Ketoconazole Gel 2% in the Treatment of Moderate to Severe Seborrheic Dermatitis

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Seborrheic dermatitis traditionally has been treated with topical steroids. In current practice, however, antifungal agents such as ketoconazole often are used because Malassezia *yeasts are thought to play a role in the disease pathogenesis. Ketoconazole gel 2% has been developed for the once-daily treatment of seborrheic dermatitis. This gel is almost invisible after application, unlike ketoconazole cream, and may offer advantages in patient acceptance and adherence to treatment. Three randomized, double-blinded, vehicle-controlled, multicenter, parallel-group phase 3 studies evaluated the efficacy and tolerability of ketoconazole gel 2% compared with a vehicle gel in more than 900 subjects with moderate to severe seborrheic dermatitis who applied treatment for 14 days and were followed for an additional 14 days. Two of these studies also compared a combination gel containing ketoconazole 2% and desonide 0.05%, each active gel individually, and a vehicle control. Subjects were considered effectively treated if the erythema and scaling as well as investigator global assessment (IGA) scores decreased to 0 (or 1 if the baseline score was ≥3) by day 28. Pooled data from these studies showed that the proportion of effectively treated subjects was significantly greater in the ketoconazole gel 2% treatment group compared with the vehicle group* (P<.001). *The comparison of the combination gel to its individual components revealed that the efficacy of ketoconazole alone was comparable to the combination gel as well as desonide gel alone for up to 2 weeks after the end of treatment. These data suggest that once-daily ketoconazole gel 2% is an effective treatment for seborrheic dermatitis and a viable alternative to the ketoconazole cream 2% formulation.*

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Seborrheic dermatitis is a common inflammatory scaling disease that affects areas of the skin containing sebaceous glands. It is characterized by oily, yellowish, scaly patches with poorly defined margins over erythematous skin. The disorder is more common in adults and patients with AIDS or Parkinson disease. The cause of seborrheic dermatitis is not known, and often it is a lifelong condition.[1] In the past, topical corticosteroids were the primary methods of treating patients with seborrheic dermatitis in an effort to reduce inflammation. Currently, however, antifungal agents such as ketoconazole are used more frequently. The success of ketoconazole in the treatment of seborrheic dermatitis provides support for the idea that *Malassezia* yeasts play a role in the etiology of this disease.[2-4] Ketoconazole cream 2% twice daily has been shown to reduce the number of *Malassezia* yeasts and the symptoms of seborrheic dermatitis on the skin nearly as well as hydrocortisone cream 1%.[5] Ketoconazole creams, unlike topical steroid creams, are suitable for long-term therapy.

Ketoconazole gel 2% has been formulated to help improve cosmetic appeal and promote patient acceptability compared with the commercially available ketoconazole cream, particularly when applied

Table 1.

Clinical Assessment Scores

	Signs or Symptoms		
Grade	Erythema*	Scaling*	Pruritus†
0 (none)	No evidence of erythema	No evidence of scaling on lesions	No evidence of pruritus
1 (mild)	Barely perceptible erythema that is faint or patchy; blanches to the touch	Barely detectable, scattered, small, flaking scales	Present with minimal discomfort
2 (moderate)	Distinct erythema; more difficult to blanch	Scales clearly visible and prominent	Appreciable discomfort that interferes with daily activities
3 (severe)	Intense (fiery red) erythema; does not blanch	Coarse thick scales, with flaking onto clothes or skin	Extreme discomfort that prevents the completion of daily activities and may disrupt sleep

*Rated by the investigator.
†Rated by the subject.

to the hairline near the scalp, which often is affected in patients with seborrheic dermatitis. It has been reported that some patients prefer gel preparations over creams, particularly when applied to the face.[6] The gel formulation does not leave a greasy residue after application and, unlike the cream formulation, the gel can be applied easier to hair-bearing areas of skin.

Unlike some ketoconazole topical creams, ketoconazole gel does not contain sodium sulfite; therefore, the associated risks, such as local skin reactions, asthma, and anaphylaxis, are removed.[7,8] During a double-blind patch test that compared the gel and cream formulations, anhydrous ketoconazole gel 2% was found to be consistently less irritating to the skin than ketoconazole cream 2% throughout 3 weeks of observation.[9] Because ketoconazole gel 2% is administered once daily, it also is expected to be associated with improved patient compliance.

Three phase 3 studies assessed the efficacy and safety of once-daily anhydrous ketoconazole gel 2% compared with vehicle gel in the treatment of seborrheic dermatitis. We report data describing the combined efficacy of ketoconazole gel 2% from these studies in subjects with moderate to severe seborrheic dermatitis.

Materials and Methods

Subjects—Subjects in the pivotal phase 3 study had to be at least 12 years of age with moderate to severe seborrheic dermatitis, a baseline score of 2 (moderate) for erythema and scaling and at least 1 (mild) for pruritus, and a baseline investigator global assessment (IGA) of at least 3 (moderate). Eligible subjects in the 2 supporting phase 3 studies (United States, 1; international, 1) had to be 18 years or older with moderate to severe seborrheic dermatitis, a baseline score of 2 (moderate) or 3 (severe) for erythema and scaling and at least 1 (mild) for pruritus, and a baseline IGA of at least 3 (moderate). In all 3 studies, the subjects were excluded if they had a known sensitivity to any of the formulation components or if they exhibited any skin condition or disease that confounded the evaluation of the study drug or necessitated concurrent therapy.

Treatment—The phase 3 studies were randomized, double-blinded, vehicle-controlled, multicenter, parallel-group studies that consisted of 1 pivotal study and 2 supporting studies. In the pivotal study, subjects were assigned in a 1:1 fashion to ketoconazole gel 2% or vehicle gel; in the 2 supporting studies, subjects were assigned in a 2:2:1:1 fashion for treatment with ketoconazole gel 2%, ketoconazole 2% plus desonide gel 0.05% (combination gel), desonide gel 0.05%, or vehicle gel. All treatments were prepared by Clinical Trial Services; blinding was maintained by a 2-part tear-off labeling system where the study drug identity was hidden under a scratch-off layer. After cleansing the affected area, subjects were asked to apply a thin layer of study medication once daily to the affected areas of the

Table 2.

Demographics and Baseline Characteristics (Intent-to-Treat Population; N=933)

Characteristic	Ketoconazole Gel 2% (n=545)	Vehicle Gel (n=388)
Age, y		
Mean (SD)	47.7 (17.6)	48.0 (17.5)
Range	13–91	13–87
Sex, n (%)		
Male	335 (61)	235 (61)
Female	210 (39)	153 (39)
Race, n (%)		
White	481 (88)	353 (91)
Black	32 (6)	16 (4)
Hispanic	25 (5)	17 (4)
Other	7 (1)	2 (0.5)
Mean duration of seborrheic dermatitis, y (SD)	9.7 (11.4)	10.1 (11.4)
Mean duration of current episode, mo (SD)	41.9 (97.6)	49.4 (102.5)
Prior treatment, n (%)	375 (69)	271 (70)

scalp hairline, postauricular area, eyebrows and/or bridge of the nose, nasolabial folds, and sternum for 14 consecutive days. When the 2-week treatment period was completed, subjects were followed for 14 additional days. After the treatment application, subjects were asked not to cleanse the affected areas for at least 3 hours. Changes in the frequency of study drug application or missed applications were documented.

The use of systemic antifungal agents and corticosteroids was not permitted within 30 days of the baseline visit. Furthermore, the use of other local treatments for seborrheic dermatitis was not permitted within 14 days of baseline. During these studies, application of other topical medications or moisturizers to the affected areas was not permitted, and if the administration of other medication became necessary, it was reported. To monitor compliance, subjects were asked to return study medication tubes at each visit.

These studies were conducted in accordance with the Declaration of Helsinki and were approved by the local institutional review boards and/or ethics committees at all participating institutions. All subjects provided written informed consent before study enrollment.

Assessments—In the pivotal study, subjects were assessed at baseline, on days 7 and 14 (treatment days), and at day 28 (the end of follow-up); this visit schedule was similar in the supporting studies, except that subjects in the supporting studies made an additional study visit on day 3. In all studies, the clinical evaluation of signs and symptoms was made at each visit and the IGA was performed at baseline and on days 7, 14, and 28. Adverse events were followed at each visit. The overall severity of erythema, scaling, and pruritus was evaluated on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe) (Table 1). The IGA was rated on a 5-point scale (0=completely clear, 1=almost clear, 2=mild [pink to red color, slight scaling], 3=moderate [distinct redness, clearly visible scaling], 4=severe [severe score in erythema or scaling]).

Table 3.

Effectively Treated Subjects*†

	Ketoconazole Gel 2%	Vehicle Gel	*P* Value
PP population	(n=447)	(n=342)	
Effective treatment, n (%)	136 (30.4)	48 (14.0)	<.001
95% CI for % success	26.2-34.9	10.5-18.2	
ITT population	(n=545)	(n=388)	
Effective treatment, n (%)	160 (29.4)	55 (14.2)	<.001
95% CI for % success	25.6-33.4	10.9-18.0	

*PP indicates per protocol; CI, confidence interval; ITT, intent to treat.

†Effectively treated defined as erythema and scaling scores of 0 (none) if baseline score was ≤2 (moderate) or a score of ≤1 (mild) if baseline score was 3 (severe), and an investigator global assessment score of 0 (completely clear) or 1 (almost clear) if the baseline score was ≥3 (moderate) by day 28.

Adverse events were defined as any untoward medical occurrence in a subject who had been treated, regardless of whether the event was considered treatment related. Preexisting conditions that worsened during the study were reported as adverse events. A serious adverse event was defined as death; a life-threatening event; or an event that either required hospitalization, resulted in persistent disability or incapacity, or was medically significant or required intervention to prevent a serious outcome. The severity of adverse events was rated by the investigator as mild, moderate, or severe (1=mild, 2=moderate, 3=severe).

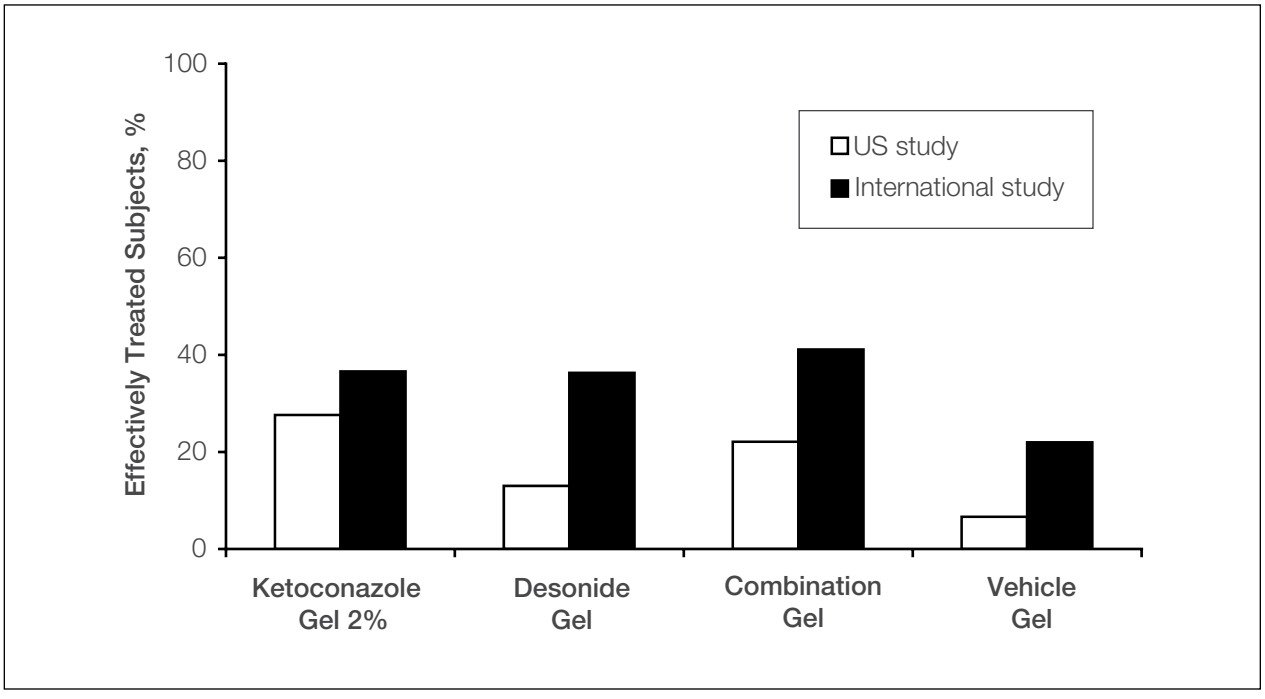

Figure 1. The percentage of effectively treated subjects from supporting studies comparing ketoconazole gel 2% with a combination gel containing ketoconazole 2% and desonide 0.05% (intent to treat). Effectively treated was defined as erythema and scaling scores of 0 (none) if baseline score was ≤2 (moderate) or a score of ≤1 (mild) if baseline score was 3 (severe), and an investigator global assessment score of 0 (completely clear) or 1 (almost clear) if the baseline score was ≥3 (moderate) by day 28.

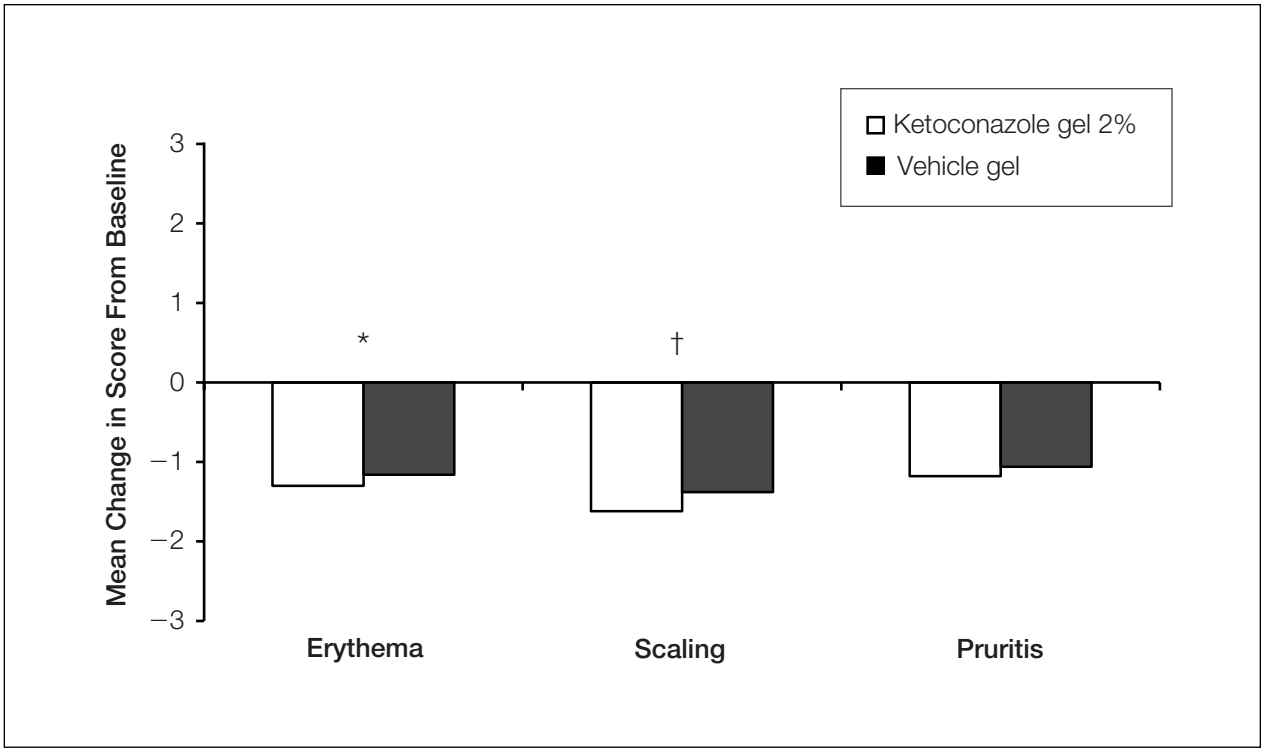

Figure 2. Mean reduction from baseline in erythema, scaling, and pruritus scores reported at day 14 during all phase 3 studies. *P* values (mean change vs baseline for ketoconazole gel 2%) were based on a Cochran-Mantel-Haenszel row mean scores test stratified by study. Asterisk indicates $P=.045$; dagger, $P<.001$.

The primary efficacy end point in all studies was the proportion of subjects effectively treated, defined as subjects who had erythema and scaling scores of 0 (none) if baseline score was ≤2 (moderate) or 0 or 1 (mild) if the baseline score was 3 (severe), and an IGA score of 0 (completely clear) or 1 (almost clear) if the baseline score was 3 (moderate) or greater by day 28. The secondary efficacy end points in the pivotal study were change from baseline in ratings of erythema, scaling, and pruritus on day 14. Because 2 of 4 treatment arms in the supporting trials included a steroid, the secondary end points were assessed at day 3 to detect early reductions of inflammation. However, day 14 data, which also were collected in the supporting trials, were used for this pooled analysis.

Statistical Analyses—For the purpose of these analyses, only common treatment groups from each study were integrated and analyzed. Within each study, categorical variables were compared among treatment groups using the Cochran-Mantel-Haenszel test, stratified by grouped study center, for nominal (general association test) and ordinal (row mean scores test) variables. Continuous variables were compared among treatment groups using a 2-way analysis of variance with factors for treatment and grouped study center. For the 4-arm supporting studies, pairwise differences between the groups were significant if both the overall test and the pairwise test were significant ($\alpha=.05$). The pooled results of all 3 studies were analyzed using the Cochran-Mantel-Haenszel test, stratified by study.

For all studies, the primary efficacy population was the intent-to-treat (ITT) population, which included all subjects who were randomized and received study drug. In these analyses, any subjects with missing values for any of the primary response criteria at day 28 were classified as treatment failures. The secondary efficacy population was the per-protocol (PP) population, which included those who completed the 14-day treatment period and the day 28 evaluation without any significant protocol violations.

In the pivotal study, a sample size of 220 subjects per group was estimated to provide at least 95% power in the ITT population to detect a significant difference between the treatment groups at a type 1 error rate of $\alpha=.05$. For each supporting study, it was estimated that a sample size of 150 subjects in the ketoconazole gel 2% and combination gel treatment groups would provide at least 90% power in the ITT population to distinguish between the groups using a .05-level χ^2 test. Furthermore, a sample size of 75 subjects in the desonide gel and vehicle gel groups was estimated to provide 99% power in the

Table 4.

Effectively Treated Subjects by Severity and Duration of Disease (Intent-to-Treat Population; N=933)

	Ketoconazole Gel 2% (n=545)	Vehicle Gel (n=388)
Disease severity,* n (%)		
Moderate	97/358 (27.1)	40/271 (14.8)
Severe	63/187 (33.7)	15/117 (12.8)
Disease duration, n (%)		
0–36 mo	56/197 (28.4)	23/130 (17.7)
>36–84 mo	33/123 (26.8)	13/86 (15.1)
>84–180 mo	33/110 (30.0)	9/94 (9.6)
>180 mo	38/115 (33.0)	10/78 (12.8)

*According to baseline investigator global assessment score.

ITT population to detect differences between each of these groups and the combination gel group. Assuming a drop out rate of 20%, the power was estimated to remain the same.

Results

Nine hundred thirty-three subjects (ITT population) received ketoconazole gel 2% (n=545) or vehicle gel (n=388). Of these subjects, 897 completed the study and 789 were included in the PP population. Thirty-six subjects discontinued the study. In the ketoconazole gel 2% treatment group, reasons for study discontinuation included lost to follow-up (n=6), adverse events (n=5), treatment failure (n=5), subject choice (n=4), and protocol violation (n=2); reasons for study discontinuation in the vehicle treatment group included lost to follow-up (n=2), adverse events (n=2), treatment failure (n=1), subject choice (n=6), protocol violation (n=1), and other reasons (n=2). Demographics and baseline characteristics for each group are shown in Table 2. All subjects had moderate or severe erythema and scaling at baseline, and most subjects had mild or moderate pruritus. Furthermore, all subjects had moderate or severe IGA scores at baseline.

The proportion of subjects from all studies effectively treated on day 28 is shown in Table 3. Significantly more subjects in the ketoconazole gel 2% treatment group ($P<.001$) were effectively treated compared with the vehicle group. In each individual study, the percentages of effectively treated subjects ranged from 25.3% to 36.6% in the ketoconazole gel 2% treatment group and 6.6% to 22.0% in the vehicle gel group.

In the supporting studies, the proportion of effectively treated subjects was comparable between the ketoconazole gel and desonide gel treatment groups, and between the ketoconazole gel and combination gel treatment groups (Figure 1). In the international supporting study, pairwise comparisons of the ITT treatment groups revealed that the combination treatment was significantly more effective than vehicle gel ($P=.003$) but not more effective than ketoconazole gel 2% ($P=.353$) or desonide gel ($P=.442$) alone. Similarly, in the US supporting study, combination treatment was significantly more effective than the vehicle gel ($P=.003$) but not more effective than ketoconazole gel 2% ($P=.25$) or desonide gel ($P=.10$) alone in the ITT population. Results were similar between the ITT and PP populations in each study.

In the ITT population from all studies, the changes from baseline to day 14 in erythema and scaling were significantly greater in the ketoconazole gel 2% treatment group. No erythema was observed in 32.1% of the ketoconazole gel 2% treatment group and 26.5% of the vehicle gel group ($P=.045$) at day 14. No scaling was observed in 43.8% of the vehicle gel group and 53.2% of the ketoconazole gel 2% group ($P<.001$). With regard to pruritus, no significant differences were observed between the groups ($P=.100$)(Figure 2).

When the data from all studies were analyzed according to age, sex, and race, the proportion

Table 5.

Application Site Adverse Events (Safety Evaluable Population; N=933)*†

System Organ Class Preferred Term	Ketoconazole Gel 2% (n=545)	Vehicle Gel (n=388)	Total (N=933)
Any application site reaction, n (%)	30 (5.5)	17 (4.4)	47 (5.0)
Burning	23 (4.2)	12 (3.1)	35 (3.8)
Dermatitis	0 (0)	1 (0.3)	1 (0.1)
Discharge	1 (0.2)	0 (0)	1 (0.1)
Dryness	0 (0)	1 (0.3)	1 (0.1)
Erythema	5 (0.9)	3 (0.8)	8 (0.9)
Irritation	2 (0.4)	0 (0)	2 (0.2)
Pain	1 (0.2)	0 (0)	1 (0.1)
Pruritus	2 (0.4)	1 (0.3)	3 (0.3)
Reaction	1 (0.2)	4 (1.0)	5 (0.5)

*Includes events reported as possibly, probably, or certainly related to study medication.

†The same adverse event recorded by a subject at different visits counts as one event for that subject, and the strongest intensity and relationship to treatment are used. At each level of summarization (system organ class), subjects are counted only once.

of effectively treated subjects remained higher for ketoconazole gel 2% in all subgroups except for those racial subgroups with few subjects. No evidence suggested that race had an impact on the percentage of effectively treated subjects. Furthermore, ketoconazole gel 2% was more effective than vehicle gel regardless of baseline signs and symptoms score, baseline IGA score, or history of seborrheic dermatitis (Table 4).

At least one adverse event was reported by 16.3% of subjects in the ketoconazole gel 2% treatment group and by 17.3% in the vehicle gel group (total, 156 of 933 subjects). Treatment-related adverse events were observed in 7% (65/933) of subjects (ketoconazole group, n=40; vehicle group, n=25). The most common treatment-related adverse reactions in both groups were application site reactions (Table 5). No serious treatment-related adverse events and no deaths were reported during these studies. Twelve subjects interrupted or discontinued treatment because of adverse events, including 7 subjects who discontinued the study.

Comment

Data from these phase 3 studies in more than 900 subjects confirm the superior efficacy of ketoconazole gel 2% over vehicle gel as assessed by reduced erythema and scaling and global ratings from investigators. The percentage of subjects effectively treated with ketoconazole gel 2% was nearly twice as high as the percentage of subjects effectively treated with vehicle gel in both the ITT and PP populations. Furthermore, improvements were observed regardless of baseline disease severity or duration, and the signs and symptoms of seborrheic dermatitis continued to improve during treatment. The safety and tolerability of ketoconazole gel 2% was similar to vehicle gel.

During the supporting studies, comparable efficacy was observed in subjects treated with ketoconazole gel 2%, desonide gel 0.05%, or the combination of these 2 agents for up to 2 weeks after the end of treatment. This finding indicates that adding a topical steroid to the treatment regimen did not provide an additional benefit in these subjects during this time period. Additionally, good symptom suppression was maintained with ketoconazole gel 2% alone for up to 2 weeks after the end of treatment. The efficacy of ketoconazole gel 2% in this population provides support for the involvement of *Malassezia* species in the pathogenesis of the disorder; it also may reflect a direct anti-inflammatory effect of ketoconazole gel 2% alone, which has been reported,[10] or perhaps both pathways contribute to the efficacy of ketoconazole gel 2%. Early

studies of ketoconazole demonstrated it has potent activity against *Malassezia* species–related conditions, such as seborrheic dermatitis,[2,3,11] and that it also has anti-inflammatory and antibacterial properties.[10,12]

Other studies have been reported that support the use of ketoconazole cream 2% in the treatment of seborrheic dermatitis.[5,13-15] The earliest of these trials compared the use of twice-daily ketoconazole cream 2% with its vehicle alone during a 4-week double-blind trial of 37 subjects with seborrheic dermatitis.[13] Of 20 subjects treated with ketoconazole cream, 11 subjects had clear skin (95%−100% improvement) at the end of treatment, 7 subjects had good results (75%–95% improvement), and 2 subjects had poor results. Most subjects (9/17) who received the vehicle cream had poor results and none had clear skin at the end of the study.[13] Later double-blind trials comparing ketoconazole cream 2% with hydrocortisone cream 1% for the treatment of seborrheic dermatitis found that although hydrocortisone cream 1% resulted in higher clinical response rates, the treatment difference was not statistically significant in either study.[5,15] Among more than 60 subjects treated in one of the studies, the clinical response rate was 94.4% in the hydrocortisone cream treatment group compared with 80.5% in the ketoconazole cream treatment group.[15] In the other study, symptomatic improvement was observed in 87.2% of subjects who received hydrocortisone cream and 81.6% of subjects who received ketoconazole cream.[5] The approved dosage of ketoconazole cream 2% for this indication is twice daily for 4 weeks or until clearing.[16]

In contrast to the older studies, the current trials found that the efficacy of treatment with ketoconazole gel 2% was superior to treatment with topical steroids. Differences in study design and formulation characteristics may partly explain the discrepancy in results from earlier studies and the present analysis.

Although no studies have been done to date comparing the efficacy of the gel formulation with the cream formulation of ketoconazole, results of a 21-day double-blind patch test comparing the safety of ketoconazole gel 2% versus ketoconazole cream 2% demonstrated less skin irritation with ketoconazole gel 2%.[9] The once-daily administration of ketoconazole gel 2% combined with cosmetic advantages and lower potential for irritation compared with the cream formulation may enhance subject satisfaction and improve subject adherence, which ultimately can influence efficacy.

Conclusion

The results of this pooled analysis of data from 3 phase 3 studies suggest that ketoconazole gel 2% applied once daily is well-tolerated and effective in treating moderate to severe seborrheic dermatitis, with a clinical response that is significantly better than vehicle gel ($P<.001$) and similar to desonide gel 0.05%.

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