

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-013**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## NEW DRUG APPLICATION

### CLINICAL STUDIES

**NDA/Serial Number:** 22-013 / N-000  
**Drug Name:** Primolux (clobetasol propionate) foam, 0.05%  
**Indication(s):** Corticosteroid responsive dermatoses  
**Applicant:** Connetics  
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## 1 Executive Summary

### 1.1 Conclusions and Recommendations

Clobetasol foam has been demonstrated to be statistically superior to vehicle foam in two studies, one in moderate to severe atopic dermatitis and one in mild to moderate psoriasis. The clinical development plan for this 505 (b) 2 application was to demonstrate the efficacy of clobetasol foam against its vehicle in one atopic dermatitis and one psoriasis study and to build a clinical bridge to the Agency's findings of safety for Temovate (clobetasol) Ointment by including a Temovate arm in the psoriasis study. Treatment success rates for the two studies are presented in Table 1. Clobetasol foam was superior to its vehicle in both studies ( $p \leq 0.0005$ ). Although not specified as an efficacy comparison in the protocol, clobetasol foam had much lower efficacy than the active comparator, Temovate ointment.

**Table 1 – Treatment Success at Week 2**

	Clobetasol Foam	Vehicle Foam	TEMOVATE Ointment
<i>Study 301 (Atopic Dermatitis)</i>	N=251	N=126	
Treatment Success <sup>1</sup>	131 (52%)	18 (14%)	--
P-value		<0.0001	
<i>Study 302 (Psoriasis)</i>	N=253	N=123	N=121
Treatment Success <sup>2</sup>	41 (16%)	5 (4%)	38 (31%)
P-value (vs. Clob. Foam)		0.0005	(0.0007) <sup>3</sup>

<sup>1</sup> ISGA = 0 or 1 with 2 grades reduction, erythema = 0 or 1, and induration/papulation = 0 or 1

<sup>2</sup> ISGA = 0 or 1 with 2 grades reduction, erythema = 0 or 1, scaling = 0 or 1, and plaque thickness = 0

<sup>3</sup> Clobetasol foam versus Temovate Ointment was not a planned efficacy comparison

### 1.2 Brief Overview of Clinical Studies

The sponsor conducted a study of clobetasol foam and vehicle foam in atopic dermatitis (301) and a study of clobetasol foam, vehicle foam, and Temovate (clobetasol) ointment in psoriasis (302) to support a 505 (b) 2 application for the treatment of corticosteroid-responsive dermatoses. Each study enrolled subjects age 12 and older and the treatment period was two weeks. The Temovate arm of Study 302 and a comparative bioavailability study (202) provide the clinical bridge to the Agency's findings of safety for Temovate ointment.

The primary efficacy endpoint in Studies 301 and 302 was treatment success and was a composite of successes on an Investigator's Static Global Assessment (ISGA) and individual signs at Week 2. For atopic dermatitis, the ISGA was based on erythema, induration/papulation, and oozing/crusting. Erythema and induration/papulation were also individually globally assessed. Treatment success was defined as achieving a score of clear or almost clear on the ISGA with at least two grades reduction from baseline, and scores of absent or minimal for erythema and induration/papulation. For psoriasis, the ISGA was based on erythema, scaling, and plaque thickness. Erythema, scaling, and

plaque thickness were also individually assessed on a target lesion. Treatment success was defined as achieving a score of clear or almost clear on the ISGA with at least two grades reduction from baseline, and scores of no evidence or faint/minimal for erythema and scale, and no elevation for plaque thickness.

### **1.3 Statistical Issues and Findings**

Both the atopic dermatitis study (301) and the psoriasis study (302) demonstrated statistical significance versus vehicle for treatment success, the primary efficacy endpoint. Both studies also had significant results for the secondary endpoints based on individual signs and symptoms. The secondary endpoints for Study 301 were success on pruritus, lichenification, erythema, and induration/papulation. The secondary endpoints for Study 302 were success on pruritus, erythema, scaling, and plaque thickness. Although the Temovate arm was included in Study 302 to build a safety bridge and it was not intended to build an efficacy bridge, the success rate on clobetasol foam was about half the success rate on Temovate (16% vs. 31%) and clobetasol foam was nominally inferior to Temovate ( $p=0.0007$ ).

The sponsor included incorrect versions of the scales for erythema and scaling with the final protocol for Study 302. This version mapped the descriptors for the none, minimal, mild, moderate, and marked to numbers 1 – 5 rather than 0 – 4. An additional different description of none was included as 0 and the description for severe was deleted. This mistake was discovered one week into the study after 46 subjects had been enrolled. Corrected versions of the scales were faxed to the investigators and the sponsor queried the investigators to ensure that the subjects enrolled under the incorrect version of the scales were mapped to the correct numerical scores. The problem with the scales affected all treatment arms. Sensitivity analyses demonstrated that the mistake did not impact the conclusions of the study.

The treatment by pooled center interaction, based on the Breslow-Day test, was significant in both studies ( $p = 0.0013$  and  $p=0.0339$ ). In Study 301, all centers had higher success rates on clobetasol foam than vehicle, but three centers had larger treatment effects and four centers had smaller treatment effects. The results, however, were not driven by any one center. In Study 302, two centers had higher success rates on vehicle than clobetasol foam, but again the results were not driven by any one center.

## **2 Introduction**

### **2.1 Overview**

Clobetasol propionate is a potent corticosteroid. It has previously been approved in various formulations (lotion, shampoo, spray, cream, gel, ointment, solution, and foam) at the 0.05% concentration. The formulations are variously approved for corticosteroid-responsive dermatoses, scalp psoriasis, or psoriasis. Most formulations are recommended for up to two weeks of use, but some formulations permit up to four weeks of use in psoriasis. The sponsor of this application has already received approval for clobetasol propionate in a different foam vehicle, Olux, which is approved to treat corticosteroid-responsive dermatoses of the scalp and non-scalp psoriasis. In this application for

Primolux foam, the sponsor is seeking approval for corticosteroid-responsive dermatoses in patients age 12 and older, with treatment limited to two weeks.

### 2.1.1 Regulatory History

This application is a 505 (b) 2 application with reference drug Temovate ointment. Interactions with the Agency included an End-of-Phase 2 meeting (November 29, 2004), a Special Protocol Assessment [SPA] (Agency letter date January 19, 2005), and a Post-SPA meeting (March 2, 2005). The Agency and sponsor agreed at the Post-SPA Meeting that a bridge to the Agency's findings of safety for clobetasol in a 505 (b) 2 application could be supported by

- A 3-arm study in psoriasis (clobetasol foam, vehicle foam, and reference clobetasol product) that demonstrated that clobetasol foam is not superior to the reference drug and did not have a worse safety profile than the reference drug.
- A comparative HPA axis suppression study or very robust PK study that demonstrated that clobetasol foam did not have greater systemic bioavailability than the reference drug.

The sponsor did not attempt to bridge to the Agency's findings of efficacy for clobetasol and is supporting the efficacy of clobetasol foam through a vehicle-controlled study in atopic dermatitis and the vehicle comparison in the 3-arm psoriasis study. The efficacy evaluation scales and endpoints were agreed upon through the SPA process.

### 2.1.2 Clinical Studies Program

The sponsor conducted two safety and efficacy studies that are reviewed here. Study 301 was a vehicle controlled study that enrolled subjects age 12 and older with moderate to severe atopic dermatitis, and Study 302 was a vehicle and active controlled study that enrolled subjects age 12 and older with mild to moderate psoriasis. The number of subjects enrolled in each study is presented in Table 2. Both studies were conducted in the United States. The sponsor also conducted a comparative bioavailability study and an HPA axis suppression study that are not further discussed in this review.

**Table 2 – Clinical Study Program**

Study	Indication/Purpose	No. Subjects
CPE.C.301	Atopic Dermatitis Efficacy & Safety	251 Clobetasol Foam 126 Vehicle Foam
CPE.C.302	Psoriasis Efficacy and Safety	253 Clobetasol Foam 123 Vehicle Foam 121 TEMOVATE Ointment
CPE.C.202	Psoriasis Bioavailability	16 Clobetasol Foam 16 TEMOVATE Ointment
CPE.C.201	Atopic Dermatitis HPA Axis Suppression	52 Clobetasol Foam

## 2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted electronically using the CTD format but not the XML backbone. The datasets used in this review are archived at \\Cdsub1\N22013\N\_000\2006-03-14\N22013\m5\53-clin-stud-rep\537-crf-ip\crt\datasets.

## 3 Statistical Evaluation

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study Design

The sponsor conducted a vehicle controlled Phase 3 study in moderate to severe atopic dermatitis (301) and a vehicle and active controlled study in mild to moderate psoriasis (302) to support a 505 (b) 2 application. Both studies enrolled subjects age 12 and older and were designed to establish efficacy via the vehicle control comparisons. Study 302 included a Temovate (clobetasol propionate) ointment arm to establish a safety bridge to the Agency's findings of safety for Temovate ointment.

##### 3.1.1.1 Study 301

Study 301 is a randomized, double-blind, vehicle controlled study of the safety and efficacy of clobetasol foam in the treatment of moderate to severe atopic dermatitis in subjects age 12 and older. Study treatment was applied twice daily for two weeks. Subjects were evaluated at baseline, Week 1, Week 2, and Week 4 (two weeks post-treatment). At baseline, subjects were to have moderate to severe atopic dermatitis (a score of 3 or 4 on the Investigator's Static Global Assessment [ISGA], see Table 29 in the Appendix), at least 5% treatable body surface area (BSA), and a sum score for erythema, induration/papulation, and oozing/crusting of at least 4 (see Table 31 in the Appendix).

The primary efficacy endpoint was treatment success at Week 2. Treatment success had 3 components and was defined as achieving (1) a score of 0 or 1 on the ISGA with at least 2 grades reduction from baseline, (2) a score of 0 or 1 for erythema, and (3) a score of 0 or 1 for induration/papulation. Since the inclusion criteria for this study required a baseline ISGA of 3 or 4, all subjects who reached a score of 0 or 1 at Week 2 would automatically have at least 2 grades reduction. Treatment success was analyzed with a Cochran-Mantel-Haenszel (CMH) test stratified on pooled center. The secondary endpoints were success for pruritus, lichenification, erythema, and induration/papulation. Success was defined as achieving a score of 0 or 1 with at least 2 grades reduction for each secondary endpoint. Success on the secondary endpoints was also analyzed with a CMH test. The sponsor also proposed a number of additional endpoints based on alternate definitions of treatment success, success on other signs, and success at post-treatment.

The principal method of handling missing data in the ITT population was LOCF. The ITT population included all subjects randomized and dispensed study drug. The per protocol population excluded subjects who missed more than 4 applications or 3 consecutive drug applications, did not have efficacy evaluations at baseline and Week 2, or used prohibited medications at any time during the study. The sponsor provided results based on the ITT and per protocol population and also proposed sensitivity analyses imputing data using a series of iterative sequential generalized logistic models and using average response rates.

### 3.1.1.2 Study 302

Study 302 is a randomized, evaluator-blind, vehicle and active controlled study of the safety and efficacy of clobetasol foam in the treatment of mild to moderate psoriasis in subjects age 12 and older. Study treatment (clobetasol foam, Temovate (clobetasol) ointment, or vehicle foam) was applied twice daily for two weeks. The investigator was blinded to treatment assignment. Subjects and the study nurse/coordinator knew whether the subject was using a foam or ointment. The goal of the study was to establish the efficacy superiority of clobetasol foam to vehicle foam and construct a clinical safety bridge from clobetasol foam to Temovate ointment.

Subjects were evaluated at baseline, Week 1, Week 2, and Week 4 (two weeks post-treatment). At baseline, subjects were to have mild to moderate psoriasis atopic (a score of 2 or 3 on the Investigator's Static Global Assessment [ISGA], see Table 34), at most 10% body surface area (BSA), and a target lesion  $> 2 \text{ cm}^2$  on the trunk or extremities with a score of 2-3 each for erythema, scaling, and plaque thickness (see Table 33).

The primary efficacy endpoint was treatment success at Week 2. Treatment success had 4 components and was defined as achieving (1) a score of 0 or 1 on the ISGA with at least 2 grades reduction from baseline, (2) a score of 0 or 1 for erythema, (3) a score of 0 or 1 for scaling, and (4) a score of 0 for plaque thickness. Treatment success was analyzed with a Cochran-Mantel-Haenszel (CMH) test stratified on pooled center. The secondary endpoints were success for pruritus, erythema, scaling, and plaque thickness. Success for pruritus and plaque thickness was defined as achieving a score of 0. Success for scaling was defined as achieving a score of 0 or 1. Success for erythema was defined in the final protocol as achieving a score of 0 and in the statistical analysis plan as achieving a score of 0 or 1. See further discussion on this endpoint in Section 3.1.6 below. Success on the secondary endpoints was also analyzed with a CMH test. The sponsor also proposed a number of additional endpoints.

The principal method of handling missing data in the ITT population was LOCF. The ITT population included all subjects randomized and dispensed study drug. The per protocol population excluded subjects who missed more than 5 applications or 3 consecutive drug applications, did not have efficacy evaluations at baseline and Week 2, or used prohibited medications at any time during the study. The sponsor provided results based on the ITT and per protocol population and also proposed sensitivity analyses imputing data using a series of iterative sequential generalized logistic models and using average response rates.

### 3.1.2 Subject Disposition

Study 301 enrolled 377 subjects, 251 on clobetasol foam and 126 on vehicle at 20 centers. The 20 centers were pooled into 7 analysis centers. A higher percentage of vehicle subjects (16%) than clobetasol subjects (5%) terminated the study early. The most common reason for discontinuation from the vehicle arm was disease progression (6%) and subject request (4%). One study center located in New Orleans, LA was disrupted by Hurricane Katrina in August 2005. Complete data records for 5 subjects and partial records for 3 additional subjects were lost in the storm. All other reasons for study discontinuation had rates of 2% or less on each arm. The reasons for study discontinuation are presented in Table 3.

**Table 3 – Reason for Study Discontinuation (Study 301)**

	Clobetasol Foam N=251	Vehicle Foam N=126
<i>Early Terminations</i>	12 (5%)	20 (16%)
Adverse Event	1 (<1%)	3 (2%)
Subject Non-compliance	1 (<1%)	1 (1%)
Disease Progression	1 (<1%)	7 (6%)
Subject Request	2 (1%)	5 (4%)
Hurricane	5 (2%)	3 (2%)
Other <sup>1</sup>	2 (1%)	1 (1%)

<sup>1</sup> Includes Lost to follow-up and pre-existing condition.

Study 302 enrolled 497 subjects, 253 to clobetasol foam, 123 to vehicle foam and 121 to Temovate ointment. The early termination rate was low (3%) and similar across all three arms. The reasons for early discontinuation are presented in Table 4.

**Table 4 – Reason for Study Discontinuation (Study 302)**

	Clobetasol Foam N=253	Vehicle Foam N=123	TEMOVATE Ointment N=121
<i>Early Terminations</i>	7 (3%)	5 (4%)	4 (3%)
Adverse Event	1 (<1%)	1 (1%)	0 (0%)
Subject Non-compliance	2 (1%)	0 (0%)	2 (2%)
Subject Request	2 (1%)	1 (1%)	1 (1%)
Other <sup>1</sup>	2 (1%)	3 (2%)	1 (1%)

<sup>1</sup> Includes Lost to follow-up and enrollment closed by sponsor.

### 3.1.3 Baseline and Demographic Data

In Study 301, the race and age groups were generally balanced across the treatment arms. The distribution of the gender groups was slightly less balanced with a higher percentage of female subjects randomized to clobetasol foam than vehicle (67% vs. 56%). Most of the subjects were Caucasian (59%) or African American (27%). The average subject age was 35 and 27% of subjects were age 12 to 17. Demographic data for 5 subjects is unavailable due to Hurricane Katrina. The demographic data is presented in Table 5.

**Table 5 – Demographic Data (Study 301)**

		Clobetasol Foam N=251	Vehicle Foam N=126
Gender	Male	80 (32%)	53 (42%)
	Female	168 (67%)	71 (56%)
	Missing	3 (1%)	2 (2%)
Race	Caucasian	148 (59%)	74 (59%)
	African-Am.	69 (27%)	31 (25%)
	Hispanic	13 (5%)	8 (6%)
	Asian	11 (4%)	7 (6%)
	Other	7 (3%)	4 (3%)
	Missing	3 (1%)	2 (2%)
Age (Years)	Mean (SD)	35.0 (18.6)	35.7 (18.5)
	Range	12 - 78	12 - 81
	12 - < 18	69 (27%)	32 (25%)
	18 - < 65	157 (63%)	79 (63%)
	≥ 65	22 (9%)	12 (10%)
	Missing	3 (1%)	3 (2%)

Race groups were generally balanced across treatment arms in Study 302 with about 88% of subjects being Caucasian and 8% Hispanic. The gender balance differed somewhat across treatment arms with the clobetasol foam arm having 50% males, vehicle foam having 58% males, and Temovate ointment having 63% males. The vehicle foam arm had a higher average age (52 vs. 47) than the two clobetasol arms and a higher percentage of subjects of subjects over 65 (22% vs. 11%). The demographic data is presented in Table 6.

**Table 6 – Demographic Data (Study 302)**

		Clobetasol Foam N=253	Vehicle Foam N=123	TEMOVATE Ointment N=121
Gender	Male	127 (50%)	71 (58%)	76 (63%)
	Female	126 (50%)	52 (42%)	45 (37%)
Race	Caucasian	221 (87%)	111 (90%)	105 (87%)
	African-Am.	5 (2%)	0 (0%)	2 (2%)
	Hispanic	20 (8%)	12 (10%)	10 (8%)
	Asian	3 (1%)	0 (0%)	1 (1%)
	Other	4 (2%)	0 (0%)	3 (2%)
Age (Years)	Mean (SD)	46.7 (15.1)	52.0 (15.6)	47.3 (14.2)
	Range	12 - 79	17 - 89	19 - 81
	12 - < 18	8 (3%)	1 (1%)	0 (0%)
	18 - < 65	216 (85%)	95 (77%)	108 (89%)
	≥ 65	29 (11%)	27 (22%)	13 (11%)

The treatment arms were balanced with regard to baseline severity in both Studies 301 and 302. In Study 301, the majority of subjects had moderate ISGA scores at baseline

(87%) and the median body surface area (BSA) was 9%. In Study 302 about one-third of subjects had mild ISGA scores and two-thirds had moderate scores. The median BSA was 4%. In Study 302 individual signs were evaluated on a target lesion. The location of the target lesion was balanced across treatment arms with the leg being the most common lesion location. Baseline severity for Study 301 is presented in Table 7 and for Study 302 in Table 8.

**Table 7 – Baseline Severity (Study 301)**

	Clobetasol Foam N=251	Vehicle Foam N=126
<b>ISGA</b>		
Moderate (3)	217 (86%)	111 (88%)
Severe (4)	31 (12%)	13 (10%)
Missing	3 (1%)	2 (2%)
<b>% BSA</b>		
Median	9.0	8.5
Range	5 - 98	5 - 70

**Table 8 – Baseline Severity (Study 302)**

	Clobetasol Foam N=253	Vehicle Foam N=123	TEMOVATE Ointment N=121
<b>ISGA</b>			
Mild (2)	93 (37%)	37 (30%)	34 (28%)
Moderate (3)	155 (61%)	85 (69%)	84 (69%)
Marked (4)	4 (2%)	1 (1%)	3 (2%)
Severe (5)	1 (< 1%)	0 (0%)	0 (0%)
<b>%BSA</b>			
Median	3.0	4.0	4.0
Range	1-10	1-10	1-10
<b>Target Lesion Location</b>			
Missing	2 (1%)	0 (0%)	0 (0%)
Leg	88 (35%)	48 (39%)	34 (28%)
Arm	52 (21%)	24 (20%)	26 (21%)
Trunk	52 (21%)	20 (16%)	23 (19%)
Knee	24 (9%)	7 (6%)	14 (12%)
Elbow	35 (14%)	24 (20%)	24 (20%)

### 3.1.4 Primary Efficacy Endpoint

Clobetasol foam was superior to vehicle in Study 301 in the treatment of atopic dermatitis for the primary efficacy endpoint of treatment success (52% vs. 14%). Treatment success was defined as an ISGA score of 0 or 1 with at least 2 grades reduction, an erythema score of 0 or 1 and an induration/papulation score of 0 or 1 at Week 2. Since the inclusion criteria stated that subjects should have ISGA scores of 3 or 4 at baseline, all

subjects who achieved an ISGA score of 0 or 1 would have achieved at least 2 grades reduction. Results for the ITT and per protocol population were similar and are presented in Table 9. The sponsor also conducted two additional sensitivity analyses regarding the handling of missing data (an iterative sequential generalized logistic model and a mean imputation) which led to the same conclusions. Refer to Appendix 6.2 for discussion and results of the sensitivity analyses.

**Table 9 – Treatment Success for Atopic Dermatitis at Week 2 (Study 301)**

	Clobetasol Foam	Vehicle Foam
<i>ITT</i>	N=251	N=126
Treatment Success <sup>1</sup>	131 (52%)	18 (14%)
P-value		<0.0001
<i>PP</i>	N=230	N=108
Treatment Success <sup>1</sup>	125 (54%)	18 (17%)
P-value		<0.0001

<sup>1</sup> ISGA = 0 or 1 with 2 grades reduction, erythema = 0 or 1, and induration/papulation = 0 or 1

Clobetasol foam was also superior to vehicle in Study 302 in the treatment of psoriasis for the primary efficacy endpoint of treatment success (16% vs. 4%). Treatment success was defined as an ISGA of 0 or 1 with at least 2 grades reduction, erythema and scaling scores of 0 or 1 and a plaque thickness score of 0. Erythema, scaling, and plaque thickness were evaluated on a target lesion identified at baseline. A Temovate ointment arm was included in the study to build a safety bridge to an approved clobetasol product. No formal efficacy comparisons between clobetasol foam and Temovate ointment were planned in the protocol. However, the success rate for clobetasol foam is about half that for Temovate ointment (16% vs. 31%) and clobetasol foam is nominally statistically inferior to Temovate. The results from the ITT and per protocol populations are similar and are presented in Table 10. The sponsor also conducted two additional sensitivity analyses regarding the handling of missing data (an iterative sequential generalized logistic model and a mean imputation) which led to the same conclusions. Refer to Appendix 6.2 for discussion and results of the sensitivity analyses.

**Table 10 – Treatment Success for Psoriasis at Week 2 (Study 302)**

	Clobetasol Foam	Vehicle Foam	TEMOVATE Ointment
<i>ITT</i>	N=253	N=123	N=121
Treatment Success <sup>1</sup>	41 (16%)	5 (4%)	38 (31%)
P-value (vs. Clob. Foam)		0.0005	(0.0007) <sup>2</sup>
<i>PP</i>	N=234	N=112	N=111
Treatment Success <sup>1</sup>	39 (17%)	5 (4%)	34 (31%)
P-value (vs. Clob. Foam)		0.0011	(0.0031) <sup>2</sup>

<sup>1</sup> ISGA = 0 or 1 with 2 grades reduction, erythema = 0 or 1, scaling = 0 or 1, and plaque thickness = 0

<sup>2</sup> Clobetasol foam versus Temovate Ointment was not a planned efficacy comparison

### 3.1.5 Components of Treatment Success

The ISGA in Study 301 (atopic dermatitis) incorporates erythema, induration/papulation, and oozing/crusting. In addition to the ISGA, erythema and induration/papulation were separately evaluated globally and incorporated into the definition of treatment success. The ISGA in Study 302 (psoriasis) incorporates erythema, scaling, and plaque thickness. The individual signs of erythema, scaling, and plaque thickness were evaluated separately on a target lesion and incorporated into the definition of treatment success. The success rates for the two studies for the individual components of treatment success are presented in Table 11 and Table 12. The overall definition of success was largely driven by the ISGA in Study 301, but in Study 302 the treatment success rates were substantially lower than for any of the individual components. This might be due to the fact that the scores on a target lesion may not directly correspond to the overall impression of the entire treated area.

**Table 11 – Components of Treatment Success (Study 301)**

	Clobetasol Foam N= 251	Vehicle Foam N= 126
Treatment success	131 (52%)	18 (14%)
Components of treatment success		
ISGA clear (0) or almost clear (1) with at least 2 grades reduction	149 (59%)	20 (16%)
Erythema absent (0) or minimal (1)	156 (62%)	27 (21%)
Induration/papulation absent (0) or minimal (1)	182 (73%)	28 (22%)

**Table 12 – Components of Treatment Success (Study 302)**

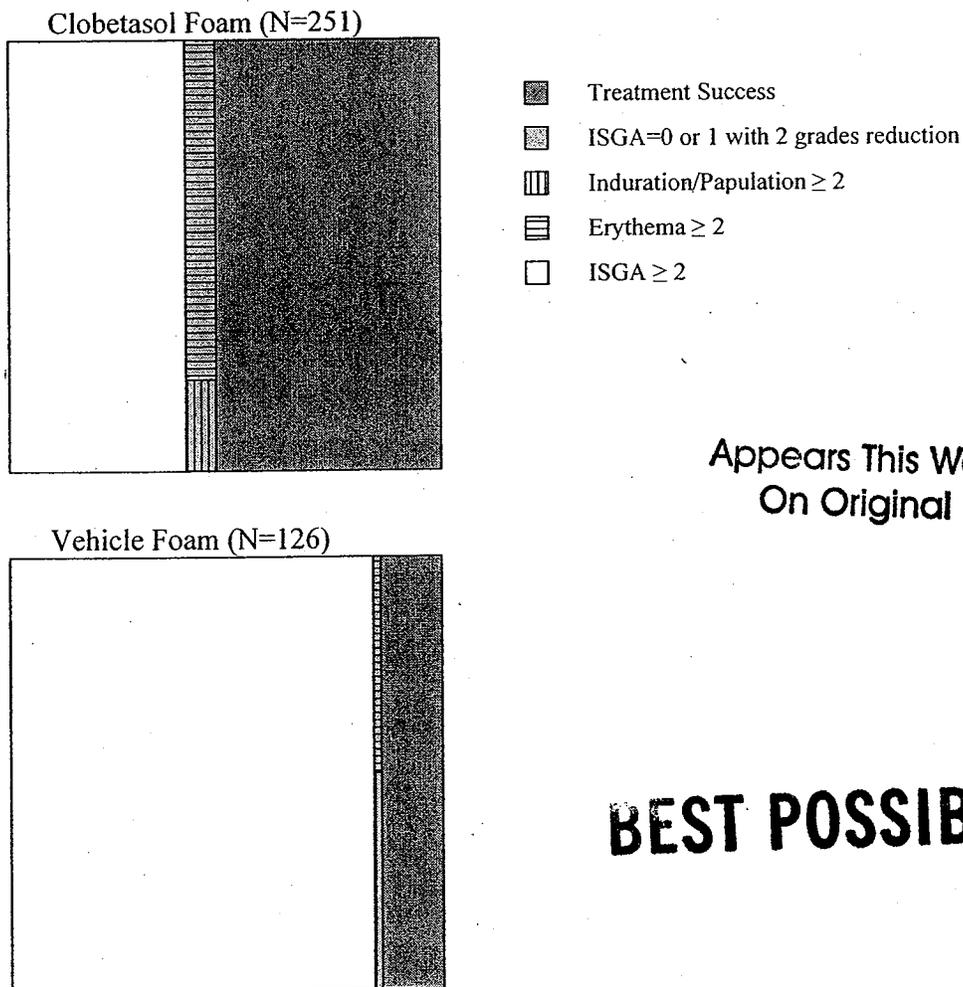
	Clobetasol Foam N=253	Vehicle Foam N=123	TEMOVATE Ointment N=121
Subjects with treatment success	41 (16%)	5 (4%)	38 (31%)
Components of treatment success			
ISGA clear (0) or almost clear (1) with at least 2 grades improvement	73 (29%)	11 (9%)	69 (57%)
Erythema none (0) or faint (1)	135 (53%)	25 (20%)	83 (69%)
Scaling none (0) or minimal (1)	180 (71%)	34 (28%)	107 (88%)
Plaque thickness none (0)	78 (31%)	6 (5%)	59 (49%)

Although in recent years the Agency has consistently used global evaluations like the ISGA to assess efficacy for atopic dermatitis and psoriasis, the use and specifics of additional requirements on the individual signs has varied from study to study. In particular for Study 302, where the composite success rate is about half of the success rate from the ISGA alone, it may be of interest to understand how the additional requirements on treatment success are impacting the overall success rate. Figure 1 and Figure 2 display the success rates and the key components leading to a classification of

treatment failure for subjects with ISGA scores of 0 or 1 in Studies 301 and 302. Area on these graphs is proportional the percentage of subjects in a particular classification. These figures indicate the proportion of subjects who met the full definition of treatment success ['responders'] (brown or darkest shading), did not achieve 0 or 1 on the ISGA ['non-responders'] (no shading), or achieved 0 or 1 on the ISGA but not all of the additional requirements ['partial responders'] (yellow/orange or lighter shading and hash marks).

In Study 301, as noted previously, most subjects who achieved 0 or 1 on the ISGA also met the requirements for 0 or 1 on erythema and induration/papulation. That is, there were few 'partial responders'. Most of the 'partial responders' had erythema scores of 2 or greater. These results are presented graphically in Figure 1.

**Figure 1 - Components Leading to Treatment Failure among Subjects with ISGA = 0 or 1 (Study 301)**

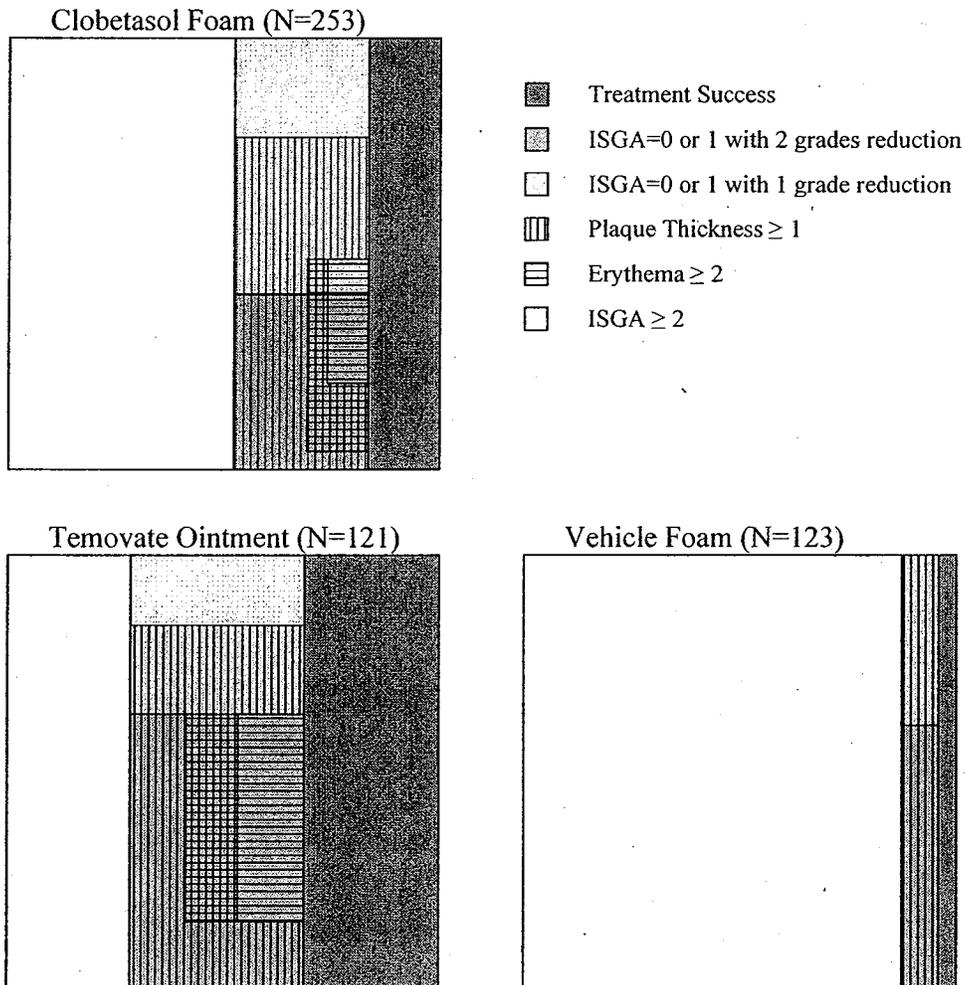


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In Study 302 there was a much larger proportion of subjects who achieved ISGA scores of 0 or 1 but did not meet at least one of the other requirements for treatment success. Although a scaling score of 0 or 1 was required for treatment success, scaling alone was never responsible for preventing treatment success. All subjects with an ISGA of 0 or 1 but a scaling score of 2 or greater also had a plaque thickness score of 1 or greater. Therefore scaling is not incorporated into Figure 2 for simplicity. Plaque thickness scores of 1 or greater appear to be the largest factor in preventing subjects with ISGA scores of 0 or 1 from achieving success. Although the success rates on Temovate are higher than on clobetasol foam, it does not appear that Temovate influences a particular sign differently than clobetasol foam.

**Figure 2 – Components Leading to Treatment Failure among Subjects with ISGA = 0 or 1 (Study 302)**



### 3.1.6 Secondary Endpoints

#### 3.1.6.1 Study 301

Study 301 had four secondary endpoints: success on pruritus, lichenification, erythema, and induration/papulation at Week 2. Success for pruritus and lichenification was defined as a score of 0 with at least 2 grades reduction. Success for erythema and induration/papulation was defined as a score of 0 or 1 with at least 2 grades reduction. Results of the secondary endpoints were consistent with the primary analysis. Clobetasol foam was superior to vehicle for each secondary endpoint. The results of the secondary analyses are presented in Table 13.

**Table 13 – Success<sup>1</sup> on Secondary Efficacy Endpoints (Study 301)**

	Clobetasol Foam N= 251	Vehicle Foam N= 126	p-value
Pruritus = 0	104 (41%)	10 (8%)	<0.0001
Lichenification = 0	56 (22%)	5 (4%)	<0.0001
Erythema = 0 or 1	134 (53%)	19 (15%)	<0.0001
Induration/Papulation = 0 or 1	141 (56%)	14 (11%)	<0.0001

<sup>1</sup> All definitions of success required at least 2 grades reduction from baseline.

#### 3.1.6.2 Study 302

Study 302 had four secondary endpoints: success on pruritus, erythema, scaling, and plaque thickness at Week 2. Success for pruritus and plaque thickness was defined as a score of 0. Success for scaling was defined as a score of 0 or 1. The definition of erythema success differed in the different amendments of Protocol 302. The study report uses a definition for erythema success as a score of 0 or 1. This definition of success is included in the Statistical Analysis Plan (dated December 15, 2005) and in an earlier version (Amendment 1) of the protocol (dated December 6, 2004). However, the final version of the protocol, Amendment 2 (dated March 10, 2005), defines erythema success as a score of 0. The sponsor does not discuss the discrepancy in the definition of erythema success between the final version of the protocol and the Statistical Analysis Plan and study report. Results from both definitions are provided in Table 14. Clobetasol foam is superior to vehicle foam under both definitions of erythema success. Unlike Study 301, 2 grades reduction from baseline was not required for the secondary endpoints in Study 302. For each secondary endpoint clobetasol foam was superior to vehicle foam. Except for the endpoint with erythema = 0, clobetasol foam was inferior to Temovate ointment.

**Table 14 – Success<sup>1</sup> on Secondary Efficacy Endpoints (Study 302)**

	Clobetasol Foam N= 253	Vehicle Foam N= 123	TEMOVATE Ointment N=121	p-value <sup>2</sup>	p-value <sup>3</sup>
Pruritus = 0	106 (42%)	23 (19%)	71 (59%)	<0.0001	0.0022
Erythema = 0	39 (16%)	3 (2%)	24 (20%)	0.0002	0.2284
Erythema = 0 or 1	135 (53%)	25 (20%)	83 (69%)	<0.0001	0.0042
Scaling = 0 or 1	180 (71%)	34 (28%)	107 (88%)	<0.0001	0.0002
Plaque Thickness = 0	78 (31%)	6 (5%)	59 (49%)	<0.0001	0.0006

<sup>1</sup> Definitions of success do *not* require at least 2 grades reduction from baseline.

<sup>2</sup> P-value for clobetasol foam versus vehicle foam.

<sup>3</sup> P-value for clobetasol foam versus TEMOVATE Ointment.

### 3.1.7 Protocol Changes during the Study

#### 3.1.7.1 Study 301

One of the inclusion criteria in Study 301 was for subjects to have a score of at least 2 for pruritus at baseline. Investigators informed the sponsor that this criterion might be limiting enrollment. Pruritus scores are not involved in the primary efficacy endpoint. On May 25, 2005, after about one-third of the subjects had been enrolled, the sponsor removed this inclusion criterion. In the end, a higher proportion of subjects were enrolled with pruritus scores of 0 or 1 *before* the criterion was removed (9/140 [6%]) than after (8/232 [3%]). Eight of the nine subjects enrolled with scores of 0 or 1 before the criterion was removed were enrolled at one site. Efficacy results under the two sets of inclusion criteria were similar. Among subjects enrolled before the change, the treatment success rates were 51% (48/95) for clobetasol foam and 16% (7/45) for vehicle foam. After the change, the treatment success rates were 54% (83/153) for clobetasol foam and 14% (11/79) for vehicle foam. Removal of the pruritus entrance criterion does not appear to have significantly impacted the level of pruritus at baseline or the final success rates.

#### 3.1.7.2 Study 302

Typographical errors regarding the scaling and erythema components of the Psoriasis Grading Scale were included in the final version of the protocol and this scale was used to enroll the first 46 subjects. The error involved the scaling and erythema components and essentially mapped correct textual descriptions of the levels to incorrect numerical scores, added an incorrect '0' score and deleted the highest level. The sponsor provided the following timeline of events:

- December 14, 2004: Protocol 302 was submitted to the Agency for a Special Protocol Assessment (SPA) which included the following Psoriasis Grading Scale (Table 15).

**Table 15 – Original Psoriasis Grading Scale in SPA**

<b>Score</b>	<b>Scaling</b>	<b>Erythema</b>	<b>Induration</b>
0	No evidence of scaling	No evidence of erythema, hyperpigmentation may be present	No evidence of plaque elevation
1	Minimal; occasional fine scale over less than 5% of the lesion	Faint erythema	Minimal plaque elevation, 0.5mm
2	Mild, fine scales predominate	Light red coloration	Mild plaque elevation, 1 mm
3	Moderate; coarse scales predominate	Moderate red coloration	Moderate plaque elevation, 1.5mm
4	Marked; thick non-tenacious scale predominates	Bright red coloration	Marked plaque elevation, 2mm
5	Severe; very thick tenacious scale predominates	Dusky to deep red coloration	Severe plaque elevation, 2.5mm or more

- January 19, 2005: The Agency provided the following comment on the Psoriasis Grading Scale in the SPA response:  
 “Please provide information on the reliability and reproducibility of investigator assessments of differences in plaque elevation of 0.5 mm increments. Alternatively, provide verbal descriptions for the grades of plaque elevation in both the ISGA and plaque thickness scale for the target lesion.”
- March 18, 2005: The sponsor revised the plaque thickness scale to address the Agency’s comment, but in the process inadvertently changed the scales for scaling and erythema. Additional incorrect descriptions for Score 0 were added, the remaining categories were shifted down one row, and the ‘severe’ categories were deleted. This version of the Psoriasis Grading Scale was provided to the investigative centers in the final protocol (Table 16 - Highlighting Added).

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**Table 16 – Incorrect Psoriasis Grading Scale in Final Protocol (Highlighting Added)**

	Score	Scaling	Erythema	Plaque Thickness
<i>Added Description</i>	0	No Scale	Hyperpigmentation, pigmented macules, diffuse faint pink or red coloration	No elevation over normal skin
<i>Shifted Categories</i>	1	No evidence of scaling	No evidence of erythema, hyperpigmentation may be present	Possible but difficult to ascertain whether there is a slight elevation above normal skin
	2	Minimal; occasional fine scale over less than 5% of the lesion	Faint erythema	Slight but definite elevation, typically edges are indistinct or sloped
	3	Mild, fine scales predominate	Light red coloration	Moderate elevation with rough or sloped edges
	4	Moderate; coarse scales predominate	Moderate red coloration	Marked elevation typically with hard or sharp edges
	5	Marked; thick non-tenacious scale predominates	Bright red coloration	Very marked elevation typically with hard sharp edges

- April 18, 2005: First subject enrolled using incorrect scale for erythema and scaling.
- April 25, 2005: Sponsor notifies sites of the incorrect scale and provides a corrected version (Table 17). Forty-six subjects were enrolled prior to the correction.

**Table 17 - Corrected Final Psoriasis Grading Scale**

Score	Scaling	Erythema	Plaque Thickness
0	No evidence of scaling	No evidence of erythema, hyperpigmentation may be present	No elevation over normal skin
1	Minimal; occasional fine scale over less than 5% of the lesion	Faint erythema	Possible but difficult to ascertain whether there is a slight elevation above normal skin
2	Mild, fine scales predominate	Light red coloration	Slight but definite elevation, typically edges are indistinct or sloped
3	Moderate; coarse scales predominate	Moderate red coloration	Moderate elevation with rough or sloped edges
4	Marked; thick non-tenacious scale predominates	Bright red coloration	Marked elevation typically with hard or sharp edges
5	Severe; very thick tenacious scale predominates	Dusky to deep red coloration	Very marked elevation typically with hard sharp edges

After the corrected scale was distributed to the sponsor, the sponsor mapped the old scores for erythema and scaling to the correct numbers (e.g. 'Old' 3 to 'New' 2) since the textual descriptions for the relevant levels did not change. The sponsor queried the

investigators to ensure the mappings were correct. One investigator had been using the (correct) scale provided at the investigator's meeting rather than the (incorrect) scale provided in the protocol and her 6 subjects' scores did not need to be mapped. Two other subjects were mapped to scores other than what a direct mapping would imply based on the investigator's input and source data. The remaining 38 subjects were mapped directly by shifting their scores down one level.

Because the inclusion criteria stated that subjects were to have scores of 2-3 on a target lesion for each of the 3 components of the Psoriasis Grading Scale, the incorrect numbering of the levels could lead to subjects not meeting the inclusion criteria after mapping. However, only 1 subject was enrolled with scores of 2 for erythema and scaling on the incorrect scale that were mapped to scores of 1 on the correct scale. This subject was enrolled with an ISGA score of 2 and randomized to clobetasol foam. At Week 2, this subject had worsened on the ISGA to a score of 3 and was not a treatment success.

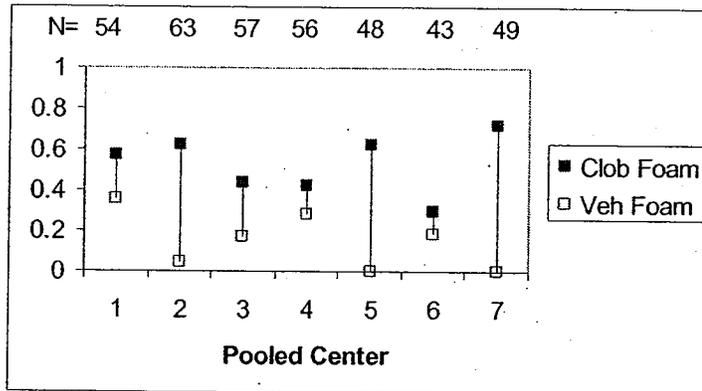
The sponsor conducted a sensitivity analysis excluding the 46 subjects enrolled under the incorrect scale. The results were similar to the ITT analysis for treatment success (14% (32/228) for clobetasol foam versus 4% (4/113) for vehicle foam, p-value = 0.0027). In summary, the mistake of including an incorrect version of the Psoriasis Grading Scale during the first week of the study does not appear to have significantly impacted the baseline severity of the subjects or the conclusions of the study.

### **3.1.8 By Center Results**

#### **3.1.8.1 Study 301**

Study 301 enrolled subjects in 20 centers which the sponsor pooled into 7 analysis centers. Treatment success rates by pooled center are presented in Figure 3. Results from all of the pooled centers favored clobetasol foam over vehicle foam, though three of the pooled centers had larger treatment effects than the remaining four pooled centers. The Breslow-Day test was significant with a p-value of 0.0013. The significance of the treatment by center interaction appears to be related to the magnitude of the treatment effect rather than the direction. The results of the primary analysis are still statistically significant if the three pooled centers with the largest treatment effects (2, 5, 7) are removed from the analysis.

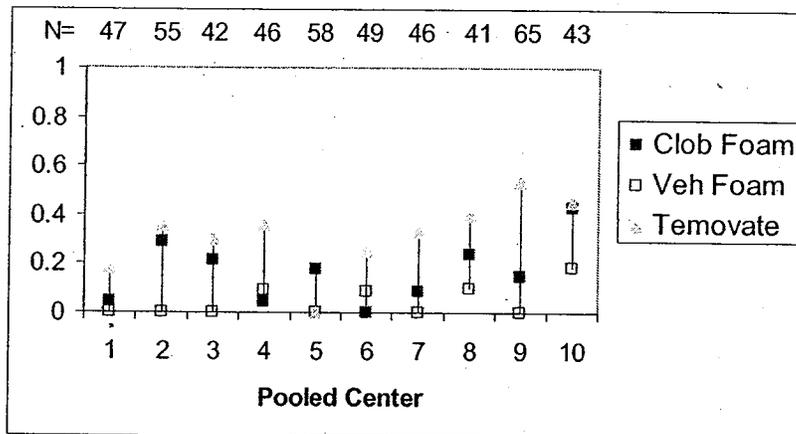
**Figure 3 – Treatment Success Rates by Pooled Center (Study 301)**



**3.1.8.2 Study 302**

Study 302 enrolled subjects in 20 centers which the sponsor pooled into 10 analysis centers. Treatment success rates by pooled center are presented in Figure 4. Results from 8 of the 10 pooled centers favored clobetasol foam over vehicle foam. The Breslow-Day test for clobetasol foam versus vehicle foam was significant with a p-value of 0.0339. Even though the Breslow-Day test is significant, the results do not appear to be driven by any particular center.

**Figure 4 – Treatment Success by Pooled Center (Study 302)**



**3.2 Evaluation of Safety**

**3.2.1 Extent of Exposure**

In Study 301, clobetasol foam and vehicle foam subjects had similar drug usage levels with vehicle subjects using slightly more drug product than clobetasol subjects (73 g vs. 69 g). The labels for Temovate and other clobetasol products recommend limiting use to no more than 50 g of drug per week and limiting use to at most 2 weeks (100 g total). In Study 301, 23% of subjects used more than 100 g during the treatment period (or more than 50 g if the number of treated days was one week or less). A similar percentage of

vehicle foam subjects (20%) used more than 100g as well. The maximum usage of clobetasol foam was 188 g over 15 days and the maximum treatment period was 36 days. The study drug exposure summary for Study 301 is presented in Table 18.

**Table 18 – Study Drug Exposure (Study 301)**

	Clobetasol Foam N= 251	Vehicle Foam N= 126
Days on study drug	(N=248)	(N=124)
Mean	15.1	14.2
Range	1 - 36	1 - 22
Study drug usage (g)	(N=243)	(N=121)
Mean	69.25	72.99
Range	4.1 - 188.2	5.2 - 179.4
No. > 50 g/week <sup>1</sup>	56 (23%)	24 (20%)

<sup>1</sup> Number of subjects using >100 g during study or > 50 g if treated period was 1 week or less.

In Study 302, clobetasol foam and vehicle foam subjects also had similar drug usage levels, but both foam groups used roughly twice as many grams of drug product as the Temovate ointment group. A similar percentage of foam subjects in Study 302 used more than 100 g of study drug during the treatment period as in Study 301 (20% on clobetasol foam and 18% on vehicle foam). No Temovate subjects used more than 100 g during the treatment period. The maximum usage of clobetasol foam was 201 g over 14 days and the maximum treatment period was 22 days. The study drug exposure summary for Study 302 is presented in Table 19.

**Table 19 – Study Drug Exposure (Study 302)**

	Clobetasol Foam N= 253	Vehicle Foam N= 123	TEMOVATE Ointment N=121
Days on study drug	(N=253)	(N=121)	(N=120)
Mean	14.6	14.6	14.6
Range	1 - 22	7 - 21	12 - 21
Study drug usage (g)	(N=250)	(N=119)	(N=117)
Mean	62.32	57.95	28.98
Range	1.6 - 200.7	4.5 - 200.6	1.6 - 100
No. > 50 g/week <sup>1</sup>	49 (20%)	21 (18%)	0 (0%)

<sup>1</sup> Number of subjects using >100 g during study or > 50 g if treated period was 1 week or less.

### 3.2.2 Adverse Events

Similar proportions of clobetasol and vehicle subjects experienced adverse events during Study 301 (20% on clobetasol and 17% on vehicle). Reported local adverse events (administration site conditions, infections, and skin and subcutaneous disorders) are presented in Table 20. Most local adverse events occurred at similar rates on the clobetasol and vehicle foam arms.

**Table 20 – Application Site Reactions, Infections, and Skin Disorders (Study 301)**

	Clobetasol Foam N=251	Vehicle Foam N=126
<b>Subjects with any adverse experience</b>	51(20%)	21(17%)
<b>Administration Site Conditions</b>		
Application site atrophy	5(2%)	1(1%)
Application site burning	1(< 1%)	1(1%)
Application site dermatitis	1(< 1%)	1(1%)
Application site dryness	1(< 1%)	0(0%)
Application site eczema	0(0%)	2(2%)
Application site erythema	0(0%)	1(1%)
Application site pain	1(< 1%)	0(0%)
Application site pigmentation changes	2(1%)	0(0%)
Application site pruritus	1(< 1%)	6(5%)
Application site reaction	5(2%)	2(2%)
Application site urticaria	1(< 1%)	0(0%)
<b>Infections</b>		
Application site folliculitis	1(< 1%)	0(0%)
Application site infection	1(< 1%)	1(1%)
Dermatitis infected	0(0%)	1(1%)
Folliculitis	1(< 1%)	0(0%)
<b>Skin/Subcutaneous Disorders</b>		
Heat rash	1(< 1%)	0(0%)
Dermatitis atopic	0(0%)	1(1%)
Skin burning sensation	0(0%)	1(1%)
Telangiectasia	2(1%)	0(0%)

Similar proportions of clobetasol foam and vehicle foam subjects experienced adverse events during Study 302, but these rates were higher than on the Temovate ointment arm (17% on clobetasol foam, 16% on vehicle foam, and 9% on Temovate ointment). Reported local adverse events (administration site conditions, infections, and skin and subcutaneous disorders) are presented in Table 21. Most local adverse events occurred at similar rates on the clobetasol and vehicle foam arms, though fewer Temovate ointment subjects experienced local adverse events.

**Table 21 - Application Site Reactions, Infections, and Skin Disorders (Study 302)**

	Clobetasol Foam N=253	Vehicle Foam N=123	Temovate Ointment N=121
<b>Subjects with any adverse experience</b>	42 (17%)	20 (16%)	11 (9%)
<b>Administration Site Conditions</b>			
Application site atrophy	6 (2%)	1 (1%)	0 (0%)
Application site burning	4 (2%)	2 (2%)	0 (0%)
Application site dryness	1 (< 1%)	0 (0%)	0 (0%)
Application site hypersensitivity	1 (< 1%)	0 (0%)	0 (0%)
Application site pruritus	0 (0%)	1 (1%)	0 (0%)
<b>Infections</b>			
Application site folliculitis	2 (1%)	0 (0%)	0 (0%)
<b>Skin/Subcutaneous Disorders</b>			
Dermatitis	0 (0%)	0 (0%)	1 (1%)
Dermatitis atopic	1 (< 1%)	0 (0%)	0 (0%)
Dermatitis contact	0 (0%)	1 (1%)	0 (0%)
Post-inflammatory pigmentation change	0 (0%)	0 (0%)	1 (1%)
Urticaria generalised	0 (0%)	0 (0%)	1 (1%)

The severities of cutaneous signs (atrophy, pigmentation, telangiectasia, and striae) were recorded at each visit. The numbers of subjects in Study 301 who worsened from baseline at any visit (Week 1, 2, or 4) are presented in Table 22. The rates of worsening were about 1-2% higher for clobetasol foam than vehicle foam for each sign.

**Table 22 – Worsening of Cutaneous Signs from Baseline at any Visit (Weeks 1, 2, or 4) (Study 301)**

	Clobetasol Foam N=251	Vehicle Foam N=126
Atrophy	5 (2%)	1 (1%)
Pigmentation	14 (6%)	5 (4%)
Telangiectasia	2 (1%)	0 (0%)
Striae	1 (<1%)	0 (0%)

The results for Study 302 on the worsening of cutaneous signs at any visit are similar to those for Study 301. The worsening rates for atrophy and telangiectasia were 1-2% higher on clobetasol foam than vehicle foam. Clobetasol foam had a lower rate of pigmentation changes than Temovate ointment (5% vs. 9%) and a similar rate of telangiectasia (2%). The numbers of subjects in Study 302 who worsened from baseline at any visit (Week 1, 2, or 4) are presented in Table 23.

**Table 23 – Worsening of Cutaneous Signs from Baseline at any Visit (Weeks 1, 2, or 4) (Study 302)**

	Clobetasol Foam N=253	Vehicle Foam N=123	TEMOVATE Ointment N=121
Atrophy	6 (2%)	1 (1%)	0 (0%)
Pigmentation	12 (5%)	6 (5%)	11 (9%)
Telangiectasia	4 (2%)	1 (1%)	2 (2%)
Striae	0 (0%)	0 (0%)	0 (0%)

## 4 Findings in Special/Subgroup Populations

### 4.1 Gender, Race, and Age

Success rates and treatment effects were generally consistent across gender, race, and age subgroups in Study 301. The subgroup results for treatment success are presented in Table 24.

**Table 24 – Treatment Success at Week 2 by Subgroup (Study 301)**

	Clobetasol Foam	Vehicle Foam
Gender Male	37/80 (46%)	5/53 (9%)
Female	94/168 (56%)	13/71 (18%)
Race Caucasian	76/148 (51%)	13/74 (18%)
Afr.-Amer.	37/69 (54%)	3/31 (10%)
Other	18/31 (58%)	2/19 (11%)
Age 12 <- 18	38/69 (55%)	3/32 (9%)
18 <- 65	85/157 (54%)	13/79 (16%)
≥ 65	8/22 (36%)	2/12 (17%)

Treatment success rates for males and females were similar in Study 302. The vast majority of subjects in Study 302 were Caucasian and in the 18-64 age group and it is difficult to assess subjects outside of these groups due to the small numbers. However, the success rates for non-Caucasians are lower than for Caucasians in each treatment group and no non-Caucasians achieved treatment success on clobetasol foam or vehicle foam. Subgroup results for Study 302 are presented in Table 25.

**Table 25 – Treatment Success at Week 2 by Subgroup (Study 302)**

	Clobetasol Foam	Vehicle Foam	TEMOVATE Ointment
Gender Male	21/127 (17%)	4/71 (6%)	23/76 (30%)
Female	20/126 (16%)	1/52 (2%)	15/45 (33%)
Race Caucasian	41/221 (19%)	5/111 (5%)	35/105 (33%)
Other	0/32 (0%)	0/12 (0%)	3/16 (19%)
Age 12 <- 18	2/8 (25%)	0/1 (0%)	--
18 <- 65	37/216 (17%)	3/95 (3%)	31/108 (29%)
≥ 65	2/29 (7%)	2/27 (7%)	7/13 (54%)

## 4.2 Other Special/Subgroup Populations

In Study 301, treatment success rates were higher in subjects with moderate severity at baseline than severe. Severe subjects would have needed to improve further to achieve success than moderate subjects. In Study 302, subjects with mild and moderate severity at baseline had similar success rates on the clobetasol foam and vehicle foam arms, but on the Temovate arm, moderate subjects had higher success rates than mild subjects. Note that in Study 302, mild subjects needed to achieve clearance to be a success, but moderate subjects needed to achieve an almost clear state. Treatment success rates by baseline ISGA severity are presented in Table 26 and Table 27 for the two studies.

**Table 26 – Treatment Success at Week 2 by Baseline Severity (Study 301)**

		Clobetasol Foam	Vehicle Foam
ISGA	Moderate	122/217 (56%)	18/111 (16%)
	Severe	9/31 (29%)	0/13 (0%)

**Table 27 – Treatment Success at Week 2 by Baseline Severity (Study 302)**

		Clobetasol Foam	Vehicle Foam	TEMOVATE Ointment
ISGA	Mild	15/93 (16%)	2/37 (5%)	7/34 (21%)
	Moderate	24/155 (15%)	3/85 (4%)	30/84 (36%)
	Marked/Severe	2/5 (40%)	0/1 (0%)	1/3 (33%)

In Study 302, the individual signs were evaluated on a target lesion. The success rates for subjects with target lesions on the leg, arm, and trunk were higher than for those with lesions on the elbow or knee for clobetasol foam. On the Temovate arm, however, subjects with a target lesion on the knee did not have lower efficacy than other locations. Success rates by target lesion location are presented in Table 28.

**Table 28 – Treatment Success at Week 2 by Target Lesion Location (Study 302)**

	Clobetasol Foam	Vehicle Foam	TEMOVATE Ointment
Leg	19/88 (22%)	1/48 (2%)	10/34 (29%)
Arm	8/52 (15%)	2/24 (8%)	9/26 (35%)
Trunk	10/52 (19%)	1/20 (5%)	9/23 (39%)
Knee	2/24 (8%)	0/7 (0%)	6/14 (43%)
Elbow	2/35 (6%)	1/24 (4%)	4/24 (17%)
Missing	0/2 (0%)	--	--

## 5 Summary and Conclusions

### 5.1 Statistical Issues and Collective Evidence

The sponsor is supporting a 505 (b) 2 application for clobetasol foam by establishing efficacy by way of two vehicle-controlled studies, one in moderate to severe atopic

dermatitis and one in mild to moderate psoriasis. To bridge to the Agency's findings of safety for Temovate (clobetasol) ointment, the sponsor included a Temovate arm in the psoriasis study. Both studies demonstrated that clobetasol foam was superior to vehicle foam for treatment success; however, clobetasol foam appears to be less efficacious than Temovate ointment. Efficacy is also supported by results on the secondary endpoints and results were generally consistent across subgroups. Treatment by center interactions were significant in both studies, but this appears to be primarily due to the magnitude of the treatment effect varying across centers. The efficacy conclusions did not rely on any one center.

Each study had one protocol change during the study involving the inclusion criteria. In Study 301, the requirement that subjects have a baseline pruritus score of at least 2 was removed about one-third of the way through the study. After the change most subjects still had baseline pruritus scores of at least 2, and the overall baseline severity and the efficacy results were similar before the change and after. In Study 302, incorrect scales for erythema and scaling were initially provided to the investigators. The problem was discovered one week into the trial and corrected scales were provided to the investigator. With the investigator's input, the sponsor was able to map the scores for the 46 subjects evaluated using the incorrect scale to the corrected scale. Sensitivity analyses demonstrated that the impact of the mis-specified scale was minimal.

In each study approximately 20% of subjects using a foam treatment used more than the recommended 50 g per week. On average, clobetasol foam subjects used twice as much medication as Temovate ointment subjects. Adverse event rates on the clobetasol foam, vehicle foam, and Temovate ointment arms were similar. Rates for local adverse events were generally low.

## **5.2 Conclusions and Recommendations**

The efficacy of clobetasol foam in the treatment of corticosteroid-responsive dermatoses has been demonstrated by the superiority of clobetasol foam to its vehicle in one atopic dermatitis and one psoriasis study. The treatment success rate in moderate to severe atopic dermatitis was 52% versus 14% ( $p < 0.0001$ ). The treatment success rate in mild to moderate psoriasis was 16% versus 4% ( $p = 0.0005$ ). In the psoriasis study, clobetasol foam had similar rates of adverse events as the reference drug Temovate ointment and lower efficacy (16% vs. 31%).

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## 6 Appendix

### 6.1 Efficacy Scales

**Table 29 - Investigator's Static Global Assessment (Study 301)**

Score	Definition
0	Clear; minor residual discoloration; no erythema or induration/papulation, no oozing/crusting
1	Almost Clear; trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting
2	Mild; faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate; pink-red erythema with moderate induration/papulation with or without oozing/crusting
4	Severe; deep or bright red erythema with severe induration/papulation and with oozing/crusting

**Table 30: Subject's Assessment of Pruritus**

Score	Definition
0	No itching
1	Minimal; very rarely aware of localized itching; only present when relaxing and lasts for very short time
2	Mild; only aware of itching at times; only present when relaxing; not present when focused on other activities
3	Moderate; often aware of itching; annoying; sometimes disturbs sleep and daytime activities
4	Severe; constant itching; distressing; frequent sleep disturbance; interferes with activities

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**Table 31: Erythema, Induration/Papulation, Lichenification, Scaling and Oozing/Crusting Scoring**

<b>Erythema</b>	<b>Definition</b>
0	Absent; no erythema present (may be minor discoloration)
1	Minimal; faint pink, barely apparent
2	Mild; light pink, noticeable
3	Moderate; pink-red, easily noticeable
4	Severe; deep or bright red, may feel warm to the touch
<b>Induration/Papulation</b>	
0	Absent; no evidence of elevation
1	Minimal; barely perceptible elevation
2	Mild; perceptible but not extensive elevation
3	Moderate; marked and somewhat extensive elevation
4	Severe; marked and extensive elevation
<b>Lichenification</b>	
0	Absent; no lichenification present
1	Minimal; slightly accentuated superficial skin lines, not palpable
2	Mild; minor epidermal thickening in one or two areas
3	Moderate; moderate epidermal thickening in few areas, moderately accentuated skin lines
4	Severe; prominent epidermal thickening with deep skin lines, 4 or more areas involved
<b>Scaling</b>	
0	Absent; no evidence of scaling
1	Minimal; occasional fine scale
2	Mild; fine, flaky scale predominates
3	Moderate; coarse scale predominates
4	Severe; thick, coarse, crusted scale predominates
<b>Oozing/Crusting</b>	
0	Absent; no evidence of oozing or crusting
1	Minimal; rare oozing/crusting
2	Mild; occasional oozing/crusting
3	Moderate; diffuse oozing/crusting
4	Severe; marked oozing/crusting

**Table 32: Subject's Global Assessment**

Score	Definition
0	My dermatitis is clear
1	My dermatitis is minimal; there may be a few light pink areas
2	My dermatitis is mild; there may be occasional light pink areas
3	My dermatitis is moderate; there may be easily noticeable pink-red areas
4	My dermatitis is severe; there may be deep or bright red areas which may be warm to the touch

**Table 33: Psoriasis Grading Scale**

Score	Scaling	Erythema	Plaque Thickness
0	No evidence of scaling	No evidence of erythema, hyperpigmentation may be present	No elevation over normal skin
1	Minimal; occasional fine scale over less than 5% of the lesion	Faint erythema	Possible but difficult to ascertain whether there is a slight elevation above normal skin
2	Mild, fine scales predominate	Light red coloration	Slight but definite elevation, typically edges are indistinct or sloped
3	Moderate; coarse scales predominate	Moderate red coloration	Moderate elevation with rough or sloped edges
4	Marked; thick non tenacious scale predominates	Bright red coloration	Marked elevation typically with hard or sharp edges
5	Severe; very thick tenacious scale predominates	Dusky to deep red coloration	Very marked elevation typically with hard sharp edges

**Table 34: Investigator's Static Global Assessment**

Score	Definition
0	Clear; minor residual discoloration, no erythema, scaling, or plaque thickness
1	Almost Clear; occasional fine scale, faint erythema, and barely perceptible plaque thickness (possible but difficult to ascertain whether there is a slight elevation above normal skin)
2	Mild; fine scales predominate with light red coloration and mild plaque thickness (slight but definite elevation, typically edges are indistinct or sloped)
3	Moderate; coarse scales predominate with moderate red coloration and moderate plaque thickness (moderate elevation with rough or sloped edges)
4	Marked; thick, non-tenacious scale predominates with bright red coloration and marked plaque thickness (marked elevation typically with hard or sharp edges)
5	Severe; very thick tenacious scale predominates with dusky to deep red coloration and severe plaque thickness (very marked elevation typically with hard sharp edges)

**Table 35: Subject's Assessment of Pruritus**

Score	Definition
0	No itching
1	Minimal: very rarely aware of localized itching; only present when relaxing and lasts for very short time
2	Mild: only aware of itching at times; only present when relaxing; not present when focused on other activities
3	Moderate: often aware of itching; annoying; sometimes disturbs sleep and daytime activities
4	Severe: constant itching; distressing; frequent sleep disturbance; interferes with activities

**Table 36: Subject's Global Assessment**

Score	Definition
0	My skin is completely clear, except for possible residual hyperpigmentation
1	My psoriasis is almost clear; however, patchy remnants of fine scaling may be present
2	My psoriasis is mild, with a small amount of psoriasis remaining (i.e., fine to coarse scales in some areas, definite redness, and/or barely visible plaque thickness)
3	My psoriasis is moderate, between slight and definitely noticeable
4	My psoriasis is very noticeable with redness, scaling, and/or plaque thickness
5	My psoriasis is severe with severe redness, and thick scaling and plaques

### 6.2 Sensitivity Analyses for Handling of Missing Data

The sponsor proposed two sensitivity analyses for the handling of missing data for the primary efficacy endpoint for Studies 301 and 302. The first analysis computed the average response rate for completers by treatment arm and imputed this value for subjects with missing data. The second analysis imputed values based on a series of iterative sequential generalized logistic models. The sponsor's method is based on work by Horton, Lipsitz, and Parzen (2003) and Allison (2002). This method uses multiple imputation from a generalized logistic model. The sponsor used a software package called IVEware to create the multiple imputations. Due to the use of specialized software, this reviewer did not verify the sponsor's analyses; however, in each case the estimated success rates using these two imputations were within 1-2% of the primary imputation method of LOCF. The results of the sensitivity analyses are presented in Table 37 and Table 38.

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**Table 37 – Sensitivity Analyses for Missing Data (Study 301)**

	Clobetasol Foam N=251	Vehicle Foam N=126
<i>Sequential Regression Method</i>		
Treatment Success <sup>1</sup>	136 (54%)	20 (16%)
P-value		<0.0001
<i>Mean Imputation Method</i>		
Treatment Success <sup>1</sup>	134 (53%)	18 (14%)
P-value		<0.0001

<sup>1</sup> ISGA = 0 or 1 with 2 grades reduction, erythema = 0 or 1, and induration/papulation = 0 or 1

**Table 38 – Sensitivity Analyses for Missing Data (Study 302)**

	Clobetasol Foam N=253	Vehicle Foam N=123	TEMOVATE Ointment N=121
<i>Sequential Regression Method</i>			
Treatment Success <sup>1</sup>	41 (16%)	5 (4%)	39 (32%)
P-value (vs. Clob. Foam)		0.0013	
<i>Mean Imputation Method</i>			
Treatment Success <sup>1</sup>	42 (17%)	5 (4%)	38 (31%)
P-value (vs. Clob. Foam)		0.0004	

<sup>1</sup> ISGA = 0 or 1 with 2 grades reduction, erythema = 0 or 1, scaling = 0 or 1, and plaque thickness = 0

### 6.3 References

Horton, N.J., S.R. Lipsitz, and M. Parzen, A Potential for Bias When Rounding in Multiple Imputation. American Statistical Association, 2003. 57(4): p. 229–232.

Allison, P., Missing Data, in Series: Quantitative Applications in the Social Sciences. 2002, Sage Publications: Thousand Oaks, CA. p. 64–73.

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