Clinical Pharmacology Review

NDA:	19-452
SUBMISSION TYPE:	Pediatric Supplement (S024)
SUBMISSION DATE:	February 12, 2007
PRODUCT:	Derma-Smoothe/FS® (0.01% fluocinolone acetonide)
INDICATION:	Atopic Dermatitis
SPONSOR:	Hill Dermaceuticals, Inc, FL 32773
REVIEWER:	Tapash K. Ghosh, Ph.D.

Introduction and Background

The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. Although several topical corticosteroids are approved for the treatment of atopic dermatitis, few have been formally studied for the age group described in the studies submitted for this NDA efficacy supplement

Derma-Smoothe/FS® (0.01% fluocinolone acetonide) topical oil was initially approved for the treatment of atopic dermatitis on February 3, 1988 and subsequently approved for the treatment of scalp psoriasis on February 16, 1995, both in adult population. Later Derma-Smoothe/FS was approved for pediatric patients 2 years and older for the treatment of atopic dermatitis in October 10, 2001. The current submission contains a phase 4 study (See Study 38) pursuant to CFR § 314.55 that contains clinical data to support use of Derma-Smoothe in pediatric atopic dermatitis patients from 3 months to 2 years old.

Clinical formulation:

Each gram of Derma-Smoothe FS topical oil contains approximately 0.11 mg of fluocinolone acetonide in a blend of oils which contains isopropyl alcohol, isopropyl myristate, light mineral oil, oleth-2, refined peanut oil NF and fragrances.

Ingredient	Percentage
Fluocinolone Acetonide, USP	0.010
Refined peanut Oil, NF[a]	
[redacted] Mineral Oil, USP	
Oleth-2	
Isopropyl Myristate, NF	
Isopropyl Alcohol, NF	
[redacted]	
[redacted]	

[redacted]

Labeling: Based on the review of Study 38, this reviewer suggests the following changes (Strikeout denotes deletion and underline denotes addition) in the sponsor's proposed language under clinical studies:

CLINICAL STUDIES

[redacted]

Recommendation:

The Clinical Pharmacology section of pediatric efficacy supplement of NDA 19-452 (S024) and the proposed label are acceptable .

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Senior Clinical Pharmacology Reviewer

Concurrence:

Sue-Chih Lee, Ph.D./TL

CC: NDA 19, 452 (S024)
HFD-540/Div File
HFD-540/CSO/Buerlien/DFS

Individual Study Review:

NDA: 19-452/ (S024) Protocol 38 **Study Dates: Apr, 05 – Nov, 06**

An Open-label Safety Study of Derma-Smoothe/FS® Topical Oil in Pediatric Patients, 3 months to 2 years old, with Atopic Dermatitis.

Objectives: The primary objective of the study was to evaluate the potential of Derma-Smoothe/FS® Topical Oil to suppress the HPA axis in a controlled, open-label, Phase 4 trial with pediatric patients, 3 months to 2 years old, with atopic dermatitis; effectiveness was also evaluated as a secondary objective.

Methodology: This study was conducted as an open-label study involving pediatric patients 3 months to 2 years of age with moderate to severe atopic dermatitis covering at least 20% total body surface area, meeting specific inclusion/exclusion criteria in 2 sites. A total of 32 patients were enrolled in this study with the patient identification numbers listed below in Table 1:

Table 1 Patient Identification Numbers by Investigator

Site #	Patient Identification Numbers	Number of Patients Enrolled
1	1 to 25	22
2	201 to 210	10

The study involved 4 weeks twice daily treatment with Derma-Smoothe/FS® Topical Oil and a follow-up visit one week post-treatment. Upon enrollment (Day 1/Baseline), morning plasma Cortisol level was determined prior to the administration of Cortrosyn®. Serum sample was again collected and tested for Cortisol level 30 minutes after the Cortrosyn® administration. Patients were required to return to the office within 1-3 days after administration of Cortrosyn® injection, for the Cortisol level results and dispensing of study medication. The same procedure for Cortisol level determination was repeated at the end of the treatment period, on Day 29 (4th week visit, 28+1). At Day 35, 1-week post-treatment, final evaluation was conducted. If any patient had subnormal cortisol levels at the end of the treatment period they were to be retested 14 days following the last dose, and followed clinically until recovery of HPA axis function was demonstrated. The patient was to be referred to an endocrinologist if the cortisol level was still abnormal at the 14 days post-treatment retest.

Criteria for normal HPA axis function as outlined in Package Insert for CORTROSYN®, were used by the sponsor to evaluate patients' HPA axis function. Each patient had to have a normally functioning HPA axis as defined by: (1) 8:00 AM (drawn no later than 10:00 AM) plasma cortisol level exceeding 5 mcg/100 mL prior to study entry; (2) demonstrate a response to cosyntropin stimulation exceeding 18 mcg/100 mL cortisol 30 minutes after stimulation with 0.125 mg of cosyntropin; and (3) the 30-minute level had to show an increment of at least 7 mcg/100 mL above the basal level.

Efficacy Evaluations: Since the primary purpose of this study was safety, all efficacy parameters collected are considered secondary. The investigator evaluated individual signs and symptoms (pruritus, prurigo, eczematous lesions and lichenification), global severity and global response at each visit. He/she also assessed the patient's condition

(relapse or not) at the 1-week post-treatment visit (Day 35). Efficacy results have not been reviewed here.

Results: Thirty two (32) patients enrolled in the study. Two patients did not receive any study drug. One patient (204) was withdrawn as his baseline cortisol level was < 5 µg/dL; he did not receive study drug. Subject 206 was enrolled in the study but did not return for a baseline blood draw, did not receive study drug and was lost to follow up. Neither Subject 204 nor Subject 206 was included in the ITT database. Therefore, there were 30 patients in the ITT population.

Another two subjects did not complete the study. Patient 205 did not return for the final (follow up) visit and was lost to follow up. Subject 210 withdrew from the study at Day 14 due to an adverse event (abscess on the right anticubital area). Both Subject 205 and Subject 210 were included in the ITT database. Therefore, a total of 4 patients were withdrawn from the study (Table 2) and only 28 patients completed the study.

Table 2 Reasons for Patient-Withdrawal from the Study

	N
Number of subjects enrolled	32
Number of subjects who did not complete study:	4
Baseline Cortisol < 5 µg/dL† (not included in the ITT)	1
Did not return for BL cortisol evaluation† (not included in the ITT)	1
Did not return for final F/U visit (included in the ITT population)	1
W/D for Adverse event at Day 14 (included in the ITT population)	1
ITT Population	30

† These subjects did not receive study drug and were not included in the ITT population

Although there were 30 subjects in the ITT database, subject 210 was excluded from the data analysis due to having no Day 29 blood draws. Therefore, in the ITT analysis, data from 29 subjects were analyzed.

Moreover, for the other analysis, an additional 5 patients were excluded by the sponsor because they did not meet the definition of "evaluable patients." One patient (#201) had a baseline cortisol value < 5 µg/dL at the Baseline Visit and three (#3, #13, and #205) had cortisol values < 5 µg/dL at Day 29; Another subject (Subject 209) had a post-stimulation increase < 7 µg/dL at Day 29 (Table 3). Therefore, the analyses of the cortisol levels were performed on the population of subjects who met the criteria for inclusion in the HPA axis evaluation (N = 24; evaluable subjects; excluded subjects #s: 201, 204, 205, 206, 209, 210, 3 and 13).

Table 3 Patients Who Did Not Meet the Criteria for the HPA Axis Evaluation

Visit	Baseline Value < 5 µg/dL	Post-Stimulation Value < 18 µg/dL	Post-Stimulation Inc < 7 µg/dL
Baseline	1	0	0
Day 29	3	0	1

Note: Patient (#201) had a baseline cortisol value of 4.9 mcg/dL, below the < 5 µg/dL criterion, but was included in the study after discussion between the sponsor and the site

primary investigator. (Per [redacted] the acceptable normal values for Cortisol levels fall within a range, i.e., 2.4 to 22.9 for the age group 2 months to 13 years old). Moreover, this patient responded normally to the Cosyntropin test: post-stimulation cortisol value of 20.7 mcg/dL. Patients (#3, #13 and #205) had post-treatment pre-stimulation cortisol values less than 5 mcg/dL (3.9, 4.3 and 4.6 mcg/dL respectively), which were again within the normal range of cortisol values for this age group Per [redacted]. Again, the post-stimulation cortisol values were normal responses above 18mcg/dL, and > 7 mcg/dL increase. Hence, these patients did not need further follow-up. Patient (#209) had cortisol values in the normal range at the pre-treatment test point, for both pre- and post-stimulation, 16.6 mcg/dL and 26.5 mcg/dL respectively. According to the sponsor, an explanation for the normal but slightly higher pre-stimulation cortisol value at baseline is possibly an effect of stress and anticipation to this 1 year old from an injection to draw blood. Nevertheless, the cortisol value increased after stimulation, although the increment was < 7 mcg/dL. This patient responded to the cortisol stimulation and was deemed to have normal cortisol response, and no suppression. No further follow up was performed.

The medical reviewer considered the single criterion of >18 micrograms per deciliter post-treatment post-stimulation cortisol levels as the evidence of no HPA axis suppression. Therefore, no consideration was given to the patients discussed above. The following Table 4 summarizes the overall results of the study:

Table 4 Summary Results

Pt Id	Gend	Race	Age (Yrs)	BSA	Severity	BL Cortisol Levels			Day 29 Cortisol Levels		
						Pre-Stim	Post-Stim	Incr	Pre-Stim	Post-Stim	Incr
1	Male	Other	1.03	20%	Moderate	**15.5**	**36.0**	**20.5**	**14.5**	**39.7**	**25.2**
2	Female	Caucasian	1.66	20%	Moderate	**9.9**	**32.4**	**22.5**	**14.6**	**30.2**	**15.6**
3	Male	Asian	0.52	50-75%	Moderate	**6.9**	**35.9**	**29.0**	**3.9**	**27.5**	**23.6**
4	Male	Other	2.55	20%	Moderate	**20.6**	**31.3**	**10.7**	**17.7**	**32.2**	**14.5**
5	Male	Caucasian	2.33	20%	Moderate	**14.2**	**38.5**	**24.3**	**10.6**	**26.4**	**15.8**
6	Male	Caucasian	1.43	20%	Moderate	**8.6**	**29.8**	**21.2**	**6.0**	**36.3**	**30.3**
7	Male	Black	0.35	20%	Moderate	**5.1**	**33.7**	**28.6**	**5.4**	**27.3**	**21.9**
8	Male	Black	0.31	>75%	Moderate	**13.4**	**47.0**	**33.6**	**17.8**	**32.7**	**14.9**
9	Male	Black	1.16	20%	Moderate	**16.6**	**38.9**	**22.3**	**10.9**	**30.6**	**19.7**
10	Male	Other	1.29	20%	Moderate	**6.8**	**32.1**	**25.3**	**14.6**	**41.9**	**27.3**
11	Female	Other	1.36	20%	Moderate	**11.3**	**29.2**	**17.9**	**11.5**	**35.3**	**23.8**
12	Female	Asian	2.69	50-75%	Moderate	**18.5**	**34.4**	**15.9**	**11.1**	**26.6**	**15.5**
13	Female	Caucasian	0.42	50-75%	Moderate	**18.4**	**46.9**	**28.5**	**4.3**	**29.0**	**24.7**
14	Male	Asian	0.70	50-75%	Moderate	**5.5**	**27.2**	**21.7**	**6.6**	**30.4**	**23.8**
15	Female	Other	1.66	50-75%	Moderate	**6.3**	**24.5**	**18.2**	**22.8**	**40.1**	**17.3**
16	Male	Asian	0.64	20%	Moderate	**9.7**	**29.8**	**20.1**	**13.0**	**26.0**	**13.0**
18	Female	Asian	0.45	>75%	Moderate	**8.5**	**66.0**	**57.5**	**6.9**	**36.8**	**29.9**
19	Female	Caucasian	0.31	>75%	Moderate	**17.6**	**42.1**	**24.5**	**9.4**	**23.9**	**14.5**

20	Male	Asian	0.53	>75%	Moderate	**5.5**	**31.8**	**26.3**	**10.3**	**38.4**	**28.1**
21	Female	Other	0.35	>75%	Moderate	**5.4**	**24.4**	**19.0**	**5.6**	**21.6**	**16.0**
22	Female	Caucasian	0.31	>75%	Moderate	**7.4**	**34.4**	**27.0**	**8.4**	**35.1**	**26.7**
25	Female	Caucasian	0.52	>75%	Severe	**10.6**	**31.3**	**20.7**	**6.7**	**30.8**	**24.1**
201	Female	Black	1.69	50-75%	Moderate	**4.9**	**20.7**	**15.8**	**8.2**	**18.1**	**9.9**
202	Male	Black	0.55	>75%	Severe	**19.1**	**33.5**	**14.4**	**10.6**	**21.8**	**11.2**
203	Female	Other	1.19	50-75%	Moderate	**12.7**	**32.5**	**19.8**	**7.1**	**26.4**	**19.3**
205	Male	Black	0.77	50-75%	Moderate	**6.4**	**27.3**	**20.9**	**4.6**	**23.7**	**19.1**
207	Female	Black	1.45	50-75%	Moderate	**8.1**	**32.9**	**24.8**	**12.0**	**23.8**	**11.8**
208	Male	Black	1.54	50-75%	Severe	**9.0**	**27.9**	**18.9**	**7.3**	**22.0**	**14.7**
209	Female	Black	1.04	50-75%	Moderate	**16.6**	**26.5**	**9.9**	**25.3**	**30.6**	**5.3**
210	Female	Black	0.58	50-75%	Moderate	**13.2**	**26.0**	**12.8**			

Table 5 summarizes the sponsor's analysis results of the pre- and post-stimulation cortisol levels and the post-stimulation increases for evaluable subjects. The mean post-stimulation increase at baseline was not much different from the post-stimulation value at Day 29.

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%)

Table 6 summarizes the pre- and post-stimulation cortisol levels at baseline and on Day 29, as well as the post-stimulation increases in cortisol levels for the ITT population per the sponsor's analysis. The post-stimulation increase at Day 29 was less than at baseline, but again the difference was probably not clinically significant.

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 increase (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

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Conclusions: This study was done in pediatric patients 3 months to 2 years of age with atopic dermatitis, who applied Derma-Smoothe/FS® to at least 20% of their bodies twice daily for 4 weeks. All of the cortisol response were above 20 µg/dL post-treatment. Based on the Agency's current single criterion of >18 micrograms per deciliter post-treatment post-stimulation cortisol levels as the evidence of no HPA axis suppression,

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. This study also confirmed a previous study, which showed no HPA axis suppression for Derma-Smoothe/FS® for the treatment of atopic dermatitis in a pediatric population, ages between 2 and 13 years of age.

Comment: *Some deviations have been noted based on sponsor-defined criteria for normal HPA axis function as outlined in package insert for CORTROSYN®. However, the Agency's current thinking on the new and sole criterion for HPA axis states that, for the purposes of corticosteroid drug development, the single criterion of <18 micrograms per deciliter post-stimulation is sufficient as the determinant of adrenal suppression. Out of 32 subjects entered in the study, morning pre-stimulation cortisol levels and post-Cortrosyn® stimulation cortisol levels were obtained in 28 subjects at the beginning of the trial and at the end of 4 weeks of treatment. As all these 28 subjects had >18 micrograms per deciliter post-treatment post-stimulation cortisol levels, no subject appeared to have HPA axis suppression following 4 weeks twice daily treatment with Derma-Smoothe/FS® Topical Oil.*

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/s/

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8/15/2007 02:08:02 PM
BIOPHARMACEUTICS

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