CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-644

MEDICAL REVIEW

Medical Officer's Memo to File Re: NDA 21-644

Drug: CLOBEX™ Shampoo, 0.05%
Sponsor: Galderma
Pharmacologic Category: psoriasis product
Proposed Indication: moderate to severe scalp psoriasis
Project Manager: Jacqueline Smith
Reviewer: Jill Lindstrom, MD

This memo is written to identify two typographical errors on the Labeling Review for NDA 21-644, which was entered into DFS on January 13, 2004.

1. The Title of the above review incorrectly states the NDA number as 20-664; the correct NDA number is 21-644.

2. The header beginning on page 2 should be N 21-644 rather than N 20-539.

Jill Lindstrom, M.D.
Medical Officer/Dermatology

For concurrence:
HFD-540/TL/LukeM
HFD-540/aDD/KukichS

In DFS: January 15, 2004

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/s/

Jill Lindstrom
1/15/04 12:15:41 PM
MEDICAL OFFICER

Markham Luke
1/15/04 12:35:03 PM
MEDICAL OFFICER

Stanka Kukich
1/16/04 02:52:55 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 20-664

Labeling Review

Drug: CLOBEX™ Shampoo, 0.05%
Sponsor: Galderma
Pharmacologic Category: psoriasis product
Proposed Indication: moderate to severe scalp psoriasis

Review start date: January 13, 2004
Review completion date: January 13, 2004
Project Manager: Jacqueline Smith
Reviewer: Jill Lindstrom, MD

Background and Regulatory History: The Sponsor submitted a New Drug Application for CLOBEX™ (clobetasol propionate) Shampoo, 0.05%, on May 6, 2003. As of this date, all reviews have been completed and the approval letter is pending. Internal division labeling meetings were held on December 11, 2003 and December 15, 2003. Teleconferences with the Sponsor to negotiate changes to the label were held on December 17, 2003 and December 30, 2003.

Summary: The major changes requested by FDA and agreed to by the Sponsor include the reformatting of the results table in the Clinical Studies section so that the data from the two pivotal studies was presented in parallel; alteration of the Indications and Usage section to reflect approval for use in patients 18 years of age and older; restatement of the risk of hypothalamic-pituitary-adrenal axis suppression to reflect FDA analysis of the data; and inclusion of a table listing selected adverse events in the Adverse Reactions section. Wording of various sections of the Package Insert and Patient Package Insert was synchronized with the CLOBEX™ Lotion labeling.

Comments for the Sponsor: none

Recommended Regulatory Action: approval of the label, of which the Package Insert and Patient Package Insert are attached below.

Jill Lindstrom, M.D.
Medical Officer/Dermatology

For concurrence:
HFD-540/TL/LukeM
HFD-540/aDD/KukichS

In DFS: January 13, 2004

14 page(s) of draft labeling has been removed from this portion of the review.

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/s/

Jill Lindstrom
1/13/04 05:23:32 PM
MEDICAL OFFICER

Markham Luke
1/14/04 12:56:08 PM
MEDICAL OFFICER
Concur with Labeling as modifed post-discussion with Sponsor.

Stanka Kukich
1/15/04 08:45:45 AM
MEDICAL OFFICER

CLINICAL REVIEW

Medical Officer's Review of NDA 21-644
Original

Medical Officer: Jill Lindstrom, M.D.
DDDDP HFD-540

NDA #21-644

Submission date: 5/2/03
CDER Stamp date: 5/8/03
Assignment date: 6/2/03
Review began: 6/11/03
Review completed: 11/30/03
Revised: 12/30/03

Sponsor:	Galderma Laboratories, L.P. 14501 North Freeway Fort Worth, TX 76177 USA
Generic name:	Clobetasol Propionate
Trade name:	Clobex
Chemical name:	Clobetasol Propionate
Pharmacologic Category:	Corticosteroid, topical
Indication:	moderate to severe scalp psoriasis
Dosage Form(s):	Shampoo
Route of Administration:	Topical

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Clinical Review for NDA 21-644

Executive Summary

I. Recommendations

A. Recommendation on Approvability

This reviewer recommends that Clobetasol Propionate Shampoo, 0.05% be approved for the treatment of moderate to severe psoriasis of the scalp in subjects 18 years of age and older. Clinical review of NDA 21-644 reveals that Clobetasol Propionate Shampoo, 0.05% is effective and has an acceptable safety profile in this population when applied for 15 minutes once daily for up to four weeks.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The following Phase 4 commitments are recommended:

1. Conduct an HPA axis suppression study in no less than 60 evaluable subjects (30 adults and 30 adolescents 12 to 17 years of age) using cosyntropin stimulation testing conducted as labeled with stimulated serum cortisol levels at 30 minutes obtained at baseline and 4 weeks. Enrolled subjects should have at least 25% scalp surface area involvement and normal baseline stimulated cortisol levels, and any suppressed subjects should be followed to recovery.
2. Conduct a safety and efficacy study in non-Caucasian subjects.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Clobetasol Propionate Shampoo, 0.05% is a super-high potent topical corticosteroid in a shampoo vehicle intended for 15 minute application once daily for up to four weeks for the treatment of moderate to severe scalp psoriasis. To achieve this indication, the Sponsor conducted five Phase 2 and five Phase 3 studies in subjects with moderate to severe scalp psoriasis. The Phase 2 program consisted of a proof-of-concept efficacy study, two dose-range finding studies and two HPA axis suppression studies involving a total of 158 subjects, 107 of whom were exposed to Clobetasol Propionate Shampoo, 0.05%. The Phase 3 program entailed two pivotal trials involving 290 total subjects, of whom 194 were randomized to received active drug, and three non-pivotal Phase 3 studies involving 455 subjects of whom 259 received active drug. In Phases 2 and 3 combined, 558 subjects received treatment with Clobetasol Propionate Shampoo, 0.05%. All studies enrolled subjects with moderate to severe scalp psoriasis.

B. Efficacy

In NDA 21-644, the Sponsor demonstrated that Clobetasol Propionate Shampoo, 0.05% is superior to vehicle in the treatment of moderate to severe scalp psoriasis in subjects 12 years of age and older. This reviewer's conclusion of efficacy relies primarily on analysis of data from two pivotal Phase 3 trials, but the three non-pivotal Phase 3 studies were also supportive. All of the Phase 3 studies enrolled subjects with moderate to severe scalp psoriasis. The two pivotal trials and one non-pivotal study enrolled both adults and adolescents, and the remaining two non-pivotal studies enrolled adults only.

Both pivotal trials were adequate and well controlled: they were of sound design, sufficiently powered, multi-center, randomized, vehicle-controlled, and double blind. The primary efficacy variable, success rate, was based on Global Severity Scale dichotomized to success or failure. The Global Severity Scale is a static six-point (0–5) integer scale for investigator global assessment, in which a score of 0 or 1 corresponds to success (clear or almost clear). A score of three, or moderate, was necessary for enrollment, so subjects had to improve by at least two units to achieve success. Secondary efficacy variables included erythema, scaling, plaque thickening and pruritus. The primary endpoint was four weeks, and the ITT (LOCF) population was specified as primary in the statistical analysis plan.

In both pivotal trials, the proportion of subjects who achieved success at week 4 in the ITT (LOCF) population was significantly greater in the Clobetasol Propionate Shampoo, 0.05% group than the Vehicle Shampoo group. In pivotal trial **18075**, 28.3% of subjects in the Clobetasol Propionate Shampoo, 0.05% achieved success versus 10.2% of subjects in Vehicle Shampoo group, for a p-value of 0.012. In pivotal trial **18076**, 42.1% of subjects in the Clobetasol Propionate Shampoo, 0.05% achieved success versus 2.1% of subjects in Vehicle Shampoo group, for a p-value of <0.001. In both pivotal trials, the proportions of subjects with success in the individual secondary endpoints of scaling, erythema, plaque thickness and pruritus were significantly greater in the Clobetasol Propionate Shampoo, 0.05% group than the Vehicle Shampoo group.

These nearly identical trials resulted in different rates of success, although the reason for this difference is not clear. Disease severity at enrollment was similar for both groups, and the amount of medication applied was also similar (subjects in **18075** actually averaged 1.8 gms more Clobetasol Propionate Shampoo, 0.05% use per week than subjects in **18076**). The centers with highest efficacy from both trials were evaluated by DSI and found to be without deficiency.

The three non-pivotal studies were active-controlled [calcipotriol solution, Polytar Liquid®, and Dermoval (clobetasol propionate, 0.05%) Gel, respectively], and one (Dermoval Gel) was also vehicle-controlled. The primary efficacy measures in the non-pivotal studies were a static investigator global assessment scale, similar to the scale used in the pivotal trials but not dichotomized, and a total severity score, computed from the individual secondary endpoints of erythema, scaling and plaque thickening. The primary endpoint was four weeks. Although Clobetasol Propionate Shampoo, 0.05% was found non-inferior to calcipotriol solution, Polytar Liquid® and Dermoval Gel™, and superior to calcipotriol solution and Polytar Liquid®, the lack of vehicle arms (calcipotriol solution and Polytar Liquid®), absence of subject blinding, and

large delta for non-inferiority are weakness that compromise the contribution of these studies to the finding of efficacy. Clobetasol Propionate Shampoo, 0.05% was also found to be superior to Vehicle Shampoo in the study with Dermoval Gel™ as active comparator, which substantively supports the efficacy findings of the pivotal trials.

C. Safety

In addition to the five Phase 3 studies, five early phase studies were also included in the safety review: **18032**, a contact irritation and sensitization study; **2577** and **2591**, dose-range finding studies; and **2620** and **18070**, HPA axis suppression studies. The subjects in **18032** were only exposed to Vehicle Shampoo, so they are not included in the safety population.

Nine hundred subjects were included in the safety population, 558 of who received Clobetasol Propionate Shampoo 0.05%. Of these, 468 were enrolled in studies of 4 weeks treatment duration. Four weeks is sufficient duration of exposure for the development of HPA axis suppression, ocular hypertension, cutaneous atrophy or telangiectasia to occur.

Two Phase 2 studies, **18070** and **2620**, evaluated the potential of clobetasol propionate shampoo to suppress the HPA axis in subjects with scalp psoriasis. Both of these studies had design flaws: enrollment of subjects with abnormal baseline HPA axes, suboptimal sampling times, and weekly stimulation of subjects' HPA axes (**2620** only). Study **18070** enrolled thirteen adolescents (PP population = 12), five of who demonstrated HPA axis suppression. Study **2620** enrolled 14 adults in the Clobetasol Propionate Shampoo, 0.05% group, but the study was so severely flawed as to make the data uninterpretable. The high incidence of HPA axis suppression among adolescents warrants further investigation in Phase 4, clear documentation of the risk in labeling, and restriction of use to adults for not longer than 4 weeks.

No serious adverse events were attributed to study drug use. A serious adverse event, surgery of the internal meniscus of the right knee was reported for one subject in the Clobetasol Propionate Shampoo, 0.05% group. The percentages of subjects with AEs and AEs attributable to study drug were both higher for Vehicle Shampoo group than for Clobetasol Propionate Shampoo, 0.05% group. The body system with the highest proportions of both AEs and AEs related to study drug was Skin and Appendages. The two most frequent AEs related to study drug were skin discomfort and pruritus; both were more frequent in the Vehicle Shampoo group (12.6% and 5.5%, respectively) than the Clobetasol Propionate Shampoo, 0.05% group (4.5% and 0.5% respectively). The higher incidence of skin discomfort and pruritus in the Vehicle Shampoo group suggests that vehicle ingredients (such as coco-betaine or sodium laureth sulfate, known cutaneous irritants) rather than the drug substance provoked the irritation, and the drug moiety mollified or prevented the vehicle-induced irritation in the active group.

Ocular safety was assessed in study **2620**. No clinically significant changes were noted in intraocular pressure, slit lamp examination or visual acuity in either treatment group throughout the study. In the pivotal trials, one subject in the Clobetasol Propionate Shampoo, 0.05% group reported eye irritation, which resolved after one day.

Three studies, **2620**, **2638** and **2648**, actively assessed for cutaneous atrophy and telangiectasia. One subject in the Clobetasol Propionate Shampoo, 0.05% group developed "mild" atrophy at study end. Two subjects in the Clobetasol Propionate Shampoo, 0.05% developed "mild" telangiectasia during the course of treatment. The risk of atrophy and telangiectasia is addressed in standard language in labeling for topical corticosteroids.

In study **18032**, a standard, repeat insult patch test study was performed using vehicle shampoo in closed patches and open application to determine the risk of contact irritation or sensitization. Fourteen of 217 subjects developed greater than no or mild erythema from closed application during the irritation/induction phase, but none from open application. The absence of an irritancy signal with undiluted preservative-containing Vehicle Shampoo in open application suggests that occlusion itself magnified the irritancy seen with the shampoo dilutions. No subjects demonstrated a response indicative of sensitization during the challenge phase.

D. Dosing

Dose range finding studies investigated ranges in duration of application (2.5 to 15 minutes) and condition of application (wet versus dry scalp). A trend toward increased efficacy was noted with longer application, independent of conditions of application. Because of greater subject convenience, application to dry scalp was selected as the condition of use, with duration for 15 minutes. All other formulations of clobetasol propionate marketed in the US are at 0.05% concentration and dosed twice daily. No concentrations other than 0.05% were studied for the shampoo vehicle, nor were dosing frequencies other than once daily.

The Sponsor has proposed limiting the duration of use of Clobetasol Propionate Shampoo, 0.05% to 4 weeks. In light of the HPA axis suppression identified in study **18070**, this limitation is prudent. All other marketed formulations of clobetasol propionate restrict the quantity of use to 50 gms/week. The Sponsor intends to package Clobetasol Propionate Shampoo, 0.05% in 4 fl oz/ [redacted] bottles, [redacted]

E. Special Populations

Clobetasol Propionate Shampoo, 0.05% appears to have comparable safety and efficacy in both genders. It appears to be effective for adolescents and adults, although on subgroup analysis statistical significance for the primary efficacy variable, success rate, was not achieved (p=0.055) for subjects 65 years of age and older. A high incidence of HPA axis suppression was seen among adolescents.

Subgroups analysis by race using the combined data from the two pivotal trials (**18075** and **18076**) for the primary efficacy endpoint, Success Rate at week 4 for the ITT population, revealed that only the Caucasian only and Caucasian + non-Caucasian (all races) subgroups achieved statistical significance. The non-Caucasian subgroup failed to achieve significance for success rate (p=0.462). [redacted]

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Clobex™ (clobetasol propionate) Shampoo, 0.05%, is a super-high potent topical corticosteroid with a proposed indication [redacted] moderate to severe forms of scalp psoriasis [redacted] The shampoo is intended for short contact application: once daily for 15 minutes (followed by rinsing) for up to four weeks

B. State of Armamentarium for Indication(s)

Clobetasol propionate is currently marketed in various formulations including lotion, cream, emollient cream, ointment, gel, solution, scalp application, and foam. The solution, scalp application and foam products are indicated for the short-term treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp, which encompasses the indication of psoriasis. Clobetasol propionate is not currently available in a shampoo vehicle. Capex® shampoo (fluocinolone acetonide) is a medium-potency corticosteroid indicated for the topical treatment of seborrheic dermatitis of the scalp.

C. Important Milestones in Product Development

PreIND/End-of-Phase 2 Meeting – January 13, 2000

- FDA concurred with the Sponsor that clobetasol 0.05% shampoo is suitable for short contact treatment (15 minute application) once daily for moderate to severe forms of [redacted]
- Preclinical and clinical data support application over 4 weeks, but a 24-week extension phase would require HPA axis suppression studies as well as clinical safety and efficacy data.
- The primary endpoint should be the proposed global severity scale dichotomized to success or failure at the end of the treatment period.

PreNDA Meeting – March 8, 2002

- Phase 3 clinical trials qualify application for submission under 505(b)(1), or 505(b)(2) if no reference product is used to support the application and the basis for 505(b)(2) is published literature.
- The adequacy of study **18070** for adrenal suppression, which enrolled only 12 subjects, will be a review issue.
- Sponsor was requested to provide UV absorption profiles of the ingredients in their product in the NDA submission; waiver of phototoxicity and photoallergenicity studies will be based on provision of this information.

IND 60,934/SN:000 -- submitted September 8, 2000 -- Special Protocol Assessment

- The ITT population should be used to establish superiority over vehicle.
- The number of secondary endpoints will require adjustment for multiplicity.

IND 60,934/SN:004 -- submitted December 6, 2000

- It is unclear in the protocol how surface area involvement can be accurately estimated on the scalp
- Protocol definition of HPA axis suppression is too restrictive; abnormality in any single parameter (pre-stimulation or post-stimulation) indicates suppression.

D. Other Relevant Information

Clobetasol propionate 0.05% shampoo is not registered in any foreign country at this time nor has the drug product been withdrawn from marketing in any foreign country for any reason. This New Drug Application is the first filing for clobetasol propionate shampoo, 0.05% in the world; further submission in Europe is planned.

E. Important Issues with Pharmacologically Related Agents

Clobetasol propionate is a Class 1, or super-high potent, topical corticosteroid. The main safety concern with super-high potent topical corticosteroids is HPA axis suppression. To reduce this risk, treatment with other clobetasol propionate formulations is restricted to 50 gms per week use for — 4 weeks duration. Clobetasol propionate 0.05% shampoo is the first formulation to use short-contact application, rinsing off the product after 15 minutes. There is not a shampoo formulation in this class.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Chemistry

The Sponsor describes Clobetasol Propionate Shampoo, 0.05% as a, ——— The proposed drug product contains clobetasol propionate, USP, 0.05% — (0.5 mg/g) ——— shampoo dosage form."[1] Clobetasol Propionate Shampoo, 0.05% will be packaged in a commercial trade size 4 fl oz bottle and a physician sample size 0.5 fl oz bottle. The composition of the to-be-marketed formulation, ——— is described in Table 1, below. This formulation was used in the two pivotal trials, three non-pivotal safety and efficacy studies, two HPA axis suppression studies, vasoconstrictor assay study and the topical safety study. A second formulation, ———, which differed only by the additional ingredient ——— ———, was used concurrently in the topical safety study.

[1] Sponsor's NDA sumission, Volume 1.2, p.39.

Table 1: Formulation

Ingredients	Percent (w/w)	Per gram
Clobetasol propionate, USP	0.05%	
Alcohol, USP		
Coco-betaine		
Sodium laureth sulfate		
Polyquaternium-10		
Sodium citrate dihydrate, USP		
Citric acid monohydrate, USP		
Purified water, USP		

Source: Sponsor's NDA submission, Volume 1.2, page 39

The reader is referred to the review of Dr. Saleh Turujman, chemistry reviewer, which was not available at the time of completion of this review.

III. Human Pharmacokinetics and Pharmacodynamics

The Sponsor conducted a vasoconstrictor study (1.CG.03.SPR.**2618**) to determine the skin blanching capacity of clobetasol propionate shampoo, 0.05% compared to its vehicle, two marketed formulations of clobetasol propionate (Temovate® Scalp Application, 0.05% and Temovate® Cream, 0.05%) and a marketed formulation of betamethasone dipropionate cream (Diprolene® Cream, 0.05%). Twelve healthy male subjects were enrolled. Per the Sponsor's summary, Clobetasol Propionate Shampoo, 0.05% produced "significantly less vasoconstriction than the Temovate® products but significantly more vasoconstriction than Diprolene® Cream, categorizing Clobetasol Propionate Shampoo, 0.05% as a superpotent corticosteroid."[2]

The Sponsor conducted two HPA axis suppression studies in adolescents and adults, respectively, with moderate to severe scalp psoriasis. These studies are reviewed in the safety section of this review.

The reader is referred to the clinical pharmacology and biopharmaceutics review of Dr. Chandra S. Chaurasia for further detail; Dr. Chaurasia's review was not available at the time of completion of this review.

IV. Description of Clinical Data and Sources

A. Overall Data

This review was based on data contained in the Sponsor's NDA submission, volumes 1.1, 1.2, and 1.21 through 1.53. These NDA volumes contained data from studies conducted by the Sponsor. The Cortrosyn label was used to determine the criteria for normal adrenal response to cosyntropin stimulation. Additional data sources include tables from the biostatistician, Dr. Steve Thomson (full biostatistics review not available at the time of completion of this review) and the clinical pharmacology and toxicology review of Dr. Paul Brown.

B. Tables Listing the Clinical Trials

[2] Sponsor's NDA submission, vol. 1.2, p121-2.

Table 2: Phase 1 Studies

Study Number	Study Design	Treatment	Number of Subjects	Treatment Duration
1.CG.03.SPR.**2618**	Evaluation of vasoconstriction capacity	Clobetasol Propionate Shampoo 0.05% Temovate® Cream 0.05% Temovate® Scalp Application 0.05% Diprolene® (betamethasone dipropionate) Cream 0.05% Vehicle Shampoo	12	15-minute application on two days
1.GUS.04.SPR.**18032**	Evaluation of contact irritation sensitization potential	Vehicle Shampoo Formulations Petrolatum	219	23-day treatment/6-week study duration

Table 3: Phase 2 Studies

Study Number	Study Design	Treatment	Number of Subjects	Treatment Duration
1.CG.03.SPR.**2620**	Evaluation of ocular safety and HPA axis suppression potential: Single-center, randomized, investigator-masked, active-controlled comparison in subjects with scalp seborrheic dermatitis or scalp psoriasis	Clobetasol Propionate Shampoo 0.05% Once daily for scalp psoriasis, twice weekly for seborrheic dermatitis 15 minutes on dry scalp Dermoval® (clobetasol propionate) Gel 0.05% Once daily on dry scalp	52	4 weeks
RD.06.SPR.**18070**	Evaluation of HPA axis suppression potential: Multicenter, open-label study in subjects 12 to 17 years old with scalp psoriasis	Clobetasol Propionate Shampoo 0.05% Once daily, 15 minutes on dry scalp	13	4 week treatment then 2-week follow-up
1.CG.03.SPR.**2555**	Pilot study evaluation of efficacy and safety: Single-center, randomized, double-blind cross-over study in subjects with scalp psoriasis	Clobetasol Propionate Shampoo 0.05% Vehicle Shampoo 10 minutes on wet scalp Once daily for 2 weeks then crossed over to the other treatment for 2 weeks	12	4 weeks (2 weeks on each treatment)
1.CG.03.SPR.**2577**	Evaluation of efficacy and tolerance: Single-center, randomized, investigator-masked, active- and vehicle-controlled comparison in subjects with scalp psoriasis	Clobetasol Propionate Shampoo 0.05% Once daily, 2.5 min on wet scalp Once daily, 5 min on wet scalp Once daily, 10 min on wet scalp Vehicle Shampoo Once daily, 10 min on wet scalp Dermoval® Gel, 0.05% Once daily on dry scalp	60	2-week treatment then 2-week post-treatment follow-up
1.CG.03.SPR.**2591**	Evaluation of efficacy and tolerance: Multi-center, randomized, investigator-masked, active-controlled comparison in subjects with scalp psoriasis	Clobetasol Propionate Shampoo, 0.05% Once daily, 10 min on dry scalp Once daily, 10 min on wet scalp Once daily, 15 min on dry scalp Daivonex® (calcipotriol) Scalp Solution, 0.05% 4 mL twice daily on dry scalp	59	3-week treatment period 3-week post-treatment follow-up period

Table 4: Phase 3 Studies

Study Number	Study Design	Treatment	Number of Subjects	Treatment Duration
RD.06.SPR.**18075**	Multi-center, randomized, vehicle-controlled, double-blind, parallel group comparison	Clobetasol Propionate Shampoo, 0.05% 15 min on dry scalp before rinsing qd Vehicle Shampoo 15 min on dry scalp before rinsing qd	99 49	4-week treatment then 2-week post-treatment follow-up
RD.06.SPR.**18076**	Multi-center, randomized, vehicle-controlled, double-blind, parallel group comparison	Clobetasol Propionate Shampoo, 0.05% 15 min on dry scalp before rinsing qd Vehicle Shampoo 15 min on dry scalp before rinsing qd	95 47	4-week treatment then 2-week post-treatment follow-up
RD.03.SPR.**2638**	Multi-center, randomized, active-controlled, investigator-blind, parallel group comparison	Clobetasol Propionate Shampoo, 0.05% 15 min on dry scalp before rinsing qd Daivonex® Solution on dry scalp without rinsing BID	76 75	4-week treatment
RD.03.SPR.**2648**	Multi-center, randomized, active-controlled, investigator-blind, parallel group comparison	Clobetasol Propionate Shampoo, 0.05% 15 min on dry scalp before rinsing qd Polytar® Liquid Shampoo on wet scalp BID	121 41	4-week treatment
RD.03.SPR.**2665**	Multi-center, randomized, active- and vehicle-controlled, investigator-blind, parallel group comparison	Clobetasol Propionate Shampoo, 0.05% 15 min on dry scalp before rinsing qd Vehicle Shampoo 15 min on dry scalp before rinsing qd Dermoval® Gel on dry scalp without rinsing qd	63 20 61	4-week treatment

C. Postmarketing Experience

This is a new formulation of clobetasol propionate and is not approved in any country

V. Clinical Review Methods

A. How the Review was Conducted

The two pivotal Phase 3 trials were reviewed individually and in detail with regard to both efficacy and safety. The three non-pivotal Phase 3 trials served a supportive role in the efficacy evaluation, but were integral to the safety evaluation. All of the Phase 2 and 3 studies for scalp psoriasis were included in the Integrated Analysis of Safety. The Phase 1 cutaneous safety study was reviewed for safety, but the drug exposure in this trial was minimal.

B. Overview of Materials Consulted in Review

C.

The Sponsor's NDA submission, the Cortrosyn® label and tables generated by Dr. Steve Thomson were used for this portion of the review.

D. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations (DSI) was asked to investigate the site with highest efficacy on subgroup analysis in each of the pivotal trials: Dr. Mark Lebwohl (RD.06.SPR.**18075**) and Dr. Michael Jarratt (RD.06.SPR.**18075**). Both sites were found to have conducted their clinical investigation for the respective trials in compliance with applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. The data from subjects at both sites was found acceptable for inclusion in the analysis of NDA 21-644.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials did seem to be conducted with accepted ethical standards and the sponsor states such in the NDA submission.

E. Evaluation of Financial Disclosure

The Sponsor states that during the course of development, financial disclosure forms were collected from each investigator and sub-investigator who participated in a "covered clinical study" as defined in 21 CFR Part 54.2 (e). The Sponsor further stated that on these financial disclosure forms, none of the investigators reported that they had received funding from the Applicant outside of the current clinical study.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In two pivotal trials, Clobetasol Propionate Shampoo, 0.05% was superior to vehicle for the treatment of moderate to severe scalp psoriasis in subjects 12 years of age and older. Both pivotal trials were adequate and well controlled. The primary efficacy variable in the pivotal trials, success rate for the ITT population, was based on a static investigator global assessment scale dichotomized to success or failure. The primary endpoint was four weeks. In both pivotal trials, the proportion of subjects who achieved success at week 4 was significantly greater in the Clobetasol Propionate Shampoo, 0.05% group than the Vehicle Shampoo group. In both pivotal trials, the secondary endpoints of scaling, erythema, plaque thickness and pruritus were significantly better in the Clobetasol Propionate Shampoo, 0.05% group than the Vehicle Shampoo group.

The three non-pivotal studies were active-controlled [calcipotriol solution, Polytar Liquid®, and Dermoval (clobetasol propionate, 0.05%) Gel, respectively], and one (Dermoval Gel) was also vehicle-controlled. The primary efficacy measures in the non-pivotal studies were a static investigator global assessment scale, similar to the scale used in the pivotal trials but not dichotomized, and a total severity score, computed from the individual secondary endpoints of erythema, scaling and plaque thickening. The primary endpoint was four weeks. Although Clobetasol Propionate Shampoo, 0.05% was found non-inferior to calcipotriol solution, Polytar Liquid® and Dermoval Gel™, and superior to calcipotriol solution and Polytar Liquid®, the lack of vehicle arms (calcipotriol solution and Polytar Liquid®), absence of subject blinding, and large delta for non-inferiority are weakness that dilute the contribution of these studies to the finding of efficacy. Clobetasol Propionate Shampoo, 0.05% was also found to be superior to Vehicle Shampoo in the study with Dermoval Gel™ as active comparator, which substantively supports the efficacy findings of the pivotal trials.

B. General Approach to Review of the Efficacy of the Drug

The efficacy evaluation of Clobetasol Propionate Shampoo 0.05% is based on a detailed review of the two pivotal Phase 3 trials, RD.06.**18075** and RD.06.**18076**, and supported by a more brief review of three non-pivotal Phase 3 trials, RD.03.SPR**2638**, RD.03.SPR**2648** and RD.03.SPR**2665**. Table 5 provides an overview of these trials.

Table 5: Overview of Phase 3 Trials

Study Number	Pivotal Trials		Non-pivotal Trials		
	RD.06.SPR.18075	**RD.06.SPR.18076**	RD.03.SPR.**2638**	RD.03.SPR.**2648**	RD.03.SPR.**2665**
Population	Scalp Psoriasis	Scalp Psoriasis	Scalp Psoriasis	Scalp Psoriasis	Scalp Psoriasis
Objective	Safety and Efficacy	Safety and Efficacy	Safety and Efficacy	Safety and Efficacy	Safety and Efficacy
Formulations and Treatment Dose(s)	-Clobetasol Propionate Shampoo 0.05% -Vehicle Shampoo Once daily, 15 minutes on dry scalp before rinsing	-Clobetasol Propionate Shampoo 0.05% -Vehicle Shampoo Once daily, 15 minutes on dry scalp before rinsing	-Clobetasol Propionate Shampoo 0.05% Once daily, 15 minutes on dry scalp before rinsing -Daivonex® Solution (calcipotriol 0.005%) Twice daily, on dry scalp without rinsing	-Clobetasol Propionate Shampoo 0.05% Once daily, 15 minutes on dry scalp before rinsing -Polytar Liquid® Shampoo (tar blend 1%) Twice weekly, on wet scalp before rinsing	-Clobetasol Propionate Shampoo 0.05% Once daily, 15 minutes on dry scalp before rinsing -Vehicle Shampoo Once daily, 15 minutes on dry scalp before rinsing Dermoval® Gel (clobetasol propionate 0.05%) Once daily, on dry scalp without rinsing
Enrollment	142 adults and 6 adolescents	138 adults and 4 adolescents	147 adults and 4 adolescents	162 adults	144 adults
Duration of Treatment	4-week treatment 2-week follow-up	4-week treatment 2-week follow-up	4-week treatment	4-week treatment	4-week treatment
Number of Visits	4	4	3	3	3
Measurement Timepoints	Baseline, weeks 2, 4, and 6	Baseline, weeks 2, 4, and 6	Baseline, weeks 2 and 4	Baseline, weeks 2 and 4	Baseline, weeks 2 and 4

C. Detailed Review of Trials by Indication

Pivotal Trials for Scalp Psoriasis

Reviewer's comment: *The two pivotal trials, **18075** and **18076**, are similar in design and differ only in safety monitoring and study site locations. Study **18075** assessed for adverse events and obtained basic laboratory studies (CBC, chemistries, urinalysis) and plasma clobetasol levels, while study **18076** assessed only for adverse events. All of the sites for study **18075** were located in the US, while the study sites for study **18076** were located in the US and Canada.*

Pivotal Study #1: Protocol Number: RD.06.SRE.**18075**

Title: "A Randomized, Double-Blind, Parallel Group Evaluation of Clobetasol Propionate Shampoo, 0.05% Versus Its Vehicle – An Efficacy and Safety Study in Subjects with Scalp Psoriasis"

Investigators

Analysis Center	Investigator Number/Name/Location	Patients Enrolled Active/Vehicle/Total
01	[redacted]	14/7/21
02		12/6/18
03		12/6/18
04		10/5/15
05		10/4/14
06		9/4/13
07		7/4/11
08		6/3/9
09		6/3/9
10		2/1/3
10	[redacted]	4/2/6
10	2128/Mark Lebwohl, MD/New York, NY	7/4/11

Reviewer's Comment: *Enrollment in some centers was low. Centers 2001, 2028 and 2128 were combined for analysis by the Sponsor.*

Objective/Rationale

The primary objective of the study was to evaluate the efficacy and safety of Clobetasol Propionate Shampoo, 0.05%, vs. its corresponding vehicle, Clobetasol Propionate Shampoo Vehicle, in subjects aged 12 years and older with moderate to severe scalp psoriasis.

Overall Study Design

This study was conducted as a multi-center, randomized, vehicle-controlled, double-blinded, parallel-group comparison involving subjects aged 12 years and older with moderate to severe scalp psoriasis. Qualified subjects, who met specific enrollment criteria, were randomized in a 2:1 ratio to receive either Clobetasol Propionate Shampoo, 0.05%, or Clobetasol Propionate Shampoo Vehicle, respectively. Subjects were dispensed two 4-oz bottles (approximately 120 gms) of study drug every two weeks; the amount of study drug applied per week by each subject was determined by weighing the bottles used during the treatment period. Subjects were to apply the study drug once daily to the affected areas of the scalp (then wait 15 minutes before lathering and rinsing) for a period of 4 weeks (or shorter if the condition cleared), with a 2-week treatment-free follow-up period to assess psoriasis recurrence after treatment discontinuation. Subjects were evaluated at baseline and weeks 2, 4, and 6.

Reviewer's Comment: *Subjects who cleared before the week 4 endpoint were allowed to terminate treatment and enter the treatment-free follow-up period at the time of clearing, rather than continuing treatment to the week 4 endpoint, to avoid unnecessary exposure to a super-high potent topical steroid.*

Protocol

Inclusion Criteria

- Male or female subjects, 12 years of age or older.
- Female subjects of childbearing potential having a negative urine pregnancy test (UPT) at the beginning of the study. Pre-menses females and those who had undergone a hysterectomy, bilateral ovariectomy, or tubal ligation or had been post-menopausal for at least 2 years were not considered to be of childbearing potential.
- Subjects with moderate to severe scalp psoriasis (defined as global severity score of at least three: moderate plaque elevation, coarser scale with most lesions at least partially covered, moderate erythema with definite red coloration)
- Subjects who provided written informed consent and, if applicable, whose parent/guardian provided written informed consent.
- Subjects willing and capable of cooperating to the extent and degree required by the protocol.

Exclusion Criteria

- Subjects with medical conditions that would have put the subject at increased risk from study participation, confounded study assessments, or interfered with subject participation.
- Female subjects of childbearing potential not practicing an acceptable form of contraception (abstinence; implanted, injectable, or oral contraceptive; intrauterine contraceptive device, vasectomized partner).
- Subjects whose scalp psoriasis necessitates systemic or other concomitant topical therapies during the study (concomitant treatment of *body* psoriasis with topical emollients, coal tars, vitamin D derivatives, tazarotene, and salicylic acid was allowed).
- Allergy to one of the components of the test products
- Subjects who participated in a biomedical research trial in the month preceding enrollment.
- Subjects who were pregnant, nursing or planning a pregnancy.
- Subjects who used the following topical treatments on the scalp within the given washout periods
  - Topical corticosteroids 2 weeks
  - Topical anti-psoriatics (vit D derivatives, tazarotene, salicylic acid, coal tars) 2 weeks
- Subjects who used topical corticosteroids on the body within the two week washout period
- Subjects who used the following systemic treatments within the given washout periods
  - Systemic corticosteroids 4 weeks
  - Psoralen plus ultraviolet light (PUVA) therapy 6 weeks
  - Systemic immunosuppressive drugs (such as azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate) 8 weeks
  - Systemic retinoids (such as isotretinoin, acitretin) 16 weeks
  - Other treatment that could have aggravated psoriasis*:
    - β-blockers 2 weeks
    - Lithium preparations 2 weeks
    - Antimalarials 2 weeks
    - Nonsteroidal anti-inflammatory drugs 2 weeks

- Subjects who were known to be immunocompromised
- Subjects with a history of adverse response to topical or systemic steroid therapy
- Subjects with prolonged exposure to ultraviolet light during the 2-week period before study entry

*If the drug had been used for more than 6 months without worsening of the psoriasis, then the subject could have been included in the study.

Withdrawal Criteria

Reasons for withdrawal may have included but were not limited to the following:

- Psoriasis flare that needed an interfering therapy
- Pregnancy
- Investigator's request for safety reasons
- Subject's request
- Major protocol violation that would have confounded interpretation of results
- Loss to follow-up

Procedures and Observations

Each subject was to receive both verbal and written instructions as to the proper dosing and study medication application techniques at the time the study drug was dispensed during the baseline visit. The study agent was to be applied to affected areas of the scalp by moving the hair to expose the affected scalp, applying the study drug directly from the bottle onto the scalp, spreading the study drug to cover the entire lesion with a thin film and then repeating for each additional scalp lesion. The study drug was to be left in place for 15 minutes, then water added to lather and rinse thoroughly. The study agent was to be applied daily for a period of four weeks (or shorter if the condition cleared). At the conclusion of the treatment period (end of week four or time of clearing), a 2-week, treatment-free period commenced.

Table 6 documents the assessments that were to be made throughout the trial.

Table 6: Efficacy and Safety Evaluations

Parameter	Baseline	Week 2	Week 4	Week 6
Efficacy Variables				
Global Severity	X	X	X	X
Erythema	X	X	X	X
Scaling	X	X	X	X
Plaque Thickening	X	X	X	X
Pruritus	X	X	X	X
Scalp surface area of involvement	X	X	X	X
Global Assessment of Improvement-Investigator		X	X	
Global Assessment of Improvement-Subject		X	X	
Safety Variables				
Laboratory testing (CBC, chemistries, UA)	X	X	X	X
Adverse Events	X	X	X	X
Plasma clobetasol levels			X	
Source: Sponsor's NDA submission: Volume 1.33, page 4431				

Reviewer's Comment: *The Division agreed to Global Severity, dichotomized to success or failure, as the primary efficacy endpoint at the pre-IND/EOP-2 meeting. The Division has historically recognized the individual parameters of erythema, scaling and plaque thickening as relevant secondary endpoints for psoriasis. No agreement on secondary endpoints is mentioned in the preIND/EOP2 minutes or SPA, other than the need for statistical correction for multiple endpoints.*

Efficacy Endpoints

The primary efficacy variable was success rate versus failure rate, assessed for the ITT population. Success rate was defined as the proportion of subjects with a global severity score of clear or minimal. The Global Severity Scale is a static six-point integer scale (0 to 5) with morphologic descriptors, shown below in Table 7. The primary efficacy endpoint was week 4.

Table 7: Global Severity Scale

Score	Category	Category Description
0	Clear	Plaque thickening = none (no elevation or thickening over normal skin) Scaling = none (no evidence of scaling) Erythema = ± (hyperpigmentation or residual red coloration)
1	Minimal	Plaque thickening = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin level) Scaling = ± (residual surface dryness and scaling) Erythema = up to mild (up to light red or pink coloration)
2	Mild	Plaque thickening = slight (slight but definite elevation) Scaling = fine (fine scales partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque thickening = moderate (moderate elevation with rounded or sloped edges) Scaling = coarser (most lesions at least partially covered) Erythema = moderate (definite red coloration)
4	Severe	Plaque thickening = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (non-tenacious scale predominates, covering most or all of the lesions) Erythema = very severe (very bright red coloration)
5	Very Severe	Plaque thickening = very marked (very marked elevation typically with hard or sharp edges) Scaling = very coarse (thick tenacious scale covers most or all of the lesions) Erythema = very severe (extreme red coloration; deep red coloration)

Source: Sponsor's NDA submission vol. 1.33 p. 4432

Reviewer's Comment: *The Global Severity Scale above is an acceptable static integer scale with morphologic descriptors of approximately equal decrement delineating progressively worse disease. The Division's definition of success, clear or almost clear, corresponds with Grades 0 or 1, Clear or Minimal, on the Global Severity Scale. A baseline Global Severity score of 3, or*

Moderate, was necessary for enrollment. Hence a subject needed to improve by at least two units to achieve success (grade 0 or 1).

The secondary efficacy variables include global severity (full scale, not dichotomized); total severity score (TSS), which is the sum of erythema, plaque thickening, and scaling scores; individual scores for erythema, plaque thickening, scaling, and pruritus; percent scalp surface area of involvement; global assessment of improvement by the investigator; and global assessment of improvement by the subject.

Total Severity Score (TSS): the sum of the individual scores for erythema, scaling, and plaque thickening. Each individual parameter was scored on a 4-point scale from 0 to 3 on the whole scalp.

Reviewer's Comment: *TSS is a computed score that is not clinically relevant. It is not used by clinicians to assess or follow patients with psoriasis. It is doubtful that a particular score or magnitude of change would be meaningful to practicing physicians or their patients. TSS will not be reviewed.*

Erythema (abnormal redness of the skin)

0	None	No erythema
1	Mild	Slight pinkness present
2	Moderate	Definite redness; easily recognized
3	Severe	Intense redness

Source: Sponsor's NDA submission vol. 1.33 p. 4432

Reviewer's Comment: *The Division has recognized erythema as a meaningful secondary endpoint in psoriasis trials. A score of 0 (none) or 1 (mild) on the above scale corresponds with clear or almost clear for erythema.*

Scaling (scales attached to the scalp)

0	None	No scale visible on the scalp
1	Mild	Some scales, which may often be fine, on the scalp
2	Moderate	Numerous flakes of scaling present on the scalp
3	Severe	Presence of very numerous flakes of scaling, usually large, on the scalp

Source: Sponsor's NDA submission vol. 1.33 p. 4433

Reviewer's Comment: *The Division has recognized scaling as a meaningful secondary endpoint in psoriasis trials. A score of 0 (none) on the above scale corresponds with clear or almost clear for scaling.*

Plaque Thickening (a thickening or elevation of a circumscribed lesion or plaque)

0	None	No plaque thickening
1	Mild	Slight thickening
2	Moderate	Definite but not solid thickening
3	Severe	Marked, solid thickening

Source: Sponsor's NDA submission vol. 1.33 p. 4433

Reviewer's Comment: *The Division has recognized plaque thickening as a meaningful secondary endpoint in psoriasis trials. A score of 0 (none) on the above scale corresponds with clear or almost clear for plaque thickening.*

Pruritus (an itching sensation)

0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching, somewhat bothersome, without loss of sleep
3	Severe	Intense itching that has caused pronounced discomfort; night rest interrupted. Excoriation of the skin from scratching may be present.

Source: Sponsor's NDA submission vol. 1.33 p. 4433

Reviewer's Comment: *The Division has not historically recognized pruritus as a secondary endpoint in psoriasis trials. However, pruritus is often a symptom of scalp psoriasis.*

Scalp Surface Area: The method used to estimate the percent involved area was not described in the protocol.

Reviewer's Comment: *In comments provided to the Sponsor regarding IND 60,934 SN004, the medical reviewer informed the Sponsor that it was"... unclear from the protocol how surface area of involvement can be accurately estimated on the scalp."*[3] *No further elaboration was provided, and this reviewer is similarly uncertain about the accuracy of the estimations obtained. The endpoint Scalp Surface Area will not be reviewed.*

Global Assessment of Improvement (As Per Investigator)

Score	Category	Category Description
5	Clear	All signs and symptoms of disease have resolved (100% improvement from Baseline)
4	Almost clear	Nearly all signs and symptoms of disease have cleared (about 90% improvement from Baseline); only minimal residual signs and symptoms remain
3	Marked improvement	Majority of the signs and symptoms have resolved (about 75% improvement from Baseline)
2	Moderate improvement	Significant improvement, but many signs and symptoms remain (about 50% improvement from Baseline)
1	Minimal improvement	Slight overall improvement, but not clinically significant (about 25% improvement from Baseline)
0	No change	Overall severity similar to baseline
-1	Worse	Worse than Baseline

Source: Sponsor's NDA submission vol. 1.33 p. 4434

Reviewer's Comment: *The endpoint global assessment of improvement per investigator used a dynamic scale. Dynamic scales are subject to recall bias. Additionally, this scale incorporates both objective and subjective criteria but defines neither. This endpoint will not be reviewed.*

[3] Sponsor's NDA submission, vol. 1.1, p. lxxxix.