Evaluation of the Efficacy and Safety of Clobetasol Propionate Spray in the Treatment of Plaque-Type Psoriasis

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Treatment of the inflammatory component of plaque psoriasis is an important part of psoriasis management. A new and unique spray formulation of clobetasol propionate 0.05% may provide advantages over the currently available formulations through easy application to hard-to-reach areas and the ability to deliver a fixed dose of corticosteroid per spray. The purpose of this study was to evaluate the efficacy and safety of clobetasol propionate spray 0.05% in the treatment of moderate to severe plaque-type psoriasis. This study was conducted as a multicenter, randomized, double-blinded, vehicle-controlled, parallel-group, comparative study in subjects with plaque psoriasis. Subjects were randomized to receive either clobetasol propionate spray 0.05% (n=60) or vehicle spray (n=60) twice daily for 4 weeks, followed by a 4-week treatment-free follow-up period. Efficacy evaluations at all visits included assessment of scaling, erythema, plaque elevation, pruritus, and overall disease severity.

Success rates for each of the signs and symptoms evaluated, as well as for the overall disease severity assessment, were significantly in favor of clobetasol propionate (P≤.001). The additional 2 weeks of treatment from weeks 2 to 4 increased the number of cleared subjects from 2% to 25%; treatment success was still in favor of clobetasol propionate (P<.001) at week 8 (4 weeks post-treatment). No treatment-related serious adverse events occurred during the course of the study. Mild application site burning/stinging was the most common treatment-related adverse event, with similar frequency and severity for both active and vehicle groups. There were no reports of skin atrophy, telangiectasia, folliculitis, or hypothalamus-pituitary-adrenal axis suppression. Overall, clobetasol propionate spray 0.05% administered twice daily for 4 weeks was effective and safe in reducing scaling, erythema, plaque elevation, and overall disease severity and demonstrates durable clinical response up to 4 weeks after treatment end.

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Psoriasis has a considerable effect on a patient's quality of life, with many patients complaining about the messiness of the topical agents used to treat the disease, as well as the profound psychologic impact of the treatments and the disorder.[1-5]

Clobetasol propionate is known for its anti-inflammatory, antipruritic, vasoconstrictive, and immunomodulatory properties. It currently is used for the treatment of certain hyperproliferative and/or

inflammatory dermatoses, including psoriasis and atopic dermatitis. The drug's efficacy and safety is well-defined in the medical literature, and it is the most common corticosteroid used to treat psoriasis.[6,7]

In the past, different vehicles containing clobetasol propionate 0.05% (eg, foams, solutions) have been evaluated, and results showed that patients preferred easy-to-spread foams and solutions to creams, gels, and ointments, suggesting that the characteristics of solutions and foams may favor improved compliance to topical therapy.[8]

In an effort to expand on the current treatment options, a new spray formulation of this superpotent corticosteroid was developed for patients experiencing difficulties in adequately treating their psoriasis (eg, patients living alone, patients with physical disabilities, elderly patients, patients with lesions difficult to reach) or patients seeking to minimize the time spent on their treatment. The spray formulation is based on a cosmetically elegant emollient, isopropyl myristate, and alcohol carrier. A recent intraindividual study conducted in 27 subjects with moderate to severe psoriasis demonstrated that the spray formulation of clobetasol propionate 0.05% is highly efficient and safe in the treatment of moderate to severe psoriasis.[9]

The aim of the present study was to confirm the efficacy and safety of clobetasol propionate spray 0.05% compared with its vehicle spray in a larger group of patients with moderate to severe plaque-type psoriasis.

Methods

The study received approval from the appropriate institutional review board for each center prior to subject enrollment and was conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent prior to entering the study.

Study Design and Population—For this 4-week, multicenter, randomized, double-blinded, vehicle-controlled, parallel-group, comparative study, 120 subjects with moderate to severe psoriasis were to be recruited. Subjects could be of either sex, had to be at least 18 years of age, and had to present with an area of plaque psoriasis covering at least 2% of the body surface area (BSA)(excluding the face, scalp, groin, axillae, and other intertriginous areas). The overall disease severity score on the area of the target lesion that was treated, accounting for scaling, erythema, and plaque elevation, had to be scored as at least 3 (moderate) on a scale ranging from 0 (none) to 4 (severe/very severe). Women of childbearing potential had to have a negative urine pregnancy test and had to agree to use an effective nonprohibited form of birth control for the duration of the study. Prior to entering the study, subjects had to respect treatment-specific wash-out periods as defined by the protocol regarding any topical and systemic treatments known to affect psoriasis, including immunomodulatory therapies and exposure to natural or artificial UV radiation.

Treatment—Suitable subjects were randomized in a 1:1 ratio to receive either clobetasol propionate spray 0.05% or the vehicle spray. Subjects were instructed to apply the study medication twice daily for 4 weeks to all active psoriasis plaques.

Subjects were further instructed to allow at least 8 hours between applications, not to wash the treated area for at least 4 hours following an application, and not to apply the study medication within 4 hours prior to any study visit. The treatment phase was followed by a 4-week treatment-free follow-up period.

Efficacy and Safety Parameters—Study evaluations took place at baseline and on weeks 1, 2, 4, and 8 (follow-up 4 weeks after the end of treatment). Scaling, erythema, plaque elevation, pruritus, and overall disease severity were assessed using a 5-point scale (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe/very severe).

The primary response measure was the calculated success rate, dichotomized as failure or success in overall disease severity, defined as a grade of 2 (mild) or less on the 5-point scale at week 2 and defined as a grade of 1 (almost clear) or less on the same scale at the end of treatment at week 4. Secondary parameters included the comparison of the clobetasol propionate spray group with the vehicle group at weeks 1 and 8 for overall disease severity; psoriasis signs and symptoms (scaling, erythema, plaque elevation, and pruritus), scored on a 5-point scale, at all other visits; and calculated treatment success (graded 1 or less) at week 8. Overall safety was evaluated throughout the study by adverse events reported (eg, skin atrophy, telangiectasia, burning/stinging, and folliculitis), as well as for clinical signs and symptoms of hypothalamus-pituitary-adrenal axis suppression.

Statistical Methods—There were 3 study populations: the intent-to-treat population (all subjects enrolled and randomized), the per-protocol population (only those subjects and visits that were considered evaluable), and the safety population (all subjects who received treatment). A sample size of 53 subjects (treatment group) was deemed sufficient to detect a true difference in success rate of 30% in the overall disease severity (45% vs 15%) with a power of 0.9 and a type I error rate of 0.05 (2-tailed). A total of 108 to 124 subjects were to be enrolled and randomized.

Demographics and baseline characteristics were evaluated by the Cochran-Mantel-Haenszel test, while group differences in age and percentage of BSA involved were assessed by the Wilcoxon rank sum test. Frequency distributions for overall disease

severity, psoriasis signs and symptoms, and dichotomized success rates were summarized by treatment group with frequency counts and percentages for all visits. The success rate of all parameters measured was calculated for each time point using a Cochran-Mantel-Haenszel test to confirm the superiority of clobetasol propionate spray 0.05%. Statistical significance of the above efficacy parameters was based on 2-tailed tests of the null hypothesis, resulting in *P* values of .05 or less.

Results

Subject Demographics and Baseline Data—A total of 120 subjects, 60 in each treatment group, were included and completed the trial (Table). There were no statistically significant differences for any of the demographic variables or baseline data between the 2 treatment groups. More men (38; 63%) than women (22; 37%) were recruited for the clobetasol propionate group. Most subjects in the clobetasol propionate group were white (95%). The mean percentage of BSA involved was 7.19; 93% of subjects in the clobetasol propionate group presented with moderate overall disease severity and 7% of subjects presented with severe/very severe overall disease severity.

In the vehicle group, the man/woman ratio was somewhat more balanced (57% men, 43% women). Most of the subjects in the vehicle group were white (93%). The mean percentage of BSA involved was 8.19; 88% of subjects presented with moderate overall disease severity and 12% of subjects presented with severe/very severe overall disease severity.

Efficacy—The analysis of the primary efficacy criteria at week 2 demonstrated a statistically significant ($P<.001$) success rate in favor of clobetasol propionate spray 0.05%: 52 subjects (87%) were considered to be successfully treated with clobetasol propionate versus 17 subjects (28%) treated with the vehicle spray. Despite the more restrictive criteria for success at week 4 than at week 2 (subjects had to be almost or completely clear at week 4, but mild disease or better was considered success at week 2), 47 subjects (78%) were qualified as successfully treated after 4 weeks of treatment with clobetasol propionate compared with 2 subjects (3%) treated with vehicle. The difference was statistically significant ($P<.001$). The additional treatment period of 2 weeks after week 2 resulted in 14 additional subjects (23%) (increased from 2% to 25%) with total clearing of their disease and a higher percentage of cleared or almost cleared subjects (78% vs 55%) with clobetasol propionate. Percentages of cleared and almost cleared overall disease severity in subjects at weeks 2 and 4 are shown in Figure 1.

Success rates at week 1 for overall disease severity and for signs and symptoms of psoriasis and pruritus reached statistically significant differences ($P<.001$, $P<.01$, and $P<.001$, respectively). At weeks 2 and 4, success rates for psoriasis signs and symptoms were all in favor of clobetasol propionate, and the differences were statistically significant (all $P<.001$)(Figure 2).

The clinical evaluation of the overall disease severity at the 4-week posttreatment follow-up visit (week 8) demonstrated that 25 of 57 subjects (44%) in the clobetasol propionate group (data missing for 3 subjects) remained a treatment success compared with 2 of 54 subjects (4%) in the vehicle group (data missing for 6 patients) (Figure 3). The difference was statistically significant ($P<.001$). This result was paralleled by outcomes for signs and symptoms: most subjects in the clobetasol propionate group remained clear or almost clear, and the differences to the vehicle were statistically significant for scaling, erythema, plaque elevation, and pruritus ($P\leq.001$). Figure 4 shows photographs of a subject treated with clobetasol propionate at baseline, week 4, and week 8.

Safety—Burning/stinging was the only queried adverse event associated with the topical application of the study medication, both active and vehicle. This adverse event was reported by 14 subjects (23%) within 15 minutes following the first application of clobetasol propionate and by 13 subjects (22%) following the application of the vehicle. The incidence of burning/stinging decreased throughout the study (Figure 5), but most of those reports were mild in severity. The similarity of burning/stinging between the active and placebo groups suggests this is very likely to be a vehicle effect, possibly related to the alcohol content. No cutaneous signs of skin atrophy, telangiectasia, or folliculitis were detected in either group throughout the duration of the study.

Although clinical signs and symptoms of hypothalamus-pituitary-adrenal axis suppression were not anticipated during this study, the investigator or designee examined and directly queried the subjects for clinical signs and symptoms of adrenal suppression at each study visit. No adrenal suppression was described during the study.

Comment

Subjects with psoriasis have a wide choice of topical treatments and selecting the right product is important for treatment success.[10] A 2003 study confirmed that patients prefer easy-to-use and easy-to-spread formulations, especially when treatments have to be used regularly and over a long period.[11]

Superpotent topical steroids such as clobetasol propionate 0.05% are used in the management of

Subject Demographics and Baseline Data*

	Clobetasol Propionate Spray 0.05%	Vehicle Spray
No. of subjects	60	60
Age, y		
Mean±SD	46.72±12.73	49.30±13.05
Range	21.0–76.0	24.0–73.0
Sex, n (%)		
Men	38 (63)	34 (57)
Women	22 (37)	26 (43)
Race, n (%)		
White	57 (95)	56 (93)
Black	2 (3)	1 (2)
Hispanic/Latino	1 (2)	2 (3)
American/Alaskan native	0 (0)	1 (2)
BSA involved, %		
Mean±SD	7.19±5.33	8.19±6.9
Scaling, n (%)		
2 (mild)	2 (3)	0 (0)
3 (moderate)	49 (82)	52 (87)
4 (severe/very severe)	9 (15)	8 (13)
Erythema, n (%)		
2 (mild)	4 (7)	2 (3)
3 (moderate)	48 (80)	49 (82)
4 (severe/very severe)	8 (13)	9 (15)
Plaque elevation, n (%)		
2 (mild)	4 (7)	4 (7)
3 (moderate)	53 (88)	50 (83)
4 (severe/very severe)	3 (5)	6 (10)
Pruritus, n (%)		
0 (none)	3 (5)	4 (7)
1 (almost clear)	4 (7)	3 (5)
2 (mild)	22 (37)	13 (22)
3 (moderate)	26 (43)	34 (57)
4 (severe/very severe)	5 (8)	6 (10)
Overall disease severity, n (%)		
3 (moderate)	56 (93)	53 (88)
4 (severe/very severe)	4 (7)	7 (12)

*BSA indicates body surface area.

psoriasis as short-term "pulsed" therapy. The present study demonstrates a significant ($P<.001$) reduction in disease with 47 subjects (78%) achieving treatment success of clear or almost clear at week 4 when treated with clobetasol propionate spray 0.05%. In the United States, most marketed superpotent topical steroids are indicated for 2 weeks of treatment. The additional 2 weeks of treatment in this study increased the number of cleared and almost cleared subjects from 33 subjects (55%) to 47 subjects (78%) in the clobetasol propionate group without affecting the overall and local tolerability of the medication. Treatment success was maintained during the 4-week treatment-free follow-up period with 25 subjects (44%) remaining cleared or almost cleared compared with only 2 subjects (4%) in the vehicle group.

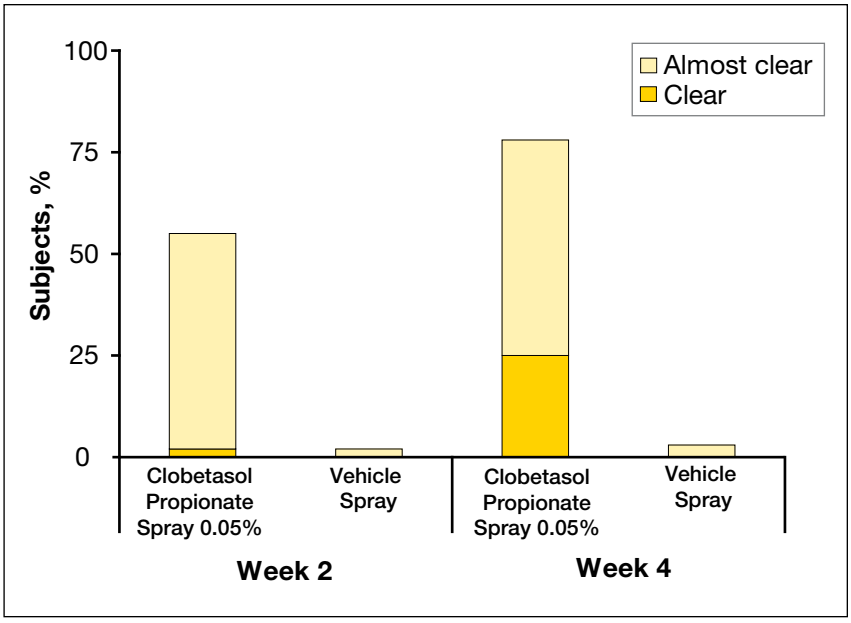

Figure 1. Subjects in the intent-to-treat population who were clear or almost clear in overall disease severity at weeks 2 and 4.

In a separate safety study, 41 subjects with at least moderate to severe plaque psoriasis on at least 20% of their BSA (excluding the face, scalp, groin, axillae, and other intertriginous areas) were enrolled and randomized to treatment for either 14 or 28 days with clobetasol propionate spray 0.05%.[12] The study was designed to determine the

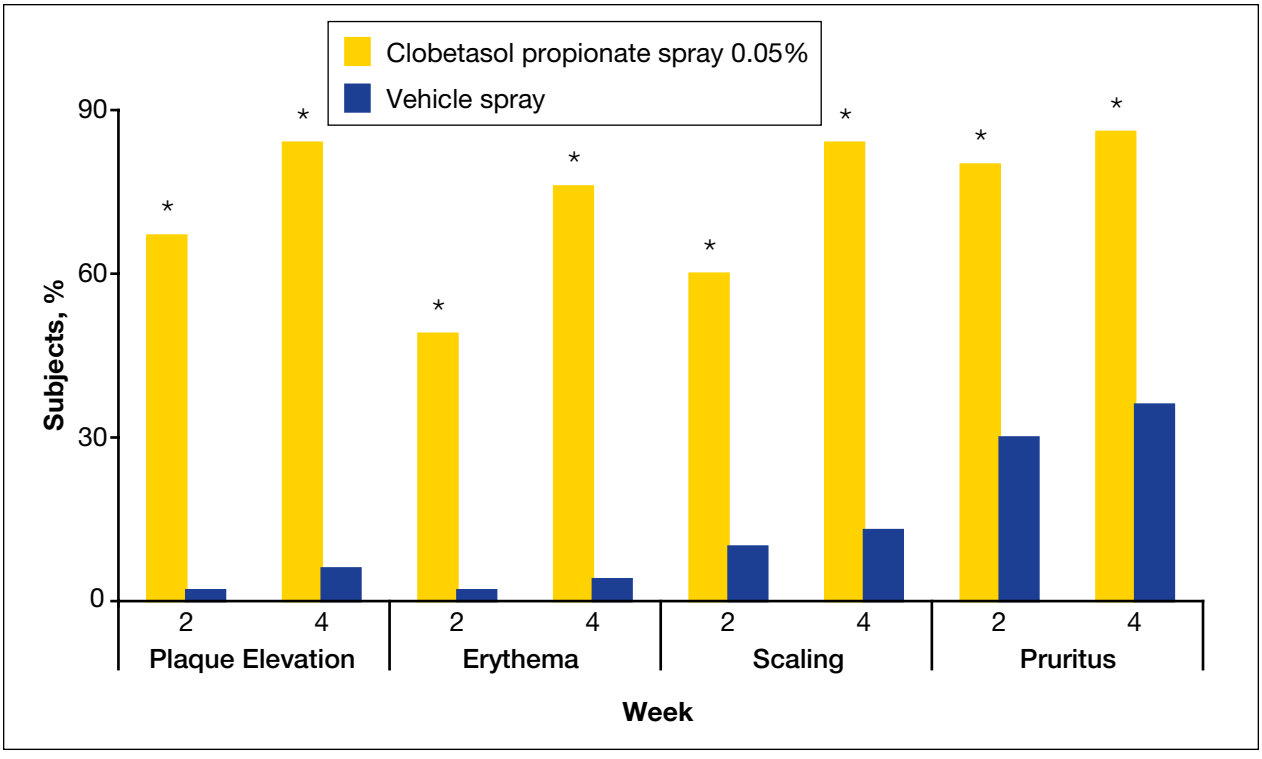

Figure 2. Subjects in the intent-to-treat population who were clear or almost clear of psoriasis signs and symptoms at weeks 2 and 4 (end of treatment). Asterisk indicates $P<.001$.

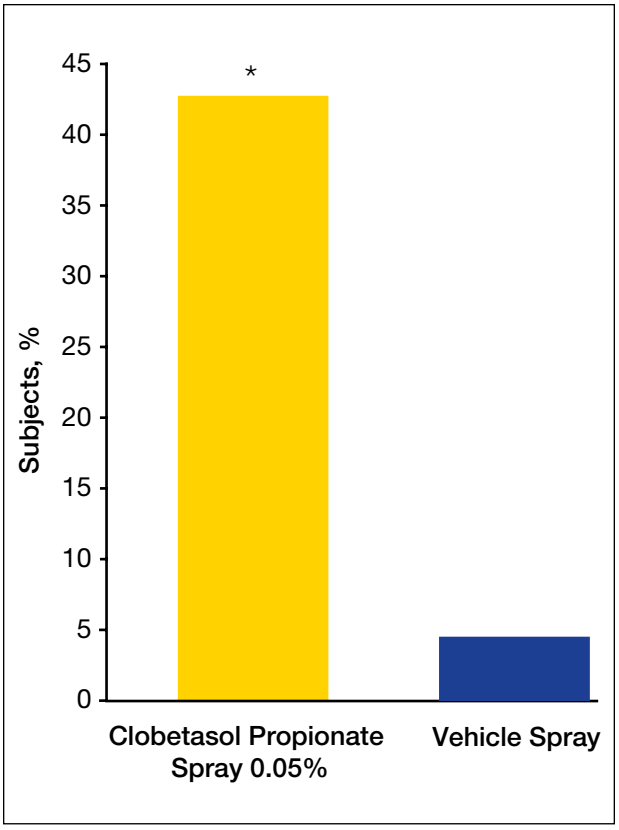

Figure 3. Percentage of subjects who demonstrated success in overall disease severity for both groups at the 4-week posttreatment follow-up visit (week 8) based on the intent-to-treat population. Data were missing for 3 subjects in the clobetasol propionate group and 6 subjects in the vehicle group. Asterisk indicates $P<.001$.

adrenal suppression potential of the study medication when the subject applied a maximum of 7 g/d (3.5 g twice daily) for a total of approximately 50 g/wk. All subjects had a cosyntropin stimulation test to assess their hypothalamus-pituitary-adrenal system response at visit 1 and at the end of the scheduled treatment period (or earlier if the investigator verified the subject's psoriasis has cleared). In addition to the cosyntropin stimulation test, subjects had samples for routine 8-hour fasting hematology, chemistry, and urinalysis.[12]

Of the 41 subjects enrolled in the study, 36 subjects had data that were included in the modified intent-to-treat analysis.[12] Nineteen subjects applied the medication twice daily for 2 weeks, and 17 subjects applied the medication twice daily for 4 weeks. Of these evaluable subjects, laboratory-based adrenal suppression was documented in 4 subjects in each treatment group. In all subjects, adrenal function had returned to normal within 2 weeks.[12] The extent of laboratory-based suppression reported in this study is consistent with other class 1 steroids,[13] and the length of treatment does not appear to increase the incidence or the duration of the adrenal suppression. In addition, the lack of any clinically significant drug-related events in any of these subjects is consistent with other currently marketed clobetasol formulations.

Conclusion

Clobetasol propionate spray 0.05% is effective and safe in the treatment of moderate to severe plaque-type psoriasis. The increase of the usually prescribed 2-week treatment period for corticosteroids of this potency to 4 weeks yielded an increased clinical benefit, including additional clearing and improvement of disease, with no substantial change in the safety profile. The spray formulation of clobetasol propionate 0.05% may provide an appealing, easy-to-apply, and potent short-term treatment alternative for specific patient groups.

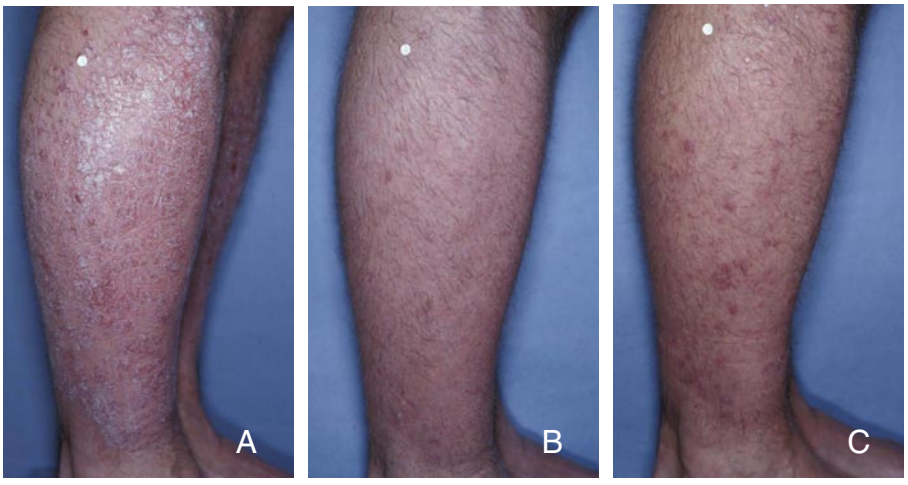

Figure 4. Subject treated with clobetasol propionate spray 0.05% at baseline (A), week 4 (B), and week 8 (follow-up 4 weeks after completion of treatment)(C).

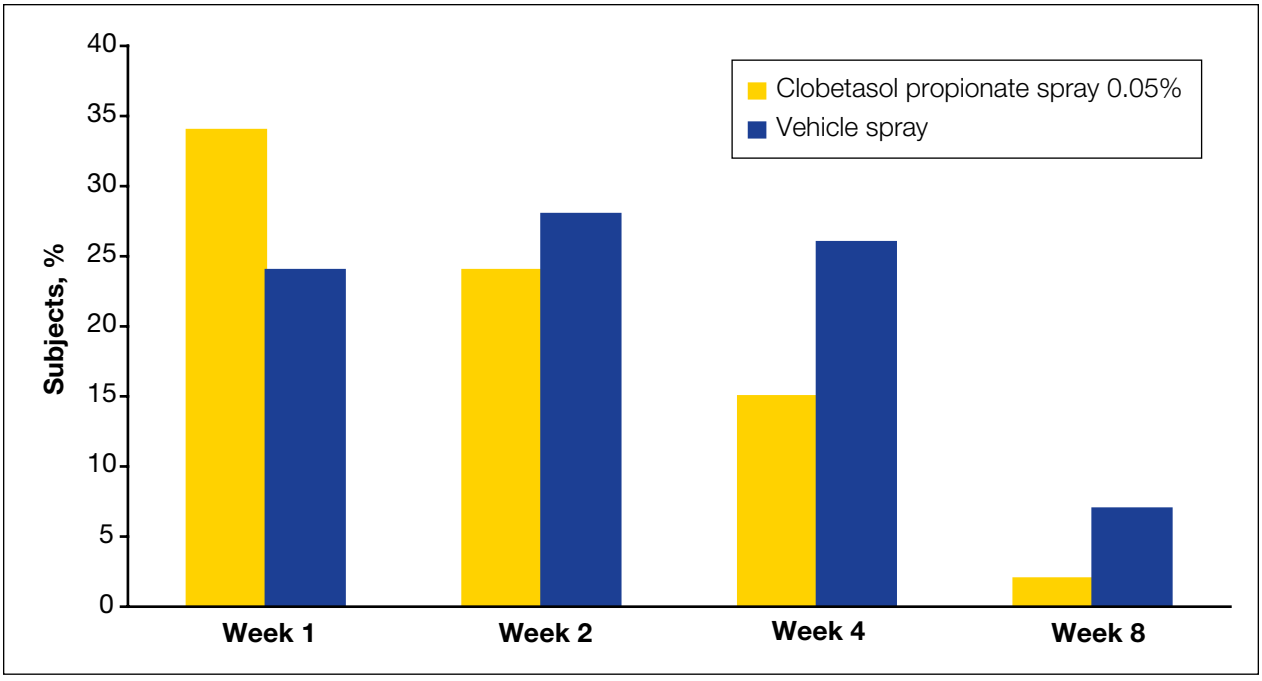

Figure 5. The incidence of burning/stinging decreased throughout the study, from weeks 1 to 4 and at week 8 (4 weeks after completion of treatment) based on the intent-to-treat population.

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