Total Severity Score (0-9)	5.51±1.46	5.51±0.1.70	5.59±1.29

Source: Sponsor's NDA submission, vol. 1.49, p10409.

Reviewer's Comment: *The baseline scores for the primary efficacy endpoints, Global Severity Score and Total Severity Score, appear to be comparable between the two treatment groups.*

Efficacy Endpoint Outcomes

Table 39: Total Severity Score , Summary Statistics by Visit

		Group			
		Clobetasol Propionate Shampoo, 0.05%	Dermoval Gel	Vehicle Shampoo	Total
ITT(LOCF)					
Baseline	N	63	61	20	144
	Mean (SD)	5.5 (1.5)	5.5 (1.7)	5.6 (1.3)	5.5 (1.5)
Week 4	N	63	61	20	144
	Mean (SD)	2.0 (1.9)	1.2 (1.6)	2.9 (2.0)	1.8 (1.9)
PP					
Baseline	N	57	55	16	128
	Mean (SD)	5.5 (1.5)	5.6 (1.6)	5.8 (1.1)	5.6 (1.5)
Week 4	N	57	55	16	128
	Mean (SD)	1.8 (1.7)	1.1 (1.3)	2.4 (1.6)	1.6 (1.6)

Source: Sponsor's NDA submission, vol 1.49, pp.10461, 10469.

Analysis of covariance for treatment comparison with and without interaction (treatmentXcenter) suggested that an interaction was likely for the ITT(LOCF) but not the PP population, therefore the model with interaction for ITT(LOCF) and without interaction for PP were used, respectively, in the table below (Table 40).

Table 40: Total Severity Score, Estimated Difference (Clobetasol-Comparator and Clobetasol-Vehicle) , Analysis of Covariance for Treatment Comparison

ANCOVA: Model	Visit	Comparison	Estim. Diff.	SE	95% CI	p-Value
W inter. TreatXcenter ITT(LOCF)	Week 4	Clobetasol vs. Dermoval	0.70	0.27	0.16, 1.24	0.011
		Clobetasol vs. vehicle	-1.03	0.39	-1.81, -0.25	0.010
W/o inter. TreatXcenter PP	Week 4	Clobetasol vs. Dermoval	0.77	0.26	0.25, 1.29	0.004
		Clobetasol vs. vehicle	0.71	0.27	0.18, 1.25	0.009

Source: Sponsor's NDA submission, vol 1.49, pp.10461, 10469.

The difference in the reduction in TSS from baseline to week 4 between the clobetasol propionate shampoo and the Dermoval™ Gel treatment groups was significant for both the ITT(LOCF) and the PP populations. The statistical analysis plan in the protocol prespecified that non-inferiority would be achieved if the upper limit of the confidence interval was below the target delta of 1.5 for TSS in both the ITT(LOCF) and PP population. This was achieved.

Reviewer's Comments: *Non-inferiority of Clobetasol Propionate Shampoo, 0.05% relative to Dermoval™ Gel was demonstrated by the criteria pre-specified in the protocol statistical analysis plan, but the lack of blinding of subjects to treatment groups may have introduced bias. The large delta for non-inferiority (1.5) also a weakness of this study.*

Table 41: Global Severity Score, Summary Statistics by Visit

		Group			
		Clobetasol Propionate Shampoo, 0.05%	Dermoval Gel	Vehicle Shampoo	Total
ITT(LOCF)					
Baseline	N	63	61	20	144
	Mean (SD)	3.5 (0.6)	3.5 (0.6)	3.7 (0.6)	3.5 (0.6)
Week 4	N	63	61	20	144
	Mean (SD)	1.7 (1.3)	1.1 (1.0)	2.4 (1.2)	1.5 (1.2)
PP					
Baseline	N	57	55	16	128
	Mean (SD)	3.5 (0.6)	3.5 (0.6)	3.6 (0.6)	3.5 (0.6)
Week 4	N	57	55	16	128
	Mean (SD)	1.6 (1.2)	1.1 (0.9)	2.0 (1.0)	1.4 (1.1)

Source: Sponsor's NDA submission, vol 1.49, pp.10477, 10487.

Analysis of covariance for treatment comparison with and without interaction (treatmentXcenter) did not suggest an interaction, therefore the model without interaction was used in the table below (Table 42).

Table 42: Global Severity Score, Estimated Difference (Clobetasol-Comparator and Clobetasol-Vehicle), Analysis of Covariance for Treatment Comparison

ANCOVA: Model	Visit	Comparison	Estim. Diff.	SE	95% CI	p-Value
W/o inter. TreatXcenter ITT(LOCF)	Week 4	Clobetasol vs. Dermoval	0.55	0.18	0.21, 0.90	0.002
		Clobetasol vs. vehicle	-0.64	0.25	-1.14, -0.14	0.012
W/o inter.	Week 4	Clobetasol	0.55	0.18	0.21, 0.90	0.002

TreatXcenter PP		vs. Dermoval				
		Clobetasol vs. vehicle	-0.48	0.26	-1.00, 0.05	0.074

Source: Sponsor's NDA submission, vol 1.49, pp.10477, 10487.

The difference in the reduction in GSS from baseline to week 4 between the clobetasol propionate shampoo and the Dermoval™ Gel treatment groups was significant for both the ITT(LOCF) and the PP populations. The difference in the reduction in GSS from baseline to week 4 between the clobetasol propionate shampoo and the Vehicle Shampoo treatment groups was significant for the ITT(LOCF) but not the PP population. The statistical analysis plan in the protocol pre-specified that superiority to vehicle would be achieved if a significant difference in favor of clobetasol propionate was detected in both primary efficacy criteria, TSS and GSS, for the ITT(LOCF) population. This was achieved. Superiority to Dermoval™ Gel was not a primary objective of this study.

Reviewer's Comments: *Superiority of Clobetasol Propionate Shampoo, 0.05% relative to Vehicle Shampoo was demonstrated by the criteria pre-specified in the protocol statistical analysis plan. The Clobetasol Propionate Shampoo, 0.05% and Vehicle Shampoo groups were blinded to one another. The achievement of this objective, demonstration of the superiority of Clobetasol Propionate Shampoo, 0.05% to Vehicle Shampoo in the ITT (LOCF) population, is supportive of the efficacy of Clobetasol Propionate Shampoo, 0.05% as demonstrated in the pivotal trials.*

The secondary endpoints of erythema, scaling/desquamation and plaque thickening decreased in all three treatment groups at 4 weeks relative to baseline. The decrease was largest in the Dermoval Gel group, followed by the Clobetasol Propionate Shampoo, 0.05% group and least in the Vehicle Shampoo group.

D. Efficacy Conclusions

Clobetasol Propionate Shampoo, 0.05% is efficacious in the treatment of moderated to severe scalp psoriasis in subjects 12 years of age and older. The two pivotal trials were adequate and well-controlled, and both demonstrated effectiveness. Although two of the three non-pivotal studies were not compelling (**2638, 2648**), they did not contradict the results obtained in the pivotal trials, and the one non-pivotal study that was vehicle-controlled (**2665**) was substantially supportive.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Clobetasol Propionate Shampoo 0.05% has an acceptable safety profile for the treatment of moderate to severe psoriasis of the scalp. Hypothalamic-pituitary-adrenal (HPA) axis suppression was identified and will need to be further investigated. Local adverse effects include skin discomfort and atrophy.

B. Description of Patient Exposure

Eleven studies are included in the review of safety. The studies are grouped according to phase, with Phases 2 and 3 considered together. The trials in each phase are summarized in tabular form, followed by discussion.

Table 43: Phase 1 Studies

Study Number	1.CG.03.SPR.2618	1.GUS.04.SPR.18032
Design	intra-individual, investigator blinded, randomized, active- and vehicle controlled	intra-individual, evaluator blinded, randomized, controlled
Location	France – single center	US - single center (two sites)
Objective	Vasoconstriction Assay	Contact Irritation and Sensitization/Repeat Insult Patch Test
Formulations	CP shampoo Temovate® Cream Temovate® Scalp Application Diprolene® Cream Vehicle shampoo	Vehicle Shampoo (662.064P), 5% dilution Vehicle Shampoo (662.066P), 5% dilution White petrolatum ointment
Enrollment	12 healthy adult males	219 healthy adults
Dose	50 uL of test agent applied for 15 minutes	0.1gm of test agent (occluded) and 0.02gm of test agent (open)
Number of Doses per Study Time Frame	One application, 15 minutes under occlusion	Test materials were applied under occlusive and open conditions every 48 hours for nine applications, and again after a 9 to 11 day rest
Number of Visits	4	13
Measurement Timepoints	Pre-test (-2, -1), application, 4h, 6h, 8h, 10h, 12h, 14h, 24h	Baseline (d1), day 3, 6, 8, 10, 13, 15, 17, 20, 34, and follow-up at day 36 and possibly day 38
Measurements Related to Safety	Adverse Events (AE)	Irritation, sensitization, AE

Source: Sponsor's NDA submission, ISS, vol. 1.52, p.11452; vol. 1.21 p.250; vol. 1.22, p.474.

Subject Accountability, Phase 1

In Phase 1, 243 subjects were exposed to the study agent. In study **2618**, which assessed vasoconstriction, 12 subjects were enrolled and completed the study. In study **18032**, which assessed cumulative irritancy and sensitization, 219 subjects were enrolled and 210 completed the study. Six subjects discontinued the study at the subject's request, 2 were lost to follow-up, and 1 was discontinued due to a protocol violation. 217 subjects returned for at least one evaluation and were assessed for cumulative irritancy. Two hundred and eleven subjects entered the challenge phase; one was discontinued, resulting in 210 evaluable subjects for sensitization.

Treatment Duration, Phase 1

The extent of exposure in study **2618** (vasoconstriction) was brief: a single application 15 minutes under occlusion. In study **18032,** a 5% dilution of the vehicle shampoo was applied every 48 hours for 9 consecutive applications, followed by a tenth application after a 9 to 11 day rest. However, study **18032** did not use active clobetasol propionate shampoo.

Reviewer's comment: In study 18032, the repeat insult patch test study to assess for cumulative irritancy and sensitization, vehicle shampoo was used to avoid masking an irritant or allergic reaction by the active ingredient clobetasol propionate.

Exposure to Study Drugs, Phase 1

The exposure to study drug in Phase 1 was minimal: 0.05mL for a single exposure, or approximately 1% of the daily exposure in Phase 3. This exposure was exclusively in study **2618**, as only vehicle shampoo was used in study **18032**.

Table 44: Phase 2 Studies

Study Number	1.CG.03.SPR.2577	1.CG.03.SPR.2591	1.CG.03.SPR.2620	RD.06.SPR.18070
Design	Single center, randomized, investigator-masked, active and vehicle controlled, parallel group comparison	Multi-center, randomized, investigator-masked, active-controlled, parallel group comparison	Single center, randomized, investigator-masked, active-controlled, parallel group comparison	Multi-center, open-label
Location	France	France	France	U.S.
Objective	Dose response/regimen finding	Dose response/regimen finding	HPA Axis Suppression	HPA Axis Suppression
Formulations and Regimen/Comparators (regimen includes rinsing unless otherwise specified)	CP shampoo wet scalp 2.5 min qd CP shampoo wet scalp 5 min qd CP shampoo wet scalp 10 min qd Vehicle shampoo wet scalp 10 min qd Dermoval® Gel dry scalp qd w/o rinsing	CP shampoo dry scalp 10 min qd CP shampoo wet scalp 10 min qd CP shampoo dry scalp 15 min qd Daivonex® Solution on dry scalp BID without rinsing	CP shampoo dry scalp 15 min qd Dermoval® Gel dry scalp qd w/o rinsing (up to 40 mL/week)	CP shampoo dry scalp 15 min qd
Enrollment	60 adults	59 adults	26 adults	13 adolescents
Randomization	1:1:1:1:1	1:1:1:1	1:1	Active only

ratio				
Mean weekly usage of CP shampoo	67.5 gm/wk (2.5 min) 73.9 gm/wk (5 min) 80.2 gm/wk (10 min)	48.2gm/wk (10min,dry) 59.9gm/wk (10min,wet) 65.3gm/wk (15min,dry)	65 gm/wk	22.7 gm/wk
Number of Doses per Study Time Frame	2weeks treatment, once daily	3 weeks treatment, once daily	4 weeks treatment, once daily	4 weeks treatment, once daily
Number of Visits	4	5	6	
Measurement Timepoints	Baseline, wk 1, 2, 4	Baseline, wk 1, 2, 3, and 6	Inclusion, baseline, wk 1, 2, 3, and 4	Screening, baseline, wk 2, 4 and wk 6 follow-up
Measurements Related to Safety	Plasma clobetasol levels, irritation/burning, AE	Irritation/burning, AE	HPA axis function assessment, intraocular pressure, slit lamp exam, visual acuity, plasma clobetasol levels, routine labs, telangiectasia, skin atrophy, AE	HPA axis function assessment, routine labs, plasma clobetasol levels, vital signs, AE

Source: Sponsor's NDA submission, ISS, vol. 1.52, pp.11461-2, 11468; vol. 1.28, pp.2741-4; vol. 1.31, pp. 3716-7; vol. 1.23, pp.805-6, 812; vol. 1.26, pp.2016.

Table 45: Phase 3 Studies

Study Number	**RD.06.SPR.18075**	**RD.06.SPR.18076**	**RD.03.SPR.2638**	**RD.03.SPR.2648**	**RD.03.SPR.2665**
Design	Multi-center, randomized, vehicle-controlled, double-blind, parallel group comparison	Multi-center, randomized, vehicle-controlled, double-blind, parallel group comparison	Multi-center, randomized, active-controlled, investigator-blind, parallel group comparison	Multi-center, randomized, active-controlled, investigator-blind, parallel group comparison	Multi-center, randomized, active- and vehicle-controlled, investigator-blind, parallel group comparison
Location	U.S.	U.S.	Europe	Europe	Europe
Objective	Safety and efficay	Safety and efficay	Safety and efficay	Safety and efficay	Safety and efficay
Formulations and Regimen/Comparators (regimen includes rinsing unless otherwise specified)	CP shampoo dry scalp 15 min qd Vehicle shampoo dry scalp 15 min qd	CP shampoo dry scalp 15 min qd Vehicle shampoo dry scalp 15 min qd	CP shampoo dry scalp 15 min qd Daivonex® Solution dry scalp BID w/o rinsing	CP shampoo dry scalp 15 min qd Polytar® Liquid Shampoo wet scalp twice weekly	CP shampoo dry scalp 15 min qd Vehicle shampoo dry scalp 15 min qd Dermoval® Gel dry scalp qd w/o rinsing
Enrollment	148	142	151	162	144
Randomization ratio	2:1	2:1	1:1	3:1	3:1:3
Mean weekly usage of CP shampoo	34.5 gms/wk	32.7 gms/wk	60.1 gms/wk	39.2 gms/wk	46.2 gms/wk
Number of	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks

Doses per Study Time Frame	treatment, once daily	treatment, once daily	treatment, once daily	treatment, once daily	treatment, once daily
Number of Visits	4	4	3	3	3
Measurement Timepoints	Baseline, wk 2, 4, and week 6 follow-up	Baseline, wk 2, 4, and week 6 follow-up	Baseline, wk 2 and 4	Baseline, wk 2 and 4	Baseline, wk 2 and 4
Measurements Related to Safety	Plasma clobetasol levels, AE, skin atrophy, telangiectasis, burning, irritation, and acne	AE, skin atrophy, telangiectasis, burning, irritation, and acne	Local (telangiectasis, skin atrophy, burning), Ocular (burning/stinging), blood pressure, AE	Local (telangiectasis, skin atrophy, burning), Ocular (burning/stinging), blood pressure, AE	Stinging/burning Pustules/folliculitis, AE

Source: Sponsor's NDA submission, vol 1.52, pp. 11462-3,11468; vol. 1.43, pp. 8126, 8146; vol. 1.46, pp. 9071, 9099; vol. 1.49, pp. 10361, 10382.

Subject Accountability, Phases 2 and 3

A total of 900 subjects with scalp psoriasis were included in the safety population in Phase 2 and 3 studies. One hundred fifty-eight subjects (17.6%) were enrolled in the Phase 2 studies; 119 (13.2%) were in the dose-finding studies and 39 (4.3%) were enrolled in the HPA axis studies. Seven hundred forty-two subjects (82.4%) were enrolled in the Phase 3 studies; 287 (31.9%) were enrolled in the pivotal vehicle-controlled studies and 455 (50.6%) were in the active-controlled, supportive studies.[5]

Of the subjects in the integrated safety database, 558 subjects (62%) received Clobetasol propionate Shampoo, 0.05%, 127 (14.1%) received Vehicle Shampoo, 85 (9.4%) received Dermoval® Gel, 90 (10.0%) received Daivonex® Solution, and 40 (4.4%) received Polytar® Liquid Shampoo. [6]

In the Clobetasol propionate Shampoo, 0.05% group, 94.3% of the subjects completed the study, as did 92.9% of the Vehicle Shampoo subjects, 97.6% of the Dermoval® Gel subjects, 82.2% of the Daivonex® Solution subjects, and 90.0% of the Polytar® Liquid Shampoo subjects. Within each treatment group, fewer than 2% of the subjects discontinued for any given reason except as follows: 3.1% of the Vehicle Shampoo group discontinued due to subject request; for the Daivonex® Solution group, 2.2% discontinued due to lack of effect or worsening of condition, 8.9% discontinued due to adverse event, and 5.6% discontinued due to subject request; 5.0% of the subjects in the Polytar® Liquid Shampoo group discontinued due to subject request, and 2.5% each discontinued due to protocol violation and lost to follow up.[7]

Treatment Duration, Phases 2 and 3

[5] Sponsor's NDA submission vol. 1.52, p. 11464.
[6] Sponsor's NDA submission, vol. 1.52, p.11464.
[7] Sponsor's NDA submission, vol. 1.52, p. 11464.

The mean treatment duration for the safety population in the Phase 2 and 3 studies was 26.4 days, and was similar across all treatment groups: 26.6 days for the Clobetasol Propionate Shampoo, 0.05%, 26.4 days for Vehicle Shampoo, 26.1 days for Dermoval® Gel, 25.0 days for Daivonex® Solution, and 26.9 days for Polytar Liquid. The majority of subjects received treatment for 21 or more days.[8]

Exposure to Study Drugs, Phases 2 and 3

Weekly medication usages were calculated for each of the studies in Phases 2 and 3 and are summarized in the table below.

Table 46: Mean Weekly Usage of Clobetasol Propionate Shampoo, 0.05% per Study

Study Number	Weekly Average Use (gms/wk)	Number subjects using > 50 gms/wk	Application Instructions*
U.S. HPA Axis Suppresion			
RD.06.SPR.**18070**	22.7	1(2)[§]	120gm bottle/2wk; apply to at least 25% scalp
U.S. Phase 3			
RD.06.SPR.**18075**	34.5	17	120 gm bottle/2wk; apply thin film to affected areas
RD.06.SPR.**18076**	32.7	6	120 gm bottle/2wk; apply thin film to affected areas
U.S. Subtotal		24/205 (11.7%)	
European HPA Axis Suppression			
1.CG.03.SPR.**2620**	65 gm/wk	14	10mL/d from unit-dose vials
European Dose Ranging			
1.CG.03.SPR.**2577** 3.5 min wet scalp 5 min wet scalp 10 min wet scalp	 67.5 73.9 80.2	24	5ml (short) or 10ml(long) per day depending on hair length; cosmetic shampoo NOT allowed
1.CG.03.SPR.**2591** 10min dry scalp 10 min wet scalp 15 min dry scalp	 48.2 59.9 65.3	18	5ml (short) or 10ml(long) per day depending on hair length; cosmetic shampoo NOT allowed
European Phase 3			
RD.03.SPR.**2638**	60.1	54	100gm tube/wk; apply usual quantity of shampoo

[8] Sponsor's NDA submission, ISS, vol. 1.52, p.11591.

RD.03.SPR.**2648**	39.2	24	100gm tube/wk; apply usual quantity of shampoo
RD.03.SPR.**2665**	46.2	33	100gm tube/wk; apply usual quantity of shampoo
European Subtotal		167/353 (47.3%)	

*Use of cosmetic (non-medicated) shampoo allowed unless otherwise noted.
[§]Reviewer's calculations identify 2 subjects with >50 g/wk study drug useage (calculations based on Sponsor's submission vol.1.27, p.2517).
Source: Sponsor's NDA submission vol. 1.52, pp. 11468, 11592.

The European studies had a higher mean weekly usage of CP Shampoo (39.2 gm/wk to 80.2 gm/wk) than did the U.S. studies (22.7gm/wk to 34.5gm/wk), and a higher percentage of European subjects used greater than 50gms/wk (47.3%) than did U.S. subjects (11.7%). Several factors may have contributed to this difference.

First, in the European phase 2 trials, subjects were instructed to apply either 5mL (short-haired subjects in dose-ranging studies) or 10mL (long-haired subjects in dose-ranging studies and all subjects in HPA axis suppression studies) per application, regardless of the extent of lesional skin. Subjects in the European dose-ranging studies were prohibited from using non-medicated shampoo, so subjects with long hair were assigned the higher volume for cosmetic purposes. In the U.S. Phase 2 studies, subjects were instructed to apply a thin film of shampoo to lesional and non-lesional skin covering at least 25% of the scalp.

Second, in the Phase 3 European trials, subjects were instructed to apply their usual quantity of shampoo onto dry scalp and then massage the scalp, especially the lesions. In the Phase 3 U.S. trials, subjects were instructed to move the hair away from the scalp, apply a small amount of the shampoo directly onto each lesion and then spread the product so that the entire lesion was covered with a thin uniform film. Thus the U.S. instructions were more precise and aimed at directing the product specifically onto lesional skin.[9]

Reviewer's Comment: The unit dosing (5 or 10mL/application) and restriction on use of non-medicated shampoo are conditions that did not apply to the Phase 3 pivotal studies and will not apply to labeled use. Thus the average weekly usage for the Phase 3 pivotal studies is expected to be more predictive of U.S. marketed use.

The higher weekly usage in the European studies provides useful safety data for extremes of use.

Weekly usage of study agent exceeded 50gm/wk in a higher percentage of subjects who received CP shampoo (34.2%) than vehicle (22.0%). This is skewed by the Phase 2 studies that used a set doses (5 and/or 10 mL/application) resulting in higher weekly usage, but which with one exception were not vehicle-controlled. In the Phase 3 studies that were vehicle-controlled, weekly useage that exceeded 50 gm/wk was similar between the active and vehicle groups.

[9] Sponsor's NDA submission, vol. 1.52, p. 11465.

Table 47: Subjects with Study Medication Useage >50 g/week in Phase 3, Vehicle-Controlled Trials

Study Number	Clobetasol Shampoo n/N (%)	Vehicle Shampoo n/N (%)
SPR **18075**	17/99 (17.2%)	7/49 (14.3%)
SPR **18076**	6/95 (6.3%)	6/47 (12.8%)
SPR **2665**	33/63 (52.3%)	10/20 (50.0%)
Total	56/257 (21.8%)	23/116 (19.8%)

n = number of subjects with study medication useage >50 gm/week
N = number of subjects in study arm
Source: Sponsor's submission vol 1.52, p. 11593 and reviewer's calculations.

C. Methods and Specific Findings of Safety Review

The safety review of clobetasol propionate shampoo, 0.05% will focus on adverse events in Phase 2 and Phase 3 studies, systemic safety as indicated by the rate of hypothalamic-pituitary-adrenal (HPA) axis suppression in Phase 2 trials, and local safety as indicated by ocular safety, cutaneous irritancy and allergenicity, and cutaneous adverse events (skin atrophy and telangiectasia).

Adverse Events (AEs)

Table 48 summarizes the adverse events that occurred in ≥ 1% of the subjects in the Phase 2 and 3 studies for scalp psoriasis.

Table 48: Summary of Adverse Events ≥ 1% by Body System, Safety Population

Body System	Clobetasol Propionate Shampoo N=558	Vehicle Shampoo N=127
Total Number of AEs	166	69
Total Number of Subjects with AEs	129 (23.1%)	**40 (31.5%)**
Skin and Appendages	49 (8.8%)	**28 (22.0%)**
Discomfort Skin	26 (4.7%)	**16 (12.6)**
Pruritus	3 (0.5%)	**9 (7.1%)**
Body As A Whole	33 (5.9%)	**12 (9.4%)**
Headache	**10 (1.8%)**	1 (0.8%)
Injury/Accident	8 (1.4%)	**3 (2.4%)**
Flu Syndrome	6 (1.1%)	**3 (2.4%)**
Respiratory System	20 (3.6%)	**6 (4.7%)**
Pharyngitis	12 (2.2%)	**4 (3.1%)**
Digestive System	16 (2.9%)	**4 (3.1%)**

Tooth Disease	**6 (1.1%)**	0 (0.0%)
Gastroenteritis	**6 (1.1%)**	0 (0.0%)
Urogenital System	**9 (1.6%)**	1 (0.8%)

Source: Sponsor's NDA submission, vol. 1.52, pp. 11644-7.

The percentage of subjects with AEs was higher among subjects that received vehicle shampoo than those that received clobetasol propionate shampoo, as was the incidence of Skin and Appendages AEs. The rates of headache, tooth disease, gastroenteritis and urogential system AEs were higher in the clobetasol propionate shampoo group.

Table 49 lists the adverse events that Investigators ascribed as related to study drug use in the nine Phase 2 and Phase 3 studies.

Table 49: Summary of Adverse Events Related to Study Drug, Phase 2 and 3 Safety Population

Body System/COSTART Term	Clobetasol propionate Shampoo N=558	Vehicle Shampoo N=127
Total Number of AEs	48	32
Total Number of Subjects w/AEs	40 (7.2%)	**23 (18.1%)**
Skin and Appendages	37 (6.6%)	**22 (17.3%)**
Discomfort Skin	25 (4.5%)	**16 (12.6%)**
Pruritus	3 (0.5%)	**7 (5.5%)**
Acne	**2 (0.4%)**	0 (0.0%)
Infect Skin	**2 (0.4%)**	0 (0.0%)
Edema Skin	**2 (0.4%)**	0 (0.0%)
Urticaria	**1 (0.2%)**	0 (0.0%)
Psoriasis	**1 (0.2%)**	0 (0.0%)
Skin Dry	1 (0.2%)	**1 (0.8%)**
Irritant Dermatitis	1 (0.2%)	**2 (1.6%)**
Folliculitis	**1 (0.2%)**	0 (0.0%)
Alopecia	**1 (0.2%)**	0 (0.0%)
Worse Treated Disease	**1 (0.2%)**	0 (0.0%)
Erythema	0 (0.0%)	**1 (0.8%)**
Desquamation	0 (0.0%)	**1 (0.8%)**
Dermatitis Contact	0 (0.0%)	**1 (0.8%)**
Body as a Whole	1 (0.2%)	**2 (1.6%)**
Headache	**1 (0.2%)**	0 (0.0%)
Lab Test Abnormality	0 (0.0%)	**1 (0.8%)**
Edema Face	0 (0.0%)	**1 (0.8%)**
Musculoskeletal System	**1 (0.2%)**	0 (0.0%)
Arthralgia	**1 (0.2%)**	0 (0.0%)
Nervous System	**1 (0.2%)**	0 (0.0%)
Dizziness	**1 (0.2%)**	0 (0.0%)

Special Senses	**1 (0.2%)**	0 (0.0%)
Conjunctivitis	**1 (0.2%)**	0 (0.0%)

Source: Sponsor's NDA submission, vol. 1.52 pp11648-9.

The incidence of overall AE as well as Skin and Appendages AEs were higher among subjects who received vehicle shampoo than those who received clobetasol propionate shampoo. Additionally, the incidences of Discomfort Skin and Pruritus were both higher among subjects receiving vehicle shampoo.

Reviewer's Comment: *The higher incidence of skin discomfort and pruritus in the Vehicle Shampoo group than the Clobetasol Propionate Shampoo, 0.05% group suggests that vehicle ingredients rather than the drug substance are responsible for the irritation, and the drug substance mollified the vehicle-induced irritation in the active group. Coco-betaine and sodium laureth sulfate are known cutaneous irritants.*

Five subjects had serious adverse events (SAE): three subjects in the Vehicle Shampoo group (amygdalectomy, fever, and bronchitis, respectively) and one subject each in the Clobetasol Propionate Shampoo, 0.05% group (surgery of the internal meniscus of the right knee) and Dermoval® Gel group (appendicectomy). All of these SAE were non-dermatologic and assessed as either definitely unrelated or unlikely related to study drug.

Systemic Safety: HPA Axis Suppression

Two phase 2 studies, **SPR.18070** and **SPR.2620**, were performed to evaluate the potential of clobetasol propionate shampoo to suppress the HPA axis of subjects with scalp psoriasis. The first, **SPR.18070**, was conducted in adolescents (ages 12 to 17 years), involved daily application of clobetasol propionate shampoo to at least 25% of the scalp, and measured HPA axis function at screening and week 4. The second, **SPR.2620**, was conducted in adults (18 years and older), involved application of 10mL clobetasol propionate shampoo or an unspecified amount of Dermoval®/Temovate® gel (not to exceed 40 gm/wk), and measured HPA axis function at screening and at weeks 1, 2, 3 and 4.

Study RD.06.SPR.18070

Study Design

13 subjects aged 12 to 17 years with moderate to severe scalp psoriasis affecting at least 25% of their scalp were enrolled in this multi-center, open-label study of clobetasol propionate shampoo, 0.05%. Subjects were required to have a normally functioning HPA axis, defined as a pre-stimulation serum cortisol level of at least 7 ug/dL and a post-stimulation serum cortisol of at least 18 ug/dL 60 minutes after receiving 0.25mg of cosyntropin via IV injection. The subjects applied clobetasol propionate shampoo once daily to the affected areas of the dry scalp, waiting 15 minutes before lathering and rinsing, for a period of four weeks. HPA axis function was measured again at week 4, and weekly thereafter in those subjects with suppression until they returned to normal. Plasma clobetasol levels were measured at week four.

Reviewer's comment: *The Division prefers the labeled criteria for normal HPA axis function in response to Cortrosyn® stimulation: pre-stimulation plasma cortisol level greater than 5 ug/dL, post-stimulation measurements taken at 30 (rather than 60) minutes after IV injection of 0.25mg of cosyntropin, post-stimulation levels at least 7ug/dL greater than pre-stimulation levels as well as greater than 18 ug/dL. The Cortrosyn® label indicates that if the post-stimulation plasma cortisol level is measured at 60 rather than 30 minutes, "...the criterion for a normal response is an approximate doubling of the basal plasma cortisol value."*[10]

Results

Table 50 HPA Axis Parameters, Study 18070

Subject #	Serum cortisol values, ug/dL								HPA axis suppression?
	screening				Week 4				
	Prestimulation	2X prestim (computed value)	Post-stimulation	Change (post – pre)	Prestimulation	2X prestim (computed value)	Post-stimulation	Change (post – pre)	
001	17.3	34.6	24.4	7.1	19.2	38.4	32.6	13.4	**Yes**
002	11.0	22.0	24.1	13.1	18.8	**37.2**	**29.0**	10.2	**Yes**
003	14.8	29.6	34.9	20.1	*27.7*	*55.4*	37.5	8.0	**Yes***
004	9.5	19.0	30.9	21.4	16.9	33.8	32.3	15.4	No
005	11.8	23.6	29.5	17.7	14.4	**28.8**	**19.1**	**4.7**	**Yes**
006	16.9	33.8	28.8	11.9	12.3	**24.6**	**10.4**	**-1.9**	**Yes**
019	11.2	22.4	39.3	28.1	13.6	27.2	35.8	22.2	No
020	7.4	14.8	25.2	17.8	8.2	16.4	23.8	15.6	No
007	15	30	26.5	11.5	16.2	32.4	35.3	19.1	No
008	9.2	18.4	28.9	19.7	7.8	15.6	32.4	24.6	No
009	19.6	39.2	33.6	14.0	11.4	22.8	32.4	21.0	No
010	8.7	17.4	25.1	16.4	13.0	29.0	26.0	16.0	No
011	11	22	33.2	22.2	7.5	42	15	34.5	No

*Although the 4 week pre-stimulation value exceeded the normal range, the post-stimulation value was less than twice the approximate doubling of the upper range of normal and therefore the subject was considered suppressed.

Pre-stimulation values that exceed the upper range of normal (23ug/dL) and the corresponding doubled values are italicized.

Source: Sponsor's NDA submission vol. 1.27, pp. 2524-6, and reviewer's computations.

Subjects 001, 002, 003, 005 and 006 demonstrated HPA axis suppression based on the 60 minute criteria of failing to double the baseline plasma cortisol level 60 minutes after stimulation with Cortrosyn®. Subjects 005 and 006 also manifested HPA axis suppression by failing to show a ≥5 ug/dL rise in serum cortisol after Cortrosyn® stimulation relative to baseline, which should be demonstrable even 30 minutes after stimulation.

Subject 020 missed 8 consecutive doses of study drug, a major protocol violation.

[10] Cortrosyn® package insert.

Reviewer's comment: *Five of 12 subjects manifested evidence of HPA axis suppression. The Sponsor discounted subject 006 stating that the low post-stimulation level was a laboratory error. No substantiation was provided. This reviewer therefore accepted the value, and the subject is considered suppressed. The subject was not reported to have used concomitant medications. Subject 020 was not included in the PP population by the Sponsor, and the results for Subject 020 were discounted by this reviewer as the 8 consecutive missed doses may have resulted in a falsely negative (normal) Cortrosyn stimulation result.*

Two subjects used greater than 50 g/wk of study medication: subjects 010 and 011, who used 54.975 and 50.975 g/wk, respectively.[11] None of the subjects who were identified as having HPA axis suppression, subjects 001, 002, 003, 005, 006, used greater than 50 g/wk of clobetasol propionate shampoo, 0.05%. Weight of study medication use among subjects with definite or equivocal HPA axis suppression ranged from 8.375 to 40.55 g/wk.[12]

Study CG.03.SPR.2620

Study Design

Twenty-six subjects aged 18 years and older with moderate to severe scalp psoriasis affecting at least 25% of their scalp were enrolled in this single-center, randomized, investigator-masked study of HPA axis suppression with use of clobetasol propionate shampoo, 0.05%, or Dermoval®/Temovate® gel. Subjects were required to have a normally functioning HPA axis, defined as a pre-stimulation serum cortisol level of at least 10 ug/dL and a post-stimulation change in serum cortisol of at least 8 ug/dL (greater than baseline) 60 minutes after receiving 0.25mg of cosyntropin via IV injection. The subjects applied either 10 mL clobetasol propionate shampoo once daily to the affected areas of the dry scalp, waiting 15 minutes before lathering and rinsing, or Dermoval®/Temovate® gel (not to exceed 40 g/wk) twice daily for a period of four weeks. HPA axis function was measured at inclusion, baseline, weekly through week four, and weekly thereafter in those subjects with suppression until they returned to normal. Plasma clobetasol levels were measured at week four. Ophthalmologic safety was also assessed in this trial, and will be discussed in a subsequent section.

Reviewer's comment: *Using the labeled criteria for determination of normal HPA axis function, when the post-stimulation plasma cortisol level is measured at 60 rather than 30 minutes, "...the criterion for a normal response is an approximate doubling of the basal plasma cortisol value."[13] Ideally, Cortrosyn® stimulation should be performed at baseline and again at the conclusion of therapy (e.g., at week 4) rather than weekly, as weekly stimulation may mask suppression.*

Results
(next page)

[11] Reviewer's calculations, based on data in Sponsor's submission vol. 1.27, p. 2518.
[12] Reviewer's calculations, based on data in Sponsor's submission vol. 1.27, p. 2518.
[13] Cortrosyn® package insert.

Table 51 HPA Axis Parameters, Study 2620

Subject #	Serum cortisol values, ug/dL								HPA axis suppression?
	inclusion				Week 4				
Clobetasol propionate shampoo	Prestimulation	2X prestim (computed value)	Post-stimulation	Change (post – pre)	Pre-stimulation	2X prestim (computed value)	Post-stimulation	Change (post – pre)	
32	*35.2*	*70.4*	43.5	8.3	*41.4*	*82.8*	46.8	5.4	No*
33	*24.7*	*49.4*	32.7	8.0	*27.5*	*55.0*	43.3	15.8	No*
35	17	34	30	13	25.2	***50.4***	**29.4**	**4.2**	**Yes**
38	14.9	29.8	25.7	10.8	10.8	21.6	23.4	12.6	No
39	16.6	33.2	26.3	9.7	19.9	**39.8**	**28.9**	9	**Yes**
41	19.3	38.6	30.5	11.2	20.6	**41.2**	**33.8**	13.2	**Yes**
44	*42.5*	*83*	50.1	7.5	*49.6*	*99.2*	63.8	14.2	No*
46	18.1	36.2	27.8	9.7	17.9	**35.8**	**27**	17.9	**Yes**
47	17.8	35.6	25.5	7.7	15.2	**30.4**	**26.8**	11.6	**Yes**
50	22.3	44.6	35.5	13.2	*23.5*	*47*	**31.1**	7.6	**Yes**
51	*25.8*	*51.6*	36.9	11.1	22.2	**44.4**	**30.5**	8.3	**Yes**
54	22.9	45.8	31.9	9	22.1	**44.2**	**31.8**	10.7	**Yes**
55	17.4	34.8	28.3	10.9	10.6	21.2	26.4	15.8	No
56	22.8	45.6	36.6	13.8	22.9	**45.8**	**31.7**	8.8	**Yes**
Dermoval® gel									
31	*23.5*	*47*	42.7	19.3	*25.7*	***51.4***	**34.6**	8.9	**Yes**
34	11	22	28.4	17.4	6.9	13.8	22.2	15.3	No
36	22.3	44.6	30.1	7.8	*24.1*	***48.2***	**27.3**	3.2	**Yes**
37	*24*	*48*	32	8	22.7	**45.4**	**28.2**	5.5	**Yes**
40	16.8	33.6	26.3	9.5	9.8	19.6	18.2	8.4	No
42	17.4	34.8	25	7.6	21.7	**43.4**	**25.3**	3.6	**Yes**
43	11.7	23.4	25.8	14.1	20	**40**	**28.6**	8.6	**Yes**
45	20.7	41.4	30.3	10.4	*29.8*	***59.6***	**36.5**	6.7	**Yes**
48	*24.8*	*49.6*	40.3	15.5	21.2	42.4	43	21.8	No
49†	*31.9*	*63.8*	40.3	8.4	*25.4*†	***50.8***†	**34.8**†	9.4†	**Yes**
52	31.3	62.6	42	10.7	32.6	65.2	45.1	12.5	No*
53	21.7	43.4	30.6	8.9	*27*	***54***	**33.7**	6.7	**Yes**

*Although the post-stimulation value was less than twice the pre-stimulation value, it was not less than the approximate doubling of the upper range of normal (23 ug/dL) and therefore the subject was not considered suppressed.

Pre-stimulation values that exceed the upper range of normal (23ug/dL) and the corresponding doubled values are italicized.

Subject numbers of subjects with HPA axis suppression at baseline based on sixty-minute criteria are underlined.

†These values represent Week 1 sampling in subject 49, the last stimulation values available for this subject.

Source: Sponsor's NDA submission vol. 1.24, pp.1368-72, and reviewer's computations.

Using the labeled criteria for HPA axis suppression when serum cortisol is measured 60 minutes after stimulation with cosyntropin, 9 of 14 subjects in both the clobetasol propionate shampoo group and 8 of 12 subjects in the Dermoval®/Temovate® gel group are suppressed. However, 11 of 14 subjects in the clobetasol propionate shampoo group and 9 of 12 in the Dermoval/Temovate gel group would not have qualified as having a normal HPA axis based on the criteria of approximate doubling of the pre-stimulation baseline serum cortisol level when measured 60 minutes after cosyntropin stiumlation. Four subjects in the Clobetasol Propionate Shampoo, 0.05% group and five in the Dermoval® Gel group had baseline prestimulation levels that exceeded the normal range; these subjects are not ideal for inclusion in a study of HPA axis suppression.

Reviewer's comment: *In study **2620**, the Sponsor selected a suboptimal sampling time, failed to exclude subjects with abnormal baseline HPA axes, and stimulated the subjects' HPA axes weekly with cosyntropin. Because of these issues in study design, the high incidence of apparent HPA axis suppression is difficult to interpret.*

Plasma Clobetasol Levels

Plasma clobetasol levels were obtained in four studies, which included 141 subjects who received Clobetasol Propionate Shampoo 0.05%. Two of the studies were HPA axis suppression studies, studies **2620** and **18070**. In both of these studies, no subject had quantifiable amounts (———) of clobetasol propionate in blood. The remaining two studies, **18075** and **2577**, were Phase 3 trials. In study **18075**, a U.S. pivotal trial, one subject in the Clobetasol Propionate Shampoo 0.05% group had a plasma clobetasol level of ——— In study **2577**, three subjects had plasma clobetasol levels below the limit of quantification (———) but above the limit of detection (———

*Reviewer's comment: The paucity of subjects with quantifiable levels of serum clobetasol would only be reassuring in the absence of the signal for HPA axis suppression. In light of the HPA axis suppression seen in **18070**, the absence of quantifiable levels of serum clobetasol suggests that the HPA axis is exquisitely sensitive to this drug moiety.*

Other Laboratory Parameters

Routine clinical laboratory data was collected in studies **2620, 18070** and **18075**. No clinically significant laboratory abnormalities were identified.

Local Safety – Ocular

Ocular burning/stinging:

Three studies actively assessed for ocular burning/stinging: **1.CG.03.SPR.2620**, **RD.03.SPR.2638** and **RD.03.SPR.2648**. Study **2620** is a Phase 2 safety study that assessed HPA axis suppression (above) and ocular safety, and studies **2638** and **2648** are non-pivotal Phase 3 safety and efficacy studies. In study **2620**, ocular burning/stinging was assessed by the

subject at inclusion, baseline, and week 1, 2, 3 and 4, and in studies **2638** and **2648** at baseline and weeks 2 and 4.

No subjects reported ocular burning/stinging at any timepoint in study **2620**.

In study **2638**, ocular burning/stinging was reported in both treatment groups at all time points. In the active group (clobetasol propionate shampoo), the incidence of ocular burning/stinging decreased from 11.8% at baseline to 8.1% at week 4. In the comparator group (Daivonex® solution, which was not rinsed), the incidence of ocular burning/stinging increased from 4.0% at baseline to 6.3% at week 4.

In study **2648**, ocular burning/stinging was reported in both treatment groups and decreased in incidence in both groups over time. In the active group (clobetasol propionate shampoo), 7.5% of subjects reported ocular burning/stinging at baseline and 0.9% at week 4. In the comparator group (Polytar® Liquid Shampoo), 5.0% of subjects reported ocular burning/stinging at baseline and no subjects (0%) at either week 2 or 4.

Other measures of ocular safety

Study **2620**

In addition to HPA axis suppression (previous subsection), ocular safety was also assessed in Study **2620**. Briefly, 26 subjects with moderate to severe scalp psoriasis were randomized to receive either clobetasol propionate shampoo, 0.05%, 10ml to be applied to dry scalp once daily for 15 minutes before rinsing, or Dermoval/Temovate gel, 0.05%, applied to the scalp BID in amounts not to exceed 40 gm/week. Treatment was continued for four weeks. Ocular safety was assessed at inclusion and baseline and then weekly throughout treatment.

Ocular safety parameters included visual acuity, intraocular pressure, slit lamp examination (conjunctival hyperemia, chemosis, discharge, follicles, papillae and giant papillae; corneal edema and fluoroscein staining); and ocular subjective symptoms (overall ocular tolerance, burning and stinging). There were no clinically significant changes in visual acuity in either treatment group during the study. There were no clinically significant changes in intraocular pressure in either treatment group throughout the study, and no subject had elevated intraocular pressure at any time point in either treatment group. No subject had abnormalities in any of the assessed parameters on slit lamp examination at any time point during the study, nor were there any clinically significant changes noted in any slit lamp parameter. No subject in either treatment group reported ocular burning or stinging at any time point, and all subjects scored the overall ocular tolerance as acceptable (vs. not acceptable) at all time points.

Ocular AEs

Two ocular AEs were reported in the Phase 2 and 3 studies. In Study **2577**, a non-pivotal Phase 3 study, one subject in the clobetasol propionate shampoo group reported a bilateral ocular tight sensation/swelling sensation of the eyelids of mild severity with onset on study day 1 and resolution on day 18. In Study **18076**, a pivotal Phase 3 trial, one subject in the clobetasol

propionate shampoo group reported eye irritation/conjunctivitis of mild severity with onset on study day 8 and resolution on day 9.

Local Safety – Cutaneous Irritation and Sensitization

A standard, repeat insult patch test study was performed using two formulations of clobetasol propionate vehicle shampoo (with and without preservative) to determine their potential to cause contact irritation or sensitization.

Study 1.GUS.04.SPR.18032

Study Design

Two hundred and nineteen subjects enrolled in this single-center, randomized, controlled, evaluator-blinded, intra-individual study consisting of a 3-week induction phase, a 2-week rest period, and a single-application challenge phase. A 5% dilution of a preservative and a non-preservative-containing Vehicle Shampoo along with petrolatum control were applied under occlusion, and undiluted preservative-containing Vehicle Shampoo was applied and not occluded. Applications were left in place for 48 hours, after which the site was evaluated and study agents reapplied three times weekly for the first three weeks. After a two-week rest period during which no applications were made, test materials were reapplied to naïve sites on the back for 48 hours and evaluated at the time of patch removal (48 hours) and 24 hours later (72 hours), and again after 24 hours (96 hours) if there was any reaction at 72 hours after challenge. Sensitization was defined as a reaction score of 2 (erythema with mild edema) or greater on the sensitization response scale.

Reviewer's comment: The two formulations of the vehicle shampoo used in study 18032 differed only by the presence or absence of the preservative [redacted] *is a known sensitizer. The Vehicle Shampoo formulation without* [redacted] *is identical to the marketed formulation less the active ingredient, clobetasol propionate.*

The study evaluated only vehicle shampoo. The active ingredient in clobetasol propionate shampoo, clobetasol propionate, is a super high potent topical steroid and as such may obscure an irritant or allergic response. Clobetasol propionate itself can be a sensitizer, albeit infrequently.

Results

Two hundred and seventeen subjects completed the irritation/induction phase of the study. For the preservative-containing Vehicle Shampoo under occlusion, 203 subjects had maximum responses of Grade 0 (no reaction) or Grade 1 (mild erythema), while six had maximum responses of Grade 2 (intense erythema), six of Grade 2D (damage to epidermis: oozing, crusting and/or superficial erosions) and two of Grade 2P (papular > 50%). For the preservative-free Vehicle Shampoo under occlusion, 197 subjects had maximum responses of Grade 0 or 1, 8 of

Grade 2, 9 of Grade 2D, and 3 of Grade 2P. No Grade 2, 2D, or 2P reactions were recorded for petrolatum or preservative-containing Vehicle Shampoo not under occlusion.

Reviewer's comment: The irritancy seen with the 5% dilution of the two formulations of Vehicle Shampoo (with or without [redacted]) under occlusion was similar. The vehicle contains sodium laureth sulfate and coco-betaine, both known cutaneous irritants. 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.

Two hundred and ten subjects completed the sensitization phase of the study. No subjects had a score of 2 or greater during the challenge phase. Fifty-four subjects in the group receiving Vehicle Shampoo with preservative under occlusion, fifty-two subjects in the group receiving Vehicle Shampoo without preservative under occlusion, and no subjects in the group receiving Vehicle Shampoo with preservative not under occlusion had a score of one.

Reviewer's comment: No safety signal for sensitization emerged from this study. However [redacted] coco-betaine and clobetasol propionate are recognized potential sensitizers, hence allergic contact reactions may be seen with wider use in the post-marketing phase.

Local Safety-Cutaneous Atrophy

Three studies, **1. CG.03.SPR.2620**, **RD.03.SPR.2638** and **RD.03.SPR.2648**, actively assessed for skin atrophy using either ultrasound (**2620**) or clinical exam (**2638** and **2648**).

In study **2620**, skin atrophy was measured using a B-Scan Ultrasound at baseline and weeks 2 and 4. Skin thickness was ascertained at three sites on the forehead scalp margin, and the means for all patients determined for each date. As a group, the mean skin thickness at baseline was 1.931mm, at week 2 1.867mm, and at week 4 1.878 mm.

Studies **2638** and **2648** assessed atrophy clinically using a 0 to 3 scale (none, mild, moderate, severe) again at baseline and weeks 2 and 4. In study **2638**, one subject in the Clobetasol Propionate Shampoo, 0.05% group increased from "none" at baseline to "mild" at weeks 2 and 4. No other subjects in either study had increased scores over baseline.

*Reviewer's Comment: Cutaneous atrophy is a recognized adverse effect of topical steroids, for which thin-skinned areas such as the face are at greater risk. The mean thicknesses from study **2620** are difficult to interpret because pooling of the ultrasound data would blunt outliers and may have masked individual occurrences of atrophy. The slight downward trend in the average thicknesses in study **2620** and the development of clinical atrophy in a subject in study **2638** warrants mention of atrophy in labeling.*

Local Safety – Telangiectasia

Three studies actively assessed for telangiectasia: **1. CG.03.SPR.2620**, **RD.03.SPR.2638** and **RD.03.SPR.2648**. All three studies used a clinical scale from 0 to 3 (none, mild, moderate, severe). In study **2620**, no subjects in either treatment group (Clobetasol Propionate Shampoo, 0.05% and Dermoval® Gel) had an increase over baseline score. In study **2638**, one subject in the Clobetasol Propionate Shampoo 0.05% group had an increase from "none" at baseline to "mild" at weeks 2 and 4. No subjects in the Daivonex® group had and increase over baseline. In study **2648**, one subject in the Clobetasol Propionate Shampoo 0.05% group had an increase from "none" at baseline and week 2 to "mild" at week 4, and one subject in the Polytar® Liquid Shampoo group also had an increase from "none" at baseline to "mild" at weeks 2 and 4. Telangiectasia was not reported as an adverse event in any of the Phase 2 or 3 studies of Clobetasol Propionate Shampoo 0.05%.

D. Adequacy of Safety Testing

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 treatment is adequate exposure for the development of HPA axis suppression or ocular hypertension to occur. Cutaneous atrophy or telangiectasia may also develop within four weeks time, although the risk of these local adverse effects may be expected to increase with increased duration of exposure. It would not be ethical to extend treatment beyond four weeks to monitor the rate of late development of local cutaneous adverse effects because of the risk of HPA axis suppression.

The Sponsor addressed the important areas of risk: HPA axis suppression, ocular safety and cutaneous safety. The evaluations of ocular and cutaneous safety were generally well conceived and executed. In contrast, the HPA axis studies were not of ideal design. The HPA axis studies enrolled subjects with abnormal baseline HPA axes and deviated from labeled criteria for Cortrosyn. Both HPA axis studies measured serum cortisol at 60 rather than 30 minutes post-stimulation, and the European adult study (**2620**) stimulated the adrenal glands weekly. Despite these shortcomings, a signal for HPA axis suppression was identified, but a Phase 4 study will be needed to further delineate the magnitude of risk.

E. Summary of Critical Safety Findings and Limitations of Data

Clobetasol Propionate Shampoo, 0.05% induced HPA axis suppression at a substantial rate under study conditions. In study **18070**, "HPA Axis Suppression Potential of Clobetasol Propionate Shampoo, 0.05% - An open-label study in adolescents with scalp psoriasis," five of twelve adolescent subjects manifested HPA axis suppression by this reviewer's analysis. In study **2620**, "Ocular Safety and HPA Axis Suppression Potential of Clobetasol Propionate Shampoo, 0.05% - A Study on Both Scalp Psoriasis and Scalp Seborrheic Dermatitis Subjects," nine of fourteen adult subjects with scalp psoriasis manifested HPA axis suppression by this reviewer's analysis; however, poor study design invalidates the data.

Both study **18070** and **2620** assessed adrenal function 60 rather than 30 minutes after cosyntropin stimulation. Additionally, study **2620** measured adrenal function weekly, which may have masked suppression by the repeated cosyntropin stimulation. Neither study used the criteria for

suppression recommended in the Cortrosyn® label. In study **18070**, this only affected the analysis of results, as all subjects had normal adrenal function at baseline by both the protocol criteria and the labeled criteria. In study **2620**, however, 12 of 14 subjects had abnormal adrenal function at baseline using labeled criteria (but not protocol criteria), including all 9 of the subjects that manifested HPA axis suppression at week 4, making it difficult to interpret the data from this study. Using labeled criteria for normal adrenal response, these subjects would not have been enrolled in the study.

The Cortrosyn® label recommends assessing adrenal function exactly 30 minutes after stimulation with Cortrosyn®. However, the label states that, "if the 60-minute test period is used, the criterion for a normal response is an approximate doubling of the basal plasma cortisol value." Using the labeled criterion for a normal adrenal response 60 minutes post-stimulation, 5 of 12 adolescents in study **18070** manifested adrenal suppression after 4 weeks of treatment with Clobetasol Propionate Shampoo, 0.05%.

In study **2620**, 9 of 14 adult subjects with scalp psoriasis treated for 4 weeks with Clobetasol Propionate Shampoo, 0.05% manifested HPA axis suppression using labeled criteria.

VIII. Dosing, Regimen, and Administration Issues

The Sponsor conducted two dose-range finding studies (**2577** and **2591**) to investigate the effect of duration of application and conditions of application (wet versus dry scalp) for Clobetasol Propionate Shampoo, 0.05% in scalp psoriasis. In the first (study **2577**), application for 10 minutes to wet scalp was found to be more effective than application for either 5 or 2.5 minutes to wet scalp. In the second (**2591**), application to dry scalp for 15 minutes was found to be comparable to application to application for 10 minutes to either wet or dry scalp, with a trend toward increased efficacy for the longer application. Because of greater subject convenience, application to dry scalp was selected as the condition of use, with duration for 15 minutes.

The only concentration of clobetasol propionate in the shampoo vehicle that was studied was 0.05%. All other formulations of clobetasol propionate marketed in the US are also of 0.05% concentration.

Once daily dosing was the only frequency of application of Clobetasol Propionate Shampoo, 0.05% that was studied. Although all other clobetasol propionate formulations marketed in the US are dosed twice daily, it seems logical to have pursued once daily (rather than BID) dosing for the shampoo.

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. Labeling will need to clearly instruct patients not to exceed recommended duration of use, as of familiarity with cosmetic shampoo may lead to the erroneous conclusion that Clobetasol Propionate Shampoo, 0.05% can be used on a continuous basis.

Additionally, all other marketed formulations of clobetasol propionate restrict the quantity of use to 50 gms/week. The pivotal trials assessed but did not limit weekly use; the mean grams per week used in the pivotal trials **18075** and **18076** was 34.5 and 32.7 gms respectively, although 17 and 6 subjects (of 99 and 95, respectively) in these two studies exceed 50gms/week useage. The Sponsor intends to package Clobetasol Propionate Shampoo, 0.05% in 4 fl oz/120 gm bottles. Packaging in 100gm bottles may be helpful in discouraging over-use.

IX. Use in Special Populations.

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The Sponsor performed subgroup analyses by gender of the primary efficacy endpoint, Success Rate at 4 weeks for the ITT population, using combined data from the two pivotal trials (**18075** and **18076**). At Week 4, for the ITT(LOCF) population, significantly more subjects in the Clobetasol Propionate Shampoo, 0.05% subgroups (Male only, Female only, Male and Female) had achieved Success (clear or almost clear) than in the Vehicle Shampoo subgroups (Male only, Female only, Male and Female).

Table 53: Comparison of Success Rates [N (%), p-value], Clobetasol Propionate Shampoo, 0.05% Vehicle Shampoo Vehicle Shampoo, ITT (LOCF), Combined Data for Studies 18075 and 18076, Subgroup Analyses by Gender

Visit	Male + Female		Male		Female	
Treatment	C P Shampoo	Vehicle Shampoo	C P Shampoo	Vehicle Shampoo	C P Shampoo	Vehicle Shampoo
N at baseline	194	96	84	42	110	54
	Success Rates					
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 4 (LOCF)	68 (35.1%) p<0.001	6 (6.3%)	32 (38.1%) p<0.001	1 (2.4%)	36 (32.7%) p<0.001	5 (9.3%)

Source: Sponsor's NDA submission vol 1.51, pp.11289, 11347-8.

Reviewer's Comment: *Clobetasol Propionate Shampoo, 0.05% appears to be effective for both genders for the treatment of moderate to severe psoriasis of the scalp.*

E. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Age

The Sponsor performed subgroup analysis of the primary efficacy endpoint, Success Rate at 4 weeks for the ITT population, using combined data from the two pivotal trials (**18075** and **18076**), to compare the response rate of adolescents (12 – 17 years), adults 18 to 64 years, adults 65 years and above, and all ages. At Week 4, for the ITT(LOCF) population, significantly more subjects treated with Clobetasol Propionate Shampoo, 0.05% achieved Success (clear or almost clear) than those treated with Vehicle Shampoo in the adolescent, adult and all ages subgroups. While proportionately more subjects treated with Clobetasol Propionate Shampoo, 0.05% than Vehicle Shampoo improved in the subgroup of adults aged 65 years and older, significance was not achieved; the Sponsor attributed non-significance to small numbers in this subgroup.

Table 54: Comparison of Success Rates [N (%), p-value], Clobetasol Propionate Shampoo, 0.05% Vehicle Shampoo Vehicle Shampoo, ITT (LOCF), Combined Data for Studies 18075 and 18076, Subgroup Analysis by Age

Visit	All ages (12-65yrs)		12 – 17 years		18 – 64 years		65 years and above	
Treatment	C P Shampoo	Vehicle Shampoo	C P Shampoo	Vehicle Shampoo	C P Shampoo	Vehicle Shampoo	C P Shampoo	Vehicle Shampoo
N at baseline	194	96	5	5	162	76	27	15
	Success Rates							
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 4 (LOCF)	68 (35.1%) p<0.001	6 (6.3%)	4 (80.0%) p=0.014	0 (0.0%)	55 (34.0%) p<0.001	5 (5.6%)	9 (33.3%) p=0.055	1 (6.7%)

Source: Sponsor's NDA submission vol. 1.51, p. 11199.

Reviewer's Comment: *Clobetasol Propionate Shampoo, 0.05% appears to be effective for the treatment of moderate to severe psoriasis of the scalp across the age ranges studied, although it is less clearly the case for subjects aged 65 and older (p=0.055).*

Study **18070** identified significant HPA axis suppression in adolescents; see pages 62-64 of this review.

Reviewer's comment: *Pediatric subjects are at greater risk for HPA axis suppression than are adults. Because of the significant HPA axis suppression seen among adolescents, Clobetasol Propionate Shampoo, 0.05% should not be approved for use by patients younger than 18 years of age.*

Race

Subgroup 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, reveals that significantly more subjects treated with Clobetasol Propionate Shampoo, 0.05% than with Vehicle Shampoo achieved Success in the Caucasian Only and Caucasian + Non-Caucasian subgroups. No significant difference in the success rate between treatment groups was found for the non-Caucasian subgroup, however. The Sponsor attributed the non-significance to the low numbers of non-Caucasian subjects enrolled.

Table 55: Comparison of Success Rates [N (%), p-value], Clobetasol Propionate Shampoo, 0.05% Vehicle Shampoo Vehicle Shampoo, ITT (LOCF), Combined Data for Studies 18075 and 18076, Subgroup Analysis by Race

Visit	Caucasian + Non-Caucasian		Caucasian		Non-Caucasian	
Treatment	C P Shampoo	Vehicle Shampoo	C P Shampoo	Vehicle Shampoo	C P Shampoo	Vehicle Shampoo
N at baseline	194	96	173	88	21	8
	Success Rates					
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 4 (LOCF)	68 (35.1%) p<0.001	6 (6.3%)	59 (34.1%) p<0.001	5 (5.7%)	8 (40.0%) p=0.462	2 (25.0%)

Source: Sponsor's NDA submission vol. 1.51, p.11200.

Table 56: Subject Demographics by Race, Combined Data for Studies 18075 and 18076, and US Census 2000 Data

Race	Clobetasol Propionate Shampoo, 0.05%	Vehicle Shampoo	Total	US population[14]
Caucasian	173	88	261 (90%)	75.1%
Black	5	2	7 (2.4%)	12.3%
Asian	2	0	2 (0.7%)	3.6%
Hispanic	12	6	18 (6.2%)	12.5%*
Other	2	0	2 (0.7%)	-
Total	194	96	290 (100%)	§

Source: Sponsor's NDA submission, vol. 1.33 p.4449 and 1.39 p.6718; reviewer's computations; US Census Bureau (see footnote citation).

*In the Census 2000, race was evaluated separately from ethnicity; "Hispanic or Latino" was a category for ethnicity but not for race. In the pivotal studies, "Hispanic" was a category for race.

§Because the categories used in the pivotal studies involved both race and ethnicity in the 2000 census, it is not possible to sum them together for the Census data.

[14] Overview of Race and Hispanic Origin, U.S. Census Bureau Census 2000 Brief, March 2001; p.3.

Reviewer's Comment: *The number of non-Caucasian subjects is low, both absolutely and relative to the US population. African Americans have fewer hair follicles per unit area of scalp*[15]*. Although the transappendegeal contribution to percutaneous absorption is likely small and early, it may be relatively more significant for this drug which uses short-contact application limited to the scalp. The lack of significant efficacy in non-Caucasians merits mention in labeling and further study in the non-Caucasian population.*

C. Evaluation of Pediatric Program

Pediatric subjects 12 to 17 years of age were studied to determine the safety and efficacy of Clobetasol Propionate Shampoo, 0.05% in this population for the treatment of moderate to severe scalp psoriasis. Children younger than 12 years were not included in any of the studies of this product. Clobetasol propionate in any other vehicle formulation is not approved for use in children younger than 12 years of age.

The sponsor conducted a phase 2 HPA axis suppression study of 13 adolescent subjects, aged 12 to 17 years. Although this study was not of ideal design, 5 of 12 subjects (PP population) manifested HPA axis suppression. This is a significant safety signal.

Additionally, both pivotal trials (**18075** and **18076**) and one non-pivotal trial (**2638**) enrolled adolescents as well as adults. The number of adolescents enrolled was small: 13 adolescents total in these three trials, 6 of whom were randomized to receive Clobetasol Propionate Shampoo, 0.05%. Despite the small numbers, subgroup analysis of adolescents in the two pivotal trials demonstrated efficacy for the primary efficacy endpoint.

Reviewer's Comment: *Clobetasol Propionate Shampoo, 0.05% appears efficacious for adolescent subjects 12 to 17 years of age with moderate to severe scalp psoriasis, but the high incidence of HPA axis suppression among adolescents makes the risk-benefit ratio unacceptable. Clobetasol Propionate Shampoo, 0.05% should therefore not be approved for patients less than 18 years of age.*

D. Comments on Data Available or Needed in Other Populations

Clobetasol propionate is absorbed systemically following topical administration, but serum levels are typically below the limit of detection. After absorption, clobetasol propionate, like other glucocorticoids, is metabolized by the liver and excreted by the kidneys. A search of PubMed using a combination of the terms "clobetasol", "metabolism" and "hepatic disease" did not yield any citations. It would be interesting to know the effect of hepatic impairment on HPA axis suppression in subjects treated with Clobetasol Propionate Shampoo, 0.05%. However, it is expected that the number of patients with hepatic impairment who will require use of this drug will be small, and a mandatory Phase 4 investigation of HPA axis suppression in this population would be impractical.

[15] Sperling LC. Hair densityin African Americans. Arch Dermatol 199; 185:656-8.

X. Conclusions and Recommendations

A. Conclusions

Clobetasol Propionate Shampoo, 0.05% is a super-high potent topical corticosteroid in a shampoo vehicle for which the Sponsor seeks approval for 15 minute application once daily for up to four weeks for the treatment of moderate to severe scalp psoriasis

In NDA 21-644, the Sponsor demonstrated in two pivotal Phase 3 trials, supported by one non-pivotal Phase 3 trial, that Clobetasol Propionate Shampoo, 0.05% is superior to vehicle for the above population. Both pivotal trials were adequate and well controlled. The primary efficacy variable, success rate, was based on Global Severity Scale dichotomized to success or failure, and was assessed at week four in the ITT (LOCF) population. 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 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. In the three non-pivotal trials, Clobetasol Propionate Shampoo, 0.05% was demonstrated to be non-inferior to comparator drugs (calcipotriol solution, Polytar Liquid® and Dermoval™ Gel), although weaknesses in study design limit the value of these findings. 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.

No serious adverse events were attributed to study drug use. The two most frequent AEs related to study drug were skin discomfort and pruritus; both were more frequent in the Vehicle Shampoo group than the Clobetasol Propionate Shampoo, 0.05% group. Telangiectasia and cutaneous atrophy were infrequently noted. No clinically significant increase in intraocular pressure was seen with four weeks of use. A signal for HPA axis suppression among adolescents was identified, but the studies were not optimally designed; a Phase 4 study to better characterize this risk is warranted, and Clobetasol Propionate Shampoo, 0.05% should be approved only for adults.

B. Recommendations

This reviewer recommends, from a clinical perspective, that the new drug application for Clobetasol Propionate Shampoo, 0.05% be approved for use in patients 18 years of age and older.

Additionally, this reviewer recommends that the Sponsor 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 pre- and exactly-30-minutes-post-stimulation serum cortisol levels 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.

Finally, this reviewer recommends that the Sponsor conduct a safety and efficacy study in non-Caucasian subjects, with particular attention to subjects of African-American and Asian ethnicity.

X. Appendix

A 4-Month Safety Update was received on September 26, 2003. Review did not reveal new information that would affect labeling.

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

/s/

Jill Lindstrom
1/13/04 01:27:42 PM
MEDICAL OFFICER

Markham Luke
1/14/04 12:54:20 PM
MEDICAL OFFICER
See also labeling review.

Stanka Kukich
1/15/04 08:42:02 AM
MEDICAL OFFICER
signing for Dr. Jonathan Wilkin, Division Director