Clinical Pharmacology Review

NDA #	21-152/S-004
Submission Date (s)	April 22nd, 2010, July 22nd, 2010, July 30th, 2010 and August 6th, 2010
Brand Name	Cutivate® Lotion, 0.05 %
Generic Name	Fluticasone Propionate
Reviewer	Abimbola Adebowale, Ph.D.
Team Leader	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology (DCP) 3
OND Division	Division of Dermal and Dental Products (DDDP)
Applicant	Nycomed US Inc.
Relevant IND(s)	54,894
Submission Type	Pediatric Efficacy Supplement
Formulation; Strength(s)	Topical Lotion, 0.05%
Approved Indication	Relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 1 year of age and older.

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1 Executive Summary

Cutivate (fluticasone propionate) Lotion, 0.05% is a topical corticosteroid that was approved on March 31st, 2005 for the relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 1 year of age and older. The lotion is labeled to be applied once daily to the affected skin areas. (b) (4) 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.***

(b) (4)

Cutivate (fluticasone propionate) is also currently marketed as Cutivate ® 0.005% ointment (NDA 19-957, approved Dec. 14th, 1990) and, Cutivate ® 0.05 % cream (NDA-19-958, approved Dec.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).

(b) (4)

(b) (4)

1.2 Phase IV Commitments

Not Applicable

1.3 Summary of Clinical Pharmacology Findings and Biopharmaceutics Findings

Nycomed submitted one HPA axis suppression study, ALT 0434-01-01 (b) (4) .

HPA Axis Suppression:

Study ALT 0434-01-01 was 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 ≥ 35 % Body Surface Area (BSA). Cutivate® Lotion was applied twice daily for 3- or 4-weeks. A normal adrenal response was one in which the 30 minute post-injection cortisol level ≥18 micrograms/dL. Results of this study indicated that 1 of 49 (~2%) evaluable subjects demonstrated adrenal suppression as documented by a post-stimulation cortisol level of 15 micrograms/dL following 27 days of treatment. Notably, this subject (4 month old male) had a BSA of 94% treated with Cutivate® Lotion at baseline and a post-stimulation cortisol level of 31 microgram/dL at baseline. This subject appeared to recover from the adrenal suppression within one week as documented by a post-stimulation cortisol level of 22.1 micrograms/dL at follow-up. (b) (4)

2 Question-Based Review

2.2 General Clinical Pharmacology

Q What is the systemic exposure of Cutivate ® Lotion in pediatric atopic dermatitis (AD) patients aged 3 months to 12 months?

In study ALT-0434-01-01, HPA axis suppression was used as a surrogate marker to assess the potential for systemic exposure of Cutivate® Lotion. This study demonstrated that Cutivate lotion has the potential to cause suppression of the HPA axis when used over a large body surface (≥ 35 %) twice a day for up to 4 weeks in pediatric patients aged 3 months to 11 months old. This suggests that fluticasone is absorbed following topical application of Cutivate Lotion. The study also demonstrated that the suppression is reversible upon cessation of the drug product.

Study ALT-0434-01-01 was an open-label, multi-center study that enrolled 56 pediatric subjects aged 3 months to 11 months old with moderate to severe AD. Local and systemic safety after 3 or 4 weeks of twice-daily applications of Cutivate® Lotion was evaluated. The study medication was applied to the affected areas of atopic dermatitis (AD) covering 35% to 94.0 % Body Surface Area (BSA). The eyelids, perioral area, around the nostrils, and in the diaper area of those subjects who wore diapers and plastic pants were excluded. The primary safety parameter was the response of the adrenal gland to the Cosyntropin Stimulation Test (CST) at baseline and end of treatment/ final visit. A normal HPA response was defined as a 30-minute post-stimulation serum cortisol level ≥18 micrograms/dL at the end of treatment.

Of the 56 subjects enrolled, 49 were considered evaluable with respect to their adrenal axis function post-treatment. The distribution of subjects by age cohort was as follows: 27 subjects were 3 months to 6 months old and 29 subjects were 7 months to 11 months old.

Table 1: CST Results

	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 micrograms/dL.

As shown in the table above, one out of 49 (~2%) evaluable subjects, Subject # 2-134 (4 month old male) demonstrated adrenal suppression at the end of 27 days treatment as documented by a post-stimulation cortisol level of 15 micrograms/dL. Notably, this subject had a BSA of 94% treated with Cutivate® Lotion at baseline and a post-stimulation cortisol level of 31 microgram/dL at baseline. This subject appeared to recover from the adrenal suppression within one week as documented by a post-stimulation cortisol level of 22.1 micrograms/dL at follow-up.

Reviewer's Comments: There were no 12 month old AD subjects enrolled in this study as requested in the PMC. However, it is noted that 12 month old subjects were included in the previous study conducted (FPL 10005) in 4 months to 5 year old subjects. The currently approved label also includes subjects 12 months and older indicating that we have adequate safety data for this age group. (b) (4)

It is also noted that the twice daily dosing regimen used in this study is an exaggerated dosing regimen. Currently, only a once daily dosing regimen is approved for use in pediatric patients as young as 1 year of age. However, Nycomed stated that the current study was designed to include twice daily dosing to maximally challenge patients with respect to possibly eliciting a suppression response. This is consistent with the dosing regimen that was used in the previous HPA axis suppression study (FPL 10005) conducted by the sponsor in patients aged 4 months to 5 years old. This dosing regimen was also found acceptable by the clinical reviewer who reviewed the protocol prior to the initiation of the study.

2.6 Analytical Section

Q What bioanalytical methods were used to assess the active moiety in biological fluids and were they adequately validated?

The applicant did not measure the active moiety (fluticasone propionate) in biological fluids. The blood samples were analyzed for serum cortisol levels using an FDA validated and approved cortisol chemiluminescent immunoassay kit (FDA 510 (K) # is K962559) by CIBA Corning Diagnostic Corporation with a minimum detectable level of 0.2 micrograms/dL.

Reviewer's Comments: *The clinical reviewer had the following statement documented in their review for the original NDA "the sponsor stated that the decision not to measure plasma fluticasone levels in children less than 2 years of age was based (on) experience from an HPA axis study for fluticasone cream. Specifically, the sponsor states that in that study "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, Volume 14, p.18)" Therefore,* plasma fluticasone levels were not determined in *children less than 2 years of age in this study as well. .*


(b) (4)

Appendix

Individual Study Review

Significant Regulatory Interactions with regards to Study ALT-0434-01-01:

March 31st, 2005: Cutivate Lotion, 0.05 % was approved for marketing in the USA with 2 PMCs included in the approval letter as follows: (1) Evaluation of the safety ad systemic exposure of the drug product in pediatric patients aged 3 months to 1 year. (2) Study to determine the photo-carcinogenic potential of the drug product.

November 30th, 2005: The sponsor submitted the protocol (ALT 0434-01-01) to evaluate the potential effect of Cutivate Lotion, 0.05% on the HPA axis in a pediatric population aged 3 months to 12 months (b) (4)

February 10th, 2006: Review of the protocol by the clinical division was signed off in DARRTS (IND 54,894)

February 23rd, 2006: The clinical reviewer's comments for the protocol were faxed to the Sponsor (IND 54,894)

May 16th, 2006: The sponsor sent a revised protocol to the Agency that incorporated the changes suggested by the Agency in the February 23rd fax sent by the Agency to the sponsor.

June 29th, 2006: The clinical reviewer noted in his review (IND 54,894) that the study protocol incorporated the changes suggested by the Agency to amend the previously submitted protocol for the pediatric study commitment of HPA suppression. No further comments were conveyed to the sponsor

Protocol # ALT 0434-01-01 Review

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

Investigators and Study Centers: 10 sites in the US

1. Elizabeth Connelly, M.D. 2. Lawrence Eichenfield, M.D. 3. Alan B. Fleischer, Jr., M.D. 4. Adelaide Hebert, M.D. 5. Kenneth Bloom, M.D. 6. Craig L. Leonardi, M.D. 7. Sharon S. Raimer, M.D. 8. Lawrence C. Parish, M.D. 9. David L. Kaplan, M.D. 10. Stephen W. Shewmake, M.D.

Study Centers:
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4. The University of Texas Health Science Center at Houston, 6655 Travis, Suite 600, Houston, TX 77030
5. Dermatology Center for Children & Young Adults, P.A., 2795 Pilot Knob Road, Suite 300, Eagan, MN 55121
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Development Phase: 4

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

Reviewer's Comments: The approval letter had the following time-lines for the PMC Protocol Submission: by November 15, 2005; Study Start: by May 15, 2006; Final Report Submission: by May 15, 2008. The study started about 14 months late and the final report was submitted about 4 months late. It is not clear from the history of interactions with the Agency whether the applicant requested an extension.

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 ≥ 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

Reviewer's Comments: This reviewer only reviewed safety assessment # 1 (i.e. the effects on the HPA axis as determined by the cosyntropin stimulation tests). Please see clinical review for the review of safety assessment #'s 2, 3 and 4.

Study Design: 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% (Nycomed US Inc.). Up to six clinic visits (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.

Reviewer's Comments: The applicant stated that the current study was designed to include twice daily dosing to maximally challenge patients with respect to possibly eliciting a suppression response. A once-daily dose for up to 4 weeks is currently approved for use in pediatric patients as young as 1 year of age for the treatment of atopic dermatitis, but safety and efficacy in pediatric patients below 1 year of age has not been established per the Cutivate (FP) Lotion, 0.05 % package insert.

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 4months to < 6 years old for cutivate lotion. This dosing regimen was also found acceptable by the clinical reviewer who reviewed this protocol prior to the initiation of the study.

Plasma Fluticasone Levels: The applicant did not measure Plasma Fluticasone blood levels in this study based on their previous communications with the Agency. For the previous HPA axis suppression study (FPL 10005) conducted with cutivate lotion in patients aged 3 months to 5 years. The clinical reviewer had the following statement documented in their review for the original NDA "the sponsor stated that the decision not to measure plasma fluticasone levels in children less than 2 years of age was based (on) experience from an HPA axis study for fluticasone cream. Specifically, the sponsor states that in that study "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, Volume 14, p.18)".

Therefore, plasma fluticasone levels were not determined in children less than 2 years of age in this study as well. Please note that plasma fluticasone levels were not determined in children less than 2 years of age in approved NDA 19-958 (cutivate cream, 0.05%) and NDA 19-957 (cutivate ointment, 0.005%) for the same reasons cited for cutivate lotion and the sponsor's reasons were found acceptable.

Study Population: 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. Of the four subjects that did not complete the study; one (1) was related to an adverse event (Subject 5-095, 8 month old female), one (1) was lost to follow-up (Subject 8-082, 4 month old female) and 2 were related to abnormal CST testing at Baseline (Subjects 3-101, 7 month old male and 5-166, 4 month old male). Subject 5-095 had a flare of a Herpes Simplex Virus infected skin lesion which led to the discontinuation of the subject from the study. The applicant stated that Subject 8-082 completed all visits prior to the Final Visit.

When the site subsequently contacted the parent, she refused to reschedule their final visit but later returned the study drug.

Table 1: 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%)

Reviewer's Comments: The table above indicates that 12 month old patients were enrolled in the study. However, an examination of the individual subject listing indicated that there was no 12 month old subject enrolled in this study.

Table 2: Demographics of Age: ALL 56 Subjects

Age (months)	**Number of subjects**
3	5
4	10
5	8
6	4
7	8
8	5

9	5
10	5
11	6
Total	**56**

(b) (4)

The breakdown of Race in the applicant summary table above also indicates that there were a total of 61 subjects enrolled instead of 56 subjects however on further examination of the individual subject listings it was observed that there was an overlap between races. For example, 3 subjects were counted as white or African American and counted twice, one subject was listed as White/American Indian and counted twice and two other subjects were listed as Other/White/Japanese/Fillipino or White/Asian and counted twice.

Table 3: Subject age and Sex (from listing 16.2.4.3)

Site	Subject	Age(mth) /Sex	Site	Subject	Age(mth) /Sex	Site	Subject	Age(mth) /Sex	Site	Subject	Age(mth) /Sex
1	84	5/M	4	111	4/M	5	95	8/F	8	17	9/M
	85	3/M		112	7/M		96	7/F		18	4/M
	87	11/M		113	7/F		97	4/M		19	8/F
	88	10/M		114	10/F		98	6/M		76	8/M
	89	6/M		115	7/M		99	8/M		77	4/F
2	132	11/M		151	9/M		163	10/F		78	11/F
	133	5/M		152	7/M		164	5/F		79	7/M
	134	4/M		153	11/M		165	9/F		80	4/M
	135	5/M		154	6/M		166	4/M		81	10/F
3	100	10/F		155	3/M		167	5/F		82	4/F
	101	7/M		156	9/M	6	116	6/M		83	4/M
4	108	11/M	5	92	3/M		117	5/F		148	4/F
	109	8/M		93	9/F		118	7/M		149	3/M
	110	11/F		94	5/M	7	140	3/M	10	157	5/M

Treatments Administered: Cutivate (Fluticasone Propionate) Lotion 0.05% (Nycomed US Inc.). Three subjects (# 17, 18 and 19) at Site 08 received Cutivate Lotion 0.05 %, lot #5L017 (expiration 10/31/2007). All other subjects received Cutivate Lotion 0.05 %, lot # 7C005 (Expiration 3/31/2009).

Mode of Administration: 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. Prior to applying the study medication, the subject's parent/guardian was instructed to wash the area to be treated with mild soap and water. The area was to be allowed to dry for at least 10 minutes. Subjects' parents/guardians were instructed to wash their hands before applying the lotion. Subjects should not have bathed within 2 hours after study medication applications. Subjects' parents/ guardians were instructed not to apply study medication to the subject on the morning of the next visit. No study medication should have been applied for 4 hours prior to study visits. 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), unless the subject had reached his/her maximum treatment schedule.

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.

Extent of Exposure: Number of applications ranged from 6 to 62 and averaged 50.8±10.2. Five subjects (5/55~ 9.1 %) missed 10 to < 20% of the study medication application and 50/55 ~ 90.1 % missed less than 10 % of the study medication application.

Table 4: Extent of Exposure

	Overall	1-7 Days	8-14 Days	15-21 Days	22-28 Days	29+ Days
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

Reviewer's Comments: From the table above, 48/55 (~ 85.7 %) subjects were treated for > 21 days with the study medication.

Efficacy Assessment: Although efficacy assessment was not the primary objective of this study, disease severity was relevant for assessing safety and 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)]. ***Please see the clinical review for a detailed review of the efficacy assessment.*** A summary of the baseline assessment of the BSA and the total severity score is inserted below:

Table 5: Summary of Subject Baseline Characteristics (contd.)

Body Surface Area	BSA Affected	BSA Treated
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

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

The table above shows that the mean BSA treated at Baseline was 54.5 % with a range of 35.0 to 94.0 %. The total severity score for atopic dermatitis ranged from 7-19.

Safety Assessment: ***Please note that this reviewer only reviewed the HPA axis suppression component of the safety assessment. The clinical reviewer will be assessing the hematology, chemistry, adverse events and cutaneous effects component.***

Cosyntropin Stimulation Test (CST)

The primary systemic safety parameter was the response to the CST at baseline and end-of-treatment. 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 CST result at baseline were removed from the study.

After application of a topical anesthetic (EMLA®), an intravenous catheter was placed for blood sampling and cosyntropin administration. The cosyntropin injection was reconstituted by adding 1 mL of 0.9% sodium chloride to the labeled vial containing 0.25 mg cosyntropin. One-half of the reconstituted solution was injected. Therefore the dose of cosyntropin administered was 0.125 mg. At approximately 8:00 AM on Day 1 (Screening/Baseline Visit), a blood sample (3-5 mL) was taken from subjects immediately prior to intravenous (IV) or intramuscular (IM) injection of cosyntropin solution. An additional sample (after offering food and/or drink) was obtained thirty (30) minutes after IV or IM injection of 0.125 mg of Cortrosyn®. This test was conducted prior to the morning application of study medication. The End of Treatment CST was performed within one hour of the Baseline (Day 1) CST.

The preferred route for administration of the Cortrosyn® was intravenous. Every effort was made to ensure intravenous administration of Cortrosyn® throughout the study; 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.

Reviewer's Comments: Cosyntropin was administered at both baseline and end of treatment to 15 subjects (by IV) and 24 subjects (by IM). All the other subjects had either IV or IM administration before and after treatment. Subject 2-134 who demonstrated HPA axis suppression had IV administration only. There does not appear to be a correlation between post-stimulation cortisol levels and the route of administration (IV or IM) of cosyntropin.

The blood samples were analyzed for serum cortisol levels using an FDA validated and approved cortisol chemiluminescent immunoassay kit (FDA 510 (K) # is K962559) by CIBA Corning Diagnostic Corporation with a minimum detectable level of 0.2 micrograms/dL.

Baseline and post-treatment cortisol levels were summarized with descriptive statistics including mean, standard deviation, and range as are the change from Baseline (post-treatment minus Baseline).

CST RESULTS

Table 6: 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 micrograms/dL.

In the 49 evaluable subjects, at Baseline, post-stimulation cortisol levels averaged 28.2 micrograms/dL compared to 26.5 micrograms/dL at the End of treatment which resulted in a mean change of -1.8 micrograms/dL.

Baseline:

Reviewer's Comments: As per the table above, the 3 subjects with abnormal adrenal response (i.e. < 18 micrograms/dL) at baseline are summarized in the table below:

Table 7: Subjects with Abnormal Adrenal Response at Baseline

Subject #	Age (months)/Sex	Baseline Post-CST (micrograms/dL)
2-135	5/M	17.4
3-101	7/M	11.3
5-166	4/M	16.9

Subject #'s 3-101 and 5-166 were determined to be non-evaluable for CST testing, while subject # 2-135 was determined to be evaluable by the applicant. Subject (2-135) had a baseline CST of 17.4 micrograms/dL, which on re-analysis yielded 20.3 micrograms/dL (the applicant stated that the clinical laboratory commented that this reanalyzed cortisol value may be increased due to aging of the specimen). However, this subject completed the study and was found to have normal adrenal axis function with a post-stimulation cortisol level of 20.9µg/dL. Following discussions with the clinical reviewer we agreed that this subject could be considered evaluable since the cortisol levels did not decrease after treatment with cutivate lotion.

End of Treatment (EOT):
Of the 56 subjects initially enrolled, 49 were considered evaluable with respect to their adrenal axis function post treatment. 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. Notably, this subject had a BSA of 94% treated with Cutivate® Lotion 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). All the other 48 subjects had normal adrenal axis function at the End of Treatment evaluation. Of note, within this group there was one subject (5-095) who developed a herpes simplex infection during the trial that resulted in discontinuation. This subject had normal adrenal axis function (post-stimulation cortisol levels 26.7 micrograms/dL) at the conclusion of the study and was considered evaluable as the subject completed a minimum of 21 days of treatment.

Reviewer's comments:

Although subject # 2-134 who was suppressed had a BSA of 94 % treated with cutivate lotion at baseline, this does not definitively indicate a correlation between %BSA treated and adrenal suppression. There were 4 other subjects who had a % BSA treated value between 90 and 92 and none of them were suppressed.

Notably, subject 5-095 completed 24 days of dosing. The clinical reviewer is currently evaluating whether this subject # 5-095 is evaluable as stated by the applicant. This is because it is not clear whether the Herpes Simplex infection could have affected the CST testing results. This reviewer could not find any information that indicated that the herpes Simplex infection may have an effect on the CST results.

As per the current practices in the Division of Dermal and Dental Products, administration of cosyntropin to the same patient repeatedly at intervals of less than 4 weeks may result in higher stimulated cortisol levels after each successive cosyntropin injection, leading to invalid data. Notably, none of the subjects treated for less than 21 days demonstrated adrenal suppression as documented by post-CST cortisol levels ≥ 20 micrograms/dL (which exceeds the levels needed to demonstrate abnormal adrenal response) as shown in the table below.

Table 8: Subjects who had their Final Visit on Day 22 (N=10)

Subject #	**Age (months)/ sex**	**% BSA**	**Baseline Post-CST level (mcg/dL)**	**EOT Post-CST level (mcg/dL)**	**Difference from Baseline (mcg/dL)**
1-084	5/M	40	30.8	23.1	-7.7
1-085	3/M	50	20.6	20.8	0.2
1-087	11/M	50	22.2	21.3	-0.9
2-133	5/M	38	24.8	19.9	-4.9
4-110	11/F	53	38.3	22.8	-15.5
4-111	4/M	61	26.3	27.0	0.7
4-114	10/F	54	33.4	31.4	-2.0
4-152	7/M	36	27.9	29.2	1.3
4-155	3/M	57	29.9	26.7	-3.2
4-156	9/M	38	26.6	31.9	5.3
Mean			**28.1**	**25.4**	**-2.7**
Minimum			**20.6**	**19.9**	**-15.5**
Maximum			**38.3**	**31.9**	**5.3**
Standard Deviation (STDEV)			**5.3**	**4.4**	**5.8**

Ref: Listing Appendix 16.2.6.3

Based on the data for the full study (n=49), the mean change from baseline was -1.8 µg/dL. Assuming that the degree of HPA suppression at 3 weeks is equal to that obtained at 4 weeks (worst case), if there were stimulation due the short CST testing interval of 3 weeks we would expect the 3 weeks data to show less change from baseline than the -1.8 obtained for the whole study. As shown in the table above the calculated mean change was -2.7µg/dL for the 10 subjects with data on day 22. This data suggests that the CST testing at 3 weeks did not over-

stimulate cortisol levels. Therefore, administration of cosyntropin to the same patient repeatedly at an interval of 3 weeks did not appear to result in over stimulated cortisol levels leading to invalid data in this study. In addition, since everyone in this group had cortisol levels ≥ 19.9 µg/dL (i.e., ~2 units higher than the 18 µg/dL limit), we could conclude a lack of HPA axis suppression in these subjects.

Non-evaluable Subjects:
Of the 56 subjects enrolled seven (7) subjects were considered not-evaluable for HPA axis suppression for a variety of reasons; 2 with abnormal Baseline CST (Subjects 3-101, 5-166) already mentioned above, 3 with venous access difficulties/insufficient samples (Subjects 6-117, 8-019, 8-076), 1 withdrew consent (Subject 08-082), 1 with normal post-treatment CST but the analysis was delayed due to a specimen handling error by the lab (Subject 08-083) as detailed in the Table below:

Table 9: Adrenal Axis Assessment – Subjects Determined Non-Evaluable*

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

Reviewer's Comments: Center # 8 seemed to have the highest number of subjects that were not evaluable.

Reviewer's Summary: One subject out of 49 (~2%) evaluable subjects, Subject 2-134 (4 month old male) demonstrated adrenal suppression after 27 days of treatment as documented by a post-stimulation cortisol level of 15 micrograms/dL. Notably, this subject had a BSA of 94% at baseline that was treated with Cutivate® Lotion and a post-stimulation cortisol level of 31micrograms/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). Therefore, the study was able to demonstrate that Cutivate Lotion has the

potential to cause suppression of the HPA axis when used over a large body surface (≥ 35 %) twice a day for up to 4 weeks in pediatric patients aged 3months to 11 months old. The study also demonstrated that the suppression is reversible upon cessation of the drug product.

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/s/

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09/28/2010

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