US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

New Drug Application

Clinical Studies

NDA/Serial Number:	19-452/SE-5-024
Drug Name:	Derma-Smoothe/FS® Topical Oil
Indication(s):	Atopic Dermatitis
Applicant:	Hill Dermaceuticals, Inc.
Dates:	Submitted: 2/15/07 PDUFA: 12/15/07
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics III
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Concurring Reviewer:	Mohamed Alosh, Ph.D.
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Keywords:	HPA-axis study, atopic dermatitis

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1 Executive Summary

1.1 Conclusions and Recommendations

Derma-Smoothe/FS® Topical Oil is currently approved for the treatment of atopic dermatitis in patients at least 2 years of age. The current supplement contains results from an HPA-axis suppression study in subjects 3 months to 2 years of age. The HPA-axis study resulted in zero out of thirty subjects with post-stimulation cortisol level less than 18 mcg/dL. One subject had a post-stimulation increment of less than 7 mcg/dL. However this subject was determined to have normal cortisol response by the sponsor due to a high pre-stimulation cortisol level that was speculated to be a result of stress from anticipation of pain. Therefore, zero subjects were determined to have shown adrenal suppression.

1.2 Brief Overview of Clinical Studies

The supplement to the original NDA contains one HPA-axis suppression study, Protocol 38, to study adrenal suppression in pediatric subjects 3 months to 2 years of age with atopic dermatitis. This study is used to support the sponsor's claim that Derma-Smoothe/FS® Topical Oil is safe and effective in pediatric patients, 3 months and older. A total of 32 subjects were enrolled in the study, however two subjects did not receive the study drug and were excluded from the intent-to-treat (ITT) population. Subjects applied the drug twice daily for four weeks. Each subject's plasma cortisol level was evaluated at Baseline and Day 29, pre- and post- cosyntropin stimulation. Normally functioning HPA axis was defined as (1) pre-stimulation cortisol level $>$ 5 mcg/dL; (2) post-stimulation cortisol level $>$ 18 mcg/dL; and (3) post-stimulation increment $>$ 7 mcg/dL. Efficacy and local safety was evaluated at Day 29. Hypothesis testing was not planned in the protocol and therefore none were conducted in this review.

1.3 Statistical Issues and Findings

In the HPA-axis suppression study of twice daily application of Derma-Smoothe/FS® Topical Oil in the treatment of atopic dermatitis in subjects 3 months to 2 years of age, zero of thirty subjects had a post-stimulation cortisol level less than 18 mcg/dL and one subject had a post-stimulation increment of less than 7 mcg/dL, after 4 weeks of treatment.

2 Introduction

2.1 Overview

Derma-Smoothe/FS® Topical Oil (Flucinolone Acetonide 0.01%) is a low to medium strength topical steroid in a combination oil base containing refined peanut oil and mineral oil, which

was approved on February 3, 1988 for the indication of atopic eczema in adults. The product was approved for psoriasis of the scalp in adults on February 16, 1995 and for atopic dermititis (AD) in pediatric patients at least 6 years of age on August 18, 1999. On October 10, 2001, approval was extended to pediatric patients at least 2 years of age.

The sponsor submitted an open-label safety study assessing HPA axis function of Derma-Smoothe/FS® Topical Oil in AD pediatric subjects, 3 months to 2 years of age with the intentions to change the labeling to include patients of this age group. Note that the primary objective of the study was to evaluate the potential of Derma-Smoothe/FS® Topical Oil to suppress the HPA axis and though efficacy was evaluated, it was as a secondary objective.

2.2 Data Sources

The review of this study (Protocol 38) was based on the data located at \\CDSESUB1\N19452\S_024\2007-05-29.

3 Statistical Evaluation

3.1 Study Design

The HPA axis suppression trial, Protocol 38, enrolled 32 subjects from two investigational sites. Subjects enrolled in the study were ages from 3 months to 2 years with moderate to severe AD covering at least 20% total body surface area. The study was designed as 4 weeks twice daily treatment with Derma-Smoothe/FS® Topical Oil and a follow-up visit one week post-treatment. The product vehicle was used as a skin moisturizer and applied as often as needed between treatments.

Morning plasma cortisol level was determined by drawing blood, prior to and after the administration of ACTH (Cortrosyn®) Stimulation Test. This was done upon enrollment (Day 1/Baseline) and repeated at the end of the treatment period, Day 29. Subjects were required to return to the office within 1-3 days after the Cortrosyn® administration, for the Cortisol level results and dispensing of the study medication. At Day 35, 1 week post-treatment, final evaluation was conducted.

A normally functioning HPA axis was defined as an 8:00 AM (drawn no later than 10:00 AM) plasma cortisol level exceeding 5 mcg/100 mL prior to study entry and a response to cosyntropin stimulation (0.125mg) exceeding 18 mcg/100 mL 30 minutes after stimulation. The 30-minute cortisol level had to show an increment of at least 7 mcg/100 mL above the basal level. Subjects with subnormal cortisol levels at the end of the treatment period were to be retested 14 days following the last dose and followed clinically until recovery of HPA axis function was demonstrated.

For efficacy, the investigators evaluated individual signs and symptoms (pruritus, prurigo, eczemtous lesions and lichenification), global severity and global response at each visit. The subjects' condition (relapse or not) were assessed at the 1 week post-treatment visit (Day 35). The scales used for these evaluations were as the following:

Static Global Severity		Assessment of patient's disease 1-week post treatment	
0	None	0	Completely cleared of signs/symptoms of atopic dermatitis
1	Mild	1	Has residual signs/symptoms but do not require further treatment
2	Moderate	2	Although signs/symptoms were gone at the last visit, patient now requires further treatment for atopic dermatitis
3	Severe	3	Patient was not cleared at any point during the study and requires further treatment for atopic dermatitis

Global Response (on Days 14 and 29)

0 Complete Clearing; 100% improvement/clearance from baseline;
1 Excellent Response; 75% - 99% improvement/clearance from baseline; residual traces of disease may be present;
2 Good Response; 50% - 74% improvement/clearance from baseline;
3 Fair Response; 25% - 49% improvement/clearance from baseline;
4 Slight Response; less than 25% improvement/clearance from baseline;
5 No change from baseline;
6 Exacerbation of Condition as compared to baseline

Other signs and symptoms (pruritus, prurigo, eczematous lesions and lichenification) were assessed on a scale of 0 - 3. The study protocol stated that efficacy evaluation will be descriptive and that no hypothesis testing was planned.

3.2 Subject Disposition

The study enrolled 32 subjects. Subjects 204 and 206 did not receive the study drug because Subject 204's baseline cortisol level was $< 5\mu$g/dL and Subject 206 did not return for the baseline blood draw and was lost to follow up. These subjects were not included in the intent-to-treat (ITT) population. All thirty subjects who received the study drug were included in the ITT population. Table 1 presents the reasons for subject withdrawal from the study.

Table 1: Reasons for Subject Withdrawal

	N
Subjects enrolled	32
Subjects who discontinued	4
Reason	
Baseline cortisol <5μg/dL[†]	1
Did not return for BL cortisol evaluation[†]	1
Did not return for final F/U visit	1
W/D for adverse event at Day 4	1

[†] Subjects who did not receive study drug and were excluded from the ITT population

Source: Protocol 38 Final Report, p. 30.

3.3 Demographic Data

Table 2 presents the demographics of the ITT population. The study included equal number of males and females. The racial distribution was also relatively balanced. Subjects' ages ranged from 3 months to 32 months (2.7 years) and were fairly uniformly distributed across the 6-month cohorts.

Table 2: Demographics (ITT)

	Number of Subjects (%) N=30
Gender	
Male	15 (50%)
Female	15 (50%)
Age (months)	
- 6	7 (23%)
6 - 12	8 (27%)
12 - 18	8 (27%)
18 - 24	4 (13%)
24 - 30	1 (3%)
30 - 36	2 (7%)
Race	
Caucasian	7 (23%)
African American	10 (33%)
Asian	6 (20%)
Other	7 (23%)

Source: Protocol 38 Final Report, p. 32 and Reviewer's Analysis

3.4 Evaluation of Efficacy

No hypothesis testing was proposed in the protocol of this study. Table 3 on the following page presents the distribution of Global Severity and Global Improvement from baseline at each visit which was confirmed by this reviewer. Note that one subject missed the Day 14 visit. For that subject, last observation carried forward was used to impute the Global Severity. The distribution of Global Improvement from Baseline was based on 29 subjects.

Table 3: Physician Assessments of Global Severity and Improvement

	Number of subjects (%)		
	Baseline N=30	Day 14 N=30†	Day 29 N=30
Global Severity			
0	0 (0%)	1 (3%)	12 (40%)
1	0 (0%)	23 (77%)	16 (53%)
2	27 (90%)	6 (20%)	2 (7%)
3	3 (10%)	0 (0%)	0 (0%)
Global Improvement from Baseline			
0		1 (3%)	12 (40%)
1		10 (34%)	7 (23%)
2		13 (45%)	10 (33%)
3		2 (7%)	1 (3%)
4		2 (7%)	0 (0%)
5		1 (3%)	0 (0%)
6		0 (0%)	0 (0%)

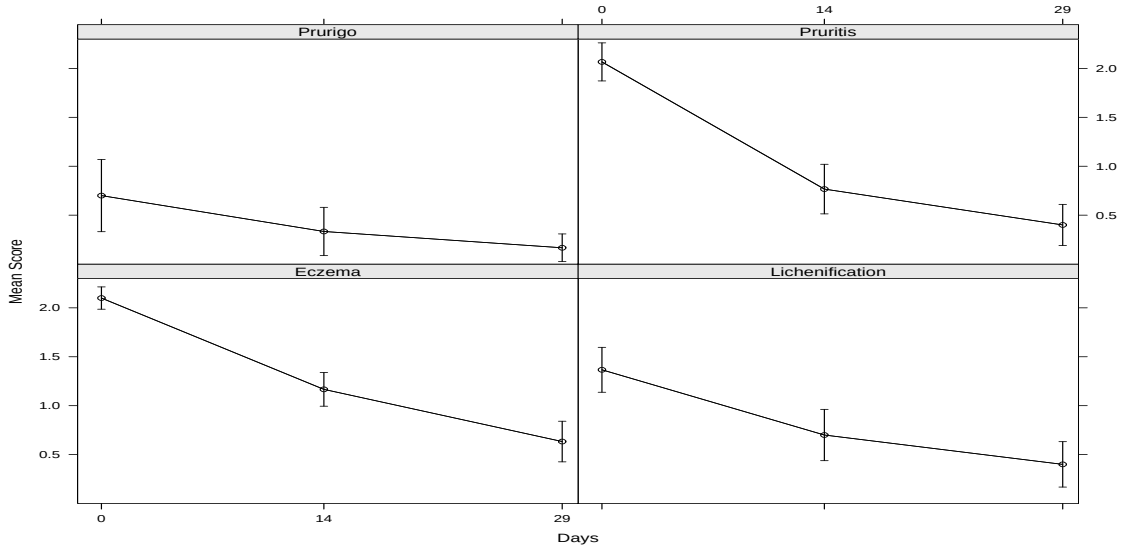
† One subject missed the Day 14 Visit. Last observation carried forward was used for Global Severity. Global Improvement was based on twenty nine subjects for the Day 14 assessments.

Source: Protocol 38 Final Report, p. 33

There were more subjects who scored a 0 or 1 on Day 29 than on Day 14 for both global endpoints. The disease status generally improved with time. Twenty seven (27) subjects returned for the one-week post treatment evaluation. According to the sponsor, 12 of the 27 subjects (44%) did not require further treatment, and 13 (46%) subjects required further treatment for atopic dermatitis at the judgement of the investigator.

Figure 1 on the following page presents the mean score of prurigo, pruritis, eczema and lichenification at baseline, and Days 14 and 29. The corresponding unadjusted 95% confidence intervals at these time points are also displayed. The mean score decreased over time in all four signs and symptoms assessments.

Figure 1: Mean Score of Signs and Symptoms Over Time and Corresponding Unadjusted 95% CIs



3.5 HPA-Axis Suppression Trial

Each subject had to have a normally functioning HPA axis defined by an 8:00 AM (no later than 10:00 AM) plasma cortisol level exceeding 5 mcg/100 mL prior to study entry. Post-stimulation cortisol level $\leq$ 18 mcg/100 mL, 30 minutes after 0.125 mg of cosyntropin indicates adrenal suppression. Additionally, the cortisol level 30 minutes post-stimulation had to show an increment of at least 7 mcg/100 mL above the basal level.

Among the thirty ITT population subjects, one subject (Subject ID # 210) was excluded from the HPA-axis study due to not having a Day 29 blood draw. Table 4 presents the number of subjects that did not meet the pre-specified criteria of normally functioning HPA axis, the Patient ID of those, and the value of the corresponding evaluation.

One subject (ID # 201) and three subjects (ID #s 3, 13, 205) had pre-stimulation values less than 5 mcg/dL at Baseline and at Day 29, respectively. One subject (ID # 209) had a post-stimulation increment less than 7 mcg/dL at Day 29. The sponsor determined to include Subject ID # 201 in the HPA-axis analysis because the subject's cortisol level was 4.9, which they considered to be within the normal A.M. cortisol level range for this age group. The three subjects with pre-stimulation less than 5 mcg/dL at Day 29 did not require follow-up because the pre-stimulation values, 3.9, 4.3, 4.6, were considered within the normal cortisol level range for this age group and their post-stimulation levels were larger than 18 mcg/dL with increments larger than 7 mcg/dL. The sponsor's reasoning for the one subject with an increment of less than 7 mcg/dL was the subject's anticipation of pain that might have raised cortisol levels. This

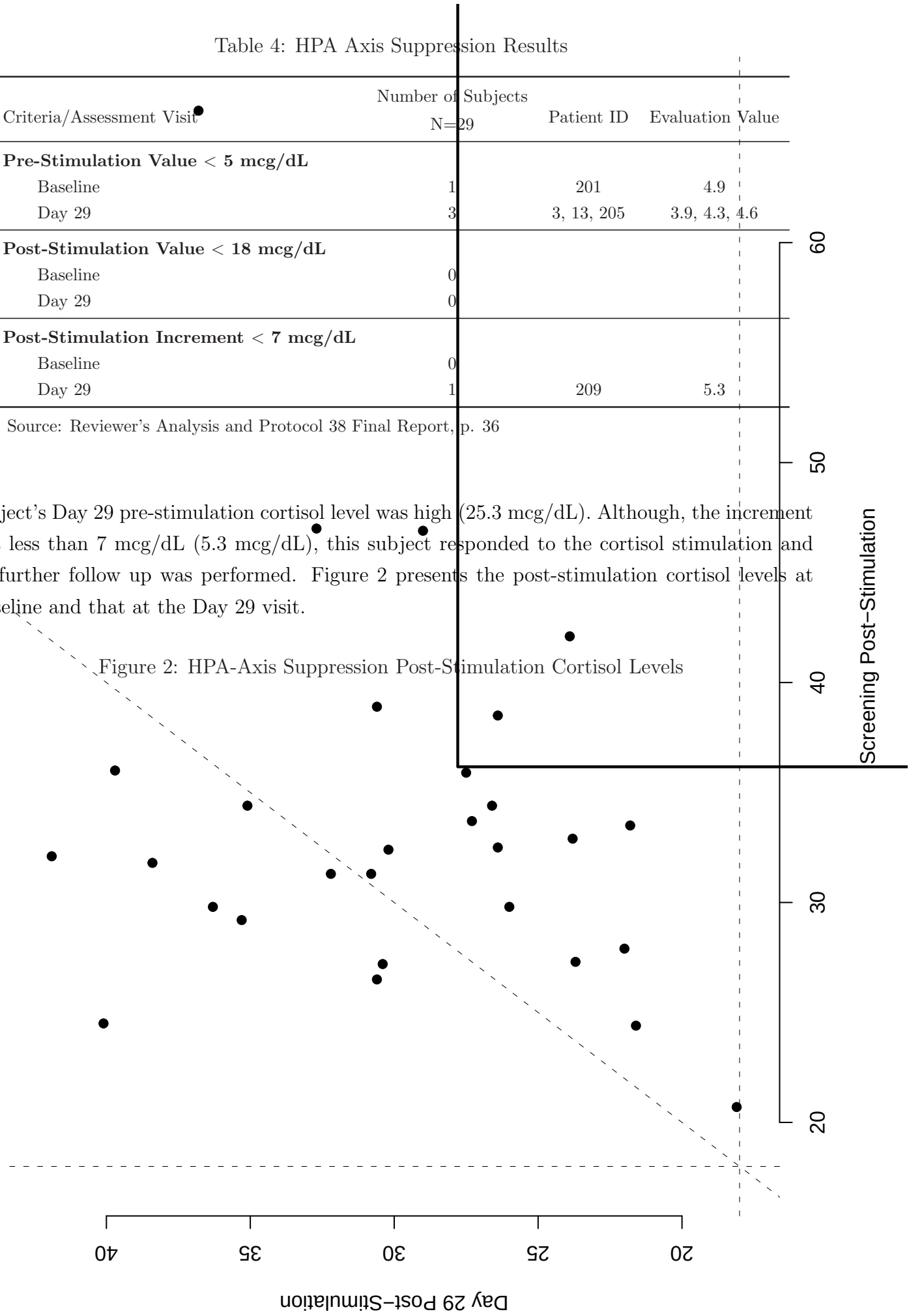
Table 4: HPA Axis Suppression Results

Criteria/Assessment Visit	Number of Subjects N=29	Patient ID	Evaluation Value
Pre-Stimulation Value < 5 mcg/dL			
Baseline	1	201	4.9
Day 29	3	3, 13, 205	3.9, 4.3, 4.6
Post-Stimulation Value < 18 mcg/dL			
Baseline	0		
Day 29	0		
Post-Stimulation Increment < 7 mcg/dL			
Baseline	0		
Day 29	1	209	5.3

Source: Reviewer's Analysis and Protocol 38 Final Report, p. 36

subject's Day 29 pre-stimulation cortisol level was high (25.3 mcg/dL). Although, the increment was less than 7 mcg/dL (5.3 mcg/dL), this subject responded to the cortisol stimulation and no further follow up was performed. Figure 2 presents the post-stimulation cortisol levels at Baseline and that at the Day 29 visit.

Figure 2: HPA-Axis Suppression Post-Stimulation Cortisol Levels



4 Summary and Conclusions

4.1 Statistical Issues and Collective Evidence

In the HPA-axis suppression study of twice daily application of Derma-Smoothe/FS® Topical Oil in the treatment of atopic dermatitis in subjects 3 months to 2 years of age, zero of thirty subjects had a post-stimulation cortisol level less than 18 mcg/dL and one subject had a post-stimulation increment of less than 7 mcg/dL, after 4 weeks of treatment.

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August 30, 2007

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