An Open-label, Multicenter Study of the Efficacy and Safety of a Weekday/Weekend Treatment Regimen With Calcitriol Ointment 3 µg/g and Clobetasol Propionate Spray 0.05% in the Management of Plaque Psoriasis

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High-potency topical corticosteroids are the cornerstone of psoriasis therapy. Although highly effective, long-term use of topical steroids can cause adverse side effects. Additionally, steroids alone do not address the multiple pathophysiologic factors that cause the disease. Psoriasis regimens that utilize high-potency steroids combined with nonsteroid-containing products such as vitamin D analogs have been used for many years to manage the disease, not only for the short-term treatment of the disease but also for long-term

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treatment to minimize the recurrence of symptoms. We report an open-label, multicenter study designed to evaluate a weekday/ weekend treatment regimen involving calcitriol ointment 3 μ g/g and clobetasol propionate spray 0.05% for moderate plaque psoriasis. Participants applied calcitriol ointment 3 μ g/g twice daily on the weekdays and clobetasol propionate spray 0.05% twice daily on the weekends for up to 4 weeks. Participants were evaluated at baseline, week 2, and week 4. The results of this study

consultant and investigator for and has received grants and honoraria from Eli Lilly and Company; a consultant for and has received honoraria from Genentech, Inc; an advisory board member and investigator for and has received grants and honoraria from Graceway Pharmaceuticals, LLC; a consultant and investigator for and has received grants and honoraria from GlaxoSmithKline; a consultant, investigator, and speaker for and has received grants and honoraria from Stiefel, a GSK company; and an advisory board member, consultant and investigator for and has received grants and honoraria from UCB. Dr. Smith is a consultant for Aqua Pharmaceuticals, LLC, and Galderma Laboratories, LP, and is a speaker for Abbott Laboratories and Centocor Ortho Biotech Inc. He also reports ownership in Therapeutics, Inc. Dr. Sofen is an advisory board member and is a clinical trial investigator for Galderma Laboratories, LP. Ms. Colón and Drs. Johnson and Gottschalk are employees of Galderma Laboratories, LP.

This study was registered on October 1, 2009, at www.clinicaltrials .gov with the identifier NCT00988637.

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demonstrate that a 4-week regimen of calcitriol ointment $3\mu g/g$ treatment on weekdays and clobetasol propionate spray 0.05% on weekends is effective and well-tolerated for the treatment of moderate plaque psoriasis.

Cutis. 2011;88:201-207.

soriasis is a chronic inflammatory skin condition that affects approximately 2% of the worldwide population and carries substantial physical and psychological burden.¹⁻³ As a serious and chronic disease, long-term treatment applications are desired, and specific treatment regimens often are designed for individual patient needs. Topical corticosteroids have been a standard of care in the treatment of plaque psoriasis since the 1950s.³ They are effective in treating plaque psoriasis because of their antiinflammatory and antiproliferative properties; however, prolonged use can cause a number of adverse side effects, including hypopigmentation, folliculitis, skin atrophy, telangiectases, and potential suppression of the hypothalamic-pituitary-adrenal axis.^{4,5} Vitamin D analogs also have become a mainstay of psoriasis treatment since their introduction in the 1990s.⁶ Vitamin D helps normalize dysfunctional cellular differentiation and also possesses antiproliferative activity. Therefore, combining agents such as corticosteroids and vitamin D analogs that have unique and complementary mechanisms of action could provide substantial benefit to psoriatic patients.⁷

Consensus guidelines recommend combination therapies for patients with plaque psoriasis that provide efficacy and safety while minimizing exposure to high-potency steroids and other agents with potential adverse events (AEs) from longer-term use.⁴ Clobetasol propionate spray 0.05%, a super highpotency steroid, currently is indicated and used for the treatment of moderate to severe plaque psoriasis in adults.⁸ Calcitriol ointment 3 μ g/g, which contains the naturally occurring and biologically active form of vitamin D, has been developed for the treatment of mild to moderate plaque psoriasis with a twice-daily application in patients 18 years and older.⁹ Long-term use of calcitriol ointment 3 $\mu g/g$ has been shown to be well-tolerated,¹⁰ and its use in treatment regimens with a super high-potency steroid is a treatment option consistent with consensus guideline recommendations.⁴

The objective of this study was to evaluate the efficacy and safety of a weekday/weekend dosing regimen involving calcitriol ointment 3 μ g/g and clobetasol propionate spray 0.05% for participants with moderate plaque psoriasis. Participants applied calcitriol ointment 3 μ g/g twice daily on the weekdays

and clobetasol propionate spray 0.05% twice daily on the weekends for up to 4 weeks.

Methods

The study was conducted in accordance with the Declaration of Helsinki, Finland (1964), and its Tokyo, Japan (1975); Venice, Italy (1983); Hong Kong (1989); Somerset West, South Africa (1996); and Edinburgh, Scotland (2000) amendments, as well as the International Conference on Harmonisation Good Clinical Practice principles, US Food and Drug Administration Code of Federal Regulations, Health Insurance Portability and Accountability Act, and local regulatory requirements.

Study Design and Treatment—This open-label, multicenter study was conducted in participants aged 18 to 80 years inclusive with moderate plaque psoriasis. For inclusion in this study, female participants of childbearing potential must have had a negative urine pregnancy test at the beginning of the study and must have agreed to practice an effective method of contraception for the duration of the study. Participants with 3% to 10% treatable body surface area (most areas were treated with the exception of the face, scalp, groin, axillae, and other intertriginous areas) also were included in this study. Participants using medication(s) to treat a concurrent medical condition were allowed to participate in the study if the type and dose of the medication(s) were stable for at least 3 months prior to study entry and were not expected to change during the study. Participants receiving treatment with beta-blockers or lithium, whose dose had been stable for at least 6 months and who had shown no worsening of their psoriasis, were included in the study at the discretion of the investigator. Participants meeting the specific enrollment criteria followed a weekday/weekend treatment regimen, applying calcitriol ointment 3 μ g/g twice daily on the weekdays and clobetasol propionate spray 0.05% twice daily on the weekends for 4 weeks.

Female participants who were pregnant, nursing, or planning a pregnancy during the study were excluded from this study. Participants with a known allergy to any of the components of the study products; participants with intakes of more than 50 μ g per day of vitamin D and/or more than 1000 mg per day of calcium; participants who foresaw intensive UV exposure during the study; and participants whose psoriasis involved only the face, scalp, groin, axillae, and/or other intertriginous areas also were excluded from this study. Participants with a washout period for topical treatment (any steroid-containing medication, calcipotriene, anthralin, tar, and/or UVB treatment) less than 30 days and a washout period for systemic treatment (corticosteroids, biologics, and/or

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psoralen plus UVA treatment) less than 12 weeks also were excluded from this study.

Assessments—Participants were evaluated at each visit for overall disease severity (ODS), global assessment of improvement (GAI), signs of psoriasis, and percentage treatable body surface area (BSA). In this study, most areas were treated with the exception of the face, scalp, groin, axillae, and other intertriginous areas. The ODS score at week 4 (intent-to-treat [ITT] population) was the primary efficacy assessment. Overall disease severity is comprised of the assessment of 3 key characteristics of plaque psoriasis: (1) scaling, (2) erythema, and (3) plaque elevation (Table 1). The secondary end points included the ODS score at week 2 (ITT population), GAI scores at weeks 2 and 4, signs of psoriasis at weeks 2 and 4, and percentage change from baseline in percentage treatable BSA at weeks 2 and 4.

Safety evaluations included tolerability assessments and incidence of AEs. For the tolerability assessments, pruritus, telangiectases, burning/ stinging, skin atrophy, and folliculitis were evaluated at each visit.

Participants completed a satisfaction questionnaire at the final visit. Participants also completed the Koo-Menter psoriasis index 12-item quality of life questionnaire (PQOL-12) at baseline and the final visit.

Statistical Analysis—Descriptive statistics were provided to summarize demographic data, efficacy end points, tolerability end points, AEs, participant satisfaction, and quality of life data at all appropriate study visits. For the primary efficacy end point, the full-scale ODS scores at week 4 were compared to baseline using the Cochran-Mantel-Haenszel test after ridit transformation. For the secondary efficacy

Table 1.

Score	Assessment	Description			
0	Clear	Scaling: no evidence of scaling			
		Erythema: no evidence of erythema (except possible residual discoloration)			
		Plaque elevation: no evidence of plaque elevation above normal skin level			
1	Almost clear	Scaling: limited amount of very fine scales partially covers some of the plaques			
		Erythema: very few of the plaques are light red			
		Plaque elevation: very slight elevation above the normal skin level, easier felt than seen			
2	Mild	Scaling: mainly fine scales; some plaques are partially covered			
		Erythema: some plaques are light red			
		Plaque elevation: slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped, on some of the plaques			
3	Moderate	Scaling: somewhat coarser scales; most plaques are partially covered			
		Erythema: most plaques are red			
		Plaque elevation: moderate elevation with rounded or sloped edges on most of the plaques			
4	Severe	Scaling: coarse, thick scales; virtually all or all plaques are covered; rough surface			
		Erythema: virtually all or all plaques are bright to dusky red			
		Plaque elevation: marked to very marked elevation with hard to very hard sharp edges on virtually all or all of the plaques			

Overall Disease Severity

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end points, the full-scale ODS scores at week 2 were compared to baseline using the Cochran-Mantel-Haenszel test after ridit transformation. The GAI scores and the percentage change from baseline in percentage treatable BSA were summarized at week 2 and 4. Signs of psoriasis and participant satisfaction were summarized at each applicable time point with frequency tables. No statistical analyses were conducted for these variables. Adverse events, tolerability, and compliance data were summarized using descriptive statistics on the safety population. No statistical analyses were conducted for these variables.

Results

Demographics—Table 2 outlines the participant demographics for the ITT population (N=70). Most of the participants were male (43/70 [61%]) and white (65/70 [93%]) with Fitzpatrick skin types II (24/70 [34%]), III (19/70 [27%]), or IV (19/70 [27%]). The mean age was 46.4 years with a mean history of psoriasis for 20.6 years and a mean percentage treatable BSA at baseline of 5.8%. The range of treatable BSA in participants was 3% to 10%.

Primary Efficacy Assessment—The study results demonstrate that the weekday/weekend treatment regimen was efficacious with a significant improvement in ODS at week 4 of the treatment regimen (P<.001). Figure 1 summarizes the ODS distribution at week 4 in the ITT population. At baseline, all participants had an ODS of moderate (70/70 [100%]) (not shown). At week 4, 79% (55/70) of the participants were deemed clear, almost clear, or mild.

Secondary Efficacy Assessments—Improvement in ODS at week 2 also is shown in Figure 1. At week 2, 59% (41/70) of the participants were deemed clear, almost clear, or mild. The ODS distribution was significantly different between baseline and week 2 (P<.001).

The GAI at weeks 2 and 4 is shown in Figure 2. At weeks 2 and 4, 74% (52/70) and 81% (57/70) of participants, respectively, had global improvement scores of definite improvement, considerable improvement, and clearing.

The signs of psoriasis also were evaluated at weeks 2 and 4. At baseline, 14% (10/70), 9% (6/70), and 16% (11/70) of participants had mild scores for scaling, erythema, and plaque elevation, respectively. At week 2, 89% (62/70), 50% (35/70), and 67% (47/70) had clear/almost clear/mild scores for scaling, erythema, and plaque elevation, respectively, while at week 4, 91% (64/70), 60% (42/70), and 77% (54/70) had clear/almost clear/mild scores for scaling, erythema, and plaque elevation, respectively. The distribution of scores for each of the signs of psoriasis was significantly different between

Table 2.

Participant Demographics

	1			
	ITT Population (N=70)			
Age, y				
Mean (SD)	46.4 (14.0)			
Median	48.0			
Minimum, Maximum	18.0, 74.0			
Gender, n (%)				
Male	43 (61)			
Female	27 (39)			
Race, n (%)				
White	65 (93)			
Black	4 (6)			
American Indian/ Alaska Native	1 (1)			
Other or mixed	0 (0)			
Fitzpatrick skin type, n (%)				
1	1 (1)			
II	24 (34)			
III	19 (27)			
IV	19 (27)			
V	4 (6)			
VI	3 (4)			
History of psoriasis, y				
Mean (SD)	20.6 (14.1)			
Treatable BSA at baseline, %				
Mean (SD)	5.8 (2.3)			
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Abbreviations: ITT, intent to treat; SD, standard deviation; BSA, body surface area.

baseline and week 2 (P<.001) as well as baseline and week 4 (P<.001).

The final secondary efficacy assessment was the percentage change from baseline in percentage treatable BSA at weeks 2 and 4. The median percentage change from baseline in percentage treatable BSA at weeks 2 and 4 was -16.7% and -33.3%, respectively (Figure 3), which is significantly different compared to baseline at week 2 (*P*<.003) and at week 4 (*P*<.002).



Figure 1. Percentage of participants who achieved overall disease severity scores of clear, almost clear, or mild at weeks 2 and 4 of treatment with calcitriol ointment 3 μ g/g on weekdays and clobetasol propionate spray 0.05% on weekends (N=70). Overall disease severity scores were significantly improved at weeks 2 and 4 compared to baseline (*P*<.001).



Figure 2. Percentage of participants with scores of definite improvement, considerable improvement, or clearing on the global assessment of improvement at weeks 2 and 4 of treatment with calcitriol ointment 3 μ g/g on weekdays and clobetasol propionate spray 0.05% on weekends compared to baseline (N=70).



Figure 3. Median percentage change from baseline in percentage treatable body surface area at weeks 2 and 4 of treatment with calcitriol ointment 3 μ g/g on week-days and clobetasol propionate spray 0.05% on week-ends (N=70).

Safety Assessments—Table 3 shows the tolerability assessments. At week 4, there were no reports of skin atrophy, and most of the participants had no pruritus (36/70 [51%]), no telangiectases (65/70 [93%]), no burning/stinging (55/70 [79%]), and no folliculitis (65/70 [93%]).

There were 12 AEs reported by 12 participants on the weekday/weekend regimen and all AEs were mild or moderate in severity (12/12 [100%]). Adverse events included 1 report each of application-site irritation, pain, skin burning sensation, skin irritation, sinusitis, tooth infection, headache, and lower respiratory tract infection, and 4 reports of upper respiratory tract infection. Most of the AEs were definitely unrelated or unlikely related (8/12 [67%]) to the study medications. There were no serious AEs reported in this study.

Participant Satisfaction—Table 4 summarizes the results of the participant satisfaction questionnaire at week 4 (safety population). Most participants on the weekday/weekend regimen strongly agreed/moderately agreed that the treatment program was easy to follow (63/70 [90%]). Most participants also strongly agreed/moderately agreed that they were satisfied with their appearance (49/70 [70%]), satisfied with the results of the treatment program (58/70 [83%]), and would use the treatment program again (58/70 [83%]).

Comment

Treatment regimens that combine high-potency steroids with nonsteroid-containing products such as vitamin D or vitamin D analogs are important therapeutic options for psoriatic patients. Psoriasis is a multifactorial disease and regimens that utilize agents with complementary mechanisms of actions can be of great benefit. Additionally, combination regimens can help minimize potential adverse side effects associated with the long-term use of topical steroids. Several studies have been done testing the efficacy of high-potency corticosteroids in combination with the vitamin D analog calcipotriene.¹¹⁻¹⁵ There is 1 published study evaluating a treatment regimen that combines a high-potency corticosteroid with calcitriol in the management of plaque psoriasis.¹⁶

Our study reports the efficacy and safety of a combined treatment regimen for moderate plaque psoriasis consisting of calcitriol ointment 3 μ g/g twice daily on the weekdays and clobetasol propionate spray 0.05% twice daily on the weekends. The results of the study demonstrate a significant improvement in ODS at weeks 2 and 4 of the study (*P*<.001 for both) as well as significant reduction in signs of psoriasis (*P*<.001 for both) and percentage treatable BSA at weeks 2 and 4 (*P*<.003 and *P*<.002,

Table 3. Tolerability Assessments (Safety Population; N=70)^{a,b}

	Participants, n (%)				
Tolerability Assessments	None	Mild	Moderate	Severe	Present
Baseline					
Pruritus	6 (9)	24 (34)	25 (36)	15 (21)	
Telangiectases	68 (97)	1 (1)	1 (1)	O (O)	
Burning/stinging	49 (70)	10 (14)	9 (13)	2(3)	
Skin atrophy					1 (1)
Folliculitis					1 (1)
Week 2 ^c					
Pruritus	33 (47)	29 (41)	7 (10)	0 (0)	
Telangiectases	68 (97)	1 (1)	0 (0)	0 (0)	
Burning/stinging	51 (73)	16 (23)	2 (3)	0 (0)	
Skin atrophy					0 (0)
Folliculitis					0 (0)
Week 4 ^d					
Pruritus	36 (51)	29 (41)	2 (3)	0 (0)	
Telangiectases	65 (93)	2 (3)	0 (0)	0 (0)	
Burning/stinging	55 (79)	11 (16)	1 (1)	0 (0)	
Skin atrophy					0 (0)
Folliculitis					2 (3)

^aTolerability assessments are reported for the safety population, which includes all participants who received at least 1 dose of any of the study products. Percentages may not add up to 100% due to missing assessments and/or rounding.

^bTolerability assessments of pruritus, telangiectases, and burning/stinging were rated as none, mild, moderate, or severe; skin atrophy and folliculitis were considered present (or not present [not shown]).

°Assessments were not available for 1 participant.

^dAssessments were not available for 3 participants.

respectively). The weekday/weekend regimen resulted in improved quality of life scores (data not shown) and most participants agreed that the treatment program was easy to follow. This treatment regimen also was welltolerated, with reported AEs being mild or moderate in severity and primarily unrelated to the study medications. There were no serious AEs reported in this study. Consistent with prior studies of clobetasol propionate spray 0.05% over 4 weeks,^{17,18} there were no reports of skin atrophy or telangiectases in this 4-week study. Previously 1 case of skin atrophy and 1 case of telangiectasis were reported in a clinical trial with clobetasol propionate spray 0.05%, which indicated that even in 4 weeks of use, skin atrophy and telangiectases may occur.¹⁹ Two limitations of this study are the small number of participants and the lack of a vehicle arm. However, the results of the study do show that a combination regimen using 2 agents with complementary mechanisms of action provides an efficacious and well-tolerated treatment option in the management of plaque psoriasis.

Conclusion

The treatment regimen of calcitriol ointment $3 \mu g/g$ twice daily on the weekdays and clobetasol propionate spray 0.05% twice daily on the weekends was efficacious, well-tolerated, and resulted in high participant satisfaction, thus making it a viable

Table 4.

Participant Satisfaction Questionnaire at Week 4 (Safety Population; N=70)

Survey Statement	Response	Participants, n (%)
The treatment program was easy to follow.	Strongly agree/ moderately agree	63 (90)
I am satisfied with my appearance.	Strongly agree/ moderately agree	49 (70)
I am satisfied with the results of the treatment program.	Strongly agree/ moderately agree	58 (83)
l would use this treatment program again.	Strongly agree/ moderately agree	58 (83)

alternative treatment regimen for patients with moderate plaque psoriasis.

Acknowledgment—The authors would like to thank Renée M. McKay, PhD, for her role in writing this article. Her work was funded by Galderma Laboratories, LP. Revisions of the manuscript for important intellectual content were performed by each of the listed authors.

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