Overview of clinical studies

The following clinical studies were performed on 1% Ciclopirox shampoo.

Phase 1 studies		
Study No.	Design	# subjects
101	Local tolerance	20
102	Sensitization potential	207
103	Phototoxicity potential	25
104	Photosensitization potential	25

Pharmacokinetic studies			
Study No.	Design	Treatment/duration	# Subjects
201	Pharmacokinetics, safety and efficacy	Exaggerated use/ 4 weeks	18
202	Pharmacokinetics, safety and efficacy	Exaggerated use/ 4 weeks	14

Phase 2 studies				
Study #	Design	Condition	Treatment/ duration	# pts
203	Safety and efficacy of 0.1%, 0.3%, 1% ciclopirox shampoos	Seborrheic dermatitis	BIW x 4 weeks	203
204	Safety and efficacy of 1% ciclopirox shampoo	Seborrheic dermatitis	QW, BIW, TIW x 4 weeks	183

Phase 3 studies				
Study #	Design	Condition	Treatment/ duration	# pts
3001	Part A: Safety and efficacy of 1% shampoo as treatment (DB,VC) Part B: Safety and efficacy of 1% shampoo as prophylaxis (DB,VC)	Seborrheic dermatitis	Part A: QW or BIW x 4 weeks Part B: QW or QOW x 12 weeks	Part A: 949 Part B: 428
3003	Safety and efficacy of 1% ciclopirox vs 2% ketoconazole shampoo (DB,AC)	Seborrheic dermatitis	BIW x 4 weeks	737
DB = double blind VC = vehicle controlled AC = active controlled				

Studies # 204 and 3001 were the pivotal studies for a determination of effectiveness.

Studies # 101, 102, 103, 104, 201, and 203 were performed with the to-be-marketed formulation. The formulations used in Studies # 3001 and 3003 differed in that a) t

; these differences were not felt by the Chemistry reviewer to be significant.

Financial Disclosure statement

Hoechst Marion Roussel, Inc. Has provided the following statement.

'As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of

significant payments of other sorts as defined in 21 CFR 54.2(f).'

Listed are all the investigators and subinvestigators in Studies 201, 202, 203, 204, 3001, and 3003.

Phase 1 studies

These studies were sponsored by Hoechst Dermatology Clinical Research, Frankfurt, Germany. The investigator was Prof. Dr. Irene Tausch, Hamburg, Germany.

1. Study # 101: Local tolerance.

This study was a comparison of local tolerance to 1% ciclopirox shampoo and to a 2% ketoconazole shampoo marketed by Janssen under a German trade name, in 20 normal subjects, when applied as an exaggerated exposure to the antecubital areas during a five day period.

In the study procedure, the test product and the control were randomly assigned to contralateral antecubital areas, each measuring 10 cm^2. One ml of each shampoo was applied to its respective site, then lathered with water and washed by hand for one minute, and rinsed with water. A second application was then applied, with washing for one minute. The shampoo was then left on the skin site for 3 minutes, and rinsed with water. This procedure was performed on the evening of day 1, twice daily on days 2 through 4, and once in the morning of day 5.

At one to three hours following the last wash local skin reactions were assessed by a blind observer, using the following scores.

Score	Description
0	no reaction/normal skin
1	mild erythema, no infiltrate
2	moderate erythema with or without infiltrate
3	strong erythema with infiltrate and/or papules
4	deep erythema with infiltrate, vesicles, erosions

All 20 subjects completed the study. No subject had a reaction with a score of greater than 1. Scores of 1 were recorded for 8 of the subjects with ciclopirox shampoo, and for 9 of the subjects with ketoconazole shampoo. Mild to moderate itching and/or burning were reported by 2 subjects in the ciclopirox-treated areas, and strong itching and burning occurred in one subject and slight itching in another subject in the ketoconazole-treated areas.

The investigator's conclusion was that on the basis of these results it can be assumed that the product will be well tolerated when used as intended. The mild erythematous reactions and subjective symptoms (itching and burning) observed after repeated washing with both ciclopirox shampoo and the control preparation ketoconazole were attributable to increasing exsiccation accompanying the intensive use of the products in the sensitive antecubital areas.

2. Study 102: sensitization potential.

This was a repeat insult patch test study on 198 subjects, using 1% ciclopirox shampoo, 0.3% ciclopirox shampoo, and the shampoo vehicle. The test products were randomly assigned to three skin sites of the back, and an additional site was an untreated occluded control.

During the induction phase, applications of 50 ul of each product were made using a ——— test chamber attached to an occlusive adhesive patch, having an area of 1 cm^2. The patches were removed after 24 hours. This was repeated three times a week for a total of 10 applications. At 17-24 days after the last induction application the test products were reapplied in the challenge phase at new skin sites, with occlusion for 24 hours. Scoring of reactions was made by a blinded observer at patch removal, and at 24, 48, and 72 hours after patch removal, according to the following scale.

Score	Description
0	no reaction
1	erythema
2	erythema with infiltration
3	erythema with papulovesiculae
4	erythema with blisters, blebs, erosions

A total of 207 subjects were enrolled in the study, of which 9 subjects were discontinued from the study and 198 completed the study. Seven subjects discontinued for reasons unrelated to the study, and one subject discontinued for unknown reasons.

One subject was discontinued from the study on day 15 of the induction phase due to erythema and papules on the face, neck, and breast. At the time there was slight erythema and itching at the test areas on the back. After clearing of the lesions patch and photo patch tests were done with the test products, and no allergic or photoallergic reactions were found.

One subject had erythema and itching with all three preparations from the second to the sixth application. The subject removed the patch after 14 hours following the sixth treatment, and the itching subsided and the patches remained in place thereafter for the full time. One subject had intense erythema, apparently at all test sites during induction, and the length of exposure was shortened to six hours after the first application. Another subject had very strong eczematous reactions at all test sites after the sixth application; this subject had had erythema and itching following earlier applications. The patches were removed after six hours on days 15 and 17, and the last induction application was omitted.

Although reactions were not scored during the induction phase, numerous reactions were seen, which varied from very mild to severe erythema. These were most frequently seen with the 1% shampoo, followed by the 0.3% shampoo.

One subject in the challenge phase developed erythema, papules, and itching on both arms and erythema of the face. After resolution of the dermatitis a patch/photopatch with the test preparations was performed; no allergic or photoallergic reactions were observed.

At challenge patch removal there were 115 reactions with 1% ciclopirox shampoo, 58 reactions with 0.3% ciclopirox shampoo, and 25 reactions with the vehicle. At 72 hours after patch removal there were 3 reactions with 1% ciclopirox shampoo, 4 reactions with 0.3% ciclopirox shampoo, and 7 reactions with the vehicle. All reactions with 1% ciclopirox shampoo were of Grade 1, except for two patients, as follows.

In one subject reactions after challenge patch removal were as follows.

	Immediate	24 hrs	48 hrs	72 hrs
1% ciclopirox	1	3	2	0
0.3% ciclopirox	1	3	2	1
Vehicle	1	3	2	1
1 = erythema 2 = erythema with infiltration 3 = erythema with blisters, blebs, erosions				

During the induction phase this subject had shown erythema after the first application and very strong eczematous reactions with all test products after the sixth application. The length of exposure was decreased to 6 hours at the end of the induction phase, and the last exposure was omitted because of the severity of the reactions.

In a second subject reactions after challenge patch removal were as follows.

	Immediate	24 hrs	48 hrs	72 hrs
1% ciclopirox	1	3	2	2
0.3% ciclopirox	1	2	2	2
Vehicle	1	1	2	2
1 = erythema 2 = erythema with infiltration 3 = erythema with blisters, blebs, erosions				

Strong reactions were also found in this subject during the induction period.

The investigator's evaluation was that on the basis of these results it can be assumed that ciclopirox shampoo 1% will not produce frequent sensitization reactions when used as intended. She further states that preparations containing surfactants are known to cause impairment of the stratum corneum when applied occlusively. The dose-dependent increase in erythematous reactions which occurred following occlusive application can be explained by the increased penetration of the active ingredient following barrier impairment and is not to be expected in normal rinse-off use. Allergic reactions which are defined by a crescendo course and characteristic morphologic changes (erythema

with papulae and vesiculae) were not observed in any of the test fields.

3. Study 103: Phototoxic potential.

This double blind study was performed on 25 subjects. The test materials were 1% ciclopirox shampoo, 0.3% ciclopirox shampoo, and the shampoo vehicle.

A total of eight test sites were used, with four sites on each side of the back. On the left side three sites were treated and irradiated, and one site was irradiated but not treated. On the right side three sites were treated and one site was untreated; none were irradiated.

Applications of 50 ul of each test product were made in duplicate to the two sides of the back, using a ——— test chamber having an area of 1 cm^2 which was mounted on an occlusive foil. These were left in place for six hours. After the occlusion period the foil on the left side was removed and the test sites were cleaned with tissue. The left side was then irradiated with a UVA dose of 10 Joule/cm^2. (The light source was a metal halide sun simulator with H1 filter for pure UVA light.) The foil was then removed from the right side, and all test sites were assessed for skin reactions. The right side was again covered, and the subjects were later assessed for skin reactions at 24, 48, and 72 hours after irradiation. Reactions were scored on the following scale.

Score	Description
0	no reaction
1	erythema
2	erythema with infiltration
3	erythema with papulovesiculae
4	erythema with blisters, blebs, erosions

All reactions observed were a Grade 1, i.e., erythema without infiltration. The frequency of reactions at the 1% ciclopirox shampoo sites and the vehicle sites were as follows.

Frequency of Grade 1 scores				
	0 hr	24 hrs	48 hrs	72 hrs
1% ciclopirox and irradiation	6	10	4	0
1% ciclopirox w/o irradiation	9	7	3	1
Vehicle and irradiation	0	6	1	0
Vehicle w/o irradiation	0	4	2	1

No reactions were seen at the untreated radiated and non-irradiated control sites.

The investigator's conclusion was that on the basis of these results it can be assumed that ciclopirox shampoo 1% will be well tolerated without phototoxic reactions when used as intended. The mild erythematous reactions observed were felt to be due to the occlusive applications.

4. Study 104: photosensitization potential.

This double blind study was performed on 25 subjects. The test materials were 1% ciclopirox shampoo, 0.3% ciclopirox shampoo, and the shampoo vehicle.

Applications of 50 ul of each test product were made in duplicate to the two sides of the back for 24 hours, using a [redacted] test chamber having an area of 1 cm^2 which was mounted on an occlusive foil. After patch removal one set of test sites were irradiated with 3 MED of ultraviolet light using a solar simulator. The other set of patches were removed but the test sites were not irradiated. This procedure was repeated every three or four days for a total of six applications and UV exposures.

At ten days after the last induction exposure the test materials were reapplied at new duplicate skin sites, with occlusion for 24 hours. After patch removal one set of test sites was exposed to 5 Joules/cm^2 of UVA. All test sites were evaluated for skin reactions immediately after patch removal/UV exposure, and at 24, 48, and 72 hours later, using the following scale.

Score	Description
0	no reaction
1	erythema
2	erythema with infiltration
3	erythema with papulovesiculae
4	erythema with blisters, blebs, erosions

All reactions were Grade 1. Seven subjects had erythema with 1% ciclopirox shampoo and eight subjects had erythema with the vehicle shampoo. The distribution of the reactions was as follows.

Distribution of grade 1 scores				
Subject #	1% ciclopirox shampoo		Vehicle shampoo	
	Irradiated	Non-irradiated	Irradiated	Non-irradiated
2	24 hrs	24 hrs	24 hrs	24 hrs
3	24 hrs	24 hrs	24 hrs	24 hrs
8	24 hrs	24 hrs	24 hrs	24 hrs
15	24 hrs	-	24,48,72 hrs	24 hrs
19	-	-	24 hrs	24 hrs
23	0, 24 hrs	0, 24 hrs	0, 24 hrs	-
24	24 hrs	-	-	-

The investigator's evaluation was that during the study no allergic or photoallergic reactions were observed in any subject. The mild erythematous reactions both at the irradiated and non-irradiated sites were related to the occlusive applications. Reactions were no more frequent with the 1% shampoo than with the 0.3% shampoo or the vehicle.

Reviewer's evaluation of Phase 1 studies: The dermal tolerance study was not of the preferred duration of 21 days for topical products. However, it was an exaggerated exposure for a shampoo formulation, and the results, together with the results of the occlusive repeat insult patch tests in the sensitization study are felt to be adequate to conclude that the product should have

a low potential for irritation under the intended conditions of use.

The sensitization study showed a high frequency of mild irritant reactions with the 1% shampoo under these conditions of repeat insult occlusive patches. Although the investigator did not feel that sensitization reactions were seen, the reactions in 2 of the 198 subjects were indicative, while not typical, of sensitization. One of these occurred with the vehicle as well as with the active test products.

The results of the phototoxicity and photosensitization studies are adequate to demonstrate little or no potential for phototoxicity or photosensitization.

Dose ranging studies

1. Study 203.

The investigators for this study were as follows.

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Prof.Dr. P. Altmeter, MD Bochum, Germany	Dr. G.Klovekorn, MD Gilching, Germany
Prof.Dr. Brocker, MD Wurzburg, Germany	Dr. F. Kornlewski, MD Ludinghausen, Germany
Dr. E. Gensch, MD Kirchhain, Germany	Dr. Kuster, MD Marburg, Germany
Dr. K. Grunder, MD Giessen, Germany	Dr. G. Ludwig, MD Rheine, Germany
Dr. G. Von Hake, MD Frankfurt a. Main, Germany	Dr. D. Meier, MD Neu-Isenberg, Germany
Dr. S. Heilmann, MD Marburg, Germany	Dr. E. Morgenstern, MD Siegburg, Germany
Dr. K. Jablonski, MD Herne, Germany	Dr. M. Neumann, MD Bonn, Germany
Prof.Dr. J.Stefan, MD Hennef, Germany	Frau Dr. E. Thomas Marburg, Germany

1) Study title: Efficacy and Safety of Ciclopirox shampoo in the Treatment of Seborrheic Dermatitis of the Scalp. A Randomized Double-Blind Placebo-Controlled Comparison of Different Concentrations.

2) Study objectives: The primary objective was to assess the efficacy of different concentrations of Ciclopirox shampoo in the treatment of seborrheic dermatitis of the scalp. The secondary objectives were to assess the safety of different concentrations of Ciclopirox shampoo, and the semi-quantitative evaluation of infection with *Pityrosporum ovale*.

3) Study design: This was a double blind, multicenter, randomized, parallel group comparison of 0.1%, 0.3%, and 1.0% ciclopirox shampoos and the shampoo vehicle, with usage twice weekly for four weeks in the treatment phase. In the followup phase a non-medicated shampoo was used two to three times weekly for four weeks.

4) Inclusion criteria: Patients who met the following criteria were enrolled into the study.

   a. 18-75 years of age, in good physical health.
   b. A diagnosis of stable or exacerbating seborrheic dermatitis of the scalp, as evidenced by a scaling score of 2 to 4, and an inflammation score of 2 to 4, on a scale as described below. This evaluation was made at the end of a two week 'run-in' phase (see 'Treatment Regimen' below).

5) Exclusion criteria: Patients with the following were excluded from enrollment in the study.

   a. Pregnancy, breast feeding, childbearing potential without adequate contraception, irregular menstrual cycles.
   b. History of drug or alcohol abuse.
   c. A mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study.
   d. A history or suspicion of unreliability, poor co-operation or non-compliance with medical treatment.
   e. Shoulder-length or longer hair.
   f. Psoriasis or atopic dermatitis.
   g. Topical treatment of the scalp with antifungal medication or with corticosteroids in the two weeks before the start of the run-in phase.
   h. Systemic use of retinoids, erythromycin, tetracycline or any of its derivatives, trimethoprim/sulfamethoxazole, or metronidazole within 28 days before the start of the run-in phase.
   I. Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol.
   j. History of hypersensitivity to the study medication or to drugs with similar chemical structures.

k. Uncontrolled diabetes.
l. Clinical signs and/or history of immunosuppression, such as recent or recurrent herpes zoster, or known HIV infection.
m. Abnormal baseline findings considered by the investigator to be indicative of conditions that might affect study results.
n. Impaired hepatic function, as shown by but not limited to values for SGOT, SGPT, or γ-GT more than two fold above the upper limit.
o. Severe disease, likely to jeopardize the planned termination of the study, e.g., cancer, cardiac infarction, unstable angina.
p. Treatment with any other investigational drug in the 4 weeks before study entry.

6) Treatment regimen: Applications of the test products were made twice weekly for four weeks in the treatment phase of the study.

During a two week 'run-in' phase prior to treatment, the patients applied the shampoo base twice weekly and alternating with these applications also used a non-medicated shampoo, ——— shampoo, twice weekly. After clinical evaluation the patients were randomized into the treatment phase. The procedure was the same in the treatment phase, with the test products applied twice weekly, alternating with twice weekly applications of ——— -shampoo, for four weeks. In a four week followup phase ——— shampoo was applied two to three times weekly. Except for hair spray, no other cosmetic or non-cosmetic treatment of the scalp was permitted.

At each application, 5 ml of the shampoo was to be used, and the patients were instructed to wet the hair, lather and massage with the shampoo, observe an incubation time of 3 minutes which was measured by a timer provided to each patient, and then rinse the hair. The interval between successive applications was to be about three days.

The rationale for the concurrent use of the non-medicated shampoo was that it was felt that the patients were likely to prefer more than two hair washings per week for cosmetic reasons. Use of the shampoo provided by the sponsor was intended to standardize conditions for all the patients.

7) Efficacy parameters. The following assessments were made.

a. Signs and symptoms. Itching, scaling, and inflammation were scored at weekly return visits on the following scales.

Itching	
Score	Description
0	None
1	Slight
2	Mild
3	Moderate
4	Pronounced
5	Severe

Scaling	
Score	Description
0	None
1	Slight: small flakes resembling a coarse grayish powder
2	Mild: intermediate
3	Moderate:large flakes very loosely attached to the scalp and given an irregular whitish surface
4	Pronounced: flakes apparently congealed together into yellowish plates adhering to the scalp
5	Severe: asbestos-like scaling

Inflammation (erythema)	
Score	Description
0	None
1	Slight
2	Mild
3	Moderate
4	Pronounced
5	Severe

For statistical evaluation the results of the three single scores were added, for a combined score of from 0 to 15.

b. Investigator's global evaluation. The provision for this efficacy parameter, to be done at the end of the treatment period, was made in an amendment to the protocol after the study was in progress. For those patients who had already completed the four week treatment period the global assessment was done retrospectively.

The status of the disease and the change in the disease from baseline was assessed on the following scales.

Investigator's Global Evaluation Status of condition at week 4	
Score	Description
0	No: complete absence of signs or symptoms
1	Slight: Weak presence of signs or symptoms
2	Mild: slight but obvious involvement
3	Moderate: easily observed involvement
4	Pronounced: evident involvement
5	Severe: extreme involvement

Investigator's Global Evaluation Change in condition at week 4	
Score	Description
0	Normalised: 100% clearance of signs/symptoms
1	Markedly improved: 75 to < 100% clearance of disease
2	Moderately improved: 50 to < 75% clearance of disease
3	Slightly improved: < 50% clearance of disease
4	Unchanged: no detectable improvement from baseline
5	Deteriorated: exacerbation of disease in treated area

The primary efficacy variables were the sum of the scores for itching, scaling, and inflammation in the ITT population, which was defined as all randomized patients with at least one assessment after the start of treatment. This differs from the Agency definition of ITT population, which is all randomized patients, regardless of whether they have had subsequent assessments.

c. Percentage of scalp affected: This was estimated as 0-10%, >10-20%, >20-30%, >30-50%, >50-75%, >75-100%.

d. Assessment of *P. Ovale*: Scales from the most affected area were taken and assessed semi-quantitatively for the presence of *P. Ovale*.

8) Safety parameters: Hematology and clinical chemistries were done at screening and after completion of the study, as follows: Hemoglobin, hematocrit, RBC, creatinine, SGOT, SGPT, Y-GT, LDH, cholesterol, and triglycerides. A brief physical examination was performed at screening and at the end of the study phase. Adverse events observed by the investigator or reported by the patient were recorded. A global evaluation of local tolerance at the end of treatment was rated by the patient as excellent, good, fair, or poor.

Results were as follows.

1) Patient enrollment and demographic characteristics: Of 210 screened patients, the following number of patients were included in the different analysis populations.

No. of patients in analyses populations			
Treatment	Safety	ITT	Valid
Vehicle	53	50	45
Ciclopirox 0.1%	49	48	41
Ciclopirox 0.3%	53	53	46
Ciclopirox 1.0%	48	47	41
Total	203	198	173

Safety = all patients who received randomized study medication.
ITT = all patients randomized to treatment who received at least one dose of assigned treatment and had a subsequent rating of the primary efficacy variable
Valid = all patients of the ITT population who also had a rating of the primary efficacy variable at the end of the experimental study phase (visit 4) and for whom no major protocol violations occurred.

The age and gender distribution of the safety population were as follows.

Demographic characteristics				
	Ciclopirox 0.1% n=49	Ciclopirox 0.3% n=53	Ciclopirox 1.0% n=48	Vehicle n=53
Gender				
Male	42 (86%)	29 (55%)	34 (71%)	37 (70%)
Female	7 (14%)	24 (45%)	14 (29%)	16 (30%)
Age				
Mean	39.1	38.6	36.5	38.9
Range	19-69	18-72	18-71	18-72

The number of dropouts and the reasons given were as follows.

All dropouts			
Reason	Prior to randomisation	During treatment	Total
Non-appearance		2	2
Insufficient compliance	1	19	20
Screening failure	2		2
Consent withdrawn		3	3
Inefficacy		9	9
Adverse event	1	1	2
Violation of incl/exc criteria	3	1	4
Total	7	35	42

Two patients dropped out due to an adverse event. One dropped out after the screening period due to the appearance of a generalised eczema after two prewashes of the hair. The other, in the 0.1% ciclopirox group, had a severe worsening of the seborrheic dermatitis.

The distribution of the dropouts in the ciclopirox and the placebo groups during the treatment phase was as follows.

Dropouts during the treatment phase			
Reason	Ciclopirox (all)	Ciclopirox 1.0%	Placebo
Non-appearance	-	-	2
Insufficient compliance	15	4	4
Consent withdrawn	1	1	2
Inefficacy	7	-	2
Adverse event	1	-	-
Violation of incl/exc criteria	1	1	-
Total	25	6	10

2) Efficacy variables.

These are presented for the ITT population, defined as all randomized patients with at least one assessment after the start of treatment.

a. Sumscores for clinical signs/symptoms.

The mean sumscores (the sum of the scores for erythema, itching, and inflammation) and the changes from baseline in mean sumscores were as follows.

Mean sumscores				
	Ciclopirox 0.1%	Ciclopirox 0.3%	Ciclopirox 1.0%	Placebo
Baseline	8.1	8.5	8.3	8.4
2 weeks	7.0	6.1	5.6	6.5
4 weeks	5.1	5.0	4.2	5.4
Endpoint	5.6	5.3	4.4	5.5

Change in mean sumscores from baseline				
	Ciclopirox 0.1%	Ciclopirox 0.3%	Ciclopirox 1.0%	Placebo
2 weeks	- 1.1	- 2.3	- 2.7	- 1.9
4 weeks	- 2.9	- 3.5	- 4.1	- 3.0
Endpoint	- 2.5	- 3.2	- 3.8	- 3.0

The p values for pairwise comparisons of the mean sumscores at endpoint were as follows.

Treatment comparisons	p value
Ciclopirox 0.1% vs placebo	0.6646
Ciclopirox 0.3% vs placebo	0.4431
Ciclopirox 1.0% vs placebo	0.3178

b. Individual clinical signs/symptoms.

The frequency distribution of scores for itching, erythema, and inflammation at baseline and at 4 weeks, by percentages of patients in each category, was as follows.

Itching Frequency distribution by percentage of patients						
	none	slight	mild	moderate	pronounced	severe
0.1% ciclopirox						
Baseline	2.1	8.3	35.4	37.5	14.6	2.1
Week 4	14.0	27.9	25.6	25.6	7.0	-
0.3% ciclopirox						
Baseline	5.7	7.5	18.9	43.4	20.8	3.8
Week 4	23.4	25.5	19.1	17.0	14.9	-
1.0% ciclopirox						
Baseline	4.3	10.6	14.9	57.4	12.8	-
Week 4	34.9	27.9	16.3	9.3	11.6	-
Placebo						
Baseline	6.0	10.0	16.0	36.0	30.0	2.0
Week 4	29.8	12.8	25.5	17.0	12.8	2.1

Scaling Frequency distribution by percentage of patients						
	none	slight	mild	moderate	pronounced	severe
0.1% ciclopirox						
Baseline	-	4.2	20.8	54.2	20.8	-
Week 4	16.3	23.3	23.3	27.9	9.3	-
0.3% ciclopirox						
Baseline	-	-	17.0	62.3	20.8	-
Week 4	21.3	23.4	25.5	19.1	8.5	2.1
1.0% ciclopirox						
Baseline	-	-	25.5	46.8	27.7	-
Week 4	18.6	39.5	16.3	11.6	14.0	-
Placebo						
Baseline	-	-	18.0	58.0	24.0	-
Week 4	17.0	14.9	25.5	27.7	12.8	2.1

Inflammation Frequency distribution by percentage of patients						
	none	slight	mild	moderate	pronounced	severe
0.1% ciclopirox						
Baseline	-	-	52.1	39.6	8.3	-
Week 4	37.2	14.0	27.9	16.3	4.7	-
0.3% ciclopirox						
Baseline	-	-	50.9	30.2	18.9	-
Week 4	27.7	23.4	34.0	12.8	2.1	-
1.0% ciclopirox						
Baseline	2.1	-	44.7	42.6	10.6	-
Week 4	48.8	20.9	4.7	16.3	7.0	2.3
Placebo						
Baseline	-	-	52.0	38.0	10.0	-
Week 4	25.5	27.7	19.1	21.3	4.3	2.1

c. Investigator's global evaluation.

The status of the seborrheic dermatitis and the change from baseline at week 4 was as follows.

Status of condition at week 4 Investigator's global evaluation				
	Ciclopirox 0.1%	Ciclopirox 0.3%	Ciclopirox 1.0%	Placebo
None	4 (8.9%)	5 (10.6%)	10 (23.3%)	7 (14.9%)
Slight	10 (22.2%)	13 (27.7%)	19 (44.2%)	8 (17.0%)
Mild	15 (33.3%)	17 (36.2%)	4 (9.3%)	18 (38.3%)
Moderate	12 (26.7%)	7 (14.9%)	5 (11.6%)	9 (19.1%)
Pronounced	4 (8.9%)	5 (10.6%)	5 (11.6%)	4 (8.5%)
Severe	-	-	-	1 (2.1%)

Change from baseline at week 4 Investigator's global evaluation				
	Ciclopirox 0.1%	Ciclopirox 0.3%	Ciclopirox 1.0%	Placebo
Normalized	3 (6.7%)	5 (10.6%)	10 (23.3%)	7 (14.9%)
Markedly improved	14 (31.1%)	15 (31.9%)	12 (27.9%)	9 (19.1%)
Moderately improved	11 (24.4%)	10 (21.3%)	9 (20.9%)	6 (12.8%)
Slightly improved	3 (6.7%)	7 (14.9%)	3 (7.0%)	13 (27.7%)
Unchanged	13 (28.9%)	8 (17.0%)	5 (11.6%)	11 (23.4%)
Deteriorated	1 (2.2%)	2 (4.3%)	4 (9.3%)	1 (2.1%)

The results of the treatment comparisons with the vehicle based on the status of the seborrheic dermatitis at week 4 were as follows.

Treatment comparisons	p value
Ciclopirox 0.1% vs placebo	0.6523
Ciclopirox 0.3% vs placebo	0.5039
Ciclopirox 1.0% vs placebo	0.0551

The rates of 'therapy responders', defined as those patients classified as 'none' or 'slight' at week 4 in the evaluation of the status of the seborrheic dermatitis, were as follows.

Rate of therapy responders	
Ciclopirox 0.1%	14 (31.1%)
Ciclopirox 0.3%	18 (38.3%)
Ciclopirox 1.0%	29 (67.4%)
Placebo	15 (31.9%)

3) Safety assessments.

The adverse events of the skin and appendages which occurred after randomization, as listed in standardized terminology, were as follows.

Adverse events Skin and appendages				
	Ciclopirox 0.1%	Ciclopirox 0.3%	Ciclopirox 1.0%	Placebo
Skin disorder	1 (2.0%)	-	1 (2.1%)	-
Eczema	-	2 (3.8%)	-	-
Hair disorder	-	1 (1.9%)	-	-
Rash	-	1 (1.9%)	1 (2.1%)	1 (1.9%)
Acne	-	-	1 (2.1%)	1 (1.9%)
Dry hair	-	-	1 (2.1%)	-
Photosensitivity reaction	-	-	1 (2.1%)	-

Additional descriptions of the reactions which appeared to this reviewer to be possibly related to treatment, provided in the patient data listings, were as follows.

Adverse events possibly treatment related Skin and appendages		
Pt No.	Term	Description
Ciclopirox 0.1%		
163	Skin disorder	Worsening of skin disease
Ciclopirox 0.3%		
222	Hair disorder	Hair matted and dull
Ciclopirox 1%		
198	Skin disorder	Worsening of scalp, moistening cruston, to 100% of scalp
244	Dry hair	Dry hair
Placebo		
None		

The adverse events of the skin and appendages which did not appear to be treatment-related were as follows: rash in 2, described as perioral dermatitis; rash in 1, described as rubeoliform exanthem; and photosensitivity reaction, described as phototoxic reaction unlikely to be related to the drug.

The local tolerance, as rated by the patients as good or excellent, was as follows.

Local tolerance Patient rating of good or excellent			
Ciclopirox 0.1%	Ciclopirox 0.3%	Ciclopirox 1.0%	Placebo
73%	75%	88%	77%

The laboratory parameters showed a few abnormalities. These did not appear to be severe or dose-related, and were considered by the investigator to be not clinically relevant.

Reviewer's evaluation of Study 203: No evaluation of this study is made, as this is not considered to be a pivotal study for the determination of effectiveness.

2. Study 204

The investigators for this study were as follows.

Dr. D. Abeck, M.D. Hamburg, Germany	Dr. Bettina Post, M.D. Hamburg, Germany
Dr. med. S. Blitz, M.D. Munich, Germany	Dr.med. H. Pres, M.D. Berlin, Germany
Prof.Dr.B.Czarnetzki, M.D. Berlin, Germany	Dr.med.K.Streckenbach, M.D. Hamburg, Germany
Dr.med.A.Donhauser, M.D. Munich, Germany	Dr.med.M. Theiler, M.D. Hannover, Germany
Dr. Thomas-M. Ernst, M.D. Berlin, Germany	Dr.med.F.Vennemann, M.D. Langenhagen, Germany
Dr.med.G. Hartmann, M.D. Hamburg, Germany	Dr.med.H. Janssen, M.D. Kassel, Germany
Dr.med.B. Kanze, M.D. Hamburg, Germany	Dr. G. Klovekorn, M.D. Gilching, Germany
Dr.E. Meyer-Latzke, M.D. Berlin, Germany	Dr. M. Corte, M.D. Berlin, Germany
Dr.med.H. Neuber, M.D. Berlin, Germany	

1) Study title: Efficacy and Safety of Ciclopirox shampoo in the Treatment of Seborrheic Dermatitis of the Scalp. A Randomized Double-Blind Placebo-Controlled Comparison of Different Application Frequencies.

2) Study objectives: The primary objective was to assess the efficacy of 1% Ciclopirox shampoo in relation to application frequency in the treatment of seborrheic dermatitis of the scalp. The secondary objectives were to assess the safety of Ciclopirox shampoo and the shampoo base in relation to application frequency, and the semi-quantitative evaluation of infection with *Pityrosporum ovale*.

3) Study design: This was a double blind, multicenter, randomized, parallel group comparison of 1% Ciclopirox shampoo applied QW, BIW, and TIW, and the shampoo vehicle applied TIW, in the treatment phase of the study.

4) Inclusion criteria: Patients who met the following criteria were enrolled into the study.

a. 18-75 years of age, in good physical health.
b. A diagnosis of stable or exacerbating seborrheic dermatitis of the scalp, as evidenced by a scaling score of 2 to 4, and an inflammation score of 2 to 4, on a scale as described below. This evaluation was made at the end of a two week 'run-in' phase (see 'Treatment Regimen' below).

5) Exclusion criteria: Patients with the following were excluded from enrollment in the study.

a. Pregnancy, breast feeding, childbearing potential without adequate contraception, irregular menstrual cycles.
b. History of drug or alcohol abuse.
c. A mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study.
d. A history or suspicion of unreliability, poor co-operation or non-compliance with medical treatment.
e. Shoulder-length or longer hair.
f. Psoriasis or atopic dermatitis.
g. Topical treatment of the scalp with antifungal medication or with corticosteroids in the two weeks before the start of the run-in phase.
h. Systemic use of retinoids, erythromycin, tetracycline or any of its derivatives, trimethoprim/sulfamethoxazole, or metronidazole within 28 days before the start of the run-in phase.
I. Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol.
j. History of hypersensitivity to the study medication or to drugs with similar chemical structures.
k. Uncontrolled diabetes.
l. Clinical signs and/or history of immunosuppression, such as recent or recurrent herpes zoster, or known HIV infection.
m. Abnormal baseline findings considered by the investigator to be indicative of conditions that might affect study results.
n. Impaired hepatic function, as shown by, but not limited to, values for SGOT, SGPT, or y-GT more than two fold above the upper limit.
o. Severe disease, likely to jeopardize the planned termination of the study, e.g., cancer, cardiac infarction, unstable angina.
p. Treatment with any other investigational drug in the 4

weeks before study entry.

6) Treatment regimen: During a two week 'run-in' phase prior to treatment, the patients applied the shampoo base twice weekly. After clinical evaluation the patients were then randomized into parallel groups in the treatment phase. Except for hair spray, no other cosmetic or non-cosmetic treatment of the scalp was permitted besides that provided for the trial.

During the treatment phase of the study applications of 5 ml of 1% ciclopirox shampoo were made QW, BIW, and TIW, and applications of 5 ml of the vehicle were made TIW, for four weeks.

The weekly application schedule for the four treatment groups was as follows.

Weekly application schedule				
	Vehicle	Ciclopirox QW	Ciclopirox BIW	Ciclopirox TIW
1st application	Vehicle	Vehicle	Ciclopirox	Ciclopirox
2nd application	Vehicle	Ciclopirox	Vehicle	Ciclopirox
3rd application	Vehicle	Vehicle	Ciclopirox	Ciclopirox

At each application, 5 ml of the shampoo was to be used.The patients were instructed to wet the hair, lather and massage with the shampoo, leave the lather in place for three minutes (measured by a timer provided to each patient), and then rinse the hair. The interval between successive applications was to be 2-3 days.

During a four week followup phase after treatment, the patients applied a non-medicated shampoo, [redacted]-shampoo, two to three times weekly.

7) Efficacy parameters. After the screening visit, the patients returned at baseline, at 2 and 4 weeks after baseline, and for a followup visit at 8 weeks after baseline.

a. Signs and symptoms. Itching, scaling, and inflammation were scored at each return visit. Itching and inflammation were scored on the following scale.

Itching/Inflammation	
Score	Description
0	None
1	Slight
2	Mild
3	Moderate
4	Pronounced
5	Severe

Scaling was scored on the following scale.

Scaling	
Score	Description
0	None
1	Slight: small flakes resembling a coarse grayish powder
2	Mild: intermediate
3	Moderate:large flakes very loosely attached to the scalp and given an irregular whitish surface
4	Pronounced: flakes apparently congealed together into yellowish plates adhering to the scalp
5	Severe: asbestos-like scaling

For statistical evaluation the results of the three single scores were added, for a combined sumscore of from 0 to 15.

b. Investigator's global evaluation. After the study was underway, the protocol was amended on the recommendation of the FDA to add two investigator's global evaluations to the efficacy assessment. These were the status of the seborrheic dermatitis at week 4, and the change in the seborrheic dermatitis at week 4. However, a number of patients had already completed the treatment period before the protocol was amended, and the global evaluation for these patients was done retrospectively by the investigators and the patients.

The global evaluation was scored on the following scales.

Investigator's Global Evaluation Status of condition at week 4	
Score	Description
0	No: complete absence of signs or symptoms
1	Slight: Weak presence of signs or symptoms
2	Mild: slight but obvious involvement
3	Moderate: easily observed involvement
4	Pronounced: evident involvement
5	Severe: extreme involvement

Investigator's Global Evaluation Change in condition at week 4	
Score	Description
0	Normalised: 100% clearance of signs/symptoms
1	Markedly improved: 75 to < 100% clearance of disease
2	Moderately improved: 50 to < 75% clearance of disease
3	Slightly improved: < 50% clearance of disease
4	Unchanged: no detectable improvement from baseline
5	Deteriorated: exacerbation of disease in treated area

c. Percentage of scalp affected: This was estimated as 0-10%, >10-20%, >20-30%, >30-50%, >50-75%, >75-100%.

d. Assessment of *P. Ovale*: The degree of infection with *P. ovale* was assessed semi-quantitatively.

8) Safety parameters: Hematology and clinical chemistries were done at screening and at visit 4, as follows: Hemoglobin, hematocrit, RBC, creatinine, SGOT, SGPT, y-GT, LDH, cholesterol, and triglycerides. A brief physical examination was performed at screening and at the end of the study phase.

Adverse events observed by the investigator or reported by the patient were recorded, and a global evaluation of local tolerance at the end of treatment was rated by the patient as excellent, good, fair, or poor.

Results were as follows.

1) Patient enrollment and demographic characteristics: The following number of patients were included in the different analysis populations.

No. of patients in analyses populations			
Treatment	Safety	ITT	Valid
Vehicle	48	46	40
Ciclopirox QW	44	43	36
Ciclopirox BIW	47	46	35
Ciclopirox TIW	44	42	38
Total	183	177	149

Safety = all patients who received randomized study medication.
ITT = all patients randomised to treatment who received at least one dose of assigned treatment and had a subsequent rating of the primary efficacy variable.
Valid = all patients of the ITT population who also had a rating of the primary efficacy variable at the end of the treatment phase, with no major protocol violations.

The age and gender distribution of the safety population were as follows.

Demographic characteristics				
	Ciclopirox QW n=44	Ciclopirox BIW n=47	Ciclopirox TIW n=44	Vehicle n=48
Gender				
Male	25 (57%)	27 (57%)	29 (66%)	28 (58%)
Female	19 (43%)	20 (43%)	15 (34%)	20 (42%)
Age				
Mean	41.8	41.5	41.6	41.4
Range	20-72	19-68	20-71	18-69

All patients except four were Caucasian. The others were designated as three Oriental or Asian and one Arabian.

The number of dropouts and the reasons given were as follows.

All dropouts			
Reason	Prior to randomisation	During treatment	Total
Non-appearance	8	7	15
Insufficient compliance	2	3	5
Screening failure	4		4
Consent withdrawn	2		2
Inefficacy		2	2
Prohibited comedication	1		1
Total	17	12	29

There were no dropouts due to adverse events.

The 12 dropouts which occurred after randomization were distributed as follows.

Dropouts after randomization			
Ciclopirox QW n=44	Ciclopirox BIW n=47	Ciclopirox TIW n=44	Vehicle n=48
3	2	2	5

2) Efficacy variables.

These are presented for the ITT population, defined as all randomized patients who received at least one dose of assigned treatment and had a subsequent rating of the primary efficacy variable.

After finalization of the study report, two additional response variables were calculated for this study at the request of the FDA, namely, 'Effectively Treated' and 'Cleared'; these were to be the primary efficacy variables. Both categories were based on the investigator's global evaluation status score, which had been added by protocol amendment after initiation of the study, and the scores for

scaling and inflammation. However, the global evaluation is not considered by the Agency to be a valid assessment, because a number of patients had already completed the study when the protocol was amended, and were given retrospective evaluations. The Agency then determined that alternative definitions of 'Cleared' and 'Effectively Treated' based on the clinical signs and symptoms, would be acceptable. These results are described below.

A. Primary efficacy variable.

The Agency definition of the categories of 'Clear' and 'Almost Clear' at the end of treatment is as follows.

Response categories	
Category	Definition
Almost Clear	Inflammation: score = 0
	Scaling: score = 0, or score = 1 if the baseline score was =/> 3
	Itching: score = 0, or score = 1 if the baseline score was =/> 3
Clear	Inflammation: score = 0
	Scaling: score = 0
	Itching: score = 0

The response rates and p values provided by the sponsor for the ITT population were as follows. (It should be noted that the sponsor's definition of ITT population was all randomized patients that had at least one assessment, whereas the Agency definition of ITT population is all randomized patients.)

Effectively Treated (Cleared or Almost Cleared)			
Ciclopirox QW	Ciclopirox BIW	Ciclopirox TIW	Placebo
36.4%	21.3%	29.5%	20.8%

Cleared			
Ciclopirox QW	Ciclopirox BIW	Ciclopirox TIW	Placebo
20.5%	14.9%	20.5%	14.6%

Effectively Treated	p value
Ciclopirox QW vs placebo	0.1003
Ciclopirox BIW vs placebo	0.9580
Ciclopirox TIW vs placebo	0.3377

Cleared	p value
Ciclopirox QW vs placebo	0.4604
Ciclopirox BIW vs placebo	0.9662
Ciclopirox TIW vs placebo	0.4604

B. Other efficacy variables.

a. Sumscores for clinical signs/symptoms.

The mean sumscores (the sum of the scores for erythema, itching, and inflammation) and the changes from baseline in mean sumscores were as follows.

Mean sumscores				
	Ciclopirox QW	Ciclopirox BIW	Ciclopirox TIW	Placebo
Baseline	7.8	7.9	8.2	7.8
2 weeks	5.0	4.8	5.1	6.2
4 weeks	3.5	3.5	3.6	5.1
Endpoint	3.5	3.5	3.6	4.9

Change in mean sumscores from baseline				
	Ciclopirox QW	Ciclopirox BIW	Ciclopirox TIW	Placebo
2 weeks	- 2.9	- 3.0	- 3.0	- 1.5
4 weeks	- 4.3	- 4.2	- 4.5	- 2.9
Endpoint	- 4.3	-4.3	- 4.6	- 2.9

b. Individual clinical signs/symptoms.

The frequency distribution of scores for itching, erythema, and inflammation at baseline and at 4 weeks, by percentages of patients in each category, was as follows.

Itching Frequency distribution by percentage of patients						
	none	slight	mild	moderate	pronounced	severe
Ciclopirox QW						
Baseline	7.0	11.6	32.6	37.2	9.3	2.3
Week 4	53.5	16.3	11.6	14.0	4.7	-
Ciclopirox BIW						
Baseline	6.5	10.9	32.6	34.8	15.2	-
Week 4	40.0	31.1	17.8	8.9	2.2	-
Ciclopirox TIW						
Baseline	7.1	7.1	38.1	31.0	14.3	2.4
Week 4	52.4	14.3	16.7	11.9	4.8	-
Placebo						
Baseline	4.3	17.4	32.6	32.6	13.0	-
Week 4	26.7	24.4	20.0	20.0	6.7	2.2

Scaling Frequency distribution by percentage of patients						
	none	slight	mild	moderate	pronounced	severe
Ciclopirox QW						
Baseline	-	-	23.3	67.4	9.3	-
Week 4	25.6	30.2	20.9	20.9	2.3	-
Ciclopirox BIW						
Baseline	-	4.3	21.7	47.8	26.1	-
Week 4	22.2	33.3	26.7	13.2	4.4	-
Ciclopirox TIW						
Baseline	-	-	16.7	59.5	23.8	-
Week 4	23.8	28.6	23.8	19.0	2.4	2.4
Placebo						
Baseline	-	2.2	21.7	47.8	28.3	-
Week 4	17.8	20.0	28.9	26.7	6.7	-

Inflammation Frequency distribution by percentage of patients						
	none	slight	mild	moderate	pronounced	severe
Ciclopirox QW						
Baseline	-	7.0	32.6	58.1	2.3	-
Week 4	48.8	18.6	16.3	14.0	2.3	-
Ciclopirox BIW						
Baseline	-	10.9	41.3	37.0	8.7	2.2
Week 4	33.3	37.8	20.0	6.7	2.2	-
Ciclopirox TIW						
Baseline	2.4	-	35.7	54.8	7.1	-
Week 4	52.4	11.9	19.0	14.3	2.4	-
Placebo						
Baseline	2.2	8.7	39.1	41.3	8.7	-
Week 4	33.3	20.0	24.4	20.0	2.2	-

c. Investigator's global evaluation.

The status of the seborrheic dermatitis and the change from baseline at week 4 was as follows.

Status of condition at week 4 Investigator's global evaluation				
	Ciclopirox QW	Ciclopirox BIW	Ciclopirox TIW	Placebo
None	10 (23.3%)	8 (17.8%)	11 (26.8%)	7 (15.6%)
Slight	16 (37.2%)	17 (37.8%)	12 (29.3%)	10 (22.2%)
Mild	8 (18.6%)	12 (26.7%)	10 (24.4%)	11 (24.4%)
Moderate	7 (16.3%)	8 (17.8%)	6 (14.6%)	12 (26.7%)
Pronounced	2 (4.7%)	-	1 (2.4%)	4 (8.9%)
Severe	-	-	-	1 (2.2%)

Change from baseline at week 4 Investigator's global evaluation				
	Ciclopirox QW	Ciclopirox BIW	Ciclopirox TIW	Placebo
Normalized	11 (25.6%)	7 (15.6%)	12 (29.3%)	9 (20.0%)
Markedly improved	15 (34.9%)	17 (37.8%)	13 (31.7%)	9 (20.0%)
Moderately improved	7 (16.3%)	11 (24.4%)	7 (17.1%)	7 (15.6%)
Slightly improved	6 (14.0%)	6 (13.3%)	4 (9.8%)	9 (20.0%)
Unchanged	2 (4.7%)	4 (8.9%)	4 (9.8%)	9 (20.0%)
Deteriorated	2 (4.7%)	-	1 (2.4%)	2 (4.4%)

3) Safety assessments.

The incidence of adverse events of the skin and appendages, in standardized terminology, was as follows.

Adverse events Skin and appendages				
	Ciclopirox QW n=44	Ciclopirox BIW n=47	Ciclopirox TIW n=44	Placebo n=48
Eczema	2 (4.5%)	1 (2.1%)	1 (2.3%)	1 (2.1%)
Pruritus	1 (2.3%)	-	-	1 (2.1%)
Alopecia	-	1 (2.1%)	-	-
Cyst	-	1 (2.1%)	-	-
Acne	-	-	1 (2.3%)	-
Fungal dermatitis	-	-	1 (2.3%)	-
Photosensitivity reaction	-	-	1 (2.3%)	-
Rash	-	-	-	2 (4.2%)
Skin disorder	-	-	-	3 (6.3%)

Those reactions that were considered to be at least possibly related to treatment were as follows.

Adverse events possibly treatment related Skin and appendages			
Pt No.	Term	Description	Severity
Ciclopirox QW			
14/10	Pruritus	Pruritus and tenseness of forehead and neck	Moderate
Ciclopirox BIW			
3/126	Hair disorder	Hair loss	Mild
Ciclopirox TIW			
None			
Placebo			
1/1	Skin disorder	Tenseness of scalp after shampooing	
3/34	Pruritus	Pruritus	Moderate
3/34	Skin disorder	Moist areas of scalp	
7/25	Skin disorder	Parietal erythema	Severe

The percentages of patients who rated the local tolerance as good or excellent was as follows.

Local tolerance Patient rating of good or excellent			
Ciclopirox QW	Ciclopirox BIW	Ciclopirox TIW	Placebo
93%	89%	88%	73%

The laboratory parameters showed a few abnormalities. These did not appear to be dose-related, and were considered by the investigator to be not clinically relevant or as unrelated to the study drug.

Reviewer's comments: In summary, this study was a comparison of Ciclopirox shampoo QW, BIW, and TIW and the vehicle, with administration for four weeks. The efficacy parameters were a scoring of itching, inflammation, and scaling. An investigator's global evaluation was made, but this is not considered to be valid, as it was done retrospectively after some patients had completed the study.

The Agency determined that definitions of 'Cleared' and 'Almost Cleared' based on the clinical signs and symptoms would be acceptable as comprising the primary efficacy variable. Clear was defined as scores of 0 at the end of treatment for inflammation, itching, and scaling. Almost Clear at the end of treatment was defined as an inflammation score of 0, and scores for itching and scaling of 0, or of 1 if the baseline score was =/> 3 at baseline. The category 'Effectively Treated' included those patients that were Cleared or Almost Cleared at the end of treatment, and was the primary efficacy variable.

Statistical analyses for those patients that were Effectively Treated showed no significant difference between Ciclopirox shampoo QW, BIW, or TIW and the vehicle. There is no evidence of a dose related trend in the proportion of patients that were Cleared or were Effectively Treated. This study, therefore, does not show the effectiveness of the product at any of these application frequencies.

Phase 3 studies

1) Study 3001.

The investigators for this study were as follows.

Monsieur le Docteur Abirached, MD Nanterre, France	Dr. Gunter Klovekorn, MD Gilching, Germany
Dr. M. Adler, MD Middlesex, UK	Dr.H. Lachner, MD Mainz, Germany
Dr. W. Aitchison, MD Renfrewshire, UK	Monsieur le Docteur Lanternier, MD Clamart, France
Monsieur le Docteur Alirezai, MD Montpelier, France	Dr. Gunter Ludwig, MD Rheine, Germany
Dr. Barbara Anegg, MD Vienna, Austria	Madame le Docteur Massis, MD Clamart, France
Madame le Docteur Beout, MD. Clichy, France	Dr. D. McKeith, MD Irvine, UK
Dr. D. Binder, MD Witzburg, Germany	Prof. Dr. Merk, MD Aachen, Germany

Frau Dr. M. Bisco, MD Mannheim, Germany	Dr. Monika Neumann, MD Bonn, Germany
Dr. J. Budde, MD Marl, Germany	Madame le Docteur Ochonisky, MD Paris, France
Dr. L. Campbell, MD Glasgow, UK	Monsiieur le Docteur Payenneville, MD Rouen, France
Madame le Docteur Dabeaux-Merger, MD Marseille, France	Dr. P. Pierchalla, MD Recklinghausen, Germany
Monsieur le Docteur Drouault, MD Boulogne, France	Madame le Docteur Reverat, MD Brunoy, France
Madame le Docteur Durande, MD Paris, France	Dr. J. Ross, MD Glasgow, UK
Madame le Docteur Farcet, MD Athis Mons, France	Madame le Docteur Ruer-Mulard, MD Martigues, France
Dr. Ernst-Gunther Gensch, MD Kirchhain, Germany	Prof. Dr. Schill, MD Giessen, Germany
Prof.Dr. F. Gschnait, MD Vienna, Austria	Dr. M. Sebastian MD, Mahlow, Germany
Prof. Dr. Hagedorn, MD Darmstadt, Germany	Madame le Docyeur Serrero, MD Montpelier, France
Monsieur le Professeur Humbert, MD Besancon, France	Dr. P. Shearer, MD Ayr, UK
Dr. J. Hutchison, MD Glasgow, UK	Dr. D. Spence, MD Glasgow, UK
Prof. Dr. Jorg Keller, MD Stuttgart, Germany	Prof Dr. Josef-Andreas Stefan, MD Hennef, Germany
Prof. Dr. Helmut Kerl, MD Graz, Austria	Frau Dr. Elisabeth Thomas Marburg, Germany
Frau Dr. E. Wolf Mainz-Kastel, Germany	Dr. med. F. Vennemann, MD Langenhagen, Germany
	Frau Dr. Wichmann-Hendricks, MD Grunberg, Germany

1) Study title: A Randomized, Double Blind, Multinational, Multicenter Study of the Efficacy and Safety of Ciclopirox Shampoo in the Treatment and Prophylaxis of Seborrheic Dermatitis/Dandruff of the Scalp.

Segment A (Treatment): Comparison of 1% Ciclopirox twice a week versus once a week versus vehicle for four weeks.

Segment B (Prophylaxis): Comparison of 1% Ciclopirox once a week versus once every fortnight versus vehicle for three months.

2) Study objectives: The primary objective of Segment A was to assess the efficacy of 1% Ciclopirox shampoo in the therapeutic treatment of seborrheic dermatitis of the scalp. The primary objective of Segment B was to assess the efficacy of 1% Ciclopirox shampoo in the prophylaxis of seborrheic dermatitis of the scalp in the responders from Segment A.

The secondary objective was to assess the safety and tolerability of 1% Ciclopirox shampoo in the treatment and prophylaxis of seborrheic dermatitis of the scalp.

3) Study design: This was a multinational, multicenter, parallel group, randomized, double blind, (double dummy) Phase III study.

4) Inclusion criteria: Patients who met the following criteria were enrolled into the study.

a. 18-75 years of age, in good physical health.
b. A score of 3 or higher for each of the categories 'Status of seborrheic dermatitis', 'Inflammation' and 'Scaling'.

5) Exclusion criteria: Patients with the following were excluded from enrollment in the study.

a. Psoriasis of the scalp.
b. Topical treatment of the scalp with other antifungal medication, including Ciclopirox, or with corticosteroids in the 4 weeks before start of the active treatment.
c. Use of systemic corticosteroids, retinoids, erythromycin, tetracycline or its derivatives (e.g., minocycline hydrochloride, doxycycline) trimethoprim/sulfamethoxazole, cytostatic or immunomodulating drugs or any other antimycotic within 4 weeks before the start of active treatment.
d. A likelihood of requiring treatment during the study

period with drugs not permitted by the study protocol.

e. Asthma requiring regular treatment with >800 ug corticosteroids of inhaler therapy.
f. A history of hypersensitivity to the study medication or to drugs with similar chamical structure.
g. Uncontrolled diabetes.
h. Clinical signs and/or history of immunosuppression.
I. Abnormal baseline findings which the investigator considered might affect the study results.
j. Severe disease likely to jeopardize the planned termination of the study, e.g., cancer, cardiac infarct, unstable angina pectoris.
k. Pregnancy, lactation, childbearing potential without adequate contraception.
l. Treatment with any other investigational drug in the last 4 weeks before study entry.
m. History of drug or alcohol abuse.
n. History or suspicion of unreliability, poor co-operation or non-compliance with medical treatment.
o. A mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study.

6) Treatment regimen: During a two week 'run-in' phase prior to treatment the patients used —— shampoo at least twice weekly. At each application during the treatment phases of Segments A and B, 5 ml of the shampoo was to be used, as measured with a measuring jug. The patients were instructed to wet the hair, lather and massage with the shampoo, leave the shampoo on for 3 minutes, which was measured by a timer provided to each patient, and then rinse the hair. The interval between successive applications was to be 3-4 days. The patients were permitted to use —— shampoo, provided by the sponsor, for additional shampoos during treatment as desired.

After the run-in phase, the patients were randomized at baseline on a 2:2:1 basis into the treatment groups of Segment A, namely, Ciclopirox shampoo QW, Ciclopirox shampoo BIW, and vehicle BIW, respectively. The duration of applications was four weeks.

The weekly application schedule in Segment A was as follows.

Weekly application schedule Segment A			
	Vehicle	Ciclopirox QW	Ciclopirox BIW
1st application	Vehicle	Ciclopirox	Ciclopirox
2nd application	Vehicle	Vehicle	Ciclopirox

During the prophylaxis phase (Segment B) patients who had responded to treatment in Segment A were newly randomized into three treatment groups on a 1:1:1 basis: Ciclopirox shampoo QW, Ciclopirox shampoo once every second week, and the vehicle once weekly, for 12 weeks. A response to treatment was defined as a score of 0, or a score of 1 if the baseline score was equal to or greater than 3, to be met simultaneously by the global status, inflammation, and scaling at individual endpoint.

The application schedule for Segment B was as follows.

Application schedule Segment B			
	Vehicle	Ciclopirox QW	Ciclopirox QOW
Week 1	Vehicle	Ciclopirox	Ciclopirox
Week 2	Vehicle	Ciclopirox	Vehicle

This sequence was repeated throughout the 12 week treatment period.

7) Efficacy parameters: Return visits were scheduled as follows.

Schedule of return visits	
Visit 1	Screening
Visit 2	Baseline for Segment A
Visit 3	At 2 weeks of treatment - Segment A
Visit 4	At 4 weeks of treatment - Segment A Final visit Segment A, baseline Segment B
Visit 5	At 4 weeks of treatment - Segment B
Visit 6	At 12 weeks of treatment - Segment B Final visit, Segment B

a. Signs and symptoms. Itching, scaling, and inflammation were scored at each return visit on the following scale.

Signs/symptoms	
Score	Description
0	None
1	Slight
2	Mild
3	Moderate
4	Pronounced
5	Severe

For statistical evaluation the results of the three single scores were added, for a combined score of from 0 to 15.

b. Investigator's global evaluation: The status of the diease was rated at each visit on the following scale.

Global evaluation	
Score	Description
0	None
1	Slight
2	Mild
3	Moderate
4	Pronounced
5	Severe

The change in the condition was calculated from the score during treatment minus the score at the baseline of the study segment.

The percentage of scalp affected was estimated as 0-10%, >10-20%, >20-30%, >30-50%, >50-75%, or >75-100%.

The sponsor considered the primary efficacy variable for Segment A to be the 'Primary Response'. This was defined as a score of 0, or a score of 1 if the baseline score was equal to or greater than 3, to be met simultaneously by the global status, inflammation, and scaling at individual endpoint. For Segment B the primary efficacy variable was the relapse rate, defined as a worsening of the global status score from the start of Segment B by 2 or more points.

8) Safety parameters: The following hematology and clinical chemistries were done at screening, at visit 4, and at visit 6: Hemoglobin, hematocrit, RBC, creatinine, SGOT, SGPT, y-GT, and urinalyses. Adverse events observed by the investigator or reported by the patient were recorded as mild, moderate, or severe, and local tolerance was rated by the investigator as excellent, good, fair, or poor at each return visit.

Serum and urine drug levels were measured at selected centers. It was intended to collect data from 20 patients with the highest exposure to the drug during Segment B, i.e., Ciclopirox once weekly. Since these patients could only be identified after unblinding, it was planned to measure drug levels on 180 patients chosen at screening. Blood and 24 hour urine samples for drug levels were taken at screening, after

4 weeks of treatment in Segment A, and after 12 weeks of treatment in Segment B. The patients were advised to wash their hair with the study medication on the day before a sampling visit.

Results in Segment A were as follows.

1) Patient enrollment and demographic characteristics: Of 949 screened patients, the following number of patients were included in the different analysis populations in Segment A.

No. of patients in analyses populations
Segment A

Treatment	Safety	ITT	Valid
Vehicle	192	190	158
Ciclopirox QW	377	376	321
Ciclopirox BIW	380	376	324
Total	949	942	803

Safety = all patients who received at least one dose of randomized medication.
ITT = all patients randomised to treatment who received at least one dose of assigned treatment and had a subsequent rating of the primary efficacy variable (response rate) or who dropped out due to lack of efficacy.
Valid = all patients of the ITT population who also had a rating of the primary efficacy variable at the end of the experimental study phase, (Visit 4 in Segment A and visit 6 in Segment B) with no major protocol violations.

It should be noted that the Agency definition of the ITT population is all randomized patients.

The age and gender distribution of all randomized patients were as follows.

Demographic characteristics			
	Ciclopirox QW n=377	Ciclopirox BIW n=380	Vehicle n=192
Gender			
Male	215 (57%)	213 (56%)	109 (57%)
Female	162 (43%)	167 (44%)	83 (43%)
Age			
Mean	28.1	28.4	28.4
Range	18-38	18-38	18-38

The number of dropouts and the reasons given were as follows.

Dropouts			
Reason	Ciclopirox QW	Ciclopirox BIW	Vehicle
Adverse event	5	3	4
Insufficient compliance	4	1	4
Inefficacy	2	3	4
Consent withdrawn	1	2	-
Major protocol violation	-	-	1
Other	1	3	2
Total	13	12	15

2). Efficacy variables.

The following results of Segment A were for the ITT population, defined as all patients randomised to treatment who received at least one dose of assigned treatment and had a subsequent rating of the primary efficacy variable (response rate) or who dropped out due to lack of efficacy.

A. Primary efficacy variable.

The sponsor considered the primary efficacy variable for Segment A to be the 'Primary Response'. This was defined as a score of 0, or a score of 1 if the baseline score was

equal to or greater than 3, to be met simultaneously by the global status, inflammation, and scaling at individual endpoint.

Primary response rate			
	Ciclopirox QW	Ciclopirox BIW	Vehicle
Responders	171 (45.5%)	220 (58.5%)	60 (31.6%)
Non-responders	205 (54.5%)	156 (41.5%)	130 (68.4%)

p values - Primary response rate	
Comparison	p value
Ciclopirox QW vs vehicle	0.0008
Ciclopirox BIW vs vehicle	<0.0001

B. Secondary efficacy variables.

a. 'Cleared' response rate.

The proportions of patients that cleared, with scores of 0 for status of seborrheic dermatitis, inflammation, scaling, and itching, were as follows.

Cleared response rate			
	Ciclopirox QW	Ciclopirox BIW	Vehicle
Responders	64 (17.0%)	87 (23.1%)	19 (10.0%)
Non-responders	312 (83.0%)	289 (76.9%)	171 (90.0%)

p values - Cleared response rate	
Comparison	p value
Ciclopirox QW vs vehicle	0.0367
Ciclopirox BIW vs vehicle	0.0001

b. Clinical signs/symptoms

The mean sumscores (the sum of the scores for scaling, itching, and inflammation) and the changes from baseline in mean sumscores were as follows.

Mean sumscores			
	Ciclopirox QW	Ciclopirox BIW	Vehicle
Baseline	9.0	9.2	9.4
2 weeks	5.7	5.0	6.8
4 weeks	3.7	2.9	5.1
Endpoint	3.8	3.0	5.3

Change in mean sumscores from baseline			
	Ciclopirox QW	Ciclopirox BIW	Vehicle
2 weeks	- 3.3	- 4.1	- 2.6
4 weeks	- 5.3	- 6.2	- 4.2
Endpoint	- 5.2	- 6.1	- 4.1

No statistical analyses were done on the changes in mean sumscores from baseline.

The frequency distribution of scores for itching, scaling, and inflammation at baseline and at 4 weeks, by percentages of patients in each category, was as follows.

Itching Frequency distribution by percentage of patients						
	none	slight	mild	moderate	pronounced	severe
Ciclopirox QW						
Baseline	3.2	8.2	20.5	43.6	18.9	5.6
Week 4	41.9	27.1	14.8	11.8	3.6	0.8
Ciclopifox BIW						
Baseline	3.2	8.8	17.8	41.5	24.2	4.5
Week 4	48.1	28.3	13.3	7.3	2.4	0.5
Vehicle						
Baseline	3.2	7.4	17.9	32.6	32.6	6.3
Week 4	28.3	27.8	18.3	16.1	8.3	1.1

Scaling Frequency distribution by percentage of patients						
	none	slight	mild	moderate	pronounced	severe
Ciclopirox QW						
Baseline	-	-	18.4	50.0	26.9	4.8
Week 4	23.3	38.4	14.8	16.4	6.0	1.1
Ciclopirox BIW						
Baseline	-	-	11.7	50.0	33.2	5.1
Week 4	32.1	38.9	12.5	12.5	3.3	0.8
Vehicle						
Baseline	-	-	16.8	42.6	32.1	8.4
Week 4	15.6	27.2	20.0	21.7	13.3	2.2

Inflammation Frequency distribution by percentage of patients						
	none	slight	mild	moderate	pronounced	severe
Ciclopirox QW						
Baseline	-	-	30.3	44.9	21.8	2.9
Week 4	41.9	26.8	13.7	14.0	3.3	0.3
Ciclopirox BIW						
Baseline	-	-	30.9	45.2	21.0	2.9
Week 4	52.7	23.9	13.0	8.75	1.1	0.5
Vehicle						
Baseline	-	-	31.1	40.5	24.2	4.2
Week 4	31.1	17.8	22.2	20.0	7.83	1.1

c. Investigator's global evaluation.

The status of the seborrheic dermatitis and the change from baseline at week 4 was as follows.

Status of condition at week 4 Investigator's global evaluation			
	Ciclopirox QW	Ciclopirox BIW	Placebo
None	73 (20.0%)	107 (29.1%)	26 (14.4%)
Slight	148 (40.5%)	154 (41.8%)	50 (27.8%)
Mild	59 (16.2%)	52 (14.1%)	39 (21.7%)
Moderate	61 (16.7%)	42 (11.4%)	44 (24.4%)
Pronounced	22 (6.0%)	11 (3.0%)	19 (10.6%)
Severe	2 (0.5%)	2 (0.5%)	2 (1.1%)

Change from baseline at week 4 Investigator's global evaluation			
	Ciclopirox QW	Ciclopirox BIW	Vehicle
-5	3 (0.8%)	7 (1.9%)	1 (0.6%)
-4	22 (6.0%)	35 (9.5%)	12 (6.7%)
-3	71 (19.5%)	93 (25.3%)	21 (11.7%)
-2	116 (31.8%)	121 (32.9%)	49 (27.2%)
-1	84 (23.0%)	74 (20.1%)	52 (28.9%)
0	65 (17.8%)	34 (9.2%)	29 (16.1%)
1	4 (1.1%)	4 (1.1%)	14 (7.8%)
2	-	-	2 (1.1%)

3) Safety assessments.

The adverse events in Segment A which were related to the skin and appendages, and occurred in at least two patients, were as follows.

Adverse events - skin and appendages - Segment A Occurring in at least 2 patients			
	Ciclopirox QW n=377	Ciclopirox BIW n=380	Vehicle n=192
Seborrhea	3 (0.7%)	5 (1.3%)	4 (2.1%)
Rash	1 (0.3%)	4 (1.1%)	1 (0.5%)
Pruritus	1 (0.3%)	3 (0.8%)	1 (0.5%)
Skin disorder	4 (1.1%)	1 (0.3%)	2 (1.0%)
Herpes simplex	1 (0.3%)	2 (0.5%)	-
Acne	-	2 (0.5%)	-
Eye disorder	2 (0.5%)	-	-
Skin hypertrophy	2 (0.5%)	-	-

Adverse events in Segment A which were related to the scalp occurred in 7 (1.8%) on Ciclopirox QW, 11 (3%) on Ciclopirox BIW, and 7 (3.6%) on the vehicle, with several patients having more than one event. (The sponsor's tabulation differs slightly from the tabulation below, as they listed 3 events that were not treatment related). These events, as listed first for all treatment groups in standardized terminology, and then with additional descriptive data for the Ciclopirox QW and BIW groups provided in the data listings, were as follows.

Adverse events related to scalp - standard terminology Segment A All patients			
	Ciclopirox QW n=377	Ciclopirox BIW n=380	Vehicle n=192
Seborrhea	3 (0.7%)	3 (0.8%)	2 (1.0%)
Rash	-	4 (1.1%)	-
Application site reaction	1 (0.3%)	-	1 (0.5%)
Pruritus	1 (0.3%)	3 (0.8%)	2 (1.0%)
Skin disorder	1 (0.3%)	-	2 (1.0%)
Hair discoloration	-	1 (0.3%)	-
Dry skin	-	1 (0.3%)	-
Alopecia	1 (0.3%)	-	-

Additional descriptions of events related to the scalp provided in the patient data listings were as follows.

Adverse events -scalp - data listings Ciclopirox BIW			
Pt #/Site	Term	Description	Severity
2/104	Hair discoloration	Dyed off strands	Moderate
26/106	Pruritus	Itching after use of AII (AII not defined)	Mild
4/111	Seborrhea	Scaling	Mild
23/111	Dry skin	Dry skin, discomfort after hair washing	Moderate
29/111	Rash	Erythema of scalp	Mild
29/111	Pruritus	Itching of scalp	Mild
47/111	Pruritus	Itching after use of shampoo	Moderate
10/113	Seborrhea	Exacerbation of seborrheic dermatitis	Severe
6/116	Rash	Redness on scalp	Mild
6/116	Rash	Papules on scalp	Mild
8/116	Rash	Redness after application of shampoo	Moderate
7/309	Rash	Pruriginous erythema on the head	Severe
12/309	Seborrhea	Seborrheic dermatitis, scalp and ears	Severe

Adverse events - scalp - data listings Ciclopirox QW			
Pt #/Site	Term	Description	Severity
25/111	Pruritus	Itching	Moderate
34/111	Application site reaction	Slight burning after first use of shampoo	Mild
17/116	Seborrhea	Prūritus, scaling, deterioration of seborrheic eczema	Moderate
2/302	Alopecia	Alopecia	Mild
9/343	Seborrhea	Serious growth of seborrheic dermatitis or intolerance	Severe
1/351	Seborrhea	Increase in the seborrheic dermatitis on the head	Moderate
10/352	Skin disorder	Increase in the dermatitis	Severes

Adverse events - scalp Vehicle			
Pt #/Site	Term	Description	Severity
29/103	Seborrhea	Seborrheic dermatitis	Moderate
17/106	Pruritus	Pruritus scalp	Severe
4/116	Skin disorder	Worsening of study disease	Moderate
18/116	Seborrhea	Deterioration of seborrheic dermatitis	Moderate
18/302	Application site reaction	Intolerance	Mild
4/309	Pruritus	Scalp pruritus	Moderate
13/309	Skin disorder	Erythema and pruritus, neck and face	Severe

Most of the cases of seborrhea, skin disorder, and pruritus reflected a worsening of the condition. Adverse events of the scalp which led to withdrawal were seborrhea in 3 patients in the Ciclopirox QW group, hair discoloration in 1 and seborrhea in 2 in the BIW group, and seborrhea in 2 and application site reaction in 1 in the vehicle group.

The duration and outcome of the cases of rash which occurred in the Ciclopirox BIW group, as described in the data listings, were as follows. The three mild cases were of one day's duration, and resolved spontaneously. The moderate case lasted one month and resolved spontaneously. The severe case lasted two days; the patient was given remedial drug therapy and it resolved. Information is not given as to when in the course of treatment the rashes occurred, but it appears that all the patients completed the study.

No serious events occurred which were treatment-related.

The investigator's rating of local tolerance at week 4 was as follows.

Investigator rating of local tolerance Percentage of patients				
	Excellent	Good	Fair	Poor
Ciclopirox QW	42.5%	51.0%	4.9%	1.6%
Ciclopirox BIW	48.1%	44.6%	6.0%	1.4%
Vehicle	32.6%	58.6%	6.1%	2.2%

Laboratory abnormalities which were considered adverse events were liver function test abnormalities in 2 patients in the Ciclopirox twice weekly group and in 2 patients in the once weekly Ciclopirox group; none of these was considered to be treatment related, although no explanation was provided. The outcome in these patients was also not provided. The values for the liver function tests were as follows.

Liver function abnormalities U/L				
Pt No.	Visit	SGOT	SGPT	GGT
Ciclopirox BIW				
106/13	Screening Visit 4	Hemolysis 23	Hemolysis 20	Hemolysis 530*
111/44	Screening Visit 4 2 weeks after	15 20 23	29 78* 42	24 42 37
Ciclopirox QW				
116/2	Screening Visit 4	20 17	37 33	45 57
205/13	Screening Visit 4	12 21	16 31	61* 89*
* considered clinically relevant Normal values: SGOT - 0 to 19 SGPT - 0 to 23 GGT - 4 to 28				

Results for Segment B were as follows.

1) Patient disposition: The number of patients who were responders in Segment A, those re-randomized into Segment B into new treatment groups, and the number which completed Segment B, were as follows.

Patient disposition - end of Segment A				
	Ciclopirox QW	Ciclopirox BIW	Vehicle	Total
Completed Segment A	364	368	177	909
Responders in Segment A	221	261	76	558
Transferred to Segment B	162	205	61	428

Patient disposition - Segment B				
	Ciclopirox QW	Ciclopirox QOW	Vehicle	Total
Randomized in Segment B	138	149	141	428
Premature terminations	10	20	13	43
Completed Segment B	128	129	128	385

The reasons for premature terminations in Segment B were as follows.

Premature terminations - Segment B			
	Ciclopirox QW	Ciclopirox QOW	Vehicle
Adverse event	2	6	3
Inefficacy	2	5	4
Major protocol violation	1	3	2
Insufficient compliance	2	2	-
Consent withdrawn	1	2	-
Other	2	2	4
Total	10	20	13

The distribution of the populations for analysis was as follows.

No. of patients in analyses populations			
Treatment	Safety	ITT	Valid
Ciclopirox QW	138	136	97
Ciclopirox QOW	149	145	103
Vehicle	141	140	91
Total	428	421	291

2) Efficacy.

The primary efficacy variable for Segment B was the relapse rate, defined as a worsening of the global status score by 2 or more points at endpoint, as compared to the score at the start of Segment B. The relapse rate for the ITT population was as follows.

Relapse rate			
	Ciclopirox QW n=136	Ciclopirox QOW n=145	Vehicle n=140
Relapse	20 (14.7%)	32 (22.1%)	49 (35.0%)

The p values for pairwise comparisons with the vehicle were as follows.

p values - relapse rate	
Comparison	p value
Ciclopirox QW vs vehicle	0.0001
Ciclopirox QOW vs vehicle	0.0149

The frequency distribution of the investigator's global evaluation was as follows.

Investigator's global evaluation, Segment B ITT population - percentage of patients						
	None score 0	Slight score 1	Mild score 2	Moderate score 3	Pronounced score 4	Severe score 5
Ciclopirox QW n=136						
Visit 4	33.8	66.2	-	-	-	-
Visit 5	32.4	50.0	9.6	6.6	0.7	0.7
Visit 6	34.8	40.2	15.2	6.1	3.8	-
Endpt	33.8	39.7	15.4	6.6	3.7	0.7
Ciclopirox QOW n=145						
Visit 4	36.6	62.8	0.7	-	-	-
Visit 5	24.8	49.0	11.0	12.4	2.1	0.7
Visit 6	28.7	42.6	14.7	9.6	4.4	-
Endpt	26.9	42.1	14.5	10.3	5.5	0.7
Vehicle n=140						
Visit 4	40.0	59.3	0.7	-	-	-
Visit 5	21.7	40.6	15.2	16.7	5.1	0.7
Visit 6	29.5	28.8	17.4	15.2	9.1	-
Endpt	28.8	28.8	16.5	15.8	10.1	-

3) Safety.

Adverse events of the skin and appendages in Segment B were as follows.

Adverse events - skin and appendages - Segment B			
	Ciclopirox QW	Ciclopirox QOW	Vehicle
Eczema	2 (1.4%)	3 (2.0%)	1 (0.7%)
Fungal dermatitis	1 (0.7%)	1 (0.7%)	-
Seborrhea	1 (0.7%)	3 (2.0%)	3 (2.1%)
Skin disorder	1 (0.7%)	1 (0.7%)	1 (0.7%)
Contact dermatitis	-	1 (0.7%)	-
Nail disorder	-	1 (0.7%)	-
Rash	-	2 (1.3%)	-
Urticaria	-	1 (0.7%)	-
Furunculosis	-	-	1 (0.7%)
Pruritus	-	-	1 (0.7%)

Adverse events related to the scalp occurred in 1 patient (1%) in the Ciclopirox QW group, in 7 patients (5%) in the Ciclopirox QOW group, and in 4 patients (3%) in the vehicle group; these were as follows.

Adverse events related to scalp			
	Ciclopirox QW n=138	Ciclopirox QOW n=149	Vehicle n=141
Seborrhea, application site reaction	1 (0.7%)	-	-
Seborrhea	-	3 (2.0%)	2 (1.4%)
Rash	-	2 (1.3%)	-
Skin disorder	-	1 (0.7%)	1 (0.7%)
Application site reaction	-	1 (0.7%)	-
Pruritus	-	-	1 (0.7%)

Most of these events were related to worsening of the seborrheic dermatitis.

No dose-related changes in laboratory parameters were found. Predefined abnormal increases in liver enzymes occurred in 4 (3%) of the Ciclopirox QW group, in 3 (2%) of the Ciclopirox QOW group, and in 4 (3%) of the vehicle group.

The number of patients who had analyses of drug serum levels, and the number of patients with drug serum levels equal to or greater than the LOQ of ——— were as follows.

Ciclopirox serum levels - Segment A			
	Ciclopirox BIW	Ciclopirox QW	Vehicle
Screening # pts sampled # pts >/= LOQ	110 -	108 -	54 -
After 4 wks treatment # pts sampled # pts >/= LOQ	104 3'	106 1**	53 -
* Drug levels were: ——— ** ———			

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Ciclopirox serum levels - Segment B			
Treatment Segment B	Ciclopirox QW		
Treatment Segment A	BIW	QW	Vehicle
After 12 wks treatment # pts sampled # pts >/= LOQ	13 -	15 1*	4 -

Treatment Segment B	Ciclopirox QOW		
Treatment Segment A	BIW	QW	Vehicle
After 12 wks treatment # pts sampled # pts >/= LOQ	12 -	12 -	7 -

Treatment Segment B	Vehicle		
Treatment Segment A	BIW	QW	Vehicle
After 12 wks treatment # pts sampled # pts >/= LOQ	18 1**	9 -	4 -

*)
**

There was no concomitant administration recorded of other medication containing Ciclopirox in any of the patients for whom the drug serum levels were equal to or greater than the LOQ ——— The value in the one patient in the vehicle group in Segment B was considered to be an artifact.

The number of patients with at least one 24 hour urine sample containing quantifiable levels of drug (=/> 20 ng/ml) at the end of Segment A and at the end of Segment B (after 4 and 12 weeks of treatment, respectively,) was as follows.

24 hour urine drug levels =/> 20 ng/ml End of Segment A		
	# pts sampled	# pts with drug levels
Ciclopirox BIW	98	77 (79%)
Ciclopirox QW	102	70 (69%)
Vehicle	52	6 (11%)

24 hour urine drug levels =/> 20 ng/ml End of Segment B		
	# pts sampled	# pts with drug levels
Ciclopirox QW	31	20 (65%)
Ciclopirox QOW	29	20 (69%)
Vehicle	27	3 (11%)

The amounts of drug excreted in ug was as follows.

Urine drug excretion (ug) End of Segment A			
	Range	Median	Mean
Ciclopirox BIW		240	359
Ciclopirox QW	———	259	421
Vehicle		35	37

Urine drug excretion (ug) End of Segment B			
	Range	Median	Mean
Ciclopirox QW		242	351
Ciclopirox QOW	———	137	258
Vehicle		91	91

Assuming that a dose of 50 mg of Ciclopirox was administered per application (5 ml of shampoo), the calculated median amounts excreted in the urine at the end of four weeks of treatment would represent 0.48% of the administered dose in the Ciclopirox BIW group and 0.52% of the administered dose in the Ciclopirox QW group. The maximum value found in one patient was ———, or 4.5% of the administered dose, in the Ciclopirox QW group.

The calculated median amounts excreted in the urine at the end of twelve weeks of treatment would represent 0.48% of the administered dose in the Ciclopirox QW group and 0.27% of the administered dose in the Ciclopirox QOW group. The maximum value found in one patient was ——— or 3.1% of the administered dose, in the Ciclopirox QW group.

There was no evidence of an effect of drug excretion on liver function.

Ciclopirox was found in 9 of 414 urine samples that should not have contained any drug, that is, samples taken at screening or after vehicle treatment. In one of these patients this was due to administration of a concomitant vaginal cream containing Ciclopirox. The others were just above the level of detection, in the range of [redacted] and it was felt that these might be due to interfering compounds such as food or spices.

Reviewer's comments: In the primary efficacy variable, defined as a score of 0, or a score of 1 if the baseline score were 3 or greater, to be met simultaneously by the global status, inflammation and scaling, Ciclopirox QW and Ciclopirox BIW were significantly superior to the vehicle at endpoint after four weeks of treatment. For patients who met the primary efficacy variable and were treated for an additional twelve weeks, it was found that Ciclopirox QW and Ciclopirox QOW were significantly superior to the vehicle in the relapse rate, defined as a worsening of the condition by 2 or more points in the global status scale during this period. It is felt that this study adequately demonstrates the effectiveness Of Ciclopirox shampoos QW and BIW in the treatment of seborrheic dermatitis, and the effectiveness of Ciclopirox shampoos QW and QOW in the prevention of recurrence of seborrheic dermatitis in those patients who have responded to a first four week course of Ciclopirox shampoos QW and BIW. The data also suggest that for treatment Ciclopirox shampoos BIW are superior to QW, and for prophylaxis Ciclopirox shampoos QW are superior to QOW.

2) Study 3003.

This was a double blind, randomized, multicenter study of the efficacy and safety of 1% Ciclopirox shampoo as compared to 2% ketoconazole shampoo in the treatment of patients with seborrheic dermatitis. Because the study was not adequately controlled, as it did not include a vehicle control, it was reviewed only for safety.

The safety population consisted of 373 patients in the 1% Ciclopirox group and 364 patients in the ketoconazole group. Applications of the shampoos were made twice weekly for four weeks. After lathering and thorough massage of the scalp, the patients were to leave the shampoo on the scalp for as close to 3 minutes as possible before rinsing.

The patients returned for evaluation every 2 weeks during treatment. Adverse events were recorded and local tolerance was scored at each return visit. The following hematology and clinical chemistries were done before and at the end of treatment: Hemoglobin, hematocrit, RBC, creatinine, SGOT, SGPT, γ-GT, cholesterol, triglycerides, and urinalyses.

The adverse events related to the skin and appendages were as follows.

Adverse events Skin and appendages		
	1% ciclopirox n=373	2% ketoconazole n=364
Acne	2 (0.5%)	3 (0.8%)
Alopecia	4 (1.0%)	3 (0.8%)
Eczema	1 (0.2%)	3 (0.8%)
Fungal dermatitis	2 (0.5%)	1 (0.3%)
Nail disorder	2 (0.5%)	-
Pruritus	5 (1.3%)	6 (1.6%)
Rash	6 (1.6%)	4 (1.0%)
Seborrhea	4 (1.0%)	1 (0.3%)

Additional descriptions of the reactions which were related to the scalp were as follows.

Adverse events related to the scalp			
Site/Pt No.	Term	Description	Severity
Ciclopirox 1.0%			
104/21	Alopecia	Alopecia	Mild
126/22	Alopecia	Alopecia	Moderate
325/9	Alopecia	Alopecia	Mild
325/11	Alopecia	Alopecia	Mild
106/1	Hair disorder	Reddening of hair	Mild
111/6	Psoriasis	Psoriasis of head	Moderate
209/3	Photosensitivity	Sunburn	Mild
211/6	Pruritus	Scalp pruritus	Severe
216/1	Pruritus	Increased scalp itching	Moderate
216/6	Pruritus	Increased scalp itching	Moderate
318/3	Pruritus	Increase of itching	Severe
219/1	Rash	Irritation of scalp	Moderate
219/6	Rash	Scalp irritation	Moderate
Ketoconazole 2%			
104/13	Alopecia	Alopecia	Moderate
104/18	Alopecia	Alopecia	Mild
325/13	Alopecia	Alopecia	Mild
202/15	Rash	Scalp irritation	Mild
206/3	Pruritus	Scalp itching	Severe

One patient in the Ciclopirox group withdrew from the study because of an adverse event related to the scalp; this patient had severe pruritus of the scalp.

Predefined abnormal changes in laboratory parameters occurred as follows.

Predefined abnormal changes in laboratory values		
Abnormalities	Ciclopirox n=373	Ketoconazole n=364
Increased blood lipids	4	3
Increased liver enzymes	3	12
Increased creatinine	2	1
Decreased hematological parameters	1	3

Reviewer's comments: This study was not reviewed for efficacy because it did not include a vehicle control.

Summary and evaluation: The proposed labeling indication for Loprox shampoo is the topical treatment of seborrheic dermatitis of the scalp and its minor form, dandruff, in adults. The clinical studies provided in support of the safety and effectiveness for this indication are four Phase 1 studies and two pivotal Phase 3 studies.

The Phase 1 studies were on local tolerance, sensitization potential, phototoxicity, and photosensitization potential. It is felt that the results of these studies show a low potential for irritation under the intended conditions of use, and little or no potential for phototoxicity or photosensitization. There also appeared to be a low potential for sensitization, although in the sensitization study, reactions in 2 of the 198 subjects were indicative, though not typical, of sensitization.

The pivotal Phase 3 studies were Studies # 204 and 3001. Study 204 was a controlled comparison of 1% Ciclopirox shampoo applied QW, BIW, and TIW with the vehicle applied TIW for four weeks in 177 patients. The efficacy variables were scores for itching, scaling, and inflammation. (The protocol was amended after the study had been initiated to include a global evaluation of the status of the disease, but this was applied retroactively after some patients completed the study and so was not considered to be valid.) The primary efficacy variable was determined to be the proportion of patients who were 'Effectively Treated', which included those patients who were 'Cleared' or 'Almost Cleared' at

the end of treatment. Cleared was defined as a score of 0 for inflammation, scaling, and itching. Almost Cleared was defined as a score of 0 for inflammation, and scores of 0 for itching and scaling, or scores of 1 if the baseline score were 3 or greater.

Statistical analyses of the results of Study 204 showed no significant differences between Ciclopirox shampoo QW, BIW, or TIW, and the vehicle in the proportion of patients that were Effectively Treated. It is therefore concluded that this study has not demonstrated the effectiveness of Loprox shampoo for the labeling indication.

Study 3001 was a controlled comparison of Ciclopirox shampoo QW and BIW and the vehicle when applied for four weeks in 942 patients. This was followed by twelve weeks of treatment with Ciclopirox shampoo QW or QOW or the vehicle in those patients who were considered to have responded during the first four weeks of treatment. The efficacy variables were scores for itching, scaling, and inflammation, and scores for the investigator's global evaluation of the status of the disease. The primary efficacy variable for the first four weeks of active treatment was the 'Primary Response', which was defined as scores of 0 for the global status, inflammation, and scaling, or scores of 1 if the baseline score were 3 or greater. The primary efficacy variable for the second part of the study, the twelve week prophylaxis phase, was the relapse rate, defined as the worsening of the condition by 2 or more points.

Results of statistical analyses at the end of the four week active treatment period showed a significant superiority of Ciclopirox shampoo QW and BIW over the vehicle in the Primary Response rate. At the end of the twelve week prophylactic treatment period, Ciclopirox QW and QOW were significantly superior to the vehicle in the relapse rate. It is concluded that the results of this study adequately demonstrate the effectiveness of Ciclopirox shampoo QW and BIW in the treatment of seborrheic dermatitis, and the effectiveness of Ciclopirox shampoo QW and QOW in the prevention of recurrence in those patients who have responded to the first four week active treatment period.

Adverse events which appeared to be possibly related to treatment were a low incidence of minor dermatological events.

It is noted that several items that were discussed with the sponsor at the pre-NDA meeting have not been addressed or provided by the sponsor. These include:

a. *a demonstration of the applicability of the data and organisms studied to the US population and US medical practice.*
b. *subset analyses of patients with dandruff, HIV infection, non-scalp seborrheic dermatitis, and different racial heritage.*
c. *An explanation of the discrepancy in the results of Study 3001, in which there was a higher disease relapse rate in the once per four day treatment arm than in the once per seven day treatment arm.*

Conclusions: It is concluded that the results of one of the two pivotal studies (#3001) has adequately demonstrated the effectiveness for the proposed labeling indication, but that the other study (#204) has not demonstrated a similar effectiveness. It is felt that an additional clinical study is needed which supports the results of Study 3001.

Recommendations: It is recommended that this application for the use of Loprox shampoo 1% for the treatment ——— of seborrheic dermatitis ——— not be approved.

/S/ M.D.

Phyllis A. Huene, M.D.

Cc: Orig NDA 21-159
HFD-540 Division files
HFD-540/Wilkin
HFD-540/Okun
HFD-540/Huene
HFD-540/Lutwak
HFD-540/Kumar
HFD-540/Nostrandt
Not in DFS

5/16/00
/S/ 5/15/00
See TL Addendum

Study #203 was sufficient dose-ranging evidence for 1% formulation.
See TL Addendum 5/21/00