

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-835**

**STATISTICAL REVIEW(S)**



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

## STATISTICAL REVIEW AND EVALUATION

### NEW DRUG APPLICATION

#### CLINICAL STUDIES

**NDA/Serial Number:** 21-835 / N-000  
**Drug Name:** Clobex (clobetasol propionate) spray 0.05%  
**Indication(s):** Psoriasis  
**Applicant:** Dow Pharmaceutical Sciences  
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## **1 Executive Summary**

### **1.1 Conclusions and Recommendations**

Clobetasol spray was statistically superior to vehicle spray in two studies (TI01-01008 and TI01-01010) in the treatment of psoriasis. Efficacy was demonstrated after both 2 and 4 weeks of treatment though success rates (clear/almost clear) were higher after 4 weeks of use than after 2 weeks. Efficacy was evaluated using the following sequence of endpoints to control for multiplicity: (1) Clear/Almost Clear/Mild at Week 2, and (2) Clear/Almost Clear at Week 4. After 2 weeks of treatment, 87% of clobetasol subjects were clear, almost clear, or mild versus 28% of vehicle subjects in Study 8, and 87% of clobetasol subjects were clear, almost clear, or mild versus 27% of vehicle subjects in Study 10. After 4 weeks of treatment, 78% of clobetasol subjects were clear or almost clear versus 3% of vehicle subjects in Study 8, and 82% of clobetasol subjects were clear or almost clear versus 2% of vehicle subjects in Study 10. All of the primary efficacy results were statistically significant at  $p < 0.0001$ . For comparison with the Week 4 clear/almost clear results, at Week 2, 55% of clobetasol subjects were clear or almost clear versus 2% of vehicle subjects in Study 8, and 47% of clobetasol subjects were clear or almost clear versus 0% of vehicle subjects in Study 10.

Adverse event rates were similar on the clobetasol and vehicle arms. The most common adverse event was burning or stinging in the application area, and was reported by approximately 40% of subjects in both the clobetasol and vehicle arms. Reports of burning persisted throughout the treatment period with a slight increase in rates over time in one study and a slight decrease in rates over time in the other study on the clobetasol arm.

### **1.2 Brief Overview of Clinical Studies**

The sponsor conducted two Phase 3 studies (TI01-01008 and TI01-01010) evaluating the safety and efficacy of clobetasol spray versus its vehicle in the treatment of psoriasis. Subjects in the studies were evaluated for up to 8 weeks, 4 weeks of treatment and 4 weeks of post-treatment follow-up. Each study enrolled 120 subjects, 60 to clobetasol and 60 to vehicle. Subjects were enrolled with moderate to severe plaque psoriasis. Efficacy was measured with the Overall Disease Severity scale, a global evaluation incorporating scaling, erythema, and plaque elevation. All study centers for the two studies were in the United States.

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

The sponsor has conducted two studies that consistently and by a large margin demonstrated that clobetasol spray is superior to its vehicle in the treatment of psoriasis. The sponsor conducted the studies under protocols that were agreed upon with the Agency with regard to study design and endpoints. Due to the fact that safety concerns might limit treatment duration to 2 weeks (though the sponsor was interested in labeling for 4 weeks use), the sponsor specified both Week 2 and Week 4 as primary timepoints, using a pre-specified sequence to control multiplicity (success at Week 4 could only be evaluated if success at Week 2 was significant). Subjects were evaluated on the Overall

Disease Severity (ODS) scale which was a 5-point (clear, almost clear, mild, moderate, severe/very severe) global evaluation of scaling, erythema, and plaque elevation. A looser definition of treatment success was agreed upon for the Week 2 endpoint (clear/almost clear/mild) than for the Week 4 endpoint (clear/almost clear). The Week 2 and Week 4 success rates were statistically significant in both studies ( $p < 0.0001$ ). Subjects were also evaluated on the individual signs and symptoms of psoriasis (scaling, erythema, plaque elevation, and pruritus). The results on the individual signs and symptoms were consistent with the results on the ODS scale. The proportion of subjects who were clear or almost clear increased from Week 2 to Week 4 on the clobetasol arm (55% to 78% in Study 8 and 47% to 82% in Study 10), while the clear/almost clear rate on the vehicle arm remained low throughout the treatment period in both studies (0 – 3%). Subjects were also followed four weeks post-treatment. At the Week 8 follow-up visit the clear/almost clear rate on the clobetasol arm dropped to 41% in Study 8 and 57% in Study 10 compared with rates of 3% and 7% on the vehicle arms for the two studies.

## 2 Introduction

### 2.1 Overview

Clobetasol propionate is a super-high potency corticosteroid. It has previously been approved in various formulations for various sponsors to treat corticosteroid responsive dermatoses or scalp psoriasis. CLOBEX (clobetasol propionate) is currently approved in lotion and shampoo formulations. The shampoo formulation is indicated for the treatment of moderate to severe scalp psoriasis in patients age 18 and older -- treatment should be limited to at most 4 weeks. The lotion formulation is indicated for the treatment of corticosteroid responsive dermatoses in patients age 18 and older -- although treatment should be limited to 2 weeks, localized lesions of plaque psoriasis that have not responded after 2 weeks may be treated for an additional 2 weeks. In the current application for CLOBEX spray, the sponsor is seeking an indication of moderate to severe plaque psoriasis in patients age 18 and older, with treatment limited to at most 4 weeks. This indication reflects the population that was studied in the two Phase 3 studies.

The protocols for the two Phase 3 studies (TI01-01008 and TI01-01010) were discussed in an End of Phase 2 Meeting held March 18, 2002 and were evaluated as Special Protocol Assessments in August 2002. Through this process, the sponsor and the Division came to agreement on the key aspects of the study design and endpoints. The Phase 3 studies are the focus of this review. In addition to the Phase 3 studies, the sponsor also conducted two HPA axis suppression studies. The key features of the clinical studies supporting CLOBEX spray for the treatment of psoriasis are presented in Table 1. This review evaluates the two Phase 3 efficacy and safety studies.

**Table 1 – Clinical Study Program for CLOBEX Spray**

Study	Description	Duration	# Subjects
TI01-01008	Safety and Efficacy	8 weeks (4 weeks treatment/ 4 weeks follow-up)	60 clobetasol 60 vehicle
TI01-01010	Safety and Efficacy	8 weeks (4 weeks treatment/ 4 weeks follow-up)	60 clobetasol 60 vehicle
TI01-0109	HPA Axis Suppression	4 weeks	14 clobetasol
D02-0204-03	HPA Axis Suppression	2 weeks and 4 weeks	19 (2 wks clob.) 17 (4 wks clob.)

## 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 in eCTD format and was entirely electronic. The datasets used in this review are archived at [\\Cdesub1\evsprod\N021835\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5351-stud-rep-contr\study-report-ti01-01008\datasets\analysis](#) and [\\Cdesub1\evsprod\N021835\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5351-stud-rep-contr\study-report-ti01-01010\datasets\analysis](#).

## 3 Statistical Evaluation

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study Design

The sponsor conducted two Phase 3 studies (TI01-01008 and TI01-01010) to evaluate the safety and efficacy of clobetasol spray in the treatment of moderate to severe plaque psoriasis. Studies 8 and 10 were conducted under identical protocols. Protocol 10 was evaluated as a Special Protocol Assessment in August 2002. Studies 8 and 10 were randomized, double-blind vehicle controlled studies each conducted at 6 centers. The subjects enrolled were 18 years of age or older with plaque psoriasis covering at least 2% body surface area and an Overall Disease Severity score of at least 3 (moderate) on a 0-4 scale. Subjects applied test medication twice daily for 4 weeks (or less if the psoriasis completely cleared before 4 weeks). Subjects were evaluated at baseline, Week 1, Week 2, Week 4 (end of treatment), and Week 8 (four weeks post-treatment). Each study enrolled 120 subjects, 60 to clobetasol and 60 to vehicle.

The primary efficacy evaluations were based on the Overall Disease Severity scale (ODS). The ODS scale was defined as

0 - Clear

Scaling: no evidence of scaling

Erythema: no evidence of erythema (except possible residual discoloration)

Plaque elevation: no evidence of plaque elevation above normal skin level

1 - Almost clear

Scaling: limited amount of very fine scales partially covers some of the plaques

Erythema: very few of the plaques are light red

Plaque elevation: very slight elevation above normal skin level, easier felt than seen.

2 - Mild

Scaling: mainly fine scales; some plaques are partially covered

Erythema: some plaques are light red

Plaque Elevation: slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped, on some of the plaques

3 - Moderate

Scaling: somewhat coarser scales; most plaques are partially covered

Erythema: most plaques are red

Plaque Elevation: moderate elevation with rounded or sloped edges on most of the plaques

4 - Severe/Very Severe

Scaling: coarse, thick scales; virtually all or all plaques are covered; rough surface

Erythema: virtually all or all plaques are bright to dusky red

Plaque elevation: marked to very marked elevation, with hard to very hard sharp edges on virtually all or all of the plaques

Subjects were also evaluated on the individual signs of scaling, erythema, and plaque elevation on a 0-4 scale. The definitions of the grades of the individual signs match the individual descriptions used in the ODS scale. Subjects were also evaluated on their level of pruritus according to the following scale

0 - Clear: no evidence of pruritus

1 - Almost clear: pruritus is infrequently noticeable and never disrupts daily activity

2 - Mild: pruritus is noticeable but does not disrupt daily activity

3 - Moderate: Urge to scratch occasionally disrupts daily activity

4 - Severe/Very Severe: Marked to extreme urge to scratch routinely disrupts daily activity and may disrupt sleep.

The study evaluated two primary efficacy endpoints analyzed in a pre-specified order. The first primary efficacy endpoint was treatment success at Week 2, defined as a score of 0, 1, or 2 on the ODS at Week 2. The second primary efficacy endpoint was treatment success at Week 4, defined as a score of 0 or 1 on the ODS at Week 4. Because the endpoints were analyzed in a pre-specified order, no other adjustment for multiplicity is needed. The secondary efficacy endpoints were defined as the success rates for scaling, erythema, plaque elevation, and pruritus. The success rate for each individual sign or symptom was defined as grade 0 or 1 at each time period. The success rates were analyzed with the Cochran-Mantel-Haenszel test stratified on investigator.

The ITT population was defined as all subjects randomized and dispensed test medication. Subjects were excluded from the per protocol population if they missed the

Week 2 or Week 4 visits (unless due to cleared psoriasis), or were outside the Week 2 or Week 4 visit window of  $\pm 3$  days, applied fewer than 80% or more than 120% of required doses, or took a concomitant medication excluded by the protocol.

### 3.1.2 Subject Disposition

Study 8 enrolled 120 subjects, 60 to clobetasol and 60 to vehicle at 6 centers. Study 10 also enrolled 120 subjects, 60 to clobetasol and 60 to vehicle at 6 centers. The reasons for study discontinuation are presented in Table 2. The most common reasons for discontinuation were adverse events and treatment failure. Three clobetasol subjects and seven vehicle subjects discontinued early due to adverse events. In Study 8, one clobetasol subject discontinued on Day 2 due to stinging and one clobetasol subject discontinued on Day 52 due to a flare of guttate psoriasis on untreated areas. In Study 10 one clobetasol subject discontinued on Day 18 due to burning. In Study 8, two vehicle subjects discontinued due to burning and stinging (Day 14 and Day 50) and one due to infected eczema (Day 24). In Study 10, three vehicle subjects discontinued due to burning, stinging or discomfort (Day 7, Day 13, Day 15), and one due to lesions recurring and severe itching (Day 46). Three of the discontinuations for adverse events occurred during the post-treatment follow-up period (flare of guttate psoriasis, lesions recurring/itching, and burning/stinging). In Study 10, 8 subjects completed the study, but were considered discontinuations due to protocol violations. One subject was inappropriately enrolled due to incomplete washout of topical medications (last visit was on Day 72). The first 7 subjects (out of 20) enrolled at Site 2 were improperly scheduled for their final visits in Week 5 (Day 35 or 36) rather than Week 8 and are counted as discontinuations in the sponsor's report due to this procedural error. Table 3 presents the distribution of the subjects' last day of follow-up and the reasons for discontinuation for subjects discontinuing during the first 52 days.

**Table 2 – Reason for Study Discontinuation**

	Study 8		Study 10	
	Clobetasol	Vehicle	Clobetasol	Vehicle
<b>Number of Subjects</b>	60	60	60	60
<b>Subjects who Discontinued</b>	5	8	5	13
<i>Reason</i>				
Adverse Event	2	3	1	4
Treatment Failure	1	4	0	2
Lost to Follow-up	1	0	1	1
Non-Compliance	0	1	0	0
Subject's Decision to Withdraw	0	0	0	1
Ineligible <sup>1</sup>	0	0	0	1
Other <sup>2</sup>	1	0	3	4

<sup>1</sup> Subject 253 in Study 10 completed study but is included above for being inappropriately enrolled due to incomplete washout of topical medications

<sup>2</sup> Includes: moved out of town (Subject 7 in Study 8) and prematurely attended Visit 5 (Subjects 229 through 235 in Study 10)

Source: study-report-ti-01-01008.pdf, pg 54, and study-report-ti-01-01010.pdf, pg 52.

**Table 3 – Day of Last Attended Visit**

	Study 8		Study 10	
	Clobetasol	Vehicle	Clobetasol	Vehicle
≤ Day 10 (Week 1)	1 (AE)	0	1 (LTF)	2 (AE, SD)
Day 11 – Day 17 (Week 2)	0	2 (TF, AE)	0	3 (LTF, AE)
Day 18 – Day 24 (Week 3)	0	2 (NC, AE)	1 (AE)	0
Day 25 – Day 31 (Week 4)	2 (LTF, SM)	1 (TF)	0	2 (TF)
Day 32 – Day 38 (Week 5)	0	1 (TF)	3 (VS)	4 (VS)
Day 39 – Day 45 (Week 6)	2 (CS, TF)	1 (TF)	0	0
Day 46 – Day 52 (Week 7)	2 (CS, AE)	3 (CS, AE)	1 (CS)	2 (CS, AE)
Day 53 + (Week 8+)	53	50	54	47

AE = Adverse Event, TF = Treatment Failure, NC = Non-Compliance, LTF = Loss to Follow-up, SD = Subject's Decision, SM = Subject Moved, CS = Completed Study, VS = Visit Scheduling Error.

Source: Reviewer analysis.

### 3.1.3 Baseline and Demographic Data

The baseline demographic variables were generally balanced across treatment arms. Studies 8 and 10 enrolled slightly more males than females. About 94% of subjects in Study 8 and 86% of subjects in Study 10 were white. The average subject age was about 46 to 48 years and the range was 18 to 81 years. The baseline demographic data is presented in Table 4.

**Table 4 – Baseline Demographic Data**

	Study 8		Study 10	
	Clobetasol N=60	Vehicle N=60	Clobetasol N=60	Vehicle N=60
Gender				
Male	38 (63%)	34 (57%)	31 (52%)	37 (62%)
Female	22 (37%)	26 (43%)	29 (48%)	23 (38%)
Race				
White	57 (95%)	56 (93%)	50 (83%)	53 (88%)
Black	2 ( 3%)	1 ( 2%)	3 ( 5%)	1 ( 2%)
Hispanic	1 ( 2%)	2 ( 3%)	4 ( 7%)	4 ( 7%)
Asian	0 ( 0%)	0 ( 0%)	2 ( 3%)	1 ( 2%)
Am/AK Native	0 ( 0%)	1 ( 2%)	1 ( 2%)	0 ( 0%)
Other	0 ( 0%)	0 ( 0%)	0 ( 0%)	1 ( 2%)
Age				
Mean	46.7	49.3	46.2	45.9
Range	21 - 76	24 - 73	18 - 81	18 - 77

Source: study-report-ti-01-01008.pdf, pg 60, and study-report-ti-01-01010.pdf, pg 58.

The subjects enrolled in Studies 8 and 10 had either moderate or severe psoriasis according to the ODS scale at baseline, with the majority of subjects having moderate psoriasis (91% in Study 8 and 78% in Study 10). Baseline severity scores were fairly balanced between the clobetasol and vehicle arms. All subjects had psoriasis on at least 2% of their body, excluding the face, scalp, groin, axillae, and other intertriginous areas. The median body surface area was 6% in each study and the maximum surface area was

35% in Study 8 and 63% in Study 10. Baseline ODS scores and percent BSA measurements are presented in Table 5.

**Table 5 – Baseline Severity**

	Study 8		Study 10	
	Clobetasol N=60	Vehicle N=60	Clobetasol N=60	Vehicle N=60
<i>ODS</i>				
0 (Clear)	0	0	0	0
1 (Almost Clear)	0	0	0	0
2 (Mild)	0	0	0	0
3 (Moderate)	56 (93%)	53 (88%)	45 (75%)	48 (80%)
4 (Severe/Very Severe)	4 (7%)	7 (12%)	15 (25%)	12 (20%)
<i>% BSA</i>				
Mean	7.2	8.2	9.3	8.5
Minimum	2	2	2	2
Q1	3.5	3	4	4
Median	6	5	7	6
Q3	8	12	10.5	10
Maximum	24	35	40	63

Source: study-report-ti-01-01008.pdf, pg 60, and study-report-ti-01-01010.pdf, pg 58.

### 3.1.4 Primary Efficacy Endpoints

#### 3.1.4.1 ITT Analyses

Clobetasol propionate is currently marketed in various formulations to treat psoriasis. Some products are labeled for two weeks use while others are labeled for up to four weeks use. Length of use is limited due to concern for HPA axis suppression. The Phase 3 studies in this application were designed to evaluate four-week use, however, since it was possible that safety concerns might limit use to two consecutive weeks, the sponsor considered two primary timepoints, Week 2 and Week 4. The sponsor and Agency agreed to evaluate efficacy using the following sequence of primary endpoints: (1) scoring  $\leq 2$  (clear, almost clear, mild) on the ODS scale at Week 2, and (2) scoring  $\leq 1$  (clear, almost clear) on the ODS scale at Week 4. Since different success criteria were used to evaluate treatment success at Weeks 2 and 4, this review also includes success rates for clear/almost clear at Week 2 to facilitate comparisons. Both primary endpoints are statistically significant at  $p < 0.0001$  in each study, establishing the efficacy of clobetasol at Weeks 2 and 4. The ITT efficacy results are presented in Table 6. At Week 2, 47-55% of clobetasol subjects had achieved clear or almost clear status compared to 0-2% of vehicle subjects, while at Week 4, 78-82% of clobetasol subjects had achieved clear or almost clear status compared to 2-3% of vehicle subjects.

**Table 6 – Efficacy Results (ITT)**

	Study 8			Study 10		
	Clobetasol N=60	Vehicle N=60	p-value	Clobetasol N=60	Vehicle N=60	p-value
<b>Week 2 ODS</b>						
0 (Clear)	1 (2%)	0 (0%)		0 (0%)	0 (0%)	
1 (Almost Clear)	32 (53%)	1 (2%)		28 (47%)	0 (0%)	
2 (Mild)	19 (32%)	16 (27%)		24 (40%)	16 (27%)	
3 (Moderate)	7 (12%)	38 (63%)		7 (12%)	36 (60%)	
4 (Severe)	1 (2%)	5 (8%)		1 (2%)	8 (13%)	
Clear/Almost Clear/ Mild <sup>1</sup>	52 (87%)	17 (28%)	<0.0001	52 (87%)	16 (27%)	<0.0001
Clear/Almost Clear	33 (55%)	1 (2%)	<0.0001	28 (47%)	0 (0%)	<0.0001
<b>Week 4 ODS</b>						
0 (Clear)	15 (25%)	0 (0%)		18 (30%)	0 (0%)	
1 (Almost Clear)	32 (53%)	2 (3%)		31 (52%)	1 (2%)	
2 (Mild)	6 (10%)	17 (28%)		6 (10%)	11 (18%)	
3 (Moderate)	6 (10%)	37 (62%)		4 (7%)	38 (63%)	
4 (Severe/Very Severe)	1 (2%)	4 (7%)		1 (2%)	10 (17%)	
Clear/Almost Clear <sup>2</sup>	47 (78%)	2 (3%)	<0.0001	49 (82%)	1 (2%)	<0.0001

<sup>1</sup> First Primary Endpoint<sup>2</sup> Second Primary Endpoint

Source: study-report-ti-01-01008.pdf, pg 66, and study-report-ti-01-01010.pdf, pg 64.

### 3.1.4.2 Per Protocol Analyses

Approximately 10% of subjects were excluded from the per protocol population, with comparable numbers of exclusions from the both the clobetasol and vehicle arms. Subjects were excluded from the per protocol population for missing the Week 2 or Week 4 visits, having Week 2 or Week 4 visits outside the visit window of  $\pm 3$  days, applying less than 80% or more the 120% of required doses, or taking excluded concomitant medications. The number of subjects excluded from the per protocol population by reason are listed in Table 7. The analyses on the per protocol population were very similar to those on the ITT population with similar success rates and p-values. The per protocol results are presented in Table 8. The protocols for Studies 8 and 10 state only that subjects with major protocol violations will be excluded from the per protocol population, but not what constitutes a major protocol violation. The per protocol population is defined in the statistical analysis plan dated April 22, 2003, about 2 weeks after the last patient completed the studies. However, since the results of the ITT population and the per protocol population are so similar, the choice of the subjects for the per protocol population has not impacted the results or conclusions.

**Table 7 – Primary Reason for Exclusion from Per Protocol Population**

	Study 8		Study 10	
	Clobetasol	Vehicle	Clobetasol	Vehicle
<b>Number of Subjects</b>	60	60	60	60
<b>Excluded from PP Population</b>	5	7	7	6
<i>Reason</i>				
Missed Week 2 or 4 visit	1	2	2	2
Week 2 or 4 visit outside window	3	4	1	2
Prohibited concomitant med.	1	1	4	1
Ineligible <sup>1</sup>	0	0	0	1

<sup>1</sup> Insufficient washout at baseline.

Source: study-report-ti-01-01008.pdf, pg 58, and study-report-ti-01-01010.pdf, pg 55-56.

**Table 8 – Efficacy Results (PP)**

	Study 8			Study 10		
	Clobetasol N=55	Vehicle N=53	p-value	Clobetasol N=53	Vehicle N=54	p-value
<b>Week 2 ODS</b>						
0 (Clear)	1 (2%)	0 (0%)		0 (0%)	0 (0%)	
1 (Almost Clear)	29 (53%)	1 (2%)		23 (43%)	0 (0%)	
2 (Mild)	18 (33%)	12 (23%)		23 (43%)	15 (28%)	
3 (Moderate)	6 (11%)	35 (66%)		6 (11%)	33 (61%)	
4 (Severe)	1 (2%)	5 (9%)		1 (2%)	6 (11%)	
Clear/Almost Clear/ Mild <sup>1</sup>	48 (87%)	13 (25%)	<0.0001	46 (87%)	15 (28%)	<0.0001
Clear/Almost Clear	30 (55%)	1 (2%)	<0.0001	23 (43%)	0 (0%)	<0.0001
<b>Week 4 ODS</b>						
0 (Clear)	14 (25%)	0 (0%)		14 (26%)	0 (0%)	
1 (Almost Clear)	31 (56%)	2 (4%)		29 (55%)	1 (2%)	
2 (Mild)	3 (5%)	14 (26%)		6 (11%)	10 (19%)	
3 (Moderate)	6 (11%)	33 (62%)		3 (6%)	34 (63%)	
4 (Severe)	1 (2%)	4 (8%)		1 (2%)	9 (17%)	
Clear/Almost Clear <sup>2</sup>	45 (82%)	2 (4%)	<0.0001	43 (81%)	1 (2%)	<0.0001

<sup>1</sup> First Primary Endpoint

<sup>2</sup> Second Primary Endpoint

Source: study-report-ti-01-01008.pdf, pg 106, and study-report-ti-01-01010.pdf, pg 105.

### 3.1.5 Secondary Efficacy Endpoints

The protocols for Studies 8 and 10 specified the success rates for scaling, erythema, plaque elevation, and pruritus at each time point as the secondary endpoints. The success rate for each endpoint was defined as scoring 0 or 1 (clear or almost clear) at each

timepoint. The protocols also specified the success rates on the ODS scale at Weeks 1 and 8 as secondary endpoints. With several endpoints each evaluated at a number of timepoints, these studies have 18 secondary endpoints, and the sponsor did not propose any method of controlling for multiple comparisons. However, the sponsor has also not proposed to include any secondary efficacy results in labeling. Results for the success rates for the individual signs at Weeks 2 and 4 are presented in Table 9. The results for the individual signs and symptoms are generally comparable to those for the ODS scale and support the primary results. The success rates for the individual signs are also presented in Figure 3 and Figure 4 below.

**Table 9 – Secondary Endpoint Success Rates (Clear/Almost Clear) - ITT**

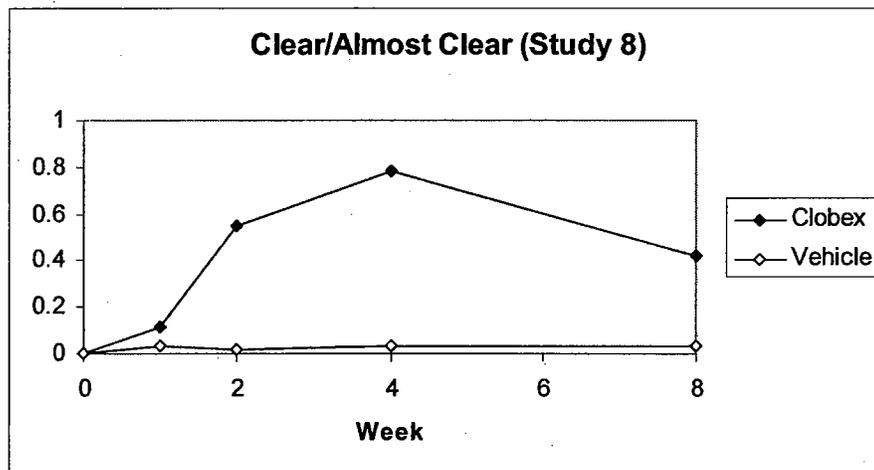
	Study 8			Study 10		
	Clobetasol N=60	Vehicle N=60	p-value	Clobetasol N=60	Vehicle N=60	p-value
<b>Week 2</b>						
Scaling	36 (60%)	6 (10%)	<0.001	34 (57%)	6 (10%)	<0.001
Erythema	29 (48%)	1 (2%)	<0.001	27 (45%)	4 (7%)	<0.001
Plaque Elevation	40 (67%)	3 (5%)	<0.001	32 (53%)	3 (5%)	<0.001
Pruritus	48 (80%)	18 (30%)	<0.001	46 (77%)	24 (40%)	<0.001
<b>Week 4</b>						
Scaling	49 (82%)	8 (13%)	<0.001	49 (82%)	4 (7%)	<0.001
Erythema	44 (73%)	2 (3%)	<0.001	50 (83%)	3 (5%)	<0.001
Plaque Elevation	48 (80%)	4 (7%)	<0.001	51 (85%)	6 (10%)	<0.001
Pruritus	51 (85%)	21 (35%)	<0.001	51 (85%)	19 (32%)	<0.001

Source: study-report-ti-01-01008.pdf, pg 68-72, and study-report-ti-01-01010.pdf, pg 66-70.

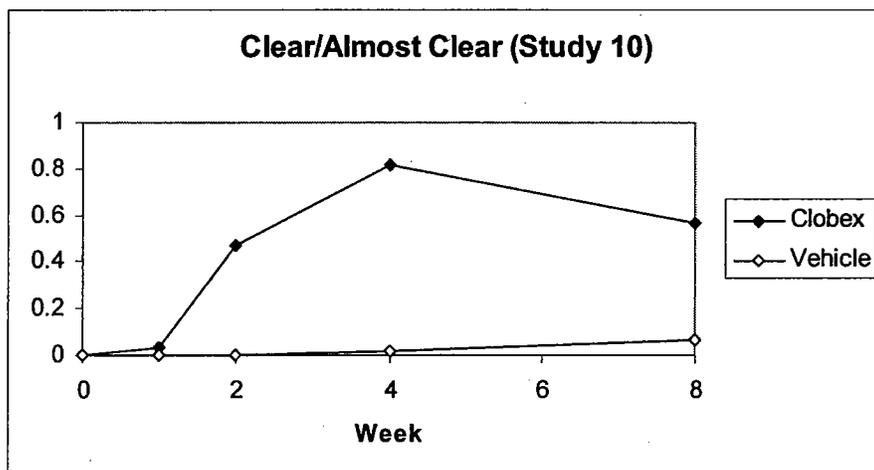
### 3.1.6 Efficacy Results over Time

Subjects were followed for 8 weeks with a 4-week treatment followed by a 4-week follow-up period. Subjects were evaluated on the ODS and the individual signs and symptoms at baseline, Week 1, Week 2, Week 4, and Week 8. The ODS rates for clear/almost clear by visit are presented in Figure 1 and Figure 2. The success rates on clobetasol continued to increase throughout the treatment period, demonstrating no difference over vehicle at Week 1 and continuing to increase from Weeks 2 and 4. Once treatment ended at Week 4, the success rates dropped off again by the Week 8 follow-up. The success rates on vehicle remained at very low levels throughout the study. The ODS scores at Week 8 are presented in Table 10. By Week 8, 41% of clobetasol subjects in Study 8 and 57% of clobetasol subjects in Study 10 were still clear or almost clear (down from peaks of 78% and 82% respectively at Week 4), compared with 3-7% of vehicle subjects.

**Figure 1 – Success Rates (Clear/Almost Clear) on the ODS over Time (Study 8)**



**Figure 2 – Success Rates (Clear/Almost Clear) on the ODS over Time (Study 10)**



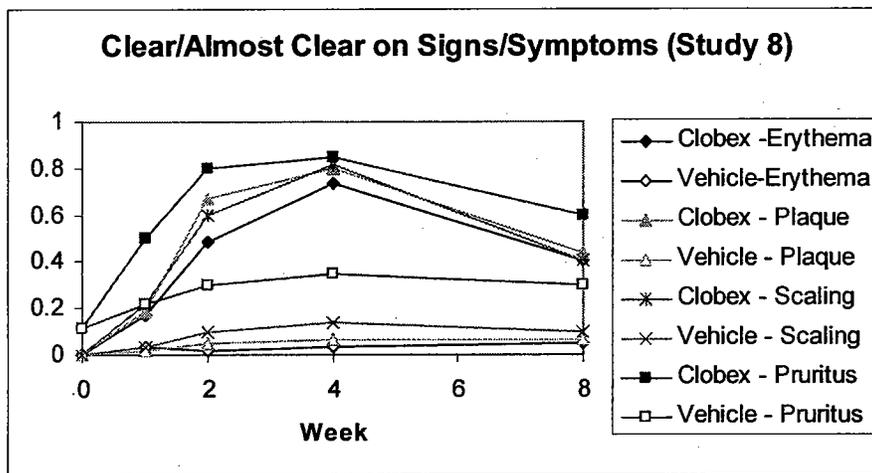
**Table 10 – Week 8 ODS Scores (4 Weeks Post-Treatment) (ITT)**

	Study 8			Study 10		
	Clobetasol N=60	Vehicle N=60	p-value	Clobetasol N=60	Vehicle N=60	p-value
<b>Week 8 ODS</b>						
0 (Clear)	5 (8%)	0 (0%)		6 (10%)	0 (0%)	
1 (Almost Clear)	20 (33%)	2 (3%)		28 (47%)	4 (7%)	
2 (Mild)	16 (27%)	15 (25%)		10 (17%)	10 (17%)	
3 (Moderate)	15 (25%)	30 (50%)		10 (17%)	24 (40%)	
4 (Severe)	1 (2%)	7 (12%)		4 (7%)	15 (25%)	
Missing	3 (5%)	6 (10%)		2 (3%)	7 (12%)	
<b>Clear/Almost Clear</b>	<b>25 (41%)</b>	<b>2 (3%)</b>	<b>&lt;0.001</b>	<b>34 (57%)</b>	<b>4 (7%)</b>	<b>&lt;0.001</b>

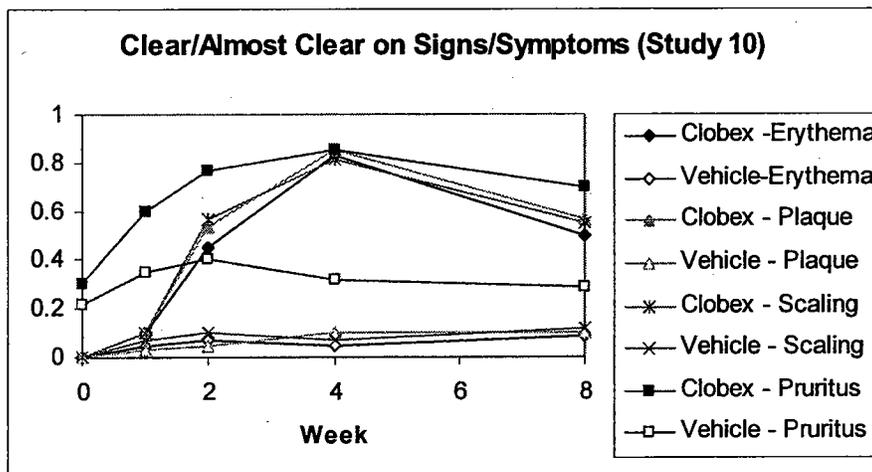
Source: study-report-ti-01-01008.pdf, pg 77, and study-report-ti-01-01010.pdf, pg 75.

The success rates (clear/almost clear) on the individual sign and symptom scores over time were very similar to the scores on the ODS. The success rates for scaling, erythema, and plaque elevation were very similar to each other, while the success rates for pruritus were somewhat higher, especially at the earlier visits. The success rates for the individual signs and symptoms are presented in Figure 3 and Figure 4. Since the results for scaling, erythema, and plaque elevation track so closely, and these three signs are globally assessed as part of the ODS, it appears that the ODS score is not driven by any one particular sign.

**Figure 3 – Success Rates (Clear/Almost Clear) for Erythema, Plaque Elevation, Scaling, and Pruritus over Time (Study 8)**



**Figure 4 - Success Rates (Clear/Almost Clear) for Erythema, Plaque Elevation, Scaling, and Pruritus over Time (Study 10)**



One reason for following subjects for four weeks post-treatment is to assess how the subjects who had a successful treatment outcome respond once the medication is stopped. The Week 8 ODS results for clobetasol subjects who were treatment successes at Week 4 are presented in Table 11. None of the subjects who were successes at Week 4 rebounded to a score that was worse than at baseline (e.g. from a 3 at baseline to a 4 at follow-up), but 8 subjects in Study 8 and 4 subjects in Study 10 returned to their baseline score of 3 at the follow-up and 2 subjects in Study 10 returned to their baseline score of 4 at follow-up. In addition, of the subjects who were successful at Week 4, 2 subjects in Study 8 and 1 subject in Study 10 who had a score of 4 at baseline went to a score of 3 at follow-up.

**Table 11 – Week 8 ODS Score among Clobetasol Subjects who were Clear/Almost Clear at Week 4 (ITT)**

	Study 8	Study 10
	Clobetasol N=47	Clobetasol N=49
<b>Week 8 ODS</b>		
0 (Clear)	5 (11%)	6 (14%)
1 (Almost Clear)	17 (36%)	26 (53%)
2 (Mild)	14 (30%)	9 (18%)
3 (Moderate)	10 (21%)	5 (10%)
4 (Severe)	0 (0%)	2 (4%)
Missing	1 (2%)	1 (2%)

Source: Reviewer analysis.

### 3.1.7 Efficacy Results by Center

Each study involved six investigators, and each investigator enrolled between 16 and 24 subjects. The sponsor had specified in the protocol that centers with fewer than 10 subjects per treatment arm would be pooled. In Study 8, Centers 2 and 6 which enrolled 16 subjects each (8 per treatment arm) were pooled in the analysis, and in Study 10, Centers 3 and 4 which also enrolled 16 subjects each (8 per treatment arm) were pooled in the analysis. The success rates by center for the two primary efficacy endpoints are presented in Table 12 and Table 13. Study 8 did not demonstrate evidence of treatment by center interaction at either Week 2 or Week 4 (Breslow-Day p-values of 0.2368 and 0.6511). Study 10 has a significant Breslow-Day p-value at Week 2 ( $p=0.0635$ ) and the Week 4 p-value can not be computed since every analysis center had at least one empty cell in its 2x2 treatment by success table (either no successes on vehicle or no failures on clobetasol). The significant p-value at Week 2 appears to be driven by the results of Site 6 which had a 100% (12/12) success rate on clobetasol and a 0% (0/12) success rate on vehicle, while the remaining 5 sites averaged an 83% success rate on clobetasol and a 33% success rate on vehicle. At Week 4 the results are comparable, with Site 6 have a 100% success rate on clobetasol and a 0% success rate on vehicle, while the remaining sites averaged 77% on clobetasol and 2% on vehicle. Site 6 in Study 10 was run by the principal investigator of the study, Karl Beutner. The site was inspected by DSI and no irregularities were noted. The study results are still highly significant, even if the data from Site 6 is not used in the analysis.

**Table 12 – Week 2 ODS Success Rates (Clear/Almost Clear/Mild) by Center**

	Study 8		Study 10	
	Clobetasol N=60	Vehicle N=60	Clobetasol N=60	Vehicle N=60
Site 1	10/10 (100%)	2/10 (20%)	9/10 (90%)	6/10 (60%)
Site 2	7/8 (88%)	0/8 (0%)	9/10 (90%)	4/10 (40%)
Site 3	11/12 (92%)	8/12 (67%)	7/8 (88%)	2/8 (25%)
Site 4	9/12 (75%)	4/12 (33%)	4/8 (50%)	2/8 (25%)
Site 5	8/10 (80%)	1/10 (10%)	11/12 (92%)	2/12 (17%)
Site 6	7/8 (88%)	2/8 (25%)	12/12 (100%)	0/12 (0%)
Total	52 (87%)	17 (28%)	52 (87%)	16 (27%)
Bres.-Day <sup>1</sup>	0.2368		0.0635	

<sup>1</sup> Centers 2 and 6 were pooled in the analysis in Study 8, and Centers 3 and 4 were pooled in the analysis in Study 10.

Source: Reviewer analysis

**Table 13 – Week 4 ODS Success Rates (Clear/Almost Clear) by Center**

	Study 8		Study 10	
	Clobetasol N=60	Vehicle N=60	Clobetasol N=60	Vehicle N=60
Site 1	9/10 (90%)	0/10 (0%)	8/10 (80%)	0/10 (0%)
Site 2	7/8 (88%)	0/8 (0%)	6/10 (60%)	0/10 (0%)
Site 3	9/12 (75%)	0/12 (0%)	7/8 (88%)	0/8 (0%)
Site 4	8/12 (67%)	0/12 (0%)	4/8 (50%)	0/8 (0%)
Site 5	7/10 (70%)	0/10 (0%)	12/12 (100%)	1/12 (8%)
Site 6	7/8 (88%)	2/8 (25%)	12/12 (100%)	0/12 (0%)
Total	47 (78%)	2 (3%)	49 (82%)	1 (2%)
Bres.-Day <sup>1</sup>	0.6511		NA	

<sup>1</sup> Centers 2 and 6 were pooled in the analysis in Study 8, and Centers 3 and 4 were pooled in the analysis in Study 10.

Source: Reviewer analysis

## 3.2 Evaluation of Safety

### 3.2.1 Extent of Exposure

Most subjects in both treatment arms used treatment for the full 4 weeks. In Study 8, the median number of days of use was 28 on the clobetasol arm (range 2 – 32 days) and the median number of days of use was 29 on the vehicle arm (range 15 - 34 days). One clobetasol subject used treatment for less than 1 week (2 days) and one clobetasol subject used treatment for two weeks (14 days). All other clobetasol subjects in Study 8 used treatment for at least 22 days. Similarly in Study 10, the median number of days of use was 29 on the clobetasol arm (range 1 – 39 days) and the median number of days of use was 29 on the vehicle arm (range 5 - 36 days). One clobetasol subject used treatment for

less than 1 week (1 day) and one clobetasol subject used treatment for about two weeks (16 days). All other clobetasol subjects in Study 10 used treatment for at least 23 days.

### 3.2.2 Adverse Events

The adverse event rates were pretty comparable for both the clobetasol and vehicle arms in the two studies. Over half of the subjects experienced adverse events (Study 8: 52% clobetasol, 48% vehicle; Study 10: 62% clobetasol, 68% vehicle). The adverse event rates for events occurring in at least 3% of subjects per treatment arm are presented in Table 14. The most common adverse event was application site burning, which occurred in approximately 40% of subjects. The reports of burning were similar for the clobetasol and vehicle study arms. The next most common adverse events were upper respiratory tract infection (8% of clobetasol and 2% of vehicle subjects) and nasopharyngitis (5% of clobetasol and 3% of vehicle subjects).

**Table 14 – Adverse Events Occurring in at least 3% of Subjects per Treatment Arm**

	Study 8		Study 10	
	Clobetasol N=60	Vehicle N=60	Clobetasol N=60	Vehicle N=60
All Adverse Events	31 (52%)	29 (48%)	37 (62%)	41 (68%)
Application Site Burning	27 (45%)	24 (40%)	21 (35%)	32 (53%)
Application Site Dryness	0 (0%)	0 (0%)	2 (3%)	0 (0%)
Application Site Pruritus	2 (3%)	1 (2%)	2 (3%)	2 (3%)
Influenza	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Nasopharyngitis	1 (2%)	1 (2%)	5 (8%)	2 (3%)
Upper Respiratory Tract Infection	3 (5%)	0 (0%)	7 (12%)	2 (3%)
Back Pain	2 (3%)	0 (0%)	2 (3%)	2 (3%)
Myalgia	1 (2%)	2 (3%)	1 (2%)	1 (2%)
Headache	1 (2%)	2 (3%)	3 (5%)	1 (2%)
Pharyngolaryngeal Pain	0 (0%)	2 (3%)	0 (0%)	1 (2%)
Eczema Asteatotic	2 (3%)	0 (0%)	0 (0%)	0 (0%)

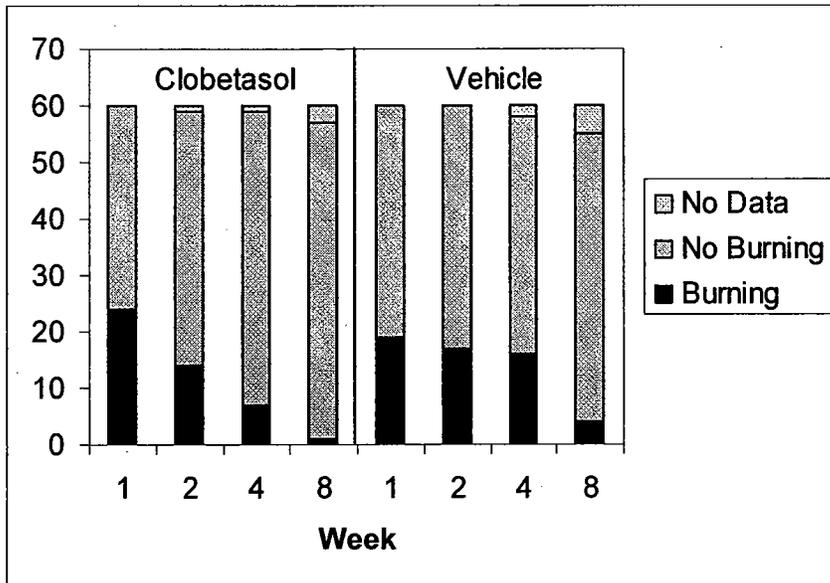
Source: study-report-ti-01-01008.pdf, pg 92-93, and study-report-ti-01-01010.pdf, pg 91-92.

### 3.2.3 Burning/Stinging over Time

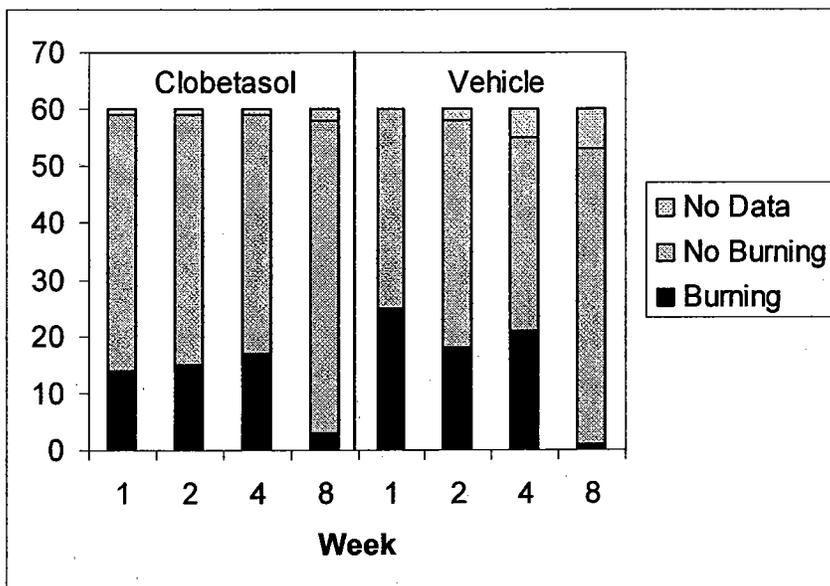
Burning and stinging were the most common adverse events in the clinical trials and occurred at similar rates in both clobetasol and vehicle subjects. The occurrence of burning and stinging was specifically queried by the investigator at each visit. The number of subjects reporting burning or stinging by visit are displayed in Figure 5 and Figure 6. The number of clobetasol subjects reporting burning and stinging decreased throughout the treatment period in Study 8, but slightly increased in Study 10. The rates on the vehicle arm remained fairly constant throughout the treatment period, and were similar to somewhat higher on the vehicle arm than the clobetasol arm. A few subjects reported burning and stinging in the post-treatment period. In the following figures, the Week 1 results combine the reports of burning and stinging within the first 15 minutes of the first application (recorded at the baseline visit) and the reports of burning and stinging

from the first week (recorded at the Week 1 visit). This reviewer also modified the counts slightly from what was presented in the Sponsor's datasets. The reasons for the modifications are detailed in the Appendix.

**Figure 5 – Number of Subjects with Burning/Stinging by Week (Study 8)**



**Figure 6 – Number of Subjects with Burning/Stinging by Week (Study 10)**



## 4 Findings in Special/Subgroup Populations

### 4.1 Gender, Race, and Age

Efficacy does not appear to be affected by gender, race, or age, though the number of non-white and geriatric subjects was very small. The success rates and treatment effects for male and female subjects were similar in the two studies. The Week 2 and Week 4 success rates by gender, race (white/non-white), and age (< 65, ≥ 65) are presented in Table 15 and Table 16.

**Table 15 – Week 2 and 4 Success Rates by Gender, Race, and Age (Study 8)**

		Week 2 <sup>1</sup>		Week 4 <sup>2</sup>	
		Clobetasol	Vehicle	Clobetasol	Vehicle
Gender	Male	31/38 (82%)	8/34 (24%)	29/38 (76%)	0/34 (0%)
	Female	21/22 (95%)	9/26 (35%)	18/22 (82%)	2/26 (8%)
Race	White	50/57 (88%)	15/56 (27%)	45/57 (79%)	2/56 (4%)
	Non-White	2/3 (67%)	2/4 (50%)	2/3 (67%)	0/4 (0%)
Age	< 65 years	48/56 (86%)	13/51 (25%)	45/56 (80%)	1/51 (2%)
	65+ years	4/4 (100%)	4/9 (44%)	2/4 (50%)	1/9 (11%)

<sup>1</sup> Week 2 Success is defined as clear/almost clear/mild on the ODS.

<sup>2</sup> Week 4 Success is defined as clear/almost clear on the ODS.

Source: study-report-ti-01-01008.pdf, pg 82-84.

**Table 16 – Week 2 and 4 Success Rates by Gender, Race, and Age (Study 10)**

		Week 2 <sup>1</sup>		Week 4 <sup>2</sup>	
		Clobetasol	Vehicle	Clobetasol	Vehicle
Gender	Male	28/31 (90%)	9/37 (24%)	26/31 (84%)	1/37 (3%)
	Female	24/29 (83%)	7/23 (30%)	23/29 (79%)	0/23 (0%)
Race	White	42/50 (84%)	15/53 (28%)	39/50 (78%)	1/53 (2%)
	Non-White	10/10 (100%)	1/7 (14%)	10/10 (100%)	0/7 (0%)
Age	< 65 years	47/55 (85%)	15/57 (26%)	44/55 (80%)	1/57 (2%)
	65+ years	5/5 (100%)	1/3 (33%)	5/5 (100%)	0/3 (0%)

<sup>1</sup> Week 2 Success is defined as clear/almost clear/mild on the ODS.

<sup>2</sup> Week 4 Success is defined as clear/almost clear on the ODS.

Source: study-report-ti-01-010010.pdf, pg 81-83.

### 4.2 Other Special/Subgroup Populations

Success rates were slightly higher for subjects with moderate disease at baseline than severe disease, though the number of subjects with severe disease at baseline was fairly small, especially in Study 8. The Week 2 and Week 4 success rates by baseline severity are presented in Table 17.

**Table 17 – Week 2 and 4 Success Rates by Baseline ODS**

	Week 2 <sup>1</sup>		Week 4 <sup>2</sup>	
	Clobetasol	Vehicle	Clobetasol	Vehicle
<b>Study 8</b>				
Moderate	50/56 (89%)	17/53 (32%)	45/56 (80%)	2/53 (4%)
Severe	2/4 (50%)	0/7 (0%)	2/4 (50%)	0/7 (0%)
<b>Study 10</b>				
Moderate	41/45 (91%)	15/48 (31%)	38/45 (84%)	1/48 (2%)
Severe	11/15 (73%)	1/12 (8%)	11/15 (73%)	0/12 (0%)

<sup>1</sup> Week 2 Success is defined as clear/almost clear/mild on the ODS.

<sup>2</sup> Week 4 Success is defined as clear/almost clear on the ODS.

Source: Reviewer analysis.

## 5 Summary and Conclusions

### 5.1 Statistical Issues and Collective Evidence

The sponsor has conducted two studies (Study 8 and Study 10) that consistently and by a large margin demonstrated that clobetasol spray is superior to its vehicle in the treatment of psoriasis. The sponsor conducted the studies under protocols that were agreed upon with the Agency in terms of study design and endpoints. Due to the fact that safety concerns might limit treatment duration to 2 weeks, though the sponsor was interested in labeling for 4 weeks use, the sponsor specified both Week 2 and Week 4 as primary timepoints, using a pre-specified sequence to control multiplicity (success at Week 4 could only be evaluated if success at Week 2 was significant). Subjects were evaluated on the Overall Disease Severity (ODS) scale which was a 5-point (clear, almost clear, mild, moderate, severe/very severe) global evaluation of scaling, erythema, and plaque elevation. A looser definition of treatment success was agreed upon for the Week 2 endpoint (clear/almost clear/mild) than for the Week 4 endpoint (clear/almost clear). The Week 2 and Week 4 success rates were statistically significant in both studies ( $p < 0.0001$ ). Subjects were also evaluated on the individual signs and symptoms of psoriasis (scaling, erythema, plaque elevation, and pruritus). The results on the individual signs and symptoms were consistent with the results on the ODS. The proportion of subjects who were clear or almost clear increased from Week 2 to Week 4 on the clobetasol arm (55% to 78% in Study 8 and 47% to 82% in Study 10), while the clear/almost clear rate on the vehicle arm remained low throughout the treatment period in both studies (0 – 3%). Subjects were also followed four weeks post-treatment. At the Week 8 follow-up visit the clear/almost clear rate on the clobetasol arm dropped to 41% in Study 8 and 57% in Study 10 compared with rates of 3% and 7% on the vehicle arms for the two studies.

### 5.2 Conclusions and Recommendations

Clobetasol spray was statistically superior to vehicle spray in two studies in the treatment of psoriasis. Efficacy was demonstrated after both 2 and 4 weeks of treatment, though success rates (clear/almost clear) were higher after 4 weeks of use than after 2 weeks. Efficacy was evaluated using the following sequence of endpoints to control for multiplicity: (1) Clear/Almost Clear/Mild at Week 2, and (2) Clear/Almost Clear at Week

4. After 2 weeks of treatment, 87% of clobetasol subjects were clear, almost clear, or mild versus 28% of vehicle subjects in Study 8, and 87% of clobetasol subjects were clear, almost clear, or mild versus 27% of vehicle subjects in Study 10. After 4 weeks of treatment, 78% of clobetasol subjects were clear or almost clear versus 3% of vehicle subjects in Study 8, and 82% of clobetasol subjects were clear or almost clear versus 2% of vehicle subjects in Study 10. All of the primary efficacy results were statistically significant at  $p < 0.0001$ . For comparison with the Week 4 clear/almost clear results, at Week 2, 55% of clobetasol subjects were clear or almost clear versus 2% of vehicle subjects in Study 8, and 47% of clobetasol subjects were clear or almost clear versus 0% of vehicle subjects in Study 10.

Adverse event rates were similar on the clobetasol and vehicle arms. The most common adverse event was burning or stinging in the application area, and was reported by approximately 40% of subjects in both the clobetasol and vehicle arms. Reports of burning persisted throughout the treatment period with a slight increase in rates over time in one study and a slight decrease in rates over time in the other study on the clobetasol arm.

### Appendix – Reviewer Changes to Burning/Stinging Counts

This reviewer made the following changes to the burning and stinging counts by visit to adjust for idiosyncrasies in the way data was recorded on the CRFs. This reviewer made changes for the following reasons. (1) Some subjects who discontinued before Week 4 had data recorded on the Week 4 (discontinuation) CRF page and were counted as attending the Week 4 visit in the database, even though the information was from an earlier visit; these subjects were deleted from the counts for Week 4 and counted as having no data. (2) Some subjects missed a visit but at a later visit reported experiencing burning during the window of the missed visit; these subjects were added to the counts for the week of the missed visit rather than being counted as missing.

**Table 18 – Changes to Burning/Stinging Counts due to Missed Visits**

Subject	Treatment	Change	Reason
Study 8			
34	Clobetasol	From Burning to No Data at Week 4	Subject stopped treatment on Day 14 due to complete clearing. Subject reported burning from Day 11-13.
102	Clobetasol	From Burning to No Data at Week 4	Subject discontinued on Day 2. Subject reported burning from Day 0 – 1.
14	Vehicle	From No Data to Burning at Week 1	Subject missed Week 1 visit, but reported burning from Day 0 – 28.
Study 10			
211	Clobetasol	From No Data to Burning at Week 4	Subject missed Week 4 visit, but reported burning from Day 0 – 28.

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## **Signatures/Distribution List**

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Date: 9/14/2005

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