evidence of adrenal suppression at Week 4. While one subject had the post-stimulation

cortisol level obtained outside the 35-minute window, this subject's response at the 40-minute mark was robust (post-stimulation cortisol level was 35.1 mcg). While three subjects may seem a relatively small number of subjects, in the reviewer's opinion, recruitment of subjects with at least 20% BSA involvement in the age group of 3 to 4 months might have proven challenging, since infantile atopic dermatitis most often begins on the face (the sponsor did not address this issue in the study report).

7.4 General Methodology

See Section 7.1

8 ADDITIONAL CLINICAL ISSUES

8.3 Special Populations

See Section 7.1

8.4 Pediatrics

See Section 7.1

9 OVERALL ASSESSMENT

9.1 Conclusions

In the reviewer's opinion, the sponsor has adequately demonstrated that subjects down to 3 months can safely tolerate the product for use twice daily for up to 4 weeks. There were three subjects between the ages of 3 and 4 months in the study, all of whom had Cortrosyn testing done at Week 4, and two of whom had cortisol levels drawn ≤ 35 minutes post-stimulation; the third subject was tested 40 minutes post-stimulation. All three of these subjects (each 3.7 months of age) had extensive disease with > 75% body surface area involvement. Two of these subjects missed ≤ 2 doses (one of these missed no doses), and the third missed 2 to 4 doses. Thus, the equivalent of two days of treatment was the most that any of these three subjects missed. None of these three subjects showed evidence of adrenal suppression at Week 4. While one subject had the post-stimulation cortisol level obtained outside the 35-minute window, this subject's response at the 40-minute mark was robust (post-stimulation cortisol level was 35.1 mcg). While three subjects may seem a relatively small percentage of subjects, in the reviewer's opinion, recruitment of subjects with at least 20% BSA involvement in the age group of 3 to 4 months might have proven challenging, since infantile atopic dermatitis most often begins on the face (the sponsor did not address this issue in the study report).

9.2 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that the supplement be approved, pending agreement on labeling.

9.3 Recommendation on Postmarketing Actions

None

9.3.1 Risk Management Activity

None

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

The labeling review will be entered as an addendum to the review.

9.5 Comments to Applicant

None

10 APPENDICES

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

The labeling review will be entered as an addendum to the review.

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

/s/

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