

Clinical Review
 Patricia C. Brown, MD
 NDA 22-013
 Primolux Foam, 0.05% (clobetasol propionate)

Table 36: Subject's Global Assessment (Study 301)

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

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 26.

As noted in the comments for the SPA submitted on 12/7/2004, the Subject's Global Assessment addresses only erythema. Information on the validation of this scale does not appear to be present. This scale is not appropriate for labeling and will not be discussed further.

Table 37: Scoring for Signs of Atopic Dermatitis (Study 301)

Erythema	Definition
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
Induration/ Papulation	
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
Lichenification	
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

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Scaling	
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
Oozing/Crusting	
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

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 25.

Safety Assessments

At each study visit a complete examination of the skin was to be performed as well as assessments for changes in atrophy, striae, telangiectasia, and pigmentation.

Table 38: Assessment of Cutaneous Signs (Study 301)

	None	Mild	Moderate	Severe
Atrophy	None	Skin slightly shiny with barely noticeable transparency.	Shiny thinned skin, vessels transparent; no signs of fragility	Fragile, thinned skin with purpura or erosions; increased transparency with small and deeper vessels detectable
Telangiectasia	None	Few fine, small red blood vessels (0.1 mm or less in diameter)	Several easily visible fine vessels and/or few large vessels (0.2 mm or greater in diameter)	Many prominent fine blood vessels and/or large blood vessels
Pigmentation changes	None	Minimal loss of normal skin color	Partial loss of normal skin color	Total loss of normal skin color
Striae	Absent	Present		

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 26.

Efficacy Endpoints:

Primary Efficacy Parameter:

The primary efficacy endpoint for the study was the proportion of subjects who had the following at Week 2: An ISGA score of 0 or 1, a score of 0 or 1 for both erythema and induration/papulation, and a minimum improvement in the ISGA score of two grades from Baseline to Week 2.

Secondary Efficacy Parameter:

The proportion of subjects who had the following at Week 2: (1) a score of 0 for pruritus, (2) a score of 0 for lichenification, (3) a score of 0 or 1 for erythema, and (4) a score of 0 or 1 for induration/papulation. A reduction of at least two grades was required for success with these endpoints.

The ITT population was defined as all subjects randomized and dispensed study drug. For the primary, secondary, and additional endpoints; the ITT population was used as the primary efficacy analysis population. The Per Protocol Population was defined by the exclusion of subjects who: 1) missed more than 4 applications or 3 consecutive applications of study drug during the treatment period and/or 2) did not have efficacy evaluations at the Baseline and Week 2 visits and/or 3) used prohibited medicines at any time during the study period. The Per Protocol Population was used only for analysis for the primary and secondary endpoints.

Additional evaluations:

The sponsor evaluated a number of additional endpoints only in the ITT population. These included items such as success post-treatment, different definitions of success, and success with other signs.

A number of endpoints were analyzed descriptively.
The endpoints analyzed descriptively will not be discussed further.

Subgroup Analyses:

Subgroup analyses were performed only using the ITT population and only on the primary efficacy endpoint.

Quality of Life:

Quality of life analyses were only performed on the ITT population and were analyzed descriptively.

Efficacy findings

Study CPE.C.301 was conducted at 20 investigational sites in the United States from March 22, 2005 to November 7, 2005. In total, 377 subjects were randomly assigned to one of two drug treatments: 251 to EF Clobetasol Foam and 126 to Vehicle Foam. Enrollment and disposition of subjects are summarized by treatment group for the ITT population in Table 39.

Table 39: Subject Disposition (ITT Population Study 301)

	EF Clobetasol Foam	Vehicle Foam
Number of Subjects	251	126
Subjects who completed study treatment	239 (95%)	106 (84%)
Number of subjects at each visit		
Baseline (Day 1)	248 (99%)	124 (98%)
Week 1	246 (98%)	118 (94%)
Week 2	241 (96%)	113 (90%)
Post-treatment follow-up (Week 4)	239 (95%)	106 (84%)
Subjects who terminated study early	12 (5%)	20 (16%)
Reasons for discontinuation		
Adverse experience	1 (<1%)	3 (2%)
Subject non-compliance	1 (<1%)	1 (1%)
Disease progression	1 (<1%)	7 (6%)
Subject request to withdraw	2 (1%)	5 (4%)
Other	7 (3%)	4 (3%)

Note: Five subjects were dispensed drug but their baseline date and information were not recorded. Also, 8 subjects had a missing TERM CRF page due to Hurricane Katrina and were coded as 'Early Termination'.

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 39.

Overall, more subjects from the vehicle arm terminated early from the study, 20 (16%), than from the EF Clobetasol arm, 12 (5%). The most common reasons for vehicle arm termination were disease progression and subject request to withdraw. Subjects withdrawing for reasons described as "Other" included 7 (3%) from the active arm and 4 (3%) from the vehicle arm. This category included subjects lost to follow-up 2 (1%) in the active arm and 1 (1%) in the vehicle arm. Due to the effects of hurricane Katrina, data was lost for 3 subjects (1%) in the active arm and 2 subjects (2%) in the vehicle arm. Partial loss of data for 3 additional subjects from this site also occurred due to the hurricane.

Protocol deviations:

Overall, protocol deviations were reported for 39 (10%) of subjects enrolled in the study. This included 21 (8%) in the EF Clobetasol arm and 18 (14%) in the vehicle arm. Among the deviations were; not meeting eligibility criteria 5 (1%) of subjects, use of prohibited medications by 7 (2%) of subjects, procedural deviations 19 (5%) of subjects, and missing more than 5 applications or 3 consecutive applications of study drug 8 (2%) of subjects.

Protocol Changes during the Study:

The inclusion criteria for pruritus in protocol Amendment 2 (dated March 4, 2005) was that a subject's assessment of pruritus score be 2 or greater. Investigators informed the sponsor that this requirement might be limiting enrollment. Connetics decided to remove this inclusion criterion since in the SPA Meeting March 2, 2005; "The sponsor acknowledged that their proposed secondary endpoint, the proportion of subjects with a pruritus score of 0 at week 2, would not have regulatory utility."⁶ This change was included in the protocol Amendment 3, dated June 28, 2005. Investigative sites were notified of this change on May 25, 2005. Before the change, 95 subjects had been randomized to EF Clobetasol foam and 45 to vehicle foam. After the change 153 subjects were randomized to EF Clobetasol foam and 79 to vehicle foam.⁷ An analysis by the FDA biostatistician shows that a higher proportion of subjects 9/140 (6%) were enrolled with pruritus scores of 0 or 1 before the change than after, 8/232 (3%).

Furthermore, efficacy results under the two sets on inclusion criteria were similar:

Table 40: Efficacy Results and Pruritus Inclusion Criteria (Study 301)

Treatment Success	Before Criteria Change	After Criteria Change
EF Clobetasol Foam	51% (48/95)	54% (83/153)
Vehicle Foam	16% (7/45)	14% (11/79)

Source: Based on analysis by Kathleen Fritsch, Statistical Review and Evaluation, NDA 22-013, p. 16.

A third amendment to the protocol, dated June 28, 2005, changed the criteria for success on the secondary endpoints to require a reduction of at least two grades. This affected about a third of the patients in the study. An analysis has been performed by the FDA biostatistician to show the effect of not requiring a two grade reduction from baseline for the secondary endpoints.

Table 41: Success on secondary Efficacy Endpoints (Study 301)

	Clobetasol Foam N= 251	Vehicle Foam N= 126	p-value
Pruritus = 0	109 (43%)	13 (10%)	<0.0001
Lichenification = 0	86 (34%)	15 (12%)	<0.0001
Erythema = 0 or 1	156 (62%)	27 (21%)	<0.0001
Induration/Papulation = 0 or 1	182 (73%)	28 (22%)	<0.0001

Definitions of success do not require reduction of at least two grades from baseline.

Source: Kathleen Fritsch, FDA biostatistician.

As shown, the rates on both arms increase by roughly the same amount for each endpoint. Please compare with Table 50.

⁶ Connetics; NDA 22-013/Amendment 002, EF Clobetasol Foam, 0.05%, Response to Filing Communication, June 9, 2006, p.42.

⁷ *Ibid*, p. 43.

Analysis Populations:

The ITT population was defined as all subjects randomized and dispensed study drug. For the primary, secondary, and additional endpoints; the ITT population was used as the primary efficacy analysis population. The Per Protocol Population was defined by the exclusion of subjects who: 1) missed more than 4 applications or 3 consecutive applications of study drug during the treatment period and/or 2) did not have efficacy evaluations at the Baseline and Week 2 visits and/or 3) used prohibited medicines at any time during the study period. The Per Protocol Population was used only for analysis for the primary and secondary endpoints. It was also used to make certain that the results were not driven by the method of dealing with missing responses.

Demographic and Baseline Characteristics:

The treatment groups in the ITT population were generally balanced with regard to baseline age, age category, and baseline weight. More females 239 (63%) than males 133 (35%) were enrolled in the study. Additionally, more females (67%) were randomized to EF Clobetasol foam than to vehicle foam (56%). Of note, 101 (27%) of subjects enrolled were in the age category 12 to < 18 years.

**Table 42: Demographic Information and Baseline Weight
 (ITT Population Study 301)**

	EF Clobetasol Foam	Vehicle Foam
Number of Subjects	251	126
Age		
n	248	123
mean (std)	35.0 (18.6)	35.7 (18.5)
median	33.0	34.0
min, max	(12.0,78.0)	(12.0,81.0)
Age Category		
Missing †	3 (1%)	3 (2%)
12 < 18 years	69 (27%)	32 (25%)
18 < 65 Years	157 (63%)	79 (63%)
≥ 65 Years	22 (9%)	12 (10%)
Gender		
Missing †	3 (1%)	2 (2%)
Male	80 (32%)	53 (42%)
Female	168 (67%)	71 (56%)
Race		
Missing†	3 (1%)	2 (2%)
Caucasian	148 (59%)	74 (59%)
African-American	69 (27%)	31 (25%)

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Hispanic	13 (5%)	8 (6%)
Asian	11 (4%)	7 (6%)
Other	7 (3%)	4 (3%)
Weight (kg)		
n	248	124
mean (std)	77.41 (22.60)	79.24 (21.39)
median	76.61	76.05
min, max	(33.6,164.0)	(42.2,141.2)

†Demographic data on 5 subjects missing due to Hurricane Katrina.

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 42.

The treatment groups in the ITT population were balanced with respect to Baseline ISGA score and extent of atopic dermatitis. Most subjects had a moderate ISGA score (86% active arm, 88% vehicle arm) at baseline. The median percentage of body surface area (% BSA) involved was 9% for active and 8.5 % for vehicle.

Table 43: Baseline ISGA and % BSA (ITT Population Study 301)

	EF Clobetasol Foam	Vehicle Foam
Number of Subjects	251	126
Investigator's Static Global Assessment Score		
Moderate	217 (86%)	111 (88%)
Severe	31 (12%)	13 (10%)
Missing	3 (1%)	2 (2%)
Extent of Atopic Dermatitis (% BSA)		
n	248	124
mean (std)	14.9 (16.1)	13.8 (13.1)
median	9.0	8.5
min, max	(5,98)	(5,70)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 43.

With respect to Baseline assessments of erythema, induration/papulation, oozing/crusting, lichenification, and scaling the treatment arms in the ITT population were balanced.

Table 44: Baseline Erythema, Induration/Papulation, Oozing/Crusting, Lichenification, and Scaling Scores (ITT Population Study 301)

	EF Clobetasol Foam	Vehicle Foam
Number of Subjects	251	126
Erythema		
Minimal	1 (0%)	2 (2%)
Mild	45 (18%)	19 (15%)
Moderate	176 (70%)	90 (71%)
Severe	26 (10%)	13 (10%)
Missing	3 (1%)	2 (2%)
Induration/papulation		
Absent	0 (0%)	1 (1%)
Minimal	9 (4%)	4 (3%)
Mild	65 (26%)	39 (31%)
Moderate	153 (61%)	70 (56%)
Severe	21 (8%)	10 (8%)
Missing	3 (1%)	2 (2%)
Oozing/Crusting		
Absent	66 (26%)	32 (25%)
Minimal	78 (31%)	36 (29%)
Mild	60 (24%)	36 (29%)
Moderate	37 (15%)	18 (14%)
Severe	7 (3%)	2 (2%)
Missing	3 (1%)	2 (2%)
Lichenification		
Absent	13 (5%)	6 (5%)
Minimal	34 (14%)	19 (15%)
Mild	77 (31%)	42 (33%)
Moderate	104 (41%)	46 (37%)
Severe	20 (8%)	11 (9%)
Missing	3 (1%)	2 (2%)
Scaling		
Absent	9 (4%)	5 (4%)

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Minimal	54 (22%)	25 (20%)
Mild	94 (37%)	54 (43%)
Moderate	85 (34%)	37 (29%)
Severe	6 (2%)	3 (2%)
Missing	3 (1%)	2 (2%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, pp. 44, 45.

With respect to baseline grades for skin atrophy, striae, telangiectasia, and pigmentation change, the treatment arms in the ITT population were balanced.

Table 45: Baseline Cutaneous Signs (ITT Population Study 301)

	EF Clobetasol Foam	Vehicle Foam
Number of Subjects	251	126
Atrophy		
None	217 (86%)	106 (84%)
Mild	29 (12%)	17 (13%)
Moderate	2 (1%)	0 (0%)
Severe	0 (0%)	1 (1%)
Missing	3 (1%)	2 (2%)
Telangiectasia		
None	237 (94%)	113 (90%)
Mild	10 (4%)	11 (9%)
Moderate	1 (0%)	0 (0%)
Missing	3 (1%)	2 (2%)
Pigmentation Change		
None	160 (64%)	84 (67%)
Mild	49 (20%)	19 (15%)
Moderate	38 (15%)	20 (16%)
Severe	1 (0%)	1 (1%)
Missing	3 (1%)	2 (2%)
Striae		
Absent	233 (93%)	115 (91%)
Present	15 (6%)	9 (7%)
Missing	3 (1%)	2 (2%)

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Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 46.

Treatment Compliance:

Among the subjects treated with clobetasol foam, 59% did not miss any treatment applications while 40% reported missing at least one application. Among those treated with vehicle foam, 61% did not miss any treatment applications while 37% reported missing at least one treatment application.

Efficacy Endpoint Outcomes:

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Success Rate

Primary Efficacy Endpoint

EF Clobetasol Foam was superior to vehicle foam as measured by subjects achieving treatment success at week 2. This finding held true for both the ITT and Per Protocol populations.

Table 46: Subjects with Treatment Success at Week 2 (Study 301)

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

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

Note: Success is defined as the proportion of subjects who have the following at Week 2: An ISGA score of 0 or 1, a score of 0 or 1 for both erythema and induration/papulation, and a minimum improvement in the ISGA score of 2 grades from Baseline to Week 2.

Treatment success was analyzed with a Cochran-Mantel-Haenszel test on pooled center.

Source: Kathleen Fritsch, Biostatistician, FDA, statistical Review and Evaluation, NDA 22-013, Table 9.

Both the FDA and the sponsor analysis are in agreement regarding the results of the primary efficacy endpoint.

As previously agreed upon, this study uses a composite endpoint consisting of four components at week 2; an ISGA score of 0 or 1, a minimum improvement in the IGSA score of 2 grades from baseline to week 2, and a score of 0 or 1 for both erythema and induration/papulation. To be noted the ISGA itself includes erythema, induration/papulation, and oozing/crusting.

Table 47: Response for Individual Components of Composite Primary Endpoint at Week 2 (ITT Population Study 301)

	EF Clobetasol Foam	Vehicle Foam
Number of Subjects	251	126
Success ITT	131(52%)	18 (14%)
ISGA Score of 0 or 1	149 (59%)	20 (16%)
Erythema Score of 0 or 1	156 (62%)	27 (21%)
Induration/papulation score of 0 or 1	182 (73%)	28 (22%)
Minimum 2 Grade Improvement	160 (64%)	21 (17%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, pp. 54, 55.

As shown in Table XXX success rates for the individual components of the primary endpoint were higher than the overall success rate. As stated by the FDA statistician, the overall definition of success was largely driven by the IGSA in this study. "In Study 301.....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'."⁸

Combined Site Analysis:

Study sites, originally 20, were combined prior to unblinding if enrollment was less than 10 subjects per treatment group per site. This resulted in 7 combined investigational sites. Combination was based on geographical and climate similarities.

All of the results from the pooled centers favored EF Clobetasol Foam over Vehicle Foam. Three of the pooled centers had larger treatment effects than the other four pooled centers. According to the FDA analysis the Breslow-Day test was significant with a p-value of 0.0013. According to the FDA biostatistician the significance of the treatment center interaction appears to be related to the magnitude of the treatment effect rather than the direction. If the three largest centers are removed from the analysis the results of the primary analysis are still significant. See FDA biostatistician's review, p. 19.

Subgroup Analyses:

Subgroup analyses were performed on subjects in the ITT population and included; gender, race, age cohort and baseline ISGA score. The results of subgroup analysis for gender, age cohort, and race are shown in Table 48. As shown, treatment effects are generally consistent across these subgroups.

⁸ Kathleen Fritsch, FDA, Statistical Review and Evaluation, NDA 22-013, p. 13.

Table 48: 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%)

†For purposes of analysis, Hispanic and Asian subjects were combined with the “Other” race category.

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 24.

Subjects with severe disease at baseline showed less treatment success than those with moderate disease as defined by ISGA. This is most likely a result of the requirement that the ISGA score be 0 or 1 for success in the composite primary efficacy endpoint. To meet this requirement, subjects with baseline severe disease (ISGA 4) would have to improve by 3 grades as opposed to only two grades for those of baseline moderate severity (ISGA 3).

Table 49: Treatment Success at Week 2 by Baseline Severity (Study 301)

	EF Clobetasol Foam	Vehicle Foam
Overall Success		
n (% success)	131/251 (52%)	18/126 (14%)
Moderate (ISGA = 3)		
n (% success)	122/217 (56%)	18/111 (16%)
Severe (ISGA = 4)		
n (% success)	9/31 (29%)	0/13 (0%)

Data for 3 subjects in EF Clobetasol Foam group and 2 subjects in Vehicle Foam group were not available due to effects of hurricane Katrina.

Source: Sponsor’s NDA submission, module 5, Final Study Report CPE.C.301, adapted from Table 27, p.63.

Secondary Efficacy Analysis:

The four secondary endpoints included the proportion of subjects who had the following at Week 2: (1) a score of 0 for pruritus, (2) a score of 0 for lichenification, (3) a score of 0 or 1 for erythema, and (4) a score of 0 or 1 for induration/papulation. A reduction of at least two grades at week 2 was required for success with these endpoints. As shown in Table 50, EF Clobetasol Foam was superior to vehicle foam for all four secondary endpoints.

Table 50: Success¹ 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

¹ All definitions of success required at least 2 grades reduction from baseline.

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 13.

Note, under Amendment 3 of the protocol, subjects could enter with a pruritus score of less than two at baseline. Amendment 3 also made the change to require at least a 2 grade reduction for success. Subjects with pruritus less than 2 at baseline were considered failures in the pruritus analysis regardless of their final pruritus score. From the table above (Table XX), 104 Clobetasol foam subjects and 10 vehicle subjects all had ≥ 2 pruritus at baseline and 0 at week 2. If subjects with 0 or 1 pruritus at baseline are counted as successes, having 0 pruritus at Week 2, the success rates would be: EF Clobetasol foam 109/251 (43%), Vehicle foam 13/126 (10%). The lichenification analysis has the same issue. About 20% of subjects had 0 or 1 lichenification at baseline and these subjects were counted as failures since they could not achieve 2 grade reductions. The analyses of erythema and induration/papulation also have the same issue, however the numbers are smaller. Only 1% of subjects came in with erythema scores less than 2 and only 4% of subjects came in with induration/papulation scores less than 2.

Safety:

There were no deaths reported in this study.

One serious adverse event, streptococcal pneumonia, was reported in the EF Clobetasol foam group. A 78 year old white female (subject 109-1417) was enrolled May 10, 2005, randomized to EF Clobetasol foam, underwent study treatment, and discontinued study drug. The subject's medical history was remarkable for hypertension, hypothyroidism, asthma, hysterectomy, renal insufficiency, insomnia, allergic rhinitis, depression, pneumonia in January 2004, penicillin and sulfa allergy, history of previous right leg vein graft surgery following an infection requiring skin grafts, history of smoking (quit 30 years ago), and anxiety. After discontinuing study drug, the patient was found at home, in a state of confusion. The same day, the subject was admitted to the hospital and was found to have a right upper lobe streptococcal pneumonia. The subject was treated with IV antibiotics. The subject also developed respiratory failure and was placed on mechanical ventilation. Additionally, during the course of hospitalization, the subject developed sepsis. The subject recovered and was discharged. The investigator considered the event of streptococcal pneumonia and the subsequent events as not related to study drug.

Four, (1%), of subjects discontinued from the study due to adverse events. In the EF-Clobetasol foam group, one subject, 301-110-1474, had moderate application site urticaria, considered to be

probably related to study drug. In the vehicle foam group, 3 subjects discontinued prematurely. Subject 301-102-1052 experienced irritant contact dermatitis, definitely related to study drug. Subject 301-103-1113 experienced generalized increased pruritus, possibly related to study drug. Subject 301-117-1835 experienced bacterial infection of atopic dermatitis classified as probably not related to study drug. However, this subject initially experienced itching. On this subject's CRF, the relationship of the itching to study drug is reported as probably related and the action taken as permanent withdrawal of study drug.

Severe adverse events were reported by 1% (2/251) subjects in the EF Clobetasol foam group. One of these was considered treatment related (15 year old subject 117-1830, probably related to study drug) and consisted of a severe application site reaction (stinging on neck area after study drug application and lasting less than one minute). The other was the case of subject 109-1417, discussed above (78 years old), having streptococcal pneumonia and subsequent sepsis (classified as a severe adverse event), events not considered related to study drug.

A severe adverse event was experienced by 1% (1/126) of subjects in the vehicle foam group. This event consisted of a hand fracture, considered not to be related to study drug.

Common adverse events:

During the study, 20% (51/251) of subjects in the EF Clobetasol foam arm reported adverse events. Of these the investigator considered 8% (21/251) to be treatment related. In the vehicle foam arm, 17% (21/126) of subjects reported adverse events. Of these the investigator considered 10% (13/126) to be treatment related. Local adverse events are shown in Table 51.

Table 51: Local Adverse Events (Study 301)

SYSTEM ORGAN CLASS Preferred Term	EF Clobetasol Foam	Vehicle Foam	Total	p-value ^a
Number of Subjects	251	126	377	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Application site atrophy	5(2%)	1(1%)	6(2%)	
Application site burning	1(< 1%)	1(1%)	2(1%)	
Application site dermatitis	1(< 1%)	1(1%)	2(1%)	
Application site dryness	1(< 1%)	0(0%)	1(< 1%)	
Application site eczema	0(0%)	2(2%)	2(1%)	
Application site erythema	0(0%)	1(1%)	1(< 1%)	
Application site pain	1(< 1%)	0(0%)	1(< 1%)	
Application site pigmentation changes	2(1%)	0(0%)	2(1%)	
Application site pruritus	1(< 1%)	6(5%)	7(2%)	0.0031
Application site reaction	5(2%)	2(2%)	7(2%)	
Application site urticaria	1(< 1%)	0(0%)	1(< 1%)	

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INFECTIONS AND INFESTATIONS			
Application site folliculitis	1(< 1%)	0(0%)	1(< 1%)
Application site infection	1(< 1%)	0(0%)	1(< 1%)
Folliculitis	1(< 1%)	0(0%)	1(< 1%)
Dermatitis Infected	0(0%)	1(1%)	1(< 1%)
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS			
Excoriation	2(1%)	0(0%)	2(1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Skin burning sensation	0(0%)	1(1%)	1(< 1%)
Telangiectasia	1(< 1%)	0(0%)	1(< 1%)
Heat rash	1(< 1%)	0(0%)	1(< 1%)
Telangiectasia	2(1%)	0(0%)	2(1%)

^a P-values are based on comparing EF Clobetasol Foam versus Vehicle Foam based on the Chi-Square test ($\alpha = 0.10$) and are calculated when the incidence is at least five percent in any one treatment group.

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, adapted from Table 57, pp. 97-100.

Local adverse events are notable for 5(2%) of subjects showing application site atrophy in the EF Clobetasol foam arm and for 6(5%) showing application site pruritus in the Vehicle foam arm.

Changes in skin signs (atrophy, striae, telangiectasia, and pigmentation) were evaluated for the ITT population at Baseline, Week 1, Week 2, and 2 weeks post-treatment. With respect to baseline grades for these signs, the treatment arms in the ITT population were balanced. Please see Table 45.

Table 52: Grade Change in Atrophy at Week 2 (Study 301)

Week 2	EF Clobetasol Foam	Vehicle Foam
Missing	11 (4%)	13 (10%)
1-Grade Improvement	4 (2%)	4 (3%)
No Change	232 (92%)	108 (86%)
1-Grade Worsening	4 (2%)	1 (1%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 116.

Table 53: Subjects with Striae Present (Study 301)

	EF Clobetasol Foam	Vehicle Foam
Number of Subjects	251	126
Baseline	15 (6%)	9 (7%)
Week 2	14 (6%)	6 (5%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 117.

Table 54: Grade Change in Telangiectasia at Week 2 (Study 301)

Week 2	EF Clobetasol Foam	Vehicle Foam
Missing	11 (4%)	13 (10%)
1-Grade Improvement	3 (1%)	1 (1%)
No Change	237 (94%)	112 (89%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 118.

Table 55: Grade Change in Pigmentation at Week 2 (Study 301)

Week 2	EF Clobetasol Foam	Vehicle Foam
Missing	12 (5%)	13 (10%)
2-Grade Improvement	4 (2%)	1 (1%)
1-Grade Improvement	19 (8%)	6 (5%)
No Change	203 (81%)	106 (84%)
1-Grade Worsening	13 (5%)	0 (0%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 119.

The results with the evaluation of skin signs present a mixed picture with generally small overall changes. For the EF Clobetasol foam groups a 1% excess of worsening was noted as compared with vehicle foam for atrophy and striae. For telangiectasia no worsening was noted. For pigmentation a 5% excess of worsening was noted as compared with vehicle foam. This was noted in the context of a 1% excess in 2-grade improvement and a 3% excess in one-grade improvement compared with vehicle foam.

The FDA biostatistician has performed an analysis of worsening of cutaneous signs from baseline at any visit (Week 1, 2, or 4).

Table 56: 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%)

Source: Kathleen Fritsch, Statistical Review and Evaluation, NDA 22-013, Table 22, p. 24.

According to this analysis the rates of worsening for EF Clobetasol foam were 1% higher than for Vehicle foam for atrophy and telangiectasia (and less than 1% higher for striae). The rate of worsening for EF Clobetasol foam was 2% higher than Vehicle foam for pigmentation. These results do not differ greatly from the Week 2 analysis.

Extent of exposure (dose/duration):

Table 57: Study Drug Exposure (ITT Population Study 301)

	EF Clobetasol Foam	Vehicle Foam
Number of Subjects	251	126
Days on study drug	N = 248 ¹	N = 124 ¹
mean (std)	15.1 (3.0)	14.2 (3.2)
range	1 - 36	1 - 22
Study Drug Usage(g)	N = 243	N = 121
mean (std)	69.25 (39.57)	72.99 (39.57)
range	4.1 - 188.2	5.2 - 179.4
Daily Mean Drug Usage(g)	N = 243	N = 121
mean (std)	4.66 (2.77)	5.09 (2.63)
range	0.4 - 15.1	0.4 - 12.8
No. > 50 g/week ²	56 (23%)	24(20%)

Note: Study drug usage is defined as total container weight dispensed minus total container weight returned. Mean drug usage is defined as the average amount of drug subjects use per study day.

¹ Complete dosing information was not available for 3 (1%) subjects in the EF Clobetasol Foam group and 2 (2%) subjects in the Vehicle Foam group because these subjects were lost to follow-up following Hurricane Katrina.

² Number of subjects using > 100g during study or > 50 g if treated period was 1 week or less. (Analysis of this information provided by Kathleen Fritsch, Statistical Review and Evaluation, NDA 22-013, Table 18, p. 21.

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, adapted from Table 56, p. 95.

In study CPE.C.301 the total study drug used and the mean daily dose was similar for the EF Clobetasol foam arm and the vehicle foam arm. Note also that a similar percentage of subjects in both study arms (23% versus 20%) used more than 100 grams of study drug during the treatment period.

Adverse Experiences for Subjects 12 to < 18 Years Old

As stated in the minutes from the End-of-Phase 2 meeting (11/29/2004); "Approval will largely rest upon adequate demonstration of safety in the pediatric population." The sponsor has enrolled 101 (27%) of subjects in the 12 to < 18 year old age group in study CPE.C.301.

In the pediatric age group studied there were no deaths and no serious adverse events.

One subject in the pediatric age group studied discontinued study participation because of an adverse event. This subject, 301-117-1835, was randomized to the vehicle foam group experienced bacterial infection of atopic dermatitis, probably not related to study drug, and moderate itching lasting 30 minutes after study medicine application, probably related to study drug.

A severe application site reaction was experienced by one subject in the EF Clobetasol foam group. This reaction (considered to be probably related to study drug) was reported as stinging on the neck area after study medication application and lasting less than one minute.

Common Adverse Events (Subjects 12 to < 18 years old):

During the study, 23% (16/69) of pediatric subjects in the EF Clobetasol foam arm reported adverse events. In the vehicle foam arm, 13% (4/32) of subjects reported adverse events.

Local adverse events for the pediatric age group are shown in Table 58.

Table 58: Local Adverse Events (Age 12 to < 18 years), ITT Population Study 301

SYSTEM ORGAN CLASS Preferred Term	EF Clobetasol Foam	Vehicle Foam	Total
Number of Subjects	69	32	101
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Application site pruritus	1(1%)	2(6%)	3(3%)
Application site reaction	3(4%)	0(0%)	3(3%)
INFECTIONS AND INFESTATIONS			
Application site infection	1(1%)	0(0%)	1(1%)
Dermatitis infected	0(0%)	1(3%)	1(1%)
Folliculitis	1(1%)	0(0%)	1(1%)
Herpes ophthalmic	1(1%)	0(0%)	1(1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Excoriation	2(3%)	0(0%)	2(2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Skin atrophy	1(1%)	0(0%)	1(1%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, adapted from Table 61, pp. 108-9.

The local adverse events for the pediatric age group studied, as shown in Table XX, do not differ substantially in nature or in number from those reported for all age groups.

Changes in skin signs (atrophy, striae, telangiectasia, and pigmentation) were evaluated for the ITT population. In the pediatric age group studied (12 to < 18 years old) changes in these signs

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from baseline to Week 2 were generally small and did not differ meaningfully from the changes noted in the general study population.

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10.1.2 Pivotal Study: CPE.C.302

Title: "A Multicenter, Randomized, Double-Blinded Study of the Safety and Efficacy of Ethanol-Free Clobetasol Propionate Foam, 0.05%, versus Vehicle Foam and Temovate® (clobetasol propionate) Ointment, 0.05%, (Investigator-Blinded) in the Treatment of Mild to Moderate Plaque-Type Psoriasis"

Investigators:

Table 59: Investigators CPE.C.302 or Study 302

Site Number	Investigator	Center	Patients Enrolled N = 497
201	Alicia Barba, MD	International Dermatology Research Miami, FL	28 (6%)
202	Debra Breneman, MD	University Dermatology Consultants, Inc. Cincinnati, OH	31 (6%)
203	Ellen Frankel, MD	Clinical partners, LLC Johnston, RI	32 (6%)
204	Toni Funicella, MD	Derm Research, Inc. Austin, TX	25 (5%)
205	Michael Gold, MD	Tennessee Clinical Research Center Nashville, TN	30 (6%)
206	Terry Jones, MD	Terry Jones, MD, PA Bryan, TX	14 (3%)
207	Robert Kalb, MD	Buffalo Medical Group Williamsville, NY	4 (1%)
208	Steven Kempers, MD	Minnesota Clinical Study Center Fridley, MN	47 (9%)
209	Alexa Boer Kimball, MD, MPH	Brigham and Women's Hospital Boston, MA	41 (8%)
210	Christopher Moeller, MD	Compliant Clinical Research, Inc. Wichita, KS 67206	42 (8%)
211	John Proffitt, MD	Compliant Clinical Research Shawnee, KS	43 (9%)
212	Thomas J. Russell, MD	Affiliated Dermatologists, S.C. Milwaukee, WI	24 (5%)
213	Brett C. Shulman, MD	The Center for Dermatology Rochester, NY	23 (5%)
214	Stacy R. Smith, MD	Therapeutics Clinical Research San Diego, CA	36 (7%)
215	Leonard Swinyer, MD, PC	Dermatology Research Center Salt Lake City, UT	23 (5%)
216	Cindy Lamerson, MD	Nevada Center for Dermatology Reno, NV	8 (2%)
217	Steven Andrew Davis, MD	Dermatology Clinical Research Center of San Antonio San Antonio, TX	18 (4%)
218	David Pariser, MD	Virginia Clinical Research, Inc. Norfolk, VA	5 (1%)

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219	Paul Yamauchi, MD	Southern California Dermatology Santa Monica, CA	-
220	Bernard Goffe, MD	Dermatology Associates, PLLC Seattle, WA	6 (1%)
221	Zoe Diana Draelos, MD	2444 N. Main St High Point, NC	17 (3%)

Source: Sponsor's NDA submission module 5, Final Study Report CPE.C.302, pp. 125, 412, 413.

Objectives: The objectives of this study were to evaluate the safety and efficacy of Emulsion Formulation Clobetasol Propionate Foam, 0.05% (EF Clobetasol Foam) by demonstrating the superiority of EF Clobetasol Foam to its vehicle in subjects 12 years and older with mild to moderate plaque-type psoriasis. In addition, Temovate® (clobetasol propionate) Ointment, 0.05%, was included as a RLD to establish a clinical bridge to the safety database of Temovate Ointment by showing non-superior efficacy and comparable safety of EF Clobetasol Foam compared to Temovate Ointment. A vehicle ointment arm was not included in the study since there was no intention to establish comparative efficacy to RLD for the purpose of making claims.

Study Design: This was conducted as a 21 (only 20 enrolled subjects) center, randomized, trial comparing EF Clobetasol Foam to vehicle foam (double-blind) and to Temovate® Ointment (investigator-blinded). Subjects were 12 years of age and older and had mild to moderate plaque-type psoriasis. Qualified subjects were randomized into one of three parallel treatment groups in a 2:1:1 ratio (EF Clobetasol Foam: Temovate Ointment: Vehicle Foam). Subjects applied study drug twice daily for two weeks to cover all lesions (excluding face, scalp, and intertriginous areas). Study visits were Baseline, Week 1, Week 2, and two weeks post-treatment (Week 4).

Protocol:

Subjects were not enrolled under the original protocol or the first amendment. Subjects were enrolled under the second amendment to the protocol. After the first subject was enrolled no further amendments were made to the protocol.

The remainder of the review will address the protocol version including the second amendment.

Inclusion Criteria:

1. Male or female subjects at least 12 years old and in good general health.
2. Mild to moderate plaque-type psoriasis, as defined by an ISGA score of 2-3 at Baseline (Table XX) involving less than or equal to 10% of total BSA, excluding the face, scalp, and intertriginous areas.
3. Subjects must have a target lesion (> 2 cm²) on the trunk or extremities (excluding palms/soles) with a score of 2-3 (on a 0 to 5 scale) for each of erythema, scaling, and plaque thickness (Table XX).
4. The ability and willingness to follow all study procedures, attend all scheduled visits, and successfully complete the study.
5. The ability to understand and sign a written informed consent form, which must be obtained prior to treatment.

6. The ability to understand and sign a HIPAA authorization form which shall permit the use and disclosure of subject's individually identifiable health information.

Exclusion Criteria:

1. Known allergy to clobetasol propionate or other topical corticosteroids; or to any component of the investigational formulations.
2. Other serious skin disorder or any chronic condition that is not well controlled.
3. Use of systemic anti-psoriatic therapy (e.g., corticosteroids, psoralen and ultraviolet A [PUVA], ultraviolet B [UVB], retinoids, methotrexate, cyclosporine) or biologics (e.g., alefacept, etanercept, adalimumab) within the past 4 weeks.
4. Use of topical treatments which have a known beneficial effect on psoriasis, including but not limited to corticosteroids, retinoids, Vitamin D derivatives, tar, or anthralin, within the past 2 weeks.
5. Introduction or change in dosage of systemic medications for other medical conditions that are known to affect psoriasis (e.g., lithium, beta-adrenergic blockers, etc.) within the past 4 weeks.
6. Use of any investigational therapy within the past 4 weeks.
7. Pregnant women, women who are breast feeding, or women of childbearing potential who are not practicing an acceptable method of birth control (abstinence, birth control pill, patch, implant, barrier with spermicidal jelly, intrauterine device, etc.), as determined by the Investigator. An acceptable method of birth control must be used during the entire study.
8. Current drug or alcohol abuse (drug screening not required).
9. Any other condition which, in the judgment of the Investigator, would put the subject at unacceptable risk for participation in the study.

Concomitant Medications/Allowed Therapy:

- 1) The use of concomitant medications for other medical conditions (e.g., hypertension, diabetes, acute infections, etc.) was permitted during this study.
- 2) The use of topical and systemic antihistamines was permitted as long as the subject had not changed dose or drug within the past 2 weeks and did not expect to change the dose or discontinue use during the study.
- 3) Use of inhaled/intranasal steroids was permitted prior to and during the conduct of the study if already being used by the subject.
- 4) Only a bland moisturizer such as Eucerin Cream was permitted for use on areas that were not to be treated with study drug (i.e., the face, scalp, and intertriginous areas). The bland moisturizer could be used between applications on areas to be treated with the study drug, but not within 4 hours of a study visit.

Proscribed Therapy:

- 1) Other than the study drugs, no concomitant topical treatment to psoriatic lesions was permitted.
- 2) The introduction of drugs or therapies for other medical conditions that are known to affect psoriasis (e.g., corticosteroids, PUVA, UVB, cyclosporine, azathioprine, methotrexate, etc.) was not permitted during the study.

Withdrawal Criteria:

- 1) Intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree, require discontinuation of drug, or both
- 2) Unacceptable toxicity
- 3) Subject noncompliance
- 4) Subject's request to withdraw

Blinding:

Study CPE.C.302 was designed as a randomized, vehicle controlled trial. With respect to the use of EF Clobetasol Foam or vehicle foam, the study was double-blind. With respect to the use of Temovate Ointment, the study was investigator-blind. The study drug treatments, EF Clobetasol Foam and vehicle foam, were packaged in identically appearing containers to ensure that, for these treatments, neither the subject nor the study nurse/coordinator nor the Investigator would know the identity. The study drug, Temovate Ointment, was packaged in over-labeled 60 gram tubes and subjects and study coordinators were aware that the subject was receiving either foam or ointment. Subjects and study coordinators were not to divulge treatment assignments to the Investigator/assessor.

Study Procedures:

Subjects were to apply study treatments twice daily (morning and evening) for two weeks. Subjects were to be instructed to apply the amount of study drug sufficient to cover all lesions (excluding the face, scalp, and intertriginous areas), and not to exceed using 50 g of study drug per week.

Each study subject was assigned one kit containing either two cans of EF Clobetasol Foam (Batch number UFB-1C, product size 100g)⁹ or vehicle foam (Batch number UEBA-C, product size 100g)¹ or two tubes of Temovate Ointment (60g). Subjects were dispensed one can or tube at the Baseline visit and the other can or tube at the Week 1 visit. Additional cans/tubes could be requested at or between study visits. Study drug was to be weighed prior to dispensing and when returned by subject.

Subjects were issued 100 gram cans of study drug. It is not clear to this reviewer that subjects could follow instructions to use no more than 50 grams a week since it is not possible to know when the can is halfway depleted.

The study consisted of two weeks of treatment. Visits occurred at Baseline, Week 1, Week 2, and two weeks following the last study drug administration. At the first visit (Baseline, Day 1), written informed consent was obtained; a medical history/review of systems was conducted; vital signs (blood pressure, pulse, temperature), weight, and height were measured; a urine pregnancy test was performed on all females of childbearing potential; subjects were to complete the Dermatology Life Quality Index (DLQI) or the Children's Dermatology Life Quality Index (CDLQI) questionnaire; and clinical photography was performed at two investigational sites.

⁹ Sponsor's NDA submission, NDA 22-013, Amendment 11 (Response to clinical reviewer's request), p. 2.

Efficacy was evaluated at all study visits. This included ISGA (Investigator's Static Global Assessment), subject self-evaluation of pruritus, and complete examination of the skin. In addition an evaluation was performed of the target lesion on the trunk or extremities (excluding the palms and soles) for erythema, scaling and plaque thickness. Also performed was a Subject's Global Assessment (SGA) of treated areas.

Safety was evaluated at all study visits. Beginning with the Week 1 visit, subjects were questioned about adverse experiences (AEs) and their use of concomitant medications. Skin was assessed for changes in atrophy, striae, telangiectasia, and pigmentation at the treated sites.

At the Week 2 visit, subjects were to complete the DLQI or CDLQI questionnaire, a urine pregnancy test was performed on all females of childbearing potential, and clinical photography was performed at two investigational sites. All subjects were required to complete the Week 2 evaluation independent of their response to treatment prior to Week 2.

Table 60: Schedule of Study Procedures (Study 302)

Parameter	Baseline	Week 1	Week 2	Follow-Up Visit
	(Day 1)	(Day 8 ± 2 days)	(Day 15 ± 2 days)	(4 weeks ± 4 days)
Written informed consent	X			
Medical history/review of systems	X			
Vital signs measurements	X		X	
Height and weight measurement	X			
Subject's assessment of pruritus	X	X	X	X
Subject's Global Assessment	X	X	X	X
Complete skin examination (% BSA)	X	X	X	X
Evaluation of target lesion for erythema, scaling, and plaque thickness	X	X	X	X
Investigator's Static Global Assessment	X	X	X	X
Cutaneous signs of atrophy, striae, telangiectasia, and pigmentation changes assessment at treated sites	X	X	X	X
Concomitant medications query	X	X	X	X
Adverse experience query		X	X	X
Urine pregnancy test	X		X	
DLQI or CDLQI	X		X	

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Clinical photography (selected sites)	X		X	
Weigh and dispense study drug	X	X		
Collect and weigh study drug		X	X	
Subject Post-Study Questionnaire			X	

Source: Sponsor's NDA submission, Module 5, Final Study Report CPE.C.302, p. 27.

Table 61: Psoriasis Grading Scale (Study 302)

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

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 28.

Table 62: Investigator's Static Global Assessment (Study 302)

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)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 28.

Table 63: Subject's Assessment of Pruritus (Study 302)

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

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 29.

Table 64: Subject's Global Assessment (Study 302)

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

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 29.

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Safety Assessments:

At each study visit a complete examination of the skin was to be performed as well as assessments of treated areas for changes in atrophy, striae, telangiectasia, and pigmentation.

Please see Table 65 next page.

Table 65: Assessments of Cutaneous Signs (Study 302)

	None	Mild	Moderate	Severe
Atrophy	None	Skin slightly shiny with barely noticeable transparency	Shiny thinned skin, vessels transparent; no signs of fragility	Fragile, thinned skin with purpura or erosions; increased transparency with small and deeper vessels detectable
Telangiectasia	None	Few fine, small red blood vessels(0.1 mm or less in diameter)	Several easily visible fine vessels and/or few large vessels (0.2 mm or greater in diameter)	Many prominent fine blood vessels and/or large blood vessels
Pigmentation changes	None	Minimal loss of normal skin color	Partial loss of normal skin color	Total loss of normal skin color
Striae	Absent	Present		

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 30.

Efficacy Endpoints:

Primary Efficacy Parameter:

The primary endpoint is defined as treatment success at Week 2. Treatment success was defined as proportion of subjects achieving all of the following: 1) a score of clear (0) or almost clear (1) on the ISGA with at least a reduction of 2 grades 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.

Secondary Efficacy Parameter:

This included the proportion of subjects who had the following at Week 2: 1) a score of 0 for pruritus, 2) a score of 0 or 1 for erythema, 3) a score of 0 or 1 for scaling, or 4) a score of 0 for plaque thickness.

It should be noted, for pruritus, that there was no minimum entry requirement.

The ITT population was defined as all subjects randomized and dispensed study drug. For the primary, secondary, and additional endpoints the ITT population was used as the primary efficacy analysis population.

Additional Evaluations:

The sponsor evaluated a number of additional endpoints only in the ITT population. These included items such as success post-treatment, other definitions of success, and success with other signs.

Quality of Life:

Quality of life analyses were performed on the ITT population and were analyzed descriptively.

Comments to the sponsor from the SPA reviewed 1/19/05 indicated that these additional evaluations will not have regulatory utility. They will not be discussed further.

Efficacy Findings:

Study CPE.C.301 was conducted at 21 investigational sites (twenty enrolled subjects) in the United States from April 18, 2005 to August 5, 2005. In total, 497 subjects were randomized to one of three study drug treatments: 253 to EF Clobetasol Foam, 123 to vehicle foam, and 121 to Temovate ointment. Subject enrollment and disposition are summarized by treatment group for the ITT population in Table 66.

Table 66: Subject Disposition (ITT Population Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects	253	123	121
Subjects who completed study	246 (97%)	118 (96%)	117 (97%)
Number of subjects at each visit			
Baseline (Day 1)	253 (100%)	123 (100%)	121 (100%)
Week 2	251 (99%)	118 (96%)	120 (99%)
Post-treatment follow-up (Week 4)	246 (97%)	118 (96%)	117 (97%)
Subjects who terminated study early	7 (3%)	5 (4%)	4 (3%)
Reasons for study discontinuation			
Adverse experience	1 (<1%)	1 (1%)	0 (0%)
Subject non-compliance	2 (1%)	0 (0%)	2 (2%)
Subject request to withdraw	2 (1%)	1 (1%)	1 (1%)
Other reason	2 (1%)	3 (2%)	1 (1%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 43.

Subjects who terminated early from the study included 7 (3%) subjects in the EF Clobetasol Foam group, 5 (4%) subjects in the vehicle foam group, and 4 (3%) subjects in the Temovate ointment group. The most commonly reported reason for early study discontinuation was "Other", including 6 subjects. This category was composed predominantly of subjects lost to follow-up; 1 (<1%) in the EF Clobetasol foam group, 3 (2%) in the vehicle foam group, and 1 (<1%) in the Temovate ointment group. One subject was discontinued early from the study; in the EF Clobetasol foam group, because the subject had been enrolled after enrollment was complete. The second most common reason for early study discontinuation was subject request to withdraw which was evenly distributed across treatment arms; 2 (1%) in the EF Clobetasol foam group, 1 (1%) in the vehicle foam group, and 1 (1%) subject in the Temovate ointment group. Non-compliance with study visits was the reason for subject withdrawal for 2 (1%) in the EF Clobetasol foam group and 2 (2%) in the Temovate ointment group. The least common

reason for early subject study withdrawal was due to an adverse experience; 1 (<1%) in the EF Clobetasol foam group and 1 (1%) in the vehicle foam group.

Early study terminations described above are low in number and generally balanced across treatment groups.

Protocol Deviations:

Overall, protocol deviations (a total of 45) were reported for 40 (8%) of subjects enrolled in the study. This included 19 (8%) in the EF Clobetasol foam arm, 11 (9%) in the vehicle foam arm, and 10 (8%) in the Temovate ointment group. Among the deviations were; not meeting eligibility criteria 19 (4%) of subjects, use of prohibited medications by 7 (1%) of subjects, procedural deviations 10 (2%) of subjects, and missing more than 5 applications or 3 consecutive applications of study drug 4 (1%) of subjects (2 or 1% in the EF Clobetasol foam group and 2 or 2% in the vehicle foam group). Of note, the Investigator/assessor was unblinded to foam vs. ointment treatment for 5 subjects; 2 (1%) in the EF Clobetasol foam group, 2 (2%) in the vehicle foam group, and 1 (1%) in the Temovate ointment group.

Protocol Changes during the Study:

The Psoriasis Grading Scale that was used to enroll the first 46 subjects contained typographical errors. These errors involved the scaling and erythema components of the scale. The version of the psoriasis grading scale provided in the final protocol is shown in Table 67.

Table 67: Incorrect Version of Psoriasis Grading Scale (Study 302)

Score	Scaling	Erythema	Plaque Thickness
0	No Scale	Hyperpigmentation pigmented macules, diffuse faint pink or red coloration	No elevation over normal skin
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

Gray shading has been added, by reviewer, to areas of incorrect description.

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 341.

After the error was discovered, the sponsor implemented a corrected grading scale as shown in Table 68.

Table 68: Corrected Psoriasis Grading Scale (Study 302)

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

Gray shading has been added to areas of description deleted by incorrect scale.

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 28.

The incorrect scale added incorrect descriptions under the categories of scaling and erythema and shifted the categories such that the description that should have gone with 1 now went with 2, the one that should have gone with 2 now went with 3, and so on, culminating with the one that went with 5 being deleted altogether (thus leaving no severe category).

To correct this, the sponsor mapped the old scores for erythema scaling to the correct numbers (for example 1 became 0, 2 became 1, and so on). The sponsor queried sites to ensure that previously enrolled subjects had been mapped to the correct grading scale. Inclusion criteria stated that subjects were to have scores of 2 or 3 on a target lesion for each of the 3 components of the Psoriasis Grading Scale. According to the review by the FDA biostatistician, only one subject was enrolled with scores of 2 for erythema and scaling that should have properly been graded as scores of 1. This subject was enrolled with an ISGA score of 2, randomized to EF Clobetasol foam, and found at Week 2 to have worsened to an ISGA score of 3, a treatment failure. The sponsor also analyzed the data excluding the 46 subjects enrolled under the incorrect scale and the results were similar to those obtained with ITT analysis for treatment success (14% (32/228) for EF Clobetasol foam versus 4% (4/113) for vehicle foam, p value = 0.0027). Please see also FDA biostatistician's review, pp. 16-19, for further discussion.

Analysis Populations:

The ITT population was defined as all subjects randomized and dispensed study drug. For the primary, secondary, and additional endpoints; the ITT population was used as the primary

Table 69: Demographic Information and Baseline Weight (ITT Population Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment	p-value ^a
Number of Subjects	253	123	121	
Age (yrs)				
n	253	123	121	0.0090
mean (std)	46.7 (15.1)	52.0 (15.6)	47.3 (14.2)	
median	47.7	54.3	46.3	
min, max	(12.2, 79.9)	(17.8, 89.8)	(19.0, 81.6)	
Age Category				
12 < 18 Years	8 (3%)	1 (1%)	0 (0%)	0.0067
18 < 65 Years	216 (85%)	95 (77%)	108 (89%)	
≥ 65 Years	29 (11%)	27 (22%)	13 (11%)	
Sex				
Male	127 (50%)	71 (58%)	76 (63%)	0.0580
Female	126 (50%)	52 (42%)	45 (37%)	
Race				
Caucasian	221 (87%)	111 (90%)	105 (87%)	0.5354
African-American	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%)	
Weight (kg)				
n	253	123	121	0.5960
mean (std)	89.13 (24.14)	88.02 (21.63)	87.76 (32.26)	
median	84.44	84.44	83.54	
min, max	(40.9, 204.3)	(47.7, 181.6)	(34.1, 370.0)	

^a P-values are derived using the Kruskal-Wallis test ($\alpha=0.05$) for age (continuous) and weight and the Chi-square test ($\alpha=0.05$) for age (categorical), sex, and race.

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, pp. 46, 47.

The treatment groups in the ITT population were balanced at baseline with respect to ISGA score, extent of body surface involved, target lesion location, and subject evaluation of pruritus. The majority of subjects had a moderate (3) ISGA at baseline: (62% EF Clobetasol arm, 69% vehicle foam arm, and 69% Temovate arm. Roughly a third of subjects across the three treatment arms had mild (2) ISGA scores. The median percentage of body surface area (% BSA) involved was 3% for EF Clobetasol foam, 4% for vehicle foam, and 4 % for Temovate ointment.

Table 70: Baseline ISGA, %BSA, Pruritus Scores, and Target Lesion Location (Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects	253	123	121
Investigator's Static Global Assessment score			
2	93 (37%)	37 (30%)	34 (28%)
3	155 (61%)	85 (69%)	84 (69%)
4	4 (2%)	1 (1%)	3 (2%)
5	1 (< 1%)	0 (0%)	0 (0%)
Extent of Psoriasis (% BSA)			
n	253	123	121
mean(std)	4.3 (2.9)	4.6 (2.9)	4.3 (2.7)
median	3.0	4.0	4.0
min, max	(1, 10)	(1, 10)	(1, 10)
Subject Evaluation of Pruritus			
Missing	0 (0%)	1 (1%)	0 (0%)
0	18 (7%)	10 (8%)	10 (8%)
1	38 (15%)	16 (13%)	11 (9%)
2	80 (32%)	48 (39%)	48 (40%)
3	90 (36%)	42 (34%)	41 (34%)
4	27 (11%)	6 (5%)	11 (9%)
Target Lesion Location			
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%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p 48.

With respect to baseline assessments of erythema, scaling, and plaque thickness the treatment arms in the ITT population were generally balanced.

**Table 71: Baseline Erythema, Scaling, and Plaque Thickness Scores
 (ITT Population Study 302)**

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects	253	123	121
Erythema			
1	3 (1%)	0 (0%)	0 (0%)
2	107 (42%)	43 (35%)	43 (36%)
3	141 (56%)	79 (64%)	75 (62%)
4	1 (< 1%)	1 (1%)	3 (2%)
5	1 (< 1%)	0 (0%)	0 (0%)
Scaling			
1	2 (1%)	0 (0%)	2 (2%)
2	130 (51%)	53 (43%)	52 (43%)
3	118 (47%)	70 (57%)	64 (53%)
4	2 (1%)	0 (0%)	3 (2%)
5	1 (< 1%)	0 (0%)	0 (0%)
Plaque thickness			
1	1 (< 1%)	0 (0%)	0 (0%)
2	106 (42%)	43 (35%)	39 (32%)
3	142 (56%)	79 (64%)	78 (64%)
4	3 (1%)	1 (1%)	4 (3%)
5	1 (< 1%)	0 (0%)	0 (0%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p 49.

With respect to baseline grades for skin atrophy, striae, telangiectasia, and pigmentation changes, the treatment arms in the ITT population were balanced.

Table 72: Baseline Cutaneous Signs (ITT Population Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects	253	123	121
Atrophy			
None	247 (98%)	120 (98%)	119 (98%)
Mild	6 (2%)	3 (2%)	2 (2%)
Striae			
Present	2 (1%)	0 (0%)	0 (0%)
Absent	251 (99%)	123 (100%)	121 (100%)
Telangiectasia			
None	250 (99%)	121 (98%)	120 (99%)
Mild	2 (1%)	1 (1%)	1 (1%)
Moderate	1 (< 1%)	1 (1%)	0 (0%)
Pigmentation Changes			
None	238 (94%)	120 (98%)	117 (97%)
Mild	12 (5%)	2 (2%)	2 (2%)
Moderate	3 (1%)	1 (1%)	1 (1%)
Severe	0 (0%)	0 (0%)	1 (1%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p 49.

Treatment Compliance:

Among the subjects treated with EF Clobetasol foam, 59 % did not miss any treatment applications while 32 % reported missing at least one application. Among those treated with vehicle foam, 67 % did not miss any treatment applications while 32 % reported missing at least one application. In the Temovate ointment treatment group, 71 % did not miss any treatment applications while 28.5 reported missing at least one application.

Efficacy Endpoint Outcomes:

Success Rate

Primary Efficacy Endpoint

EF Clobetasol foam was superior to vehicle foam as measured by the proportion of subjects achieving treatment success at Week 2. This finding held true for both the ITT and Per Protocol populations. In the ITT population, at Week 2, the proportion of subjects achieving treatment success was 16% for EF Clobetasol foam versus 4% for vehicle foam. Although not a planned efficacy comparison, note that EF Clobetasol foam was inferior to Temovate® Ointment, 16% versus 31% (p=.0007).

Table 73: 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 ¹	41 (16%)	5 (4%)	38 (31%)
P-value (vs. Clob. Foam)		0.0005	(0.0007) ²
<i>PP</i>	N=234	N=112	N=111
Treatment Success ¹	39 (17%)	5 (4%)	34 (31%)
P-value (vs. Clob. Foam)		0.0011	(0.0031) ²

¹ ISGA = 0 or 1 with 2 grades reduction, erythema = 0 or 1, scaling = 0 or 1, and plaque thickness = 0

² Clobetasol foam versus Temovate Ointment was not a planned efficacy comparison

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 10.

Treatment success was defined as proportion of subjects achieving all of the following at Week 2: 1) a score of clear (0) or almost clear (1) on the ISGA with 2) at least a reduction of 2 grades from baseline, 3) a score of 0 or 1 for erythema, 4) a score of 0 or 1 for scaling, and 5) a score of 0 for plaque thickness. The evaluation of erythema, scaling, and plaque thickness was performed on a target lesion identified at baseline. Of note, the IGSA included evaluation of erythema, scaling, and plaque thickness.

Both the FDA and the sponsor analysis are in agreement regarding the results of the primary efficacy endpoint.

As previously agreed upon, this study employs a composite endpoint consisting of five components. As shown in Table XX, the overall treatment success rate was notably lower than the success rate on the individual components. The FDA biostatistician has suggested that target lesion scores may not directly correspond to the overall impression of the entire treated area. Please see biostatistician's review, p. 12. Also, according to the FDA biostatistician, the largest factor preventing success in subjects with ISGA scores of 0 or 1 is the presence of plaque thickness scores of 1 or greater. Please see biostatistician's review, p. 14.

Table 74: Response for Individual Components of Composite Primary Endpoint at Week 2 (ITT Population Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects	253	123	121
Subjects with treatment success	41 (16%)	5 (4%)	38 (31%)
ISGA Score of 0 or 1	120 (47%)	15 (12%)	87 (72%)
Erythema score of 0 or 1	135 (53%)	25 (20%)	83 (69%)
Scaling score of 0 or 1	180 (71%)	34 (28%)	107 (88%)
Plaque thickness score of 0	78 (31%)	6 (5%)	59 (49%)
Minimum 2 Grade Improvement (ISGA)	74 (29%)	11 (9%)	69 (57%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, adapted from Table 20, p. 58.

In this study 20 original sites were combined prior to unblinding if enrollment was less than a target, per site, of 20 subjects in the EF Clobetasol foam arm, 10 subjects in the vehicle foam arm, and 10 subjects in the Temovate ointment arm. This resulted in 10 combined investigational sites. Combination was based on geographical and climate similarities.

The results from the pooled centers favored EF Clobetasol foam over vehicle foam in 8 of 10 instances. The sponsor's and the FDA analysis both yield a significant Breslow-Day test with a p-value of 0.0339. According to the FDA biostatistician, the overall results do not appear to be driven by any specific center. Please see FDA biostatistician's review, p. 20.

Subgroup Analysis:

Subgroup analyses were performed on subjects in the ITT population and included; gender, race, age, and baseline disease severity. The results of subgroup analysis for gender, age, and race are shown in Table 75.

Table 75: 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%)

† For purposes of analysis, the sponsor has combined African-American, Hispanic, and Asian subjects with the "Other" race category.

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 25.

Response to treatment was similar for both male and female subjects. The predominance of study subjects were Caucasian and in the 18 to 64 year old age group. The small numbers of subjects outside of these categories make conclusions more tentative. Treatment response did vary by race, with the proportion of subjects who achieved treatment success with EF Clobetasol foam being 19% (Caucasian) versus 0% (Other). The success rate for "Other" (or non-Caucasian) versus Caucasian was also lower in the Temovate arm, 19% versus 33%.

Treatment success for those treated with EF Clobetasol foam or foam vehicle was independent of baseline ISGA for subjects judged to have mild or moderate disease. For those treated with Temovate ointment moderate disease (ISGA = 3) versus mild disease (ISGA = 2) at baseline was associated with greater treatment success at Week 2.

Table 76: Treatment Success at Week 2 by Baseline Severity (Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Overall success			
n (% success)	41/253 (16%)	5 /123(4%)	38/121 (31%)
Mild (ISGA = 2)			
n (% success)	15/93 (16%)	2/37 (5%)	7/34 (21%)
Moderate (ISGA = 3)			
n (% success)	24 /155(15%)	3/85 (4%)	30/84 (36%)
Marked / Severe (ISGA = 4/5)			
n (% success)	2/5 (40%)	0/1 (0%)	1/3 (33%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, adapted from Table 28, p. 66.

An analysis was performed by the FDA biostatistician for success rate by target lesion location. In the EF Clobetasol foam group, subjects having target lesions located on the leg, arm, and trunk achieved higher success rates that subjects having target lesions located on the elbow or knee. In the Temovate group, only the elbow was associated with a somewhat lower success rate.

Table 77: 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%)	--	--

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 28.

Secondary Efficacy Analysis:

The four secondary endpoints included the proportion of subjects who had the following at Week 2: 1) a score of 0 or 1 for erythema, 2) a score of 0 or 1 for scaling, or 3) a score of 0 for plaque thickness, or 4) a score of 0 for pruritus. Note that a reduction of at least two grades from baseline is not required for success on these endpoints.

Table 78: Success on Secondary Efficacy Endpoints (Study 302)

	Clobetasol Foam N= 253	Vehicle Foam N= 123	TEMOVATE Ointment N=121	p-value ¹	p-value ²
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

¹ P-value for clobetasol foam versus vehicle foam

² P-value for clobetasol foam versus TEMOVATE Ointment

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 14, with minor modification.

Success for plaque thickness and pruritus was defined as a score of 0. For scaling, success was defined as a score of 0 or 1. For erythema, success was defined as a score of 0 or 1 in the Final Study report and in the Statistical Analysis Plan (dated December 15, 2005). In the protocol submitted for SPA and reviewed 1/19/05, success for erythema was defined similarly. In the original protocol issued October 27, 2004 success for erythema was defined as a score of 0 or 1 and was included as an additional evaluation. In protocol Amendment 1, dated December 6, 2004, erythema was included as a secondary efficacy endpoint with success defined as a score of 0 or 1. However, in the final protocol, Amendment 2 (dated March 10, 2005), success for erythema, a secondary endpoint, was defined as a score of 0. No explanation is given. The FDA biostatistician has performed an analysis using both definitions of erythema success.

As shown in Table XX, EF Clobetasol foam was superior to vehicle foam for all secondary endpoints, including erythema whether success defined as a score of 0 or as a score of 0 or 1. Note also that EF Clobetasol foam is inferior to Temovate ointment for all four secondary endpoints when erythema success is defined as a score of 0 or 1. When erythema success is defined as a score of 0 EF Clobetasol foam is possibly inferior to Temovate ointment, however this finding is not statistically significant.

Safety:

There were no deaths in this study.

One serious adverse event, syncope, was reported in the EF Clobetasol foam group. A 57 year old white male (subject 302-209-3446) was enrolled June 20, 2005, randomized to EF Clobetasol foam, underwent study treatment, and discontinued study drug _____ . Twelve days after

discontinuing study drug, the subject was at a party and having a cocktail when he suddenly experienced lightheadedness and within 45 seconds collapsed and passed out. The subject was at an air conditioned facility, had eaten breakfast that day, and denied excessive alcohol intake. The subject was admitted to the hospital for evaluation. Screening laboratory values were all within normal limits. Chest x-ray, stress test, and myocardial perfusion images were normal. Electrocardiogram showed few premature ventricular contractions with normal sinus rhythm and no ST or T wave changes. The subject did not have any further episodes of syncope and was discharged. The subject was continued on the same medications he had been on prior to hospitalization, Lipitor®, Atenolol®, and aspirin. The cause of the syncopal episode remained unclear. The Investigator assessed the event as not related to study drug.

Two, (<1%), of subjects discontinued the study due to adverse events. In the EF Clobetasol foam group, one subject (302-211-3553) experienced moderate atopic dermatitis of the hands, considered to be possibly related to study drug. In the vehicle foam group, one subject (302-211-3540) experienced an allergic reaction of moderate severity and considered to be probably related to study drug.

Severe adverse events were reported by 5 (1%) study subjects. Three of these were in the EF Clobetasol foam group; two of them (subject 302-205-3209-retinal detachment and subject 302-209-3547-patella fracture) were considered probably not treatment related. The third, involving subject 302-202-3066, consisted of application site (legs) burning after study drug application that was assessed as probably related to study drug.

The other severe adverse events reported involved one subject (302-205-3215-uncontrolled hypertension) in the vehicle foam arm and one subject (302-205-3212-heel spurs and plantar fasciitis) in the Temovate® Ointment arm. These were considered to be probably not treatment related.

Common adverse events:

During the study similar proportions of subjects in the EF Clobetasol foam arm, 17 % (42/253), reported adverse events as in the Vehicle foam arm, 16 % (20/123). The investigator considered 8% (20/253) in the EF Clobetasol arm and 7% (9/123) in the Vehicle arm to be treatment related. Subjects in the Temovate® ointment arm reported fewer adverse events, 9 % (11/121). Of these 2% (3/121) were considered treatment related.

Local adverse events are shown in Table 79, following.

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Table 79: Local Adverse Events (Study 302)

System Organ Class/ Preferred Term	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment	Total
Number of Subjects	253	123	121	497
General Disorders and Administrative Site Conditions				
Application site atrophy	6 (2%)	1 (1%)	0 (0%)	7 (1%)
Application site burning	4 (2%)	2 (2%)	0 (0%)	6 (1%)
Application site dryness	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)
Application site hypersensitivity	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)
Application site pruritus	0 (0%)	1 (1%)	0 (0%)	1 (< 1%)
Application site reaction	4 (2%)	3 (2%)	2 (2%)	9 (2%)
Immune System Disorders				
Hypersensitivity	0 (0%)	1 (1%)	0 (0%)	1 (< 1%)
Infections and Infestations				
Application site folliculitis	2 (1%)	0 (0%)	0 (0%)	2 (< 1%)
Tinea versicolour	0 (0%)	0 (0%)	1 (1%)	1 (< 1%)
Skin and Subcutaneous Tissue Disorders				
Dermatitis	0 (0%)	0 (0%)	1 (1%)	1 (< 1%)
Dermatitis atopic	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)
Pityriasis rosea	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)
Post-inflammatory pigmentation change	0 (0%)	0 (0%)	1 (1%)	1 (< 1%)
Urticaria generalized	0 (0%)	0 (0%)	1 (1%)	1 (< 1%)

Note: Subjects reporting a particular adverse experience more than once are counted only once for that adverse experience.

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, adapted from Table 54, pp. 100-102.

Examining the local adverse events, the largest difference between the EF Clobetasol foam arm and the Temovate® Ointment arms occurs within the categories of application site atrophy and application site burning.

A higher incidence of application site burning, 2%, was noted in the EF Clobetasol foam and the Vehicle foam arms than in the Temovate® Ointment arm, 0%. Further details regarding application site burning are provided in Table 80.

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 Patricia C. Brown, MD
 NDA 22-013
 Primolux Foam, 0.05% (clobetasol propionate)

Table 80: Subjects with Application Site Burning (ITT Population Study 302)

Subject	Study Drug Start Date	Adverse Event Start Date	Adverse Event Stop Date	Study Day of Event Start	Duration of Event (d)
EF Clobetasol Foam					
202-3066	1 Jun 05	15 Jun 05	1 Jul 05	15	17
202-3114	29 Apr 05	5 May 05	5 May 05	7	1
		6-May-05	6-May-05	8	1
203-3120	6-May-05	11-May-05	12-May-05	6	2
215-3735	17-May-05	17-May-05	19-May-05	1	3
Vehicle Foam					
209-3419	17-May-05	26-May-05	27-May-05	10	2
211-3523	19 Apr 05	21 Apr 05	2 May 05	3	12

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 103.

A higher incidence of application site atrophy was noted in the EF Clobetasol foam arm, 2%, than in the Vehicle foam arm, 1%, or the Temovate® Ointment arm, 0%. Further details regarding application site atrophy are provided in Table 81.

Table 81: Subjects with Application site Atrophy (ITT Population Study 302)

Subject	Study Drug Start Date	Adverse Event Start Date	Adverse Event Stop Date	Study Day of Event Start	Duration of Event (d)	Dose (g)
EF Clobetasol Foam						
201-3020	31 May 05	14 Jun 05	28 Jun 05	15	15	78.5
213-3648	27 Jun 05	7 Jul 05	28 Jul 05	11	22	106.8
214-3684	2 May 05	11 May 05	2 Jun 05	10	23	54.2
214-3698	9 Jun 05	16 Jun 05	11 Jul 05	8	26	141.8
214-3702	17 Jun 05	1 Jul 05	cont	15	-	62.1
214-3710	29 Jun 05	7 Jul 05	cont	15	-	33.4
Vehicle Foam						
207-3316	21 Jun 05	5 Jul 05	15 Jul 05	15	11	50.0

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 104.

The sponsor notes that every subject who received EF Clobetasol foam and who reported application site atrophy had a greater total dose of the EF Clobetasol foam than the mean total dose of Temovate® Ointment, 29g.

The preferred term with the highest number of adverse events reported was application site reaction, 9 (2%). Of these events eight were described as telangiectasia and one as mild stinging (Vehicle foam arm). The application site reactions were evenly distributed across all three treatment arms, 2% each.

Changes in skin signs (atrophy, striae, telangiectasia, and pigmentation) were evaluated for the ITT population at Baseline, Week 1, Week 2, and 2 weeks post-treatment. With respect to baseline grades for these signs, the treatment arms in the ITT population were balanced. Please see Table 72. For the following set of tables the number of subjects was 253 for EF Clobetasol foam, 123 for vehicle foam, and 121 for Temovate® Ointment.

Table 82: Grade Change in Atrophy at Week 2 (Study 302)

Week 2	EF Clobetasol Foam	Vehicle Foam	Temovate® ointment
Missing	2 (1%)	5 (4%)	1 (1%)
1-grade improvement	2 (1%)	0 (0%)	1 (1%)
No change	243 (96%)	117 (95%)	119 (98%)
1-grade worsening	6 (2%)	1 (1%)	0 (0%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 114.

Table 83: Subjects with Striae Present (Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects	253	123	121
Baseline	2 (1%)	0 (0%)	0 (0%)
Week 2	1 (< 1%)	0 (0%)	0 (0%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 115.

Table 84: Grade Change in Telangiectasia at Week 2 (Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Week 2			
Missing	2 (1%)	5 (4%)	1 (1%)
1-grade improvement	1 (< 1%)	1 (1%)	0 (0%)
No change	248 (98%)	116 (94%)	118 (98%)
1-grade worsening	1 (< 1%)	1 (1%)	2 (2%)
2-grade worsening	1 (< 1%)	0 (0%)	0 (0%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 116.

Table 85: Grade Change in Pigmentation at Week 2 (Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Week 2			
Missing	2 (1%)	5 (4%)	1 (1%)
2-grade improvement	0 (0%)	0 (0%)	1 (1%)
1-grade improvement	3 (1%)	1 (1%)	1 (1%)
No change	242 (96%)	113 (92%)	108 (89%)
1-grade worsening	4 (2%)	3 (2%)	8 (7%)
2-grade worsening	2 (1%)	1 (1%)	2 (2%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, p. 117.

The results for evaluation of skin signs at Week 2 present a mixed picture. Essentially no change in striae was noted in any treatment arm at Week 2. Changes in telangiectasia from baseline were small with a very slightly higher incidence in the Temovate® Ointment group. For atrophy, there was a greater difference across the three treatment arms, with the incidence of 1 grade worsening being 6 (2%), 1 (1%), and 0 for EF Clobetasol foam, Vehicle foam, and Temovate® Ointment respectively. For pigmentation, a higher incidence of 1 or 2 grade worsening was noted for subjects in the Temovate® Ointment arm (8% 10/121) as compared with subjects in the EF Clobetasol foam arm (2% 6/253) or the Vehicle foam arm (3% 4/123).

The FDA biostatistician has performed an analysis of worsening of cutaneous signs from baseline at any visit (Week 1, 2, or 4).

Table 86: 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%)

Source: Kathleen Fritsch, Statistical Review and Evaluation, NDA 22-013, Table 23, p. 24.

According to this analysis, worsening of atrophy and telangiectasia was not marked and was generally similar to the Week 2 analysis. Worsening of pigmentation also followed the pattern of the Week 2 analysis with Temovate® Ointment showing a higher rate (9%), than either the EF Clobetasol foam (5%), or the Vehicle foam (5%).

Extent of Exposure (dose/duration):

Table 87: Study Drug Exposure (ITT Population Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects	253	123	121
Days on Study Drug	N = 253	N = 121	N = 120
mean (std)	14.6 (1.9)	14.6 (1.8)	14.6 (1.4)
range	1 - 22	7 - 21	12 - 21
Total Study Drug Usage (g)	N = 250	N = 119	N = 117
mean (std)	62.34 (44.69)	57.95 (43.34)	28.98 (24.57)
range	1.6 - 200.7)	4.5 - 200.6	1.6 - 100.0
Daily Mean Drug Usage(g)	N = 250	N = 119	N = 117
mean (std)	4.30 (3.16)	4.08 (3.62)	2.01 (1.73)
range	0.1 - 14.5	0.3 - 28.7	0.1 - 7.9
No. > 50 g/week ¹	49 (20%)	21 (18%)	0 (0%)

Note: Study drug usage is defined as total container weight dispensed minus total container weight returned. Mean drug usage is defined as the average amount of drug subjects use per study day.

¹ Number of subjects using > 100 g during study or > 50 g if treated period was 1 week or less. (Analysis of this information provided by Kathleen Fritsch, Statistical Review and Evaluation, NDA 22-013, Table 19, p. 21.

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, adapted from Table 53, p. 97.

In study CPE.C.302 subjects displayed notably different amounts of usage for the foam products, EF Clobetasol foam and Vehicle foam, as compared with the Temovate® Ointment. Subjects using the foam products used approximately twice as many grams daily, and over the entire treatment period, as compared with the ointment product. Approximately the same number of subjects in both foam arms (18%, 20%) used more than 100g of product during the study. No subjects in the ointment arm used more than 100g of product during the study.

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10.1.3 Phase 1 Dermal Safety Studies

Study DES.C.103: “A Repeat Insult Patch Test Study to Determine the Potential of Desonide Foam, 0.05%, Desonide Vehicle Foam, and Ethanol Free Clobetasol Propionate Vehicle Foam to Induce Allergic Contact Sensitization”

A repeat insult patch test study was performed using Ethanol Free Clobetasol Propionate Vehicle Foam (EF Clobetasol Vehicle Foam), Desonide Foam, 0.05%, (Desonide Foam), and Desonide Vehicle Foam, to determine their potential to cause irritancy or allergenicity. The study was performed April 11, 2005 to June 18, 2005.

This was a single-center, evaluator-blinded trial that enrolled 240 healthy adult volunteers (male 45, female 195). Females were ineligible if they were pregnant or nursing. If females were of childbearing potential they were required to be practicing an acceptable method of birth control (abstinence, birth control pills, patch, implant, barrier with spermicidal jelly, IUD, etc.). There were three phases to the study; induction, rest, and challenge. Test articles included Desonide Foam, 0.05 %, Desonide Vehicle Foam, EF Clobetasol Vehicle Foam, 0.1% sodium lauryl sulfate (SLS) (positive control), and distilled water (negative control). During the Induction Phase (days 1-22), 0.2mL of each test article was applied under separate occlusive patches onto the subject's back 3 (M,W,F) times a week for 3 weeks in the sequence determined by the randomization scheme. Patches were placed on the backs of subjects and left in place for 48 hours (except patches applied on Fridays that were to be removed after 72 hours). Patches were then removed and the evaluator assessed for irritation at least 5 minutes but no longer than 30 minutes after removal(see table 88 for grading scale and notations).

Table 88: Grading Scale for Irritation (DES.C.103 or Study 103)

Score		Definition
0	=	No visible reaction
1	=	Minimal erythema; no sign of edema or papular response
2	=	Definite erythema with no significant edema; and/or minimal papular response
3	=	Moderate erythema with no significant edema or epidermal damage; and/or definite papular response (covering less than 50% of the site)
4	=	Moderate erythema with edema; and/or papular response covering more than 50% of the site; and/or epidermal damage
5	=	Severe erythema, edema, epidermal damage, and/or papulovesicular response

Table 88 (cont'd): Grading Scale for Irritation

Notation		Definition
X	=	Subject absent
PD	=	Patch dislodged
NA	=	Patch not applied
NP	=	No patch due to limiting irritation
N9G	=	No ninth grade in induction (i.e., missing 1 reading in the induction period)

Source: Sponsor's NDA Submission, Module 5, Study Report DES.C.103, p. 21.

Following a rest period of two weeks (days 23-35), a challenge application of each test article was applied under occlusive patches on naïve test sites on the subject's backs and remained in place for 48 hours. The patches were then removed and the test sites were then evaluated for any signs of skin sensitization at 30 minutes, and at 24, 48, and 72 hours following patch removal. A subject would be rechallenged if any sign (erythema and /or papulation) suggestive of contact sensitization in the opinion of the investigator was observed at any of the evaluations following the removal of the challenge patch. Rechallenge was conducted at naïve test sites at least two weeks after the challenge phase, with patches applied under both occlusive and semi-occlusive conditions. The scale used for grading contact sensitization is shown in table 89.

Table 89: Grading Scale for Contact Sensitization (Study 103)

Response	Symbol
No reaction	-
Minimal or doubtful response, slightly different from surrounding normal skin	?
Definite erythema; no edema	+
Definite erythema and edema	++
Definite erythema, edema, and vesiculation	+++

Response/Comment	Notation
Marked/severe erythema	E
Spreading of reaction beyond patch study site (i.e., reaction where study material was not in contact with the skin).	S
Burning or stinging sensation	B
Papular response > 50%	p
Papulovesicular response > 50%	pv
Damage to epidermis: oozing, crusting and/or superficial erosions	D
Itching	I
Subject absent	X

Source: Sponsor's NDA Submission, Module 5, Study Report DES.C.103, p. 22.

Results

A total of 240 subjects were enrolled and 206 subjects completed the study. Thirty-four subjects were dropped prior to completing the study. The following reasons were listed for dropped subjects: voluntary withdrawal (16), non-compliance (14), adverse events (2 – dizziness/nausea and a stroke), and other reasons (2 – lost to follow-up and inadvertent enrollment). During the study six subjects experienced seven adverse events. One adverse event was considered serious and consisted of a mild stroke that upon review of the narrative appears unlikely to be related to study medication. The remaining AE's appear unrelated to study medication. One subject had a positive result at the end of study urine pregnancy test. This subject completed the study. Attempts were made to contact the subject, however, the subject did not respond.

By the reviewer's calculations, 215 subjects completed the induction phase. For the Desonide Foam 0.05 %, 200 subjects had maximum scores of 0 or 1 (no or minimal erythema), 14 had maximal scores of 2 (definite erythema, no edema), and one subject had a maximal score of 4 (moderate erythema with edema; and/or epidermal damage). For the Desonide Vehicle Foam, 182 subjects had maximal scores of 0 or 1 (no or minimal erythema), 25 had maximal scores of 2 (definite erythema, no edema), 4 subjects had a maximal score of 3 (moderate erythema, no significant edema), and 4 subjects had a maximal score of 4 (moderate erythema with edema; and/or epidermal damage). For the EF Clobetasol Vehicle, 195 subjects had a maximal score of 0 or 1 (no or minimal erythema), 16 had maximal scores of 2 (definite erythema, no edema), 2 had maximum scores of 3 (moderate erythema, no significant edema), 2 had maximum scores of 4 (moderate erythema with edema; and/or epidermal damage). For the 0.1% SLS (positive control), 76 subjects has a maximal score of 0 or 1 (no or minimal erythema), 76 had a maximal score of 2 (definite erythema, no edema), 21 had a maximal score of 3 (moderate erythema, no significant edema), 41 had a maximal score of 4 (moderate erythema with edema; and/or epidermal damage), and 1 had a maximal score of 5 (severe erythema, edema, epidermal damage). For the distilled water (negative control), 214 subjects had maximum scores of 0 or 1 and 1 subject had a maximum score of 4 (moderate erythema with edema; and/or epidermal damage).

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Table 90: Summary of Induction Phase Assessments (Study 103)

	No Reaction	Minimal Erythema	definite erythema, no edema	moderate erythema, no significant edema	moderate erythema with edema; and/or epidermal damage	severe erythema, edema, epidermal damage
Desonide Foam 0.05 %, n=215	200		14	1*	1*	0
Desonide Vehicle Foam n=215	182		25	4	4	0
EF Clobetasol Vehicle n=215	195		16	2	2	0
0.1% SLS (positive control) n=215	76		76	21	41	1
Distilled water (negative control) n=215	214		0	0	1	0

* Same patient

Source: Reviewer's calculations based on Sponsor's NDA Submission, Module 5, Study Report DES.C.103, data listing 4.1, pp. 202-276.

The statistical analysis of cumulative irritancy index (CII) scores is summarized in table 91.

Table 91: Summary of Mean Irritation Scores (Study 103)

Test Article	Mean CII score (\pm SD)
Desonide Foam	0.16 (\pm 0.36)
Desonide Vehicle Foam	0.33 (\pm 0.57)
EF Clobetasol Vehicle Foam	0.26 (\pm 0.45)
0.1% SLS (positive control)	1.31 (\pm 0.73)
Distilled water (negative control)	0.02 (\pm 0.22)

P-values

Desonide Foam vs. 0.1% SLS	< .001
Desonide Foam vs. distilled water	0.002
Desonide Vehicle Foam vs. 0.1% SLS	< .001
Desonide Vehicle Foam vs. distilled water	< .001

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EF Clobetasol Vehicle Foam vs. 0.1% SLS	< .001
EF Clobetasol Vehicle Foam vs. distilled water	< .001
0.1% SLS vs. distilled water	< .001

Source: Sponsor's NDA Submission, Module 5, Study Report DES.C.103, p. 30.

The test articles; Desonide Foam, Desonide Vehicle Foam, and EF Clobetasol Foam Vehicle are more irritating than distilled water ($P = .002$) but less irritating than sodium laurel sulfate, 0.1% ($P < 0.001$).

The scores for Desonide Vehicle Foam and EF Clobetasol Foam Vehicle are very similar and slightly higher than that for the Desonide Foam. These items may be slightly more irritating than the Desonide Foam because the irritant effects of excipients may be masked by the presence of the active ingredient steroid in the Desonide Foam.

Of the components of EF Clobetasol Foam, Propylene Glycol is a recognized cause of irritant dermatitis¹. Another component, Polyoxyl 20 Cetostearyl Ether, can be an irritant at concentrations over 20%². In EF Clobetasol Foam it is found at $\frac{1}{10}$ w/w.

A total of 206 subjects completed the challenge phase of the trial. Signs suggestive of contact sensitization included erythema and/or papulation, this would be equivalent to a minimum reading of + on the grading scale for contact sensitization (see table XX). At the challenge, for both the Desonide Vehicle Foam and the EF Clobetasol Vehicle Foam a number of subjects had readings of ? (minimal or doubtful response) and + (definite erythema, no edema). Only two subjects had readings of ++ (definite erythema and edema). These were subjects 69 and 140. Subject 69 had a ++ reading at 30 minutes for both Desonide Vehicle Foam and EF Clobetasol Vehicle Foam. Subject 140 had a ++ reading at 24 hours for both Desonide Vehicle Foam and for EF Clobetasol Vehicle Foam. These subjects were rechallenged.

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¹ Riettschel RL and Fowler JF; Fisher's Contact Dermatitis, 4th Ed. ©1995, Williams & Wilkins, Baltimore, p. 282.

² Rowe-RC, Sheskey PJ, and Weller PJ; editors, Handbook of Pharmaceutical Excipients, 4th Ed. © 2003, Pharmaceutical Press and American Pharmaceutical Association, Chicago, p. 473.

TABLE 92: Re- Challenge Skin Site Assessments (Study 103)

SUBJECT NO.	PATCH TYPE	PRODUCT	PATCH SITE EVALUATIONS				DEGREE OF ITCHING			
			30 min	24 hr	48 hr	72 hr	30 min	24 hr	48 hr	72 hr
69	OCCLUSIVE	DESONIDE VEHICLE FOAM	+	+	?	?	-	-	-	-
		EF CLOBETASOL VEHICLE	+	+	?	?	-	-	-	-
	SEMI-OCCLUSIVE	DESONIDE VEHICLE FOAM	+	+	+	?	-	-	-	-
		EF CLOBETASOL VEHICLE	+	+	+	?	-	-	-	-
140	OCCLUSIVE	DESONIDE VEHICLE FOAM	++	++	+	+	S	MOD	M	-
		EF CLOBETASOL VEHICLE	++	++	+	+	S	MOD	M	-
	SEMI-OCCLUSIVE	DESONIDE VEHICLE FOAM	++	+	?	?	M	M	-	-
		EF CLOBETASOL VEHICLE	++	++	+	+	M	M	-	-

* Degree of Itching - =None, M=Mild, MOD=Moderate, S=Severe

Source: Sponsor's NDA submission, module 5, Final Report DES.C.103, data listing 4.3, p. 277.

Subject 69, while initially showing a response of "+" under occlusive and semi occlusive patches, by 72 hours demonstrated a "?" response by 72 hours for EF Clobetasol Vehicle. This is suggestive that no sensitization occurred.

Subject 140 initially showed a response of "++" that faded to "+" by 48 and 72 hours for EF Clobetasol Vehicle. This could suggest sensitization. This response was accompanied by itching that had resolved by 72 hours.

Conclusions:

The test articles; Desonide Foam, Desonide Vehicle Foam, and EF Clobetasol Foam Vehicle are more irritating than distilled water (P = .002) but less irritating than sodium laurel sulfate, 0.1% (P < 0.001).

Among the components of the EF-Clobetasol Foam Vehicle; phenoxyethanol¹, isopropyl myristate², and cetyl alcohol³ are known rare sensitizers. It is noted that this trial did not include the active ingredient, Clobetasol Propionate 0.05%. This is acceptable since its presence in the vehicle foam could mask sensitization by components of the vehicle foam. However; clobetasol propionate is itself a known sensitizer with rates of sensitization ranging between .4% and .8% of patients with suspected contact dermatitis who were tested.^{4,5} Wider use of the EF Clobetasol Foam product in the post-marketing phase may result in rare occurrences of true allergic contact dermatitis from the known sensitizing substances in the formulation.

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1 Rietschel RL and Fowler JF; Fisher's Contact Dermatitis, 4th Ed. ©1995, Williams & Wilkins, Baltimore, p. 1028.

2 *Ibid*, p. 293.

3 *Ibid*, p. 292.

4 Boffa MJ, Wilkinson SM, and Beck MH. Screening for corticosteroid hypersensitivity. Contact Dermatitis 1995; 33(3);149-51.

5 Sommer S, Wilkinson SM, English JSC et al. Type-IV hypersensitivity to betamethasone valerate and clobetasol propionate: results of a multicenter study. British J. of Dermatology 2002;147:266-269.

Study DES.C.104: “A Cumulative Irritation Study of Desonide Foam, 0.05%, Desonide Vehicle Foam, and Ethanol Free Clobetasol Propionate Vehicle Foam”

A repeat insult patch test study was conducted to evaluate the cutaneous irritation potential of Desonide Foam, 0.05% (Desonide Foam), Desonide Vehicle Foam, and Ethanol Free Clobetasol Propionate Vehicle Foam (EF Clobetasol Vehicle Foam). The study was conducted from May 2, 2005 to May 23, 2005.

This was a single-center, within subject, randomized, evaluator-blinded trial that enrolled 40 healthy adult volunteers (male 9, female 31). Females were ineligible if they were pregnant or nursing. At screening all females subjects of childbearing potential were administered urine pregnancy tests. If females were of childbearing potential they were required to be practicing an acceptable method of birth control (abstinence, birth control pills, patch, implant, barrier with spermicidal jelly, IUD, etc.). Test articles included Desonide Foam, 0.05 %, Desonide Vehicle Foam, EF Clobetasol Vehicle Foam, 0.1% sodium lauryl sulfate (SLS) (positive control), and distilled water (negative control). Approximately 0.2 mL of each test article was applied under separate occlusive patches onto the subject’s back daily for 21 days in a sequence determined by the randomization scheme. Patches were applied for 23 ± 1 hour. The patches were then removed and application sites assessed for signs of irritation and/or inflammation at least 5 minutes but no longer than 30 minutes after patch removal (see Table 93 for grading scale used).

Table 93: Integer Grading Scale for Irritation (DES.C.104 or Study 104)

Score		Definition
0	=	No visible reaction
1	=	Minimal erythema; no sign of edema or papular response
2	=	Definite erythema with no significant edema; and/or minimal papular response
3	=	Moderate erythema with no significant edema or epidermal damage; and/or definite papular response (covering less than 50% of the site)
4	=	Moderate erythema with edema; and/or papular response covering more than 50% of the site; and/or epidermal damage
5	=	Severe erythema, edema, epidermal damage, and/or papulovesicular response

Source: Sponsor’s NDA Submission, Module 5, Study Report DES.C.104, p. 21.

On study Days 2-21 previously applied patches were removed by designated personnel (not the evaluator). The test sites were evaluated for skin reaction and then new patches were applied, the same test articles to the same test sites. The patch site evaluator and the person responsible for preparing and applying test articles were located in two different rooms.

Any skin reactions that were interpreted as related to the patches or tape were documented as adverse experiences. If a score of 4 or 5 on the grading scale for irritation was observed at any site, no further applications were made to that site, and the last observed score was assigned to

that site for the duration of the study. If a subject missed more than 1 visit, that subject was not evaluable for cumulative irritancy and was dropped from the study.

Results

Of the 40 subjects who were enrolled, 34 completed the study. The following reasons were listed for discontinued subjects: one with an adverse experience (AE) described as a tape reaction, three who were non-compliant (two failed to keep the proper visit schedule and one scratched the patch sites), and two voluntarily withdrew prior to study completion.

Table 94: Histogram of Maximum Scores Achieved (Study 104)

	No Reaction	Minimal Erythema	definite erythema, no edema	moderate erythema, no significant edema	moderate erythema with edema; and/or epidermal damage	severe erythema, edema, epidermal damage
Desonide Foam 0.05 %,	23	9	2			
Desonide Vehicle Foam	14	18	2			
EF Clobetasol Vehicle	10	22	2			
0.1% SLS (positive control)		1	4		29*	
Distilled water (negative control)	26	7		1		

* These patients achieved a score of 4 and then were not further patched.

Source: Reviewer's calculations based on Sponsor's NDA Submission, Module 5, Study Report DES.C.104, data listing 4.1, pp. 126-140.

Reviewing the histogram, Desonide Vehicle Foam and EF Clobetasol Vehicle appear to have similar patterns of reaction. The Desonide Foam may have had a mildly lesser response. As might be expected, the positive control 0.1% SLS generated strong responses and the negative control distilled water generated minimal responses.

The statistical analysis of cumulative irritancy is summarized in Table 95, following.

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Table 95: Mean Cumulative Irritation Score (Study 104)

Product Tested (n = 34)	Mean Score (\pm SD)*	p Value vs.			
		B	C	D	E
Desonide Foam (A)	0.08 (0.18)	0.334	0.202	< .001	0.667
Desonide Vehicle Foam (B)	0.18 (0.25)		0.754	< .001	0.163
EF Clobetasol Vehicle (C)	0.21 (0.28)		< .001	0.089	
SLS 0.1% (D)	1.92 (0.98)		< .001		
Distilled Water (E)	0.03 (0.09)		< .001		

* See Table XX above for the 6-point integer scale used to evaluate signs of skin reaction.

Source: Sponsor's NDA Submission, Module 5, Study Report DES.C.104, p. 29.

The test articles; Desonide Foam, Desonide Vehicle Foam, and EF Clobetasol Vehicle Foam show similar levels of irritation, having mean scores of 0.08, 0.18, and 0.21, respectively. Though higher than the score for the negative control, distilled water, these scores are not significantly different. These test articles were significantly less irritating than the positive control, SLS 0.1%.

Examination of the total cumulative irritation scores for the test articles revealed a similar pattern.

Conclusions: The results of Study DES.C.104 are consistent with those found in Study DES.C.103. That study, having 215 subjects complete the induction phase and be analyzed for mean cumulative irritancy, is larger than Study DES.C.104 wherein only a total of 34 subjects completed and were analyzed for mean cumulative irritancy.

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10.1.4 Phase 2 Systemic Safety Study

Study CPE.C.201: “An Open-Label Study to Evaluate the Safety of Ethanol Free Clobetasol Propionate Foam, 0.05%, including its effect on the Hypothalamic Pituitary Adrenal (HPA) Axis”

Study CPE.C.201 was conducted to evaluate the effect of EF Clobetasol Foam on the HPA axis following twice daily (morning and evening) application for two weeks to the diseased skin of subjects with atopic dermatitis. The study was conducted from July 8, 2004 to April 6, 2005.

Study CPE.C.201 consisted of 2 weeks of treatment with visits at Screening, Baseline, Week 1, Week 2 and a conditional visit scheduled four weeks post-treatment (if needed for laboratory testing and/or adverse experience evaluations). This study enrolled 52 evaluable subjects having mild to severe atopic dermatitis (criteria of Hanifin and Rajka¹) defined as an Investigator’s Static Global Assessment (ISGA) score of 2 to 4 (see below) involving at least 30% of treatable BSA, with the exception of the face, scalp, and intertriginous areas.

Table 96: Investigator’s Static Global Assessment (CPE.C.201 or Study 201)

Score	=	Definition
0	=	Clear, except for minor residual discoloration; no erythema or scaling
1	=	Almost clear; there may be trace faint pink erythema and minimal scaling
2	=	Mild; there may be light pink erythema and mild scaling
3	=	Moderate; there may be pink-red erythema and moderate scaling
4	=	Severe; there may be deep or bright red erythema and severe scaling

Source: Sponsor’s NDA submission, module 5, Study report CPE.C.201, p. 24.

The study was to be performed under maximal use conditions as agreed upon at the Pre-IND meeting of 11/24/2003. Subjects applied treatments twice daily (morning and evening) for two weeks to a minimum of 30% treatable body surface area (BSA), defined as all affected areas with the exception of the face, scalp, and intertriginous areas. The dose was defined as the smallest amount of study drug required to cover all areas affected by atopic dermatitis. If the disease cleared the subject was to continue to apply study drug to at least 30% BSA. The total dose of EF Clobetasol foam was not to exceed more than 50 g. per week.

Subjects were enrolled in the following age cohorts:

- Cohort 1: ≥ 18 years old
- Cohort 2: $\geq 12 < 18$ years old
- Cohort 3: $\geq 6 < 12$ years old
- Cohort 4: $\geq 3 < 6$ years old
- Cohort 5: ≥ 3 months < 3 years old

¹ Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Dermatovener (Stockholm); 1980;92:44–47.

To begin the study, Cohorts 1 and 2 were concurrently enrolled. Each cohort was to enroll 15 evaluable subjects. Enrollment into Cohort 3 was not permitted until all Cohort 1 and Cohort 2 subjects had completed the study. A further condition was that HPA axis suppression be demonstrated in no more than 35% of subjects in Cohort 1 and 25% of subjects in Cohort 2. Cohort 4 enrollment was not to be allowed until all Cohort 3 subjects had completed the study, with HPA axis suppression being demonstrated in no more than 20% of subjects in Cohort 3. Cohort 5 enrollment was not to be allowed until all Cohort 4 subjects had completed the study, with HPA axis suppression being demonstrated in no more than 15% of subjects in Cohort 4. Cohort 5 enrollment was to cease if HPA axis suppression was demonstrated in more than 10% of subjects in Cohort 5.

This study was conducted at 5 investigative sites in the United States from 07/08/2004 through 04/06/2005. Enrollment totaled 52 subjects. Enrollment was as follows:

- 1) Cohort 1 - 22 subjects (This cohort was over-enrolled to ensure 15 evaluable subjects.)
- 2) Cohort 2 - 15 subjects
- 3) Cohort 3 - 15 subjects.
- 4) Cohort 4 - 0 subjects
- 5) Cohort 5 - 0 subjects

Subjects received the cosyntropin stimulation test prior to treatment, at screening (day -7 to -3) and at conclusion of therapy (day 14). Subjects received 0.25 mg of Cortrosyn either IV over a two minute period or IM. The criterion to establish a normal response was a post-injection serum cortisol level greater than 18 µg/dL. The Conditional Visit was scheduled for 4 weeks following last study drug administration if subjects had any of the following; abnormal cosyntropin stimulation test at Visit 3, other abnormal laboratory results, or study drug-related adverse experiences requiring follow-up.

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Table 97: Summary Statistics for Cosyntropin Stimulation Test in Subjects with Abnormal Response (Study 201)

Subject	Cohort	Screening ^a		Visit 3 ^b		Visit 4 ^c	
		Pre µg/dL	Post µg/dL	Pre µg/dL	Post µg/dL	Pre µg/dL	Post µg/dL
126-0001	1	23	31.1	0.9	6	19.7	27.7
151-0002	1	16.4	29	5.2	16.9	22	34.6
151-0004	1	19.2	24.7	6.7	12.6	21.4	31
152-0001	1	19.1	24.6	3	7.4	22.3	26.8
152-0002	1	21.5	37.1	2.1	12	16.9	36.3
151-0021	3	11	32	1	11	5.8	28.7
151-0024	3	8	24	0.1	5	8.1	26.8
151-0025	3	9	19	0.1	9.2	15.7	23.2
151-0029	3	15.9	22.6	0.1	2	12.3	21.5
151-0030	3	8.9	22.7	6.7	16.1	7.9	19.7
151-0032	3	16	27	7.3	15.9	17.5	23.1
155-0002	3	12	31	0.1	1.7	7.1	20

^a Screening occurred from 7 to 3 days prior to Baseline Visit.

^b This visit occurred at end of treatment (Day 15 ± 2 days).

^c This visit was scheduled for those having abnormal CST results at Visit 3. It occurred 4 weeks after treatment.

Source: Adapted from Sponsor's NDA Submission, Module 5, Study Report CPE.C.201, p. 39, data listing A_CPE201.SAS7BDAT.

Table 98: Incidence of (Reversible) HPA Axis Suppression by Cohort (Study 201)

	Cohort 1	Cohort 2	Cohort 3	Total
Number of Subjects	22	15	15	52
Week 2/End of Treatment				
n	21	15	15	51
Suppression	5 (24%)	0 (0%)	7 (47%)	12 (24%)
Conditional Visit				
n	5	0	7	12
Reversible Suppression	5 (100%)	NA	7 (100%)	12 (100%)

Note: Suppression is defined as a post-injection serum cortisol level less than or equal to 18 µg/dL. Reversible Suppression is defined as a post-injection serum cortisol level great than 18 µg/dL at the Conditional Visit after the cortisol level was less than or equal to 18 µg/dL at the Week 2/End of Treatment Visit.

Source: Sponsor's NDA submission, module 5, Study Report CPE.C.201, p 41.

Overall 24% (12/51) of subjects demonstrated HPA axis suppression. For Cohort 1 the figure was 24% (5/21) of subjects. In Cohort 2, no subjects demonstrated evidence of HPA axis suppression. The fact that the middle cohort showed no suppression could be the result of the

small numbers in the study. In Cohort 3, 47% (7/15) subjects demonstrated HPA axis suppression.

Three of the five subjects in Cohort 1 are noted to have applied greater than 150 g of study drug in the 2-week treatment period. One subject applied 152.2 g of study drug; another applied 193.7 g and a third applied 260.5 g of study drug. The subjects had been instructed to apply a thin layer of study drug to their diseased skin excluding scalp, face, and intertriginous areas for 2 weeks regardless of clearing of disease but were not to apply more than 50 g per week.

Since the level of suppression in Cohort 3 was 47% (7/15) of subjects, enrollment into Cohorts 4 and 5 was not initiated. The protocol requirement was for the proportion of subjects in Cohort 3 demonstrating suppression to be less than 20% of subjects. The study was therefore terminated after completion of Cohort 3.

The subjects who had demonstrated HPA axis suppression at Week 2, at the Conditional Visit, had serum cortisol levels greater than 18 µg/dL. They were therefore considered to have reversed their HPA axis suppression.

Comments:

For the calculation of % suppression, the sponsor has used a denominator of 52 overall, and 21 for Cohort 1. The sponsor states (p. 40 of the Final Report for Study CPE.C.301) that; "The Week 2 specimens for Subject 119-0002 were considered to be non-viable on receipt at the laboratory." This subject in Cohort 1 was enrolled and completed the study but was not included in the percentage of subjects showing suppression calculations. On Visit 3 this subject had a Pre cosyntropin stimulation value for serum cortisol of .9µg/dL. The Post cosyntropin stimulation value is missing ("non-viable"). On Visit 4 this subject had a Pre stimulation value of 17.2µg/dL and a post stimulation value of 29.2µg/dL. It appears likely that this subject's Visit 3 Post cosyntropin stimulation value would have indicated suppression. To be conservative, it would be appropriate to include this subject both in the numerator and denominator of calculations involving percentage of subjects showing suppression. Thus for Cohort 1, the value becomes 6/21(29%), for Cohorts 1&2, the value becomes 6/37(16%), and for overall the value becomes 13/52(25%).

Examination of drug usage reveals that of 12 patients who suppressed, 6 of these used more than 100 grams of study drug in the two week study period. Thus 50% of those using more than 100grams of study drug a week suppressed. This compares with a rate of 12/51(24%) for all patients and a rate of 6/41(15%) for those who used less than 100 grams of study drug. If subject 119-0002 is counted among those suppressed, the figures become 6/13(46%), 13/52(25%), and 7/42 (17%) respectively. These calculations suggest that a dose-response effect is occurring with respect to suppression, and a further caution against using more than 100 grams of the drug product over a two week period.

Cosyntropin stimulation was performed at screening (day -7 to -3) and again at conclusion of therapy (day 14), an interval shorter than the recommended 4 weeks. This may have resulted in higher stimulated cortisol levels after the second dosing.

Safety:

There were no severe AEs, serious adverse experiences (SAEs), life-threatening AEs or deaths noted during this study. Only one subject in Cohort 2 reported a treatment-related AE, mild folliculitis, and that was considered probably related to the study drug.

Conclusions:

Systemic safety was evaluated with the Phase 2 study, CPE.C.201, wherein the potential for HPA axis suppression was studied in 52 pediatric and adult patients with mild to moderate atopic dermatitis. A significant number of patients, 7 out of 15 (47%), in the youngest cohort, ages 6 to 11, showed suppression. No younger cohorts were studied since the prespecified proportion of subjects (20%) showing suppression in cohort 3 was exceeded. The proportion of subjects 12 years of age and older demonstrating HPA axis suppression was 16.2% (6 out of 37). The laboratory suppression reversed in all subjects, returning to normal by 4 weeks after last treatment

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Clinical Review
Patricia C. Brown, MD
NDA 22-013
Primolux Foam, 0.05% (clobetasol propionate)

10.2 Line-by-Line Labeling Review

Below is the draft package insert current as of the time of completion of this review. Please refer to the approval letter for the final FDA approved package insert.

6 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

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