CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-142

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Clobetasol Propionate Foam 0.05%
Olux ™ Foam
Reviewer: A. Noory
NDA 21-142

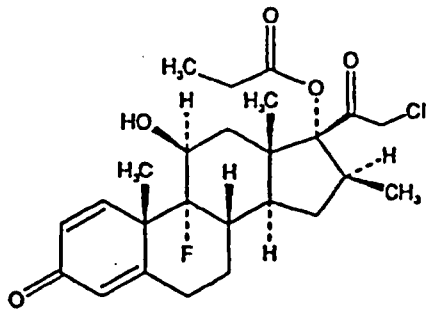
Connetics Corporation
Palo Alto, CA 94303
Submission Date: July 28,1999
September 15, 1999

Review of an NDA

I. Background:

Olux ™ Foam (clobetasol propionate foam 0.05%) is a super high potency synthetic corticosteroid and it has anti-inflammatory, antiprurtic, and vasoconstrictive properties. Olux ™ Foam is indicated for the short-term treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp. Because of their anti-inflammatory, immunosuppressive and anti-pruritic actions, topical corticosteroids, including clobetasol propionate (i.e. Temovate®), have been used effectively for many years for the treatment of corticosteroid-responsive dermatoses of the skin and scalp, including psoriasis, contact dermatitis, atopic dermatitis, and seborrheic dermatitis. Psoriasis, a chronic disorder estimated to affect about 2% of the United States (U.S.) population, usually first appears in the third decade of life. Psoriasis may occur anywhere on the skin, including the scalp. Psoriasis is characterized by raised, sharply demarcated, red plaques with a scaly surface

The chemical name of clobetasol propionate is (11β, 16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17 (1-oxopropoxy)-pregna-1,4-diene-3,20-dione ($C_{25}H_{32}ClFO_5$). It has the following structure with a molecular weight of 466.98.



As part of this NDA the applicant has submitted the results of a comparative vasoconstrictor study, a hypothalamus pituitary adrenal (HPA) axis suppression study and an in vitro absorption/bioavailability study.

II. Recommendation:

In support of the pharmacokinetic and bioavailability portion of this NDA the sponsor submitted the results of two in vivo and one in vitro studies. The topical vasoconstriction study was conducted to

evaluate the relative potency of Olux ™ Foam to currently marketed products. The HPA axis suppression study was conducted to assess the possible suppression of hypothalamic-pituitary-adrenal function. The topical vasoconstriction study adequately characterized the relative potency of Olux ™ Foam, and the HPA axis suppression study demonstrated that the suppression of the HPA axis after 14 days of treatment with Olux ™ Foam is similar (3/13) to the marketed product (Temovate® Ointment). From the biopharmaceutics perspective NDA 21-142 is approvable.

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III. Overview of pharmacokinetic section:

The human pharmacokinetic and bioavailability section of this NDA consists of two in vivo studies and one in vitro study. A comparative vasoconstriction study and a HPA axis suppression study to investigate the effect of clobetasol foam on the hypothalamic-pituitary-adrenal (HPA) function relative to a marketed clobetasol ointment. In the vasoconstriction study Olux™ foam was compared against five marketed clobetasol propionate products (Ointment, cream, gel, emollient, and scalp application), and two other marketed topical corticosteroids (fluocinonide solution and betamethasone valerate lotion). Also an in vitro study was carried out for determination of the effect of vehicle on the absorption/bioavailability of clobetasol.

Formulation:

The composition of Olux™ foam is shown in the table below. The formulation is a solution and the foam is formed at the time of use. There is [redacted] per 105 grams of the solution. The formulation does not show the [redacted] used during processing to reduce the risk of explosion.

Formulation Of Olux Foam	
Ingredient	Amount (%W/W)
Clobetasol Propionate, USP	0.05
Dehydrated Alcohol (Ethanol), USP	[redacted]
Cetyl Alcohol, NF	
Stearyl Alcohol, NF	
Polysorbate 60, NF	
Propylene Glycol, USP	
Purified Water, USP	
Citric Acid Anhydrous, USP	
Potassium Citrate, USP	

Analytical:

There were two ways of assessing the level of skin blanching in the vasoconstriction assay, one by visual inspection, the second by using a [redacted] with a precession ranging from 1.09% to 9.66% (page 14 of appendix). For the HPA suppression study the level of cortisol was determined using a [redacted]. An [redacted] was used for the determination of clobetasol in the in vitro cadaver skin study.

IV. Vasoconstrictor Study: (Study number CPCD.C.001)

The vasoconstriction test is a sensitive pharmacodynamic assay that depends upon the ability of glucocorticoids to produce vasoconstriction of superficial vessels in the skin. This activity leads to visible skin blanching at the site of application. It is the single most widely used surrogate test to assess the potency of topically applied glucocorticoids. The design of this vasoconstrictor study was discussed at the Pre-IND Meeting held February 19,1998 between applicant and the Agency. The objective of this study was to determine the vasoconstrictor potency of clobetasol propionate foam 0.05% relative to five marketed clobetasol products (ointment, cream, gel, emollient, and scalp application), and two other marketed topical corticosteroids (fluocinonide solution and betamethasone valerate lotion).

Treatments:

Product	Manufacturer	Lot #
Olux Foam 0.05% (Clobetasol propionate)	Connetics	8D976
Temovate Ointment 0.05% (Clobetasol propionate)	Glaxo Wellcome	7ZP0857
Temovate Gel 0.05% (Clobetasol propionate)	Glaxo Wellcome	7J365
Temovate Cream 0.05% (Clobetasol propionate)	Glaxo Wellcome	7ZP1765
Temovate Emollient.Cream 0.05% (Clobetasol propionate)	Glaxo Wellcome	7J378
Temovate Scalp Application 0.05% (Clobetasol propionate)	Glaxo Wellcome	6L223
Lidex Topical Solution 0.05% (Fluocinonide)	Medix Pharmaceuticals	71628
Betamethasone Valerate Lotion 0.1%	E. Fougea & Co	A761

Investigators: [redacted]

Date of Study: June29, 1998 - July 10,1998

Study Design:

The study was a single-center, masked (reader and subject), paired comparison study in healthy subjects. Thirty (30) individuals were prescreened and 24 subjects ages 18 to 65 (13 females and 11 males) showed adequate blanching response to clobetasol ointment and satisfied all inclusion and exclusion criteria. The demographics of study population are located on page 12 of the appendix. Six subjects showed inadequate blanching response to clobetasol ointment, therefore, they were excluded from the study.

Prescreening:

Subjects were screened for responsiveness to Clobetasol ointment at least 24 hours before the initiation of the study. Prescreening consisted of one unoccluded 10 µL dose applied to a 3.14 cm^2 site

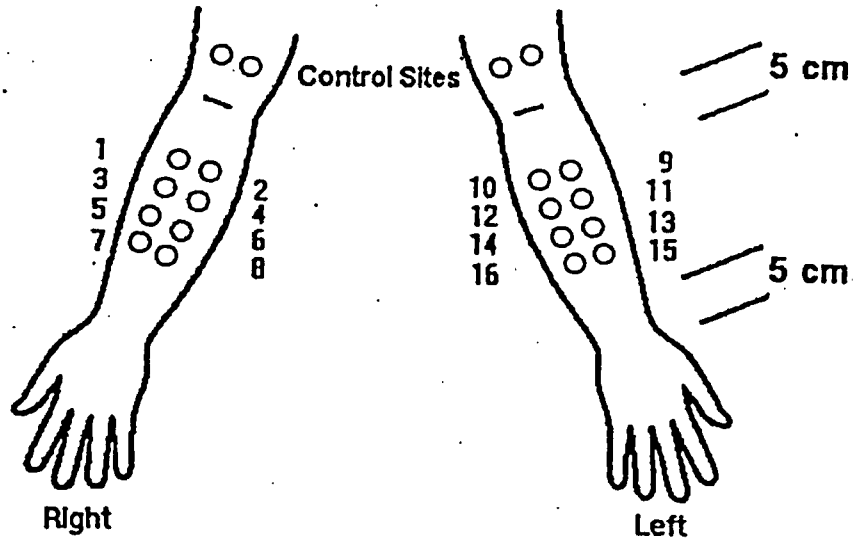
on the inner aspect of the ventral forearm. After 3 hours the site was wiped three times with dry cotton swabs and skin blanching was assessed 5 hours later using the visual rating scale given below.

0	no pallor; no change from surrounding area
1	mild pallor; slight or indistinct outline of application site
2	moderate pallor; discernible (½) outline of application site
3	moderate pallor; clean, distinct outline of application site
4	intense pallor; clean, distinct outline of application site

Eligibility of a subject for the study was contingent upon achieving a score of ≥1. The prescreening requirement was waived if the subject: (1) had participated in a vasoconstrictor study at the same site at least one, but not more than three, months before, and (2) had achieved a skin blanching score of -0.5 or lower (corrected a* scale reading, ———) 5 hours after removal of a 3-hour dose of clobetasol ointment 0.05%.

Randomization

Subjects were assigned a number in sequential order of entry (1 through 24) and randomized for assignment of the 0.5-hour and 3.0-hour dose-durations to the right or left arm and for various study drugs to individual test sites on each arm (page 13 in the appendix). All sites on one arm were used exclusively for one dose-duration, 0.5 or 3.0 hours, and all sites on the opposite arm were used exclusively for the second dose-duration. The eight test products, marked A through H, were randomly assigned to sites #1 - 8 on the right arm and the symmetrical sites #9-16 on the left arm (See Figure below).



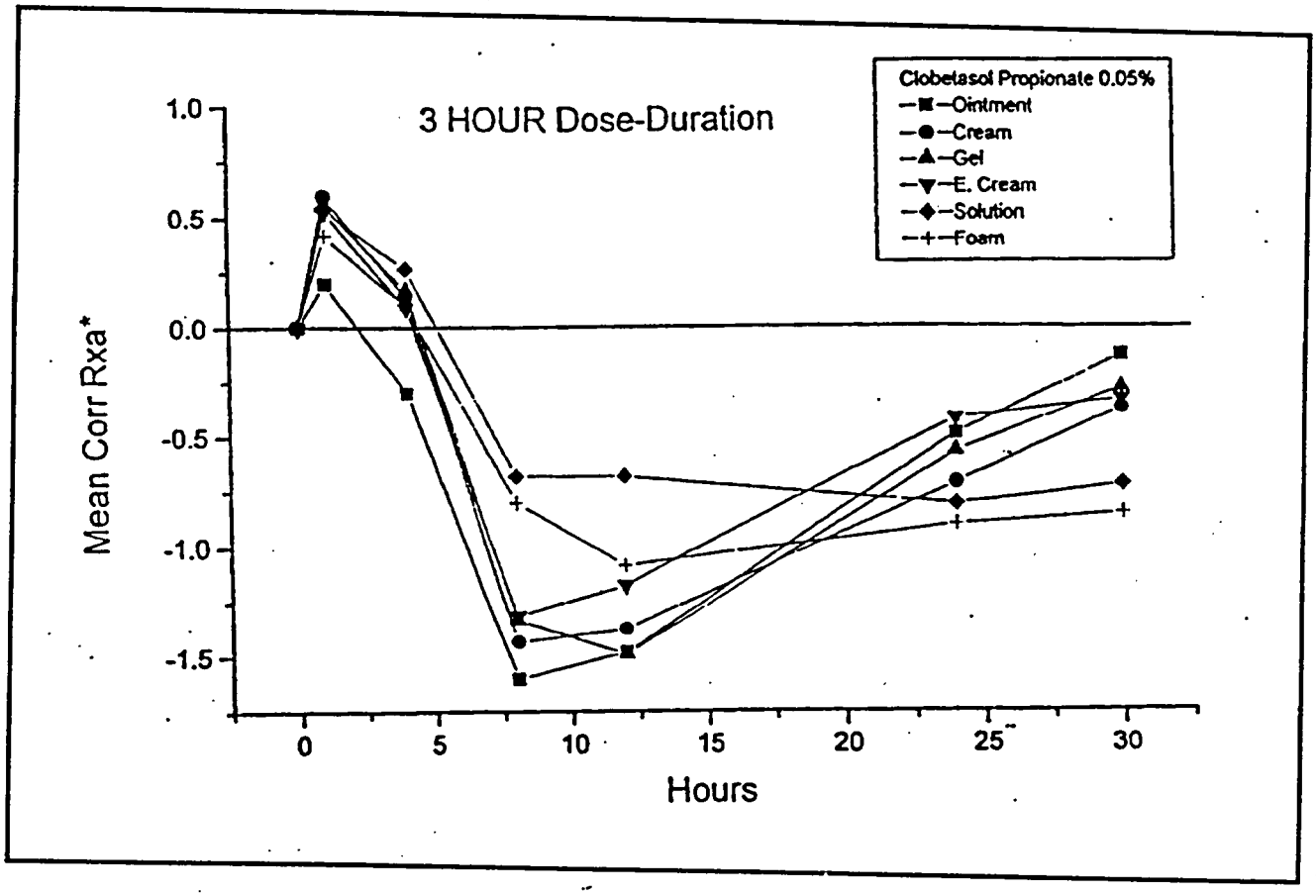
Drug Application Schematic

Skin color was measured using a ——— . Prior to use in this study, the instrument was validated to insure the reproducibility of readings. All readings were taken with the same chromameter. Skin color was initially measured 0.5 - 1 hour prior to dosing (baseline value), and again

at 1, 4, 8,12, 24 and 30 hours after dosing. A rubber 0-ring was attached with double-sided tape to the surface of the sensing head of the chromameter to prevent direct contact between sensor and skin. When taking a reading, the instrument was hand-held by the operator and the 0-ring was placed onto the skin surface lightly, to avoid compression of superficial blood vessels. The instrument was maintained perpendicular to the skin surface and the sensor activated. The chromameter was programmed to automatically take three readings at approximately 1 -second intervals.

Results:

The mean skin blanching response profile for each product as a function of time is shown on pages 15-16 of the Appendix. A representative profile for the 3.0-hour dose-duration for clobetasol containing products is shown below.



The following table shows the area under the effect curve, $AUEC_{(0-30)}$, values. Clobetasol Foam shows similar vasoconstrictor potency to Temovate Gel and Temovate E. Cream. Additionally after 3 hours dose duration Clobetasol Foam shows greater vasoconstrictor potency to than either the high potency Lidex® Topical Solution 0.05% (Fluocinonide) Topical Solution the mid-potency Betamethasone Valerate Lotion, 0.1%.

Mean $AUEC_{0-30}$ (a* Units x Hours)		
Product	0.5 Hour	3.0 Hour
Temovate Cream 0.05%	-25.2	-23.9
Temovate Ointment 0.05%	-21.6	-23.8
Temovate Gel 0.05%	-22.8	-22.9
Clobetasol Foam 0.05%	-22.8	-22.3
Temovate E. Cream 0.05%	-21.1	-19.2
Temovate Scalp Application 0.05%	-20.9	-17.2
Lidex Topical Solution 0.05%	-21.9	-16.2
Betamethasone Valerate Lotion 0.1%	-11.9	-6.7

The reason for the observed differences in rank order between the 0.5-hour and 3.0-hour dose-durations is not known. These differences may, in fact, not represent true differences in potency between products, but simply a result of the inherent variability of the method.

The rankings at both dose-durations for the Clobetasol products are as follows:

Treatment Duration	Rank Order
0.5 hour	cream > foam = gel > ointment > e. cream > scalp application
3.0 hour	cream > ointment > gel > foam > e. cream > scalp application

Conclusions

The results of this study demonstrate that the potency of Clobetasol foam falls between Temovate Cream and the Temovate Emollient Cream at both 0.5-hour and 3-hours dose duration. Since the potency of Clobetasol foam falls between Temovate Cream and Temovate Emollient Cream, and both of these formulations are classified as super-high potency corticosteroids (Stoughton and Cornell, 1993; Physicians Desk Reference, 1998), Clobetasol foam should also have a super-high potency classification.

V. HPA Suppression Study: (Study number CPCD.C.003)

One of the primary safety concerns of long term use of topical corticosteroid is the potential for suppression of adrenal function due to feedback inhibition of ACTH. This results in atrophy of the adrenal glands which are associated with major metabolic and physiologic abnormalities (Addison's disease). Current FDA guidelines call for assessment of HPA (hypothalamic-pituitary-adrenal) function using an ACTH stimulation test (cosyntropin stimulation). Determination of the HPA function in this study is done using a [redacted] .it, which utilizes [redacted] . The test is carried out both before the initiation of topical corticosteroid treatment and at the end of the treatment period. The procedure consists of a measurement of serum cortisol level before the intramuscular (IM) administration of 0.25mg of cosyntropin, and 30 minutes post administration of cosyntropin. A normal pre-stimulation cortisol level is defined as >5 µg/dL and a normal post-stimulation cortisol level is defined as >18 µg/dL. Generally, after the stimulation with cosyntropin, the plasma cortisol level will be two times the baseline level seen in the pre-stimulation indicating a lack of HPA axis suppression.

Study Title: An Open-Label Study to Evaluate the Effect of Clobetasol Propionate Foam 0.05% on the Hypothalamic-Pituitary-Adrenal Axis

Investigators: Alan Heller, MD.
San Jose Clinical Research
San Jose, CA 95128

Bruce Miller, and MD.
Clinical Research Center
Portland, OR 97223

Date of Study: September 10,1998 - November 17, 1998

Objective: The objective of this study was to compare the effects of clobetasol propionate foam, 0.05% with clobetasol propionate ointment, 0.05%, on the HPA axis ACTH stimulation.

Treatment: 0.05%, clobetasol propionate ointment, Lot # 8ZP0439, 7ZP1166
0.05%, clobetasol propionate foam, Lot # 80976

Study design: This was a multi-center (2 sites), randomized, parallel-design, open-label study in 26 subjects with psoriasis or atopic dermatitis.

Study Methods:

The effect of Clobetasol propionate, 0.05% foam and clobetasol propionate, 0.05% ointment on the HPA axis was determined following application of 3.5 grams twice daily for 14 days to the disease skin of psoriatic or dermatitis patients using the cosyntropin-stimulated change in the plasma cortisol response. Twenty-six subjects were randomly assigned to 14 days of treatment with either Clobetasol foam or Clobetasol ointment. The study population consisted of ambulatory male and female subjects, ages 23 to 72. Demographic of subjects is shown on page 17 in the appendix. Subjects were randomized to treatment with foam or ointment separately within each disease psoriasis or atopic dermatitis. The Treatment Phase consisted of a morning and an evening visit for 14 days. The subjects themselves under the supervision of the study personnel administered the treatments. The Follow-up Phase included an end of treatment visit on Day 15 for all subjects. Additional follow-up on day 20 was conducted for subjects with abnormal serum cortisol levels. Pre-stimulation and post-stimulation serum cortisol levels were measured at Baseline (Day 1), Day 8 and Day 15. Serum cortisol levels were measured prior to and 30 minutes after intramuscular (IM) injection of 0.25 mg of cosyntropin.

Results:

Serum cortisol levels were determined prior to and 30 minutes after IM injection of 0.25 mg of cosyntropin. Individual subject data are shown on page 18-19 of Appendix. Treatment groups were compared using the Fisher's Exact Test. Mean pre-injection and post-injection serum cortisol levels for the Clobetasol foam and Clobetasol ointment treatment groups on Day 1, Day 8, and Day 15 were compared using the t-test. Changes in mean serum cortisol values from Baseline to Day 8 and Day 15 were also compared using t-test (page 20 of Appendix).

Conclusions:

The results of this study show that Clobetasol foam had no greater effect on the suppression HPA axis than Clobetasol ointment and that both have similar safety profile. About 23% of the subjects experienced suppression of the HPA axis from topical clobetasol therapy.

VI. In Vitro Study:

Study Title: Effect of Vehicle on the Bioavailability of Clobetasol Propionate 0.05%

Investigator: [redacted]

Study date: April 27, 1998 to May 19, 1998

Study Objectives: To determine the relative bioavailability of clobetasol propionate from three different vehicles (Clobetasol foam; Temovate Cream, Temovate Scalp Application).

Study Design:

This was an open-label, single center study designed to assess the relative absorption/bioavailability of clobetasol propionate from three different vehicles using human cadaver skin and the [redacted]. Temovate Cream and Temovate Scalp Application are approved products manufactured by Glaxo Wellcome. The Clobetasol foam used in this study was a research batch and is claimed to be equivalent to the Clobetasol foam drug product that is the subject of this NDA except that it was an unbuffered preparation at pH 4.5.

Treatments:

Product	manufacturer	Lot number
Clobetasol foam, 0.05%	Connectics Corp.	E68/71
Temovate Cream, 0.05%	Glaxo Wellcome	7ZP1765
Temovate Scalp Application, 0.05%	Glaxo Wellcome	6L223

Study Method:

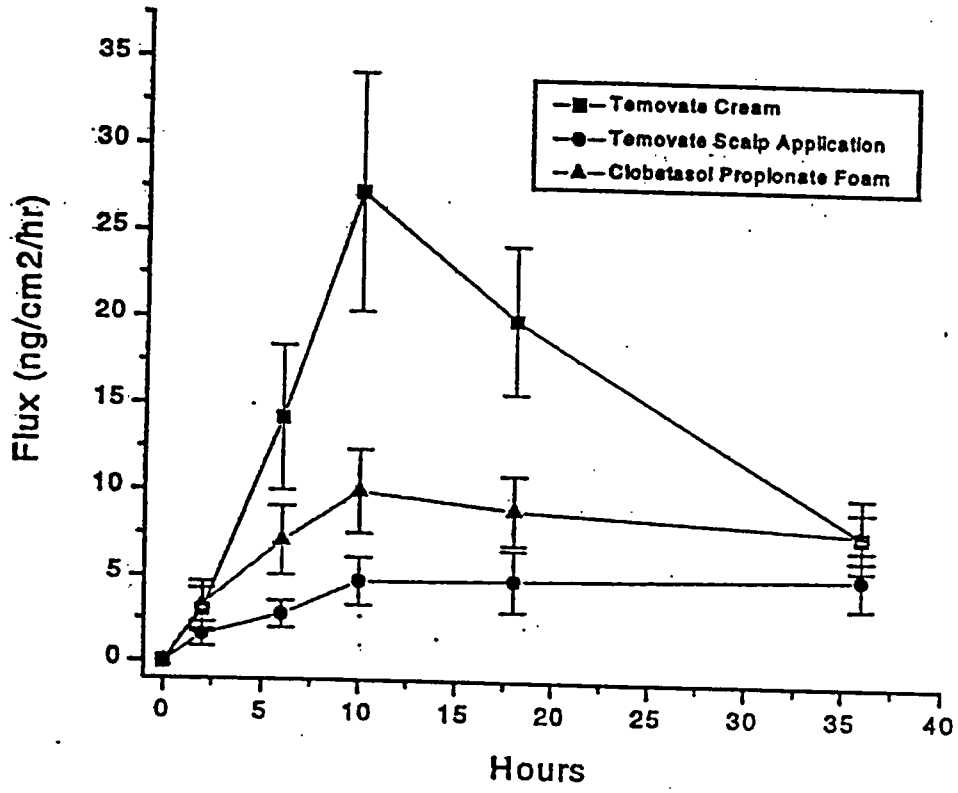
Bioavailability was assessed by determining the rate and extent of percutaneous absorption of the drug through human cadaver skin. A total of 69 skin sections obtained from five different donors that met the criteria established by the ^3H_2O validation test (An absorption of less than 1.25 µL of ^3H_2O in 0.5 hour) were used in this study. Demographics of the donors are listed in the following table.

Donor Demographics				
Donor ID	Gender	Race	Age	Body Site
[redacted]	Female	Caucasian	69	Posterior trunk
	Male	Hispanic	16	Posterior trunk
[redacted]	Female	Caucasian	56	Posterior trunk
	Male	Caucasian	38	Posterior trunk
	Male	Caucasian	32	Posterior trunk

Three donors were male and two were female, four donors were Caucasian and one was Hispanic and all skin specimens were chosen within 24 hours of death. Following the measurement of ^3H_2O absorption, the receptor solution was changed several times to remove all traces of radioactivity and then replaced with a 1:10 dilution of [redacted]. Subsequently, each test formulation was applied to multiple (4 - 7) sections of skin from the same donor skin at a dose of 5-7 mg/cm^2. At 4, 8, 12, 24 and 48 hours the receptor solution in each chamber was removed for analysis by [redacted]

Results:

The rate of absorption and total absorption was determined and the individual measurements per formulation were averaged across all skin sections from a given donor to determine the mean for that donor. Subsequently, the average data for each donor was for determination of an overall Mean ± Standard Error for the formulation. The rates of absorption are presented graphically in the following Figure.



The table below contains the total clobetasol propionate absorption at both 12 and 48-hours.

Total Absorption Across All Donors (% of dose)		
Product	12 Hours; Mean (SEM)	48 Hours; Mean (SEM)
Temovate Cream	5.79 (1 55)*	18.78 (3.40)
Clobetasol Propionate Foam	2.62 (0.70)	12.15 (2.64)
Temovate Scalp Application	1.24(0.33)	7.16(2.23)

Maximum absorption of clobetasol propionate was reached in about 10 hours. The rank order of absorption is as follows:

Temovate Cream > clobetasol foam > Temovate Scalp Application

Conclusions:

Although this in vitro study does not contribute to the regulatory requirements for approval of this NDA, the results show a rank order of the relative in vitro absorption of clobetasol foam, Temovate Cream, and Temovate Scalp Application. The rank order of absorption is Temovate Cream >clobetasol foam > Temovate Scalp Application.

VII. Labeling Comment:

Under the heading "INDICATIONS AND USAGE" first paragraph, after the second sentence, add the following.

/S/ Feb. 28, 2000

Assadollah Noory
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm.D. Ew 2/29/00

Original: NDA 21-142
CC:
HFD-540/DIV. File
HFD-540/Prj. Mgr./ Bhatt
HFD-880 (Noory)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-344 (Viswanathan)
(CDR. Attn. B. Murphy)

APPEARS THIS WAY
ON ORIGINAL

Appendix

Clobetasol Propionate Foam 0.05%
Protocol CPCD.C.001

Demography

Subject No.	Screen Date	Urine Pregnancy Test Results	Gender	Race	Date of Birth	Age (years)	All Inclusion/Exclusion criteria met?
01-00	06/29/98	Not applicable	Male	Caucasian	[redacted]	20.5	Yes
02-00	06/29/98	Not applicable	Female	Caucasian	[redacted]	38.9	Yes
03-00	06/29/98	Not applicable	Male	Caucasian	[redacted]	51.2	Yes
04-00	06/29/98	Negative	Female	Caucasian	[redacted]	26.7	Yes
05-00	06/29/98	Negative	Female	Asian	[redacted]	35.5	Yes
06-00	06/29/98	Negative	Female	Caucasian	[redacted]	45.2	Yes
07-00	06/29/98	Not applicable	Male	Caucasian	[redacted]	44.7	Yes
08-00	06/29/98	Negative	Female	Caucasian	[redacted]	44.1	Yes
09-00	07/06/98	Not applicable	Male	Caucasian	[redacted]	24.1	Yes
10-00	06/29/98	Negative	Female	Caucasian	[redacted]	21.4	Yes
11-00	07/06/98	Negative	Female	Caucasian	[redacted]	37.0	Yes
12-00	07/06/98	Negative	Female	Caucasian	[redacted]	26.0	Yes
13-00	07/06/98	Negative	Female	Caucasian	[redacted]	24.9	Yes
14-00	07/06/98	Not applicable	Male	Caucasian	[redacted]	31.5	Yes
15-00	07/06/98	Not applicable	Male	Caucasian	[redacted]	30.5	Yes
16-00	07/06/98	Negative	Female	Caucasian	[redacted]	38.9	Yes
17-00	07/06/98	Negative	Female	Caucasian	[redacted]	26.6	Yes
18-00	07/07/98	Not applicable	Male	Caucasian	[redacted]	31.4	Yes
19-00	07/06/98	Not applicable	Male	Asian	[redacted]	43.2	Yes

Clobetasol Propionate Foam 0.05%
Protocol CPCD.C.001

Demography

Subject No.	Screen Date	Urine Pregnancy Test Results	Gender	Race	Date of Birth	Age (years)	All Inclusion/Exclusion criteria met?
20-00	07/06/98	Negative	Female	Caucasian	[redacted]	27.5	Yes
21-00	07/06/98	Not applicable	Male	Caucasian	[redacted]	27.3	Yes
22-00	07/06/98	Not applicable	Male	Caucasian	[redacted]	24.0	Yes
23-00	07/07/98	Not applicable	Female	Caucasian	[redacted]	43.1	Yes
24-00	07/07/98	Not applicable	Male	Caucasian	[redacted]	23.7	Yes

APPEARS THIS WAY
ON ORIGINAL

Clobetasol Vasoconstrictor Study CPCD.C.001
Treatment Assignments for Each Patient

			Site 1 Site 9	Site 2 Site 10	Site 3 Site 11	Site 4 Site 12	Site 5 Site 13	Site 6 Site 14	Site 7 Site 15	Site 8 Site 16
Pat 01	right=0.5 hr.	left=3.0 hr.	E	B	A	F	H	D	C	G
Pat 02	right=0.5 hr.	left=3.0 hr.	C	E	B	G	F	H	D	A
Pat 03	right=3.0 hr.	left=0.5 hr.	H	F	A	G	E	D	B	C
Pat 04	right=3.0 hr.	left=0.5 hr.	A	H	G	E	D	B	F	C
Pat 05	right=3.0 hr.	left=0.5 hr.	A	G	F	D	H	B	E	C
Pat 06	right=0.5 hr.	left=3.0 hr.	E	A	D	G	C	F	B	H
Pat 07	right=3.0 hr.	left=0.5 hr.	E	D	H	B	A	C	G	F
Pat 08	right=0.5 hr.	left=3.0 hr.	A	B	E	D	H	C	F	G
Pat 09	right=0.5 hr.	left=3.0 hr.	B	E	G	F	A	C	H	D
Pat 10	right=3.0 hr.	left=0.5 hr.	B	F	G	C	D	A	E	H
Pat11	right=3.0 hr.	left=0.5 hr.	G	H	F	C	B	E	A	D
Pat 12	right=0.5 hr.	left=3.0 hr.	H	A	D	E	G	B	C	F
Pat 13	right=0.5 hr.	left=3.0 hr.	B	G	D	H	E	F	C	A
Pat 14	right=3.0 hr.	left=0.5 hr.	G	D	A	B	C	F	E	H
Pat 15	right=3.0 hr.	left=0.5 hr.	D	A	E	C	F	H	G	B
Pat 16	right=3.0 hr.	left=0.5 hr.	C	F	H	E	B	G	D	A
Pat 17	right=0.5 hr.	left=3.0 hr.	C	H	B	A	D	E	F	G
Pat 18	right=3.0 hr.	left=0.5 hr.	D	C	E	A	G	H	B	F
Pat 19	right=0.5 hr.	left=3.0 hr.	G	D	C	F	A	E	H	B
Pat 20	right=0.5 hr.	left=3.0 hr.	F	G	C	H	B	D	A	E
Pat 21	right=0.5 hr.	left=3.0 hr.	D	B	C	H	F	G	A	E
Pat 22	right=3.0 hr.	left=0.5 hr.	H	C	F	A	E	G	D	B
Pat 23	right=0.5 hr.	left=3.0 hr.	F	C	B	D	G	A	H	E
Pat 24	right=3.0 hr.	left=0.5 hr.	F	E	H	B	C	A	G	D
			A=	Clobetasol propionate foam 0.05%						
			B=	Clobetasol propionate cream 0.05%						
			C=	Clobetasol propionate emollient cream 0.05%						
			D=	Clobetasol propionate gel 0.05%						
			E=	Clobetasol propionate ointment 0.05%						
			F=	Clobetasol propionate solution 0.05%						
			G=	Flucinonide solution 0.05%						
			H=	Betamethasone valerate lotion 0.1%						

08 0303

Chromameter Validation Results

CR-300, Serial #72221032

All values are uncorrected a* scale readings

Subject: [redacted]

Site==>:	Right Arm 1	2	3	4	Left Arm 5	6	7	8
1								
2			[redacted]					
3								
4			[redacted]					
Mean:	4.21	4.86	3.90	4.03	3.65	3.77	4.01	3.65
SD:	0.41	0.31	0.14	0.39	0.13	0.26	0.18	0.17
CV	9.66	6.30	3.52	9.57	3.47	6.92	4.50	4.79

Subject: [redacted]

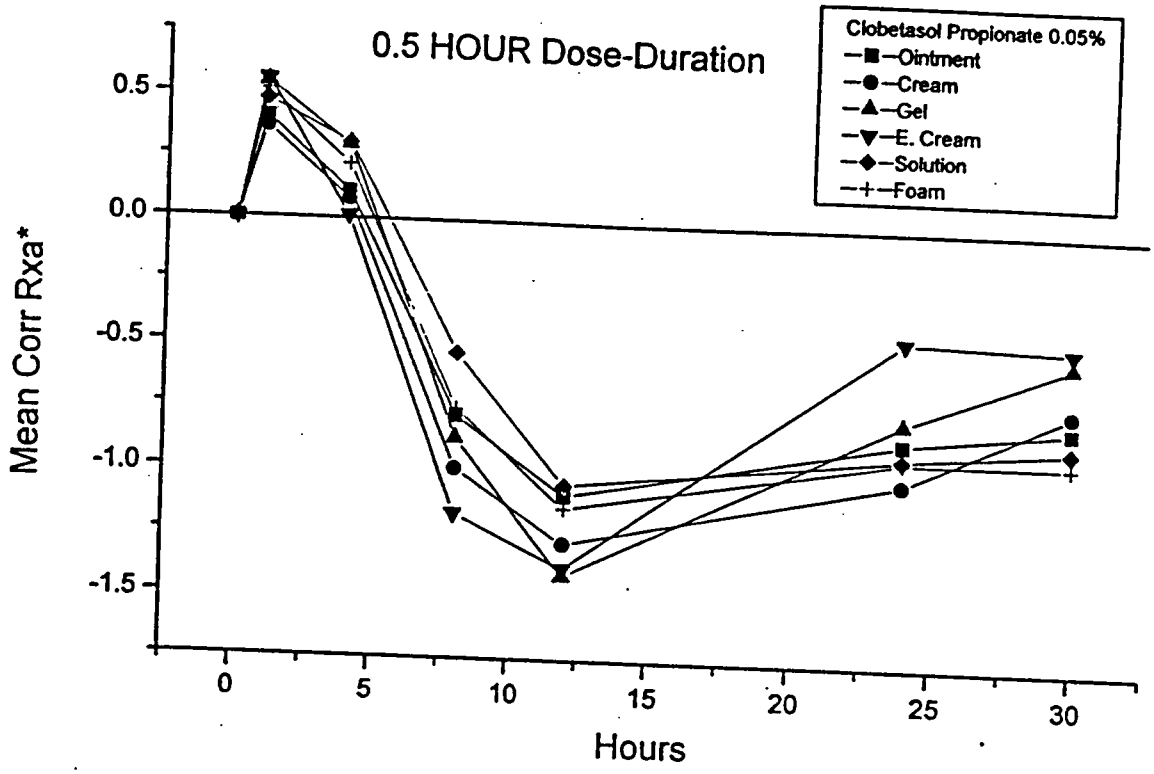
Site==>:	Right Arm 1	2	3	4	Left Arm 5	6	7	8
1								
2			[redacted]					
3								
4			[redacted]					
Mean:	6.91	6.71	7.70	6.82	7.48	6.30	7.68	6.17
SD:	0.17	0.27	0.24	0.20	0.19	0.16	0.18	0.19
CV	2.50	3.97	3.08	2.93	2.49	2.61	2.34	3.10

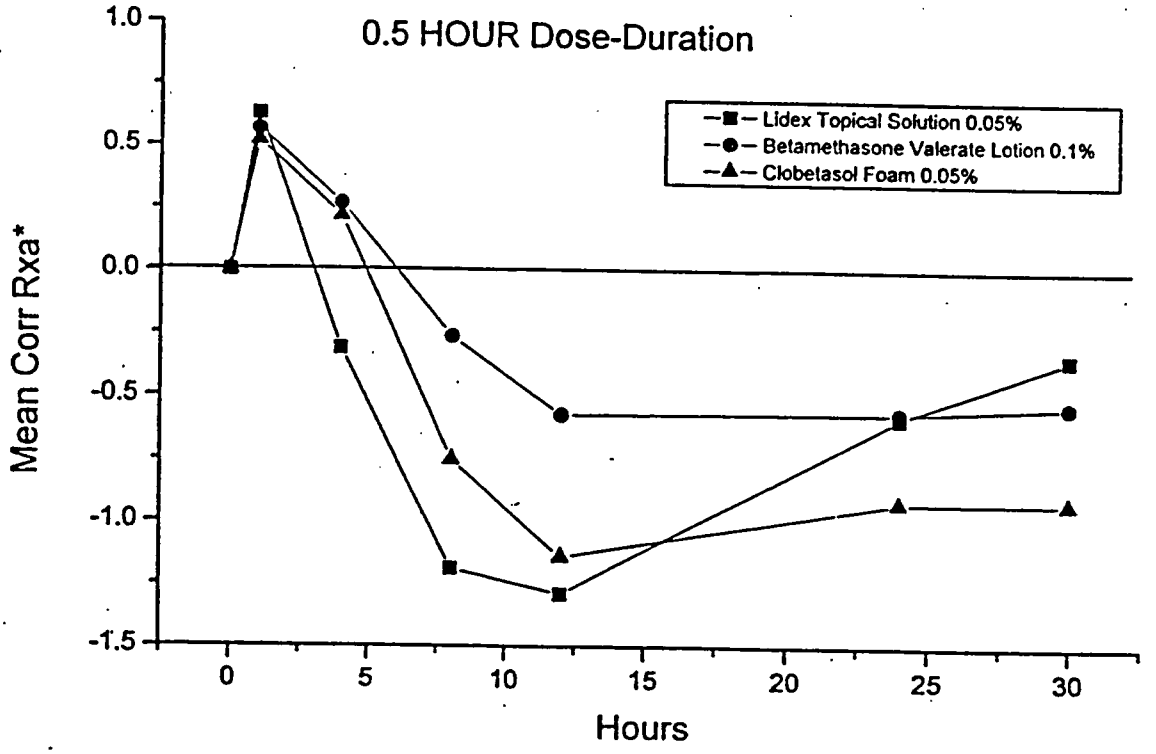
Subject: [redacted]

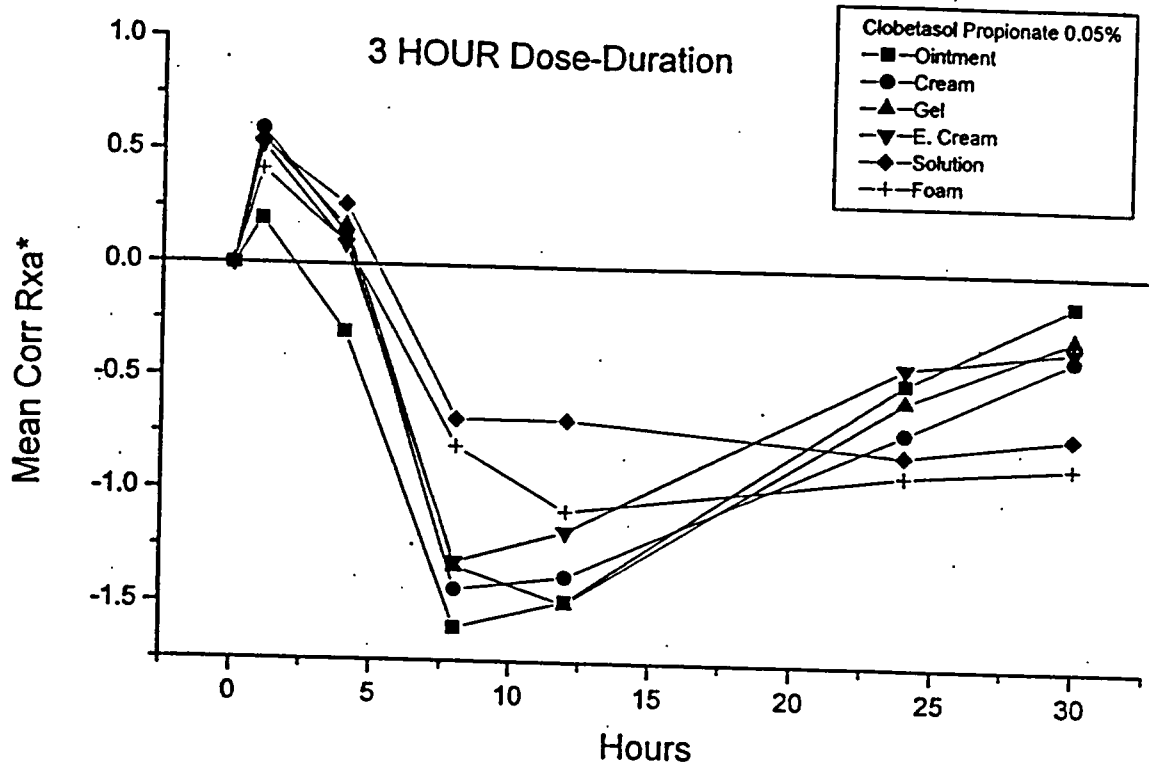
Site==>:	Right Arm 1	2	3	4	Left Arm 5	6	7	8
1								
2			[redacted]					
3								
4			[redacted]					
Mean:	5.91	4.47	6.06	5.13	5.78	4.13	6.16	4.58
SD:	0.21	0.36	0.19	0.24	0.35	0.08	0.12	0.05
CV	3.60	8.11	3.20	4.66	6.04	1.83	1.91	1.09

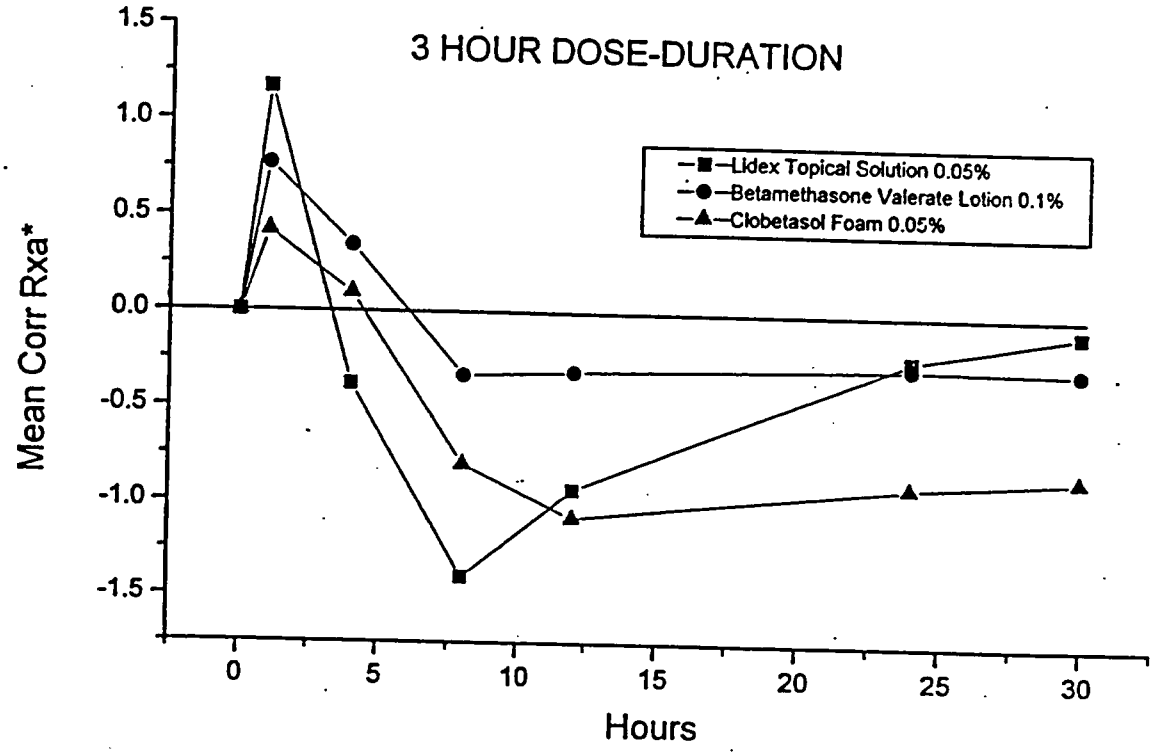
Subject: [redacted]

Site==>:	Right Arm 1	2	3	4	Left Arm 5	6	7	8
1								
2			[redacted]					
3								
4			[redacted]					
Mean:	9.05	8.05	8.85	8.11	8.98	9.11	9.10	9.03
SD:	0.33	0.33	0.29	0.09	0.31	0.29	0.12	0.51
CV	3.60	4.10	3.28	1.12	3.51	3.13	1.33	5.66


0.5 HOUR Dose-Duration
Clobetasol Propionate 0.05%
Ointment
Cream
Gel
E. Cream
Solution
Foam
Mean Corr Rxa*
0.5
0.0
-0.5
-1.0
-1.5
0
5
10
15
20
25
30
Hours


0.5 HOUR Dose-Duration
Lidex Topical Solution 0.05%
Betamethasone Valerate Lotion 0.1%
Clobetasol Foam 0.05%
Mean Corr Rxa*
1.0
0.5
0.0
-0.5
-1.0
-1.5
0
5
10
15
20
25
30
Hours


3 HOUR Dose-Duration
Clobetasol Propionate 0.05%
Ointment
Cream
Gel
E. Cream
Solution
Foam
Mean Corr Rxa*
Hours
1.0
0.5
0.0
-0.5
-1.0
-1.5
0
5
10
15
20
25
30


3 HOUR DOSE-DURATION
Lidex Topical Solution 0.05%
Betamethasone Valerate Lotion 0.1%
Clobetasol Foam 0.05%
Mean Corr Rxa*
Hours
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
0
5
10
15
20
25
30

LISTING 2

DEMOGRAPHIC INFORMATION
(PAGE 1 OF 2)

TREATMENT GROUP: CLOBETASOL FOAM 0.05%

SITE	SUBJECT	VISIT DATE	SEX	AGE	DATE OF BIRTH	RACE
1	2	10SEP98	MALE	29		CAUCASIAN
1	10	12SEP98	MALE	51		CAUCASIAN
1	15	18SEP98	MALE	47		ASIAN
1	16	21SEP98	MALE	68		CAUCASIAN
1	24	21OCT98	FEMALE	39		CAUCASIAN
1	26	28OCT98	FEMALE	34		ASIAN
2	4	10SEP98	FEMALE	23		CAUCASIAN
2	6	11SEP98	FEMALE	41		CAUCASIAN
2	7	10SEP98	MALE	64		CAUCASIAN
2	11	11SEP98	MALE	51		CAUCASIAN
2	13	14SEP98	FEMALE	55		CAUCASIAN
2	20	22OCT98	FEMALE	50		BLACK
2	21	22OCT98	MALE	38		CAUCASIAN

LISTING 2

DEMOGRAPHIC INFORMATION
(PAGE 2 OF 2)

TREATMENT GROUP: CLOBETASOL OINTMENT 0.05%

SITE	SUBJECT	VISIT DATE	SEX	AGE	DATE OF BIRTH	RACE
1	1	10SEP98	FEMALE	54		CAUCASIAN
1	14	17SEP98	FEMALE	65		CAUCASIAN
1	17	21SEP98	MALE	72		HISPANIC
1	18	22SEP98	FEMALE	41		CAUCASIAN
1	22	21OCT98	MALE	54		CAUCASIAN
1	23	21OCT98	FEMALE	55		CAUCASIAN
2	3	10SEP98	FEMALE	51		CAUCASIAN
2	5	10SEP98	FEMALE	28		CAUCASIAN
2	8	10SEP98	FEMALE	29		CAUCASIAN
2	9	11SEP98	MALE	71		CAUCASIAN
2	12	14SEP98	FEMALE	47		CAUCASIAN
2	19	22OCT98	FEMALE	43		ASIAN
2	25	28OCT98	MALE	55		CAUCASIAN

SOURCE: DEMOGLST.SAS (15APR99 22:36)

Panel G-1
Serum Cortisol Values (µg/dL) Clobetasol Foam

Subject	Visit	Pre-Stimulation Cortisol (µg/dL) (Normal Value > 5 µg/dL)	Post-Stimulation Cortisol (µg/dL) (Normal Value > 18 µg/dL)
1/2	Screening	20.0	31.2
	1	15.7	30.1
	8	17.9	24.5
	15	10.7	19.2
1/10	Screening	18.5	32.7
	1	23.4	37.2
	8	2.2	14.2
	15	<1.0	10.7
	Re-test	21.5	29.9
1/15	Screening	16.2	20.1
	1	15.9	21.0
	8	<1.0	4.9
	15	<1.0	3.2
	Re-test 1	1.6	6.6
	Re-test 2	11.5	17.6
1/16	Screening	8.7	21.6
	1	9.3	23.0
	8	3.6	19.5
	15	8.5	22.0
1/24	Screening	11.5	28.2
	Screening	11.2	27.9
	1	15.0	28.8
	8	11.7	30.6
	15	16.4	30.4
1/26	Screening	26.2	32.2
	1	26.6	32.5
	8	27.8	34.3
	15	17.8	27.7
2/4	Screening	17.8	30.0
	1	17.5	32.0
	8	8.9	21.1
	15	11.9	26.3
2/6	Screening	19.4	28.0
	1	21.9	26.8
	8	5.4	14.0
	15	12.5	18.8
2/7	Screening	16.8	27.8
	1	13.8	25.2
	8	9.9	24.1
	15	20.0	32.6
2/11	Screening	17.4	30.0
	1	17.9	28.3
	8	17.3	27.4
	15	18.1	27.5
2/13	Screening	14.0	38.5
	1	16.0	38.0
	8	11.6	29.7
	15	8.5	29.2
2/20	Screening	7.1	24.5
	1	8.0	22.1
	8	14.0	19.2
	15	2.3	12.1
	Re-test	8.9	21.8
2/21	Screening	21.0	34.8
	1	20.3	33.3
	8	21.3	35.5
	15	16.0	29.5

Data Source: 7.0

Panel G-1, cont.
Serum Cortisol Values (µg/dL) Clobetasol Ointment

Subject	Visit	Pre-Stimulation Cortisol (µg/dL) (Normal Value > 5 µg/dL)	Post-Stimulation Cortisol (µg/dL) (Normal Value > 18 µg/dL)
1/1	Screening	24.6	34.2
	1	26.0	39.4
	8	19.9	28.6
	15	20.4	28.9
1/14	Screening	22.2	30.6
	1	25.2	29.8
	8	3.8	15.7
	15	14.8	18.8
1/17	Screening	7.3	20.4
	1	10.5	19.6
	8	2.9	10.9
	15	9.7	17.1
	Re-test 1	3.7	15.1
	Re-test 2	4.6	24.2
1/18	Screening	11.5	21.7
	1	9.1	20.5
	8	6.6	16.0
	15	11.5	20.7
1/22	Screening	12.3	28.2
	1	19.2	29.8
	8	7.2	28.2
	15	4.6	24.7
	Re-test	21.4	29.4
1/23	Screening	15.2	27.3
	Screening	21.0	28.2
	1	20.3	26.7
	8	17.2	26.3
	15	14.1	26.3
2/3	Screening	11.2	27.4
	1	11.8	26.5
	8	2.4	15.3
	15	16.9	28.9
2/5	Screening	17.6	31.7
	1	11.0	27.8
	8	1.3	12.6
	15	4.9	15.8
	Re-test	8.7	21.8
2/8	Screening	24.0	36.4
	1	36.2	34.2
	8	21.7	30.6
	15	15.5	31.3
2/9	Screening	15.3	31.0
	1	21.3	27.8
	8	13.7	26.1
	15	13.1	28.1
2/12	Screening	20.4	31.5
	1	12.1	23.5
	8	9.6	23.1
	15	17.0	27.4
2/19	Screening	13.3	26.8
	1	18.7	30.9
	8	11.4	25.8
	15	14.9	24.0
2/25	Screening	6.8	15.3
	Screening	15.8	24.5
	1	13.3	25.4
	8	9.2	20.0
	15	1.5	14.2
	Re-test	4.9	12.9

Data Source: Listing 7.0

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Mean Cortisol Values
(All Subjects Randomized)

		Treatment Group		
		CP foam	CP ointment	p-value
Number of Subjects		13	13	
Mean Cortisol (µg/dL)				
Day 1	Pre-stimulation	17.02	18.05	0.698
	Post-stimulation	29.10	27.84	0.556
Day 8	Pre-stimulation	11.74	9.76	0.498
	Change (Day 1 to Day 8)	-5.28	-8.29	0.273
	Post-stimulation	23.00	21.48	0.624
	Change (Day 1 to Day 8)	-6.10	-6.36	0.920
Day 15				
	Pre-stimulation	11.13	12.22	0.653
	Change (Day 1 to Day 15)	-5.89	-5.83	0.983
	Post-stimulation	22.25	23.55	0.661
	Change (Day 1 to Day 15)	-6.85	-4.29	0.378

Note: p-values based on t-test.
Data Source: Listing 7.0

Subjects with Abnormal Cortisol Values
(All Subjects Randomized)

		Treatment Group		
		CP foam	CP ointment	p-value
Number of Subjects		13	13	
Subjects with Abnormal Response (Day 8)				
Pre-stimulation	n (%)	3 (23)	4 (31)	1.00
Post-stimulation	n (%)	3 (23)	5 (38)	0.672
Subjects with Abnormal Response (Day 15)				
Pre-stimulation	n (%)	3 (23)	3 (23)	1.00
Post-stimulation	n (%)	3 (23)	3 (23)	1.00

Note: p-values based on Fisher's Exact Test.
Data Source: Listing 7.0