CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-142

MEDICAL REVIEW(S)

Correspondence date: July 28, 1999
CDER Stamp Date: July 29, 1999

HFD-540 Trac No: 993852

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA 21-142 ORIGINAL SUBMISSION

May 15, 2000

SPONSOR: Connectics Corporation
Palo Alto, CA

DRUG: Clobetasol propionate foam 0.05%

MAY 21 2000

PROPOSED TRADE NAME: Olux Foam

CLINICAL INDICATION: [redacted]

REASON FOR ADDENDUM: Review of request for waiver of pediatric studies.

The statement on pediatric usage in the proposed labeling is as follows: '**Pediatric Use:** Safety and effectiveness of Olux foam in pediatric patients have not been established; therefore, use in children under 12 years of age is not recommended.'

The sponsor requests a full waiver of the requirement for pediatric studies on Olux foam, on the basis that a) it does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients, and b) it is not likely to be used in a substantial number of patients.

In support of their contention that Olux foam does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients, the sponsor states that the three super-high-potency corticosteroids, namely, halobetasol propionate, betamethasone dipropionate, and clobetasol propionate, are marketed in a number of vehicle formulations, and all of these products are labeled for use in children of 12 years of age or older, with use not recommended in children under the age of 12 years. Therefore the practitioner has access to at least eleven super-high-potency corticosteroid products that are already labeled for use in children 12 years of age or older. The sponsor states that the data in the studies in the NDA show that Clobetasol foam does not represent a meaningful therapeutic benefit over existing treatment for pediatric patients with moderate to severe dermatoses of the scalp.

In support of their contention that clobetasol foam is not likely to be used in a substantial number of pediatric patients, the sponsor obtained, through the Physician Drug & Diagnosis Audit database, the number of patients ages 12 through 18 who visited a physician in 1998 and were prescribed super-high-potency corticosteroids. The estimated number of patients was 55,000. Information on the number of patients with scalp involvement was not available; however, the National Psoriasis Foundation has estimated that about half of the patients with psoriasis have scalp involvement. Using this figure to extrapolate to other dermatoses, the sponsor estimated that the total number of pediatric patients aged 12 to 18 treated with a super-high-potency corticosteroid for scalp dermatoses would be about 27,500, a number which is below the 50,000 patients which the Agency defines as a substantial number of pediatric patients. In addition, the figure of 27,500 is an overestimation, since the pediatric population defined by the Agency is from 12 to 16 years of age.

Reviewer's comments: This reviewer agrees with the sponsor's position that Olux foam is not likely to be used in a substantial number of pediatric patients. It is recommended that a waiver of the requirement for pediatric studies be granted.

/S/

Phyllis A. Huene, M.D.

5/15/00

Cc: Orig NDA 21-142
HFD-540 Division file
HFD-540/Wilkin
HFD-540/Okun
HFD-540/Huene
HFD-540/Bhatt
HFD-540/Cintron

/S/ /S/ /S/ — 5/17/00 5/21/00

Not in DFS

Correspondence date: July 28, 1999
CDER Stamp Date: July 29, 1999

HFD-540 Trac No: 993852

MEDICAL OFFICER'S REVIEW OF NDA 21-142
ORIGINAL SUBMISSION

November 30, 1999

SPONSOR: Connectics Corporation
Palo Alto, CA

DRUG: Clobetasol propionate foam 0.05%

APR 22 2000

PROPOSED TRADE NAME: Olux Foam

CLINICAL INDICATION: Corticosteroid-responsive dermatoses of the scalp

Proposed labeling indication statement: 'Olux foam is a super-potent corticosteroid indicated for short-term topical treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp.'

FORMULATION:

Clobetasol propionate	0.05%
Ethanol	1%
Cetyl alcohol	%
Stearyl alcohol	%
Polysorbate 60	%
Propylene glycol	%
Citric acid anhydrous	%
Potassium citrate	%
Purified water	

DOSAGE AND ADMINISTRATION: Applications BID

DATE OF SUBMISSION: July 28, 1999

RELATED SUBMISSIONS: NDAs 19-322 and 19-323 for Temovate Cream 0.05% and Temovate Ointment 0.05% (Glaxo); NDA 19-966 for Temovate Scalp Application 0.05%; NDAs 20-337 and 20-340 for Temovate Gel 0.05% and Temovate E Cream 0.05%. NDA 20-934 and IND ——— for Clobetasol foam (Connectics).

PHARMACOLOGY AND CONTROLS REVIEWS: These are currently pending.

This NDA is submitted under FD&C Act Section 505(b)(2), using the marketed Temovate products as the reference drug product.

INDEX TO MEDICAL OFFICER'S REVIEW

Financial disclosure statement

The sponsor states that 'As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).'

Beneath this statement the sponsor has listed all the investigators in Studies CPCD.C.001, CPCD.C.002, and CPCD.C.003.

Rationale for the foam formulation

The sponsor states that Clobetasol foam is a new topical form of clobetasol that has cosmetic advantages over other currently marketed formulations of clobetasol because it is neither greasy nor runny. When the foam is applied, body heat causes the foam structure to break down and deposit the active ingredient in a vehicle most closely resembling that of a solution. The foam dosage form provides controlled application of a small amount of product over the lesion site.

The formulation is a hydroalcoholic, thermolabile foam packaged in an aluminum can with a propane/butane propellant. The excipients in Clobetasol foam are the same as those in the recently approved Luxiq (betamethasone valerate) Foam 0.1% (NDA 20-934).

Pre-IND meeting

A pre-IND meeting was held on February 19, 1998; it was agreed that submission of a 505(b)(2) application with data demonstrating comparable bioavailability of Clobetasol foam to the currently marketed forms of clobetasol would be sufficient for approval. The following three studies were to be performed in this regard:

- a comparative vasoconstrictor study.
- a comparative Phase 3 study in scalp psoriasis.
- a comparative HPA axis suppression study.

The Clinical portion of the Agency minutes of the pre-IND meeting (as paraphrased) is as follows.

- An appropriate comparative efficacy study design would include a four arm comparison, using the reference product as a comparator and including a placebo arm (active foam, placebo foam, active comparator, placebo comparator). The company has determined the comparator to be the Clobetasol Propionate Solution 0.05%. Assessment of the overall scalp should be made, rather than assessment of a specific target lesion.

- The primary endpoint 'Investigator's Global Assessment' should be a dichotomous static variable. The criteria for placing a subject into an assessment level should be clearly defined for the clinical investigators, such that the distinction between 'Cleared' and 'Almost Cleared' is apparent. Subjects who are completely cleared or almost cleared should be placed in the 'success' category for analysis, with all others placed in the 'failure' category.

- The results of the analysis of the secondary endpoint variables Erythema, Scaling, and Plaque Thickness, based on the changes from baseline to day 15 in each of the scores of signs, should reflect the results of the global static assessment.

- The intent of the vasoconstrictor study in the 505(b)(2) application is to determine potency, not comparative bioavailability. A single dose-duration [redacted] design is adequate. Comparisons should be made with multiple drug products in adjacent classes in order to adequately establish the steroid class of the clobetasol foam product.

- An HPA axis suppression study should use a cosyntropin stimulation test. The subjects should receive an amount of foam per week equal to the weekly upper limit of total dosage permitted in the final package labeling. The area treated must be clinically involved skin. The final package labeling will reflect the percentage of body surface area applied in the HPA axis suppression study, and the proposed duration of treatment in the final package labeling will reflect the duration and outcome of the HPA axis suppression test.

- The study should be performed in children, if the sponsor plans to claim use in children.

- The final package labeling will reflect the clinical trials. Whole body class labeling would not be supported by a single study in scalp psoriasis. Body psoriasis is a more appropriate paradigm than scalp psoriasis for supporting class labeling, and it includes a greater chance to enroll pediatric patients.

- HPA axis suppression testing should precede clinical trials to demonstrate an acceptable duration for the clinical pivotal trial. The sponsor should then demonstrate superiority over the vehicle and non-inferiority to the comparator at 4 weeks in the pivotal clinical trial. (Reviewer's comment: Although this statement was contained in the meeting minutes, in actuality the sponsor and the Agency agreed that the appropriate endpoint in the clinical trial is two weeks.)

- Human skin irritation studies will be waived for the proposed formulation, unless the CMC profile shows impurities or degradation products. Photoallergenicity and phototoxicity studies will be waived if the drug has no absorbance in visible, UVA, or UVB light.

The Biostatistics portion of the meeting minutes is as follows.

- For approval the sponsor should demonstrate:

  - statistical superiority of Clobetasol Propionate Foam, 0.05%, to its own vehicle, and
  - statistical non-inferiority of Clobetasol Propionate Foam, 0.05%, to the currently marketed comparator (Clobetasol Propionate Solution, 0.05%).

- To demonstrate non-inferiority of the foam formulation to the solution, a 95% confidence interval for the difference between Clobetasol Propionate Foam and the comparator should be constructed:

  - the confidence level should not fall below zero, and
  - the foam formulation should not be 10% worse than the solution.

- If the two vehicle arms are not statistically different, they can be combined for the purposes of statistical analysis.

Pre-NDA meeting

A pre-NDA meeting on Clobetasol foam was held on April 26, 1999, at which time a summary of the results of the studies was provided. In the discussion of clinical issues, the Division stated that the NDA submission should include submission of data in a manner that enables assessment of outcomes in the ITT population of treatment 'success' at day 15. Treatment 'success' was defined as:

(a) an Investigator's Global Assessment Score of completely clear or almost clear, and
(b) a plaque thickness score of zero, and
(c) a scaling score of 0 or 1, and
(d) an erythema score of 0 or 1.

To be counted as a 'success', subjects must meet all four of these criteria.

Overview of clinical studies

Three clinical studies on Clobetasol foam 0.05% are provided in this NDA submission. These are:

a. Study CPCD.C.001 - a comparative vasoconstrictor assay.
b. Study CPCD.C.003 - a comparative HPA axis suppression study.
c. Study CPCD.C.002 - a double blind, active and placebo controlled study of the safety and efficacy in the treatment of scalp psoriasis.

The conduct and results of these studies were as follows.

Study CPCD.C.001: Vasoconstrictor assay

The investigators for this study were Thomas Horn, M.D. and Paul Lehman, M.S., Department of Dermatology, University of Arkansas for Medical Sciences, Little Rock, AR.

1) Study Title: Determination of the Comparative Bioavailability of Clobetasol Propionate Products by Human Vasoconstrictor Assay.

2) Study objective: This was to determine the vasoconstrictor potency of Clobetasol propionate foam 0.05%, relative to five other dosage forms of Clobetasol propionate 0.05%, and to two corticosteroid products reported to be of lower potency (fluocinonide solution 0.05%, betamethasone valerate lotion 0.1%).

3) Study design: This was a single center, randomized, masked (reader and subject) paired comparison study in 24 healthy subjects. Using a vasoconstrictor assay, the potency of Clobetasol foam was assessed relative to the five currently marketed Clobetasol products (Temovate, Glaxo Wellcome, Inc), and to two steroids of lower potency, fluocinonide solution 0.05% (Lidex, Medicis Pharm.) and betamethasone valerate lotion 0.1% (E. Fougera & Co.).

4) Study procedures: The subjects were pre-screened for vasoconstrictive responsiveness to Clobetasol propionate ointment 0.05%. A 10 ul amount of each of the eight products was randomly applied by pipette to sites on the ventral forearms of 24 subjects, with one arm randomly assigned to receive one dose-duration (0.5 hours) and the opposite arm assigned to receive a second dose-duration (3.0 hours). Two additional sites served as untreated controls. The products were evenly spread over the skin sites. At the end of the designated times the products were removed by wiping with cotton swabs. The vasoconstrictor response (skin blanching) was assessed by [redacted] prior to application and at 1, 4, 8, 12, 24, and 30 hours after application.

5) Study results: Using the mean area-under-the-effect-curve (AUEC) from 0 to 30 hours for each product as a measure of potency, results were as follows.

$AUEC_{0-30}$		
Product	0.5 hr	3.0 hr
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 emollient cream 0.05%	- 21.1	- 19.2
Temovate scalp application 0.05%	- 20.9	- 17.2
Lidex solution 0.05%	- 21.9	- 16.2
Betamethasone Valerate lotion 0.1%	- 11.9	- 6.7

The sponsor's conclusion is that the results of this study demonstrate that the potency of Clobetasol foam is almost equal

to that of Temovate Gel, and is greater than that of Temovate Emollient Cream, Temovate Scalp Application, Lidex Topical Solution 0.05%, and Betamethasone Valerate Lotion 0.1%. Since both Temovate Gel and Temovate Emollient Cream are classified as super-high potency corticosteroids, Clobetasol foam should also have a super-high potency classification.

Reviewer's comments: This reviewer agrees with the sponsor that the results of this study show that Clobetasol foam has a potency comparable to that of the Temovate products, and intermediate among that of the Temovate products, and that it should be classified as a super-high potency corticosteroid.

Study CPCD.C.003 - HPA axis suppression

The investigators for this study were Alan Heller, M.D., San Jose Clinical Research, San Jose, CA, and Bruce Miller, M.D., Oregon Medical Research Center, Portland, OR.

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

2) Study design: This was a multicenter (two sites), randomized, parallel design, open label study in 26 subjects with psoriasis or atopic dermatitis, comparing the effect of Clobetasol Propionate foam, 0.05%, with Clobetasol Propionate (Temovate) ointment 0.05%, on the HPA axis.

3) Study objective: This was to compare the effect of Clobetasol Propionate foam, 0.05%, and Clobetasol Propionate (Temovate) ointment 0.05%, on the HPA axis, as measured by the cosyntropin stimulated change in the plasma cortisol response, following application of 3.5 gms twice daily for 14 days to the diseased skin of psoriatic or dermatitic subjects.

4) Inclusion criteria: The subjects had to meet the following criteria to be eligible for study admission:

a. Male or female subjects 18 years or older.
b. Psoriasis or atopic dermatitis involving at least 20% of the body surface area.
c. A normal cosyntropin stimulation test at least three days prior to baseline.

5) Exclusion criteria: Subjects with the following conditions were excluded from the study.

a. Any disease affecting the HPA axis, e.g., Addison's, Cushing's.
b. Known allergy or sensitivity to Clobetasol or other topical corticosteroids or any component of the investigational formulations.
c. Severe, uncontrolled manifestations of any disease, including psoriasis or dermatitis, e.g., uncontrolled diabetes, erythroderma, or exfoliative dermatitis.
d. Pregnancy or lactation.
e. Women or men of reproductive potential unless they were using effective contraception during the full course of the study.

f. Use of any topical corticosteroids in the 2 weeks prior to baseline.
g. Use of any topical retinoids in the 4 weeks prior to baseline.
h. Use of any systemic corticosteroids or systemic retinoids in the 8 weeks prior to baseline.
I. Use of any non-corticosteroid/non-retinoid systemic anti-psoriatic therapy, e.g., cyclosporin, methotrexate, PUVA, in the 4 weeks prior to baseline.
j. Use of estrogens, including estrogen-containing birth control pills, or any other medication known to affect cortisol levels or HPA axis integrity in the 8 weeks prior to baseline.
k. Use of any investigational drug or device therapy in the 4 weeks prior to baseline.
l. Known sensitivity to cosyntropin or natural ACTH.
m. Current drug or alcohol abuse.
n. Subjects who in the opinion of the investigator would not be suitable candidates for enrollment.

6) Treatment regimen: The subjects were randomized to treatment with Clobetasol foam or Clobetasol (Temovate) ointment. Randomization was performed separately for subjects with psoriasis and for subjects with atopic dermatitis.

Applications of 3.5 gm of the test products were made twice daily for 14 days under the supervision of the study personnel. The products were applied to all lesions, or, if 3.5 gm was insufficient to cover all lesions, were applied to the same lesions throughout the study. No concomitant topical treatments were allowed.

7) Study parameters: A cosyntropin stimulation test was done at screening, at baseline, and at days 8, 15, and 20. Serum cortisol levels were measured prior to and at 30 minutes after the IM injection of 0.25 mg of cosyntropin. The primary response variables were the pre-stimulation and post-stimulation serum cortisol levels at baseline, day 8, and day 15. A normal pre-stimulation cortisol level was defined as > 5 ug/dL, and a normal response to cosyntropin stimulation was defined as a cortisol level of > 18 ug/dL at 30 minutes post-injection.

Clinical laboratory tests, including hematology and chemistry profile, were done at screening and at day 15.

8) Study results: There were 13 subjects randomized into each of the two treatment groups; all subjects completed the study. There were two protocol violations: one subject missed a single application on day 4, and a second subject had received a systemic corticosteroid for one week at five weeks prior to screening.

The number of subjects with abnormal cortisol values at day 8 and day 15 were as follows.

Subjects with abnormal cortisol values *		
	Clobetasol foam	Clobetasol ointment
Number of subjects	13	13
Abnormal response - Day 8 Pre-stimulation Post-stimulation	 3 (23%) 3 (23%)	 4 (31%) 5 (38%)
Abnormal response - Day 15 Pre-stimulation Post-stimulation	 3 (23%) 3 (23%)	 3 (23%) 3 (23%)
* Defined as pre-stimulation value of ≤ 5 ug/dL, and post-stimulation value of < 18 ug/dL.		

The cortisol values in these subjects were as follows.

Clobetasol foam (abnormal values denoted by *)			
Pt #	Visit	Pre-stimulation cortisol (ug/dl)	Post-stimulation cortisol (ug/dl)
10	Screening		
	Day 8		*
	Day 15		*
	Re-test		
15	Screening		
	Day 8	) *	*
	Day 15	) *	*
	Re-test 1	*	*
	Re-test 2		
16	Screening		
	Day 8	*	
	Day 15		
6	Screening		
	Day 8		1 *
	Day 15		
20	Screening		
	Day 8		
	Day 15	*	1 *
	Re-test		

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Clobetasol ointment (abnormal values denoted by *)			
Pt #	Visit	Pre-stimulation cortisol (ug/dl)	Post-stimulation cortisol (ug/dl)
14	Screening		
	Day 8	*	*
	Day 15		
17	Screening		
	Day 8	*	*
	Day 15		*
	Re-test 1	*	*
	Re-test 2	*	
18	Screening		
	Day 8	*	*
	Day 15		
22	Screening		
	Day 8		
	Day 15	*	
	Re-test		
3	Screening		
	Day 8	*	*
	Day 15		
5	Screening		
	Day 8	*	*
	Day 15	*	*
	Re-test		
25	Screening		*
	Screening		
	Day 8		
	Day 15	*	*
	Re-test	*	*

The range of abnormal values was as follows.

Range of abnormal cortisol values (ug/dL) *		
	Clobetasol foam	Clobetasol ointment
Number of subjects	13	13
Abnormal response - Day 8 Pre-stimulation Post-stimulation	< 1.0 - 3.6 4.9 - 14.2	1.3 - 3.8 10.9 - 16.0
Abnormal response - Day 15 Pre-stimulation Post-stimulation	< 1.0 - 2.3 3.2 - 12.1	1.5 - 4.9 14.2 - 17.1
* Defined as pre-stimulation value of < 5 ug/dL, and post-stimulation value of < 18 ug/dL.		

The mean cortisol values and the mean changes in cortisol values from baseline were as follows.

Mean cortisol values Mean changes in cortisol values from baseline		
	Clobetasol foam	Clobetasol ointment
Number of subjects	13	13
Day 1 Pre-stimulation (mean) Post-stimulation (mean)	17.02 29.10	18.05 27.84
Day 8 Pre-stimulation (mean) Change from baseline Post-stimulation (mean) Change from baseline	11.74 - 5.28 23.00 - 6.10	9.76 - 8.29 21.48 - 6.36
Day 15 Pre-stimulation (mean) Change from baseline Post-stimulation (mean) Change from baseline	11.13 - 5.89 22.25 - 6.85	12.22 - 5.83 23.55 - 4.29

The sponsor's conclusion was that there was no difference between Clobetasol foam and Clobetasol (Temovate) ointment in the number of subjects with abnormal cortisol values. Mean cortisol values decreased in both treatment groups, and the

magnitude of the decrease was similar in the two groups. Therefore, the data indicate that Clobetasol foam had no greater effect on the HPA axis than did Clobetasol (Temovate) ointment.

Laboratory values showed a shift from normal baseline values to abnormal values at day 15 in 5 subjects on Clobetasol foam and 7 subjects on Clobetasol ointment; the changes were not considered to be clinically significant.

Reviewer's comments: The HPA axis suppression study appears to have been adequately designed and conducted. This reviewer is in agreement with the sponsor's conclusions that the frequency of abnormal cortisol levels and the magnitude of the decrease in cortisol levels from baseline were similar in the Clobetasol foam group and the Temovate ointment group.

Study CPCD.C.002

The investigators for this study were as follows.

Edwin Bronsky, M.D. Salt Lake City, UT	Bruce Miller, M.D. Portland, OR
Frank Dunlap, M.D. Tucson, AZ	David Miller, M.D. North Dartmouth, MA
Holly Faust, M.D. Indianapolis, IN	Jennie Muglia, M.D. Providence, RI
David Fivenson, M.D. Detroit, MI	Toivo Rist, M.D. Knoxville, TN
Alan Heller, M.D. San Jose, CA	Ronald Savin, M.D. New Haven, CT
Dale Martin, M.D. San Diego, CA	Kenneth Washenik, M.D. New York, NY

1) Study Title: A Double-Blind, Active and Placebo Controlled Study of the Safety and Efficacy of Clobetasol Propionate Foam in Treating Scalp Psoriasis.

2) Study objective: This was to evaluate whether clobetasol propionate foam, 0.05%, (Clobetasol foam) is superior to vehicle foam and not inferior to clobetasol propionate solution 0.05% (Temovate Scalp Application) with respect to safety and efficacy.

3) Study design: This was a double-blind, randomized, multicenter, double-dummy, active-controlled study in patients with moderate to severe scalp psoriasis. The patients were randomized into one of four treatment groups in a 2:1:2:1 ratio: Clobetasol foam, vehicle foam, Clobetasol solution, placebo solution.

4) Inclusion criteria: The subjects had to meet the following criteria to be eligible for study admission:

a. Male or female subjects 18 years or older.
b. Stable or worsening scalp psoriasis involving at least 10% of the scalp.
c. Moderate to severe scalp psoriasis, defined by a minimum score of 2 for each of the clinical signs erythema, scaling, and plaque thickness, using a 0 - 4 scale.

5) Exclusion criteria: Subjects with the following conditions were excluded from the study.

a. Known allergy to clobetasol or other topical corticosteroids or any component of the investigational formulations.
b. Known sensitivity to DHS shampoo.
c. Presence of a scalp condition other than psoriasis.
d. Severe, uncontrolled manifestations of any disease, including psoriasis.
e. Known failure to respond to topical corticosteroids at any time.
f. Use of systemic anti-psoriatic therapy, e.g., corticosteroids, retinoids, methotrexate, PUVA, UVB, cyclosporin, within the past 4 weeks.
g. Use of any topical drug to the scalp, e.g., corticosteroids, calcipotriene, within the past two weeks.
h. Planned treatment of non-scalp psoriatic lesions with medications, e.g., UVB, corticosteroids, etc., other than tar baths or emollients during the entire four week study.
I. The introduction of drugs for other medical conditions which are known to affect psoriasis, e.g., lithium, beta-adrenergic blockers, etc., during the period from four weeks prior to screening through day 29.
j. Use of any investigational therapy during the past four weeks.
k. Expectation of exposure to atypically strong sunlight during the course of the study, e.g., planned holiday in high sunlight location.
l. Pregnant women, women who are breast feeding, or women of child bearing potential who are not practicing an acceptable method of birth control (abstinence, birth control pill/patch, barrier with spermicidal jelly, IUD, etc.), as determined by the investigator. Acceptable contraception was to be used during the entire study.
m. Men wishing to father children during the study. Adequate means of contraception (abstinence, condom and spermicidal jelly, etc.), as determined by the investigator, must have been maintained throughout the study.
n. Current drug or alcohol abuse.
m. Any other condition which, in the judgment of the investigator or the medical monitor, would have put the subject at unacceptable risk for participation in the study.

6) Treatment regimen: Applications of the test products were made BID for 14 days.

All patients were restricted to use of DHS shampoo as the only shampoo. No other concomitant topical treatment to the scalp or medicated shampoos were permitted.

7) Efficacy parameters: After the screening visit, the patients returned at day 0 (baseline), 8, 15, and 29. The following evaluations were made.

1. Clinical signs: At each return visit an evaluation of scalp erythema, scaling, and plaque thickness was made, according to the following scales.

Grading scale for plaque thickness	
Score	Description of response
0	No plaque elevation
1	Slight, barely perceptible elevation
2	Definite elevation, but not thick
3	Definite elevation, thick plaque with sharp edge
4	Very thick plaque with sharp edge

Grading scale for scaling	
Score	Description of response
0	No scaling
1	Sparse fine scale, lesions only partially covered
2	Coarser scales, most of lesions covered
3	Entire lesion covered with coarse scales
4	Very thick, coarse scales, possibly fissured

Grading scale for erythema	
Score	Description of response
0	No erythema
1	Faint erythema, pink to very light red
2	Definite light red erythema
3	Dark red erythema
4	Very dark red, 'beefy' erythema

An evaluation of the amount of scalp pruritus was also made, using the following scale.

Grading scale for pruritus	
Score	Description of response
0	No pruritus
1	Occasional pruritus, barely noticeable
2	More frequent pruritus, not troublesome
3	Frequent and sometimes troublesome pruritus; sleeps OK
4	Frequent, troublesome pruritus; interferes with sleep and/or other activities

2. Investigator's global assessment: At days 15 and 29 the investigator evaluated the response to treatment, using the following scale.

Grading scale for Global Assessment of Response	
Score	Description of response
1	Completely clear, except for possible residual hyperpigmentation.
2	Almost clear; very significant clearance (about 90%); however, patchy remnants of dusky erythema and/or sparse fine scaling may be present.
3	Marked improvement; significant improvement (about 75%); however, a small amount of disease remaining, i.e., fine to coarse scales in some areas, definite erythema and/or barely perceptible plaque elevation.
4	Moderate improvement; intermediate between slight and marked; representing about 50% improvement.
5	Slight improvement; some improvement (about 25%); however, significant diease remaining, i.e., a moderate or greater amount of erythema, scaling, and/or plaque elevation.
6	No change. Moderate to severe erythema, scaling, and plaque elevation.
7	Worse.

The patient also made an assessment of response using the same scale.

8) Primary response variable: The primary response variable was a 'Treatment Success'; this was defined as a global assessment of Completely Clear or Almost Clear, a plaque thickness score of 0, a scaling score of 0 or 1, and an erythema score of 0 or 1.

9) Safety parameters. The patients were queried as to adverse events at each return visit. Laboratory tests were performed at screening and at day 15; these included hematology, chemistry profile, and urinalysis.

Results were as follows.

1) Baseline and demographic characteristics: 188 patients were enrolled into the study, with the following characteristics.

Demographic and baseline characteristics All patients enrolled				
	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Age (years) Mean Range 18-59 years >/= 60 years	 46.27 (20-83) 47 (76%) 15 (24%)	 47.1 (24-72) 25 (81%) 6 (19%)	 45.8 (19-75) 50 (79%) 13 (21%)	 41.9 (22-72) 30 (94%) 2 (6%)
Sex Male Female	 34 (55%) 28 (45%)	 16 (52%) 15 (48%)	 26 (41%) 37 (59%)	 17 (53%) 15 (47%)
Race Caucasian Other	 57 (92%) 5 (9%)	 26 (84%) 5 (15%)	 60 (95%) 3 (5%)	 30 (94%) 2 (6%)

2) Patient disposition: The patient disposition and premature discontinuations were as follows.

Patient disposition				
	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
# pts randomized (ITT population)	62	31	63	32
# pts randomized who applied medication (Safety population)	62	31	63	32
# pts at each visit Baseline Day 8 Day 15 Day 29	 62 (100%) 62 (100%) 62 (100%) 62 (100%)	 31 (100%) 31 (100%) 30 (97%) 29 (94%)	 63 (100%) 61 (97%) 63 (100%) 61 (97%)	 32 (100%) 31 (97%) 32 (100%) 31 (97%)
Protocol violations	0	0	0	0
# pts that completed study	62 (100%)	29 (94%)	61 (97%)	31 (97%)

The number of premature patient discontinuations and the reasons were as follows.

Premature patient discontinuations				
	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Adverse event	0	0	1	0
Patient request	0	0	1	0
Non-compliance	0	0	0	1
Other	0	2	0	0
Total # pts	0	2	2	1

3) Efficacy parameters. All efficacy analyses were performed on the ITT population, defined to include all randomized patients.

a. Clinical signs.

The results at day 15, for each of the clinical signs scaling, erythema, and plaque thickness are provided as a) the mean values, b) the change in mean values from baseline, and c) the percentage of patients with a score of 0. Mean values and change from baseline are also provided for the symptom scalp pruritus.

Results were as follows.

PLAQUE THICKNESS				
Mean values	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Baseline	2.34	2.42	2.43	2.19
Day 15	0.52	1.77	0.62	1.53
Change from baseline	- 1.82	- 0.65	- 1.81	- 0.66
p values				
CP foam vs placebo	CP solution vs placebo		CP foam vs CP solution	
0.0001	0.0001		0.9267	

PLAQUE THICKNESS Patients with score of 0 at day 15				
	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Score of 0 at day 15	41 (66%)	3 (10%)	41 (65%)	1 (3%)
p values				
CP foam vs placebo	CP solution vs placebo		CP foam vs CP solution	
< 0.0001	< 0.0001		1.0000	

ERYTHEMA				
Mean values	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Baseline	2.45	2.48	2.52	2.31
Day 15	0.84	1.97	0.95	1.94
Change from baseline	- 1.61	- 0.52	- 1.57	- 0.38
p values				
CP foam vs placebo	CP solution vs placebo		CP foam vs CP solution	
0.0001	0.0001		0.7050	

ERYTHEMA Patients with score of 0 at day 15				
	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Score of 0 at day 15	27 (44%)	2 (6%)	21 (33%)	0
p values				
CP foam vs placebo	CP solution vs placebo		CP foam vs CP solution	
< 0.0001	< 0.0001		0.2728	

SCALING				
Mean values	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Baseline	2.48	2.58	2.44	2.47
Day 15	0.47	1.81	0.83	1.84
Change from baseline	- 2.02	- 0.77	- 1.62	- 0.63
p values				
CP foam vs placebo	CP solution vs placebo		CP foam vs CP solution	
0.0001	0.0001		0.0142	

SCALING Patients with score of 0 at day 15				
	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Score of 0 at day 15	42 (68%)	3 (10%)	28 (44%)	0
p values				
CP foam vs placebo	CP solution vs placebo		CP foam vs CP solution	
< 0.0001	< 0.0001		0.0116	

SCALP PRURITUS				
Mean values	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Baseline	2.68	2.61	2.76	2.56
Day 15	0.58	1.71	0.75	1.94
Change from baseline	- 2.10	- 0.90	- 2.02	- 0.63
p values				
CP foam vs placebo	CP solution vs placebo		CP foam vs CP solution	
0.0001	0.0001		0.5741	

b. Investigator's global assessment.

The distribution of assessment categories and the percentage of patients with a global assessment of Clear or Almost Clear at day 15 were as follows.

Investigator's Global Assessment Day 15				
	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Completely clear	24 (39%)	1 (3%)	17 (27%)	0
Almost clear	22 (35%)	2 (6%)	23 (37%)	2 (6%)
Marked improvement	7 (11%)	3 (10%)	10 (16%)	5 (16%)
Moderate improvement	5 (8%)	5 (16%)	4 (6%)	10 (31%)
Slight improvement	4 (6%)	5 (16%)	6 (10%)	7 (22%)
No change	0	15 (48%)	3 (5%)	6 (19%)
Worse	0	0	0	2 (6%)

Patients evaluated as Clear or Almost Clear				
	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Clear or Almost Clear	46 (74%)	3 (10%)	40 (63%)	2 (6%)
p values				
CP foam vs placebo	CP solution vs placebo		CP foam vs CP solution	
< 0.0001	< 0.0001		0.2474	

The patient's assessment of response at day 15 was as follows.

Patient assessment of response Day 15				
	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Completely clear	14 (24%)	0	15 (24%)	0
Almost clear	26 (42%)	2 (6%)	21 (33%)	2 (6%)
Marked improvement	13 (21%)	5 (16%)	14 (22%)	5 (16%)
Moderate improvement	6 (10%)	7 (23%)	6 (10%)	4 (13%)
Slight improvement	2 (3%)	7 (23%)	5 (8%)	9 (28%)
No change	0	9 (29%)	2 (3%)	8 (25%)
Worse	0	1 (3%)	0	4 (13%)

c. Treatment Success.

Treatment Success was defined as an investigator's Global Assessment of Clear or Almost Clear, a plaque thickness score of 0, a scaling score of 0 or 1, and an erythema score of 0 or 1. The number and percent of patients with a Treatment Success at day 15 were as follows.

Patients evaluated as a Treatment Success at day 15.				
	Clobetasol foam	Vehicle foam	Clobetasol solution	Placebo solution
Treatment Success	39 (63%)	1 (3%)	36 (57%)	0
p values				
CP foam vs placebo	CP solution vs placebo		CP foam vs CP solution	
< 0.0001	< 0.0001		0.5851	

4) Safety evaluation: The adverse events of the skin and appendages in the Clobetasol foam group were 1 case each of dry skin, eczema, and skin hypertrophy. Results of the clinical laboratory tests did not indicate any safety concerns.

Reviewer's comments: In summary, the primary response variable was a Treatment Success, which was defined as an investigator's Global Assessment of Clear or Almost Clear, a plaque thickness score of 0, a scaling score of 0 or 1, and an erythema score of 0 or 1. In the percentage of patients with a Treatment Success at day 15 Clobetasol foam was significantly superior to its placebo, and was not significantly different from Clobetasol solution (Temovate Scalp Application).

For the clinical signs erythema, scaling, and plaque thickness, the results were analyzed as the mean change in scores from baseline to day 15, and as the percentage of patients with scores of 0 at day 15. In the mean change in scores from baseline and in the percentage of patients with scores of 0 for erythema and plaque thickness, Clobetasol foam was significantly superior to its vehicle, and was not significantly different from Clobetasol solution. For scaling, Clobetasol foam was significantly superior to its vehicle and to Clobetasol solution in the mean change in scores from baseline and in the percentages of patients with a score of 0.

In the percentage of patients evaluated as Clear or Almost Clear in the Investigator's Global Assessment, Clobetasol foam was significantly superior to its vehicle and was not significantly different from Clobetasol solution.

Adverse events were one case each of dry skin, eczema, and skin hypertrophy.

Statistical review

In her review of 3/8/00, Shahla Farr concludes that the analyses of Study CPCD.C.002 demonstrate that Olux Foam 0.05% is statistically significantly better than placebo in the treatment of corticosteroid-responsive dermatoses of the scalp at day 15. However, Olux Foam did not meet the criterion for non-inferiority to Clobetasol solution (Temovate Scalp Application).

The sponsor had been apprised at the pre-IND and pre-NDA meetings that for approval of the NDA it should be demonstrated that for the primary efficacy variable, Treatment Success, Olux Foam is statistically superior to its vehicle, and that Olux Foam is statistically not inferior to the comparator product, Clobetasol solution.

Although Olux Foam did not meet the criteria for statistical non-inferiority to Clobetasol solution, it is felt by this reviewer that the results show that the two products are comparable in effectiveness. The percentage of patients with a Treatment Success at day 15 was numerically higher in the Olux group than in the Clobetasol solution group. Olux foam was also numerically superior in the investigator's global assessment as Clear and Almost Clear, in the patient's assessment of response as Clear and Almost Clear, and in the percentage of patients with a score of 0 (clear) at day 15 for plaque thickness, erythema, and scaling.

Summary and evaluation

As was agreed in the pre-IND and pre-NDA meetings, the following studies have been provided to demonstrate the safety and efficacy of Clobetasol Propionate Foam 0.1% (Olux Foam): a vasoconstrictor assay, an HPA axis suppression study, and a multicenter, controlled study designed as a four arm comparison of Clobetasol Propionate Foam, the foam vehicle, the reference product Clobetasol Propionate Solution (Temovate Scalp Application), and the solution vehicle. The requirement for phototoxicity and photosensitization studies is waived, as the product does not absorb light in the 280 - 700 nm range, and the requirement for other Phase 1 studies is waived, as these were performed on Luxiq Foam under NDA 20-934 (Connectics).

In the vasoconstrictor assay Clobetasol Foam was shown to have a potency which was intermediate among the potencies of the marketed Temovate formulations, which classifies the product as a super-high potency corticosteroid.

In the HPA axis suppression study applications of 3.5 gm of Clobetasol Foam or Temovate Ointment were made twice daily for 14 days to areas of dermatitic skin comprising at least 20% of the body surface area in patients with psoriasis or atopic dermatitis. Abnormal cortisol levels were seen in several subjects treated with either Clobetasol foam or Temovate ointment; the frequency and the magnitude of the decrease in levels from baseline were similar in the Clobetasol and Temovate groups.

The clinical effectiveness study was a multicenter, double blind, randomized comparison of Clobetasol foam, the foam vehicle, Clobetasol solution (Temovate scalp application), and the solution vehicle in patients with moderate to severe scalp psoriasis. Applications of the test products were made twice

daily to the scalp for 14 days.

The efficacy parameters evaluated were scoring of the clinical signs erythema, scaling, and plaque thickness on scales of from 0 to 4 at baseline and on day 15, and an Investigator's Global Assessment of the disease status at day 15. The primary efficacy variable was the proportion of patients with a Treatment Success, which was defined as an Investigator's Global Assessment of Cleared or Almost Cleared, a plaque thickness score of 0, an erythema score of 0 or 1, and a scaling score of 0 or 1.

In the percentage of patients with a Treatment Success at day 15, Clobetasol foam was significantly superior to its vehicle and was not significantly different from Clobetasol solution. Olux Foam did not meet the criteria for statistical non-inferiority to Clobetasol solution; however, it is felt by this reviewer that the results show that the two products are comparable in effectiveness. The percentage of patients with a Treatment Success at day 15 was numerically higher in the Olux group than in the Clobetasol solution group. Olux foam was also numerically superior in the investigator's global assessment as Clear and Almost Clear, in the patient's assessment of response as Clear and Almost Clear, and in the percentage of patients with a score of 0 (clear) at day 15 for plaque thickness, erythema, and scaling.

Adverse events with Clobetasol foam were one case each of dry skin, eczema, and skin hypertrophy.

<u>Conclusions:</u> It is felt that the studies provided in the NDA adequately demonstrate the safety and effectiveness of Clobetasol Propionate Foam for the proposed labeling indication.

<u>Recommendations:</u> It is recommended that Clobetasol propionate Foam 0.05% (Olux Foam) be approved for short term topical treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp.

/S/

Phyllis A. Huene, M.D. 3/29/00

Cc: Orig NDA 21-142
HFD-540 Division file
HFD-540/Wilkin
HFD-540/Okun
HFD-540/Huene
HFD-540/Bhatt
HFD-540/Cintron
HFD-540/Pappas
HFD-540/Brown
HFD-540/Farr
HFD-540/Bashaw

NO DFS

/S/

4/19/00 Concur. Please see Team Leader Addendum

See TL Addendum

4/22/00

NDA 21-142: Team Leader Addendum

The medical reviewer has recommended approval of NDA 21-142 (a decision with which the team leader concurs), despite the fact that a statistical analysis of the primary efficacy variable could not rule out at the 95% confidence level that clobetasol propionate foam 0.05% was not inferior to the comparator (Temovate Scalp Application), which was a pre-specified criterion for approval of this 505(b)(2) application. A thorough explication of the clinical rationale underlying this decision is therefore warranted.

The primary efficacy variable prespecified in the protocol for the pivotal clinical study (CPCD.C.002) was the Investigator's Global Assessment. In the protocol, outcomes in the Investigator's Global Assessment were dichotomized such that patients classified as "cleared" or "almost cleared" were classified as successes while all others were classified as failures. The definition of the "almost cleared" category ["very significant clearance (about 90%); however, patchy remnants of dusky erythema and/or sparse fine scaling may be present"] has a dynamic component. Agency requested at the pre-NDA meeting that the primary efficacy variable be redefined so that success would be expressed in static terms. To this end, in the NDA treatment success was defined as Investigator's Global Assessment of completely clear or almost clear, and a plaque thickness score of 0, and a scaling score of 0 or 1, and an erythema score of 0 or 1. This endpoint was specified after the pivotal study was completed; thus, the clinical study was not designed with this endpoint in mind to test the hypothesis of non-inferiority of the clobetasol propionate foam to the comparator. Consequently, it is possible that the study was underpowered relative to this revised endpoint.

It was specified at the pre-IND meeting that to demonstrate non-inferiority of the active foam to the active solution, a 95% confidence interval for the difference between foam and solution should have the following characteristics: that the upper bound of the confidence interval should not fall below zero, and that at the lower bound of the confidence interval, the foam should not be 10% worse than the solution. In clinical study CPCD.C002, the bounds of the 95% confidence interval for the difference between foam and solution is (-0.11,.25). Thus, the study failed to demonstrate non-inferiority by the narrowest possible margin (1%).

Although at the lower bound of the 95% confidence interval, active foam is more than 10% worse than active solution, sufficient information in the NDA submission exists to indicate that the likelihood that the efficacy of foam is inferior to solution is small. This conclusion is based upon the following considerations:

- The point estimates of treatment success for active foam (63%) and active solution (57%) suggest that foam is <u>superior</u> to solution.
- As the medical officer has outlined in her review, outcomes for patients receiving active foam were numerically superior to outcomes for patients receiving active solution for each of the following secondary efficacy variables: change in mean plaque thickness, percentage of patients with plaque thickness score of zero at end of treatment, change in mean erythema, percentage of patients with erythema score of

zero at end of treatment, change in mean scaling, percentage of patients with scaling of zero at end of treatment, and change in mean pruritus score.

- In contrast, there was no secondary efficacy variable for which outcomes for patients receiving active solution was numerically superior to outcomes for patients receiving active foam.
- In clinical study CPCD.C.001 (the vasoconstrictor study), active foam induced more intense vasoconstriction (as measured by change in the $AUEC_{0-30}$) than did the active solution when foam and solution were applied for 0.5 hours or for 3 hours to test sites on human forearm skin. While there is not a strict correlation between potency and efficacy of a corticosteroid, these study results are not inconsistent with the foam having non-inferior clinical efficacy.

/S/ 4/20/00

Martin M. Okun, M.D., Ph.D.
Dermatology Team Leader

cc:
Archival NDA 21-142
HFD-540
HFD-540/Division Director/Wilkin
HFD-540/Dermatology Medical Reviewer/Huene
HFD-725/Biostatistics Team Leader/Al-Osh
HFD-725/Biostatistician/Farr
HFD-880/Biopharm/Bashaw
HFD-540/Pharm/Brown
HFD-540/Chemistry/Pappas
HFD-540/Project Manager/Cintron
HFD-540/Project Manager/Bhatt
NO DFS

As above. In addition the equivalence limits are conservative given the response rate of the reference drug. QJ 4/22/00

Number of Pages Redacted 11

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Draft Labeling
(not releasable