The sponsor has submitted a 505 (b)(2) application using Temovate E Cream as the reference listed drug (RLD) product. Clobetasol lotion in this context should be non-inferior to this RLD. The margin of non-inferiority that the Division has used for similar NDA applications has been a non-inferiority margin of 10%. As can be seen from table 14, clobetasol lotion has a non-inferior margin that is smaller than -10% of Temovate E in the primary efficacy variable. This is supported by the fact that three out of 4 of the secondary efficacy variables also failed to show non-inferiority to Temovate E Emollient Cream (see table 15).

Trial #3 - RD.06.SRE.2651

Reviewer's Comment: *This European conducted trial is analyzed as a supportive study. This is primarily because the formulation of the reference listed drug product (Dermoval/Temovate Cream) is unavailable for comparison to any approved topical clobetasol propionate product in the United States. Thus, equivalency cannot be definitely established through a 505 (b)(2) application route.*

Title: "The Safety and Efficacy of Clobetasol Propionate Lotion 0.05% as compared to its Vehicle and Dermoval™/Temovate™ Cream in the Treatment of Moderate to Severe Plaque-type Psoriasis"

Investigators

1.	5093/France
2.	5038/France
3.	5043/France
4	5202/France
5	5105/Belgium
6.	5116/Belgium
7.	5201/Belgium
8.	5108/Germany
9.	5204/Germany
10	5169/Germany
11.	5205/Germany
12.	5110/Germany
13.	5198/Germany
14.	5199/Germany
15.	5168/Germany
16.	5200/Germany
17.	5153/Bulgaria
18.	5196/Bulgaria

Objective/Rationale

The objectives of the study are to evaluate clobetasol propionate lotion for safety and superior efficacy to its vehicle lotion in adult patients with moderate to severe psoriasis.

Furthermore, it also aims to show non-inferiority to another clobetasol propionate product, Dermoval Cream, 0.05%.

Overall Study Design

This study was to be conducted as a multicenter, randomized, double-blind, parallel group, investigator-masked, active and vehicle controlled comparison in patients with moderate to severe psoriasis. The clobetasol propionate lotion and its vehicle were double-blinded. The clobetasol lotion and Dermoval were investigator masked as the formulations of the two substances are different. Qualified patients, who met specific inclusion criteria, were randomized in a 3:3:1 to receive either clobetasol propionate lotion, 0.05%, Dermoval Cream, or clobetasol propionate lotion, respectively. This was to minimize the number of patients receiving vehicle lotion. Patients were to apply the medication to the affected areas twice daily for 4 weeks, not to exceed 50 grams/week application of medication. A 4-week follow-up period was to assess duration of response and any late occurring safety issues.

Evaluations of patients occurred at baseline, weeks 1, 2, 4, and 8.

Protocol

Inclusion Criteria

The inclusion criteria for this study are the same as those of study 9707.R02 (see page 12) except patients were required to have psoriasis that covered a minimum body surface area of 10% (as opposed to 15% in study 9707).

Exclusion Criteria

The exclusion criteria are the same as for study 9707 (see page 12).

Procedures and Observations

The procedures and observations for this study are the same as for study 9707 (see page 13).

Efficacy Endpoints

The primary efficacy variables specified in the protocol are global severity (by the investigator), which evaluates all treated disease areas and the dermatologic sum score which comprises the sum of erythema, plaque elevation, and scaling for the target lesion. The secondary efficacy variables included erythema, plaque elevation, scaling, pruritus, Investigator's Global Assessment of Improvement from baseline, Subject's Global Assessment of Improvement from baseline, and body surface area involvement with disease. The scales for this study are the same as those for study 9707 (see pages 14-15).

Results

There was a total of 222 patients who were enrolled and randomized in this study across 18 centers in Europe. Table 16 shows the patient disposition and demographics.

Table 16
Patient Disposition and Demographics
Study 2651 - ITT Population

Subjects	Clobetasol Propionate Lotion	Dermoval	Vehicle
Enrolled and randomized	94	95	33
Gender, n (%)			
Males	47 (50%)	56 (58.9%)	21 (63.6%)
Females	47 (50%)	39 (41.1%)	12 (36.4%)
Age, mean (SD), Range	48.71 (14.1) 20–80	47.29 (15.9) 18–87	50.94 (14.6) 22–79
Race, n (%)			
White	94 (100%)	95 (100%)	33 (100%)
Completed study	91 (96.8%)	93 (97.9%)	29 (87.9%)
Withdrawn, total	3 (3.2%)	2 (2.1%)	4 (12.1%)
Condition clear	0	2	0
Lack of efficacy	0	0	1
Adverse event	1	0	0
Subject's request	2	0	3
PP population	90 (95.7%)	90 (94.7%)	27 (81.8%)
Safety population	94 (100%)	95 (100%)	33 (100%)

Source: Sponsor's NDA submission - Volume 1.36, page 6557, pages 6596-6597.

Baseline severity of disease and body surface area of involvement and treatment were similar across all arms of the study as shown in table 17.

Table 17
Baseline Characteristics of Disease
Study 2651 - ITT Population

Score at baseline	Clobetasol lotion (Mean ±SD)	Dermoval™ cream (Mean ±SD)	Clobetasol lotion vehicle (Mean ±SD)
Global severity score (Scale 0-4)	2.64 ±0.62	2.60 ±0.55	2.64 ±0.65
Erythema (Scale 0-4)	2.89 ±0.66	2.87 ±0.66	2.97 ±0.77
Plaque elevation (Scale 0-4)	2.77 ±0.65	2.69 ±0.58	2.82 ±0.58
Scaling (Scale 0-4)	2.83 ±0.71	2.76 ±0.66	2.82 ±0.77
Body surface area involved (%)	23.63 ±13.46	21.72 ±11.36	22.24 ±15.55
Treated body surface (%)	22.24 ±12.97	20.59 ±11.33	20.18 ±13.42

Source: Sponsor's NDA Submission - Volume 1.36, page

lotion does not establish non-inferiority to another of the clobetasol propionate drug products, Dermoval (clobetasol propionate) Cream. The limit of the one-sided 97.5% confidence interval for all efficacy variables, both primary and secondary, are smaller than -10%.

D. Efficacy Conclusions

Clobetasol propionate lotion is efficacious in the treatment of corticosteroid responsive dermatoses when compare to placebo. However, this is a 505 (b)(2) drug application that was relying on finding non-inferiority with a similar drug product in order to establish a bridge of findings of safety and bioequivalence to that drug product. Clobetasol, in all three trials, failed to establish non-inferiority in efficacy to an already marketed clobetasol propionate product. In the two pivotal trials this product was Temovate E Emollient Cream.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Clobetasol propionate lotion, in my opinion, confers an unacceptable risk in terms of its systemic safety profile in the treatment of corticosteroid responsive dermatoses. It causes much more HPA axis suppression than does the RLD, Temovate E Emollient Cream. The cutaneous profile of CP lotion is similar to that of Temovate E. There were no routine laboratory parameters of clinical significance attributed to clobetasol propionate lotion.

B. Description of Patient Exposure

There are 5 studies that are evaluated for safety in this NDA submission. For this section, the studies will be grouped according to disease studied, psoriasis or atopic dermatitis. For ease of review, tables of the studies with specific characteristics of the trials are reproduced below. Psoriasis data will be discussed first.

Table 20
Psoriasis Studies

Study Number	CR.U9708	1.CR.U9707.R02	RD.06.SPR.2651
Phase/Design	2/open-label	3/double-blind, parallel group comparison	3/double-blind, parallel group comparison
Location	US – multicenter	US- multicenter	Europe – multicenter
Objective	HPA Axis Safety	Safety and Efficacy	Safety and Efficacy
Formulations	-CP Lotion -Temovate E Emollient Cream	-CP Lotion -Temovate E Emollient Cream -Lotion Vehicle	-CP Lotion -Temovate Cream* -Lotion Vehicle
Enrollment	24 adults	192 adults	222 adults
Randomization ratio	1:1	3:3:1	3:3:1
Dose	-3.6g/application, ≤50 g/wk 10-20% BSA	≤50 g/wk ≥15% BSA	≤50 g/wk ≥10% BSA
Number of Doses per Study Time Frame	4 wks, twice daily	4 wks, twice daily	4 wks, twice daily
Number of Visits	6	5	4
Measurement Timepoints	Screening, Baseline, wk 1, 2, 3, 4	Baseline, wk 1, 2, 4, and wk 8 follow-up	Baseline, wk 1, 2, 4
Measurements Related to Safety	BSA, HPA Axis parameters, routine laboratory tests, plasma clobetasol levels, telangiectasia, skin atrophy, AE	Changes in vital signs and weight, telangiectasia, skin atrophy, AE	Telangiectasia, skin atrophy, AE

Source: Sponsor's NDA submission: ISS, Volume 1.39, page 8504

Subject Accountability

The safety population included 438 subjects who received at least one dose of study medication for the psoriasis studies. Of these, 188 (42.9%) received clobetasol propionate lotion, 93 (21.2%) received Temovate E Emollient Cream, and 62 (14.2%) received lotion vehicle. The final 95 (21.7%) of these patients received Temovate Cream in the supportive European trial.

Reviewer's Comment: *The safety data from the European trial, 2651, in terms of adverse events is presented for completeness but is not directly applicable to this application as it is not the reference listed drug and the sponsor is unable to provide documentation that an exact drug product is marketed in the United States.*

Twenty-eight (6.4%) subjects discontinued prematurely. The most frequent reason for discontinuation was subject request (13, 3.0%) followed by lack of efficacy (5, 1.1%), then adverse event (3, 0.7%), condition clearing (2, 0.5%), protocol violation (2, 0.5%), lost to follow-up (2, 0.5%), and other (1, 0.2%). When discontinuations are compared between treatment groups across studies, each reason for discontinuation occurred in three or fewer

subjects with the exception of subject request where nine (14.5%) subjects in the lotion vehicle group discontinued due to subject request.[1]

Extent of Exposure

The majority of subjects in **study 9708** (83.3% and 75.0% respectively for CP Lotion and Temovate Emollient groups) received study drug for 28 days. For **study 9707**, the mean days on treatment were 28.28, 28.23, and 26.93 for CP Lotion, Temovate E, and lotion vehicle respectively. The mean days on treatment were 27.65, 27.67, and 25.97 for CP lotion, Temovate Cream, and Lotion vehicle respectively, in **study 2651**. When the data are compared between treatment groups, across studies, the median treatment durations were all 29.0 days for CP Lotion, Temovate E Cream, and Temovate Cream. Therefore, within and across studies, subjects received treatment approximately the same period of time.[2]

Exposure to Study Drugs

The exposure to study drugs was measured by calculating the average daily dose (in grams) for study 9708 and total drug used for studies 9707 and 2651 (in grams, using an adjusted estimate which assumes non-returned tubes were used in the same way as returned tubes). For **study 9708**, the mean amount used was 6.74 and 6.45 grams per day for CP Lotion and Temovate Emollient Cream, respectively. The mean total drug used was 131.18 g, 140.98 g, and 121.14 g for CP Lotion, Temovate Emollient, and Lotion Vehicle, respectively in **study 9707**. The amount of drug was determined to be comparable between treatment groups. The means, in study 2651, were 149.04 g, 124.27 g, and 118.86 g total, for CP Lotion, Temovate Cream and lotion vehicle, respectively.[3]

An overview of the atopic dermatitis trials are listed in table 21.

1

[1]Sponsor's NDA Submission - ISS - Volume 1.39, pages 8505-8506.
[2]Sponsor's NDA Submission - ISS - Volume 1.39, pages 8507-8508.
[3]Sponsor's NDA Submission - ISS - volume 1.39, pages 8508-8509.

Table 21
Atopic Dermatitis Studies

Study Number	1.GUS.04.SPR.18009	RD.06.SPR.18061	1.GUS.04.SPR.18001.R02
Phase/Design	2/open label	2/open label	3/double-blind, parallel group comparison
Location	US/multicenter	US/multicenter	US/multicenter
Objective	HPA axis Safety in subjects aged 12 or older	HPA axis safety in adolescents (ages 12-17)	Safety and Efficacy in subjects aged 12 or older
Formulations	-CP Lotion -Temovate E Emollient Cream	-CP Lotion -Temovate E Emollient Cream -Temovate Cream	-CP Lotion -Temovate E Emollient Cream -Lotion Vehicle
Enrollment	23 adults 1 adolescent	36 adolescents	204 adults 24 adolescents
Randomization ratio	1:1	1:1:1	3:3:1
Dose	Twice daily application ~3.6 g/application ≤50 g/wk 10-20% BSA	Twice daily application ~3.6g /application ≤50 g/wk ≥20% BSA	Twice daily application ≤50 g/wk ≥20% BSA
Number of Doses per Study Time Frame	Twice daily for 2 wks	Twice daily for 2 wks	Twice daily for 2 wks
Number of Visits	4	6	4
Measurement Time points	Screening, Baseline, wks 1 and 2	Screening Baseline, wks 1, 2, and wk 4 and 6 wk follow-up	Baseline, wks 1, 2, and wk 4 follow-up
Measurements Related to Safety	BSA, HPA Axis parameters, routine laboratory tests, plasma clobetasol levels, AE, telangiectasia, skin atrophy	BSA, HPA Axis parameters, routine laboratory tests, plasma clobetasol levels, AE, telangiectasia, skin atrophy, blood pressure	Telangiectasia, skin atrophy, AE

Source: Sponsor's NDA submission: ISS, Volume 1.39, page 8505

Subject Accountability

A total of 288 subjects were included in the safety population in the atopic dermatitis studies. of these, 121 (42%) received CP Lotion, 122 (42.4%) received Temovate E Emollient Cream, 12 (4.2%) received Temovate Cream, and 33 (11.5%) received lotion vehicle. Twenty-five subjects (8.7%) discontinued prematurely. The most frequent reason for discontinuation was lost to follow-up (11, 3.8%), followed by subject request (7, 2.4%), protocol violation (3, 1.0%), and other (3, 1.0%), then adverse event (1, 0.3%). When discontinuations are compared between treatment groups across studies, each reason for discontinuation occurred in 2 or fewer subjects with the exception of lost to follow-up. In this case, 5 subjects (4.1%) each in the CP Lotion and Temovate Emollient groups discontinued due to lost to follow-up. In addition, 3 subjects (9.1%) in the lotion vehicle group discontinued due to subject request.[4]

2

[4]Sponsor's NDA Submission - ISS - Volume 1.39, pages 8506-8507.

Extent of Exposure

All subjects received study drugs for 14 days in **study 18009**. Mean treatment durations were 14.5, 14.3, and 14.0 days for CP Lotion, Temovate E Emollient Cream, and Temovate Cream groups, respectively, in **study 18061**. For **study 18001**, mean treatment durations were 14.2, 14.5, and 13.5 days for CP Lotion, Temovate Emollient , and lotion vehicle groups, respectively. When the treatment durations were compared between treatment groups across studies, the median days on treatment were 15.0, 15.0, 14.0, and 15.0 days for CP Lotion, Temovate E Emollient Cream, Temovate Cream, and lotion vehicle, respectively. Therefore, treatment durations were similar between treatment groups both within studies and across studies (Sponsor's NDA Submission - ISS - Volume 1.39, page 8508).

Exposure to Study Drugs

For **study 18009**, the mean daily dose was 7.46 and 7.00 g/day for the CP Lotion group and Temovate Emollient group, respectively. The mean weekly medication usage in **study 18061** was 39.13, 18.08, and 15.55 g/week for the CP Lotion, Temovate E Emollient Cream, and Temovate Cream, respectively. The amount of drug used in **study 18001** was 54.99, 44.10, and 58.21 grams for CP Lotion, Temovate Emollient Cream, and lotion vehicle, respectively.

Reviewer's Comment: *The larger amount of mean drug use in study 18061, the HPA axis study, is due to 4 patients who used more than the weekly recommended amount of CP Lotion. All 4 of these patients exhibited HPA axis suppression. Drug usage and HPA axis suppression will be discussed under the section of systemic safety.*

Global Severity At Baseline

The sponsor states in the submission, Volume 1.39, pages 8512-8513, that there was a direct correlation between the amount of drug used and the severity of the disease state in the psoriasis studies and that the correlation of increased drug use also occurred in the atopic dermatitis studies related to either severity of disease at baseline or BSA. The disease state being compared are those with a rating of severe or very severe.

Reviewer's Comment: *Severity of disease state did seem to correlate with an increase in drug usage in the 3 phase 2 studies: 9708, 18009, and 18061 and in one of the pivotal phase 3 trials, 9707. In study 9708, (psoriasis) the amount of drug used was 6.74 g/day and 6.45 g/day, respectively, in the CP Lotion and Temovate Emollient groups with a corresponding 25% and 16.7% of subjects with the severe or very severe rating. The same can be said for study 9707, (psoriasis) where a higher percentage of Temovate E subjects (37%) had that severity rating compared to CP Lotion (34.1%), corresponding to 141.0 and 131.2 grams total, respectively. In both phase 2 atopic dermatitis studies, 18009 and 18061, there was a higher proportion of subjects in the CP Lotion arm with severe disease than in the Temovate E Emollient Cream arm: 18.2% vs. 15.4% and 28.5% vs. 10%, respectively. This corresponded to a higher use of medication in the CP Lotion arm than in the Temovate E arm in both studies (7.36 vs. 7.00 gram/ day, respectively in the former study and 39.13 vs. 18.08 grams/week, respectively in the second*

study). In this reviewer's opinion, the differences in drug usage can be ascribed to the severity of the disease and seems to correlate with the discrepancies between the arms in the percentage of patients with severe or very severe disease.

However, it is not so clear in the supportive European trial in psoriasis patients, study 2651, or in the pivotal phase 3 trial in atopic dermatitis patients, study 18001. In study 2651, patients in the CP Lotion group used 149.0 grams total when compared to 124.3 grams in the Temovate E Cream group. In this reviewer's opinion, the small difference in the proportion of patients with global severity scores between CP Lotion and Temovate E Cream (57.4% vs. 56.8%, respectively) does not account for this increased usage. The same can be said for study 18001, where 25% of patients in the CP Lotion group had such a severity rating compared to 35% in the Temovate E group, yet usage of drug product in the CP Lotion group was higher (54.99 grams) compared to 44.10 grams in the Temovate E Emollient Cream Group. I do not think that the small difference in BSA treated (36.1% vs. 34.6%), as the sponsor proposes is responsible for this higher usage.

Comparison of Drug Use by Disease State

Table 22 shows the proportion of patients in the pivotal phase 3 trials and the phase 2 trials who used greater than 50g/week of study drug, either CP lotion or Temovate E Emollient Cream. In the psoriasis studies more patients in the Temovate Emollient arm used more drug than in the CP Lotion arm. The opposite was true for the atopic dermatitis studies, where more patients in the CP Lotion arm used more than the recommended amount of drug product.

Table 22
Number (%) of Subjects with Drug Usage >50 g/Week
Phase 2* and Pivotal Phase 3 Studies

	Clobetasol Lotion	Temovate E Cream	Lotion Vehicle
N 9707 and 9708	92 17 (18.5%)	91 19 (20.9%)	29 5 (17.2%)
N 18001, 18009 and 18061	118 17 (14.4%)	116 8 (6.9%)	33 3 (9.1%)
N Total	200 34 (17%)	207 27 (13%)	62 8 (21.9%)

Source: Sponsor's NDA submission -Volume 1.39, page 8510.
*The added numbers for the phase 2 trials are those of patients that were deemed "evaluable" by the reviewer. "Evaluable" patients were those who did not exhibit HPA axis suppression at baseline and who pre- and post-treatment results.

***Reviewer's Comment:** This table shows that while some patients used more than the recommended amount of drug product, the majority of patients stayed within the recommended amount to treat their disease. Usage of more CP Lotion than recommended has systemic safety implications, but does not explain the entire systemic safety profile for this drug product.*

C. Methods and Specific Findings of Safety Review

The safety review of this drug product, clobetasol propionate lotion will focus on two aspects of safety, systemic safety as measured by hypothalamic-pituitary-adrenal (HPA) axis suppression testing on patients with active disease and cutaneous adverse events (primarily skin atrophy and telangiectasia) that are known to occur with the use of topical corticosteroids to varying degrees. Patients who had atopic dermatitis and psoriasis were studied. Again, the comparator drug in which a bridge for safety is attempted is Temovate E Emollient Cream, 0.05%.

Table 23 delineates a summary of all adverse events across the 5 studies that occurred in ≥ 1% of the subjects.

Table 23
Summary of Adverse Events ≥ 1% by Body System
ITT Population

Body System	Clobetasol Lotion N =309	Temovate E Cream N=215	Temovate Cream N=107	Clobetasol Lotion Vehicle N=95	Total N=726
Total Number of AEs	68	46	13	14	141
Total Number of Subejcts with AEs	49 (15.9%)	31 (14.4%)	9 (8.4%)	9 (9.5%)	98 (13.5%)
Body As A Whole	18 (5.8%)	16 (7.4%)	2 (1.9%)	0 (0.0%)	36 (5.0%)
Flu Syndrome	6 (1.9%)	4 (1.9%)	1 (0.9%)	0 (0.0%)	11 (1.5%)
Headache	4 (1.3%)	5 (2.3%)	1 (0.9%)	0 (0.0%)	10 (1.4%)
Pain	3 (1.0%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	5 (0.7%)
Skin and Appendages	18 (5.8%)	9 (4.2%)	4 (3.7%)	4 (4.2%)	35 (4.8%)
Worse Treated Disease	3 (1.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	4 (0.6%)
Skin Dry	3 (1.0%)	1 (0.5%)	1 (0.9%)	1 (1.1%)	6 (0.8%)
Discomfort Skin	4 (1.3%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	5 (0.7%)
Respiratory System	10 (3.2%)	5 (2.3%)	1 (0.9%)	3 (3.2%)	19 (2.6%)
Pharyngitis	5 (1.6%)	4 (1.9%)	1 (0.9%)	0 (0.0%)	10 (1.4%)
Sponsor's NDA submission: ISS, Volume 1.39, page 8640					

Table 24 summarizes adverse events that were felt to be related to the study drugs across all five studies. This does not include the cutaneous events of skin atrophy and telangiectasia which will be discussed separately.

Table 24
Summary of Related Adverse Events
(Excluding Skin Atrophy and Telangiectasia)
ITT Population

Body System	Clobetasol Lotion N=309	Temovate E Cream N=215	Temovate Cream N=107	Clobetasol Lotion Vehicle N=95	Total N=726
Total Number of AEs	13	3	3	5	24
Total Number of Subejcts with AEs	13 (4.2%)	3 (1.4%)	3 (2.8%)	5 (5.3%)	24 (3.3%)
Discomfort Skin	4 (1.3%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	5 (0.7%)
Skin Dry	3 (1.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	4 (0.6%)
Irritant Dermatitis	2 (0.6%)	1 (0.5%)	0 (0.0%)	1 (1.1%)	4 (0.6%)
Pruritus	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (2.1%)	3 (0.4%)
Worse Treated Disease	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	2 (0.3%)
Paresthesia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (0.1%)
Sponsor's NDA submission: ISS, Volume 1.39, page 8658					

Reviewer's Comment: *The categories with the most adverse events are "Body As A Whole" and "Skin Appendages". Headache, flu syndrome, and pain occurred in the patients using drug product but there was not an appreciable difference between CP Lotion and the RLD, Temovate E Emollient Cream. The same can be said for the adverse events that were considered related to the use of the drug product. I would agree that most of these skin related adverse events can be attributed to drug products.*

The primary cutaneous safety endpoints to be assessed were those of telangiectasis and skin atrophy. These are cutaneous findings that are known to occur with varying degree when using topical corticosteroids and tend to occur with either high potency topical corticosteroids or after prolonged use. For evaluation of telangiectasis and skin atrophy, the following scales were used (Source: Sponsor's submission, Volume 1.26 - pages 3298-3299):

Telangiectasis (as evaluated for all treated areas): dilation of blood vessels.

None	0	No telangiectasis
Mild	1	Slight telangiectasis characterized by appearance of a few fine, small red vessels (0.1 mm or less in diameter)
Moderate	2	Pronounced telangiectasis characterized by Appearance of several fine vessels and/or a few large vessels (0.2 mm or greater in diameter)
Severe	3	Severe telangiectasis characterized by appearance of many fine vessels and/or large vessels

Skin Atrophy (as evaluated for all treated areas): increased transparency of the epidermis and a shiny appearance.

None	0	No atrophy signs detectable
Mild	1	Slightly shiny skin with barely noticeable increased transparency
Moderate	2	Shiny skin thinned and vessels transparent; no signs of increased fragility detectable
Severe	3	Increased fragility of thinned skin with purpura, Erosions, telangiectasia and increased transparency; even small and deeper vessels detectable

These cutaneous events were assessed in all the trials. However, since telangiectasis and skin atrophy are often a late events, this review will only look at the studies that had a follow-up of at least 4 weeks post treatment. These trials included the two pivotal trials, 9707 (8-week f/u) and 18001 (4-week f/u), and the phase 2 trial in adolescents with atopic dermatitis (6-week f/u). Tables 25 and 26 assess the incidence of telangiectasis and skin atrophy for psoriasis and atopic dermatitis, respectively.

Table 25
Telangiectasia and Skin Atrophy – Psoriasis
Study 9707

AE	Clobetasol Lotion		Temovate E Cream		Vehicle Lotion	
	Baseline N=82	Worst response* N=82	Baseline N=81	Worst response* N=80	Baseline N=29	Worst response* N=27
Telangiectasis						
None	82 (100%)	80 (97.6%)	78 (96.3%)	76 (95.0%)	28 (96.6%)	27 (100%)
Mild	0	2 (2.4%)	3 (3.7%)	4 (5.0%)	1 (3.4%)	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Skin Atrophy						
None	81 (98.8%)	80 (97.6%)	80 (98.8%)	76 (95.0%)	28 (96.6%)	26 (96.3%)
Mild	0	2 (2.4%)	1 (1.2%)	4 (5.0%)	1 (3.4%)	1 (3.7%)
Moderate	0	0	0	0	0	0
Severe	1 (1.2%)	0	0	0	0	0

Sponsor's NDA Submission, Volume 1.26, pages 3433-3434

Table 26
Telangiectasia and Skin Atrophy - Atopic Dermatitis
Studies 18001 and 18061

AE	Clobetasol Lotion		Temovate E Cream		Vehicle Lotion	
	Baseline N=110	Worse response* N=107	Baseline N=109	Worst response* N=106	Baseline N=33	Worst response* N=31
Telangiectasis						
None	102 (92.7%)	98 (91.6%)	103 (94.5%)	99 (93.4%)	32 (97.0%)	30 (96.8%)
Mild	8 (8.3%)	7 (7.5%)	5 (5.1%)	7 (6.6%)	1 (3.0%)	1 (3.2%)
Moderate	0	1 (1.1%)	1 (1.0%)	0	0	0
Severe	0	0	0	0	0	0
Skin Atrophy						
None	104 (94.5%)	97 (90.7%)	103 (94.5%)	97 (91.5%)	31 (93.9%)	30 (96.8%)
Mild	5 (5.2%)	8 (7.5%)	6 (6.1%)	9 (8.5%)	2 (6.1%)	1 (3.2%)
Moderate	1 (1.0%)	2 (2.2%)	0	0	0	0
Severe	0	0	0	0	0	0

Source: Sponsor's NDA submission - Volume 1.30, page 5250, and Volume 1.22, page 1941).
* Worst response is defined as the worst post baseline response during the study.

Reviewer's Comment: *There was not much appreciable difference in the incidence of telangiectasis and skin atrophy between clobetasol propionate lotion and Temovate E Cream. As would be expected, CP lotion was worse than vehicle, which did not induce any such changes.*

Systemic Safety

There were 3 phase 2 studies performed to evaluate the potential of clobetasol propionate lotion to suppress the HPA axis. There were two studies in adults, one in moderate to severe psoriasis and one in moderate to severe atopic dermatitis and one study in adolescents in moderate to severe atopic dermatitis. The comparator drug product was the RLD, Temovate E Emollient Cream in all the studies. The atopic dermatitis study in adolescents had a third arm, Temovate Cream, 0.05%.

Reviewer's Comment: *Data from the Temovate Cream arm will be included in the results. However, the results will not be analyzed in terms of the relative safety of clobetasol propionate lotion, as it is not germane to this application, which is trying to establish a bridge of safety with Temovate E Emollient Cream. The sponsor stated in the preNDA meeting that this arm was added for the European study in an effort not to duplicate studies.*

Study Design

The design of the three studies was similar. Patients were randomized to either clobetasol propionate lotion or Temovate E Emollient Cream arms. They were to apply study medication to affected areas twice a day, not to exceed 50 grams/week of study medication. Entry criteria included that for the adult studies, patients had to have a minimum BSA

involvement of 10-20%. For the adolescent study, the minimum BSA involvement was 20%. Patients who had psoriasis were treated for 4 weeks, which parallels the pivotal trial and those in the atopic dermatitis studies were treated for 2 weeks, as in the pivotal phase 3 trial.

The primary safety endpoint for these trials was evidence of HPA axis suppression. To this end the sponsor was advised in the EOP2 meeting to have at least 12 evaluable patients per arm in each study. Evaluable is defined as patients who are not suppressed at baseline as evidenced by Cortrosyn testing and who are able to have Cortrosyn testing at the end of the study (end of treatment).

In all of the studies, patients had a pre-stimulation serum cortisol drawn, followed by IV injection of 0.25 mg of Cortrosyn. The post-stimulation cortisol was drawn 60 minutes after stimulation. In the adult studies, trial number 9708 (psoriasis) and trial number 18009 (atopic dermatitis), patients were stimulated multiple times while on therapy. In the former, stimulation was performed at screening, baseline, weeks 1, 2, and 4. In the latter study, patients were stimulated at screening, baseline, weeks 1 and 2. In the adolescent atopic dermatitis study, trial number 18061, patients were stimulated at screening and at week 2, end of treatment.

Reviewer's Comment: *Usually when testing for the potential of a drug product to cause HPA axis suppression, stimulation of the adrenal gland is done before drug treatment commences and at the end of treatment. The fact that in two of the phase 2 studies the adrenal gland is constantly being stimulated, may mask any suppressant effect of the drug product. The articles submitted by the sponsor does not address the question of multiple stimulations in the same patient. Therefore, in this review, the results of the adolescent study is given more weight in assessing the potential of clobetasol propionate lotion to suppress the HPA axis, especially as compared to the RLD, Temovate E Emollient Cream.*

The criteria set forth in the protocols for the definition of HPA axis suppression is not the same for all three studies. For the adult studies, one in psoriasis and one in atopic dermatitis, HPA axis suppression is defined as a pre-stimulation serum cortisol < 10mcg/dL and a post-stimulation serum cortisol< 18mcg/dL. HPA axis suppression is defined as a pre-stimulation serum cortisol of <7mcg/dL and a post-stimulation serum cortisol of < 18mcg/dL in the adolescent atopic dermatitis study.

Reviewer's Comment: *The criteria that the sponsor chose in the protocol are not the same criteria that the Division uses for assessing HPA axis suppression. Furthermore, the value chosen for the pre-stimulation serum cortisol appears arbitrary. This reviewer is not aware of any difference in the response of the adrenal gland between adults and adolescents ages 12-17 that would warrant a difference in the required baseline value for normality.*

The Division follows the Cortrosyn label in assessing adrenal function via stimulation by this drug product. Namely, the label states, "...the following criteria have been established to denote a normal response:

1. *The control plasma cortisol level should exceed 5 micrograms/100 mL.*
2. *The 30-minute level should show an increment of at least 7 micrograms/100 mL above the basal level.*
3. *The 30-minute level should exceed 18 micrograms/100 mL..."*

The label goes on to say, "Plasma cortisol levels usually peak about 45 to 60 minutes after an injection of Cortrosyn® and some prefer the 60-minute interval for testing for this reason. While it is true that the 60-minute values are usually higher than the 30-minute values, the difference many not be significant enough in most cases to outweigh the disadvantage of a longer testing period."

The sponsor chose to wait the 60 minute interval, to get a peak response, but this does not negate the use of the 30-minute criteria to assess the HPA axis . In my review, the absence of any of these three criteria means that the patient is exhibiting HPA axis suppression.

Results

Study RD.06.SRE.18061 - Adolescents with Moderate to Severe Atopic Dermatitis

There were 36 patients ages 12-17 enrolled in the study. This included 14 patients in the clobetasol propionate arm, 10 patients in the Temovate E Emollient Cream arm, and 12 patients in the Temovate Cream arm. Interestingly, with a 50 gram/week limit, patients were dispensed 140 grams/week of CP lotion and only 65 grams of Temovate E Emollient Cream each week.

The overall mean percent BSA was comparable among treatments. Similarly, percent BSA was comparable among treatments for patients with or without HPA axis suppression. The mean percent BSA was relatively higher for patients with HPA axis suppression than that of patients without HPA axis suppression for each treatment group (32.8% vs. 27.7%; 35% vs. 25.3%; 34% vs. 23.6% for CP lotion, Temovate E and Temovate Cream, respectively).

Reviewer's Comment: *There were 4 subjects in the study where it was recorded that they used none or almost no drug product (see Appendix A, table A.1). Given the entry criteria, this is probably erroneous recording of the data. These same patients were not included in the analysis of BSA.*[5] *None of the patients are in the CP Lotion arm of the study. In this reviewer's opinion, it will skew any generalizations concerning mean drug usage in this study.*

There were 9 out of 14 (64.3%) subjects that experienced HPA axis suppression in the CP Lotion arm, 2 out 10 (20%) in the Temovate E Emollient Cream arm, and 4 out of 12 (33%) in the Temovate Cream arm. Table 27 lists the subjects with HPA axis suppression and table 28 gives the summary.

[5] The mean percent for the Temovate E and Temovate Cream arms without HPA axis suppression is an approximation since 2 patients from each arm were not included. It will not change appreciably because their BSA ranged from 20%-27%.

Table 27
Patients with Evidence of HPA Axis Suppression
Study 18061 - Atopic Dermatitis (Adolescents)

Pt. #	Age of Patient (years)	%BSA	Grams Used (2 weeks)	Clobetasol Propionate Lotion Serum Cortisol (µg/dL)[1]		
				Pre-stimulation	Post-Stimulation	Change[2]
013	16	20	17.6	[redacted]	[redacted]	**6.8**
011	14	26	29.8	[redacted]	[redacted]	**-3.1**
044*	13	22	125.6	[redacted]	[redacted]	**4.9**
009*	15	20	123.6	[redacted]	[redacted]	**2.3**
026	13	31	72.7	[redacted]	[redacted]	19.3
034*	12	35	193.2	[redacted]	[redacted]	**3.4**
047	17	42	49	[redacted]	[redacted]	**6.7**
001*	17	54	154	[redacted]	[redacted]	13.4
062*	16	45	@	[redacted]	[redacted]	@
				Temovate E Emollient Cream Serum Cortisol (µg/dL)[1]		
038	15	30	25	[redacted]	[redacted]	**5.9**
018	13	40	69.4	[redacted]	[redacted]	**2.8**
				Temovate Cream Serum Cortisol (µg/dL)[1]		
014	14	35	91.5	[redacted]	[redacted]	11.1
008	15	30	29.0	[redacted]	[redacted]	6.7
017	14	50	39.9	[redacted]	[redacted]	10.1
060	15	21	76.0	[redacted]	[redacted]	6.6

Source: Sponsor's NDA submission - Volume 1.16 Line listing SAF 1, pages 2716-2725 and Listing SUBL 10, pages 2696-2701
*Considered suppressed by the sponsor
^Below the limit of quantification
@No information but patient failed with the value given and sponsor did a f/u 2 weeks later. Specimen may have been lost as a post-stimulation time of injection and blood collection was documented. At 4 week f/u, patient was retested and showed recovery of HPA axis function.

Table 28
Summary of Patients with HPA Axis Suppression
Study 18061- Atopic Dermatitis (Adolescents)

HPA Response	Clobetasol Propionate Lotion N=14	Temovate E Emollient Cream N=10	Temovate Cream N=12
YES	9 (64.3%)	2 (20%)	4 (33%)
NO	5	8	8

Reviewer's Comment: *This study is probably the most accurate of the three HPA axis studies in assessing the potential of the drug products studied to suppress the HPA axis. Stimulation was performed at screening before treatment and at the end of treatment. It also had more than the required number of evaluable patients requested by the division in the clobetasol propionate lotion arm.*

As stated before, it appears that accurate recording of the data for grams used was not kept, at least in the case of four subjects who used little to none or even had negative drug use. This seems highly unlikely given the state of their disease at baseline (moderate to severe with ≥ 20% BSA involvement. However, if the data is analyzed as given, even though there were four patients in the CP lotion arm that used more than the recommended amount, four patients were suppressed that did not exceed the recommended amount of drug usage (4/9=44%). This is still more than twice the proportion of suppression in the Temovate E Emollient Cream arm. Since trials are controlled situations and patients had overuse of medication, the potential for overuse of a lotion formulation is probably great. Overuse of CP lotion led to 100% suppression in this study.

Four of the 9 patients with HPA axis suppression on CP lotion were restimulated at week 3 or 4 of follow-up and 3/4 had recovered, 1/1 on Temovate E Emollient Cream had recovered, and 1/3 retested on Temovate Cream recovered. Patient 009 on CP lotion remained suppressed two weeks post treatment with prestimulation cortisol of ——— post stimulation cortisol of ——— and an incremental rise of only 6.6 µg/dL.

Reviewer's Comment: *Although a small sample size, 25% of the patients retested on CP lotion remained suppressed 2 weeks after discontinuation of the drug product whereas 100% of the patients retested on Temovate E Emollient Cream recovered. The analysis for recovery of HPA axis suppression for clobetasol lotion is not complete as 5 out of 9 patients who exhibited suppression were not retested.*

Study CR.U9708 - Adults with Moderate to Severe Plaque Psoriasis

There were 24 patients enrolled in the study. Twelve subjects finished in the CP Lotion arm and 12 subjects finished in the Temovate E arm. The mean body surface area affected at baseline was 21.8% (SD 15.4%) for CP Lotion and 26.8% (SD 12.9%) for Temovate E Cream. The mean BSA treated at baseline for CP Lotion and Temovate E was 16.2% (SD 9.6%) and 17.9% (SD 9.4%), respectively. The mean BSA treated at week 4 (end of treatment) for CP lotion and Temovate E was 17.2% (SD 9.5%) and 18.8% (SD 9.5%), respectively.

Reviewer's Comment: *The percent BSA treated was comparable in the two arms of the study. Although 12 patients completed the study in each arm, there were only 10 evaluable patients in each arm, as 2 from each arm showed evidence of HPA axis suppression during pre-treatment evaluation (see Appendix A, table A.2).*

There were 8 out of 10 (80%) evaluable subjects in the clobetasol propionate arm that showed evidence of HPA axis suppression during the study. This is in contrast to Temovate E Emollient Cream, where only 3 out of 10 (30%) evaluable subjects demonstrated HPA axis suppression. Table 29 lists the patients with serum cortisol changes consistent with HPA axis suppression for both arms of the study.

Table 29
Patients with Evidence of HPA Axis Suppression
Study 9708 - Psoriasis

Pt. #	Week #	Grams Used	Clobetasol Propionate Lotion N=10 Serum Cortisol (µg/dL)[1]		
			Pre-stimulation	Post-Stimulation	Change[2]
901^*	1	59.3			12.9
904^*	2	56.9			10.6
906	2	44.6			4.5
910^	2	56.6			17.8
702	2	47.4			15.7
704^*	1	70.8			14.1
708^*	1	60.9			11.1
711	2	39.8			6.1
			Temovate E Emollient Cream N=10 Serum Cortisol (µg/dL)[1]		
907	1	52.1			6.5
912	1	56.0			5.6
706	1	42.4			19.8

Source: Sponsor's NDA Submission - Line listings, Volume 1.21, pages 1272-1289
[1]Abnormality bolded
^Patient suppressed at more than 1 time point
*Considered suppressed by the sponsor
[2]Defined as the difference between the pre- and post-stimulation cortisol

Table 30 compares the proportion of patients on CP Lotion with those on Temovate E Cream who were suppressed at each time point during the study.

Table 30
Proportion of Subjects with HPA Axis Suppression
Study 9708 - Psoriasis

Weeks of Treatment	Clobetasol Propionate Lotion N=10	Temovate E Emollient Cream N=10
1	3 (30%)	3 (30%)
2	6 (60%)	0 (0%)
4	4 (40%)	0 (0%)

Source: Sponsor's NDA Submission - Line Listings, Volume 1.21, pages 1279-1286

Reviewer's Comment: *One can note, from tables 29 and 30, that more patients had episodes of HPA axis suppression on clobetasol propionate lotion. Furthermore, the fact that patients continued to experience suppression despite the fact that the adrenal gland was constantly being stimulated suggests that the true value of suppression by clobetasol propionate lotion may be underestimated. Patients continued to exhibit suppression while using CP Lotion, even though the adrenal gland was being stimulated, 60% at week 2 and 40% at week 4. Patients using Temovate E emollient Cream, on the other hand, were able to recover with stimulation, despite*

continued use of the drug (0% of patients suppressed at week 2 and week 4). Five patients in the CP Lotion arm experienced HPA axis suppression at more than one time point compared to none in the Temovate E arm. Of the two patients that were retested because of HPA axis suppression in the CP Lotion arm, numbers 904 and 704, subject #704 remained suppressed 8 days after treatment, with a pre-stimulation serum cortisol of [redacted] a post-stimulation serum cortisol of [redacted] and an incremental change of only 6.0 µg/dL.

While it is true for clobetasol propionate that using >50 grams per week increases the risk for HPA axis suppression, the risk appears even greater for clobetasol propionate lotion, as 5/8 (63%) patients became suppressed compared to 2/7 (29%) patients in the Temovate E arm. There were some patients that suppressed at lower amounts and some that used higher amounts that did not suppress. This may have been due to the multiple stimulations that patients were given.

Study CR.U18009 - Adults with Moderate to Severe Atopic Dermatitis

There were 24 patients enrolled in the study. Eleven subjects finished in the CP Lotion arm and 13 subjects finished in the Temovate E arm. The mean body surface area affected at baseline was 28.6% (SD 23.5%) for CP Lotion and 33.4% (SD 22.3%) for Temovate E Cream. The mean BSA treated at baseline for CP Lotion and Temovate E was 19.3% (SD 8.5%) and 19.4% (SD 11.7%), respectively. The mean BSA treated at week 4 (end of treatment) for CP lotion and Temovate E was 19.8% (SD 8.4%) and 18.8% (SD 9.4%), respectively.

Reviewer's Comment: *The mean BSA treated in this study was comparable between CP Lotion and Temovate E Cream. Two of the subjects in the CP Lotion arm were suppressed at baseline and 4 subjects in the Temovate E arm were suppressed at baseline, including the only adolescent (see Appendix A, Table A.3). Therefore, there were 9 evaluable subjects in each arm.*

There were 5 out of 9 (56%) evaluable subjects in the clobetasol propionate lotion arm that showed evidence of HPA axis suppression during the study. Four out of 9 (44%) evaluable subjects demonstrated HPA axis suppression in the Temovate E arm. Table 31 lists the patients with serum cortisol changes consistent with HPA axis suppression for both arms of the study.

Table 31
Patients with Evidence of HPA Axis Suppression
Study 18009 - Atopic Dermatitis (Adults)

Pt. #	Week #	Grams Used	Clobetasol Propionate Lotion Serum Cortisol (µg/dL)[1]		
			Pre-stimulation	Post-Stimulation	Change[2]
1003^*	1	45.1	[redacted]	[redacted]	12.9
1005*	2	79.1	[redacted]	[redacted]	**7.1**
1009	2	52.2	[redacted]	[redacted]	**10.2**
1012	1	57.8	[redacted]	[redacted]	27.4
810^*	1	45.0	[redacted]	[redacted]	13.5
			Temovate E Emollient Cream Serum Cortisol (µg/dL)[1]		
1008	2	46.7	[redacted]	[redacted]	5.9
807*	2	55.2	[redacted]	[redacted]	10.4
808^*	1	48.3	[redacted]	[redacted]	**12.6**
809^	1	51.2	[redacted]	[redacted]	**2.7**

Source: Sponsor's NDA Submission - Line listings, Volume 1.22, pages 1822-1829 and 1815-1818
[1]Abnormality bolded
^Patient suppressed at more than 1 time point
*Considered suppressed by the sponsor
[2]Defined as the difference between the pre- and post-stimulation cortisol

Reviewer's Comment: *A greater proportion of patients who used clobetasol propionate lotion exhibited HPA axis suppression during this study than did those who used Temovate E (12 %). Of the patients who were tested for recovery of the adrenal gland post-treatment, 1/3, subject 1005, failed to recover after 7 days in the CP Lotion arm. This is in contrast to the Temovate E arm where 2/2 patients, who were tested for recovery of the adrenal gland post-treatment, recovered.*

Other Laboratory Parameters

In the patients studied in the trials, there were not any routine laboratory parameters that were of clinical significance.

Phase 1 Dermal Safety Studies

The sponsor was required to perform dermal safety studies with the to-be-marketed formulation of the drug product. These studies were to include cumulative irritancy, contact sensitization, phototoxicity, and photocontact allergy trials. The latter 2 trials are waived as the sponsor provided data that clobetasol propionate and the components of the vehicle do not absorb in the UV or visible light range. There may be 2 reasons that the contact sensitization trial was done with the lotion vehicle only rather than the to-be-marketed formulation. First, because of the nature of this super potent steroid, any contact sensitization that may occur in the vehicle would probably be masked and second, since this is a 505 (b)(2) application, the finding of safety

may be bridged to the RLD. Therefore, a contact sensitization study done with lotion vehicle only is acceptable.

Study # 1.CG.03.SPR.2129 - "Evaluation of Cutaneous Tolerance after Repeated Application for 21 Days on Healthy Skin of Two Formulations of Clobetasol Propionate Lotion, 0.05% and their Vehicle"

Two formulations of CP Lotion and their vehicle were assessed for skin tolerance after 21-day repeated applications under occlusion in normal healthy subjects (15 females and 11 males; ages 19.6 -40.3) using the method of **Philips (1972).**

Study Design

This study was conducted as an intra-individual, investigator-masked, controlled and randomized study. Prior to study entry, subjects were screened for enrollment according to specific protocol inclusion/exclusion criteria. After giving informed consent, the subjects were enrolled and the four materials, two treatments and two vehicles, were applied under occlusion at four different sites on the subject's back. Five applications per week were performed over three weeks. The duration of application was 24 hours and 72 hours during weekends. Cutaneous reactions were scored following the scale 0 to 4 (0 = no erythema and 4 = important erythema). For each treatment, an Individual Irritation Index was calculated for every subject by averaging the scores across evaluations. A Mean Irritation Index (M.I.I.) was calculated for each treatment.

Study Results

This three week repeated irritation study with twenty-six healthy volunteers confirmed the good clinical tolerance of both formulations of CP Lotion (formulations 661.341 and 661.337). Their corresponding vehicles were as well tolerated as the actives. None of the tested products produced more than a maximum score of 1 (slight erythema with or without edema) during the trial and overall mean Irritation Index (M.I.I.) was very low (≤ 0.131) in the study. According to the irritation classification, the 2 formulations of CP Lotion and their vehicle were therefore classified as non-irritant.

Reviewer's Comment: *According to the M.I.I. table on page 544 of Volume 1.19 of the Sponsor's submission, any substance with an index ≤ 0.25 is classified as a non-irritant. The sponsor stated that the only difference between the two products of clobetasol propionate lotion studied was the presence of* [redacted] *The sponsor did perform this study with the to-be-marketed formulation.*

Study #1.GUS.04.SPR.1802 - "Evaluation of Contact Irritation and Sensitization Potential of Clobetasol Propionate Lotion Vehicle Following Repeated Applications to the Skin of Humans (Repeat Insult Patch Test)"

CP Lotion vehicle was assessed to determine if any ingredient of the lotion vehicle causes irritation and/or sensitization after repeated application under occlusive patches to the skin of

healthy subjects (187 females and 25 males; ages 18 - 76), using a standard repeat insult patch testing (RIPT) methodology.

Study Design

This study was conducted as a single-center, randomized, controlled, evaluator-blinded, intra-individual trial that extended over a six week period and consisted of an induction phase, a 2-week rest period, and a challenge phase. Prior to study entry, subjects were screened for enrollment according to specific protocol inclusion/exclusion criteria. After giving informed consent, the subjects were enrolled and received two patches, CP Lotion vehicle and petrolatum, applied to their back. During the first 3 weeks (induction phase), each subject was instructed to leave the patch in place until the next clinic appointment, approximately 48 hours after application (72 hours over the weekend).

During weeks 4 and 5, the patch sites were allowed to rest; no applications were made during this period. The test materials were applied one last time during the sixth week to evaluate sensitization potential (challenge phase) to naïve sites on the back. Any subject with a suspected sensitization was to have been re-challenged after a rest period of approximately one week. Evaluation of patch sites consisted of irritation and sensitization grading on five point scales from 0 to 4 with a score of 0 noting no reaction. Sensitization was defined as a reaction score of 2 or greater as documented in the sensitization reaction scale in at least one of two challenge readings (any subject who developed a reaction of "1" or greater at the 72-hour evaluation was evaluated 24 hours later if possible, i.e. 96 hours after application).

Two hundred twelve subjects were enrolled and 201 subjects completed the study. Of the 212 subjects enrolled, 111 (52.4%) were White, one (0.004%) was of Asian descent, and 100 (47.2%) were Hispanic. Eleven subjects discontinued the study, nine at the request of the subject, one subject due to a serious adverse event unrelated to the test product, and one subject due to a protocol deviation.

Study Results

The mean (SD) cumulative irritancy index (CII) for CP Lotion vehicle was 0.46 (0.37), showing very slight irritancy. Nine of 207 (4.3%) subjects who generated any data showed a response of Grade 2 at the first induction reading, which resolved to Grade 1 or less by reading 2. No other Grade 2 responses were observed. The frequency of Grade 1 responses remained stable throughout the induction period. Thus, there was no evidence of cumulative irritancy. The CII for petrolatum control was significantly lower, 0.00 (0.04) than the CII for the clobetasol propionate lotion vehicle. Given the very small degree of irritancy seen with the lotion vehicle, this statistical finding was not clinically significant.

There were no subjects who showed a reaction score of 2 or greater at any challenge reading. Seventy-three subjects (36.3%) presented with a 1 at the 72-hour challenge reading at the site treated with clobetasol propionate lotion vehicle (no subjects presented with a 1 at the petrolatum sites). Of the 73 subjects, all but six returned for a 96-hour evaluation, at which they showed no progression of the response. Thus, under the conditions employed in this study, there was no evidence of cumulative irritancy or sensitization to CP Lotion vehicle or petrolatum.

Reviewer's Comment: *I would agree with the sponsor that the clobetasol propionate lotion vehicle, under the conditions of this study, does not appear to show any evidence of sensitization and slight evidence of irritancy. This degree of irritancy was not corroborated in the cumulative irritancy study for either the vehicle or the to-be-marketed formulation. At least for the to-be-marketed formulation, this degree of irritancy is probably masked by the anti-inflammatory action of the steroid moiety, clobetasol propionate.*

Four-Month Safety Update

The four-month safety update did not have any new data concerning clobetasol propionate lotion.

D. Adequacy of Safety Testing

The HPA axis suppression study of adolescents with moderate to severe atopic dermatitis was adequate and done in a manner to demonstrate the effect of clobetasol propionate lotion on the HPA axis. It showed that after 2 weeks of treatment with the drug product, a significant proportion of subjects had suppression of their HPA axis and all of the patients did not recover within two weeks. The two studies done in adults suggest that with even with continued stimulation, enough clobetasol propionate in the lotion formulation is systemically absorbed to cause HPA axis suppression. This was not the case for Temovate E Emollient Cream, the reference listed drug product.

The major cutaneous safety parameters were monitored adequately as 4-8 weeks is sufficient time to evaluate for telangiectasis and skin atrophy. These are late occurring events after topical steroid use.

E. Summary of Critical Safety Findings and Limitations of Data

The sponsor states in the proposed label under the "Precautions Section, "In total ——— patients with moderate to severe plaque-type psoriasis experienced transient reversible adrenal suppression following 4 weeks of Clobetasol Propionate Lotion, 0.05% therapy...". As stated earlier, the total is different than the sponsor's because 2 patients were suppressed before treatment commenced. Furthermore, in table 29, 4 (40%) patients, not 2 patients, according to the sponsor's data were suppressed in the CP Lotion arm compared to none (0%) in the Temovate E arm. Using the criteria based on the Cortrosyn labeling 8 out of 10 (80%) evaluable patients experienced adrenal suppression in the CP lotion arm compared to 3 out of 10 (10%) evaluable patients n the Temovate E arm. Also, it should be noted that these were adult patients.

All patients did not have transient reversible HPA axis suppression. Of the two that had a restest, subjects number 904 and 704, the latter subject remained suppressed 8 days later. For the other subjects who were suppressed there is no follow-up data.

The sponsor goes on to state in the same section of the label, "Furthermore [redacted] patients with moderate to severe atopic dermatitis experienced [redacted] adrenal suppression following 2 weeks of Clobetasol Propionate Lotion, 0.05%."

Again, these were adult patients. Actually, two of the eleven patients were not evaluable as discussed above, therefore there were 5 of 9 patients who experienced adrenal suppression following two weeks of clobetasol propionate therapy. Of the 3 that were retested, one failed to recover 7 days post-treatment. Therefore, the sponsor cannot make a claim that all of these patients experienced "[redacted] adrenal suppression."

In this same section and in the Pediatric Use Section, the label goes on to state, " [redacted] This statement is misleading as it conveys the message that non-sustained HPA axis suppression is of no clinical consequence. Indeed, patients with acute illnesses and/or injury may have increased morbidity with an adrenal gland that is intermittently suppressed.

In the "Pediatric Use" section of the label, it states, "The HPA axis suppression potential of [redacted] Lotion, 0.05% has been studied in adolescents (12-17 years of age) with moderate to severe atopic dermatitis covering a minimum of 20% of the total body surface area. In total [redacted] patients were evaluated for HPA axis function [redacted] Patients were treated twice daily for 2 weeks with [redacted] Lotion, 0.05%. After 2 weeks of treatment, [redacted] experienced [redacted] adrenal suppression." The statements that the sponsor make here are misleading. This label is about clobetasol propionate lotion and not Temovate E Emollient Cream or Temovate Cream. There were only 14 adolescent patients treated with clobetasol propionate lotion in this HPA axis study. Furthermore, 9 out of the 14 patients experienced adrenal suppression (64.3%) as compared to the sponsor's claim above of [redacted] One out of 4 (25%) patients that were retested remained suppressed 2 weeks post-treatment.

Under the Adverse Reactions Section, the sponsor states, [redacted] The Division usually lists adverse events that occur at a rate of 1% or greater. Therefore, added to the list would be "discomfort skin (1.3%) and skin dry (1.0%).

The sponsor goes on to state in the label, " Similar rates of local adverse reactions were reported in the comparator [redacted] The sponsor can only make claims compared to one marketed formulation of clobetasol propionate and that is of the RLD, Temovate E Emollient Cream, 0.05%, used in the two pivotal trials. It is true that the rates of local adverse reactions were similar to the RLD.

VIII. Dosing, Regimen, and Administration Issues

The sponsor states in the label, "Clobetasol Propionate Lotion, 0.05% contains a super-high potent topical corticosteroid; therefore treatment should be limited to:

-2 consecutive weeks for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses,

Reviewer's Comment: *The sponsor was advised to use the RLD, Temovate E Emollient Cream, as labeled. Therefore, only 5-10% of the BSA could be treated for up to 4 weeks in psoriasis. However, given the safety profile of this drug, . . . would not be recommended. Again, 80% of psoriasis patients experienced HPA axis suppression when treated with CP Lotion compared to 33% of those treated with Temovate E. At end study, the comparison was 40% vs. 0%.*

IX. Use in Special Populations

Reviewer's Comment: Sections A and B below are adapted from the statistical review of Dr. Shiowjen Lee, Division of Biometrics.

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

Efficacy results based on success rate of Global Severity over gender are generally consistent for studies 9707, 18001 and 2651 (Tables A.5 and A.8). That is, CP Lotion is better than its vehicle and similar to Temovate E Cream. For the female group in study 18001, CP Lotion and Temovate E arms had numerically higher success rates than those for males. On the other hand, females in the vehicle group had a relatively lower success rate than that in male group. The difference is not statistically significant.

For mean change from baseline in clinical signs and symptoms (Tables A.6-A.7 and A.9), results are consistent over gender. No outstanding differences are noted.

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

As the majority of the enrolled patients is Caucasian in studies 9707 and 18001, the efficacy results for Caucasians are consistent to those based on the whole ITT population. Results may vary over other race groups. Formal statistical comparison is not appropriate, as the numbers of patients for each of the other race groups are relatively small.

All enrolled patients in study 2651 are Caucasians. No subgroup efficacy results based on race could be made.

Efficacy results over pediatric, adult and geriatric groups (i.e. 12-17, 18-65 and > 65 years of age) are performed. It should be noted that there were only 24 pediatric patients (10.5%) in study 18001 (i.e. 12, 9 and 3 for CP Lotion, Temovate E and vehicle). All enrolled patients in the psoriasis studies (i.e. studies 9707 and 2651) were 18 years or older.

Efficacy results based on success rate of Global Severity and mean change from baseline of signs/symptoms are generally consistent over adult and geriatric groups in studies 9707 and 2651 (i.e. for indication of psoriasis). No outstanding differences are noted. For study 18001, even though the success rates in Global Severity for pediatric and adult groups are similar and

are relatively higher than that of the geriatric group, the efficacy trend is similar to that based on the whole ITT population.

C. Evaluation of Pediatric Program

Pediatric patients ages 12-17 were studied in this submission. As clobetasol propionate lotion is a super potent topical corticosteroid, this class of drugs is not recommended for use in pediatric patients younger than 12 years of age.

The natural history of most corticosteroid responsive dermatoses, particularly atopic dermatitis and psoriasis, as far as their response to treatment, follows the same course in pediatric patients as it does in adults. Therefore, if safety could be established in the pediatric age group studied, ages 12-17, and safety and efficacy were established in the pivotal trials with adult patients, then the efficacy data of clobetasol propionate lotion in adults would be extrapolated downward to the pediatric group where safety had been studied. However, in this submission, as has been discussed above, the risk/benefit ratio analyzed in this submission suggests that the safety risk outweighs the benefit of use of clobetasol propionate lotion in the pediatric population. It causes HPA axis suppression in a large porportion of patients. This group of patients also tended to overuse the drug product as compared to the RLD, leading to 100% HPA axis suppression in those individuals.

D. Comments on Data Available or Needed in Other Populations

This NDA covered the major concerns with the use of topical corticosteroids. One cutaneous event that was not addressed was that of pigmentary changes with use of topical corticosteroids. This is mentioned, however, not to suggest that it is a deficiency, as it is well-known that in darkly pigmented individuals, topical corticosteroids, particularly the more potent ones, can cause pigmentary changes, primarily hypopigmentation. Clobetasol propionate lotion is not expected to be any different in that regard.

X. Conclusions and Recommendations

A. Conclusions

There is no doubt that clobetasol propionate as a chemical moiety in a topical formulation is a super high potency anti-inflammatory drug product capable of treating corticosteroid responsive dermatoses. This was demonstrated in the two pivotal trials. Clobetasol propionate lotion (CP Lotion) was statistically superior to its lotion vehicle ($p \leq 0.001$). However, the demonstration of superior efficacy against its lotion vehicle was only part of the equation to attain approval of clobetasol propionate lotion. This application attempted to establish a bridge of safety and bioequivalence with a reference listed product, namely Temovate E Emollient Cream (clobetasol propionate emollient cream). The establishment of this bridge was to be two-fold, by

showing non-inferiority to this RLD in two clinical trials and by establishing that the safety profile of CP Lotion was no worse than that of clobetasol propionate emollient cream.

It is the latter part of the equation, the establishment of the bridge, in which clobetasol propionate lotion failed. In terms of efficacy, the Division allows for a 10% margin of non-inferiority compared to the RLD. In both the psoriasis trial and the atopic dermatitis trial, clobetasol propionate lotion had a margin of greater than 10% inferiority as compared to Temovate E (18.9% and 12.0%, respectively). In the atopic dermatitis trial, where the margin was closer to 10%, CP lotion failed in 3 of the 4 secondary variables, erythema, oozing/crusting, and pruritus. These variables, of course, are major symptoms of atopic dermatitis.

In terms of safety, while the cutaneous safety profiles of the two drug products are similar, the systemic safety profile, which in my opinion, is the major issue, of clobetasol propionate lotion is much worse than that of Temovate E Emollient Cream. The endpoint examined for systemic safety was the potential to suppress the HPA axis. CP Lotion wants to have an indication for psoriasis that mirrors that of Temovate E, 4 weeks of treatment. However, this drug caused HPA axis suppression at some point during treatment of psoriasis in 80% of patients as compared to 33% in patients treated with Temovate E. Furthermore, at the end of the study 40% of patients had HPA axis suppression compared to 0% treated with Temovate E. This study further demonstrates that the potential for HPA axis suppression by clobetasol propionate lotion may be underestimated as the adrenal glands of the patients were constantly being stimulated (almost q week during the study) and suppression still occurred at the endpoint (4 weeks) for patients on CP Lotion but not in patients on Temovate E. Lastly, although the BSA treated in this study was higher than that approved for Temovate E, one has to assume that the comparison of the proportion of suppression between the two drugs, although lower, would be the same.

The greater ability of CP lotion to cause HPA axis suppression is substantiated in the atopic dermatitis studies, of which the adolescent study is demonstrative. In this study 64.3% of patients experienced HPA axis suppression on CP lotion compared to 20% of those who used Temovate E.

The time to recovery from HPA axis suppression was not clear for all the patients who had follow-up. A greater number did not recover in the time tested who were treated with clobetasol propionate lotion as compared to Temovate E Emollient Cream. This imposes another safety concern.

It is clear to this reviewer that the formulation of this product, the vehicle, may be a problem. It contains a large amount of propylene glycol, an absorption enhancer, which may be responsible for the decreased efficacy at the cutaneous site as compared to the RLD, and the increased HPA axis suppression. The overuse of the lotion is two-pronged. In the adult psoriasis trial, for example, overuse of drug product was comparable between the CP Lotion and Temovate E, with 8 and 7 patients using more than 50 grams per week, respectively. However, more patients using CP lotion experienced HPA axis suppression compared to Temovate E [(63% vs. 29%, respectively), see Appendix A, table A.4]. Again, this suggests that risk of suppression with overuse is higher when treated with CP Lotion. In the adolescent study, all of the patients who went over the limit (≥123grams/2weeks) experienced HPA axis suppression. Interestingly, none of the patients in this same age group used more than the recommended amount of Temovate E Emollient Cream. Again, this underscores a concern for potential abuse of this drug product because of the nature of the formulation.

The question to be answered ultimately in review of this application, when considering the risk/benefit analysis of clobetasol propionate lotion, is, "Does clobetasol propionate lotion offer any advantage in the interest of the public health over the clobetasol propionate formulation that is currently marketed?" In my opinion, the answer is, "No, it does not offer any advantage." It is not as efficacious as Temovate E Emollient Cream in treating corticosteroid responsive dermatoses while at the same time presents an increased risk to the safety of the public health by having a poorer systemic safety profile as compared to Temovate E Emollient Cream.

B. Recommendations

It is recommended that the action taken for the new drug application of clobetasol propionate lotion be that of non-approvable. The sponsor may wish to consider the following:

1. Alteration of the drug product's vehicle such that less systemic absorption of the active chemical moiety, clobetasol propionate, takes place. Confirmation of such would require a new HPA axis suppression study. The criteria for HPA axis suppression should be agreed upon in advance with the Division such that all patients who exhibit HPA axis suppression can be followed for time to recovery.

2. [redacted]

3. [redacted]

XI. Appendix

A. Other Relevant Materials

Table A1. - Patients Recorded Using Little or No Drug Product
Study 18061 - Atopic Dermatitis (Adolescents)

Patient #	Study Arm	BSA Involvement (%)	Grams Used (total)
010	Temovate E	22	1.0
007	Temovate E	20	-3.8
006	Temovate Cream	23	-7.0
025	Temovate Cream	27	-3.6

Source: Sponsor's NDA Submission Volume 1.16, Listing SUBL 10, pages 2696-2701 and Listing EFF 1, pages 2709-2715.

Table A.2 - Patients with HPA Axis Suppression Pre-Treatment
Study 9708

Pt. #	Time point	Clobetasol Propionate Lotion Serum Cortisol (µg/dL)[1]		
		Pre-stim.	Post-stim	Change*
909	Screening	[redacted]	[redacted]	6.9
705	Screening	[redacted]	[redacted]	4.2
		Temovate E Emollient Cream Serum Cortisol (µg/dL)[1]		
911	Screening	[redacted]	[redacted]	2.3
707	Baseline	[redacted]	[redacted]	5.6

Source: Sponsor's NDA submission-Line listings, Volume 1.21, pages 1279-1289
[1]Abnormality bolded
*Defined as the difference between the pre- and post-stimulation cortisol

Table A.3 - Patients with HPA Axis Suppression - Pre-treatment
Study 18009 - Atopic Dermatitis (Adults)

Pt. #	Time point	**Clobetasol Propionate Lotion** Serum Cortisol (µg/dL)[1]		
		Pre-stim.	Post-stim	Change*
1007	Baseline	[redacted]	[redacted]	**4.8**
803	Baseline	[redacted]	[redacted]	**5.2**
		Temovate E Emollient Cream Serum Cortisol (µg/dL)[1]		
1001	Baseline	[redacted]	[redacted]	**5.9**
1006	Baseline	[redacted]	[redacted]	**6.7**
801	Baseline	[redacted]	[redacted]	**6.6**
802	Baseline	[redacted]	[redacted]	**5.0**

Source: Sponsor's NDA Submission - Line Listings, Volume 1.22, pages 1822-1829
[1]Abnormality bolded
*Defined as the difference between the pre- and post-stimulation cortisol

Table A.4 - Patients with >50grams/week Usage
Study 9708 - Psoriasis

Clobetasol Propionate Lotion N=8			
Patient #	Week #	Grams Used	HPA Axis Suppression
901	1	59.3	Yes
904^	2	56.9	Yes
908	1	61.4	No
910	2	56.6	Yes
702*	4	85.6	No
704	1	70.8	Yes
708	1	60.9	Yes
711*^	1	72.9	No
			Total = 5/8 (63%)
Temovate E Emollient Cream N=7			
902^	3	52.3	No
905	3	53.5	No
907^	1	52.1	Yes
912^	1	56.0	Yes
701^	4	53.4	No
703^	1	52.7	No
710^	4	53.9	No
			Total = 2/7 (29%)

Source: Sponsor's NDA submission, Volume 1.21, Line listings, pages 1272-1275
*Experienced suppression at another time point using < 50 grams/week
^Used >50 grams/week more than 1 week

Table A.5
Subgroup Efficacy Results in Success Rate Of Global Severity
Studies 9707 and 18001

Study	Study 9707					Study 18001				
Subgroup	Clobex (n=82)	Temovate E (n=81)	Vehicle (n=29)	Clobex vs. Vehicle	Clobex vs. Temov. E	Clobex (n=96)	Temovate E (n=100)	Vehicle (n=33)	Clobex vs. Vehicle	Clobex vs. Temov. E
Gender										
Male	22/58 (37.9%)	16/52 (30.8%)	0/16 (0)	0.010	0.608	15/39 (38.5%)	15/45 (33.3%)	3/15 (20.0%)	0.129	0.831
Female	8/24 (33.3%)	17/29 (58.6%)	0/13 (0)	0.031	0.140	26/57 (45.6%)	26/55 (47.3%)	1/18 (5.6%)	0.004	0.973
Race										
Caucasian	28/69 (40.6%)	26/66 (39.4%)	0/24	< 0.001	0.643	34/69 (49.3%)	31/67 (46.3%)	4/23 (17.4%)	0.004	0.954
Black	0/2	0/1	0/2	na	na	1/12 (8.3%)	6/27 (22.2%)	0/8	0.317	0.717
Yellow	na	na	na	na	na	3/6 (50.0%)	1/1 (100%)	na	na	na
Hispanic	2/11 (18.2%)	7/14 (50.0%)	0/3	0.482	0.089	2/6 (33.3%)	2/4 (50.0%)	0/2	na	0.157
Others	na	na	na	na	na	1/3 (33.3%)	1/1 (100%)	na	na	na
Age										
Pediatric (≤ 17)	na	na	na	na	na	6/12 (50.0%)	4/9 (44.4%)	0/3	0.480	0.876
Adult (18 - 65)	26/70 (37.1%)	28/71 (39.4%)	0/28	< 0.001	0.573	32/72 (44.4%)	34/79 (43.0%)	4/26 (15.4%)	0.006	0.711
Geriatric (> 65)	4/12 (33.3%)	5/10 (50.0%)	0/1	0.317	0.257	3/12 (25.0%)	3/12 (25.0%)	0/4	0.326	0.526
Baseline Global Severity										
1.0	na	na	na	na	na	1/1 (100%)	2/4 (50.0%)	0/1	na	na
2.0	23/49 (46.9%)	22/48 (45.8%)	0/19	< 0.001	0.965	32/71 (45.1%)	29/61 (47.5%)	4/18 (22.2%)	0.078	0.794
3.0	6/28 (21.4%)	10/30 (33.3%)	0/9	0.102	0.434	7/22 (31.8%)	10/33 (30.3%)	0/14	0.043	0.765
4.0	1/5 (20.0%)	1/3 (33.3%)	0/1	0.480	0.480	1/2 (50.0%)	0/2	na	na	na

Source: Summary is based on the Sponsor's electronic SAS datasets.
Comparison is statistical reviewer's analysis. P-value is based on CMH test adjusting for center.

Table A.6
Subgroup Efficacy Results
Mean Change from Baseline in Signs and Symptoms
Study 9707

Sign/Symptom	Erythema, mean (sd)			Plaque, mean (sd)			Scaling, mean (sd)		
Subgroup	**Clobex (n=82)**	**Temovate E (n=81)**	**Vehicle (n=29)**	**Clobex (n=82)**	**Temovate E (n=81)**	**Vehicle (n=29)**	**Clobex (n=82)**	**Temovate E (n=81)**	**Vehicle (n=29)**
Gender									
Male	1.38 (0.9)	1.29 (1.0)	0.19 (0.4)	1.91 (1.0)	1.67 (1.1)	0.50 (0.6)	1.07 (1.0)	1.83 (1.1)	0.56 (0.8)
Female	1.38 (0.6)	1.76 (0.8)	0.46 (0.5)	1.88 (0.9)	1.97 (0.9)	0.31 (0.5)	2.04 (0.8)	2.00 (0.8)	0.54 (1.0)
Race									
Caucasian	1.43 (0.8)	1.50 (0.9)	0.33 (0.5)	2.01 (1.0)	1.86 (1.1)	0.42 (0.6)	2.14 (0.9)	1.97 (1.0)	0.58 (0.9)
Black	1.0 (1.4)	3.00 (-)	0.50 (0.7)	1.0 (0)	1.0 (-)	0.50 (0.7)	1.50 (0.7)	0 (-)	0.50 (0.7)
Hispanic	1.1 (0.5)	1.14 (0.9)	0 (0)	1.36 (0.8)	1.43 (0.9)	0.33 (0.6)	1.64 (1.0)	1.64 (0.9)	0.33 (0.6)
Age									
Adult (18 - 65)	1.43 (0.8)	1.46 (0.9)	0.32 (0.5)	1.87 (1.0)	1.77 (1.1)	0.43 (0.6)	1.99 (0.9)	1.87 (1.0)	0.57 (0.9)
Geriatric (> 65)	1.08 (0.5)	1.40 (1.1)	0 (-)	2.08 (0.7)	1.80 (1.0)	0 (-)	2.50 (0.8)	2.00 (0.8)	0 (-)
Baseline Global Severity									
2.0	1.16 (0.6)	1.40 (0.9)	0.32 (0.5)	1.65 (0.8)	1.58 (0.9)	0.37 (0.5)	1.86 (0.7)	1.67 (0.8)	0.42 (0.7)
3.0	1.64 (1.0)	1.40 (0.9)	0.33 (0.5)	2.25 (1.1)	2.03 (1.2)	0.56 (0.7)	2.29 (1.2)	2.20 (1.2)	0.89 (1.2)
4.0	2.00 (1.0)	3.00 (1.0)	0 (-)	2.40 (1.1)	2.33 (0.6)	0 (-)	2.80 (0.8)	2.33 (0.6)	0 (-)

Source: Summary is based on the Sponsor's electronic SAS datasets.

Table A.7
Subgroup Efficacy Results
Mean Change from Baseline in Signs and Symptoms
Study 18001

Sign/symptom	Erythema, mean (sd)			Induration/Papulation, mean (sd)		
Subgroup	**Clobex (n=96)**	**Temovate E (n=100)**	**Vehicle (n=33)**	**Clobex (n=96)**	**Temovate E (n=100)**	**Vehicle (n=33)**
Gender						
Male	1.51 (0.9)	1.58 (1.0)	0.93 (0.7)	1.56 (0.9)	1.71 (1.0)	0.87 (1.0)
Female	1.44 (0.8)	1.49 (0.9)	0.78 (0.7)	1.77 (0.8)	1.56 (0.9)	0.78 (0.6)
Race						
Caucasian	1.52 (0.8)	1.64 (0.9)	1.0 (0.7)	1.81 (0.8)	1.73 (0.8)	0.96 (0.8)
Black	1.25 (0.8)	1.00 (0.7)	0.50 (0.8)	1.50 (0.8)	1.19 (1.1)	0.50 (0.8)
Yellow	1.50 (1.0)	3.00 (-)	na	1.83 (0.4)	3.0 (-)	na
Hispanic	1.17 (0.8)	2.50 (1.7)	0.50 (0.7)	0.83 (0.8)	2.50 (1.3)	0.50 (0.7)
Others	1.67 (1.5)	3.0 (-)	na	1.00 (2.0)	2.0 (-)	na
Age						
Pediatric (≤ 17)	1.58 (0.8)	1.11 (0.9)	1.33 (0.6)	1.92 (0.9)	2.00 (1.0)	1.33 (0.6)
Adult (18 - 65)	1.49 (0.8)	1.62 (1.0)	0.85 (0.7)	1.68 (0.8)	1.59 (0.9)	0.73 (0.8)
Geriatric (> 65)	1.25 (0.9)	1.25 (0.6)	0.50 (0.6)	1.50 (0.9)	1.58 (0.9)	1.00 (0.8)
Baseline Global Severity						
1.0	2.00 (-)	1.50 (0.6)	2.00 (-)	2.00 (-)	1.50 (0.6)	1.00 (-)
2.0	1.39 (0.8)	1.48 (0.8)	0.67 (0.6)	1.66 (0.8)	1.62 (0.9)	0.83 (0.8)
3.0	1.64 (1.0)	1.58 (1.2)	1.00 (0.8)	1.73 (0.9)	1.61 (1.1)	0.79 (0.9)
4.0	2.00 (1.4)	2.50 (0.7)	na	2.00 (0)	2.50 (0.7)	na

Sign/symptom	Oozing/Crusting, mean (sd)			Pruritus, mean (sd)		
Subgroup	**Clobex (n=96)**	**Temovate E (n=100)**	**Vehicle (n=33)**	**Clobex (n=96)**	**Temovate E (n=100)**	**Vehicle (n=33)**
Gender						
Male	0.95 (0.9)	0.71 (0.9)	0.27 (0.6)	1.92 (1.0)	1.84 (1.0)	0.87 (1.2)
Female	0.70 (0.8)	0.76 (0.7)	0.72 (0.9)	1.89 (1.0)	2.16 (1.2)	0.89 (1.2)
Race						
Caucasian	0.84 (0.9)	0.79 (0.8)	0.52 (0.8)	1.84 (1.0)	2.03 (1.0)	0.87 (1.3)
Black	0.83 (0.9)	0.59 (0.6)	0.50 (0.9)	2.25 (1.3)	1.93 (1.2)	0.75 (1.2)
Yellow	0.33 (0.5)	1.0 (-)	na	2.33 (0.5)	0 (-)	na
Hispanic	0.83 (0.8)	0.75 (1.7)	0.50 (0.7)	1.50 (1.4)	2.50 (1.3)	1.50 (0.7)
Others	0.67 (1.2)	1.0 (-)	na	2.00 (0)	4.0 (-)	na
Age						
Pediatric (≤ 17)	0.67 (0.8)	0.44 (0.5)	0.67 (1.2)	1.92 (0.9)	2.11 (1.2)	1.00 (1.0)
Adult (18 - 65)	0.75 (0.9)	0.76 (0.8)	0.42 (0.6)	1.97 (1.0)	1.99 (1.1)	0.88 (1.3)
Geriatric (> 65)	1.25 (0.9)	0.83 (0.8)	1.00 (1.4)	1.50 (0.8)	2.17 (1.2)	0.75 (1.0)
Baseline Global Severity						
1.0	0 (-)	0.50 (0.6)	0 (-)	1.00 (-)	1.50 (1.3)	-1.0 (-)
2.0	0.75 (0.8)	0.67 (0.7)	0.50 (0.9)	1.76 (0.9)	2.05 (1.0)	0.89 (1.0)
3.0	0.95 (1.1)	0.82 (0.9)	0.57 (0.6)	2.32 (1.2)	1.94 (1.3)	1.00 (1.4)
4.0	1.50 (2.1)	2.00 (1.4)	na	3.00 (1.4)	3.50 (0.7)	na

Source: Summary is based on the Sponsor's electronic SAS datasets.

Table A.8
Subgroup Efficacy Results in Success Rate of Global Severity
Study 2651

Study	Study 2651			Comparison[1]	
Subgroup	Clobex (n=94)	Dermoval (n=95)	Vehicle (n=33)	Clobex vs. Vehicle	Clobex vs. Dermoval
Gender					
Male	30/47 (63.8%)	38/56 (67.9%)	2/21 (9.5%)	< 0.001	0.751
Female	32/47 (68.1%)	31/39 (79.5%)	1/12 (8.3%)	< 0.001	0.200
Race					
Caucasian	62/94 (66.0%)	69/95 (72.6%)	3/33 (9.1%)	< 0.001	0.264
Age					
Adult (18 - 65)	54/83 (65.1%)	60/84 (71.4%)	3/28 (10.7%)	< 0.001	0.285
Geriatric (> 65)	8/11 (72.7%)	9/11 (81.8%)	0/5	0.041	0.560
Baseline Global Severity					
1.0	1/1 (100%)	na	na	na	na
2.0	31/38 (81.6%)	31/41 (75.6%)	1/15 (6.7%)	< 0.001	0.598
3.0	27/49 (55.1%)	35/51 (68.6%)	0/15	< 0.001	0.142
4.0	3/6 (50.0%)	3/3 (100%)	2/3 (66.7%)	0.414	0.221

Source: Summary is based on the Sponsor's electronic SAS datasets.
[1]Comparison is statistical reviewer's analysis. P-value is based on CMH test adjusting for center.

Table A.9
Subgroup Efficacy Results
Mean Change from Baseline in Signs and Symptoms
Study 2651

Sign/Symptom	Erythema, mean (sd)			Plaque, mean (sd)			Scaling, mean (sd)		
Subgroup	**Clobex (n=94)**	**Dermoval (n=95)**	**Vehicle (n=33)**	**Clobex (n=94)**	**Dermoval (n=95)**	**Vehicle (n=33)**	**Clobex (n=94)**	**Dermoval (n=95)**	**Vehicle (n=33)**
Gender									
Male	2.00 (0.9)	2.05 (0.9)	0.62 (0.8)	2.32 (1.1)	2.39 (0.8)	0.62 (1.0)	2.66 (0.9)	2.61 (0.8)	1.43 (1.4)
Female	2.04 (0.9)	2.28 (0.7)	0.58 (1.0)	2.21 (0.8)	2.38 (0.8)	0.83 (1.1)	2.47 (0.7)	2.46 (0.9)	1.17 (1.5)
Race									
Caucasian	2.02 (0.9)	2.15 (0.8)	0.61 (0.9)	2.27 (1.0)	2.39 (0.8)	0.70 (1.0)	2.56 (0.8)	2.55 (0.8)	1.33 (1.4)
Age									
Adult (18 - 65)	1.95 (0.9)	2.20 (0.8)	0.64 (0.9)	2.30 (1.0)	2.40 (0.8)	0.75 (1.0)	2.58 (0.8)	2.62 (0.8)	1.46 (1.3)
Geriatric (> 65)	2.55 (0.8)	1.73 (0.8)	0.40 (0.9)	2.00 (1.0)	2.27 (0.8)	0.40 (1.1)	2.45 (0.7)	2.00 (0.9)	0.60 (1.7)
Baseline Global Severity									
1.0	3.00 (-)	na	na	1.00 (-)	na	na	1.00 (-)	na	na
2.0	1.87 (0.9)	1.95 (0.8)	0.47 (0.6)	2.13 (0.8)	2.05 (0.7)	0.67 (0.9)	2.45 (0.7)	2.44 (0.8)	1.27 (1.0)
3.0	2.06 (0.9)	2.27 (0.9)	0.33 (0.5)	2.37 (1.0)	2.59 (0.8)	0.33 (0.7)	2.67 (0.8)	2.57 (0.8)	0.93 (1.4)
4.0	2.50 (1.0)	2.67 (0.6)	2.67 (0.6)	2.50 (1.2)	3.67 (0.6)	2.67 (0.6)	2.67 (1.2)	3.67 (0.6)	3.67 (0.6)

Source: Summary is based on the Sponsor's electronic SAS datasets.

B. Individual More Detailed Study Reviews (If performed)

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

/s/

Denise Cook
6/12/03 10:32:59 AM
MEDICAL OFFICER

Markham Luke
6/12/03 10:52:02 AM
MEDICAL OFFICER

Jonathan Wilkin
7/24/03 02:54:34 PM
MEDICAL OFFICER
See Division Director's Summary Review, signed in DFS on July 24, 2003