CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-535

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: **21-535**	Submission Date(s): 09/25/02
Brand Name	Clobex™ 0.05%
Generic Name	Clobetasol Propionate, 0.05%
Reviewer	Chandra S. Chaurasia, Ph. D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III (HFD-880)
OND division	ODE V (HFD-540)
Sponsor	Galderma Laboratories, L. P., Fort Worth, TX 76177
Relevant IND(s)	54,230
Submission Type; Code	New formulation
Formulation; Strength(s)	Lotion 0.05%
Indication	Relief of inflammatory and pruritic manifestations of corticosteroid- responsive dermatoses

1. EXECUTIVE SUMMARY

Clobex™ contains the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity. In the US, clobetasol is commercially available in 0.05% strength as various topical dosage forms such as, Temovate® Cream (NDA 19-322), Temovate E® Emollient Cream (NDA 20-340), Temovate® Ointment (NDA 19-323), Temovate® Gel (NDA 20-337), Temovate® Topical Solution (NDA 19-966) and Olux® Foam (NDA 21-142). Temovate Cream is marketed under the name of Dermoval® in France.

In this submission, the sponsor pursues the approval of clobetasol propionate 0.05% lotion (CP Lotion) for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (to be used not more than two consecutive weeks), and in the treatment of moderate to severe plaque-type psoriasis (to be used up to 4 consecutive weeks).

To support the NDA the sponsor has submitted a) vasoconstriction assays comparing clobetasol propionate lotion, 0.05% with Betamethasone Dipropionate (Diprolene®) Cream, Temovate® Cream, and Temovate E® Emollient Cream, b) adrenal suppression studies comparing CP lotion with Temovate E® Emollient Cream and Temovate® Cream in psoriasis and atopic dermatitis subjects, and c) in vitro liberation-penetration study comparing release profile of CP lotion with that of Temovate E® Emollient Cream and Temovate® Cream.

Based on the reported results, there appears to be a markedly higher incidence of HPA axis suppression with the Clobex Propionate Lotion compared to that observed with the Temovate Cream or Temovate E Emollient Cream in both the psoriasis and atopic dermatitis patients.

1.1. RECOMMENDATIONS

From a Biopharmaceutics perspective the firm has provided evidence of systemic availability for the test Clobex Propionate Lotion and reference Temovate E Emollient cream formulations. Based on the results of the 3 HPA axis trials, use of CP Lotion is clearly associated with a high incidence of HPA suppression compared to the Temovate E Emollient cream. Thus, from a clinical pharmacology perspective, there is a reasonable concern about the safety of this product in uncontrolled administration. While the bioavailability of clobetasol has been determined via indirect methods (i.e., HPA axis testing), the safety issues raised by the increased bioavailability relative to the reference product raises a significant concern.

/S/

_____ Date: _____

Chandra S. Chaurasia, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. /S/ Date: _____

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3. SUMMARY OF CPB FINDINGS

Clobetasol Propionate is a topical corticosteroid, and as such classical in vivo pharmacokinetic studies involving plasma drug measurement are not possible due to minimal percutaneous absorption and limit of detection issues. For a topical corticosteroid, evidence of Hypothalamus-Pituitary-Adrenal (HPA) axis suppression is typically used as a surrogate for in vivo bioavailability evaluation.

In the current submission, the biopharmaceutic/bioavailability evaluation of the lotion is based on the following comparative studies:

Vasoconstrictor Assay Studies in Healthy Subjects

1. **Report No. CG.03.SRE.2117**: Selection of a New Vehicle for Clobetasol Propionate Using the Vasoconstrictor Assay.
2. **Report No. CG.03.SRE.2570**: Vasoconstriction Assay Comparing Clobetasol Lotion with Three Commercialized Products.

Adrenal Suppression Studies in Clinical Subjects

1. **Report No. CR.U9708**: An Adrenal Suppression Study of a Clobetasol Propionate Lotion, 0.05% as compared to Temovate® E Emollient Cream, 0.05% in Subjects with Plaque-type Psoriasis.
2. **Report No. GUS.04.SRE.18009**: An Adrenal Suppression Study of a Clobetasol Propionate Lotion, 0.05% as compared to Temovate® E Emollient Cream, 0.05% in Subjects with Atopic Dermatitis.
3. **Report No. RD.06.SRE.18061**: HPA Axis Suppression Potential of Clobetasol Propionate Lotion, 0.05%, as Compared to Temovate® E Emollient Cream and Temovate® Cream in Adolescents with Atopic Dermatitis.

In Vitro Study

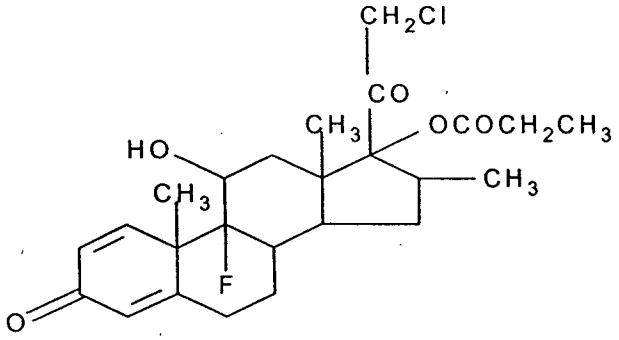
Report No. CG.03.SRE.4637: To compare the in vitro liberation-penetration of 0.05% clobetasol propionate lotion to two commercial formulations (Temovate cream and Temovate E Emollient cream) across non-occluded human skin.

4. QUESTION-BASED REVIEW

4.1. General Attributes

What are the highlights of the physicochemical properties of clobetasol propionate?

Chemically, clobetasol propionate is 11(beta),16(beta))-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy) pregna-1,4-diene-3,20-dione, and it has the following structural formula:



Clobetasol propionate has the empirical formula $C_{25}H_{32}ClFO_5$ and a molecular weight of [redacted]. It is a white to [redacted] crystalline powder insoluble in water.

What are the properties of the formulation of the drug product?

Formulation of 0.05% (w/w) lotion containing clobetasol propionate is provided below:

Component and Composition of Clobetasol Propionate Lotion, 0.05%

	Percent (w/w)			
Lot (Batch No.)	661.337	661.337P	661.341	661.341P
Clobetasol propionate, USP	0.05	[redacted]	0.05	[redacted]
Hydroxypropylmethyl cellulose, USP	[redacted]	[redacted]	[redacted]	[redacted]
Polyoxyethylene glycol 300 isostearate	[redacted]	[redacted]	[redacted]	[redacted]
Carbomer	[redacted]	[redacted]	[redacted]	[redacted]
Mineral oil, USP	[redacted]	[redacted]	[redacted]	[redacted]
Propylene glycol, USP	[redacted]	[redacted]	[redacted]	[redacted]
Sodium hydroxide, NF	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Purified Water, USP	[redacted]	[redacted]	[redacted]	[redacted]
Total				
Lot (Batch) No. used in clinical and human biopharmaceutic studies	661.337/2F1 LEHD-4 PECD	661.337/2F1 LDFH PECC	661.341/2F	661.341/2F

NF = National Formulary; USP = United States Pharmacopoeia.

What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of clobetasol propionate lotion, 0.05%?

Indication:

Clobetasol Propionate Lotion, 0.05% is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (e.g., atopic dermatitis), and in the treatment of moderate to severe plaque-type psoriasis.

Dosage and Route of Administration:

Per the Sponsor's proposed labeling, patients should be instructed to use Clobetasol Propionate Lotion, 0.05% for the minimum amount of time necessary to achieve the desired results. For atopic dermatitis treatment should be limited to 2 consecutive weeks and the total dosage should not exceed 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

In the treatment of moderate to severe plaque-type psoriasis, Clobetasol Propionate Lotion, 0.05% applied to ——— of body surface area can be used up to 4 consecutive weeks.

Mechanism of Action:

Like other topical corticosteroids, Clobetasol Propionate Lotion, 0.05% has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids in general is unclear. However, corticosteroids are thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

4.2. General Clinical Pharmacology

What studies have been conducted for biopharmaceutic/bioavailability evaluation of the drug product. What are the outcomes of these studies?

- Clobetasol Propionate 0.05% Lotion is a topical corticosteroid, and as such classical in vivo pharmacokinetic studies involving plasma drug measurement are not possible due to minimal percutaneous absorption and limit of detection issues. For a topical corticosteroid evidence of Hypothalamus-Pituitary-Adrenal (HPA) axis suppression is typically used as a surrogate for in vivo bioavailability. The firm has submitted three studies, Report Nos. CR.U9708, GUS.04.SRE.18009 and RD.06.SRE.18061 with the results of HPA axis suppression in psoriatic, atopic dermatitis in adults and adolescent populations, respectively.
- Additionally, to establish the potency of CP Lotion, the firm conducted vasoconstrictor studies (Report Nos. CG.03.SRE.2117 and CG.03.SRE.2570) comparing CP Lotion with Temovate (clobetasol propionate) Cream 0.05% and Temovate E Emollient Cream 0.05% and with Diprolene (betamethasone dipropionate) 0.05% Cream.

Results of HPA Axis Suppression Studies: Based on the reported results, there appears to be a relatively higher rate of HPA axis suppression with the Clobex Propionate Lotion compared to that observed with the Temovate Cream or Temovate E Emollient Cream in both psoriasis and atopic dermatitis patients. The comparative results are summarized in the Table below. Details of the HPA axis suppression studies are provided in **Section 6.2: Appendix II. 6.2.3, 6.2.4** and **6.2.5** of the review.

Comparative HPA Axis Suppression of Test and Reference Clobetasol Formulations in Psoriasis and Atomic Dermatitis Patients

Treatments	HPA Axis Suppression (n, %), N*		
	Week 1	Week 2	Week 4
Study No. CR.U9708 (Psoriasis, 18-75)			
Clobetasol Propionate Lotion	N/A	2 (16.7%), N=12	2 (18.2%), N=11
Temovate E Emollient Cream	N/A	0 (0%), N=12	1 (9.1%), N=11**
Study No. GUS.04.SRE.18009 (Atopic Dermatitis, 14-57 years)			
Clobetasol Propionate Lotion	3 (33.3%), N=10	5 (45.5%), N=11	N/A
Temovate E Emollient Cream	2 (15.4%, N=13	1 (7.7%), N=13	N/A
Study No. RD.06.SRE.18061 (Atopic Dermatitis, 12-17 years)			
Clobetasol Propionate Lotion	N/A	5 (35.7%), N=13	N/A
Temovate E Emollient Cream	N/A	1 (10%), N=10	N/A
Temovate Cream	N/A	3 (25%), N=12	N/A

**n = subjects with HPA suppression, N = total number of subjects completing the study at the end of the week.*

***Data at the end of Week 3: Last Observation Carried Forward.*

Results of Vasoconstrictor Studies: Based on the reported results, CP Lotion 0.05% is comparable to two known formulations containing the same active ingredient at the same concentrations (Temovate Cream and Temovate E Emollient Cream) in its ability to cause vasoconstriction. Additionally, CP Lotion does produce more vasoconstriction than Diprolene cream, a Class 1 low potency steroid. Both Temovate cream and Temovate E Emollient cream are Class I super potent steroids. Thus, the potency of clobetasol propionate lotion 0.05% is expected to be comparable to Temovate Cream and Temovate Emollient Cream. Details of the vasoconstrictor studies are provided in **Section 6.2: Appendix II. 6.2.1** and **6.2.2** of the review.

Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters?
Plasma samples were analyzed by validated [redacted] method (see Section 4.6) to determine the concentrations of clobetasol following topical administration. No quantifiable amounts of clobetasol were found in any of the plasma samples analyzed.

What are the basic pharmacokinetic parameters of clobetasol propionate lotion (ADME)?
Since the systemic plasma levels of clobetasol after topical administration are below the limit of quantitation [redacted], a basic PK profile of the drug product could not be obtained.

Are the study populations relevant to the proposed indication?
Clobetasol Propionate Lotion, 0.05% is a super-high potent corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Atopic dermatitis is prevalent in the pediatric and adolescent population. HPA axis suppression studies GUS.04.SRE.18009 and GUS.04.SRE.18061 have included atopic dermatitis patients ages 14-57 and 12-17 years, respectively. Furthermore, the firm's labeling [redacted]

Psoriasis is a common skin disorder mostly manifested in the adult populations. The HPA suppression study CR.U9708 was conducted in patients 14 to 75 years of age. Thus, the study population appears relevant to the proposed indications.

Are dose and dosing regimen appropriate for the treatment of the proposed indication?
Per proposed labeling, for the treatment of atopic dermatitis, CP lotion, 0.05% should be limited to 2 consecutive weeks and the total dosage should not exceed 50 g (approximately 2 fl.oz) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. In the treatment of moderate to severe plaque-type psoriasis, CP lotion, 0.05% applied to [redacted] of body surface area can be used up to 4 consecutive weeks.

In the current submission, the above dosing regimen was followed for atopic dermatitis and psoriatic subjects. For example, in the atopic dermatitis study #1.GUS.04.SRE 18009, the range of average daily dose of the 2 consecutive weeks treatment was 7.06 to 8.75 gm and 5.79-8.00 gm for the CP Lotion and Temovate E Emollient Cream, respectively. In the psoriasis study #CR.U9708, at the end of 4 weeks, the mean % of body surface area treated was 17.2% (range: 8-32%) and 18.8% (range: 9.5-36%) for the CP Lotion and Temovate E Emollient cream, respectively. Thus, the dose and dosing regimen seem appropriate for the treatment of the proposed indications.

4.3. Intrinsic Factors: Age, Sex, Race, Weight, Height and Disease States.

Clobetasol propionate lotion 0.05% is for topical administration. Considering the undetectable plasma concentrations of clobetasol propionate after topical administration, PK studies involving intrinsic factors (e.g., gender or age, renal and hepatic impairments) is not possible at this time.

4.4. Extrinsic Factors: Drugs, Diets and Smoking

Again, considering the undetectable plasma concentrations of clobetasol propionate after topical administration, evaluation of the effect of any extrinsic factors on clobetasol propionate lotion, 0.05% is not possible at this time.

4.5 General Biopharmaceutics

Are there any differences between clinical and to-be-marked formulations?

All batches/lots and sublots (661.337/2F1, 661.341/2F1, LECD-4 and PECD) utilized in clinical and human biopharmaceutic studies to support this application were made with the to-be-marketed formula (NDA 21-535, Vol. 1, Item 3, pp. 67 and 68).

Are there any in vitro data for clobetasol propionate 0.05% lotion?

CP Lotion was evaluated by comparing its in vitro liberation-penetration of clobetasol propionate to two commercial formulations (Temovate E Emollient Cream and Temovate Cream) across non-occluded human skin. Six skin samples from six different female donors (ages 38-58), were used to compare these formulations. Concentration of clobetasol propionate was measured using the [redacted] method validated by Bioanalysis Group of Galderma Research and Laboratories.

The penetration of clobetasol through the total skin from the lotion formulation is reported to be significantly higher, 1.2- and 1.8-times, respectively compared to Temovate cream and Temovate E Emollient cream ($p<0.02$, 95% confidence). Similar results are reported for the penetration through epidermis. Lower quantities are found in the dermis for the Temovate emollient cream compared to the CP Lotion or Temovate cream.

4.6. Analytical

What bioanalytical methods are used to assess the amount of clobetasol propionate in plasma and for in vitro analyses?

Plasma Samples. The analysis of the human plasma samples to determine the concentrations of clobetasol propionate was accomplished by use of a [redacted] method described in the validation report CG.03.VAL.4256. The method has been validated for the concentration range of [redacted] Standard curve samples and quality control samples were generated by spiking interference free human plasma samples with known amounts of clobetasol propionate and internal standard [redacted] The peak area ratios of clobetasol propionate and to IS were calculated for each sample from the measured peak areas obtained by [redacted]

No quantifiable amounts of clobetasol propionate were found in any of the plasma samples analyzed.

In Vitro Liberation-penetration Samples: The analysis of clobetasol in in vitro samples was accomplished by use of a [redacted]

[redacted] method described in the validation report CG.03.VAL.4248. The method has been validated for the concentration range of [redacted].

Are analytical methods sensitive enough to determine the extent of clobetasol propionate absorption after topical application?

The analytical method used in the current studies had a lower limit of quantitation of [redacted] At this level of sensitivity, no clobetasol propionate could be detected in the plasma samples following clobetasol propionate 0.05% lotion topical administration.

Reviewer's note: *From analytical perspective, a more sensitive assay for clobetasol propionate would have perhaps shown some PK-PD correlation between the plasma clobetasol levels and HPA suppression.*

Analytical method validation results are summarized below:

For Human Plasma Samples.

Internal Standard: [redacted]
Linearity Range: [redacted]
Lower Limit of Quantitation: [redacted]
Accuracy: [redacted]
Precision: [redacted]

For In Vitro Liberation-penetration Samples.

Internal Standard: [redacted]
Linearity Range: [redacted]
Lower Limit of Quantitation: [redacted]
Accuracy: [redacted]
Precision: [redacted]
Specificity: [redacted]

4.7. Pharmacokinetic Data:

There are no PK data as no quantifiable amounts of clobetasol propionate were found in any of the [redacted] plasma samples analyzed based on the results from Report Nos. CR.U9708 and GUS.04.SRE18009.

5. DETAILED LABELING RECOMMENDATIONS

No labeling comments are provided at this time because of the proposed "Non Approval" status on this NDA.

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ON ORIGINAL

11 Draft Labeling Page(s) Withheld

6.2. Appendix II: Individual Study Reviews

6.2.1. In Vitro Study: Report No. 1. CG.03.SRE.4637

Objectives:

To compare the in vitro liberation-penetration of 0.05% clobetasol propionate lotion to two commercial formulations (Temovate cream and Temovate E Emollient cream) across non-occluded human skin.

Study Site:

Investigational Product: Clobetasol Propionate 0.05% Lotion, Batch No. 661.337/2F1, Galderma Laboratories

Comparator Products: Temovate® Cream (Clobetasol Propionate 0.05% Cream), Glaxo. Temovate® Emollient Cream (Clobetasol Propionate 0.05% Emollient Cream), Glaxo

Method: Described in detail in NDA 21-535, Vol. 10. Item 6, pp. 101-103. Briefly, human abdominal and mammary full thickness skin removed during surgical procedures (from 6 different female donors) was used in all experiments. The permeation study was conducted using [redacted] About 10 mg of each formulation (5 mcg of clobetasol propionate) was applied to the skin surface of 1 cm^2 per cell. The skin samples were maintained in [redacted]. Concentrations of clobetasol propionate were measured using a validated [redacted] method.

The statistical analysis (described in detail in NDA 21-535, Vol. 10, Item 6, pp. 84) was performed using the variables quantities applied, and the clobetasol propionate levels in non absorbed surface excess, epidermis, dermis and total skin.

Results and Conclusions:

The individual clobetasol propionate levels obtained during the study in the compartments (receptor fluid, epidermis, dermis, and non absorbed surface excess) are given in the NDA 21-525, Item 6, Vol. 10, pp. 90-94. The mean values are reported in the following Table:

Clobetasol propionate levels (mcg) for 1 cm^2 of skin application (Arithmetic mean values ± SEM, N=12)

	CP Lotion, 0.05%	Temovate Cream	Temovate Emollient Cream
Real Applied Dose	4.75±0.19 mcg	4.72±0.16 mcg	4.82±0.11 mcg
Recovery in surface excess and upper cell washing % of the applied dose	3.97±0.27 84%	4.51±0.50 93%	4.39±0.35 91%
Epidermis: E % of applied dose	0.49±0.05 10%	0.24±0.03 5%	0.24±0.05 5%
Dermis: D % of applied dose	0.11±0.04 2%	0.12±0.03 3%	0.01* 0.1%
Total Skin: E+D % of applied dose	0.60±0.07 12%	0.36±0.05 8%	0.25±0.05 5%
Collected fractions (0-16 h) + lower cell washing	0.001*	ILQ*	0.005*
Total Skin + Collected Fractions % of applied dose	0.60±0.07 12%	0.36±0.05 8%	0.25±0.05 5%
Mass Balance % of applied dose	4.57±0.31 96%	4.86±0.48 101%	4.64±0.38 96%

**Values are ILQ (inferior to the limit of quantification) of the HPLC-MS method used (* [redacted]

The total cutaneous penetration (epidermis and dermis) were 0.60±0.07 (12% of the applied dose) for clobetasol propionate lotion, 0.36±0.05 (8% of the applied dose) for Temovate Cream and 0.25±0.05 (5% of the applied dose) for Temovate Emollient Cream.

Compared to Temovate Cream, the quantities of clobetasol propionate recovered were significantly higher for CP Lotion in Epidermis (2.2 fold higher, p=0.000) and in total skin (1.8 fold higher, p=0.013). No significant difference between the two formulations was observed in the dermis, in the mass balance and in the non penetrated excess.

Compared to Temovate Emollient Cream, the quantities of clobetasol propionate recovered were significantly higher for CP Lotion in Epidermis (2.2 fold higher, p=0.000), in dermis (1.8 fold higher, p=0.008) and in total skin (2.6 fold higher, p=0.000). No significant difference between the two formulations was observed in the mass balance and in the non penetrated excess.

6.2.2. Vasoconstrictor Study: Report 1.CG.03.SRE.2117

Selection of a New Vehicle for Clobetasol Propionate Using the Vasoconstrictor Assay.

Objectives:
To evaluate the blanching capacity of clobetasol propionate lotion, 0.05% in comparison to that of a known formulation containing the same active ingredient at the same concentration (Temovate® Cream – Glaxo Wellcome Laboratories) and to a formulation containing 0.05% betamethasone dipropionate (Diprolene® Cream – Schering-Plough Laboratories) using the vasoconstriction assay on healthy skin.

Study Site:

Investigational Product:	Clobetasol Propionate 0.05% Lotion, Batch No. 661.337/2F1, Galderma Laboratories
Comparator Products:	Temovate® Cream (Clobetasol Propionate 0.05% Cream) Temovate® Emollient Cream (Clobetasol Propionate 0.05% Emollient Cream) Diprolene® Cream (Betamethasone Dipropionate 0.05% Cream)
Treatment Duration:	One single administration over four hours.
Dose:	20 µL of each product.

Methods:

The study was conducted as monocenter, intra-individual, investigator-blinded, randomized, trial. The test products were applied without occlusion on the volar surface of the forearm. Two zones were delineated on each forearm, such that each subject received all the three products and had one non-treated zone. The products were left on the skin for four hours, after which the protection systems were removed and the excess product was wiped off using absorbent paper. Fifteen healthy male subjects were screened for the study and 12 met the criteria for study inclusion. All 12 subjects completed the study. The mean age was 28.2 +/- 3.2 years (range 25-

35 years. No treatment-related adverse events were reported. Study inclusion and exclusion criteria are described in Vol. 10, Item 6, page 213.

Evaluation Criteria: Principal criterion: Visual score (0-4), Secondary Criterion: Chromametry-parameters a* and L* taken into consideration.

Visual Score:
Visual scoring was carried out 2 hours after removal of the excess product using the scale of 0-4 (0 corresponds to unmodified skin and 4 to blanching considered being maximum). The evaluations were made by two independent evaluators.

Chromametric Measurements:
Baseline chromametric measurements were carried out before the application of the products. The evaluations were made by two independent investigators at 1, 2, 4, 6 and 24 hours after removal of the excess product. The measurements were expressed numerically by the values of the L* and a* parameters.

Statistical Methods:
To characterize vasoconstriction, the areas under the curve were calculated using trapezoid method for each subject and formulation. AUCs obtained were subjected to analysis of variance by parameters and types of application, to compare the formulation with Temovate and Diprolene and with the non treated zone using the contrast method and the least square mean.

Visual scores and Chromametric measurements of L* and a* Parameters and the corresponding descriptive statistics are provided in Vol. 10, Appendix 1, pages 169-206. AUCs values for visual scores and colorimetric measurements are summarized below

AUC Values: Visual Scores (LS Mean), Report No. 1.CG.03.SRE.2117

	No Treatment	Diprolene® Cream 0.05%	Temovate® Cream 0.05%	Clobetasol Lotion 0.05%
AUC —	0.00	10.56	26.38	21.73

AUC Values: Chromameter L* and a* Parameters (LS Mean), Report No. 1.CG. 03.SRE.2117

	No Treatment	Diprolene® Cream 0.05%	Temovate® Cream 0.05%	Clobetasol Lotion 0.05%
L* Parameter (LS Mean)				
AUC	-10.56	5.64	29.42	24.34
A* Parameter (LS Mean)				
AUC	15.51	-12.67	-27.52	-19.99

p-values for Visual Score, L* and a* Chromameter Measurements, Report No 1.CG.03.SRE.2117

CLOBETASOL PROPIONATE 0.05% Lotion versus	p-values		
	Visual Score	L*	a*
TEMOVATE® Cream	0.1620	0.4669	0.2300
DIPROLENE® Cream	0.0017	0.0109	0.2423
Untreated Control	0.0001	0.0001	0.0001

Comments on Statistical Analyses

- No statistically significant difference was found between the Clobetasol lotion and the Temovate cream for Visual Score, and L* and a* chromametric values.
- No statistically significant difference was found between the Clobetasol lotion and the Diprolene Cream 0.05% for a* chromametric value.
- A statistically significant difference was found between Clobetasol lotion and Diprolene Cream for Visual Score and L* Chromametric measurements.
- A statistically significant difference was found between the Clobetasol lotion and the untreated site for Visual Score and L* Chromameter and a* values.

Note: Please See Page 28 For Overall Comments on Vasoconstrictor Studies.

6.2.3. Vasoconstrictor Study: Report 1.CG.03.SRE.2570

VASOCONSTRICTION ASSAY COMPARING CLOBETASOL LOTION WITH THREE COMMERCIALLY AVAILABLE PRODUCTS

Objectives:
Evaluation of the blanching capacity of a new formulation of clobetasol propionate 0.05% in comparison to that of two known formulations containing the same active ingredient at the same concentrations (Temovate® Cream and Temovate E Emollient Cream – Glaxo Wellcome Laboratories) and to one formulation containing betamethasone dipropionate (Diprolene® Cream – Schering-Plough Laboratories).

Study Site:

Investigational Product:	Clobetasol Propionate 0.05% Lotion, Batch No. 661.337/2F1
Comparator Products:	Temovate® Cream (Clobetasol Propionate 0.05% Cream)
	Temovate® Emollient Cream (Clobetasol Propionate 0.05% Emollient Cream)
	Diprolene® Cream (Betamethasone Dipropionate 0.05% Cream)
	Clobetasol Lotion Vehicle, Batch No. 661.337P/2F1
Treatment Duration:	One single administration over four hours.
Dose:	20 µL of each product.

Methods:
Same as discussed above for Report No. 1.CG.03.SRE.2117. Sixteen healthy male subjects all Caucasians were screened for the study. Twelve subjects aged 24-37 years (mean 29.5 years) were selected after a "STOUGHTON" pre-test were included. One subject (#8) dropped out of the study after evaluation at 2 hr for failing to comply with the investigator's instructions. Eleven subjects completed the study.

No treatment-related adverse events were reported. Study inclusion and exclusion criteria are described in Vol. 10, Item 6, page 307. Evaluation criteria and statistical methods: Same as discussed above for Report No. 1.CG.03.SRE.2117.

Results:

Visual scores and Chromametric measurements of L* and a* Parameters and the corresponding descriptive statistics are provided in Vol. 10, Appendix 1. AUC values for visual scores and colorimetric measurements are summarized below

AUC Values: Visual Scores (LS Mean), Report No. 1.CG.03.SRE.2570

	No Treatment	Clobetasol Vehicle	Clobetasol Lotion 0.05%	Diprolene Cream 0.05%	Temovate Cream 0.05%	Temovate Emollient Cream 0.05%
AUC	0.01	0.39	30.53	17.75	33.78	25.34

AUC Values: Chromameter Measurements (LS Mean), Report No. 1.CG.03.SRE.2570

	No Treatment	Clobetasol Vehicle	Clobetasol Lotion 0.05%	Diprolene Cream 0.05%	Temovate Cream 0.05%	Temovate Emollient Cream 0.05%
L* Parameter (LS Mean)						
AUC	-2.92	-10.35	39.02	22.93	38.40	20.76
a* Parameter (LS Mean)						
AUC	8.26	3.40	-32.96	-26.55	-42.14	-28.33

p-values for Visual Score, L* and a* Chromameter Measurements, Report No 1.CG.03.SRE.2570

CLOBETASOL PROPIONATE 0.05% Lotion versus	p-values		
	Visual Score	L*	a*
TEMOVATE® Cream	0.4135	0.9337	0.0922
TEMOVATE® Emollient Cream	0.1941	0.0176	0.3908
DIPROLENE® Cream	0.0021	0.0353	0.2366
CLOBETASOL Propionate Vehicle	0.0001	0.0001	0.0001
Untreated Control	0.0001	0.0001	0.0001

Comments on Statistical Analyses

- No statistically significant difference was found between the Clobetasol lotion and either the Temovate cream or Temovate Emollient cream for Visual Score.
- No statistically significant difference was found between the Clobetasol lotion and Temovate cream for L* chromametric value.
- No statistically significant difference was found between the Clobetasol lotion and the Temovate Emollient cream, and between the Clobetasol lotion and Diprolene cream for a* chromametric value.
- A statistically significant difference was found between Clobetasol lotion and Diprolene Cream for Visual Score and L* Chromametric measures.
- A statistically significant difference was found between Clobetasol lotion and Temovate Emollient cream for L* Chromametric measure.
- A statistically significant difference was found between the Clobetasol lotion and the untreated site for each of the three parameters.

Note: Please See Page 28 For Overall Comments on Vasoconstrictor Studies.

Overall Comments on Vasoconstrictor Studies

1. The methodology of vasoconstrictor studies (report 1.CG.03.SRE 2117 and 1.CG.03.SRE 2570) conducted by the firm is different from those recommended in the Agency's Guidance "Topical Dermatologic Corticosteroids: In Vivo Bioequivalence" issued in June 1995, in that the firm has not conducted any pilot study to determine the dose response. It is noted that the applicant's study protocol states, "test product will be compared to reference product in a bioequivalence test following the FDA June 1995 guidance" (Vol. 10, pp. 216). However, from an NDA point of view, emphasis in this study is to establish a relative potency in relation to a high and low potency corticosteroid. Thus, unlike multiple point "Stoughton-McKenzie" vasoconstrictor bioassay to assess bioequivalence of topical corticosteroid, a single point vasoconstrictor assay suffices the need of establishing relative potency of the NDA. The study design is, therefore, acceptable.
2. Additionally, the firm has also not provided the type of instrument used and validations for the operators involved in the chromameter study. However, the firm has provided validation report for the visual inspectors. Since, the visual score is the primary criterion for vasoconstrictor studies, the vasoconstrictor studies is acceptable.
3. Based on the results of the study report 1.CG.03.SRE 2117, Clobetasol propionate lotion 0.05% exhibits vasoconstrictor capacity comparable to that of Temovate cream for the visual score, L* and a* parameters, and superior to Diprolene cream ($p < 0.01$), for the visual score as well as for the L* parameter. However, the analysis of a* parameter did not reveal any significant difference in the vasoconstrictor activity between Clobetasol propionate lotion and the Diprolene cream.
4. Based on the results of study report 1.CG.03.SRE 2570, Clobetasol propionate lotion 0.05% exhibits vasoconstrictor activity similar to that of Temovate cream for any of the parameters studied, and similar to that of Temovate Emollient cream for the visual and a* parameter. However, for the L* parameter, Clobetasol propionate lotion exhibits statistically superior activity over Temovate Emollient cream. With respect to Diprolene cream, Clobetasol did not demonstrate vasoconstrictor activity different for a* parameter, however it does produce more vasoconstrictor activity than Diprolene cream based on the visual score and L* parameter.
5. Additionally, Clobetasol propionate lotion demonstrated vasoconstrictor activity superior to that of Clobetasol propionate vehicle and untreated control for all the parameters.

Conclusion on vasoconstrictor studies:

Clobetasol Propionate Lotion 0.05% is comparable to two known formulations containing the same active ingredient at the same concentrations (Temovate Cream and Temovate E Emollient Cream) in its ability to cause vasoconstriction. Both Temovate cream and emollient cream are Class I super potent steroids. Clobetasol lotion does produce more vasoconstriction than Diprolene cream, a Class 1 low potency steroid. Thus, the potency of Clobetasol propionate lotion 0.05% is expected to be comparable to Temovate Cream and Temovate E Emollient Cream.

6.2.4. HPA Axis Suppression Study: Report CR. U9708

An Adrenal Suppression Study of a Clobetasol Propionate Lotion, 0.05% as compared to Temovate E Emollient Cream, 0.05% in Subjects with Plaque-type Psoriasis.

Objectives:
To evaluate the potential of Clobetasol Propionate Lotion, 0.05% to suppress the hypothalamus-pituitary-adrenal (HPA) axis as compared to a marketed corticosteroid, Temovate E Emollient Cream in subjects with plaque-type psoriasis.

Study Sites: 1. [redacted] 2. [redacted]

Investigational Product: Clobetasol Propionate 0.05% Lotion, Lot No. LEHD-4

Comparator Products: Temovate® Emollient Cream (Clobetasol Propionate 0.05% Emollient Cream)

Dose: Twice-a-day application, ~3.6 g/application covering at least 10-20% of the body surface area; not to exceed 50g/week.

Duration of Treatment: 4 weeks.

Methods:
The study was conducted as multicenter, randomized, open-label, parallel comparison involving 24 subjects (13 males and 11 females, 22 White, 1 Asian and 1 Other, ages 18 to 75 years, mean age 47.4) with plaque-type psoriasis who met specific inclusion/exclusion criteria as described in NDA 21-535, Vol. 1.11 page 552-553. Most patients (83.3%) were skin phototype II and III . The applicant pre-specified criteria for a normal adrenal response was an 8 a.m. serum cortisol levels of at least 10 mcg/dL pre-stimulation and at least 18 mcg/dL approximately 60-minutes post-stimulation with 0.25 mg cosyntropin.

Qualified subjects were randomized to receive either clobetasol propionate lotion, 0.05% or Temovate Emollient Cream, 0.05% applied twice daily for a period of 4 weeks. At weekly intervals (excluding Week 3) before morning treatment of application, blood samples for serum cortisol levels were collected before and after stimulation with cosyntropin. All cortisol measurements were obtained between 7:30 a.m. and 9:30 a.m., and within 60-65 minutes of the baseline collection time.

Blood samples for clobetasol assay were collected approximately one hour before and 4 hours after the last treatment administration at Week 4.

Of the 24 subjects enrolled, one subject (# 709, CP Lotion group) was discontinued from the study for elevated serum glucose at screening and baseline, and one subject (#707, Temovate group) was discontinued from the study for adverse events considered to be unrelated to the study medication. Thus, in all 22 subjects completed the study.

Subjects were evaluated at Screening, Baseline, and at Weeks 1,2, 3, and 4. All subjects who received at least one dose of the study medication and have at least one post-baseline safety evaluation were included in the safety analysis.

Reviewer's Note on Demography: Although, inclusion criteria in the current NDA 21-535 for Clobetasol Propionate 0.05% Lotion indicate subjects 12 years or older, the actual study did not include any subject in the age group of 12-17.

Results: The results are summarized in the Tables below. Figure 1 depicts a graphical representation of the of the cortisol levels at the end of 2nd and 4th week in relation to the baseline.

Reviewer's Note:

- *Although the applicant has provided HPA Axis function tests for Weeks 1, 2 and 4, only results from Weeks 2 and 4 are discussed in this review, as Week 1 results are not necessarily relevant to the study.*
- *It is further noted that subject 709 in the CP Lotion group was dropped from the study after the baseline screening, however it is not clear why this subject has been included in all the analysis.*

Table 1. Report CR.U9708: Pre and Post-Stimulation Cortisol Levels: Clobetasol Propionate 0.05% Lotion Treatment Group at WEEK 2 As Reported By The Applicant

		Cortisol levels (mcg/dL)						
		Baseline			Week 2			
Sub #	Age	Pre-stimulation	Post-stimulation	Change in Post-Stimulation. Baseline	Pre-stimulation	Post stimulation	Change from Baseline	HPA Suppression
901	35			15.6			12.7	NO
904	49			7.9			**10.6**	**YES**
906	61			22.9			4.5	NO
908	47			20.7			19.0	NO
909	28			14.9			12.6	NO
910	52			18.9			17.8	NO
702	72			12.4			15.7	NO
704	41			7.8			**5.2**	**YES**
705	39			6.9			8.1	NO
708	18			17.9			10.9	NO
709	65			20.0			18.2	NO
711	40			10.2			6.1	NO
Mean		14.3±2.8 (N=12)	29.0±6.1 (N=12)	-	10.8±6.1 (N=12)	22.6±5.7 (N=12)	11.8±5.1	-
HPA Axis Suppression: n (%)								2 (16.7%)

Table 2. Report CR.U9708: Pre and Post-Stimulation Cortisol Levels: Temovate Emollient Cream Treatment Group at WEEK 2 As Reported By The Applicant

		Cortisol levels (mcg/dL)						
		Baseline			Week 2			
Sub #	Age	Pre-stimulation	Post-stimulation	Change in Post-Stimulation. Baseline	Pre-stimulation	Post stimulation	Change from Baseline	HPA Suppression
902	64	[illegible]	[illegible]	-13	[illegible]	[illegible]	15.4	NO
903	23	[illegible]	[illegible]	8.4	[illegible]	[illegible]	25.1	NO
905	71	[illegible]	[illegible]	14.2	[illegible]	[illegible]	15.5	NO
907	51	[illegible]	[illegible]	10.3	[illegible]	[illegible]	7.0	NO
911	40	*	*	*	[illegible]	[illegible]	13.7	NO
912	25	*	*	*	[illegible]	[illegible]	10.4	NO
701	60	[illegible]	[illegible]	12.4	[illegible]	[illegible]	13.3	NO
703	60	[illegible]	[illegible]	19.3	[illegible]	[illegible]	12.4	NO
706	54	[illegible]	[illegible]	16.2	[illegible]	[illegible]	15.6	NO
707	34	[illegible]	[illegible]	5.6	[illegible]	[illegible]	9.2	NO
710	36	[illegible]	[illegible]	16.7	[illegible]	[illegible]	14.7	NO
712	75	[illegible]	[illegible]	25.2	16.9	28.9	12.0	NO
Mean		16.7±7.7 (N=10)	28.2±9.1 (N=10)		16.9±6.7 (N=12)	30.6±8.8 (N=12)	13.7±4.5	
HPA Axis Suppression: N (%)								0 (0%)

*Subjects 911 and 912 baseline cortisol samples were lost in the mail.

Table 3. Report CR.U9708: Pre and Post-Stimulation Cortisol Levels: Clobetasol Propionate 0.05% Lotion Treatment Group at WEEK 4 As Reported By The Applicant

		Cortisol levels (mcg/dL)						
		Baseline			Week 4			
Sub #	Age	Pre-stimulation	Post-stimulation	Change in Post-Stimulation. Baseline	Pre-stimulation	Post stimulation	Change from Baseline	HPA Suppression
901	35	[illegible]	[illegible]	15.6	[illegible]	[illegible]	17.7	NO
904	49	[illegible]	[illegible]	7.9	[illegible]	[illegible]	7.5	YES
906	61	[illegible]	[illegible]	22.9	[illegible]	[illegible]	15.5	NO
908	47	[illegible]	[illegible]	20.7	[illegible]	[illegible]	16.9	NO
909	28	[illegible]	[illegible]	14.9	[illegible]	[illegible]	9.3	NO
910	52	[illegible]	[illegible]	18.9	[illegible]	[illegible]	18.4	NO
702	72	[illegible]	[illegible]	12.4	[illegible]	[illegible]	11.8	NO
704	41	[illegible]	[illegible]	7.8	[illegible]	[illegible]	12.6	YES
705	39	[illegible]	[illegible]	6.9	[illegible]	[illegible]	9.6	NO
708	18	[illegible]	[illegible]	17.9	[illegible]	[illegible]	6.1	NO
709	65	[illegible]	[illegible]	20.0	Subject Withdrew			
711	40	[illegible]	[illegible]	10.2	[illegible]	[illegible]	9.0	NO
Mean		14.3±2.8 (N=12)	29.0±6.1 (N=12)		11.4±6.6 (N=11)	23.7±7.1 (N=11)	12.2±4.3	
HPA Axis Suppression: n (%)								2 (18.2%)

Table 4. Report CR.U9708: Pre and Post-Stimulation Cortisol Levels: Temovate Emollient Cream Treatment Group at WEEK 4 As Reported By The Applicant

		Cortisol levels (mcg/dL)						
		Baseline			Week 4			
Sub #	Age	Pre-stimulation	Post-stimulation	Change in Post-Stimulation. Baseline	Pre-stimulation	Post stimulation	Change from Baseline	HPA Suppression
902	64	[redacted]	[redacted]	-13	[redacted]	[redacted]	14.4	NO
903	23	[redacted]	[redacted]	8.4	[redacted]	[redacted]	18.4	NO
905	71	[redacted]	[redacted]	14.2	[redacted]	[redacted]	10.2	NO
907	51	[redacted]	[redacted]	10.3	[redacted]	[redacted]	10.8	NO
911	40	*	*	*	[redacted]	[redacted]	19.0	NO
912	25	*	*	*	[redacted]	[redacted]	7.0	NO
701	60	[redacted]	[redacted]	12.4	[redacted]	[redacted]	10.1	NO
703	60	[redacted]	[redacted]	19.3	[redacted]	[redacted]	16.9	NO
706	54	[redacted]	[redacted]	16.2	[redacted]	[redacted]	23.8	NO
707	34	[redacted]	[redacted]	5.6	[redacted]	[redacted]	**9.0****	**YES****
710	36	[redacted]	[redacted]	16.7	[redacted]	[redacted]	15.7	NO
712	75	[redacted]	[redacted]	25.2	[redacted]	[redacted]	21.0	NO
Mean		16.7±7.7 (N=12)	28.2±9.1 (N=12)		14.4±6.0 (N=11)	29.1±6.8 (N=11)	14.7±5.3	
HPA Axis Suppression: N (%)								1 (9.1%)**

*Subjects 911 and 912 baseline cortisol samples were lost in the mail.

** Data at the end of Week 3, subject #707 withdrew after Week 3.

Comments:

1. The results (Tables 1 and 2) show that all the 12 patients in the Clobetasol Propionate Lotion (CP Lotion) group met the pre-specified criteria representative of normal response, i.e., pre-stimulation serum cortisol level ≥ 10 mcg/dL, and post-stimulation serum cortisol level of ≥18 mcg/dL. In the Temovate E Emollient group two subjects, #703 and #706 had pre-stimulation cortisol levels of [redacted] and [redacted] respectively. These subjects do not meet pre-specified criteria. The firm has not given any justification of including these patients. However, it is noted these values are above 5 mcg/dL, and that the post-stimulation cortisol levels for these subjects are [redacted] and [redacted] respectively—twice that of their respective baseline levels. Thus, subjects 703 and 706 meet the Cortrosyn's labeling specifications for inclusion of the subject.
2. All but one subject met the criteria of post-stimulation serum cortisol level of ≥18 mcg/dL in the CP Lotion and Temovate Cream groups. However, one subject (#902) in the Temovate group was reported to have a cortisol decrease from [redacted] at pre-stimulation to [redacted] at post-stimulation. The firm's possible explanation for this opposite trend is "*possibly an unknown processing error*". It is noted that this subject exhibited a pre and post-stimulation serum cortisol levels of [redacted] and [redacted] at the end of 2-week treatment, and [redacted] and [redacted] at the end of week-4 treatment. The subject inclusion may be justified based on these results.
3. At the end of 2-week treatment, 6 out of 12 (50%) subjects in the CP Lotion group exhibit a pre-stimulation cortisol level of < 10 mcg/dL, while only one of 12 subjects (8.3%, sub. #706) in the Temovate group shows the corresponding level of below 10 mcg/dL (Tables 1 and 2).

A similar trend is seen at the end of 4-week treatment as well, with 5 out of 11 (45.5%) subjects in the CP Lotion group and 3 out of 12 (25%) exhibiting a pre-stimulation cortisol level of < 10 mcg/dL (Tables 3 and 4).

4. With respect to the HPA axis suppression, 2 subjects (or 18.2 %) in the CP Lotion group exhibited HPA function suppression compared to none in the Temovate Emollient Cream treatment group at the end of 2-weeks treatment. Based upon the statistical observation, the firm's concludes that there is no significant difference (p = 0.478, Table 3) on the HPA axis suppression between the CL Lotion and Temovate Emollient Cream. Similarly, the firm reports 2 out of 11 and 1 out of 11 subjects showing HPA suppression at the end of Week 4 in the CP Lotion, and Temovate Emollient Cream groups, respectively with no significant difference (p=0.590). The study includes only 12 for each treatment groups at the end of 2 week, and 11 subjects at the end of 4 week trials. In the absence of sufficient power, the inference that there is no significant HPA suppression with Clobetasol Propionate 0.05% Lotion compared to the Temovate Emollient Cream may be misleading.
5. All in all, there appears to be a relatively higher negative trend in HPA axis suppression—that is, relatively more subjects show pre-stimulation cortisol levels of <10 mcg/dL in the Clobex Lotion group compared to that observed with the Temovate E Emollient group at the end of 2 and 4 weeks.

6.2.5. HPA Axis Suppression Study: Report 2. GUS.04.SRE.18009

An Adrenal Suppression Study of a Clobetasol Propionate Lotion, 0.05% as compared to Temovate E Emollient Cream, 0.05% in Subjects with Atopic Dermatitis.

Objectives:
To evaluate the potential of Clobetasol Propionate Lotion, 0.05% to suppress the hypothalamus-pituitary-adrenal (HPA) axis as compared to a marketed corticosteroid, Temovate E Emollient Cream in subjects with atopic dermatitis.

Study Sites: 1. Investigator: [redacted]

2. Investigator: Bruce Miller, MD
Oregon Medical Research Center
Portland, OR 972233

Investigational Product: Clobetasol Propionate 0.05% Lotion, Lot No. LEHD-4

Comparator Products: Temovate® Emollient Cream (Clobetasol Propionate 0.05% Emollient Cream)

Dose: Twice-a-day application (~3.6 g/application), not to exceed 50g/week.

Duration of Treatment: 2 weeks.

Methods:
The study was conducted as multicenter, randomized, open-label, parallel comparison involving 24 subjects (8 males and 16 females, 20 White, 3 Black and 1 Other, ages 14 to 57 years, mean age 36.6) with atopic dermatitis who met specific inclusion/exclusion criteria as described in NDA 21-535, Vol. 1.11 page 1091-1092. Seven (29.2%), 6 (25%), 6 (25%), and 5 (20.8%) of the patients were skin phototype I, II, III, and IV, respectively. The applicant pre-specified criteria for a normal adrenal response and the study methodology were same as described in Report No. CR.U. 9708 except that the study was conducted for a period of 2 weeks only.

Of the 24 subjects enrolled, 11 were randomized to CP Lotion and 13 to Temovate Emollient Cream group. All 24 subjects completed the study, however, 2 subjects (#808 and 1002 in the Temovate group) who completed the study were excluded from the analysis as they had entered the study in violation of the protocol requirement.

Subjects were evaluated at Screening, Baseline, and at Weeks 1 and 2.

Reviewer's Note: Although, the inclusion criteria in the current NDA 21-535 indicate subjects 12 years or older, the actual study did not include any subject in the 12-13 year-old age group.

Results: Summarized in the Tables below.

Report No. 1.GUS.04.SRE.18009, Pre and Post-Stimulation Cortisol Levels: Clobetasol Propionate 0.05% Lotion Treatment Group at WEEK 1

		Cortisol levels (mcg/dL)						
		Baseline			Week 1			
Sub #	Age	Pre-stimulation	Post-stimulation	Change in Post-Stimulation. Baseline	Pre-stimulation	Post stimulation	Change from Baseline	HPA Suppression
1003	27			**7.7**			**12.9**	**YES**
1004	37			35.3			7.7	NO
1005	33			**9.8**	*	*	*	**UNKNOWN**
1007	43			4.8			12.5	NO
1009	25	*	*	*	*		*	**UNKNOWN**
1012	37			14.9			27.4	NO
1013	34			10.5			9.2	NO
803	24			**5.2**			**6.4**	**YES**
804	49			14.1			7.8	NO
805	46			11.5			15.0	NO
810	46			**13.1**			**13.5**	**YES**
Mean					10.0±9.3 (N=9)	21.9±8.2 (N=10)	12.9±6.4	
HPA Axis Suppression: N (%)								3 (33.3%)

Report No. 1.GUS.04.SRE.18009, Pre and Post-Stimulation Cortisol Levels: Temovate Emollient Cream Treatment Group at WEEK 1

		Cortisol levels (mcg/dL)						
		Baseline			Week 1			
Sub #	Age	Pre-stimulation	Post-stimulation	Change in Post-Stimulation. Baseline	Pre-stimulation	Post stimulation	Change from Baseline	HPA Suppression
1001	41			5.9			9.4	NO
1002	53			11.4			11.3	NO
1006	14			6.7			10.1	NO
1008	32			8.7			-5.1	NO
1010	32			15.3			14.1	NO
1011	26			10.7			21.3	NO
1014	47			11.0			15.4	NO
801	29			6.6			8.8	NO
802	**33**			**5.0**			**7.4**	**YES**
806	31			11.0			15.0	NO
807	57			9.5			8.5	NO
808	**47**			**11.1**			**12.6**	**YES**
809	38			8.8			2.7	NO
Mean					13.4±7.1 (N=13)	23.5±9.2 (N=13)	10.1±6.4	
HPA Axis Suppression: N (%)								2 (15.4%)

Report No. 1.GUS.04.SRE.18009, Pre and Post-Stimulation Cortisol Levels: Clobetasol Propionate 0.05% Lotion Treatment Group at WEEK 2

		Cortisol levels (mcg/dL)						
		Baseline			Week 2			
Sub #	Age	Pre-stimulation	Post-stimulation	Change in Post-Stimulation. Baseline	Pre-stimulation	Post stimulation	Change from Baseline	HPA Suppression
1003	27	[illegible]	[illegible]	7.7	[illegible]	[illegible]	12.9	YES
1004	37	[illegible]	[illegible]	35.3	[illegible]	[illegible]	18.6	NO
1005	33	[illegible]	[illegible]	9.8	[illegible]	[illegible]	7.1	YES
1007	43	[illegible]	[illegible]	4.8	[illegible]	[illegible]	16.0	NO
1009	25	*	*	*	[illegible]	[illegible]	10.2	YES
1012	37	[illegible]	[illegible]	14.9	[illegible]	[illegible]	28.8	NO
1013	34	[illegible]	[illegible]	10.5	[illegible]	[illegible]	14.7	NO
803	24	[illegible]	[illegible]	5.2	[illegible]	[illegible]	10.9	YES
804	49	[illegible]	[illegible]	14.1	[illegible]	[illegible]	10.4	NO
805	46	[illegible]	[illegible]	11.5	[illegible]	[illegible]	7.4	NO
810	46	[illegible]	[illegible]	13.1	[illegible]	[illegible]	9.6	YES
Mean					8.0±6.9 (N=11)	20.2±8.7 (N=11)	12.3±4.1	
HPA Axis Suppression: N (%)								5 (45.5%)

Report No. 1.GUS.04.SRE.18009, Pre and Post-Stimulation Cortisol Levels: Temovate Emollient Cream Treatment Group at WEEK 2

		Cortisol levels (mcg/dL)						
		Baseline			Week 2			
Sub #	Age	Pre-stimulation	Post-stimulation	Change in Post-Stimulation. Baseline	Pre-stimulation	Post stimulation	Change from Baseline	HPA Suppression
1001	41	[illegible]	[illegible]	5.9	[illegible]	[illegible]	5.9	NO
1002	53	[illegible]	[illegible]	11.4	[illegible]	[illegible]	16.1	NO
1006	14	[illegible]	[illegible]	6.7	[illegible]	[illegible]	12.2	NO
1008	32	[illegible]	[illegible]	8.7	[illegible]	[illegible]	5.9	NO
1010	32	[illegible]	[illegible]	15.3	[illegible]	[illegible]	13.8	NO
1011	26	[illegible]	[illegible]	10.7	[illegible]	[illegible]	17.0	NO
1014	47	[illegible]	[illegible]	11.0	[illegible]	[illegible]	11.4	NO
801	29	[illegible]	[illegible]	6.6	[illegible]	[illegible]	9.9	NO
802	33	[illegible]	[illegible]	5.0	[illegible]	[illegible]	3.7	NO
806	31	[illegible]	[illegible]	11.0	[illegible]	[illegible]	8.5	NO
807	57	[illegible]	[illegible]	9.5	[illegible]	[illegible]	10.4	YES
808	47	[illegible]	[illegible]	11.1	[illegible]	[illegible]	19.5	NO
809	38	[illegible]	[illegible]	8.8	[illegible]	[illegible]	6.7	NO
Mean					14.2±7.6 (N=13)	25.1±8.3 (N=13)	10.8±4.8	
HPA Axis Suppression: N (%)								1 (7.7%)

Comments:

1. All but one subject in the CP Lotion and Temovate Emollient Cream groups met the pre-specified criteria of normal response based on the baseline pre- and post-stimulation cortisol levels (Tables 8 and 9). Subject #805 in the CP Lotion group had a pre-stimulation cortisol level of [illegible] However, the post-stimulation baseline value was [illegible] allowing the subject to meet the labeling criteria for Cortrosyn.

2. At the end of 1-week treatment, 5 out of 9 (55.6%) subjects in the CP Lotion group exhibit a pre-stimulation cortisol level of < 10 mcg/dL, vs. 4 of 13 subjects (30.8%) in the Temovate group, while at the end of the 2-week, 7 out of 11 subjects (63.6%) in the CP Lotion group showed the cortisol level of below 10 mcg/dL compared to only 4 out of 13 subjects (30.8%).
3. With respect to the HPA axis function, 3 out of 9 subjects (or 33.3 %) in the CP Lotion group exhibited suppression compared to 2 out of 13 (15.4%) in the Temovate Emollient group at week-1. At week 2, 5 out of 11 subjects (45.5%) in the CP Lotion and 4 out of 13 (30.8%) in the Temovate Emollient groups showed HPA axis suppression.

6.2.6. HPA Axis Suppression Study: Report No. RD.06.SRE.18061

HPA Axis Suppression Potential of Clobetasol Propionate Lotion, 0.05%, as Compared to Temovate E Emollient Cream and Temovate Cream in Adolescents with Atopic Dermatitis.

Objectives:

To evaluate the potential of Clobetasol Propionate Lotion, 0.05% to suppress the hypothalamus-pituitary-adrenal (HPA) axis as compared to a marketed corticosteroid, Temovate E Emollient Cream, 0.05% and Temovate Cream 0.05% in adolescents subjects with atopic dermatitis.

Study Sites:
1. Investigator: [redacted]
2. Investigator: Bruce Miller, MD
   Oregon Medical Research Center
   Portland, OR 972233

Investigational Product:	Clobetasol Propionate 0.05% Lotion, Lot No. PECD
Comparator Products:	Temovate® Emollient Cream (Clobetasol Propionate 0.05% Emollient Cream)
=	Temovate® Cream (Clobetasol Propionate 0.05% Cream)

Dose: Twice-a-day application (~3.6 g/application), not to exceed 50g/week topically to affected area

Duration of Treatment: 2 weeks to provide data on systemic exposure, and 4 week follow-up for efficacy assessment.

Methods:
The study was conducted as multicenter, randomized, open-label, parallel comparison involving 36 subjects (11 males and 25 females, 24 White, 4 Black, 2 Hispanic, and 2 Mixed, ages 12 to 17 years) with atopic dermatitis who met specific inclusion/exclusion criteria as described in the NDA 21-535. The pre-specified criteria of normal response was pre- and post-stimulation cortisol levels of $\geq$ 7 and $\geq$ 18 mcg/dL, respectively.

Of the 36 subjects enrolled, 14 were randomized to CP Lotion, 10 to Temovate Emollient Cream and 12 to Temovate Cream group. Thirty-five subjects completed the study, one subject in the CP Lotion group was dropped because of protocol violation.

Subjects were evaluated at Screening, Baseline, and at Weeks 1 and 2.

Report No. 1.GUS.04.SRE.18061, Pre and Post-Stimulation Cortisol Levels: Clobetasol Propionate 0.05% Lotion Treatment Group at WEEK 2

		Cortisol levels (mcg/dL)						
		Baseline			Week 2			
Sub #	Age	Pre-stimulation	Post-stimulation	Change (Post – Pre)	Pre-stimulation	Post stimulation	Change (Post – Pre)	HPA Suppression
004	15			18.0			9.9	NO
013	16			8.9			6.8	NO
039	16			12.4			12.3	NO
050	17			20.4			13.8	NO
011	14			13.3			-3.1	NO
031	12			11.6			8.7	NO
044	**13**			**21.6**			**4.9**	**YES**
009	15			**14.2**			**2.3**	**YES**
016	14			18.5			19.7	NO
026	13			29.3			19.3	NO
034	**12**			**8.0**			**3.3**	**YES**
047	17			16.2			6.7	NO
001	**17**			**15.7**			**13.4**	**YES**
062	**16**			**10.5**			-	**YES**
Mean		16.1±5.3 (N=14)	31.7±5.2 (N=14)	-	8.8±7.6 (N=14)	18.3±9.7 (N=13)	-	
HPA Axis Suppression: n (%)								5 (35.7%)

Report No. 1.GUS.04.SRE.18061, Pre and Post-Stimulation Cortisol Levels: Temovate E Emollient Cream Treatment Group at WEEK 2

		Cortisol levels (mcg/dL)						
		Baseline			Week 2			
Sub #	Age	Pre-stimulation	Post-stimulation	Change (Post – Pre)	Pre-stimulation	Post stimulation	Change (Post – Pre)	HPA Suppression
002	14			14.3			18.6	NO
005	15			10.4			16.3	NO
015	13			16.6			10.8	NO
038	15			15.3			5.9	NO
051	17			16.4			16.8	NO
010	14			8.8			11.0	NO
007	16			19.3			14.2	NO
018	**13**			**21.3**			**2.8**	**YES**
027	13			23.7			15.7	NO
061	14			20.3			24.5	NO
		17.1±5.6 (N=10)	33.8±4.9 (N=10)	-	15.3±6.9 (N=10)	29.0±10.3 (N=10)	-	
Mean								
HPA Axis Suppression: n (%)								1 (10%)

Report No. 1.GUS.04.SRE.18061, Pre and Post-Stimulation Cortisol Levels: Temovate Cream Treatment Group at WEEK 2

		Cortisol levels (mcg/dL)						
		Baseline			Week 2			
Sub #	Age	Pre-stimulation	Post-stimulation	Change (Post – Pre)	Pre-stimulation	Post stimulation	Change (Post – Pre)	HPA Suppression
003	13	[redacted]		24.8	[redacted]		22.6	NO
006	17			7.9			16.2	NO
014	**14**			**20.4**			**11.1**	**YES**
037	12			11.7			7.1	NO
049	16			15.7			12.2	NO
012	13			17.5			14.4	NO
043	17			20.7			19.0	NO
008	15			12.3			6.7	NO
017	**14**			**9.1**			**10.1**	**YES**
025	16			17.6			7.0	NO
046	14			12.5			15.8	NO
060	**15**			**17.6**			**6.6**	**YES**
Mean		15.8±4.4 (N=12)	31.4±4.3 (N=12)	-	10.7±7.1 (N=12)	23.1±8.8 (N=12)	-	
HPA Axis Suppression: N (%)								3 (25%)

Comments:

1. All subjects in the CP Lotion, Temovate Cream, and Temovate Emollient Cream groups met the pre-specified criteria of normal response, i.e., pre- and post-stimulation cortisol levels of ≥ 7 and ≥ 18 mcg/dL, respectively.
2. At the end of 2-week treatment, 6 out of 14 (42.9%) subjects in the CP Lotion group exhibited a pre-stimulation cortisol level of < 7 mcg/dL, vs. 1 of 10 subjects (10%) in the Temovate Cream group, and 4 out of 12 (33.3%) in the Temovate Emollient Cream groups.
3. With respect to the HPA axis function, 5 out of 14 subjects (35.7%) in the CP Lotion group exhibited suppression compared to 1 out of 10 (10%) in the Temovate Cream and 3 out of 12 (25%) in the Temovate Emollient Cream groups at week 2.

6.3. OVERALL COMMENTS ON HPA AXIS FUNCTION

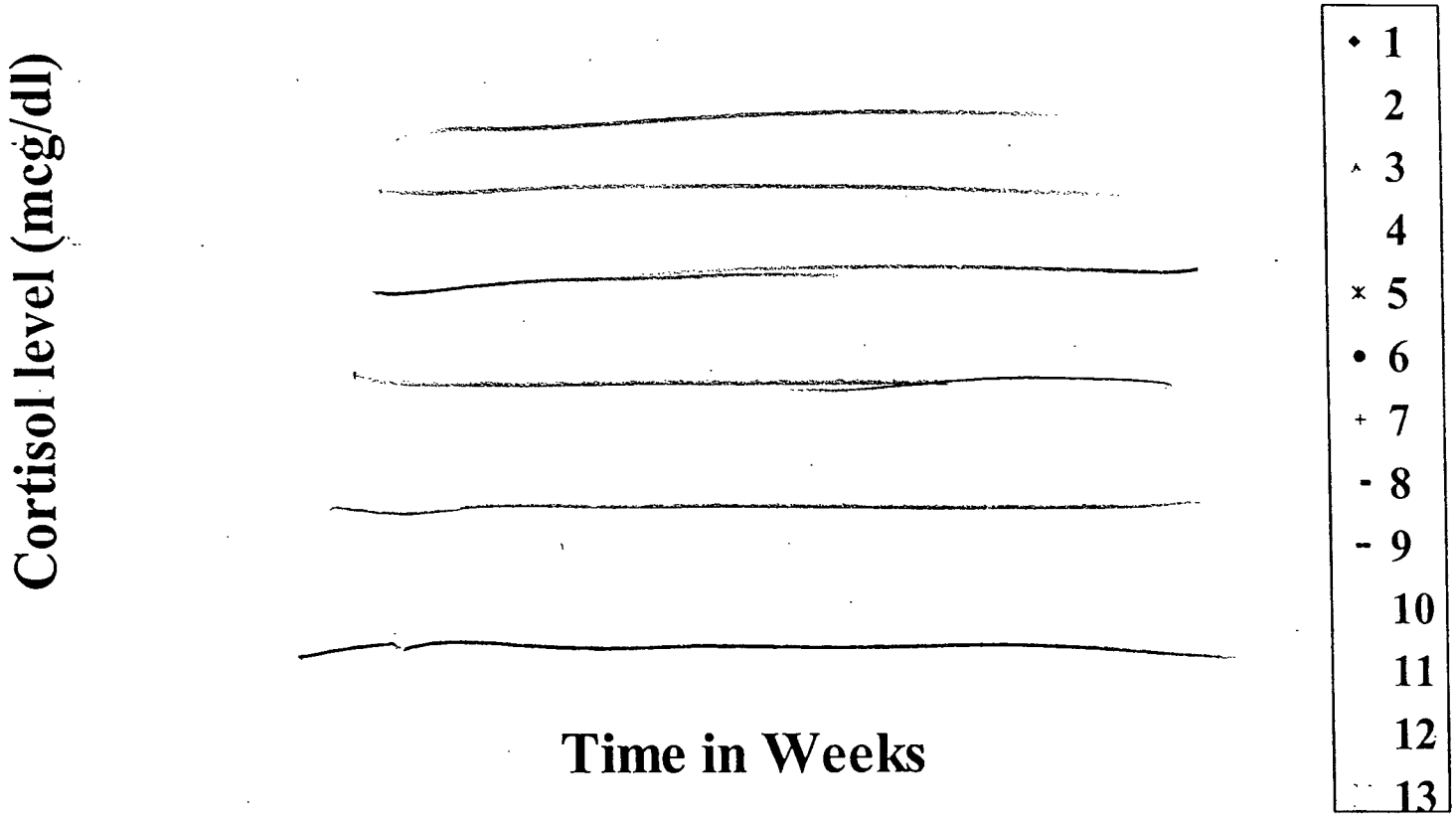
Based on the reported results, there appears to be a markedly higher incidence of HPA axis suppression with the Clobex Propionate Lotion compared to that observed with the Temovate Cream or Temovate E Emollient Cream in both the in psoriasis and atopic dermatitis patients. The observed degree of HPA suppression with Clobex Lotion is sufficient to cause concern about patient's safety in an uncontrolled administration setting.

6.4. RECOMMENDATIONS

From a Biopharmaceutics perspective the firm has provided evidence of systemic availability for the test Clobex Propionate Lotion and reference Temovate E Emollient cream formulations. Based on the results of the 3 HPA axis trials, use of CP Lotion is clearly associated with a high incidence of HPA suppression compared to the Temovate E Emollient cream. Thus, from a clinical pharmacology perspective, there is a reasonable concern about the safety of this product

in uncontrolled administration. While the bioavailability of clobetasol has been determined via indirect methods (i.e., HPA axis testing), the safety issues raised by the increased bioavailability relative to the reference product raises a significant concern.

Pre-Stimulation Cortisol Levels Baseline, Week 2, and Week 4



6.5. OCPB FILING REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics			
NEW DRUG APPLICATION FILING AND REVIEW FORM			
General Information About the Submission			
	Information		Information
NDA Number	21-535	Brand Name	Clobex™
OCPB Division (I, II, III)	DPE III	Generic Name	Clobetasol Propionate, 0.05%
Medical Division		Drug Class	Topical Steroid
OCPB Reviewer	Chandra S. Chaurasia, Ph. D.	Indication(s)	Relief of inflammatory and pruritic manifestoses of corticosteroid- responsive dermatoses
OCPB Team Leader	E. Dennis Bashaw, Pharm. D.	Dosage Form	Lotion
		Dosing Regimen	Twice daily limited to 2 or 4 consecutive weeks
Date of Submission	SEP 25, 2002	Route of Administration	Topical
Estimated Due Date of OCPB Review	March 01, 2003	Sponsor	Galderma Laboratories, L. P. Fortworth, TX 76177
PDUFA Due Date	Jul 27, 2003	Priority Classification	
Division Due Date	May 27, 2003		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**			In Vitro, CG.03.SRE.4637
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**2**		Vasoconstriction Assays: CG.03.SRE.2117 and CG.03.SRE.2570
multiple dose:				
Patients-				
single dose:				

multiple dose:		3		HPA Suppression Studies: GUS.04.SRE.18009, RD.06.SRE.1806 and CR.U9708
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X			Pooled Data
pediatrics:	X			In Adolescents Age Group 12-17-yr only for HPA Suppression study
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	3		HPA axes suppression in patient with atopic dermatitis (GUS.04.SRE.18009 and RD.06,SRE.18061) psoriasis (CR.U9708)
Phase 3:	X	2		Vasoconstriction Atopic Dermatitis: GUS.04.SRE.180001, and Psoriasis: CR.U9707.R02
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Alternate formulation as reference:	X	1		In Vitro Liberation-Penetration evaluation using In Vitro Franz-cell assay
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				

Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	3		PD articles on skin blanching
Total Number of Studies		6		Five in vivo and one in vitro studies

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• **What are the highlights of the physicochemical properties of clobetasol propionate?** • **What are the properties of the formulation of the drug product? What are the differences between clinical and to-be-marked formulations?** • *What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of clobetasol propionate?* • *Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters?* • What are the basic pharmacokinetic parameters of clobetasol propionate (ADME)? • Is the vasoconstriction assay appropriate to classify the potency class of clobetasol propionate lotion? • Is the vasoconstriction assay methodology validated? • Is the study to evaluate clobetasol propionate lotion potential to suppress the hypothalamus-pituitary-adrenal (HPA) axis appropriately designed with respect to a) the study populations relevant to the proposed indication, b) dose and dosing regimen appropriate for the treatment of the proposed indication, and c) bioanalytical methods used to assess the amount of cortisol level in study specimens. • *Is the liberation-penetration Diffusion Cell Study appropriately designed to obtain comparative in vitro evaluation of clobetasol propionate lotion?* • Are analytical methods sensitive enough to determine the extent of clobetasol in the in vitro study?	

Other comments or information not included above	
Primary reviewer Signature and Date	**Chandra S. Chaurasia, Ph. D.**
Secondary reviewer Signature and Date	**E. Dennis Bashaw, Pharm. D.**

CC: NDA 21-535, HFD-850 (P. Lee), HFD-540 (M. Harris), HFD-880 (D. Bashaw, J. Lazor, A. Selen)

End of Document

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

/s/

Chandra S. Chaurasia
7/1/03 10:56:52 AM
BIOPHARMACEUTICS

This is the final review that incorporates all recommendations made at the briefing on this NDA.

Dennis Bashaw
7/1/03 11:16:23 AM
BIOPHARMACEUTICS