

Long-term Safety of Ketoconazole Foam, 2%, in the Treatment of Seborrheic Dermatitis: Results of a Phase IV, Open-Label Study

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ABSTRACT

Background: Ketoconazole foam, 2%, is approved in the United States for seborrheic dermatitis therapy in immunocompetent patients aged ≥12 years. While short-term trials have demonstrated its safety and efficacy, seborrheic dermatitis often requires long-term treatment.
Objective: To assess the long-term safety of ketoconazole foam, 2%, twice daily, as required.
Methods: A 12-month, open-label, multicenter study. Subjects were evaluated at baseline and at weeks 4, 8, 16, 26, 39, and 52 (or early termination [ET]) for adverse events (AEs), serious AEs (SAEs), target lesion erythema, scaling, and pruritus, as well as Investigator's Static Global Assessment (ISGA) scores. Physical examinations were performed at baseline and at week 52/ET, and laboratory evaluations at baseline and at weeks 8, 26, and 52. A poststudy product-preference questionnaire was completed.
Results: Of 500 subjects enrolled, 498 were included in the safety population, and 363 completed the study. Overall, 57% of subjects reported ≥1 AE. Treatment-related AEs occurred in 14% of subjects, including application-site irritation (8%), application-site pain (4%), application-site pruritus (1%), and increased alanine aminotransferase (1%). Seven subjects were withdrawn because of treatment-related AEs. No SAEs (21 in 17 subjects) were considered to be related to study drug. Mean target lesion erythema, scaling, and pruritus scores improved by 2 units from baseline at all study visits; mean ISGA score improved by 1 unit at week 4 and by 2 units at subsequent visits. The foam vehicle was preferred by 67% of subjects.
Limitations: Evaluation of severity was limited to target lesion; no objective measure of adherence.
Conclusion: The long-term safety profile of ketoconazole foam, 2%, in subjects with seborrheic dermatitis was favorable and efficacy was maintained. This trial was registered at clinicaltrials.gov (NCT00703846).

J Drugs Dermatol. 2013;12(1):e1-e6.

INTRODUCTION

Seborrheic dermatitis is a multifactorial, recurrent inflammation of the skin that presents as pruritic, erythematous, scaly patches most commonly occurring in sebum-rich areas such as the face, scalp, and chest.[1] An inflammatory response against *Malassezia* species, opportunistic fungal pathogens that are normally present as skin commensals, underlies the etiology of the disease.[2,3]

Topical antifungal agents are the most common treatment for recurrent seborrheic dermatitis[4,5] and are not often associated with the skin atrophy or telangiectasia seen with prolonged use of topical corticosteriods.[2] Topical ketoconazole, 2%, an imidazole derivative active against species of *Malassezia*, has been approved in the United States as a cream since 1985 and as a shampoo since 1990. In 2007, ketoconazole foam, 2%, was approved in the United States for the topical treatment of seborrheic dermatitis when used twice daily for 4 weeks in immunocompetent patients 12 years and older. The vehicle used to deliver topical agents in dermatology can have a considerable effect on efficacy, and foam vehicles have advantages over creams, ointments, and solutions in drug bioavailability.[6,7] In addition, the cosmetic aspects of a foam delivery system, eg, nongreasy and low residue, may be associated with increased patient adherence,[6] particularly in hair-bearing areas, as commonly occurs in seborrheic dermatitis.

The objective of this study was to assess the long-term safety of ketoconazole foam, 2%, applied twice daily, as required, for up to 12 months in the treatment of seborrheic dermatitis.

METHODS

Study Design

This was an open-label, multicenter study to assess the long-term safety of ketoconazole foam, 2%, (Extina®; Stiefel, a GSK Company, Research Triangle Park, NC) in the treatment of seborrheic dermatitis (NCT00703846). Patients were recruited from 18 investigational centers in the United States between June 2008 and April 2010. The study was performed in accordance with Good Clinical Practice (ICH Topic E6) and the guiding principles of the Declaration of Helsinki and had institutional review board approval.

Participants

Subjects 12 years or older were eligible to participate if they had seborrheic dermatitis on the face, scalp, ears, neck, or chest with an Investigator's Static Global Assessment (ISGA) score

TABLE 1.

Subject Demographics and Baseline Characteristics

Characteristic	Ketoconazole Foam, 2% (n=498)
Age (years)	
Mean (SD)	47.2 (17.4)
Minimum, maximum	12, 89
Age category, n (%)	
12 to <18 years	14 (3)
18 to 65 years	402 (81)
>65 years	82 (16)
Sex, n (%)	
Male	259 (52)
Female	239 (48)
Race, n (%)	
American Indian or Alaska Native	20 (4)
Asian	8 (2)
Black	108 (22)
Multiracial	14 (3)
Native Hawaiian or Other Pacific Islander	2 (<1)
White	346 (69)
Ethnicity, n (%)	
Hispanic or Latino	75 (15)
Not Hispanic or Latino	423 (85)
Weight (kg)[a]	
Mean (SD)	87.3 (22.4)
Height (cm)	
Mean (SD)	170.5 (11.0)
Locations affected by seborrheic dermatitis,[b] n (%)	
Face	347 (70)
Scalp	430 (86)
Ears	188 (38)
Neck	32 (6)
Chest	30 (6)
Location of target lesion, n (%)	
Face	214 (43)
Scalp	252 (51)
Ears	18 (4)
Neck	7 (1)
Chest	7 (1)
Target area (cm^2)	
Mean (SD)	8.6 (16.30)
Median	4.0
Minimum, maximum	0.3, 192

SD, standard deviation. [a]n=497. [b]Subjects may have had ≥1 area of involvement.

of 2 to 4 at baseline and a discrete, evaluable target lesion of at least 0.5 cm^2 with a score of 2 to 4 for erythema and scaling on the seborrheic dermatitis grading scale. Exclusion criteria included use of systemic antifungal agents, corticosteroids or other immunosuppressive therapies, or systemic retinoids within 4 weeks before baseline; use of topical antifungal therapy, corticosteroid therapy, or calcineurin inhibitors to the face, scalp, ears, neck, or chest within 2 weeks before baseline; use of any investigational drugs other than the study product within 4 weeks before baseline or during the study period; use of any medication that, in the investigator's opinion, may have affected the evaluation of the study product or placed the subject at undue risk; intolerance to ketoconazole or its excipients; female subjects who were pregnant, trying to become pregnant, or lactating; any clinically relevant abnormal vital signs or findings in the physical examination; any clinically relevant history of alcohol or drug abuse; major illness within 30 days before baseline; immunocompromisation; or any clinically significant condition that would compromise the subject's participation in the study.

Interventions

All subjects attended up to 7 study visits over a 52-week period. At baseline (day 1), all subjects signed and dated an informed consent document, were evaluated against the inclusion/exclusion criteria, provided their medical history, and were given a diary card and ketoconazole foam, 2%, with application instructions. Subjects applied ketoconazole foam, 2%, topically in the morning and evening to all seborrheic dermatitis lesions on the face, scalp, ears, neck, and chest at the first sign of a symptom flare, until the treatment areas cleared. All symptom flares were treated throughout the 12-month study period.

Assessments

At all study visits (baseline, weeks 4, 8, 16, 26, 39, and 52 or early termination [ET]), subjects provided concomitant medication information, vital signs were measured, and target lesions were evaluated by the investigator for erythema, scaling, and pruritus (on individual scales of 0 to 4, no/mild symptoms to severe symptoms) and ISGA score (on a scale of 0 to 4 based on erythema and scaling scores, where the higher score indicates more severe symptoms). Used study product containers and completed diary cards were returned and replaced at each study visit except week 52 or ET. Used study product containers were weighed before dispensing and after collection, and subjects were questioned regarding their compliance with study-product application at each study visit. Every observed and reported adverse event (AE) was recorded at all postbaseline study visits. Blood and urine samples were collected at baseline and at weeks 8, 26, and 52 (or ET) for clinical laboratory analyses. At baseline and at week 52 (or ET), subjects received a physical examination and females of childbearing potential completed a pregnancy test. Subjects completed a poststudy questionnaire to collect information regarding their impressions of the foam

TABLE 2.

Adverse Events Occurring in ≥1% of Subjects by Preferred Term and Study Period (Safety Population)

Preferred Term, n (%)	Complete Study Duration[a] (n=498)	Reported in Months 0 to <3 (n=498)	Reported in Months 3 to <6 (n=427)	Reported in Months 6 to <9 (n=380)	Reported in Months 9 to <12 (n=341)
Nasopharyngitis	41 (8)	19 (4)	11 (3)	8 (2)	9 (3)
Application-site irritation	38 (8)	36 (7)	1 (<1)	2 (1)	1 (<1)
Headache	32 (6)	21 (4)	10 (2)	12 (3)	6 (2)
Upper respiratory tract infection	29 (6)	20 (4)	6 (1)	3 (1)	0
Application-site pruritus	19 (4)	16 (3)	2 (<1)	1 (<1)	1 (<1)
Sinusitis	19 (4)	9 (2)	5 (1)	3 (1)	2 (1)
Influenza	13 (3)	8 (2)	2 (<1)	0	2 (1)
Pharyngolaryngeal pain	12 (2)	5 (1)	3 (1)	4 (1)	1 (<1)
Cough	8 (2)	5 (1)	2 (<1)	0	1 (<1)
Gastroesophageal reflux disease	8 (2)	5 (1)	1 (<1)	0	0

[a]Subjects were only counted once for any particular adverse event within each study duration period. The number of subjects in the 3-month study periods, therefore, may not total the number of subjects in the complete study duration for any given adverse event.

vehicle of the study product at week 52 or ET. The questionnaire asked subjects to evaluate the study-product delivery system (ie, the foam vehicle) relative to other product forms or types (ie, gels, creams, ointments, and shampoos) that they had used previously to treat seborrheic dermatitis. The questionnaire did not ask subjects to evaluate the efficacy of the study product. The questionnaire specifically included the following items: what types of products have you ever used to treat your seborrheic dermatitis; rank the product types from 1 (product type you prefer most) to 5 (product type you prefer least); rank the product types from 1 to 5 on ease of use, speed of absorption, versatility, and overall preference.

Analysis Population

The safety analysis population was defined as all subjects who received at least one application of the study product.

Study End Points

The primary end point was the long-term safety of ketoconazole foam, 2%, applied twice daily as needed for up to 12 months in the treatment of seborrheic dermatitis. Efficacy of ketoconazole foam, 2%, was evaluated according to erythema, scaling, and pruritus assessments, and ISGA score of the target lesion.

Sample Size and Statistical Methods

A sample size of 500 subjects was originally planned for enrollment in order to obtain ≥300 and ≥100 evaluable subjects at 6 months and 12 months, respectively, to provide long-term safety information on the use of ketoconazole foam, 2%. No power calculation was performed. Statistical analyses were performed using the safety analysis population, and descriptive statistics were used to provide an overview of all evaluation endpoints. Data from all investigational centers were combined in the calculations, unless otherwise stated.

All statistical analyses were performed using SAS software (version 9.1.3; SAS Institute Inc, Cary, NC). Safety variables were tabulated using observed data only; no imputations were made for missing data.

RESULTS

Study Population

A total of 500 subjects were recruited. Of these, 498 subjects were included in the safety population (2 subjects did not apply the study product), and 363 subjects completed the 12-month study (Figure 1). The most common reasons for study discontinuation were loss to follow-up (41%; 55/135 who discontinued) or withdrawal of consent (30%; 40/135). Subjects were predominantly white (69%; 346/498) and 18 to 65 years of age (81%; 402/498; Table 1). The most common areas affected by seborrheic dermatitis were the face (70%; 347/498) and scalp (86%; 430/498). Target lesions were also most commonly located on the face (43%; 214/498) and scalp (51%; 252/498).

Primary End Point: Safety Assessments

Adverse Events

The majority of subjects (69%; 341/498) applied ketoconazole foam, 2%, for 39 weeks or more, and 48% (238/498) used the study product for at least 50 weeks. Overall, 57% (282/498) of subjects experienced at least one AE. Subjects most commonly reported

TABLE 3.

Mean Change from Baseline in Target Lesion Erythema, Scaling, and Pruritus, and ISGA Scores

	Erythema Score	Scaling Score	Pruritus Score	ISGA Score
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline (Day 1) (n=498)	3 (0.59)	3 (0.60)	3 (0.90)	3 (0.57)
Week 4 (n=451)	–2 (1.02)	–2 (1.03)	–2 (1.22)	–1 (0.94)
Week 8 (n=436)	–2 (0.98)	–2 (1.00)	–2 (1.13)	–2 (0.91)
Week 16 (n=405)	–2 (0.93)	–2 (0.93)	–2 (1.11)	–2 (0.88)
Week 26 (n=381)	–2 (0.91)	–2 (0.98)	–2 (1.13)	–2 (0.94)
Week 39 (n=370)	–2 (0.95)	–2 (1.03)	–2 (1.07)	–2 (0.98)
Week 52 (or ET) (n=420)	–2 (1.03)	–2 (1.07)	–2 (1.13)	–2 (1.04)

ET, early termination; ISGA, Investigator's Static Global Assessment; SD, standard deviation.

AEs in the first 3 months of the study (41%; 202/498), while 20% (86/427) of subjects reported AEs in months 3 to <6; 22% (82/380) in months 6 to <9, and 17% (58/341) in months 9 to <12. AEs reported by >1% of subjects are shown in Table 2. Severe AEs were experienced by 8% (38/498) of subjects; those occurring in more than one subject included application-site irritation (3 subjects), headache (3 subjects), back pain (2 subjects), depression (2 subjects), pneumonia (2 subjects), and seborrheic dermatitis (2 subjects). Of these, only application-site irritation was considered to be related to the study product. No individual AE was reported by >8% of subjects, and most were unrelated to the study product. Treatment-related AEs were reported by 14% (70/498) of subjects; those reported by ≥1% of subjects included application-site irritation (8%; 38/498), application-site pain (4%; 19/498), application-site pruritus (1%; 6/498), and increased alanine aminotransferase (ALT; 1%; 3/498).

A total of 21 serious AEs (SAEs) were reported for 17 subjects; 1 subject had an AE of hepatitis C (no treatment received), which, in the study sponsor's opinion, was serious, although it was later downgraded by the investigator to nonserious; 1 subject died of lung cancer. None of the SAEs were considered to be related to the study product or, with the exception of the subject who died, resulted in discontinuation from the study.

Nine subjects discontinued use of the study product because of AEs; 7 due to nonserious treatment-related AEs, 5 of which were related to application-site irritation and/or pain; 2 due to nonserious AEs that were not related to the study product, and 1 of which required the use of an excluded medication (Figure 1).

Clinical Laboratory Results

Overall, there were few changes in clinical laboratory results observed over the course of the study, and no new safety signals or trends were observed in association with any of the mean changes in hematology or chemistry values. Treatment-related AEs associated with clinical laboratory abnormalities included increased ALT (3 subjects; 1%), increased aspartate aminotransferase (2 subjects; <1%) and increased total protein (1 subject; <1%). Minor variations were observed in the proportions of subjects with high, normal, and low clinical laboratory values at each study visit relative to baseline. Abnormalities in clinical laboratory results were infrequent, and while clinically relevant increases were observed at a small number of visits, they were generally transient and did not suggest any trend.

Vital Signs Measurements and Physical Examination Findings

No clinically meaningful changes from baseline in temperature, sitting blood pressure, or pulse rate were observed. Changes in vital signs were reported as AEs in 12 subjects; however, none were considered to be related to the study product. No clinically significant changes from baseline or abnormal physical examination findings were reported as AEs.

Efficacy Assessments

On average, target lesions had moderate erythema, scaling, and pruritus at baseline (Table 3). A 2-unit improvement from baseline in mean (standard deviation [SD]) severity was recorded for target lesion erythema, scaling, and pruritus (baseline scores: 3 [0.59] units, 3 [0.6] units, and 3 [0.9] units, respectively) at week 4, and maintained thereafter at weeks 8, 16, 26, 39, and 52 (or ET). Target lesions had faint erythema, minimal scaling, and minimal pruritus at all postbaseline study visits. A 1-unit improvement from baseline in mean [SD] ISGA score (baseline score: 3 [0.57]) for the target lesion was observed at week 4, followed by a 2-unit improvement at week 8, which was maintained at weeks 16, 26, 39, and 52 (or ET).

The poststudy questionnaire on patient preferences showed that approximately two-thirds of patients preferred a foam to other forms of vehicle used previously for seborrheic dermatitis (Table 4a). A similar score was obtained for the overall preference of the foam vehicle (Table 4b).

DISCUSSION

The primary objective of this study was to evaluate the long-term safety of ketoconazole foam, 2%, used twice daily in the treatment of seborrheic dermatitis in immunocompetent subjects 12 years and older. Following evaluation of all reported

TABLE 4.

Poststudy Questionnaire on Patient Preferences					
(a) Ranking of Product Types Used for Seborrheic Dermatitis					
Ranking, n (%)	Gels (n=126)	Creams (n=222)	Ointments (n=184)	Shampoos (n=311)	Foams (n=385)
1st	3 (2)	33 (15)	14 (8)	98 (32)	257 (67)
2nd	20 (16)	75 (34)	46 (25)	138 (44)	72 (19)
3rd	34 (27)	65 (29)	47 (25)	39 (13)	30 (8)
4th	27 (21)	42 (19)	38 (21)	18 (6)	13 (3)
5th	42 (33)	7 (3)	39 (21)	18 (6)	13 (3)
(b) Ranking of Overall Most Preferred Product					
Ranking, n (%)	Gels (n=134)	Creams (n=228)	Ointments (n=192)	Shampoos (n=320)	Foams (n=397)
1st	6 (4)	34 (15)	15 (8)	89 (28)	266 (67)
2nd	23 (17)	73 (32)	43 (22)	142 (44)	76 (19)
3rd	32 (24)	71 (31)	54 (28)	36 (11)	30 (8)
4th	32 (24)	40 (18)	46 (24)	23 (7)	13 (3)
5th	41 (31)	10 (4)	34 (18)	30 (9)	12 (3)

Note: Percentages are based on the number of responses for each product category. Rankings were for products that subjects had used previously.

and observed AEs, SAEs, clinical laboratory results, vital signs measurements, physical examination findings, and reasons for study discontinuation, application-site reactions were the only consistent AE associated with the study product. This is consistent with the currently approved package insert for ketoconazole foam, 2%,[7] and previous studies.[8-10] Most of the treatment-related AEs that led to study discontinuation were associated with application-site pain and/or irritation, and no treatment-related SAEs were observed. Minor variations observed in the proportions of subjects with high, normal, and low clinical laboratory values over the course of the study were not unexpected owing to the age, concurrent medical conditions, and concomitant medications of the participants, as well as the duration of the study. Overall, no new safety signals or trends were identified in any of the safety parameters assessed in this 12-month study. As seborrheic dermatitis is a chronic condition requiring prolonged treatment, this study provides important safety data on the long-term use of ketoconazole foam, 2%.

Although efficacy of ketoconazole foam, 2%, was not a stated end point of the study, data collected regarding target lesion erythema, scaling, pruritus, and ISGA scores throughout the duration of the study were evaluated as efficacy variables. Improvements in lesions were evident from week 4, and although loss of subjects to follow-up limits the conclusions that can be drawn, the use of ketoconazole foam, 2%, did appear to maintain efficacy in those who continued the study.

The completed product preference questionnaire, intended to obtain information on the cosmetic acceptability of the study-product delivery system, showed that a high number of subjects preferred the foam vehicle to other types of application for seborrheic dermatitis, including shampoos. The delivery system of a topical agent is an important consideration for the patient and may influence treatment adherence. Dermatologic conditions such as seborrheic dermatitis can impact quality of life; however, this impact may be lessened through adequate adherence to treatment.[11] Foam vehicles are preferred by patients over creams and ointments, particularly in hair-bearing areas, owing to their ease of application and low residue,[9] and use of a foam vehicle may improve adherence in the treatment of seborrheic dermatitis. Poor dermatology-related quality of life is also a predictor of poor adherence.[11]

The study had some limitations. Evaluation of severity was limited to the target lesion only and did not include any additional flares that may have occurred during the study. Also, there was no objective measure of adherence. However, due to the long-term nature of seborrheic dermatitis treatment, study-product usage by subjects in this study would reflect real-world or better usage.

"The majority of subjects found ketoconazole foam, 2%, the most highly preferred delivery vehicle, which may increase treatment adherence in patients with chronic seborrheic dermatitis."

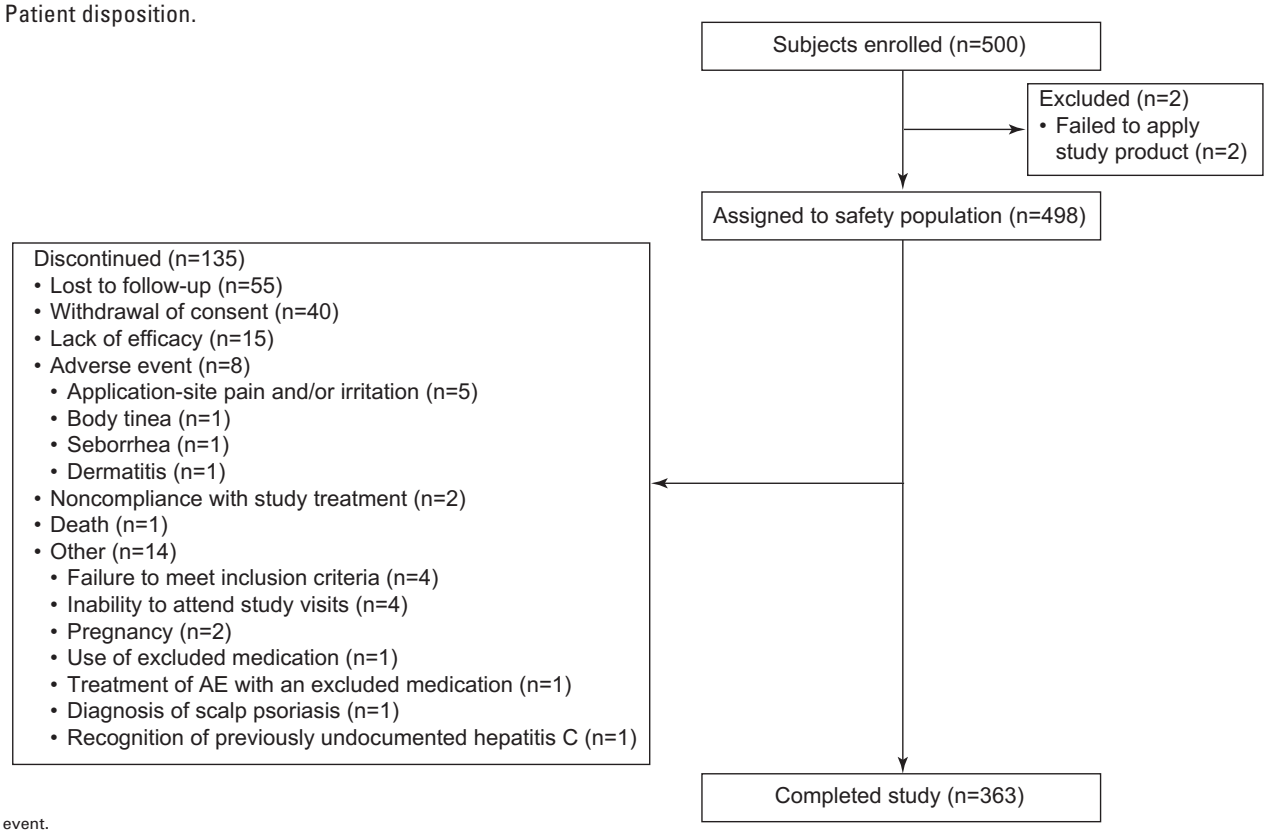
CONCLUSION

Ketoconazole foam, 2%, had a favorable safety profile when applied topically twice daily for up to 52 weeks by subjects with seborrheic dermatitis and maintained efficacy for the duration of the study. The safety profile of ketoconazole foam, 2%, observed during this study was consistent with that described in the currently approved package insert for the product. The majority of subjects found ketoconazole foam, 2%, the most highly preferred delivery vehicle, which may increase treatment adherence in patients with chronic seborrheic dermatitis.

ACKNOWLEDGMENTS

The authors thank the investigators and participants from the various centers in Study U0275-01, which included the follow-

FIGURE 1. Patient disposition.



AE, adverse event.

ing principal investigators: Texas: W. Abramovits, M. Jarratt, A. Menter, A. Moore, A. Pandya; California: E. Boh; North Carolina: Z. Draelos, S. Feldman; Alabama: B. Elewski; Rhode Island: E. Frankel; Massachusetts: A. Kimball; Virginia: D. Pariser; Florida: M. Rendon, D. Rodriguez, J. Spencer, S. Weiss; Oregon: P. Rich; Michigan: L. Stein Gold. The authors thank Alyson Bexfield PhD of Caudex Medical, Oxford, UK (supported by Stiefel, a GSK company, Research Triangle Park, NC), for assistance with preparing the initial draft of the manuscript, collating the authors' comments, and assembling the tables.

DISCLOSURES

Dr. Draelos has received research support from Stiefel, a GSK company, including in relation to the study presented here. Dr. Feldman has received speaking, research, and/or consulting support from Stiefel/GSK, Astellas, Novartis, and Galderma Laboratories. Ms. Butners and Dr. Alió Saenz are employees of Stiefel, a GSK company.

This study was supported by Stiefel, a GSK company, Research Triangle Park, NC.

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