Objective: To demonstrate the efficacy, safety, and tolerance of ciclopirox shampoo for treatment and prophylaxis of seborrheic dermatitis of the scalp.

Design: Multicenter, randomized, double-blind, vehicle-controlled study. After treatment with ciclopirox shampoo once or twice weekly or vehicle for 4 weeks (study segment A), responders were randomized to a 12-week prophylactic study arm (segment B).

Setting: Forty-five medical centers in Germany (n=19), France (n=15), the United Kingdom (n=8), and Austria (n=3).

Patients: A total of 1000 patients with stable or exacerbating seborrheic dermatitis of the scalp.

Interventions: A total of 949 patients were randomized to receive ciclopirox treatment once or twice weekly or vehicle for 4 weeks. Thereafter, 428 responders received either ciclopirox prophylaxis once weekly or every 2 weeks or vehicle for 3 months.

Main Outcome Measures: Primary and secondary: response of “effectively treated” and “cured,” with investigators and patients rating acceptability and tolerance.

Results: Ciclopirox twice and once weekly produced response rates of 57.9% and 45.4%, respectively, compared with 31.6% for vehicle. Relapses occurred in 14.7% of patients using prophylactic ciclopirox once weekly, 22.1% of those in the prophylactic group shampooing once every 2 weeks, and 35.5% in the vehicle group. The few adverse events were evenly distributed among groups. Local tolerance and cosmetic acceptability were “good” in more than 85% of subjects.

Conclusions: Seborrheic dermatitis of the scalp responds well to 1% ciclopirox shampoo once or twice weekly for 4 weeks. A low relapse rate is maintained by once-weekly shampooing or shampooing once every 2 weeks. These treatments are safe and well-tolerated.

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have not been large, and there have been no direct studies of its prophylactic efficacy, so the likely clinical potential of the drug remains to be clearly established. The present randomized, double-blind clinical trial was therefore carried out in a large cohort of patients to definitively establish the efficacy, safety, local tolerance, and cosmetic acceptability of 1% ciclopirox shampoo in the treatment and prophylaxis of seborrheic dermatitis of the scalp using different application frequencies in comparison with vehicle.

METHODS

This vehicle-controlled, randomized, double-blind, multicenter clinical trial was conducted at 45 centers in Austria, France, Germany, and the United Kingdom. The trial was divided into 2 segments: A, treatment; B, prophylaxis. The entire study lasted about 5 months for each subject (6 weeks for segment A, 12 weeks for segment B). The recruitment phase lasted 6 months.

PARTICIPANTS AND ELIGIBILITY CRITERIA

Otherwise healthy men and women of any ethnic origin, aged 18 to 88 years with stable or exacerbating seborrheic dermatitis of the scalp were enrolled. Disease severity had to be at least moderate, with a score of 3 or more on 6-point ordinal scales of “status of seborrheic dermatitis,” “inflammation,” and “scaling” (0, none; 1, slight; 2, mild; 3, moderate; 4, pronounced; 5, severe). All patients who met the inclusion criteria gave their consent in writing after receiving detailed oral and written instructions and explanations about the study, which was approved by the review board or ethics committee responsible for each center and complied with the currently valid Declaration of Helsinki.

Patients with psoriasis, asthma, or diabetes were excluded. Participants were not allowed to receive concomitant topical treatments of the scalp or any nonsystemic treatments with antifungal agents, corticosteroids, retinoids, erythromycin, tetracycline or derivatives, trimethoprim and/or sulfamethoxazole, or cytostatic or immunomodulating drugs for 4 weeks before the start of treatment.

Data were collected in 40 locations. Germany provided 19 centers (intent-to-treat [ITT] population, n=585); France, 15 centers (ITT population, n=197); United Kingdom, 8 centers (ITT population, n=136); and Austria, 3 centers (ITT population, n=24).

INTERVENTIONS

Segment A: Treatment Phase

All enrolled patients underwent a 2-week run-in during which they were required to use an open-label shampoo (Prell; Procter & Gamble, Cincinnati, Ohio) at least twice weekly. After final selection at the subsequent baseline visit, 1000 patients were enrolled, and a total of 949 were randomized on a 2:2:1 basis to 1 of the 3 parallel groups with different application frequencies of 1% ciclopirox (A1, twice weekly, n=340; A2, once weekly, n=340; A3, vehicle, n=340). Accordingly, each patient was given 2 different 90-mL bottles (bottles A I and A II). The patients were required to use 2 applications per week for 4 weeks strictly alternating use of bottles A I and A II. The patients randomized to treatment A1 were given bottles that both contained 90 mL of 1% ciclopirox shampoo. By alternating bottles, they used the active shampoo twice a week. Patients on treatment A2 received 1 bottle with 90 mL of 1% ciclopirox shampoo and 1 bottle with vehicle to achieve once-weekly shampooing with 1% ciclopirox. The bottles blindly allocated to patients in A3 both contained 90 mL of vehicle. Each application dose was 5 mL; patients with longer than shoulder-length hair could use up to 10 mL. The vehicle contained the ingredients Genapol LRO liquid (shampoo base) (Clariant, Frankfurt, Germany), Rewopol SBEA 30 (Whitico Surfactants, Steinau, Germany), Arlypon F (Henkel, Düsseldorf, Germany), sodium chloride, and water. After 4 weeks of double-blind treatment, all patients were rated as responders or nonresponders according to definition.

Segment B: Prophylaxis

Segment B of the study commenced immediately after segment A was completed to assess the prophylactic efficacy of different application frequencies of ciclopirox shampoo. A total of 428 responders from segment A proceeded with segment B before the random code for segment A was opened. The responders were randomized blindly to 3 equal groups to use ciclopirox once every week, once every 2 weeks, or vehicle. The defined relapse rate was assessed as the primary outcome measure. As in segment A, the patients were instructed to apply the shampoo from 2 different bottles (bottles B I and B II) weekly in a strictly alternating manner.

OBJECTIVES AND OUTCOME MEASURES

The primary objective of the study was to establish the efficacy, safety, and tolerance of 1% ciclopirox shampoo in the treatment and prophylaxis of seborrheic dermatitis of the scalp. The efficacy of ciclopirox treatment was assessed by comparing the responder rates of active treatment groups with vehicle as odds ratios (including 95% confidence intervals [CIs]).

Segment A

The efficacy parameters were based on 4 different 6-point ordinal scales describing the disease manifestations (status, scaling, inflammation, and itching). The outcome measures were the 2 response categories derived from the efficacy measures at each patient’s final visit. The primary outcome measure was effectively treated, defined as a score of 0 (or 1 if the baseline score was ≥3) for status, scaling, and inflammation; the secondary outcome measure was cleared, defined as a score of 0 for status, scaling, inflammation, and itching. In addition to their separate presentations, the results of 3 single scores (itching, scaling, and inflammation) were added together to form a combined sumscore ranging from 0 to 15.

The 2 active-treatment regimens were compared with the vehicle group in the Holm-Bonferroni sequential procedure. If neither of the 2 P values (2-sided Cochran-Mantel-Haenszel test adjusted for pooled centers) was .025 or lower, then the procedure was stopped without a significant result; if the smallest P value was .025 or lower, then the second P value was compared with the α level of .05 to guarantee a global α level of .05.

Segment B

The primary outcome measure for the prophylactic phase was the relapse rate, defined as a worsening from the start of segment B by 2 points or more. Secondary outcome measures consisted of relapses in inflammation, scaling, and itching, de-
fined as a worsening by more than 2 points from the start of segment B.

ASSESSMENTS OF LOCAL TOLERANCE AND COSMETIC ACCEPTABILITY

Local tolerance was assessed by the investigators, and cosmetic acceptability and tolerance were rated by the patients at each visit. These assessments were recorded at baseline (visit 2), 2 weeks ± 3 days from baseline (visit 3) and 4 weeks ± 3 days from baseline (visit 4). Visit 4 coincided with the end of segment A and with the beginning of segment B. For the segment A responders enrolled in segment B, investigators’ ratings of local tolerance and patient self-ratings of cosmetic acceptability and tolerance were documented at visits 5 and 6 of the study, which took place ± 1 weeks and 12 ± 1, respectively, after the start of segment B.

SAMPLE SIZE

The sample size was based on the following: (1) sufficient power to discriminate between active treatment and vehicle; (2) estimates of response rates; and (3) a sufficient number of responders from segment A (treatment) for inclusion in segment B (prophylaxis). Based on pilot studies, response rates of 55% were assumed for ciclopirox and 35% for vehicle. The power of a 2-sided comparison “active vs vehicle” at an adjusted α level of 2.5% (to maintain the global 5% level) was between 97% and 98%, and the 95% CI for the response rate of an active treatment arm ranged from 50% to 60%, while that of the vehicle ranged from 28% to 43%. The sample size for segment B was calculated to provide sufficient power assuming relapse rates of 22% for ciclopirox once a week, 32% for ciclopirox every 2 weeks, and 35% for vehicle. The power of the 2-sided comparison ciclopirox once every 2 weeks vs vehicle at an α level of 3% is 90%; for ciclopirox once a week vs vehicle, the power is 99.8%.

No interim analyses were performed. Segment A was analyzed immediately after its completion, ie, before the database for segment B was closed. The results for segment A were kept confidential until the database for segment B was closed.

RANDOMIZATION AND/OR SEQUENCE GENERATION

Segment A responders were randomized for segment B into 1 of the 3 different treatment arms at a ratio of 1:1:1 with the objective to obtain 3 × 105 = 315 evaluable cases.

Allocation Concealment

The investigator received a set of sealed envelopes, 1 for each patient number. The research organization and the sponsor held an identical set of sealed envelopes. The randomization envelopes were not opened until the end of the study.

Patient Identification and Randomization

On enrollment at the center, each patient was assigned a 5-digit screening number that allowed unambiguous identification. Enrolled patients who dropped out of the study before their first randomization retained their screening number without receiving a randomization number. The next patient enrolled was given the next screening number. Patients who dropped out or were withdrawn from the study after their first randomization were not replaced. Patients in segment A and segment B were randomized separately using different sets of randomization numbers.

Segment A

At each center, patients eligible for inclusion after completion of the run-in phase received their randomization number in the order in which they entered the study phase. For segment A, the number of randomized patients per center ranged from 10 to 30. The 3 treatments for segment A, ciclopirox twice a week or once a week or vehicle, were randomized on a 2:2:1 basis, respectively. The randomization code of segment A was not broken until this segment was completed and its database was closed. Although this took place while segment B was still running, the code of segment A was not disclosed to the investigators before the entire study had been completed.

Segment B

In each center selected for continuation, patients eligible for entry to segment B received their second randomization number in the order in which they entered segment B. Inclusions into segment B were stopped when the scheduled number of patients for segment B was reached; the number of randomized patients per center ranged from 3 to 12. Patients were randomized in 3 equal groups to receive the 3 treatments for segment B (application once weekly, application once every 2 weeks, and vehicle).

STATISTICAL ANALYSIS

Statistical analyses were carried out using SAS software, version 6.12 (SAS Institute, Cary, NC) according to a detailed statistical analysis plan prepared prior to unblinding. Results for segments A and B were analyzed separately. The analysis of segment A started after its completion and while segment B was still ongoing. No results of segment A were disclosed to the investigators of segment B before the entire study was finished. The 2 response rates of the once-weekly and twice-weekly applications of 1% ciclopirox were compared sequentially to the response rate of the vehicle group according to the Holm-Bonferroni procedure.

For statistical analysis, the following populations were identified separately for both segments before unblinding. The safety population comprised all randomized patients who received at least 1 dose of randomized study medication. The ITT population comprised all randomized patients who received at least 1 dose of study medication and had a subsequent rating of the primary efficacy variable or nonresponders who dropped out owing to lack of efficacy.

For segment B, the primary statistical analyses of efficacy were performed on the ITT population. A supplementary statistical analysis of efficacy was provided for the valid cases and for the all-randomized population. The analyses for the all-randomized population (with a last-observation-carried-forward for segment A and a worst-case approach for segment B) was introduced after unblinding. This population was used to assess any potential bias that might have been introduced by the requirement of at least 1 postbaseline efficacy reading in the ITT population. The results for the all-randomized population were virtually identical to those of the ITT population, confirming that no bias had been introduced by this requirement.

By definition, the all-randomized population was identical to the safety population; for the efficacy analyses, it was only used for the primary response criterion effectively treated and for the variable cleared. Safety variables were analyzed within
the safety population. To avoid the effects of too small a sample size in single centers, these were pooled before unblinding.

RESULTS

RECRUITMENT

A total of 1000 patients were enrolled in the study, 949 of whom were randomized to receive 1 of the 2 ciclopirox regimens or vehicle. The first patient was enrolled in April 1997, and the last visit of the last patient was in June 1998. The randomized population and the safety population were identical. The ITT population comprised 942 patients. A total of 40 patients (4%) dropped out prematurely, with the highest proportion in the vehicle group (2%). Adverse events considered possibly related to vehicle at the primary efficacy end point. Twice- and once-weekly shampooing produced response rates of 57.9% (220/380) (odds ratio [OR], 3.025; 95% CI, 2.096-4.366; *P* < .001 compared with vehicle) and 45.4% (171/377) (OR, 1.826; 95% CI, 1.266-2.634; *P* < .001 compared with vehicle), respectively. The response rate data are depicted in the Figure. In the ITT population, 58.5% (220/376) responded in the twice-weekly group (OR, 3.056; 95% CI, 2.114-4.416; *P* < .001 compared with vehicle) and 45.5% (171/376) in the once-weekly group (OR, 1.826; 95% CI, 1.266-2.634; *P* < .001 compared with vehicle).

For the secondary efficacy end points, the ITT analysis of cleared showed higher response rates with active treatment than with vehicle (ciclopirox twice weekly, 23.1% [P < .001]; once weekly, 17.0% [P = .04]; vehicle, 10.0%). For all response categories, rates were markedly lower with vehicle than with active treatment (Table and Figure).

### ADVERSE EVENTS

#### Segment A

In segment A, 146 adverse events were recorded in 120 patients (12.6%), with an even distribution in all treatment groups. Most were dermatologic, and the most frequent were seborrhea (n = 12) and rhinitis (n = 9). No relevant group differences were observed. A total of 12 patients dropped out owing to adverse events, with the highest proportion of dropouts leaving the vehicle group (2%). Adverse events considered possibly related

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**Table. Distribution of Seborrheic Dermatitis Severity Before Treatment and Sumscores After Treatment in the 3 Groups**

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>1% Ciclopirox Twice Weekly (n = 376)</th>
<th>1% Ciclopirox Once Weekly (n = 376)</th>
<th>Vehicle (n = 190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity at Baseline, % of Patients</td>
<td>Mild 46 (12) 56 (15) 28 (15)</td>
<td>Moderate 195 (52) 195 (52) 86 (45)</td>
<td>Pronounced 121 (32) 113 (30) 63 (33)</td>
</tr>
<tr>
<td>Severe</td>
<td>14 (4) 12 (3) 17 (7)</td>
<td></td>
<td>6 (3)</td>
</tr>
<tr>
<td>Mean ± SD Sumscore</td>
<td>Baseline 9.2 ± 2.2 9.0 ± 2.2 9.4 ± 2.3</td>
<td>Week 2 5.0 ± 3.0 5.7 ± 3.2 6.7 ± 3.3</td>
<td>Week 4 2.9 ± 3.1 3.7 ± 3.3 5.1 ± 3.8</td>
</tr>
</tbody>
</table>

*Intention-to-treat population, n=942.*
to the study drug were recorded in 19 patients. Most were dermatologic, and none of them were judged as serious. The distribution in the 3 treatment groups was similar. Treatment-emergent serious adverse events were recorded in 3 patients (shock, anxiety, and skin ulcer); none of them was related to the study drug. Pre-defined abnormal laboratory changes were recorded in 41 cases; 33 of these were increases in liver enzyme levels. This change occurred in only 4%, and a causal relationship to the study treatment was ruled out. No serious adverse event was judged to be causally related to the study medication.

The overall scores for local tolerance (investigator assessment) and cosmetic acceptability and tolerance (patient assessment) during the treatment phase were calculated. More than 85% of the patients who used ciclopirox shampoo rated local tolerance and cosmetic acceptability and tolerance at least good.

**Segment B**

In segment B, the prophylactic phase, 428 patients (median age, 37 years) were randomized to 1 of the 3 treatments. The ITT population comprised 421 patients, and the randomized population and the safety population were identical. A total of 43 patients (10.2%) dropped out prematurely (7% in the once-weekly treatment group; 13% in the once-every-2-weeks treatment group; and 9% in the vehicle group). In the ITT population, relapses occurred in 14.7% of the patients (20/136) in the once-weekly group, 22.1% (32/145) in the group shampooing once every 2 weeks, and 35.5% (50/141) in the vehicle group. Comparison of relapse between ciclopirox (both weekly and every 2 weeks) and vehicle showed a significant difference ($P<.001$), as did the primary analysis.

Adverse events during segment B were recorded in 72 (16.8%) of 428 patients, with a similar distribution in all treatment groups. Most were dermatologic; the most frequent were seborrhea (n=7) and eczema (n=6), and there was no relevant group difference. A total of 10 patients were excluded owing to adverse events, with the highest proportion in the group shampooing once every 2 weeks (4%).

Adverse events considered possibly related to the study drug were recorded in 15 patients. Most were dermatologic, and none of them was judged as serious. No group differences were apparent. No relevant differences were seen in liver enzyme, creatinine, or hematologic parameters between the treatment groups. No serious adverse events were recorded. Abnormal laboratory changes were recorded in 16 patients; 11 were increases in liver enzyme levels. A causal relationship to the study treatment was ruled out.

Local tolerance and cosmetic acceptability and tolerance during the prophylactic phase were rated at least good in more than 85% of the patients in all treatment groups, including vehicle.

**COMMENT**

This vehicle-controlled, parallel-group, randomized, double-blind, multicenter study fulfilled its objective to establish the efficacy, safety, local tolerance, and cosmetic acceptability of 1% ciclopirox shampoo for the treatment and prophylaxis of seborrheic dermatitis of the scalp. After 4 weeks of treatment, the response rates for the ITT population were significantly higher in both active treatment groups than in the vehicle group ($P<.001$). The response rates were dose-dependent, i.e., higher for the ciclopirox twice-weekly group (58.5%) than for the once-weekly group (45.5%) or the vehicle group (31.6%).

Ciclopirox shampoo was safe and well tolerated. Both investigators and patients rated local tolerance and cosmetic acceptability as high. Thus the therapeutic response, safety, and tolerance found with ciclopirox in the present study of a large cohort of patients extends and confirms the findings of smaller studies of ciclopirox and shows that its therapeutic effect is comparable to that of topical ketoconazole.

After 12 weeks of treatment, the relapse rates for the ITT population were significantly lower in both active treatment groups than in the vehicle group ($P<.001$ for the once-weekly prophylactic group; $P=.02$ for the prophylactic group shampooing once every 2 weeks) indicating the superiority of ciclopirox over vehicle in the prophylaxis of seborrheic dermatitis of the scalp. The relapse rates were lower with ciclopirox once a week (14.7%) than with treatment every 2 weeks (22.1%), in keeping with the dose-dependent relationship found in the response to initial treatment. All other efficacy parameters showed a smaller deterioration with active medication than with vehicle.

Ciclopirox shampoo proved to be safe, well tolerated, and cosmetically acceptable during the 12-week prophylactic regimen of segment B, confirming and extending the findings of segment A. Despite the efficacy studies of preparations in current use for seborrheic dermatitis of the scalp, there is a paucity of data on prophylaxis. The present study is the first to demonstrate the prophylactic response to ciclopirox shampoo; similar findings have likewise been published for ketoconazole.

Ciclopirox is a synthetic, broad-spectrum antifungal agent of the hydroxypyridone family that differs chemically and mechanistically from other antifungals such as the imidazoles and allylamines and, moreover, is without effect on cell membrane lipid synthesis or drug and hormone metabolism. Considering its efficacy, safety, and acceptability profiles, we conclude that ciclopirox is a worthwhile alternative to existing antipityrosporal therapies for the treatment and prophylaxis of seborrheic dermatitis and its minor component, dandruff.

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