

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-535

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoeconomics and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-535/N000

Drug Name: Clobetasol propionate Lotion, 0.05%

Indication(s): Treatment of corticosteroid-responsive dermatoses

Applicant: Galderma Laboratories, L.P.

Dates:
Submitted: September 25, 2002
Received: September 27, 2002
User fee: July 27, 2003
Review completion: April 15, 2003

Review Status: Standard review

Biometrics Division: Division of Biometrics III (HFD-725)

Statistics Reviewer: Shiowjen Lee, Ph.D.

Concurring Reviewers: Mohamed Alish, Ph.D.

Medical Division: Division of Dermatologic and Dental Drug Products (HFD-540)

Clinical Team: Denise Cook, M.D.

Project Manager: Melinda Harris, M.S.

Keywords: Psoriasis, atopic dermatitis, non-inferiority, superiority, clinical sign and symptom score.

TABLE OF CONTENTS

Cover Page

Table of Contents

1. Executive Summary	1
1.1 Conclusions and Recommendations	1
1.2 Brief Overview of Clinical Studies	1
1.3 Statistical Issues and Findings	2
2. Introduction	4
2.1 Overview	4
2.2 Data Sources	5
3. Statistical Evaluation	5
3.1 Evaluation of Efficacy	5
3.1.1 Pivotal Studies 9707 and 18001	5
3.1.2 Supportive Study 2651	15
3.2 Evaluation of Safety	20
3.2.1 Studies 9707 and 18001	20
3.2.2 Study 2651	22
4. Findings in Special/Subgroup Populations	23
4.1 Gender	23
4.2 Race	23
4.3 Age	23
4.4 Other Special/Subgroup Populations	23
5. Summary and Conclusions	24
5.1 Statistical Issues and Collective Evidence	24
5.2 Conclusions and Recommendations	25
6. Appendices	28
7. Primary, Concurring Reviewers, Distribution List	38

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Two pivotal trials (CR.U9707.R02 and RD.06.SPR.18001, denoted as studies 9707 and 18001) and a supportive Phase 3 trial (RD.06.SPR.2651, denoted as study 2651) were evaluated for the efficacy claim of Clobetasol propionate Lotion 0.05% (denoted as Clobex Lotion), in the treatment of corticosteroid-responsive dermatoses. The superiority efficacy claim of Clobex Lotion to its vehicle is supported for each of the trials in terms of: (a) the percentage of patients having score of 0 or 0.5 on a 6-point Global Severity scale, and (b) the mean change from baseline in each of clinical signs and symptoms. However, the overall non-inferiority efficacy claim of Clobex Lotion to Temovate E Cream is not supported for either of studies 9707 and 18001, nor the non-inferiority claim of Clobex Lotion to Dermoval Cream for study 2651. Specifically, the non-inferiority claim of Clobex Lotion to Temovate E Cream is not established for endpoint (a) in study 9707; while the non-inferiority claim is not demonstrated for the mean change from baseline in erythema, papulation, and oozing/crusting scores for study 18001. However, the non-inferiority is established for the mean change of pruritus score in study 18001. For study 2651, the non-inferiority claim of Clobex Lotion to Dermoval Cream is not established for endpoint (a), the mean change of erythema and plaque scores. However, the non-inferiority is established for the mean change of scaling score.

Safety results from studies 9707, 18001 and 2651 in terms of the incidence of adverse events and cutaneous skin reaction suggest that the safety profile of Clobex Lotion is comparable to those of Temovate E Cream (or Dermoval Cream for study 2651) and vehicle arms.

1.2 Brief Overview of Clinical Studies

The study drug product is Clobex Lotion, which is indicated for topical use twice daily for 4 weeks in the treatment of plaque-type psoriasis and 2 weeks in the treatment of atopic dermatitis.

Two pivotal trials 9707 and 18001 were conducted in the US during 2/2000 – 6/2000 and 3/2000 – 1/2001 for the indications of plaque-type psoriasis and atopic dermatitis, respectively. Total of 192 and 229 subjects were enrolled from 15 and 14 centers, respectively, for studies 9707 and 18001. The enrolled subjects were randomized in an allocation ratio of 3:3:1 to Clobex Lotion, Temovate E Cream and Lotion vehicle groups. This resulted in 82, 81 and 29 subjects in each treatment group, respectively, for study 9707; while 96, 100 and 33 subjects for study 18001. The time point for efficacy assessment was week 4 for psoriasis indication and week 2 for atopic dermatitis indication.

Study 2651 was conducted in Europe during 9/2000 – 1/2001 for the treatment of moderate to severe plaque-type psoriasis. Three treatment arms (i.e. Clobex Lotion, Dermoval Cream and Lotion vehicle) were included in the study. The drug administration was twice daily for 4 weeks. Total of 94, 95 and 33 patients were randomized to Clobex Lotion, Dermoval Cream and Lotion vehicle, respectively. It should be noted that the active-control group, Dermoval Cream, in the study differed from Temovate E Emollient Cream in pivotal studies 9707 and 18001.

1.3 Statistical Issues and Findings

Statistical Issues

Several statistical issues were identified in the Sponsor's submission. They are:

- a. The Sponsor's primary efficacy endpoint differed from those recommended by the Division. Their definition of success on Global Severity (i.e. score of 0, 0.5 or 1) is inconsistent with the Division criteria for success.
- b. The Sponsor's non-inferiority margin of 20% for success in Global Severity is large, compared to the Division's practice of using 10% in the past for drug approval in the same drug category.
- c. Investigator _____ in study 18001 has been under OCI investigation. The study site accounts for about 18% of study enrollment. Data from this study site might not be used for efficacy evaluation.
- d. Each of two investigators (i.e. Breneman and Miller) participated in the two pivotal studies. This might violate the "independence" criterion of clinical trials for efficacy and safety claims.

Efficacy Findings

The primary time point for efficacy evaluation is week 4 for the indication of plaque-type psoriasis and week 2 for atopic dermatitis. Per clinical and statistical discussions, the primary efficacy endpoints evaluated are:

- a. Success rate on Global Severity, where success is defined as a score of 0 or 0.5.
- b. Mean change from baseline to endpoint in each of the clinical signs and symptoms
 - For psoriasis indication, signs of erythema, plaque and scaling are of interest.
 - For atopic dermatitis indication, signs of erythema, induration/papulation, oozing/crusting and pruritus are of interest.

Per the Division's past practice in the same drug category (see applications of Olux Foam – NDA 21,142 and Betamethasone Valerate Foam – NDA 20,934, for the indication of moderate to severe scalp psoriasis), a non-inferiority margin of 10% for response rate has been used. Therefore, non-inferiority margins of 10% for response rate and 10% of Temovate E mean (or 10% of Dermoval mean for study 2651) for mean change from baseline are adopted for efficacy evaluation in the review.

The following summarizes the efficacy results for each study.

➤ Pivotal study 9707 (for plaque-type psoriasis):

The intent-to-treat (ITT) analysis with the last observation carried forward (LOCF) method for treating missing data demonstrates that:

- Clobex Lotion is superior to its vehicle for all primary efficacy endpoints at week 4 (p-value < 0.001).
- Clobex Lotion is non-inferior to Temovate E Cream for the mean change from baseline in each of clinical sign and symptom score (i.e. erythema, plaque and scaling). However, the non-inferiority for the success rate on Global Severity score is not established.

➤ Pivotal study 18001 (for atopic dermatitis):

1. The ITT analysis with the LOCF for missing data demonstrates that:
 - Clobex Lotion is superior to its vehicle for all primary efficacy endpoints at week 2 (p-value ≤ 0.002).
 - Non-inferiority of Clobex Lotion to Temovate E Cream is established for the mean change of pruritus score, but not the success rate in Global Severity and mean changes from baseline in erythema, induration/papulation, and oozing/crusting scores.
2. Study site ~~XXXX~~ has been under OCI investigation. The validity of data for efficacy evaluation from this site is an issue. Results after excluding this site yield the same efficacy conclusions as those based on the whole data set.
3. As the patient's participation in the two sites (i.e. Breneman and Miller) for study 9707 was earlier than for study 18001, a sensitivity analysis was performed for study 18001. The impact of the two investigators' participation in study 18001 on the efficacy results is large for Clobex group. In particular, the success rate of Global Severity was 61.9% for the two sites, compared to 37% for the remaining sites. Consequently, efficacy results are stronger for Clobex group by including the two sites. It should be noted that the non-inferiority of Clobex to Temovate E is not established even when the two sites are included in the analysis.

➤ Supportive study 2651 (for plaque-type psoriasis):

The ITT analysis with the LOCF for missing data demonstrates that:

- Clobex Lotion is superior to its vehicle with respect to all primary efficacy endpoints (p-value < 0.001).
- Non-inferiority of Clobex Lotion to Dermoval Cream is established for the mean change from baseline in scaling score, but not the success rate in Global Severity and mean changes from baseline in erythema, and plaque scores.

Safety Assessment

From statistical point of view, the three treatment groups (i.e. Clobex, Temovate E and vehicle in studies 9707 and 18001; Clobex, Dermoval and vehicle in study 2651) are comparable in terms of the incidence of adverse events and cutaneous skin reaction.

- The incidence rates of adverse event were 18.3% vs. 12.3% vs. 13.8% for Clobex, Temovate E and vehicle, respectively, in study 9707; while 14.6% vs. 11.1% vs. 12.1% for study 18001; and 7.4% vs. 5.3% vs. 3.0% for study 2651.
- For drug-related adverse event rate, it was 6.1% vs. 2.5% vs. 10.3% for Clobex vs. Temovate E vs. vehicle in study 9707; and was 4.2% vs. 1.0% vs. 6.1% in study 18001. It was 2.1% vs. 2.1% vs. 0 in study 2651 for Clobex vs. Dermoval Cream vs. vehicle. It should be noted that drug-related incidence rates in study 9707 are relatively higher than those in study 18001. This could be possibly due to a longer treatment duration for study 9707 than study 18001 (i.e. 4-week vs. 2-week). But the incidence rates for Clobex and vehicle groups in study 9707 were relatively higher than those in study 2651 even though the treatment duration and indication were the same (i.e. 4-week and psoriasis).
- Treatment groups are comparable in terms of the response of cutaneous skin reaction (i.e., telangiectasis and skin atrophy).

2. INTRODUCTION

2.1 Overview

The proposed drug product, Clobex, is a lotion formulation containing Clobetasol propionate 0.05% that has been developed to provide an alternative dosage form for the topical treatment of corticosteroid-responsive dermatoses. The dosing regimen is twice daily for 4 weeks for the indication of plaque-type psoriasis and 2 weeks for the indication of atopic dermatitis.

Twelve studies were completed for the drug application, where 6 of them were under IND 54,230 per the US regulation. phase 3 clinical trials (CR.U9707.R02, RD.06.SPR.18001, RD.06.SPR.2651, denoted as studies 9707, 18001, 2651 and respectively) were included. Studies 9707 and 18001 are designated as pivotal trials conducted in the US. The other two are supportive trials conducted in Europe.

Table 1 presents an overview of studies 9707, 18001, 2651. Three treatment arms were included in each of the pivotal trials 9707 and 18001. Study 9707 was for the indication of moderate to severe plaque-type psoriasis and study 18001 was for moderate to severe atopic dermatitis. As the NDA submission is a 505(b)(2) application, the conduct of the two pivotal trials was in agreement with the Division (meeting minutes dated 9/20/1999). The primary objectives of the trials were to demonstrate the superiority of Clobex Lotion to its Lotion vehicle, and non-inferiority of Clobex Lotion to Temovate E Emollient Cream. Studies 2651 were Phase 3 clinical trials for the indication of moderate to severe plaque-type psoriasis. Three arms were included in each trial. It should be noted that the reference arm was Dermoval Cream 0.05%, which was different from Temovate E Emollient Cream in the pivotal trials.

Table 1: Overview of the Four Phase 3 Trials

Study	Study conducted Country (mon./yr)	Patients inclusion	Treatment arms, n	Comments on treatments
Pivotal Trials				
9707	US (2/00 – 6/00)	Patients aged 18 and above with moderate to severe psoriasis	Clobex Lotion: 82 Temovate Emollient Cream: 81 Lotion Vehicle: 29	Treatment was twice daily for 4 weeks
18001	US (3/00 – 1/01)	Patients aged 12 and above with moderate to severe atopic dermatitis	Clobex Lotion: 96 Temovate Emollient Cream: 100 Lotion Vehicle: 33	Treatment was twice daily for 2 weeks
Supportive Trials				
2651	Europe (9/00 – 1/01)	Patients aged 18 and above with moderate to severe psoriasis	Clobex Lotion: 94 Dermoval Cream: 95 Lotion Vehicle: 33	Treatment was twice daily for 4 weeks

According to the Sponsor,

In agreement with the

Division, this statistical review evaluates the efficacy and safety of Clobex Lotion for studies 9707, 18001 and 2651.

2.2 Data Sources

The data summary in this review is based on the Sponsor's NDA submission, Statistical Section, Volumes 1.1, 1.18-1.39, received 9/27/2002 and electronic SAS data sets in the Electronic Document Room location of \\cdsesub1\21535\000\2002_09_25\datasets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Pivotal Studies 9707 and 18001

Study Design

Studies 9707 and 18001 were designed as randomized, investigator-masked, active- and vehicle-controlled and multicenter (i.e. 15 and 14 centers in studies 9707 and 18001), and were conducted in the US during February 2000 – June 2000 and March 2000 – January 2001, respectively. Study 9707 was for the indication of moderate to severe plaque-type psoriasis and consisted of a 4-week treatment period and a 4-week follow-up period. Study 18001 was for the indication of moderate to severe atopic dermatitis and included a treatment period of 2 weeks and a follow-up period of 2 weeks. Clinical assessment was scheduled at baseline, weeks 1, 2, 4 and 8 for study 9707 and baseline, weeks 1, 2 and 4 for study 18001, with primary time points of 4-week and 2-week for efficacy evaluation in studies 9707 and 18001, respectively. The objectives of both trials were to show the superiority of Clobex Lotion to its Lotion Vehicle, and the non-inferiority to Temovate E Emollient Cream.

Totals of 182 and 224 subjects were pre-planned in the original protocols 9707 and 18001, respectively, based on the efficacy endpoint of Dermatologic Sum Score (DSS). Totals of 192 and 229 patients were actually participated in studies 9707 and 18001. The enrolled patients in study 9707 were 18 years of age or older, had moderate to severe plaque-type psoriasis (i.e. DSS score at least 6 out of a possible maximum of 12) with a minimum of 15% body surface area involved the disease. On the other hand, the enrolled patients in study 18001 were 12 years of age or older, had moderate to severe atopic dermatitis with a minimum of 20% body surface area disease involvement. The enrolled patients were randomized in a ratio of 3:3:1 to Clobex Lotion, Temovate E Emollient Cream and Lotion Vehicle for each study. This resulted in 82, 81 and 29 patients for each treatment arm, respectively, in study 9707; while 96, 100 and 33 patients in study 18001.

Sponsor's documentation showed that the randomization list for studies 9707 and 18001 was computer-generated on 1/17/00 and 1/28/00, respectively, which were prior to the 1st patient enrollment in the trials (i.e. 2/1/00 and 3/28/00). Each of the randomization lists was based on blocks of size 7 for treatment allocation. The studies were conducted as double blind between Clobex Lotion and its Lotion Vehicle, as the appearance of the two drugs was identical. For the

blinding between Clobex Lotion and Temovate E Emollient Cream, the study was designed as investigator-masked, as the dosage forms of two drugs were different. To maintain the blinding, the medication kits were sealed when distributed to patients, so investigators would not know what treatment each patient received.

Endpoints Specified in the Protocols and Submission:

For efficacy evaluation, the following endpoints were stated in the Sponsor's submission:

- Primary: Percentage of patients with Global Severity score of 0, 0.5 or 1 at week 4 on a 6-point scale described below for study 9707, and at week 2 for study 18001.
- Secondary:
 - Global Severity score (full-scale)
 - DSS of erythema, plaque elevation and scaling for study 9707; DSS of erythema, excoriation, and induration/papulation for study 18001
 - Individual clinical signs/symptoms
 - Percentage of body surface area (BSA) involvement of disease
 - Percentage of BSA treated
 - Global Improvement

Global Severity evaluated all treated areas. The scales of Global Severity are described below:

- 0 = none; no clinical signs or symptoms detected
- 0.5 = very mild; only very slight signs or symptoms detected
- 1 = mild; slight signs or symptoms detected
- 2 = moderate; moderate, clear detectable signs or symptoms
- 3 = severe; severe signs or symptoms detected
- 4 = very severe; very severe signs or symptoms detected

Detailed description of each grade depends upon the indication (i.e. psoriasis or atopic dermatitis) and is in the Sponsor's submission (page 3298, Volume 26; page 5207, Volume 30). Sponsor's "success" criterion for Global Severity was defined as score of 0, 0.5 or 1.

Each individual clinical signs and symptoms were graded for the target lesion. Pruritus was graded for all treated area in study 18001. The degree of severity for each of signs and symptoms of psoriasis and atopic dermatitis was based on a 5-point scale. That is, 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. Detailed morphological description of the severity is in the Sponsor's submission (pages 3297-3298, Volume 26; pages 5207-5210, Volume 30).

Sponsor's investigator's Global Improvement from baseline was graded for the target lesion based on a 7-point scale:

- 5 = clear; all signs and symptoms of disease resolved (100% from baseline)
- 4 = almost clear; nearly all signs and symptoms cleared (90% from baseline); only minimal residual signs and symptoms remained
- 3 = marked improvement; majority of the signs and symptoms resolved (about 75% from baseline)
- 2 = moderate improvement; significant improvement, but many signs and symptoms remained (about 50% from baseline)
- 1 = minimal improvement; slight overall improvement, but not clinically significant (about 25%

from baseline)

0 = no change; overall severity similar to baseline

-1 = worse; worse than baseline

According to the Sponsor, the percent BSA involvement and percent BSA treated were estimated based on “rule of nines”.

Sponsor’s safety parameters included local cutaneous reactions (i.e. telangiectasis and skin atrophy), and the incidence, severity and relationship of adverse events.

Population Analyzed in the Protocols and Submission:

Intent-to-treat (ITT) and per-protocol (PP) populations were analyzed for efficacy, with ITT analysis as the primary. Their definitions of the ITT and PP populations are:

- ITT: all subjects who were randomized.
- PP: all subjects who did not have the following major protocol violations:
 - Dropping out prior to week 1 visit
 - Missing more than 3 consecutive days of dosing
 - With 2 or more visits missed through the week 4 visit for study 9707 (or including week 2 visit for study 18001)
 - Week 4 visit for study 9707 was outside 28 ± 8 days window
 - Subjects who did not meet all inclusion/exclusion criteria – blinded medical review on a case-by-case basis to determine the seriousness of the violation(s).
 - Received prohibited concomitant medications – evaluated on a case-by-case basis to determine whether the prohibited medication caused problems to warrant exclusion.

For handling missing values in the efficacy evaluation, the last observation carried forward (LOCF) method was proposed and applied to the ITT analysis.

Sponsor’s safety population was defined as the ITT population, excluding patients who never applied the assigned study drug.

Statistical Analysis Plan Used in the Submission:

- Percentage of patients with Global Severity score of 0, 0.5 or 1:
 - Cochran-Mantel-Haenszel (CMH) test adjusting for center was used for superiority comparison between Clobex Lotion and its Lotion Vehicle.
 - Two-sided 95% confidence interval for the difference between Clobex Lotion and Temovate E Emollient Cream (i.e. Clobex – Temovate E) was calculated. The non-inferiority was claimed if the lower limit of the interval was not less than -0.20.

It should be noted that the non-inferiority margin of 0.20 (or 20%), which is an issue for this application, was not proposed in the original protocol.

- Global Severity score (full-scale): CMH test adjusting for center and using RIDIT transformed score for all comparisons. The “very mild” and “mild” were collapsed before analysis (i.e. scores of 0.5 and 1).
- Individual signs/symptoms: CMH test, adjusting for center and using RIDIT transformed score.

- Percent change from baseline in DSS, percent BSA involved, and percent BSA treated: Analysis of covariance (ANCOVA) with the terms of center, treatment and baseline data.

Reviewer's Comments on Studies 9707 and 18001:

1. Each of investigators Miller and Breneman was in both pivotal trials. This might violate the "independence" criterion of clinical trials for efficacy and safety claims. It should be noted that site IDs in the two pivotal trials are the same for each investigator (i.e. 1170 for Breneman and 2029 for Miller). However, the patients enrolled in the two studies were different. An analysis is performed to examine the impact of the two sites on the efficacy results in the review.
2. Investigator [redacted] in study 18001 has been under OCI investigation. A total of 42 patients (18%) were enrolled at the study site. The validity of data for efficacy evaluation is an issue. A sensitivity analysis is performed to investigate the impact of the study site on the efficacy results in the review.
3. One randomization number was not assigned to any patients in each of studies 9707 and 18001. Seven randomization numbers (3%) were not assigned sequentially in study 18001. However, this is not expected to have an impact on the efficacy results.
4. Per the Division's comments at the End-of-Phase 2 Meeting (dated 9/20/1999), the primary efficacy endpoints should be:
 - Clinical signs/symptoms – change from baseline should be evaluated.
 - Percentage of patients with success in dichotomized Global Severity.
5. It should be noted that there were 4 amendments included in the NDA submission for study 18001. Amendments 2 and 3 were submitted to the Division on 4/18/00 and 9/28/00, respectively. However, the Division does not have records concerning amendments 1 and 4, which were dated 2/23/00 and 11/13/00. Two crucial points about amendments 1 and 4 are:
 - Sponsor's amendment 1 defined the success criterion in Global Severity as score of 0, 0.5 or 1. This endpoint was one of their secondary efficacy endpoints at the time.
 - Sponsor's amendment 4 changed the primary efficacy endpoints from Dermatologic Sum Score (DSS) and Global Severity score (full-scale) to the success rate in Global Severity. Consequently, the non-inferiority margin used for efficacy assessment between Clobex Lotion and Temovate E Cream was changed from 1 point for DSS to 20% for success rate in Global Severity.

It should be noted that the Sponsor's definition of success in Global Severity based on scores of 0, 0.5 or 1 might be inappropriate for the following reasons:

- Approximately 60% and 65% of patients were scored as 2 at baseline for studies 9707 and 18001, respectively. The distribution of patients with a score of 2 at baseline was 59.8% vs. 59.3% vs. 65.5% for Clobex vs. Temovate E vs. vehicle in study 9707; while 74.0% vs. 61.0% vs. 54.5% in study 18001. An improvement of only 1 grade would categorize patients as successes at the final time point. The clinical benefit of an improvement of 1 grade might not be significant. It should be noted also that Clobex group had a higher rate of patients with score 2 at baseline in study 18001, as compared to Temovate E and vehicle groups.
- In study 18001, 6 patients (2.6%) were categorized as successes at baseline without starting study medication. The patient distribution was 1 (1%), 4 (4%) and 1 (3%) for Clobex, Temovate E and vehicle arms, respectively.

Furthermore, per the Division's review practice in the past for drug approval in the same drug category, the 20% non-inferiority margin for the success rate in Global Severity might be too large. In agreement with the clinical team, this statistical review evaluates the efficacy claim of Clobex Lotion based on the following:

- Success in Global Severity is re-defined as a score of 0 or 0.5.
 - Non-inferiority evaluation is based on one-sided 97.5% confidence intervals.
 - Non-inferiority margin for success rate in Global Severity is based on 10% in accordance with the Division's past approved NDAs (i.e. Olux Foam for NDA 21,142 and Betamethasone Valerate Foam for NDA 20,934, for the indication of moderate to severe scalp psoriasis).
 - For mean change from baseline in clinical signs and symptoms, the non-inferiority margin of 10% of reference drug mean is used. Additionally, the clinical signs and symptoms are also evaluated based on dichotomizing the clinical sign and symptom at score of 0 as supportive.
6. Per clinical and statistical discussions, the clinical signs and symptoms to be evaluated for each study are:
- For study 9707 (psoriasis indication): erythema, plaque elevation and scaling.
 - For study 18001 (atopic dermatitis indication): erythema, induration/papulation, oozing/crusting and pruritus.
7. This statistical review will evaluate the primary efficacy endpoints recommended by the Division at the End-of-Phase 2 Meeting. Results of other efficacy endpoints are not reported. For efficacy analyses in this statistical review, study sites 2063 and 2124 are pooled in study 9707; while sites 2087, 2092 and 2139 are pooled in study 18001 to attain at least 7 patients per center, as proposed by the Sponsor.

Efficacy Results for Pivotal Studies 9707 and 18001:

1. Patient Disposition and Baseline Characteristics

To evaluate the comparability of three treatment arms, Table 2 presents the patient disposition for studies 9707 and 18001. The results of study enrollment by center, and patient demographics/baseline characteristics are given in Tables A.1-A.2 of the Appendix, respectively.

Table 2: Patient Disposition – Studies 9707 and 18001

Subjects	Study 9707			Study 18001		
	Clobex	Temovate E	Vehicle	Clobex	Temovate E	Vehicle
Subject Enrolled	82	81	29	96	100	33
Completed study	77 (94%)	77 (95%)	21 (72%)	87 (91%)	93 (93%)	26 (79%)
ITT population	82 (100%)	81 (100%)	29 (100%)	96 (100%)	100 (100%)	33 (100%)
Discontinued, total	5 (6%)	4 (5%)	8 (28%)	9 (9%)	7 (7%)	7 (21%)
Lack of efficacy	3	1	1	0	0	0
Adverse events	0	0	0	0	0	1
Lost to follow-up	0	1	1	5	4	1
Protocol violation	2	0	0	0	0	1
Subject request	0	2	6	2	3	3
Other	0	0	0	2	0	1
PP population	76 (93%)	75 (93%)	26 (90%)	90 (94%)	95 (95%)	28 (85%)
Safety population	82 (100%)	81 (100%)	29 (100%)	96 (100%)	99 (99%)	33 (100%)

Source: Sponsor's NDA submission (pages 3270-3271 and 3309, Volume 26; pages 5178 and 5226, Volume 30).

Generally, treatment groups are comparable with respect to the ITT, PP and safety populations within each trial. A higher rate of subjects in vehicle group discontinued from the trials, as compared to Clobex and Temovate E arms. For the treatment distribution by demographic and baseline characteristics, the results in Table A.2 generally show non-significant differences among treatment groups. Clobex group may have a higher rate of subjects categorized as

Hispanic and Yellow in study 18001. It is difficult to make a formal statistical comparison among treatment groups, as the numbers of subjects in these race groups are small. It should be noted that treatment groups are comparable if the race distribution is categorized as white vs. non-white (p-value = 0.761 based on CMH test).

2. Primary Efficacy Endpoints

Success Rate in Global Severity:

In agreement with the Division, success criterion is re-defined as Global Severity score of 0 or 0.5 at Week 4 (for psoriasis) and Week 2 (for atopic dermatitis), respectively, for studies 9707 and 18001. The efficacy results of success rate are presented in Table 3. The following summarizes the results:

- Generally, results of the ITT and PP analyses are consistent.
- Clobex is superior to its vehicle for each study (p-value < 0.001 and ≤ 0.003 for studies 9707 and 18001).
- For non-inferiority evaluation of Clobex to Temovate E based on the ITT analysis, it is *not* established, as the limits of the one-sided 97.5% confidence intervals are -18.9% and -12.0% for studies 9707 and 18001, respectively, which are smaller than -10%.

It should be noted that the PP analyses in Table 3 employed the LOCF method for handling missing data at final time points. This reviewer has examined the results of such analyses. They are similar to those based on the observed cases.

**Table 3: Number (%) of Patients with Success (Score of 0 or 0.5) in Global Severity
Studies 9707 (Week 4) and 18001 (Week 2)**

Analysis	Clobex n/N (%)	Temovate E n/N (%)	Vehicle n/N (%)	Clobex vs. Vehicle (p-value) ¹	Clobex vs. Temovate E	
					Difference (Clobex – Temovate E)	Limit of 97.5% CI (Asymp.) ¹
Study 9707 ITT	30/82 (36.6%)	33/81 (40.7%)	0/29	< 0.001	-4.2%	-18.9%
PP	27/76 (35.5%)	32/75 (42.7%)	0/26	< 0.001	-7.1%	-22.4%
Study 18001 ITT	41/96 (42.7%)	41/100 (41.0%)	4/33 (12.1%)	0.001	1.7%	-12.0%
PP	40/90 (44.4%)	41/95 (43.2%)	4/28 (14.3%)	0.003	1.3%	-12.9%

Source: Summary is based on the Sponsor's NDA submission (page 3317, Volume 26; page 5236, Volume 30).

¹Comparison is reviewer's analysis. P-value between Clobex and its vehicle is based on CMH test adjusting for center. Non-inferiority comparison between Clobex and Temovate E is based on one-sided 97.5% C.I. for proportion difference (Clobex – Temovate E). Asymptotic and exact results are calculated using StatXact, 5.0. Only asymptotic results are presented, as exact results are similar.

Clinical Signs and Symptoms

Per clinical and statistical discussions, the clinical signs and symptoms to be examined for studies 9707 and 18001 are:

- Study 9707 (psoriasis): erythema, plaque and scaling.
- Study 18001 (atopic dermatitis): erythema, papulation, oozing/crusting and pruritus.

For the change score from baseline to endpoint (i.e. week 4 for study 9707 and week 2 for study 18001), this reviewer has performed analyses on the mean absolute change and mean percent change from baseline. The results are generally consistent. It should be pointed out that the normality assumption on data of the absolute change and percent change from baseline is not met ($p\text{-value} \leq 0.014$). Therefore, ANCOVA analyses based on ranks were performed and yielded consistent results to those based on the original data.

Tables 4 and 5 below present results of the mean absolute change based on the original data for studies 9707 and 18001, respectively.

**Table 4: Mean Change from Baseline to Week 4 in Clinical Signs/Symptoms
Study 9707 (Psoriasis)**

Analysis Signs/symptoms	Clobex	Temovate E	Vehicle	Clobex vs. Vehicle (p-value) ¹	Limit of 97.5% CI (Clobex – Temovate E) ¹	–10% Temovate E mean
ITT Analysis	(N=82)	(N=81)	(N=29)			
Erythema	1.38	1.46	0.31	< 0.001	–0.11	–0.146
Plaque	1.90	1.78	0.41	< 0.001	–0.08	–0.178
Scaling	2.06	1.89	0.55	< 0.001	–0.05	–0.189
PP Analysis	(N=76)	(N=75)	(N=26)			
Erythema	1.42	1.51	0.31	< 0.001	–0.13	–0.151
Plaque	1.95	1.80	0.42	< 0.001	–0.085	–0.180
Scaling	2.11	1.95	0.58	< 0.001	–0.09	–0.195

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

¹Results are based on ANCOVA on the original data with terms of center, treatment and baseline data. For superiority comparison, p-value is listed. For non-inferiority assessment, limits of one-sided 97.5% C.I. for mean difference (i.e. Clobex – Temovate E) are calculated.

**Table 5: Mean Change from Baseline to Week 2 in Clinical Signs/Symptoms
Study 18001 (Atopic Dermatitis)**

Analysis Signs/symptoms	Clobex	Temovate E	Vehicle	Clobex vs. Vehicle (p-value) ¹	Limit of 97.5% CI (Clobex – Temovate E) ¹	–10% Temovate E mean
ITT analysis	(N=96)	(N=100)	(N=33)			
Erythema	1.47	1.53	0.85	< 0.001	–0.253	–0.153
Papulation	1.69	1.63	0.82	< 0.001	–0.204	–0.163
Oozing/Crusting	0.80	0.74	0.52	0.002	–0.104	–0.074
Pruritus	1.91	2.02	0.88	< 0.001	–0.159	–0.202
PP Analysis	(N=90)	(N=95)	(N=28)			
Erythema	1.53	1.60	0.89	< 0.001	–0.267	–0.160
Papulation	1.77	1.72	0.89	< 0.001	–0.238	–0.172
Oozing/Crusting	0.82	0.78	0.57	0.005	–0.098	–0.078
Pruritus	1.98	2.12	0.96	< 0.001	–0.195	–0.212

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

¹Results are based on ANCOVA on the original data with terms of center, treatment and baseline data. For superiority comparison, p-value is listed. For non-inferiority assessment, limits of one-sided 97.5% C.I. for mean difference (i.e. Clobex – Temovate E) are calculated.

The following summarizes the results of Tables 4-5:

- Clobex is superior to its vehicle for the mean change in each study (Tables 4 and 5: $p\text{-value} < 0.001$ and ≤ 0.005 for studies 9707 and 18001, respectively).
- Clobex is non-inferior to Temovate E in the mean absolute change of clinical signs/symptoms for study 9707, as limits of one-sided 97.5% confidence intervals are not

less than –10% of Temovate E means. However, the non-inferiority of Clobex to Temovate E is **not** established for clinical signs and symptoms in study 18001 except pruritus score, since limits of the mean change are less than –10% of Temovate E means for erythema, induration/papulation and oozing/crusting scores in both the ITT and PP analyses.

Additionally, a supportive analysis based on dichotomizing the clinical signs and symptoms at score of 0 is performed. The ITT results are presented in Table 6.

Table 6: Number (%) of Patients with Score of 0 at Endpoint in Clinical Signs and Symptoms – Studies 9707 and 18001 (ITT Analyses)

Study 9707	Clobex (N=82)	Temovate E (N=81)	Vehicle (N=29)	Clobex vs. Vehicle (p-value) ¹	Clobex vs. Temovate E	
					Difference (Clobex – Temovate E)	Limit of 97.5% CI (Asymp.) ¹
Erythema	13 (15.9%)	11 (13.6%)	0	0.0124	2.3%	–8.91%
Plaque elevation	45 (54.9%)	33 (40.7%)	0	< 0.001	14.1%	–1.20%
Scaling	48 (58.5%)	41 (50.6%)	2 (6.9%)	< 0.001	7.9%	–7.33%
Study 18001	(N=96)	(N=100)	(N=33)			
Erythema	34 (35.4%)	34 (34.0%)	2 (6.1%)	< 0.001	1.4%	–11.84%
Papulation	50 (52.1%)	48 (48.0%)	5 (15.2%)	< 0.001	4.1%	–9.85%
Oozing/Crusting	82 (85.4%)	88 (88.0%)	21 (63.6%)	0.0083	–2.6%	–12.50%
Pruritus	56 (58.3%)	60 (60.0%)	5 (15.2%)	< 0.001	–1.7%	–15.30%

Source: Summary is based on the Sponsor's NDA submission (page 3320, Volume 26; pages 5238-5239, Volume 30).
¹Comparison is reviewer's analysis. P-value is based on CMH test adjusting for site. For non-inferiority evaluation, limits of one-sided 97.5% C.I. based on asymptotic and exact results are calculated using StatXact, Version 5.0. Only asymptotic results are presented, as exact results are similar.

The following summarizes the results in Table 6:

- Results based on the proportion of patients with sign/symptom score of 0 are generally consistent to those based on the mean change from baseline.
- Clobex is superior to its vehicle with respect to the proportion of patients with sign/symptom score of 0 in each study (p-value ≤ 0.0124 and ≤ 0.0083 for studies 9707 and 18001).
- Clobex is non-inferior to Temovate E in each of signs and symptoms in study 9707, as the limits of one-sided 97.5% confidence intervals (i.e. –8.91%, –1.20% and –7.33%) are all greater than –10%. However, the non-inferiority of Clobex to Temovate E is **not** established in all sign and symptom scores except papulation score in study 18001.

Sensitivity Analyses:

Per the statistical comments stated previously, the participation of two investigators, Breneman (site 1170) and Miller (site 2029), in both pivotal studies 9707 and 18001 might violate the independence of clinical trials for efficacy and safety claims. Also, investigator — (i.e. site 2122) in study 18001 has been under OCI investigation due to lack of license for medicinal practice. Sensitivity analyses are performed to investigate the impact of these study sites on the efficacy results.

Total of 7 (i.e. 3, 3, and 1 in Clobex, Temovate E and vehicle) and 21 patients (i.e. 9, 9 and 3 in Clobex, Temovate E and vehicle) were enrolled in sites 1170 and 2029, respectively, for study 9707. This constitutes 14.6% of patient enrollment for study 9707. For study 18001, 21 (i.e. 9, 9

and 3 in Clobex, Temovate E and vehicle) and 28 patients (i.e. 12, 12, and 4 in Clobex, Temovate E and vehicle) were in sites 1170 and 2029. This constitutes 21.4% of patient enrollment for study 18001. There were 42 patients participated in site 2122 (i.e. 18, 18 and 6 in Clobex, Temovate E and vehicle) which constitutes 18.3% of patient population in study 18001. With such relatively large percentages of patients in these study sites, efficacy results might be affected in some certain degrees.

(1) Site in Study 18001:

Table 7 presents the results for the primary efficacy endpoints when site was excluded from the study.

Table 7: Primary Efficacy Results when Excluding Site – Study 18001

Endpoints	Success Rate in Global Severity, n/N (%)					
	Clobex	Temovate E	Vehicle	Clobex vs. Vehicle (p-value) ¹	Clobex vs. Temovate E	
					Difference (Clobex – Temovate E)	Limit of 97.5% CI (asympt.) ¹
Success Rate	37/78 (47%)	36/82 (44%)	4/27 (15%)	0.003	3.5%	-11.8%
Signs/symptoms	Clinical Signs and Symptoms, mean					
	Clobex	Temovate E	Vehicle	Clobex vs. Vehicle (p-value) ²	Clobex vs. Temovate E	
					Limit of 97.5% CI ²	-10% Temovate E mean
Erythema	1.53	1.51	0.89	< 0.001	-0.264	-0.151
Papulation	1.71	1.67	0.81	< 0.001	-0.244	-0.167
Oozing/Crusting	0.71	0.61	0.41	0.002	-0.096	-0.061
Pruritus	1.95	2.00	0.89	< 0.001	-0.140	-0.200

Source: Summary is based on the Sponsor's electronic SAS data sets.
¹ Comparison is reviewer's analysis. P-value is based on CMH test adjusting for site. For non-inferiority evaluation, limits of one-sided 97.5% C.I. based on asymptotic and exact results are calculated using StatXact, Version 5.0. Only asymptotic results are presented, as exact results are similar.
² Results are based on ANCOVA on the original data with terms of center, treatment and baseline data. For superiority comparison, p-value is listed. For non-inferiority assessment, limits of one-sided 97.5% C.I. are calculated.

Results of Table 7 are summarized by the following:

Results yield the same efficacy conclusions to those based on the whole date set. That is,

- Clobex is superior to its vehicle in all primary efficacy endpoints (p-value ≤ 0.003).
- The non-inferiority of Clobex to Temovate E is **not** established for all primary efficacy endpoints except pruritus score, as the limits of 97.5% confidence intervals are smaller than -10% for success rate of Global Severity, and -10% of Temovate E means for mean change from baseline in erythema, papulation and oozing/crusting scores.

(2) The Two Investigators Miller and Breneman:

It should be noted that the patient enrollment dates were during 2/2/00 – 4/20/00 for Investigator Miller; and 3/1/00 – 4/3/00 for Investigator Breneman in study 9707. On the other hand, patient enrollment dates were 5/3/00 – 12/11/00 for Investigator Miller and were 6/5/00 – 12/6/00 for Investigator Breneman in study 18001. Therefore, patient's participation in the two sites for study 9707 was earlier than for study 18001. The participation of the two investigators in study 18001 might violate the "independence" criterion of clinical trials for efficacy and safety claims.

Table 8 presents the results of the primary efficacy endpoints for the two sites compared to the remaining sites in study 18001.

**Table 8: Comparisons between Miller/Breneman Sites and Other Sites
in the Primary Efficacy Endpoints – Study 18001**

Study	Efficacy endpoints	Clobex	Temovate E	Vehicle
18001	Success rate in Global Severity, n/N (%)			
	Sites 1170/2029	13/21 (61.9%)	5/21 (23.8%)	1/7 (14.3%)
	Remaining sites	28/75 (37%)	36/79 (46%)	3/26 (12%)
	Erythema, mean (sd)			
	Sites 1170/2029	1.67 (0.80)	1.52 (0.98)	1.00 (0.82)
	Remaining sites	1.41 (0.84)	1.53 (0.96)	0.81 (0.69)
	Papulation, mean (sd)			
	Sites 1170/2029	1.86 (0.73)	1.81 (0.93)	0.86 (1.21)
	Remaining sites	1.64 (0.88)	1.58 (0.94)	0.81 (0.69)
	Oozing/crusting, mean (sd)			
	Sites 1170/2029	0.62 (0.97)	0.43 (0.81)	0.14 (0.38)
	Remaining sites	0.85 (0.85)	0.82 (0.76)	0.62 (0.85)
	Pruritus, mean (sd)			
	Sites 1170/2029	2.10 (0.94)	1.76 (1.18)	1.00 (1.15)
	Remaining sites	1.85 (1.02)	2.09 (1.10)	0.85 (1.26)
Source: Summary is based on the Sponsor's electronic SAS data sets.				

Results of Table 8 are summarized by the following:

The impact of the two investigators' participation in study 18001 on the results of the primary efficacy endpoints is large for Clobex group for the following reasons:

- The mean changes from baseline in each of clinical signs and symptoms, except oozing/crusting score, for study sites 1170 and 2029 are numerically higher than those of the remaining sites in Clobex group. Therefore, efficacy results are relatively stronger for Clobex group when the two sites are included.
- Clobex group had a higher success rate of Global Severity for study sites 1170 and 2029, as compared to Temovate E and vehicle arms (i.e. 61.9% vs. 23.8% vs. 14.3%). The success rate was 61.9% for the two sites in Clobex group, compared to 37% for the remaining sites. Consequently, efficacy results are stronger for Clobex group by including the two sites.

It should be noted that the non-inferiority of Clobex to Temovate E is not established with respect to the success rate of Global Severity and the mean change from baseline in some of clinical sign/symptom even when the two sites are included in the analysis.

3.1.2 Supportive Study 2651

Study Design

Study 2651 was a randomized, active- and vehicle-controlled, investigator-masked, and multicenter (i.e. 18 centers) trial conducted in Europe. The study indication was moderate to severe plaque-type psoriasis. The three treatment arms in the study were Clobex Lotion, Dermoval Cream, and Lotion vehicle. The assigned study medication was applied twice daily for 4 weeks to the affected areas. Clinical assessments were done at baseline, weeks 1, 2, and 4, with week 4 as the primary time point for efficacy evaluation. It should be noted that the active-control arm was Dermoval Cream, which differed from Temovate E Emollient Cream in the pivotal studies 9707 and 18001.

Patient's inclusion criteria included age of 18 or older, and moderate to severe psoriasis, which was defined as a total of at least 6 points out of a possible maximum of 12 points for the symptoms of erythema, plaque elevation, and scaling on a target lesion. The target lesion was a lesion identified by the investigator at baseline. Furthermore, patients were required to have psoriasis that covered a minimum body surface area of 10% (in contrast to 15% for study 9707).

According to the protocol, 210 patients were planned. The randomization was based on blocks of size 7 and the treatment allocation was based on a ratio of 3:3:1 to Clobex, Dermoval Cream and vehicle arms. Sponsor's documentation showed that two sets of randomization numbers, 001-280 and 281-308, were generated on 4/20/00 and 11/7/00, respectively, which were prior to the 1st patient enrollment (i.e. 9/12/00 and 11/22/00). The actual study enrollment was, however, 222 patients from 18 European centers. It should be noted that the Sponsor's submission does not show any patients assigned with randomization numbers 29-35 and 211-252. This reviewer requested a clarification on these points. The Sponsor's explanation was submitted on 2/19/03. Their responses seem acceptable. Review of the Sponsor's responses is provided in A.3 of the Appendix.

The study was designed as double blind between Clobex Lotion and its Lotion vehicle, and was investigator-masked between Clobex Lotion and Dermoval Cream, as the dosage forms of the two active drugs are different. To maintain the blinding, study drug package kits were sealed and distributed by designated personnel other than the investigator.

Endpoints Specified in the Protocol and Submission:

Two primary efficacy endpoints were specified in the protocol:

- a. Global Severity: is evaluated on all treated areas based on scales of 0 (none), 0.5 (very mild), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe).
- b. Dermatologic Sum Score (DSS): sum of erythema, plaque elevation, and scaling for the target lesion.

Secondary efficacy endpoints included:

- a. Erythema, plaque elevation, scaling, and pruritus: the degree of severity for each of the signs/symptoms was based on a 5-point scale (i.e. 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe).

- b. Investigator's Global Assessment of Improvement from baseline: was evaluated for the target lesion based on a 7-point scale (i.e. -1 = worse, 0 = no change, 1 = minimal improvement, 2 = moderate improvement, 3 = marked improvement, 4 = almost clear, and 5 = clear).
- c. Subject's Global Assessment of Improvement from baseline: was evaluated for all treated areas using a 7-point scale (same description as that for Investigator's Global Assessment of Improvement from baseline).
- d. Body surface area involvement with disease: was based on "*rule of nines*".

Sponsor's safety parameters included cutaneous reaction (i.e. telangiectasis and skin atrophy), and incidence of adverse events.

Population Analyzed and Statistical Analysis Planned in the Protocol and Submission:

- Efficacy analysis was based on the ITT and PP populations, with the ITT analysis as the primary. Sponsor's ITT population consisted of all subjects enrolled and randomized. PP population included patients who were considered evaluable, based on the observed deviations from the protocol. For handling missing data, the LOCF was used for the ITT analysis, but not the PP analysis.
- Sponsor's safety population included all patients enrolled and randomized, but excluded subjects who never applied the assigned study drug.
- Criteria of success of the study were:
 - Superiority between Clobex and its vehicle: a significant difference in favor of Clobex for the 2 primary efficacy endpoints.
 - Non-inferiority between Clobex and Dermoval: upper limit of the two-sided 95% confidence interval of the difference (i.e. Clobex - Dermoval) in DSS not exceeding 1 point, and the upper limit of the two-sided 95% confidence interval of the difference in Global Severity not exceeding 0.5 point.
- Except the Global Improvement endpoints, ANCOVA method with terms of treatment, center, and baseline score was planned to analyze all efficacy endpoints.
- For evaluation of the Global Improvement endpoints, and of the safety scores of telangiectasis and skin atrophy, CMH test adjusting for center using the riddit transformation, was planned.

Reviewer's Comments on Study 2651:

1. In agreement with the medical reviewer and in consistency with studies 9707 and 18001, only the primary efficacy endpoints recommended by the Division are evaluated for the study. They are:
 - Success rate in Global Severity, where success is defined as a score of 0 or 0.5.
 - Clinical signs and symptoms, including erythema, plaque, and scaling. For each sign/symptom, mean absolute change from baseline to week 4 is evaluated. Additionally, analysis based on dichotomizing the clinical signs and symptoms at score of 0 is also performed as supportive.

For non-inferiority assessment, the non-inferiority margin of 10% is used for response rate; while the non-inferiority margin of 10% of Dermoval mean is applied to the mean change from baseline.

Efficacy Results for Study 2651:

1. Patient Disposition and Baseline Characteristics

Table 9 presents the patient disposition and demographic. Patient baseline characteristics are given in Table A.4 of the Appendix.

Generally, the three treatment groups are comparable in terms of the patient disposition and demographic (Table 9). Relatively higher percentages of patients are males in Dermoval and vehicle groups, as compared to Clobex arm. However, the difference is not significant (p-value = 0.289 based on chi-square test). For the comparability of baseline characteristics, no outstanding difference among treatment groups is noted from Table A.4 of the Appendix.

Table 9: Patient Disposition and Demographic – Study 2651

Subjects	Clobex	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)	47.29 (15.9)	50.94 (14.6)
	20–80	18–87	22–79
Race, n (%)			
White	94 (100%)	95 (100%)	33 (100%)
ITT population	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 (page 6557, pages 6596-6597, Volume 34).

2. Primary Efficacy Endpoints

Results of comparing success rates of Global Severity (i.e. score of 0 or 0.5) at week 4 as well as mean change from baseline to week 4 in each of the clinical signs and symptoms for the three treatment groups are presented in Tables 10 and 11, respectively. They are summarized by the following:

- Results of the ITT and PP analyses are consistent (Tables 10-11).
- Clobex is superior to its vehicle with respect to the success rate in Global Severity and mean change from baseline for each of the clinical signs and symptoms (p-value < 0.001, Tables 10-11).
- For non-inferiority evaluation based on the ITT analysis,
 - **Success rate in Global Severity:** The non-inferiority of Clobex Lotion to Dermoval Cream is not established, as the limit of the one-sided 97.5% confidence interval for the proportion difference (Clobex – Dermoval) is –19.7%, which is smaller than –10%.
 - **Mean change from baseline in signs/symptoms:** The non-inferiority of Clobex Lotion to Dermoval Cream is not established except the mean change from baseline in scaling score. The limits of the one-sided 97.5% confidence intervals are –0.325, and –0.367, which are smaller than –10% of Dermoval means for change from baseline in erythema and plaque scores (i.e. –0.215 and –0.239).

Table 10: Success Rate in Global Severity at Week 4 – Study 2651

Study 2651	Clobex n/N (%)	Dermoval n/N (%)	Vehicle n/N (%)	Clobex vs. Vehicle (p-value) ¹	Clobex vs. Dermoval	
					Difference (Clobex – Dermoval)	Limit of 97.5% CI (Asymp.) ¹
ITT	62/94 (66.0%)	69/95 (72.6%)	3/33 (9.1%)	< 0.001	-6.7%	-19.7%
PP	60/90 (66.7%)	65/90 (72.2%)	3/27 (11.1%)	< 0.001	-5.6%	-18.9%

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

¹Comparison is reviewer's analysis. P-value between Clobex and its vehicle is based on CMH test adjusting for center. Non-inferiority comparison between Clobex and Dermoval Cream is based on one-sided 97.5% C.I. for proportion difference (Clobex – Dermoval). Asymptotic and exact results are calculated using StatXact, 5.0. Only asymptotic results are presented, as exact results are similar.

**Table 11: Mean Change from Baseline to Week 4 in Clinical Signs and Symptoms
Study 2651**

Analysis Signs/symptoms	Clobex	Dermoval	Vehicle	Clobex vs. Vehicle (p-value) ¹	Clobex vs. Dermoval	
					Limit of 97.5% CI ¹	-10% Dermoval mean
ITT Analysis	(N=94)	(N=95)	(N=33)			
Erythema	2.02	2.15	0.61	< 0.001	-0.325	-0.215
Plaque	2.27	2.39	0.70	< 0.001	-0.367	-0.239
Scaling	2.56	2.55	1.33	< 0.001	-0.183	-0.255
PP Analysis	(N=90)	(N=90)	(N=27)			
Erythema	2.01	2.16	0.67	< 0.001	-0.323	-0.216
Plaque	2.30	2.38	0.81	< 0.001	-0.343	-0.238
Scaling	2.60	2.53	1.56	< 0.001	-0.135	-0.253

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

¹Comparison is reviewer's analyses. Results are based on ANCOVA on the original data with terms of center, treatment and baseline data. For superiority comparison, p-value is listed. For non-inferiority assessment, limits of one-sided 97.5% C.I. are calculated.

In addition, a supportive analysis based on dichotomizing each of the clinical signs and symptoms at score of 0 is performed. Results are presented in Table 12. A summary of the results is:

- Clobex is superior to its vehicle with respect to the proportion of patients with score of 0 at week 4 in each of erythema, plaque and scaling (p-value < 0.001).
- The non-inferiority of Clobex to Dermoval is not established with respect to this endpoint, as limits of one-sided 97.5% confidence intervals are -16.2%, -24.8% and -16.0% for erythema, plaque and scaling, which are less than -10%.

**Table 12: Number (%) of Patients with Score of 0 at Week 4 in
Clinical Signs and Symptoms – Study 2651 (ITT Analysis)**

Study 2651	Clobex n/N (%)	Dermoval n/N (%)	Vehicle n/N (%)	Clobex vs. Vehicle (p-value) ¹	Clobex vs. Dermoval	
					Difference (Clobex – Dermoval)	Limit of 97.5% CI (Asymp.) ¹
Erythema	31/94 (33%)	34/95 (36%)	1/33 (3%)	< 0.001	-2.8%	-16.2%
Plaque	60/94 (64%)	72/95 (76%)	3/33 (9%)	< 0.001	-12.0%	-24.8%
Scaling	73/94 (78%)	78/95 (82%)	7/33 (21%)	< 0.001	-4.4%	-16.0%

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

¹Comparison is reviewer's analysis. P-value between Clobex and its vehicle is based on CMH test adjusting for center. Non-inferiority comparison between Clobex and Dermoval is based on one-sided 97.5% C.I. for proportion difference (Clobex – Dermoval). Asymptotic and exact results are calculated using StatXact, 5.0. Only asymptotic results are presented, as exact results are similar.

3. A Note on the Sponsor's Results

It should be noted that the Sponsor's primary efficacy endpoints specified in the protocol were:

- Dermatological Sum Score (DSS: i.e. sum of erythema, plaque and scaling scores) at Week 4
- Global Severity score at Week 4

To claim the non-inferiority of Clobex Lotion to Dermoval Cream, the Sponsor's non-inferiority margins were set to be 1 point for DSS and 0.5 point for Global Severity score in the protocol.

The Sponsor's ITT (LOCF) results are presented below:

Study 2651	Clobex Mean (sd)	Dermoval Mean (sd)	Vehicle Mean (sd)	Clobex vs. Vehicle (p-value)	Lower limit of two- sided 95% CI for (Clobex - Dermoval)
DSS score	1.6 (1.7)	1.2 (1.4)	6.0 (2.7)	< 0.001	-0.14
Global Severity	0.7 (0.7)	0.6 (0.6)	2.0 (0.9)	< 0.001	-0.12
Source: Sponsor's NDA submission (pages 6605-6606, 6608-6609, Volume 34).					

It can be observed from the above table that Clobex is highly superior to its vehicle for both primary efficacy endpoints. However, the non-inferiority of Clobex to Dermoval would not be established based on the non-inferiority margin criterion of 10% of Dermoval mean (i.e. 0.12 and 0.06 for DSS and Global Severity, respectively), despite the results in the above table support the Sponsor's claim using their defined margins. This could arise if the sample size was originally powered based on the Sponsor's defined primary efficacy endpoints and non-inferiority margins. A larger number of patients would be needed to conclude the non-inferiority efficacy of Clobex to Dermoval Cream based on the criterion of 10% of Dermoval mean.

**APPEARS THIS WAY
ON ORIGINAL**

3.2 Evaluation of Safety

3.2.1 Studies 9707 and 18001

The Sponsor's safety population included all randomized patients who had applied at least one dose of study medication (active or vehicle). This included 192 (100%) and 228 (99.6%) subjects in studies 9707 and 18001, respectively (per Table 2). Results of safety assessment based on drug exposure, incidence of adverse events, and cutaneous skin reactions (i.e. telangiectasis and skin atrophy) are presented in Tables 13-15. It should be noted that the p-value listed in the comments (shown below) should be interpreted loosely, as studies were not designed to test safety.

Drug Exposure:

Results in Table 13 show that treatment groups are generally comparable with respect to the mean days of treatment duration within each study. No outstanding difference is noted.

Incidence of Adverse Events:

The results in Table 14 generally show that the treatment groups are comparable in terms of incidence of adverse events.

- Clobex group may have numerically higher overall incidence rates of adverse event within each study. However, the differences are not significant (i.e. p-value ≥ 0.294 based on CMH test).
- The incidence rates of study drug related adverse events are not significant between Clobex Lotion group and each of the other two groups (i.e. p-value ≥ 0.164 based on CMH test).

Cutaneous Skin Reaction (Telangiectasis and Skin Atrophy)

Telangiectasis, defined as a dilation of blood vessels, was graded based on a 4-point scale (i.e. 0 = none, 1 = mild, 2 = moderate, and 3 = severe). Skin atrophy, defined as an increased transparency of the epidermis and a shiny appearance, was also scored based on the same scale. Table 15 presents the results of cutaneous skin reaction based on the observed data.

- Clobex group had relatively larger percentage of patients with no telangiectasis at baseline in study 9707, as compared to each of the others (i.e. p-value = 0.074 and 0.083, respectively). The worst responses post-baseline within each study are not different between Clobex and each of the other groups (i.e. p-value ≥ 0.266).
- For skin atrophy, Clobex group is comparable to each of the others at baseline (i.e. p-value ≥ 0.189). No outstanding difference is noted in terms of the percentage of patients with the worst response post baseline between groups (i.e. p-value ≥ 0.338).

Table 13: Duration of Treatment (in Days) – Studies 9707 and 18001

Study 9707	Clobex (n=82)	Temovate E (n=81)	Vehicle (n=29)
Mean (SD)	28.28 (4.032)	28.23 (4.602)	26.93 (6.808)
Median	28	29	29
Range	14 – 45	4 – 37	1 – 32
Study 18001	Clobex (n=96)	Temovate E (n=99)	Vehicle (n=33)
Mean (SD)	14.2 (2.99)	14.5 (2.82)	13.5 (3.46)
Median	15	15	15
Range	1 – 19	1 – 20	1 – 17
Source: Sponsor's NDA submission (page 3328, Volume 26; page 5262, Volume 31).			

Table 14: Incidence of Adverse Events – Studies 9707 and 18001

Events	STUDY 9707			STUDY 18001		
	Clobex (n=82)	Temovate E (n=81)	Vehicle (n=29)	Clobex (n=96)	Temovate E (n=99)	Vehicle (n=33)
Subjects with at least one AE	15 (18.3%)	10 (12.3%)	4 (13.8%)	14 (14.6%)	11 (11.1%)	4 (12.1%)
Subjects with dermatological AE	9 (11%)	5 (6.2%)	2 (6.9%)	4 (4.2%)	4 (4.0%)	2 (6.1%)
Subjects with non-derm. AE	9 (11%)	6 (7.4%)	2 (6.9%)	11 (11.5%)	9 (9.1%)	2 (6.1%)
Subjects with at least one AE related to study drug	5 (6.1%)	2 (2.5%)	3 (10.3%)	4 (4.2%)	1 (1.0%)	2 (6.1%)
Subjects with Serious AE	0	1 (1.2%)	0	0	0	0
Subject Deaths	0	0	0	0	0	0
Discontinuation due to AE	0	1 (1.2%)	0	0	0	1 (3.0%)
AE according to Body System						
Body as a Whole	6 (7.3%)	6 (7.4%)	0	7 (7.3%)	7 (7.1%)	0
Cardiovascular System	0	0	1 (3.4%)	0	1 (1.0%)	0
Digestive System	2 (2.4%)	0	1 (3.4%)	1 (1.0%)	0	1 (3.0%)
Endocrine System	1 (1.2%)	0	0	0	0	0
Metabolic and Nutritional Disorders	0	1 (1.2%)	0	0	0	0
Nervous System	0	0	1 (3.4%)	0	1 (1.0%)	0
Respiratory System	2 (2.4%)	0	0	2 (2.1%)	1 (1.0%)	2 (6.1%)
Skin and Appendages	9 (11.0%)	5 (6.2%)	2 (6.9%)	4 (4.2%)	4 (4.0%)	2 (6.1%)
Urogenital System	1 (1.2%)	0	0	0	0	1 (3.0%)
Special Senses	0	0	0	1 (1.0%)	0	0

Source: Sponsor's NDA submission (pages 3414, 3417-3418, Volume 26; pages 5338, 5340-5343, Volume 31).

Table 15: Telangiectasis and Skin Atrophy – Studies 9707 and 18001

Study 9707	Clobex Lotion		Temovate E Cream		Vehicle Lotion	
	Baseline	Worst response*	Baseline	Worst response*	Baseline	Worst response*
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
p-value			0.074	0.417	0.083	0.445
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	1 (1.2%)	0	0	0	0	0
Severe	0	0	0	0	0	0
p-value			0.400	0.415	0.189	0.682
STUDY 18001						
Telangiectasis						
None	88 (91.7%)	85 (91.4%)	93 (93.9%)	91 (94.8%)	32 (97.0%)	30 (96.8%)
Mild	8 (8.3%)	7 (7.5%)	5 (5.1%)	5 (5.2%)	1 (3.0%)	1 (3.2%)
Moderate	0	1 (1.1%)	1 (1.0%)	0	0	0
Severe	0	0	0	0	0	0
p-value			0.593	0.321	0.260	0.266
Skin Atrophy						
None	90 (93.8%)	85 (91.4%)	93 (93.9%)	89 (92.7%)	31 (93.9%)	30 (96.8%)
Mild	5 (5.2%)	6 (6.5%)	6 (6.1%)	7 (7.3%)	2 (6.1%)	1 (3.2%)
Moderate	1 (1.0%)	2 (2.2%)	0	0	0	0
Severe	0	0	0	0	0	0
p-value			0.986	0.793	1.000	0.338

Source: Sponsor's NDA submission (pages 3433-3434, Volume 26; page 5250, Volume 30).

* Worst response is defined as the worst post baseline response during the study.

3.2.2 Study 2651

All 222 patients enrolled are included for safety evaluation in study 2651. Results of safety assessment based on treatment duration, incidence of adverse events, and cutaneous skin reactions (i.e. telangiectasis and skin atrophy) are presented in Table 16.

The results in Table 16 generally suggest that the safety profile of Clobex Lotion in terms of treatment duration, incidence of adverse events and cutaneous skin reaction is comparable to that of other two treatment groups.

**Table 16: Treatment Duration, Adverse Events and Cutaneous Skin Reaction
Study 2651**

		Clobex (n=94)	Dermoval (n=95)	Vehicle (n=33)
Drug Exposure	Mean (SD)	27.65 (3.53)	27.67 (2.84)	25.97 (5.14)
	Median	28.0	28.0	28.0
	Range	13 – 53	13 – 42	13 – 36
Adverse Events				
Subjects with at least one AE		7 (7.4%)	5 (5.3%)	1 (3.0%)
Subjects with drug-related AE		2 (2.1%)	2 (2.1%)	0
Subjects withdrew due to AE		1 (1.1%)	0	0
Deaths		0	0	0
Subjects with AE by severity				
Mild		4 (4.3%)	3 (3.2%)	1 (3.0%)
Moderate		2 (2.1%)	2 (2.1%)	0
Severe		1 (1.1%)	1 (1.1%)	0
Subjects with AE by Body System				
Body as a Whole		1 (1.1%)	1 (1.1%)	0
Cardiovascular System		0	1 (1.1%)	0
Digestive System		2 (2.1%)	2 (2.1%)	0
musculoskeletal System		1 (1.1%)	0	0
Nervous System		0	1 (1.1%)	0
Respiratory System		1 (1.1%)	0	1 (3.0%)
Skin		2 (2.1%)	2 (2.1%)	0
Urogenital System		1 (1.1%)	0	0
Cutaneous Skin Reaction				
<u>Telangiectasis</u> ¹				
— Baseline				
0 (none)		94 (100%)	93 (97.9%)	33 (100%)
1 (mild)		0	1 (1.1%)	0
2 (moderate)		0	1 (1.1%)	0
Worst responses post-baseline ²				
0 (none)		91 (96.8%)	92 (96.8%)	33 (100%)
1 (mild)		1 (1.1%)	3 (3.2%)	0
2 (moderate)		2 (2.1%)	0	0
<u>Skin Atrophy</u> ¹				
Baseline				
0 (none)		93 (98.9%)	94 (98.9%)	33 (100%)
1 (mild)		1 (1.1%)	0	0
2 (moderate)		0	1 (1.1%)	0
Worst responses post-baseline ²				
0 (none)		90 (95.7%)	90 (94.7%)	33 (100%)
1 (mild)		1 (1.1%)	4 (4.2%)	0
2 (moderate)		3 (3.2%)	1 (1.1%)	0

Source: Sponsor's NDA submission (pages 6615-6617, 6657, 6660-6661, Volume 34).

¹The grades of telangiectasis and skin atrophy are 0= none, 1= mild, 2= moderate, and 3= severe.

² Worst response is defined as the worst score post-baseline.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup efficacy results by gender, race, age and baseline global severity are examined. The results are presented in Tables A.5-A.9 of the Appendix for studies 9707, 18001 and 2651. It should be noted that subgroup efficacy results are intended to observe any efficacy trend over subgroups. The studies were not designed to test efficacy within subgroups.

4.1 Gender

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, Clobex group has higher success rates than those of its vehicle and similar to those of Temovate E Cream group. For female patients in study 18001, Clobex and Temovate E arms had numerically higher success rates than those for males. On the other hand, females in vehicle group had a relatively lower success rate than that in male group. The difference is not statistically significant.

For the 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.

4.2 Race

As the majority of the enrolled patients are 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.

4.3 Age

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 Clobex, Temovate E and vehicle groups). All enrolled patients in 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 the 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.

4.4 Other Special/Subgroup Populations

Subgroup efficacy analysis by baseline Global Severity score is performed. For success rate of Global Severity at endpoint in Clobex and Temovate E groups, the response rate generally

decreases as the baseline Global Severity score increases. The response rates are similar for Clobex and Temovate E groups at each baseline Global Severity score.

On the other hand, the mean change from baseline in clinical signs and symptoms increases as the baseline Global Severity score increases. The results are generally consistent between Clobex and Temovate E groups at each baseline Global Severity score and are better than those of vehicle group.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary issues for the Sponsor's NDA submission are summarized in the following:

- a. Sponsor's primary efficacy endpoint differed from those recommended by the Division. The Division's recommendation of the primary efficacy endpoints at the End-of-Phase 2 Meeting (dated 9/20/1999) were:
 - Change from baseline in clinical signs and symptoms.
 - Dichotomized Global Severity score.
- b. Sponsor's definition of success on Global Severity was score of 0, 0.5 or 1 in the submission. The definition might be inappropriate for the following reasons:
 - Approximately 60% and 65% of patients were scored as 2 at baseline for studies 9707 and 18001, respectively. The distribution of patients with a score of 2 at baseline was 59.8% vs. 59.3% vs. 65.5% for Clobex vs. Temovate E vs. vehicle in study 9707; while 74.0% vs. 61.0% vs. 54.5% in study 18001. An improvement of only 1 grade would categorize patients as successes at the final time point. The clinical benefit of an improvement of 1 grade might not be significant. It should be noted also that Clobex group had a higher rate of patients with score 2 at baseline in study 18001, as compared to Temovate E and vehicle arms.
 - In study 18001, 6 patients (2.6%) were categorized as successes at baseline without starting study medication. The patient distribution was 1 (1%), 4 (4%) and 1 (3%) for Clobex, Temovate E and vehicle, respectively.

Per clinical and statistical discussions, success on Global Severity is re-defined as a score of 0 or 0.5 at endpoint to evaluate the efficacy claim of Clobex Lotion.

- c. For non-inferiority assessment of Clobex to Temovate E Cream in studies 9707 and 18001, the Sponsor used a non-inferiority margin of 20% for success rate in Global Severity. It should be noted that the Division did not have records of such information being submitted for review at the IND protocol stage. Per the Division's review practice in the past for drug approval in the same drug category (i.e. Olux Foam – NDA 21,142 and Betamethasone Valerate Foam – NDA 20,934, for the indication of moderate to severe scalp psoriasis), non-inferiority margin of 10% for response rate has been used.

- d. Investigator [redacted] in study 18001 has been under OCI investigation. A total of 42 patients (18%) were enrolled in the study site. Data from the study site might not be used for efficacy evaluation.
- e. Each of Investigators Miller and Breneman participated in the two pivotal trials. This might violate the "independence" criterion of clinical trials for efficacy and safety claims.

For issue (a) – (c), statistical review has evaluated the efficacy claims of Clobex Lotion based on the Division's recommendation at the EOP2 Meeting and review practice in the past. Sensitivity analyses were performed to evaluate the impact of issue (d) and (e) on the efficacy results.

5.2 Conclusions and Recommendations

The Sponsor in this submission presented results for two pivotal studies (studies 9707 and 18001) and [redacted] Phase 3 studies (studies 2651 [redacted] in support of the efficacy and safety claim of Clobetasol propionate Lotion, 0.05% (Clobex), for the treatment of corticosteroid-responsive dermatoses. The dosing of Clobex Lotion is two times daily for 2 weeks for atopic dermatitis and 4 weeks for psoriasis. Patients with moderate to severe psoriasis and atopic dermatitis were recruited in studies 9707 and 18001, respectively. Studies 2651 [redacted] enrolled patients with moderate to severe plaque-type psoriasis. [redacted]

The primary time point for efficacy evaluation is week 4 for the indication of plaque-type psoriasis and week 2 for atopic dermatitis. In agreement with the Division, the primary efficacy endpoints evaluated are:

- (i) Success rate in Global Severity score, where success is defined as a score of 0 or 0.5.
- (ii) Mean change from baseline to endpoint in each of clinical signs and symptoms
 - For psoriasis indication, erythema, plaque and scaling are of interest.
 - For atopic dermatitis indication, erythema, induration/papulation, oozing/crusting and pruritus are of interest.

Per the Division's past review practice in the same drug category, a non-inferiority margin of 10% for response rate has been used. The efficacy evaluation in this review adopted non-inferiority margins of 10% for response rate and 10% of Temovate E mean (or 10% of Dermoval mean for study 2651) for the mean change from baseline in clinical signs and symptoms. Efficacy results based on the ITT population with the last observation carried forward (LOCF) method for handling missing data are summarized by the following.

Efficacy:

➤ Pivotal study 9707 (for plaque-type psoriasis):

The ITT analysis with the LOCF for missing data demonstrates that:

- Clobex Lotion is superior to its vehicle for all primary efficacy endpoints at week 4 (p-value < 0.001).
- Non-inferiority assessment of Clobex Lotion to Temovate E Cream:
 - a. is not established for the success rate in Global Severity, as limit of the one-sided 97.5% confidence interval is -18.9%, which is less than -10%.

- b. is established for the mean change from baseline to week 4 in clinical signs and symptoms, as limits of the one-sided 97.5% confidence intervals (i.e. -0.11, -0.08 and -0.05) are greater than -10% of Temovate E means (i.e. -0.146, -0.178 and -0.189) for erythema, plaque and scaling scores, respectively.
- Pivotal study 18001 (for atopic dermatitis):
1. The ITT analysis with the LOCF for missing data demonstrates that:
 - Clobex Lotion is superior to its vehicle for all primary efficacy endpoints at week 2 (p-value ≤ 0.002).
 - Non-inferiority assessment of Clobex Lotion to Temovate E Cream:
 - a. is not established for the success rate in Global Severity, as limit of the one-sided 97.5% confidence interval is -12.0%, which is less than -10%.
 - b. is established for mean change from baseline in pruritus score, but not mean change from baseline in erythema, induration/papulation, and oozing/crusting scores. The limits of the 97.5% confidence intervals for mean difference in erythema, papulation, and oozing/crusting scores (i.e. -0.253, -0.204 and -0.104) are less than -10% of Temovate E means (i.e. -0.153, -0.163, and -0.074).
 2. Study site ~~_____~~ has been under OCI investigation. The validity of data for efficacy evaluation is an issue. Results after excluding this site yield the same efficacy conclusions as those based on the whole data set.
 3. As the patient's participation in the two sites (i.e. Breneman and Miller) for study 9707 was earlier than for study 18001, a sensitivity analysis was performed for study 18001. The impact of the two investigators' participation in study 18001 on the efficacy results is large for Clobex group. In particular, the success rate of Global Severity was 61.9% for the two sites, as compared to 37% for the remaining sites. Consequently, efficacy results are stronger for Clobex group by including the two sites. It should be noted that the non-inferiority of Clobex to Temovate E is not established even when the two sites are included in the analysis.
- Supportive study 2651 (for plaque-type psoriasis):
- The ITT analysis with the LOCF for missing data demonstrates that:
- Clobex Lotion is superior to its vehicle with respect to all primary efficacy endpoints (p-value < 0.001).
 - Non-inferiority of Clobex Lotion to Dermoval Cream:
 - a. is not established for the success rate in Global Severity, as limit of the one-sided 97.5% confidence interval is -19.7%, which is less than -10%.
 - b. is established for the mean change from baseline to week 4 in scaling score, but not the mean changes from baseline in erythema, and plaque scores. The limits of the one-sided 97.5% confidence intervals for mean difference in erythema and plaque scores (i.e. -0.325 and -0.367) are less than -10% of Dermoval means (i.e. -0.215 and -0.239).

Safety:

From statistical point of view, the safety profile of Clobex Lotion is comparable to those of Temovate E Cream (or Dermoval Cream for study 2651) and Lotion vehicle in terms of the incidence of adverse events and cutaneous skin reaction.

➤ Study 9707:

- Treatment duration is comparable among the three treatment groups.
- The incidence rate of adverse events is generally comparable among treatments (i.e. 18.3% vs. 12.3% vs. 13.8% for Clobex, Temovate E and vehicle, respectively). Clobex group may have a numerically higher rate; however, the difference is not significant.
- Vehicle group had a higher treatment-related adverse event rate (10.3%), as compared with that of Clobex and Temovate E groups (i.e. 6.1% and 2.5%). But the difference is not significant.
- The three treatment groups are comparable in terms of the responses of cutaneous skin reaction.

➤ Study 18001:

- The three treatment groups are comparable in terms of the treatment duration and responses of cutaneous skin reaction. No outstanding differences are noted.
- The incidence rates are comparable among groups (i.e. 14.6% vs. 11.1% vs. 12.1% for Clobex, Temovate E and vehicle). The treatment-related adverse event rates are 4.2% vs. 1.0% vs. 6.1% for three groups, respectively, which are relatively lower than those in study 9707 (i.e. 6.1% vs. 2.5% vs. 10.3%). This could be possibly due to a shorter treatment duration for study 18001, as compared to study 9707 (i.e. 2-week vs. 4-week).

➤ Study 2651:

- Treatment duration and responses of cutaneous skin reaction are comparable among the three treatment groups.
- The incidence rates of adverse event for the three groups are similar (i.e. 7.4% vs. 5.3% vs. 3.0% for Clobex vs. Dermoval vs. vehicle). The incidence rates of drug-related adverse event are 2.1% vs. 2.1% vs. 0, which are relatively smaller than those in study 9707 even though the treatment duration and indication were the same (i.e. 4-week and psoriasis).

**APPEARS THIS WAY
ON ORIGINAL**

6. APPENDICES

**Table A.1: Patient Enrollment and Treatment by Center
Studies 9707 and 18001 – ITT Population**

Study 9707/Center	Clobex	Temovate E	Vehicle	Total
438	6	5	2	13
740	5	5	2	12
1086	6	6	2	14
1170	3	3	1	7
2019	9	9	3	21
2028	3	3	1	7
2029	9	9	3	21
2065	9	8	3	20
2066	9	9	3	21
2094	3	3	1	7
2123	8	9	3	20
2125	3	3	1	7
2126	6	6	2	14
2063 & 2124	3	3	2	8
Total	82	81	29	192

Study 18001/Center	Clobex	Temovate E	Vehicle	Total
2122	18	18	6	42
2029	12	12	4	28
2128	9	11	3	23
1170	9	9	3	21
429	8	7	3	18
2067	7	8	3	18
2129	7	7	2	16
2089	6	6	2	14
2121	6	6	2	14
2026	5	6	2	13
2069	6	4	1	11
2087, 2092 & 2139	3	6	2	11
Total	96	100	33	229

Source: Sponsor's NDA submission (page 3336, Volume 26; page 5260, Volume 31).

**Table A.2: Patient Demographics and Baseline Characteristics:
Studies 9707 and 18001 – ITT Population**

STUDY 9707	Clobex (N=82)	Temovate E (N=81)	Vehicle (N=29)	p-value
Age, mean (range)	48.72 (19 – 76)	49.09 (21 – 77)	47.21 (26 – 78)	0.795
Gender, n (%)				
Male	58 (70.7%)	52 (64.2%)	16 (55.2%)	0.286
Female	24 (29.3%)	29 (35.8%)	13 (44.8%)	
Race, n (%)				
White	69 (84.1%)	66 (81.5%)	24 (82.8%)	0.286
Black	2 (2.4%)	1 (1.2%)	2 (6.9%)	
Hispanic	11 (13.4%)	14 (17.3%)	3 (10.3%)	
Skin Phototype, n (%)				
I	3 (3.7%)	1 (1.2%)	4 (13.8%)	0.103
II	23 (28.0%)	27 (33.3%)	6 (20.7%)	
III	28 (34.1%)	30 (37.0%)	10 (34.5%)	
IV	15 (18.3%)	20 (24.7%)	5 (17.2%)	
V	11 (13.4%)	2 (2.5%)	3 (10.3%)	
VI	2 (2.4%)	1 (1.2%)	1 (3.4%)	
Duration of disease (months) mean (range)	237.38 (6 – 780)	220.58 (12 – 552)	220.97 (36 – 600)	0.715
Duration of current episode (months)	74.07 (2 – 528)	75.75 (1 – 528)	58.0 (1 – 324)	0.666
STUDY 18001	Clobex (N=96)	Temovate E (N=100)	Vehicle (N=33)	p-value
Age, mean (range)	39.3 (12 – 84)	42.4 (12 – 83)	40.7 (12 – 86)	0.344
Gender, n (%)				
Male	39 (40.6%)	45 (45.0%)	15 (45.5%)	0.824
Female	57 (59.4%)	55 (55.0%)	18 (54.5%)	
Race, n (%)				
White	69 (71.9%)	67 (67.0%)	23 (69.7%)	0.087
Black	12 (12.5%)	27 (27.0%)	8 (24.2%)	
Yellow	6 (6.3%)	1 (1.0%)	0	
Hispanic	6 (6.3%)	4 (4.0%)	2 (6.1%)	
Other	3 (3.1%)	1 (1.0%)	0	
Skin Phototype, n (%)				
I	4 (4.2%)	8 (8.0%)	4 (12.1%)	0.351
II	28 (29.2%)	19 (19.0%)	8 (24.2%)	
III	33 (34.4%)	32 (32.0%)	8 (24.2%)	
IV	14 (14.6%)	14 (14.0%)	4 (12.1%)	
V	7 (7.3%)	6 (6.0%)	4 (12.1%)	
VI	10 (10.4%)	21 (21.0%)	5 (15.2%)	
Duration of disease (months) mean (range)	219.5 (15 – 660)	215.5 (7 – 888)	178.5 (6 – 429)	0.553
Duration of current episode (months)	60.7 (1 – 552)	80.3 (1 – 720)	44.5 (1 – 456)	0.162
Source: Sponsor's NDA submission (pages 3312-3313, Volume 26; pages 5230-5231, Volume 30).				

Appendix A.3

This reviewer made the following request for a clarification concerning the treatment allocation for this NDA on 2/6/2003:

According to the Sponsor's response for study 2651, randomization numbers 001-280 and 281-308 were generated on 4/20/00 and 11/7/00, respectively. However, the total enrollment according to the NDA submission was 222 patients.

1. Please clarify why the 2nd set of randomization numbers (i.e. 281-308) was generated.
2. Also, please provide details on why numbers 29-35 and 211-252 were skipped.

Sponsor's responses were submitted on 2/19/2003. A summary of the Sponsor's responses is:

1. The 1st randomization list 001-280 was generated on 4/20/00, where kits 001-252 were prepared for shipment to French, Flemish and German sites and kits 253-280 to Bulgarian sites. To allow non-Bulgarian sites to continue enrolling patients, and due to a relatively rapid enrollment in Bulgarian sites, the 2nd set of randomization list (i.e. 281-308) was generated on 11/7/00 to restock the Bulgarian sites.
2. Subject kits 29-35 were shipped to Pr — site in Germany on 9/8/00. However, no patients were enrolled and kits were returned 1/30/01. Subject kits 211-252 were never shipped to any sites.

Reviewer's Comments:

The following table gives a summary of patient enrollment for each site based on the Sponsor's NDA submission (page 6571, Volume 34) and Sponsor's electronic SAS datasets.

Investigator No., Country	# patients enrolled	Enrollment date	Enrolled patient ID	Randomization # assigned
5093, France	7	9/19/00 – 11/29/00	1-7	1-7
5038, France	7	9/12/00 – 11/22/00	8-14	8-14
5043, France	7	9/21/00 – 12/04/00	15-21	15-21
5202, France	2	11/02/00 – 11/09/00	92-93	92-98
5105, Belgium	21	9/25/00 – 9/25/00 10/21/00 – 10/21/00 11/21/00 – 11/21/00	106-112 120-126 197-203	106-112 120-126 197-203
5116, Belgium	14	9/18/00 – 9/27/00 10/19/00 – 11/20/00	99-105 127-133	99-105 127-133
5201, Belgium	1	11/3/00	113	113-119
5108, Germany	21	9/14/00 – 9/28/00 10/20/00 – 10/27/00 11/06/00 – 11/21/00	22-28 148-154 190-196	22-28 148-154 190-196
5204, Germany	21	9/22/00 – 10/11/00 10/24/00 – 11/07/00 11/14/00 – 11/17/00	36-42 155-161 204-210	36-42 155-161 204-210
5169, Germany	2	10/04/00 – 11/15/00	57-58	57-63
5205, Germany	21	9/14/00 – 9/19/00 10/15/00 – 10/26/00 10/27/00 – 11/17/00	43-49 134-140 169-175	43-49 134-140 169-175
5110, Germany	21	9/15/00 – 9/18/00 10/19/00 – 10/20/00 10/30/00 – 11/02/00	50-56 141-147 176-182	50-56 141-147 176-182
5198, Germany	14	9/18/00 – 11/02/00 11/03/00 – 11/22/00	64-70 183-189	64-70 183-189
5199, Germany	7	10/06/00 – 12/01/00	85-91	85-91
5168, Germany	1	11/07/00	71	71-77
5200, Germany	13	10/02/00 – 10/18/00 10/25/00 – 11/21/00	78-84 162-167	78-84 162-168
5153, Bulgaria	21	9/26/00 – 10/13/00 11/28/00 – 11/30/00	253-266 281-287	253-266 281-287
5196, Bulgaria	21	9/26/00 – 10/23/00 11/22/00 – 11/23/00	267-280 288-294	267-280 288-294
Total	222			

Sponsor's responses seem acceptable following the examination of the patient enrollment table, as

- Most sites started patient enrollment in September 2000 and the enrollment pace seems to be reasonably rapid in the two Bulgarian sites as compared to others.
- Only Bulgarian sites used the 2nd set of randomization numbers (i.e. 281-294).
- Subject kits 211-252, which were never shipped to study sites, were in blocks of size 7.

APPEARS THIS WAY
ON ORIGINAL

Table A.4: Patient Baseline Characteristics – Study 2651

Baseline Score, mean $\pm$ sd	Clobex (n=94)	Dermoval (n=95)	Vehicle (n=33)
Global Severity score (scale 0-4)	2.64 $\pm$ 0.62	2.60 $\pm$ 0.55	2.64 $\pm$ 0.65
Erythema (scale 0-4)	2.89 $\pm$ 0.66	2.87 $\pm$ 0.66	2.97 $\pm$ 0.77
Plaque (scale 0-4)	2.77 $\pm$ 0.65	2.69 $\pm$ 0.58	2.82 $\pm$ 0.58
Scaling (scale 0-4)	2.83 $\pm$ 0.71	2.76 $\pm$ 0.66	2.82 $\pm$ 0.77
Body surface area involved (%)	23.63 $\pm$ 13.46	21.72 $\pm$ 11.36	22.24 $\pm$ 15.55
Treated body surface area (%)	22.24 $\pm$ 12.97	20.59 $\pm$ 11.33	20.18 $\pm$ 13.42
Source: Sponsor's NDA submission (page 6598, Volume 34).			

**APPEARS THIS WAY
ON ORIGINAL**

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

Study Subgroup	Study 9707					Study 18001				
	Clobex (n=82)	Temovate E (n=81)	Vehicle (n=29)	p-value ¹		Clobex (n=96)	Temovate E (n=100)	Vehicle (n=33)	p-value ¹	
				Clobex vs. Vehicle	Clobex vs. Temov. E				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.

¹Comparison is 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			p-value 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 reviewer's analysis. P-value is based on CMH test adjusting for center.					

APPEARS THIS WAY
ON ORIGINAL

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.

7. PRIMARY, CONCURRING REVIEWERS, DISTRIBUTION LIST

Primary Statistical Reviewer:	Shiowjen Lee, Ph.D., Biometrics III
Date:	4/15/2003
Concurring Reviewer/ Statistical Team Leader:	Mohamed Alosch, Ph.D., Biometrics III
Biometrics Deputy Division Director:	Aloka Chakravarty, Ph.D., Biometrics III
Biometrics Division Director:	Mohammad Huque, Ph.D., Biometrics III

cc:

HFD-540/Div. File
HFD-540/Ms. Harris
HFD-540/Dr. Cook
HFD-540/Dr. Luke
HFD-540/Dr. Wilkin
HFD-725/Dr. Lee
HFD-725/Dr. Alosch
HFD-725/Dr. Chakravarty
HFD-725/Dr. Huque
HFD-710/Dr. Anello

This statistical review contains 40 pages (1 cover page, 1 page of table of contents, 27 pages of text, 10 pages of Appendix and one page of distribution list).

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

/s/

Showjien Lee
5/7/03 02:33:34 PM
BIOMETRICS

Mohamed Alosch
5/7/03 04:02:34 PM
BIOMETRICS
Concur with review