CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-159

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Medical Division: **Division of Dermatologic & Dental Drug Products (DDDDP)**
HFD-540
Biometrics Division: **Division of Biometrics III**
HFD-725

NDA NUMBER:	21-159
DATE RECEIVED BY CENTER:	9/03/2002
DRUG NAME:	Loprox (ciclopirox) Shampoo, 1%
INDICATION:	Seborrheic dermatitis of the scalp
SPONSOR:	Medicis
DOCUMENTS REVIEWED:	Vol. 1, 3-34; Electronic files: \\CDSESUB1\N21159\N_000\2002-08-29
STATISTICAL REVIEWER:	Kathleen Fritsch, Ph.D. (HFD-725)
STATISTICAL TEAM LEADER:	Mohamed Alosh, Ph.D. (HFD-725)
BIOMETRICS DIVISION DIRECTOR:	M. F. Huque, Ph.D. (HFD-725)
CLINICAL REVIEWER:	Phyllis Huene, M.D. (HFD-540)
PROJECT MANAGER:	Jacquelyn Smith (HFD-540)

Table of Contents

1 Executive Summary of Statistical Findings

1.1 Conclusions and Recommendations

The sponsor has proposed that Loprox (ciclopirox) shampoo, 1%, should be indicated for the "topical treatment of seborrheic dermatitis of the scalp in adults. Additionally, it is indicated for [redacted]." In two studies, the sponsor has demonstrated a statistically significant effect for Loprox (ciclopirox) shampoo, 1%, in the treatment of seborrheic dermatitis of the scalp. In the clinical studies, treatment occurred twice weekly for four weeks. The primary efficacy endpoint was effective treatment, defined as achieving a score of 0 (or 1 if baseline was ≥3) simultaneously for status, erythema or inflammation, and scaling at Week 4. A score of 0 corresponds to 'none' and a score of 1 corresponds to 'slight' for each measure. In Study 3001, 58% of subjects using ciclopirox twice weekly achieved effective treatment, compared with 31% of subjects using vehicle ($p = 0.0001$). In Study 017, 26% of subjects using ciclopirox twice weekly achieved effective treatment, compared with 13% of subjects using vehicle ($p=0.0001$). Thus the sponsor has statistically demonstrated the efficacy of ciclopirox shampoo used twice weekly for 4 weeks in the treatment of seborrheic dermatitis of the scalp in two studies.

In addition, the sponsor has also proposed that ciclopirox shampoo can be used [redacted] Ciclopirox shampoo for prophylaxis was evaluated in one study (Study 3001, Segment B) and found to have a statistically significant effect in the prevention of relapse, where relapse is defined as worsening by at least 2 points on the status variable. In Study 3001-B, 16% of ciclopirox once weekly subjects had a relapse, while 35% of vehicle subjects had a relapse ($p=0.0001$). The sponsor has not attempted to replicate the findings of Study 3001, Segment B. Thus prophylactic treatment with ciclopirox shampoo has been studied and demonstrated effective in only a single study.

1.2 Overview of Clinical Program and Studies Reviewed

Study 3001 and a Phase 2 study (Study 204) were reviewed when the original NDA was submitted on September 8, 1999. Of the two studies evaluated, only Study 3001 supported the sponsor's claims, as Study 204 did not achieve statistical significance for any endpoints. Thus the application was not approved. In addition, all of the sponsor's Phase 2 and 3 studies submitted in the original application were conducted in Europe. Thus the sponsor was asked to provide data demonstrating the applicability of their findings to the U.S. population. The sponsor then conducted Study 017, which is the subject of the current submission. The sponsor conducted Study 017 in the United States. Study 3001 enrolled 1000 subjects, of whom 949 were treated (380 to ciclopirox twice weekly, 377 to ciclopirox once weekly, and 192 to vehicle). Study 3001 was conducted in Europe. For the complete statistical review of Study 3001, refer to the Statistical Review and Statistical Review Addendum dated 4/11/2000 and 6/12/2000, respectively.

Study 017 enrolled 499 subjects (250 to ciclopirox twice weekly and 249 to vehicle). Study 017 was conducted in the United States and is the primary subject of this review.

1.3 Principal Findings

Both Study 3001 and Study 017 support the efficacy of ciclopirox shampoo, 1%, in the treatment of seborrheic dermatitis of scalp, when used twice weekly for 4 weeks. In Study 3001, 58% of subjects using ciclopirox twice weekly achieved effective treatment, compared with 31% of subjects using vehicle ($p = 0.0001$). In Study 017, 26% of subjects using ciclopirox twice weekly achieved effective treatment, compared with 13% of subjects using vehicle ($p=0.0001$). There were a few differences in study design and execution between Studies 3001 and 017 that may have contributed to the observed differences in effective treatment rates for the two studies. Study 3001 was conducted in Europe with a predominantly Caucasian population (97%), while study 017, in the United States, enrolled a larger proportion of minorities (20%), and some variation in efficacy among minority populations was observed in Study 017. Also, Study 3001 followed subjects for a two-week run-in period before initiating the randomized treatment, while Study 017 did not have a run-in period. One further difference between the two studies was that effective treatment was based in part on an evaluation of 'inflammation' in Study 3001, and on an evaluation of 'erythema' in Study 017.

The efficacy of ciclopirox in the treatment of seborrheic dermatitis of the scalp was also supported by secondary endpoints such as clearing, improvement, erythema, scaling, and status. Ciclopirox shampoo for prophylaxis was evaluated in one study (Study 3001, Segment B) and found to be statistically significant in the prevention of relapse, where relapse is defined as worsening by at least 2 points on the status variable.

In Study 017, all age, race, and gender subgroups favored ciclopirox over vehicle except for subjects in the racial group 'black', where the proportion of effectively treated subjects on vehicle was higher than on ciclopirox. However, relatively few subjects in the black racial group were enrolled in Study 017 (28 ciclopirox and 21 vehicle). Even fewer black subjects were enrolled in Study 3001 (4 to ciclopirox twice weekly and none to vehicle).

In Study 017, adverse event rates were similar across the two treatment arms. Approximately 27% of subjects in each arm experienced an adverse event during the study. Approximately 4% of subjects in each arm (11 on ciclopirox and 10 on vehicle) experienced treatment related adverse events. The most common treatment related adverse event was pruritus.

2 Statistical Review and Evaluation of Evidence

2.1 Introduction and Background

The sponsor originally submitted the application for Loprox (ciclopirox) Shampoo, 1%, for the treatment [redacted] of seborrheic dermatitis (NDA 21-159) on September 8, 1999. The Division evaluated the results of a vehicle-controlled Phase 2 study (Study 204), and a vehicle-controlled Phase 3 study (Study 3001) for efficacy in the treatment of seborrheic dermatitis. Study 3001 had two segments, Segment A which studied the effect of treatment with ciclopirox shampoo, followed by Segment B which studied the effect of prophylaxis with ciclopirox shampoo. Study 204 did not demonstrate statistical significance for the primary or secondary efficacy endpoints in any of the three regimens studied (once, twice, or three times per week) in the treatment of seborrheic dermatitis. Study 3001-A demonstrated a statistically significant effect for the primary and secondary endpoints for ciclopirox shampoo applied either once weekly or twice weekly in the treatment of seborrheic dermatitis. For prophylaxis, ciclopirox was found to be statistically superior to vehicle when used either once weekly or once every other week in Study 3001-B. All of the submitted studies were conducted in Europe. The reviewer concluded that the sponsor had submitted one study that supported the efficacy of ciclopirox shampoo in the treatment and prophylaxis of seborrheic dermatitis.

Since only one of the sponsor's studies demonstrated efficacy and all of the studies were conducted in Europe, the Division issued a Not Approvable letter, and requested that the sponsor conduct an additional study to support efficacy. The Division recommended that the study be conducted in the United States, since no data had been provided addressing the applicability of the European data to the U.S. population. The sponsor has conducted an additional study of ciclopirox applied twice weekly for the treatment of seborrheic dermatitis (MED 00-017) that is the basis of this amendment to the application.

2.2 Data Analyzed and Sources

Table 1 lists the studies in the clinical program for ciclopirox shampoo. Studies 203, 204, 3001, and 3003 were submitted in the original submission of the NDA (9/08/1999). From that submission, studies 204 and 3001 were subjected to detailed statistical review. The current submission contains the study report for Study MED 00-017. Study 017 is the focus of this statistical review.

Table 1 – Clinical Program for Ciclopirox Shampoo, 1% for Seborrheic Dermatitis

Study	Study Type	Arms	Frequency	Subjects	Study Location
203	Phase 2 Efficacy/Safety (Treatment)	CIC 0.1% CIC 0.3% CIC 1.0% Vehicle	2x per week	210 enrolled 203 treated	Europe
204	Phase 2 Efficacy/Safety (Treatment)	CIC 1.0% Vehicle	1x, 2x, or 3x per week	200 enrolled 183 treated	Europe
3001	Phase 3 Efficacy/Safety Segment A – (Treatment) Segment B – (Prophylaxis)	CIC 1.0% Vehicle	 1x or 2x per week 1x per week or 1x every 2 weeks	1000 enrolled 949 treated 428 treated	Europe
3003	Phase 3 Active Controlled (Treatment)	CIC 1.0% KET 2.0%	2x per week	781 enrolled 737 treated	Europe
017	Phase 3 Efficacy/Safety (Treatment)	CIC 1.0% Vehicle	2x per week	499 enrolled 499 treated	U.S.

Note: CIC = Ciclopirox, KET = Ketoconazole

The sponsor has provided electronic data sets for Study 017. Demographic variables are found in the file pxldemog.xpt. Efficacy variables (signs, symptoms, and status) are found in the file pxlasses.xpt. These files are archived in the Electronic Document Room at \\CDSESUB1\N21159\N_000\2002-08-29\crt\DATASETS\med00-017. Information on ITT and per protocol status was downloaded from Table 1, page 74 of file med00-017.pdf (corresponding to printed page 154 in Volume 3.) All derived variables, such as effective treatment, were computed by the reviewer using the protocol definitions, as only raw variables were provided in the sponsor's data sets.

2.3 Statistical Evaluation of Evidence on Efficacy and Safety

2.3.1 Study 3001

The sponsor's claims of the efficacy of ciclopirox shampoo, 1% are based on two Phase 3 clinical studies, Studies 3001 and 017. Study 3001 was reviewed in the initial submission of NDA 21-159 and was found to have statistically demonstrated the efficacy of ciclopirox shampoo in the treatment (once weekly or twice weekly use) and prophylaxis (once weekly or once every two weeks use) of seborrheic dermatitis. The efficacy findings of Study 3001, as presented in the Statistical Review and Addendum (dated 4/11/2000 and 6/12/2000, respectively) are summarized here.

Study 3001 (Segment A) was a randomized, double-blind, multi-center, vehicle controlled study of the safety and efficacy of ciclopirox shampoo in the treatment of seborrheic dermatitis. Two treatment regimens were evaluated, once weekly and twice weekly. Subjects applied treatment for 4 weeks following a two-week run-in period. The study enrolled 1000 patients with 949 randomized to treatment: 380 to ciclopirox twice weekly, 377 to ciclopirox once weekly, and 192 to vehicle. Subjects were enrolled in four European countries, Germany, UK, France, and Austria. Baseline demographic data for age, race and gender are presented in Table A.1 in the appendix. More males than females were enrolled (57% versus 43%), and over 97% of the subjects were Caucasian.

At Week 4, subjects were evaluated on their 'status of seborrheic dermatitis', itching, scaling, and inflammation, each measured on a 6-point scale with 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = pronounced, and 5 = severe. The primary efficacy endpoint was 'Effective Treatment' defined as achieving a score of 0 (or 1 if baseline was ≥3) simultaneously for status, inflammation, and scaling at Week 4. The statistical reviewer also considered one secondary endpoint, 'Cleared', defined as achieving a score of 0 simultaneously for status, inflammation, scaling, and itching at Week 4. The results, based on the reviewer's ITT population (defined as all randomized patients), are presented in Table 2.

Table 2 – Number of Successes in Study 3001 (Segment A) at Week 4 (ITT)

	Ciclopirox 2x weekly (N=380)	Ciclopirox 1x weekly (N=377)	Vehicle (N=192)
Effective Treatment	220 (57.9%)	171 (45.4%)	60 (31.3%)
*p-value**	0.0001	0.0007	
Cleared	87 (22.9%)	64 (17.0%)	19 (10.0%)
*p-value**	0.0001	0.031	

* p-value versus vehicle (CMH test, adjusted for center). To adjust for multiplicity (Holm's procedure), the smaller p-value should be compared with 0.025, and the larger p-value should be compared with 0.05 for each endpoint.
Source: Statistical Review (4/11/2000), pg. 9-10.

The success rates were analyzed with Cochran-Mantel-Haenszel (CMH) tests, stratified on center. Since the study evaluated two treatment regimens, Holm's procedure was used to adjust for multiple comparisons. For two comparisons and overall $\alpha = 0.05$, Holm's procedure compares the smaller of the two p-values with 0.025, and the larger of the two p-values with 0.05. For both the primary and secondary endpoints, the p-values for the two regimens meet these criteria. Thus the efficacy of ciclopirox shampoo in the treatment of seborrheic dermatitis of the scalp with either once weekly or twice weekly dosing has been statistically demonstrated in Study 3001 (Segment A).

Subjects completing Segment A of the study with scores ≤ 1 simultaneously for status, scaling, inflammation, and itching were eligible for Segment B, a study of the efficacy of ciclopirox in the prevention of relapse in treatment responders. Subjects entering

Segment B were re-randomized equally into 3 arms, ciclopirox once weekly, ciclopirox once every second week, or vehicle once weekly. Of the subjects completing Segment A, 428 were randomized into Segment B. Subjects were treated for 12 weeks. The primary efficacy endpoint was the 'relapse' rate defined as worsening from the start of Segment B to the end by at least 2 points on the status variable (6-point scale). The results, based on the reviewer's ITT population (defined as all randomized patients), are presented in Table 3.

Table 3 – Relapse Rates in Study 3001 (Segment B) at Week 12 (ITT)

	Ciclopirox 1x weekly (N=138)	Ciclopirox 1x per 2 weeks (N=149)	Vehicle (N=141)
Relapsed Subjects	22 (15.9%)	36 (24.2%)	50 (35.5%)
p-value[*]	0.0001	0.033	

[*] p-value versus vehicle (CMH test, adjusted for center). For the sequential step down procedure, the p-value for ciclopirox once weekly versus vehicle should be compared with 0.05, and if significant, then the p-value for ciclopirox one time every two weeks versus vehicle should be compared with 0.05.
Source: Statistical Review (4/11/2000), pg. 13.

The relapse rates were analyzed with Cochran-Mantel-Haenszel (CMH) tests, stratified on center. Since the study evaluated two treatment regimens, the sequential step down procedure was used to account for multiple comparisons. The comparison of ciclopirox once weekly versus vehicle was pre-specified as the first comparison and tested at 0.05. If this comparison was significant, then the second comparison, ciclopirox once every two weeks versus vehicle, was also tested at 0.05. The p-values for the relapse rates meet these criteria, and thus both regimens, once weekly and once every two weeks, were found to be statistically superior to vehicle in the prevention of relapse. Thus, Study 3001 provided statistically significant evidence that ciclopirox shampoo (either once or twice weekly) was effective in the treatment of seborrheic dermatitis of the scalp, and that ciclopirox shampoo (either once per week or once every two weeks) was effective in the prevention of relapse of seborrheic dermatitis of the scalp.

2.3.2 Study 017 – Study Design

After receiving the Not Approvable letter, the sponsor conducted the second study, Study 017. Study 017 was a randomized, double-blind, multi-center, vehicle-controlled study of the safety and efficacy of ciclopirox shampoo in the treatment of seborrheic dermatitis. Major aspects of the study were agreed upon with the Division through a Special Protocol Assessment. Unlike Study 3001, Study 017 evaluated only one treatment regimen (twice weekly application for 4 weeks), and did not have a prophylaxis segment. Study 017 also did not have a two-week run-in period. The study enrolled 499 patients, 250 on ciclopirox and 249 on vehicle. Subjects were enrolled at 19 centers in the U.S. Subjects were evaluated at baseline, Week 2, and Week 4.

At Week 4, subjects were evaluated on their 'status of seborrheic dermatitis', itching, scaling, and erythema, each measured on a 6-point scale with 0 = none, 1 = slight, 2 =

mild, 3 = moderate, 4 = pronounced, and 5 = severe. These evaluations are the same evaluations that were conducted in Study 3001, except that Study 017 evaluated erythema while Study 3001 evaluated inflammation. The primary efficacy endpoint was 'Effective Treatment' defined as achieving a score of 0 (or 1 if baseline was ≥3) simultaneously for status, erythema, and scaling at Week 4. The secondary endpoints were: 'Cleared', defined as achieving a score of 0 simultaneously for status, inflammation, scaling, and itching at Week 4, 'Improved 1', defined as improvement from baseline by ≥ 2 points for status, scaling, and erythema, and 'Improved 2', defined as a score ≤ 1 or improvement from baseline by ≥ 3 points for status. Results on the individual signs and symptoms endpoints were also considered.

2.3.3 Statistical Methods

The ITT population was defined as all subjects randomized and dispensed treatment. Neither the protocol nor the statistical analysis plan state how missing data was to be handled. However, in the Special Protocol Assessment letter (dated 2/16/2001) the Division advised the sponsor that LOCF should be used for missing data in the ITT population. The sponsor appears to have followed that advice.

The per protocol population was defined as all subjects with a rating of the primary efficacy variable at the end of treatment and no major protocol violations. The major protocol violations used to exclude patients were: premature study termination, insufficient compliance, prohibited pre- or concomitant medication, and baseline erythema or scaling scores < 2.

Success rates for the primary and secondary endpoints were analyzed with Cochran-Mantel-Haenszel (CMH) tests stratified on center. The sponsor did not conduct formal tests of treatment by center interaction. The two smallest centers (with 3 and 8 subjects, respectively) were each pooled with another center with similar geographic characteristics.

2.3.4 Patient Disposition and Demographics

Study 017 enrolled 499 patients, 250 on the ciclopirox arm and 249 on the vehicle arm at 19 centers. One additional center involved in the study enrolled no subjects. Seventeen ciclopirox (6.8%) and 14 vehicle patients (5.6%) terminated the study early. Table 4 lists the disposition of enrolled subjects. The most common reason for discontinuation was loss to follow up (8 subjects). Two ciclopirox and three vehicle subjects discontinued due to adverse events.

Table 4 – Patient Disposition in Study 017

	Ciclopirox (N=250)	Vehicle (N=249)
Discontinued Subjects	17	14
Adverse Event	2	3
Lost to Follow-up	5	3
Protocol Violation	3	1
Non-compliance	1	5
Patient Request	4	1
Other	2	1

Source: Table 2.5.3, Vol. 3, pg. 200 (sponsor's submission).

Table A.2 in the appendix presents the baseline demographic data for Study 017. There are no significant demographic imbalances between arms. Approximately 80% of the subjects were Caucasian, 10% were black, 7% were Hispanic, and 3% were Asian/Other. Enrollment was relatively balanced between the two genders, with slightly more females than males enrolled (53% versus 47%). The average age was 46 years, with ages ranging from 16 to 90 years.

Approximately 36% of enrolled subjects were excluded from the per protocol population (87 on ciclopirox and 92 on vehicle). The most common protocol deviation used to exclude patients from the per protocol population was poor compliance (using less than 80% of the prescribed treatment shampoo or bottle weight missing) which occurred in 38 ciclopirox and 55 vehicle patients. Other protocol violations used to exclude a number of patients included delayed termination of prior treatments, deviation from time schedule, and early termination of the study.

Study 017 involved 19 centers. Two centers with small enrollments were pooled with centers from similar geographic regions. Center 12 (8 subjects) from Texas was pooled with Center 2 (32 subjects) from New Mexico. Centers 7 and 8, with 14 and 3 subjects respectively, both from Georgia, were also pooled. The remaining centers enrolled between 10 and 58 subjects each.

2.3.5 Sponsor's Efficacy Results

The sponsor's primary efficacy endpoint was effective treatment, defined as achieving a score of 0 (or 1 if baseline was ≥3) simultaneously for status, erythema, and scaling at Week 4. The results for effective treatment in the ITT population in Study 017 are presented in Table 5. In the study, 26% of ciclopirox and 13% of vehicle patients achieved effective treatment. This comparison was statistically significant ($p = 0.0001$). The results from the per protocol population (also presented in Table 5) are similar to those from the ITT population, with 28% of ciclopirox and 11% of vehicle patients achieving effective treatment.

Table 5– Number of Successes (Derived Variables) in Study 017 at Week 4

ITT	Ciclopirox 2x weekly (N=250)	Vehicle (N=249)	p-value[a]
Primary Endpoint			
Effective Treatment	65 (26%)	32 (13%)	0.0001
Secondary Endpoints			
Cleared	25 (10%)	8 (3%)	0.0017
Improved 1	72 (29%)	38 (15%)	0.0001
Improved 2	106 (42%)	60[b](24%)	<0.0001

Per Protocol	Ciclopirox 2x weekly (N=163)	Vehicle (N=157)	p-value[a]
Primary Endpoint			
Effective Treatment	46 (28%)	17 (11%)	0.0001
Secondary Endpoints			
Cleared	19 (12%)	4 (3%)	0.0011
Improved 1	50 (31%)	17 (11%)	<0.0001
Improved 2	70 (43%)	36 (23%)	0.0001

[a] p-values based on CMH test, adjusted for center.
[b] Sponsor's analysis. In the reviewer's analysis, 59 vehicle subjects were found to be successes for 'Improved 2' in the ITT population.
Effective Treatment = score of 0 (or 1 if ≥3 at baseline) on status, scaling and erythema; *Cleared* = score of 0 for status, scaling, erythema, and itching; *Improved 1* = improvement from baseline by ≥2 points for status, scaling, and erythema, *Improved 2* = improvement from baseline by ≥3 or score ≤1 for status.
Source: Tables 7.1.2, 7.2.1.1.1, 7.2.1.1.2, 7.2.1.2.1, 7.2.1.2.2, 7.2.1.3.1, and 7.2.1.3.2, Vol. 4, pg. 003-009 (sponsor's submission)

The secondary endpoints of 'Cleared', 'Improved 1' and 'Improved 2' were also statistically significant and support the primary endpoint. Results from the ITT population are presented in Table 5. For the ITT analysis of 'Improved 2', the sponsor and this reviewer disagree on the classification of one vehicle subject. The subject had missing data for 'status' at Week 4, but had scores of 'pronounced' for erythema and scaling, and a score of 'severe' for pruritus at Week 4. ('Improved 2' is calculated using the status variable only.) The sponsor classified this subject as a success, while this reviewer believes this subject should be classified as a failure. However, since the disputed successful subject is on the vehicle arm, the sponsor's analysis is more conservative (less significant) than the reviewer's analysis. The reviewer's and sponsor's results agree on all other analyses. The results from the per protocol population were again similar to the results from the ITT population, and are also presented in Table 5.

The sponsor also analyzed scaling, erythema, and itching as individual variables. With success defined as achieving a score of 0 (or 1 if ≥3 at baseline), ciclopirox was superior to vehicle for each of the individual signs and symptoms. Results for the ITT population

are presented in Table 6. Week 4 scores for scaling, erythema, itching, and status (rated from none to severe) are presented in Table A.3 in the appendix.

Table 6– Number of Successes (Single Variables) in Study 017 at Week 4 (ITT)

	Ciclopirox (N=250)	Vehicle (N=249)	p-value[a]
Scaling	85 (34%)	50 (20%)	0.0002
Erythema	98 (39%)	51 (21%)	<0.0001
Itching	120 (48%)	74 (30%)	<0.0001

[a] p-value based on CMH test, adjusted for center.
Success defined as score of 0 (or 1 if ≥3 at baseline)
Source: Tables 7.2.1.4.1, 7.2.1.5.1, and 7.2.1.6.1, Vol. 4, pg. 010-014 (sponsor's submission)

2.3.6 Reviewer's Efficacy Analyses

The sponsor did not conduct a formal analysis of treatment by center interaction for the primary efficacy endpoint, effective treatment. Since the Breslow-Day test is commonly used to assess the treatment by center interaction for success/failure data, this reviewer performed the Breslow-Day test for effective treatment. The p-value for this test was 0.3829, indicating that a significant interaction was not detected. Two of the 19 centers for the study had a more favorable result for vehicle than ciclopirox. These centers enrolled 29 and 20 subjects respectively, and were located in Alabama and Tennessee. Four centers observed no differences between treatments, and the remaining 13 centers observed a more favorable result for ciclopirox than vehicle. The reversal of effect in some centers is not unexpected when a large number of centers are used. However, it may be of interest that all of the centers that had no differences between treatments or favored vehicle were located in the southeastern United States (Alabama, Tennessee, Georgia, North Carolina, and Florida). These 6 centers also enrolled nearly half of the black subjects (24/49, 49%), who as a group had lower efficacy than the full study population. See the discussion on racial subgroups in the following section. Treatment effects by center are presented in Figure A.1 in the appendix. Statistical significance for effective treatment is maintained if the three centers with the largest treatment effects are removed from the analysis, representing 19% of the total subjects.

2.3.7 Subgroup Analyses

The sponsor conducted subgroup analyses for race, gender and age. The results of the subgroup analyses are presented in Table 7. The observed treatment effects across the gender and age subgroups are similar, and all favor ciclopirox. However, slightly more variation is observed in the racial subgroups. Relatively small numbers of subjects in the Black, Hispanic, Asian, and Other race groups were enrolled. For black subjects, the observed response rate was higher on the vehicle arm than the ciclopirox arm. Nearly one-fourth of the black subjects were enrolled at one center (Center 4, 12/49 = 24%). This center was also the center with the worst observed treatment effect for ciclopirox, with 0/15 = 0% achieving effective treatment on ciclopirox, and 2/14=14% achieving effective treatment on vehicle. Both successes on vehicle at Center 4 were black subjects

(0/7 = 0% of black subjects achieved effective treatment on ciclopirox, while 2/5 = 40% of black subjects achieved effective treatment on vehicle). While this center appears to have extreme results, the results should be interpreted with caution as they are based on only a small number of patients. The other study conducted by the sponsor, Study 3001, enrolled only 4 black subjects on the ciclopirox 2 times weekly arm, while no black subjects were enrolled on the vehicle arm. Thus it is impossible to determine whether the results observed in Study 017 on the black patients in Study 017 are applicable to the broader population.

Table 7 – Effectively Treated Subjects by Race, Gender, and Age in Study 017 (ITT)

		Ciclopirox 2x weekly (N=250)	Vehicle (N=249)
Race	Caucasian	50/195 (26%)	20/205 (10%)
	Black	3/28 (11%)	5/21 (24%)
	Other	12/27 (44%)	7/23 (30%)
Gender	Male	33/115 (29%)	17/122 (14%)
	Female	32/135 (24%)	15/127 (12%)
Age	< 40	23/94 (24%)	12/91 (13%)
	40 - 64	35/116 (30%)	15/117 (13%)
	≥ 65	7/40 (18%)	5/40 (13%)

Source: Tables 7.2.3.1, 7.2.4.1, and 7.2.5.1, Vol. 4, pg. 018 – 030 (sponsor's submission)

2.3.8 Safety Assessment

Exposure to treatment in Study 017 ranged from 1 to 40 days with a mean of 27.3 days in the ciclopirox group, and ranged from 8 to 38 days with a mean of 26.9 days in the vehicle group. The incidence of adverse events was similar across the two treatment arms, with approximately 27% of subjects in each arm experiencing adverse events. On the ciclopirox arm, 11 subjects experienced treatment related adverse events, while 10 vehicle subjects experienced treatment related adverse events. The most common treatment related adverse events were pruritus (2.4% on ciclopirox and 0.8% on vehicle) and application site reaction (0.4% on ciclopirox and 1.6% on vehicle).

Table 8 presents the incidence of adverse events in the study, while Table 9 lists the incidence of the more common adverse events observed in the study. The most common adverse events were upper respiratory tract infection, influenza-type symptoms, and pruritus. Two subjects, both in the ciclopirox group, suffered serious adverse events during the study. One subject experienced myocardial infarction. The other subject experienced heart block and dizziness. One subject on the vehicle arm became pregnant during the study.

Table 8 – Adverse Events in Study 017

	Ciclopirox 2x weekly (N=250)	Vehicle (N=249)
All Adverse Events	67 (26.9%)	68 (27.3%)
Treatment Related	11 (4.4%)	10 (4.0%)
Serious Adverse Events	2 (0.8%)	0

Source: Table 6.1.1, Vol. 5, pg 26. (sponsor's submission)

Table 9 – Adverse Events Reported by at least 1.5% of Patients in Either Treatment Arm in Study 017

	Ciclopirox 2x weekly (N=250)	Vehicle (N=249)
SKIN & APPENDAGES		
Pruritus	7 (2.8%)	8 (3.2%)
Seborrhea	3 (1.2%)	4 (1.6%)
Skin Exfoliation	0	5 (2.0%)
RESPIRATORY SYSTEM		
Sinusitis	7 (2.8%)	4 (1.6%)
Upper Resp. Tract Inf.	7 (2.8%)	12 (4.8%)
BODY AS A WHOLE		
Influenza-like Symptoms	7 (2.8%)	7 (2.8%)
APPLIC. SITE DISORDERS		
Applic. Site Reaction	1 (0.4%)	4 (1.6%)

Source: Table 12.1, Vol. 3, pg. 137. (sponsor's submission)

2.3.9 Comments on Sponsor's Proposed Labeling

Approximately 13% of the subjects were age 65 or over. Table 10 presents the age breakdown by treatment arm for the two studies.

Table 10 – Number of Subjects by Age in Studies 3001 (Segment A) and 017

	Age	*Ciclopirox 2x Weekly*	*Ciclopirox 1x Weekly*	*Vehicle*	*Total*
Study 3001	< 65	335 (88%)	338 (90%)	171 (89%)	844 (89%)
	≥ 65	45 (12%)	39 (10%)	21 (11%)	105 (11%)
Study 017	< 65	210 (84%)	-	209 (84%)	419 (84%)
	≥ 65	40 (16%)	-	40 (16%)	80 (16%)
Total	< 65	545 (87%)	338 (90%)	380 (86%)	1263 (87%)
	≥ 65	85 (13%)	39 (10%)	61 (14%)	185 (13%)

Source: Table 6, Vol. 12, pg. 137 and 140, and Table 22, Vol. 13, pg. 97. (sponsor's submission)

In terms of the primary efficacy criterion, 18/45 (40%) of ciclopirox twice weekly subjects aged 65 and over in Study 3001 achieved effective treatment versus 10/21 (48%) of vehicle subjects aged 65 and over. In Study 017, 7/40 (18%) of ciclopirox twice weekly subjects aged 65 and over achieved effective treatment versus 5/40 (13%) of vehicle subjects aged 65 and over. Pooling the results for subjects aged 65 and over for the two studies leads to estimates for effective treatment of 25/85 (29%) for subjects using ciclopirox twice weekly and 15/61 (25%) for subjects using vehicle.

With regards to adverse reactions, 8/380 (2.1%) of ciclopirox twice weekly subjects in Study 3001 (Segment A), and 11/250 (4.4%) of ciclopirox twice weekly subjects in Study 017 experienced treatment related adverse events. This leads to a pooled total of 19/630 (3.0%) subjects experiencing treatment related adverse events for the two studies. Considering subjects using ciclopirox two times per week from Studies 203, 204, 3001, 3003, and 017, 36/1098 (3.3%) experienced treatment related adverse events. The number of subjects using ciclopirox twice weekly who discontinued treatment due to adverse events was 3/380 (0.8%) in Study 3001, 5/373 (1.3%) in Study 3003, and 4/250 (1.6%) in Study 017. In Study 017, 4/249 (1.6%) of vehicle subjects discontinued due to adverse events. In Study 3001, 7 vehicle subjects discontinued due to adverse events. However, in this submission the sponsor only has provided information on the subjects receiving vehicle during Segment A (192 subjects) and/or Segment B (119 additional subjects) combined, and it is not possible to determine which segment the 7 subjects were in when discontinued.

2.4 Statistical Evaluation of Collective Evidence and Conclusions

The sponsor has demonstrated a statistically significant effect for ciclopirox shampoo in the treatment of seborrheic dermatitis of the scalp in two studies for twice weekly treatment for four weeks. The primary efficacy endpoint was effective treatment, defined as achieving a score of 0 (or 1 if baseline was ≥3) simultaneously for status, erythema or inflammation, and scaling at Week 4. A score of 0 corresponds to 'none' and a score of 1 corresponds to 'slight'. (Inflammation was evaluated in Study 3001 and erythema was evaluated in Study 017.) In Study 3001, 58% of subjects using ciclopirox twice weekly achieved effective treatment, compared with 31% of subjects using vehicle ($p = 0.0001$). In Study 017, 26% of subjects using ciclopirox twice weekly achieved effective treatment, compared with 13% of subjects using vehicle ($p=0.0001$). There were a few

differences in study design and execution between Studies 3001 and 017 that may have contributed to the observed differences in effective treatment rates for the two studies. Study 3001 was conducted in Europe with a predominantly Caucasian population (97%), while study 017, in the United States, enrolled a larger proportion of minorities (20%) and some variation in efficacy among minority populations was observed in Study 017. Also, Study 3001 followed subjects for a two-week run-in period before initiating the randomized treatment, while Study 017 did not have a run-in period. One further difference between the two studies was that effective treatment was based in part on an evaluation of 'inflammation' in Study 3001, and on an evaluation of 'erythema' in Study 017.

The secondary endpoint 'cleared', defined as a score of 0 (none) simultaneously for status, erythema or inflammation, scaling and itching was also significant in both studies ($p \leq 0.0017$). Thus the sponsor has statistically demonstrated the efficacy of ciclopirox shampoo used twice weekly for 4 weeks in the treatment of seborrheic dermatitis of the scalp in two studies.

The sponsor has also proposed that ciclopirox shampoo can be used [redacted] Ciclopirox shampoo for prophylaxis was evaluated in one study (Study 3001, Segment B) and found to be statistically significant in the prevention of relapse, where relapse is defined as worsening by at least 2 points on the status variable. The sponsor has not attempted to replicate the findings of Study 3001, Segment B. Thus prophylactic treatment with ciclopirox shampoo has been studied and demonstrated effective in only a single study.

2.5 Appendix of Additional Tables and Figures

Table A.1 – Baseline Demographic Data in Study 3001

	Ciclopirox 2x Weekly (N=380)	Ciclopirox 1x Weekly (N=377)	Vehicle (N=192)
Age			
mean	41.6	40.8	41.9
range	18 - 88	18 - 84	18 - 84
Race			
Caucasian	369 (97.1%)	364 (96.9%)	191 (99.5%)
Black	4 (1.1%)	3 (0.8%)	0
Asian	4 (1.1%)	5 (1.3%)	1 (0.5%)
Other	3 (0.8%)	5 (1.3%)	0
Sex			
Male	213 (56%)	215 (57%)	109 (57%)
Female	167 (44%)	162 (43%)	83 (43%)

Source: Table E.13, Vol.12, pg. 40 (sponsor's submission)

Table A.2 – Baseline Demographic Data in Study 017

	Ciclopirox 2x weekly (N=250)	Vehicle (N=249)	p-value[a]
Age			
< 40	94 (38%)	92[b](37%)	0.9882
40 - 64	116 (46%)	117 (47%)	
≥ 65	40 (16%)	40 (16%)	
Race			
Caucasian	195 (78%)	205 (82%)	0.6133
Black	28 (11%)	21 (8%)	
Asian	5 (2%)	2 (1%)	
Hispanic	18 (7%)	18 (7%)	
Other	4 (2%)	3 (1%)	
Sex			
Male	115 (46%)	122 (49%)	0.5028
Female	135 (54%)	127 (51%)	

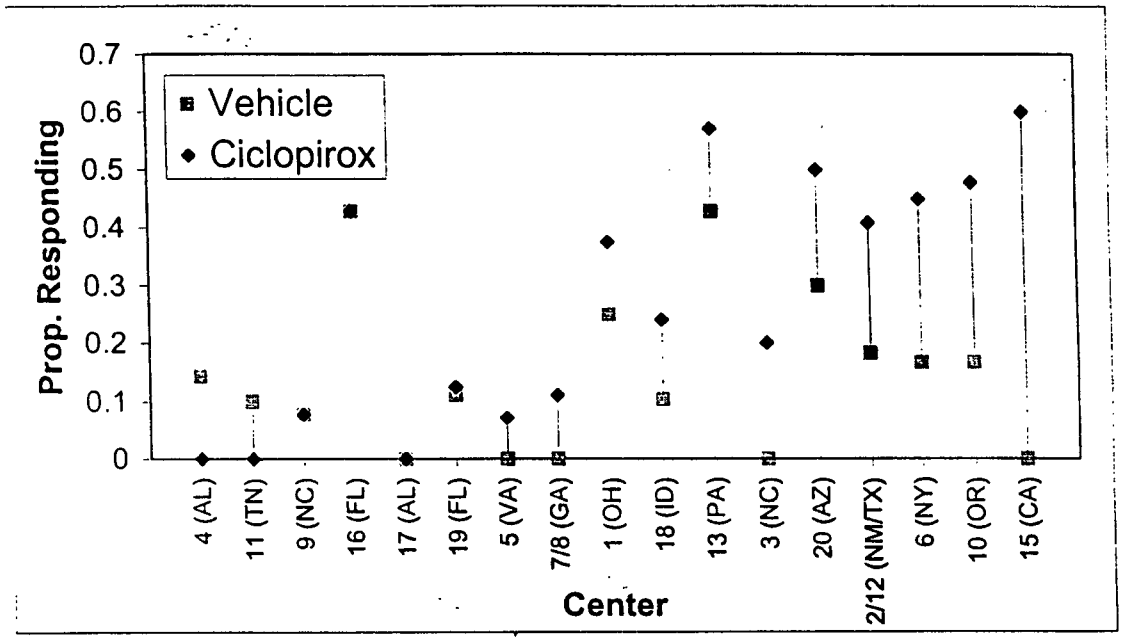
[a] p-values based on the chi-square test
[b] includes one subject with date of birth, but not date of first visit recorded, counted as age missing in sponsor's table
Source: Table 11.1, Vol. 3, pg. 121 (sponsor's submission).

Table A.3 –Status, Itching, Scaling, and Erythema Scores at Week 4 in Study 017 (ITT)

	Status		**Itching**	
	Ciclopirox (N=250)	Vehicle (N=249)	Ciclopirox (N=250)	Vehicle (N=249)
None	33 (13%)	15 (6%)	63 (25%)	39 (16%)
Slight	72 (29%)	44 (18%)	82 (33%)	61 (25%)
Mild	81 (32%)	73 (29%)	47 (19%)	59 (24%)
Moderate	46 (18%)	94 (38%)	32 (13%)	53 (21%)
Pronounced	15 (6%)	21 (8%)	14 (6%)	33 (13%)
Severe	3 (1%)	2 (1%)	12 (5%)	4 (2%)
	Scaling		**Erythema**	
	Ciclopirox (N=250)	Vehicle (N=249)	Ciclopirox (N=250)	Vehicle (N=249)
None	38 (15%)	24 (10%)	58 (23%)	31 (12%)
Slight	73 (29%)	38 (15%)	71 (28%)	53 (21%)
Mild	70 (28%)	74 (30%)	69 (28%)	78 (31%)
Moderate	48 (19%)	79 (32%)	36 (14%)	77 (31%)
Pronounced	17 (7%)	32 (13%)	13 (5%)	10 (4%)
Severe	4 (2%)	2 (1%)	3 (1%)	0

Source: Tables 7.3.1.1, 7.3.2.1, 7.3.3.1, and 7.5.1.1, Vol. 4, pg. 74, 109, 144, and 253 (sponsor's submission)

Figure A.1– Effective Treatment Rates by Center (Study 017)



Source: Reviewer analysis.

Kathleen Fritsch, Ph.D.
Mathematical Statistician, Biometrics III

Concur: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:
Archival NDA
HFD-540/Wilkin
HFD-540/Luke
HFD-540/Huene
HFD-540/Smith
HFD-700/Anello
HFD-725/Huque
HFD-725/Alosh
HFD-725/Fritsch
StatRev N 21159.doc 1/8/03

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kathleen Fritsch
1/8/03 03:17:54 PM
BIOMETRICS

Mohamed Alosh
1/8/03 03:45:57 PM
BIOMETRICS
Concur with review

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL/CLINICAL REVIEW AND EVALUATION

NDA: 21-159

APR 11 2000

Applicant: Medicis

Name of Drug: Loprox (ciclopirox) Shampoo 1%

Documents Reviewed: Volumes1.1 1.3-1.80 dated September 01, 1999

Type of Report: NDA review

Indication: Topical treatment [redacted] of seborrhoeic dermatitis of the scalp and [redacted]

Medical officer: Phyllis Huene, MD (HFD-540)

Introduction and regulatory history

The sponsor submitted reports of a Phase 2 Study 204 and Phase 3 Studies 3001, and 3003 to support the claim that treatment with 1% Ciclopirox shampoo once or twice a week is safe and effective in the treatment of seborrhoeic dermatitis of the scalp and its minor form, dandruff. In this review, Studies 204 and 3001 are considered as confirmative studies for the indication of the treatment of seborrhoeic dermatitis. As Study 3003 does not have a placebo arm, in agreement with the DDDDP, this study will not be used as a confirmative study for efficacy in this review.

Concerning the indication for [redacted], the DDDDP assumes that evidence of efficacy for the treatment of seborrhoeic dermatitis implies efficacy for the treatment of [redacted]

Prevention of recurrence of seborrhoeic dermatitis was addressed by Segment B of Study 3001. In this review, Segment B of Study 3001 is considered as a confirmative study to support the claim of the [redacted]

The protocols of the submitted pivotal clinical studies had a number of deficiencies. A dose-ranging, Phase 2 Study 204 was completed in 1994-1995 without a prior IND application. Statistical recommendations at the April 29, 1999, Pre-NDA meeting concerning [redacted] are documented in the minutes of the meeting, (see Volume 1.1, pages 19-21) but were not followed by the Sponsor as discussed below.

Reviewer's comments:

1. *Some of the FDA statistical recommendations at the Pre-NDA meeting were ignored or even distorted by the sponsor in the NDA 21-159. For example, in the Study 204 report, the sponsor presented the ANOVA results and claimed that ANOVA analysis was requested or*

recommended by the FDA (see Volume 1.1, pages 191 and 192, and Volume 1.37, pages 50 and 73). In fact, ANOVA was never requested or recommended by the FDA. On the contrary, at both the End-of-Phase-2 and Pre-NDA meetings, this reviewer specifically indicated that ANOVA analysis was not planned in the original protocol and therefore, ANOVA results have no regulatory value. To comply with the ICH E9 Document, Section 5.1, "only results from the analyses envisaged in the protocol can be regarded as confirmatory". The statistical comments of the Minutes of the April 29, 1999, Pre-NDA meeting, specifically indicate that only results of the adjusted Wilcoxon rank-sum test should be used in the efficacy analysis because this method was pre-specified in the Protocol. The ANOVA results will not be used in the FDA review because this method was not planned in the original protocol (see Volume 1.1, page 20).

2. *As was indicated in the statistical comments of the Minutes of the April 29, 1999, Pre-NDA meeting, "a placebo arm is required in equivalence and non-inferiority trials to evaluate internal validity" (see Volume 1.1, page 21). As Study 3003 does not have a placebo arm, in agreement with the medical division, this study will not be used as a confirmative study for efficacy in this review.*

3. *As was indicated in the statistical comments of the Minutes of the April 29, 1999, Pre-NDA meeting, the primary efficacy analysis in superiority comparisons of studies 204, and 3001 should be based on the ITT population. Sponsor's efficacy population, "ITT without wrong inclusions", was not pre-specified in the study protocol and, therefore, has no regulatory utility.*

STUDY 204

Design

It was a randomized, multicenter, double-blind, dose-ranging, placebo controlled, Phase 2 study to compare the effects of a 4-week treatment of 1.0% Ciclopirox shampoo 1x, 2x, and 3x per week with the effects of vehicle. The patients were randomized at the 1:1:1:1 ratio to the four treatment arms: vehicle, 1% Ciclopirox shampoo 1x per week, 2x per week, and 3x per week. Study population included subjects of either gender aged 18-75 years with the diagnosis of stable or exacerbating seborrhoeic dermatitis of the scalp.

Sponsor's primary efficacy variable was the sum of the scores (sumscore) of the three signs and symptoms of seborrhoeic dermatitis of the scalp (itching, scaling, and inflammation) at the end of treatment at week 4. Each individual sign or symptom was evaluated using an ordinal scale ranging from 0 = none to 5 = severe. Sponsor's secondary efficacy variable was the proportion of patients "effectively treated" derived from the score of the status of seborrhoeic dermatitis at Week 4.

Reviewer's Comment:

1. *In Study 204, this Reviewer used a primary efficacy variable that is different from that in Study 3001, for the following reason. In Study 3001, the primary efficacy variable is the responder rate which is based on the Investigator' Global evaluation of the "status" as well as on the inflammation and scaling scores. In Study 204, the Investigator's Global evaluation of the "status" was not measured at baseline. For this reason, the responder rate cannot be used in Study 204 as a primary efficacy variable. Reviewer's primary efficacy variable in Study 204 is the proportion of patients who have met the definition of "Cleared or almost cleared". A patient is classified as "Cleared or almost cleared" when*
   Inflammation: score = 0,
   and Scaling: score = 0 or
   score = 1 if the baseline score for scaling was ≥3,
   and Itching: : score = 0 or
   score = 1 if the baseline score for itching was ≥3.

2. *As a secondary efficacy variable in Study 204, this reviewer used the sum of the scores (sumscore) of the three signs and symptoms of seborrhoeic dermatitis of the scalp (itching, scaling and inflammation) at the end of treatment at week 4.*

3. *Sponsor's ITT population includes 177 patients. In the efficacy report, the sponsor also presented results in the "ITT population without wrong inclusions". This efficacy population ("ITT without wrong inclusions") was not pre-specified in the study protocol and, therefore, has no regulatory utility. At the April 29, 1999, Pre-NDA meeting, the sponsor was advised that the "ITT population without wrong inclusions" would not be used in the FDA review. The sponsor was advised that the ITT population should include all 183 randomized patients. Consequently, the reviewer's ITT population includes all 183 randomized patients.*

4. ***To adjust for the three multiple comparisons, the Study 204 protocol specified that the Holm procedure will be applied. However, according to page 49 of Volume 1.37, instead of the Holm procedure, the sponsor used a different approach to adjust for multiple comparisons. According to the ICH E9 Document, only results from analysis envisaged in the protocol (including amendments) can be regarded as confirmatory. Therefore, in this review the Holm procedure will be used. Any other method of adjustment for multiple comparisons has no regulatory value in this NDA.***

Statistical methods

Primary efficacy analysis in this review was based on the ITT population including all randomized patients. Primary statistical method to compare proportion of patients "Cleared or almost cleared" in the treatment groups was the CMH test. To account for the three efficacy comparisons (1x per week vs. placebo, 2x per week vs. placebo, and 3x per week vs. placebo) this reviewer applied the Holm p-value adjustment procedure. Statistical method to compare

sumscore in the treatment groups was the Wilcoxon rank-sum test adjusted for baseline severity and center (using the CMH procedure with the modified ridit scores).

Results of Study 204

Of the 200 screened patients, 17 patients dropped out before randomization and 183 were randomized to treatment arms. Of the 183 randomized patients, 6 patients dropped out between randomization and visit 3 due to non-compliance. Reviewer's ITT population included all 183 randomized patients. There was no statistically significant difference between the treatment groups relative to age or gender ($p>0.05$).

Primary efficacy analysis in Study 204

Table 1 shows the reviewer's efficacy results relative to the primary efficacy variable, proportion of patients classified as "Cleared or almost cleared" at the end of treatment.

Table 1. Primary efficacy analysis in Study 204. Proportion of patients classified as "Clear or almost clear". Reviewer's ITT population (all 183 randomized patients)

	Vehicle	Ciclopirox 1x	Ciclopirox 2x	Ciclopirox 3x
Number of patients	48	44	47	44
Number (%) of "Cleared or almost cleared"	10 (20.8%)	16 (36.4%)	10 (21.3%)	13 (29.5%)
Nominal (not adjusted for multiple comparisons) p-value versus vehicle*	-	0.10	1.0	0.34

* P-value in the CMH test.

As can be seen from Table 1, even without adjustment for 3 multiple comparisons, none of the three Ciclopirox treatment groups was statistically significantly better than vehicle ($p>0.1$). According to the protocol, to adjust for the three multiple comparisons, the Holm procedure should be applied. To apply the Holm p-value adjustment procedure, we need to compare the nominal p-values in Table 1 with alpha/3. As none of the three nominal p-values in Table 1 is smaller than 0.0167=0.05/3, we conclude that there is no statistically significant difference between any of the Ciclopirox arms and vehicle.

Secondary efficacy analysis in Study 204.

The third row in Table 2 shows the efficacy results in Reviewer's ITT populations of Study 204 relative to the secondary efficacy variable, Sumscore, at the end of treatment without adjustment to multiple comparisons. According to the protocol, to adjust for the three multiple comparisons.

the Holm procedure should be applied. To apply the Holm p-value adjustment procedure, we need to compare the nominal p-values in the third row of Table 2 with alpha/3. As none of the three nominal p-values in the third row of Table 2 is smaller than the Holm p-value 0.0167=0.05/3, we conclude that there is no statistically significant difference between any of the Ciclopirox arms and vehicle.

The fourth row in Table 2 shows the efficacy results in the Sponsor's ITT populations of Study 204 relative to the secondary efficacy variable, Sumscore, at the end of treatment. Results for the Sponsor's ITT population were similar to that in the Reviewer's ITT population. To apply the Holm p-value adjustment procedure, we need to compare the nominal p-values in the fourth row of Table 2 with alpha/3. As none of the three nominal p-values in the fourth row of Table 2 is smaller than 0.0167=0.05/3, we conclude that there is no statistically significant difference between any of the Ciclopirox arms and vehicle.

Table 2. Secondary efficacy analysis in Study 204. Nominal (not adjusted for multiple comparisons) p-values versus vehicle for the Sumscore (the sum of the scores of itching, scaling and inflammation) at the end of treatment at week 4*.

		Ciclopirox 1x	Ciclopirox 2x	Ciclopirox 3x
Reviewer's ITT population (all 183 randomized patients)		0.041	0.11	0.082
Sponsor's ITT population (177 patients)		0.046	0.17	0.057

* P-value in the Wilcoxon rank-sum test adjusted for site.

Safety in Study 204

No serious adverse events (AE) were recorded during the study. Overall a total of 40 AE occurred in total of 27 patients. Table 3 presents number of patients with at least one AE. There was no statistically significant difference between treatment groups relative to the proportion of patient with any adverse events (p=0.6) or relative to the proportion of patients with skin and appendages disorders (p=0.7).

Table 3. Safety summary in Study 204						
	Vehicle	Ciclopirox			Total	P-value
		1x	2x	3x		
Total number of patients	48	47	44	44	183	
Number (%) of patients with one or more adverse events	9 (19%)	4 (9%)	8 (17%)	6 (14%)	27 (15%)	0.6
Number (%) of patients with one or more skin and appendages disorders	6 (13%)	3 (6%)	3 (7%)	3 (7%)	15 (8%)	0.7

Reviewer's Conclusions on Study 204:

Results of the primary efficacy analysis of Study 204 fail to support the claim that at least one of the regimens of Ciclopirox shampoo (1x, 2x, or 3x per week) is statistically significantly superior in efficacy to vehicle (p>0.1).

Results of the secondary efficacy analysis of Study 204 also fail to support the claim that at least one of the regimens of Ciclopirox shampoo (1x, 2x, or 3x per week) is statistically significantly superior in efficacy to vehicle. As the smallest observed p=0.0464 in the Sumscore comparisons is larger than 0.0167=0.05/3, the Holm adjustment procedure for the 3 multiple comparisons implies that there is no statistically significant difference between any of the three Ciclopirox arms and vehicle.

STUDY 3001

Phase 3 Study 3001 had two consecutive segments (Segment A and Segment B) each of which addressed a different primary objective. The objective of Segment A of Study 3001 was to support the claim of efficacy and safety of 1% Ciclopirox shampoo twice weekly and 1% Ciclopirox shampoo once weekly in the treatment of seborrhoeic dermatitis. The objective of Segment B of Study 3001 was to support the claim of efficacy and safety of 1% Ciclopirox shampoo once weekly and 1% Ciclopirox shampoo once every second week in the prophylaxis of seborrhoeic dermatitis.

STUDY 3001, Segment A.

This was a randomized, 4-week, double-blind, multinational, placebo-controlled, multi-center study. Patients were randomized at the 2:2:1 ratio to the three arms: 1% Ciclopirox shampoo twice weekly (2x), 1% Ciclopirox shampoo once weekly (1x), and vehicle twice weekly.

Global evaluation of the "Status of seborrhoeic dermatitis", itching, scaling, and inflammation

were evaluated at baseline, week 4 and at week 12. Investigator's Global Evaluation of "Status" was based on severity of appearance and symptoms and used the following scale:
0 = none,
1 = slight
2 = mild
3 = moderate
4 = pronounced
5 = severe.

Itching, scaling, and erythema were assessed by three 6-step scales ranging from 0 = none to 5 = severe. Scaling and erythema scores were assessed by the investigator. Itching was evaluated by patients.

Inclusion criteria: Majority (>70%) of randomized patients should have a moderate grade (3 or worse) for each of the "Status", inflammation, and scaling.

The Sponsor's primary efficacy variable is the responder rate (proportion of patients classified as "Effectively treated"). The responder is defined as a patient with:

Score =0 or
Score=1 if baseline was $\geq$ 3 points to be met simultaneously for "status", inflammation, and scaling scores at individual endpoint.

Efficacy populations:

The Sponsor's primary efficacy analysis was based on the ITT population defined as all randomized patients with at least one post-baseline efficacy assessment. Drop-outs due to lack of efficacy were included in the ITT population.

Statistical methods:

Comparisons of treatment groups were performed with the CMH test adjusted for center. In order to adjust for two multiple comparisons, Holm procedure was applied. If neither of the two p-values in the CMH test was $\leq$ 0.025, then the procedure was stopped without a significant results; if the smallest p-value was $\leq$ 0.025, then the second p-value was compared to the alpha-level of 0.05 in order to guarantee a global alpha-level of 0.05.

Reviewer's Comments:

1. ***The primary efficacy variable in this review is the responder rate (the same as the Sponsor's primary efficacy variable).***

2. ***One secondary efficacy variable is used in this review: proportion of patients classified as "Cleared". "Cleared" is defined as score=0 to be met simultaneously for "status",***

inflammation, scaling, and itching scores at individual endpoint.

3. *The primary efficacy analysis in this review is based in the Reviewer's ITT population including all randomized patients.*

Results of Segment A of Study 3001

Of the 1000 patients enrolled, 949 were randomized to Segment A of Study 3001. Of the 949 randomized patients, 380 patients were randomized to Ciclopirox twice weekly, 377 patients were randomized to Ciclopirox once weekly, and 192 patients were randomized to vehicle. A total of 909 (95.8%) completed the study: 368 (96.8%) in the Ciclopirox twice daily, 364 (96.6%) in the Ciclopirox once daily group, and 177 (92.2%) in the vehicle group (p=0.021). The Reviewer's ITT population included all 949 randomized patients. The Sponsor's ITT population included 942 patients: 376 (98.9%) in the Ciclopirox twice daily group, 376 (99.7%) in the Ciclopirox once daily group, and 190 (99.0%) in the vehicle group (p=0.39). The patients were treated in four European countries: Germany, UK, France, and Austria. There was no statistically significant difference between the treatment groups at baseline relative to age or gender (p>0.05).

Primary efficacy analysis

The primary efficacy variable is the responder rate. The definition of responder is based on the Investigator's Global evaluation of the "status of seborrhoeic dermatitis" and inflammation /scaling scores at individual endpoint. The responder is defined as
Score =0 or
Score=1 if baseline was $\geq$ 3 points to be met simultaneously for "status", inflammation, and scaling scores at individual endpoint.

Primary efficacy analysis for Segment A of Study 3001 is shown in Table 4a: This table shows the responder rates in the Reviewer's ITT population of Study 3001 and the nominal p-values (not adjusted for two multiple comparisons). To adjust for the two multiple comparisons, the protocol specified that the Holm procedure should be applied. To apply the Holm p-value adjustment procedure, we need to compare the nominal p-values in Table 4a with 0.025=0.05/2. As both p-values in Table 4a are smaller than 0.025 (0.0007<0.025), we conclude that both Ciclopirox 2x and Ciclopirox 1x are statistically significantly better than vehicle with the overall Type 1 error being preserved at the 0.05 level.

Table 4a. Primary efficacy analysis for Segment A in Study 3001. Responder rates in the Reviewer's ITT population (all 949 randomized patients).

	Ciclopirox 2x	Ciclopirox 1x	Vehicle
Total number of patients	380	377	192
Number (%) of responders	220 (57.9 %)	171 (45.4 %)	60 (31.3 %)
Nominal (not-adjusted for multiple comparisons) p-value* versus vehicle	0.0001	0.0007	-

* P-value in the CMH test adjusted for center.

Table 4b shows the responder rates in the Sponsor's ITT population of Segment A in Study 3001 and the nominal p-values (not adjusted for two multiple comparisons). The results are very similar to the results in the Reviewer's ITT population of Study 3001. To adjust for the two multiple comparisons, the protocol specified that the Holm procedure should be applied. To apply the Holm p-value adjustment procedure, we need to compare the nominal p-values in Table 4b with 0.025=0.05/2. As both p-values in Table 4b are smaller than 0.025 (0.0008<0.025), we conclude that both Ciclopirox 2x and Ciclopirox 1x are statistically significantly better than vehicle with the overall Type 1 error being preserved at the 0.05 level.

Table 4b. Responder rates in the Sponsor's ITT population of Segment A in Study 3001 (942 patients).

	Ciclopirox 2x	Ciclopirox 1x	Vehicle
Total number of patients	376	376	190
Number (%) of responders	220 (58.5 %)	171 (45.5 %)	60 (31.6 %)
Nominal (not-adjusted for multiple comparisons) p-value* versus vehicle	0.0001	0.0008	-

* P-value in the CMH test adjusted for center.

Secondary efficacy analysis

The secondary efficacy analysis in Segment A of Study 3001 is shown in Table 5a. This table shows the proportion of patients "Cleared" in the Reviewer's ITT population of Study 3001 and the nominal p-values (not adjusted for two multiple comparisons). To adjust for the two multiple comparisons, the protocol specified that the Holm procedure should be applied. To apply the Holm p-value adjustment procedure, we need to compare the nominal p-values in Table 5a with 0.025=0.05/2. As the smallest of the two nominal p-values in Table 5a is smaller than 0.025 (0.0001<0.025), we conclude that Ciclopirox 2x is statistically significantly better than vehicle. The second p-value should be compared to 0.05. As the second p-value is smaller than 0.05 (0.031<0.05), we conclude that Ciclopirox 1x is statistically significantly better than vehicle and the overall Type 1 error is preserved at the 0.05 level.

Table 5a. Secondary efficacy analysis in Segment A of Study 3001. Proportion of patients "Cleared" in the reviewer's ITT population (all 949 randomized patients).			
	Ciclopirox 2x	Ciclopirox 1x	Vehicle
Total number of patients	380	377	192
Number (%) of patients "Cleared"	87 (22.9 %)	64 (17.0 %)	19 (10.0 %)
Nominal (not-adjusted for multiple comparisons) p-value* versus vehicle	0.0001	0.031	-

* P-value in the CMH test adjusted for center.

Table 5b shows the proportion of patients "Cleared" in the Sponsor's ITT population of Segment A in Study 3001 and the nominal p-values (not adjusted for two multiple comparisons). The results are very similar to the results in the Reviewer's ITT population of Study 3001. To adjust for the two multiple comparisons, the protocol specified that the Holm procedure should be applied. To apply the Holm p-value adjustment procedure, we need to compare the nominal p-values in Table 5b with 0.025=0.05/2. As the smallest of the two nominal p-values in Table 5b is smaller than 0.025 (0.0001<0.025), we conclude that Ciclopirox 2x is statistically significantly better than vehicle. The second p-value should be compared to 0.05. As the second p-value in Table 5b is smaller than 0.05 (0.037<0.05), we conclude that Ciclopirox 1x is statistically significantly better than vehicle and the overall Type 1 error is preserved at the 0.05 level.

Table 5b. Proportion of patients "Cleared" in the Sponsor's ITT population of Segment A in Study 3001 (942 patients).			
	Ciclopirox 2x	Ciclopirox 1x	Vehicle
Total number of patients	376	376	190
Number (%) of patients "Cleared"	87 (23.1 %)	64 (17.0 %)	19 (10.0 %)
Nominal (not-adjusted for multiple comparisons) p-value* versus vehicle	0.0001	0.037	-

* P-value in the CMH test adjusted for center.

Subgroup analysis of Segment A in Study 3001

The subgroup efficacy analysis of Segment A in Study 3001 shows that in younger patients (≤38 years), both Ciclopirox once weekly and Ciclopirox twice weekly were statistically significantly better than vehicle relative to the responder rates ($p \leq 0.004$). In older patients (>38 years), both Ciclopirox twice weekly and Ciclopirox once weekly groups were only numerically better than vehicle ($p > 0.07$).

In males, both Ciclopirox once weekly and Ciclopirox twice weekly were statistically significantly better than vehicle relative to responder rates ($p \leq 0.003$). In females, Ciclopirox twice weekly group was statistically significantly better than vehicle relative to responder rates ($p = 0.007$) and Ciclopirox once weekly was only numerically better than vehicle ($p = 0.2$).

Safety results in Segment A of Study 3001

All randomized 949 patients of Segment A were included in safety population. Table 6 shows number and percentage of patients with at least one adverse event in the three treatment groups. There was no statistically significant difference in the proportion of patients with at least one adverse event between Ciclopirox twice weekly and vehicle (p=0.9) or Ciclopirox once weekly and vehicle (p=0.5).

Table 6. Adverse events summary in Segment A of Study 3001

	Ciclopirox twice weekly. N=380	Ciclopirox once weekly. N=377	Vehicle N=192
Number (%) of patients with at least one adverse event	43 (11%)	54 (14%)	23 (12%)
P-value versus vehicle	0.9	0.5	-

Table 7 shows number and percentages of patients with skin and appendages disorders. There was no statistically significant difference in the proportion of patients with skin appendages disorders between Ciclopirox twice weekly and vehicle (p=0.6) or Ciclopirox once weekly and vehicle (p=1.0).

Table 7. Skin and appendages disorders in Segment A of Study 3001

	Ciclopirox twice weekly. N=380	Ciclopirox once weekly. N=377	Vehicle N=192
Number (%) of patients with at least one skin and appendages disorder	13 (3.4%)	18 (4.8%)	9 (4.7%)
P-values versus vehicle	0.6	1.0	-

STUDY 3001, Segment B

Segment B of Study 3001 was designed to assess the efficacy of two different regimens of 1% Ciclopirox in the prophylaxis of seborrhoeic dermatitis of the scalp. Before the randomization code of Segment A was open, 350 responders from Segment A were to be randomized to three equal sizes parallel groups: once weekly, once every second week, or vehicle once weekly for 12 weeks. Global evaluation, itching, scaling and inflammation were evaluated at week 4 and at week 12. Global evaluation as based on severity of appearance and symptoms was rated by the investigator using the following scale:

0 = none,
1 = slight

2 = mild
3 = moderate
4 = pronounced
5 = severe.

Change of seborrhoeic dermatitis from baseline of the study segment was defined as score under treatment minus score at baseline. **The primary efficacy variable** was relapse in the "Status" defined as worsening from start of Segment B by ≥ 2 points.

The CMH test adjusted for centers was used to compare relapse rates of the active treatment regimens with vehicle. In contrast to Segment A, tests were performed in a pre-specified sequence, in order to guarantee the global alpha level of 0.05. The first comparison was "Ciclopirox once weekly (1x) versus vehicle". The second comparison, "Ciclopirox once every second week versus vehicle" was only made if the first p-value (2-sided) was ≤ 0.05.

Results of Segment B in Study 3001

A total of 428 patients were randomized in Segment B: 138 patients were randomized to Ciclopirox once weekly, 149 to Ciclopirox once every second week, and 141 to vehicle. A total of 385 (90%) patients completed Segment B: 128 (93%) in the Ciclopirox once weekly group, 129 (87%) in the Ciclopirox once every second week, and 128 (91%) in the vehicle group (p=0.2). The reviewer's ITT population included all 428 randomized patients. The sponsor's ITT population included 421 patients because 7 patients did not have post-baseline visits. There were no statistically significant differences between the treatment groups relative to gender or age (p>0.5).

Primary efficacy analysis in Segment B of Study 3001

Table 8a shows the results of the efficacy analysis in the reviewer's ITT population of Segment B of Study 3001 relative to the proportion of patients with relapse of seborrhoeic dermatitis. Both active treatment groups were statistically significantly better than the vehicle group. Ciclopirox once weekly and once every second week groups had relapse rates of 15.9% and 24.2%, respectively, compared with 35.5% in the vehicle group. In the sequentially performed pair-wise comparison against vehicle, Ciclopirox once weekly was statistically significantly better than vehicle ($p<0.001$). This allows performing the second comparison, Ciclopirox once every second week against vehicle. In this comparison, Ciclopirox once every second week is also statistically significantly better than vehicle (p=0.033).

Table 8a. Primary efficacy analysis in Segment B of Study 3001. Relapse rates in the Reviewer's ITT population including all 428 randomized patients.			
	Ciclopirox once weekly	Ciclopirox once every second week	Vehicle
Number of patients	138	149	141
Number (%) of patients with relapse	22 (15.9%)	36 (24.2%)	50 (35.5%)
Nominal p-value (not adjusted for two multiple comparisons)	0.0001	0.033	–

Secondary efficacy analysis in Segment B of Study 3001

Table 8b shows the results of the secondary efficacy analysis in the Segment B of Study 3001 relative to the proportion of patients with relapse of seborrhoeic dermatitis in the Sponsor's ITT population. Both active treatment groups were statistically significantly better than the vehicle group. Ciclopirox once weekly and once every second week groups had relapse rates of 14.7% and 22.1%, respectively, compared with 35.0% in the vehicle group. In the sequentially performed pair-wise comparison against vehicle, Ciclopirox once weekly was statistically significantly better than vehicle ($p<0.001$). This allows performing the second comparison, Ciclopirox once every second week against vehicle. In this comparison, Ciclopirox once every second week is also statistically significantly better than vehicle ($p=0.015$).

Table 8b. Secondary efficacy analysis in Segment B of Study 3001. Relapse rates in the Sponsor's ITT population including 421 patients.			
	Ciclopirox once weekly	Ciclopirox once every second week	Vehicle
Number of patients	136	145	140
Number (%) of patients with relapse	20 (14.7%)	32 (22.1%)	49 (35.0%)
Nominal p-value (not adjusted for two multiple comparisons)	0.0001	0.015	–

Subgroup efficacy analysis in Segment B of Study 3001

In males, both Ciclopirox once weekly and Ciclopirox once every second week were statistically significantly better than vehicle relative to relapse rates ($p=0.011$ and $p=0.013$, respectively). In females, Ciclopirox once weekly group was statistically significantly better than vehicle relative to relapse rates ($p=0.008$) and Ciclopirox once every second week was only numerically better than vehicle ($p=0.7$).

In younger patients (≤38 years), Ciclopirox once weekly group was statistically significantly better than vehicle relative to relapse rates (p=0.018) and Ciclopirox once every second week was only numerically better than vehicle (p=0.1). The same pattern was true in older patients (>38 years): Ciclopirox once weekly group was statistically significantly better than vehicle relative to relapse rates (p=0.006) and Ciclopirox once every second week was only numerically better than vehicle (p=0.15).

There was no significant difference between the relapse rates in younger (≤38 years) and older patients. In all treatment groups, including vehicle, there were lower relapse rates in females than males. This may be explained by more intense care in females.

Safety results in Segment B of Study 3001

All randomized 428 patients of Segment B were included in the safety population. Table 9 shows number and percentage of patients with at least one adverse event in the three treatment groups. There was no statistically significant difference in the proportion of patients with at least one adverse event between Ciclopirox once weekly and vehicle (p=0.16) or Ciclopirox once every second week and vehicle (p=0.76).

Table 9. Adverse events summary in Segment B of Study 3001

	Ciclopirox once weekly. N=136	Ciclopirox once every second week. N=145	Vehicle N=140
Number (%) of patients with at least one adverse event	16 (12%)	30 (20%)	26 (18%)
P-value versus vehicle	0.16	0.76	-

Table 10 shows number and percentages of patients with skin and appendages disorders. There was no statistically significant difference in the proportion of patients with skin appendages disorders between Ciclopirox once weekly and vehicle (p=0.8) or Ciclopirox once every second week and vehicle (p=0.3).

Table 10. Skin and appendages disorders in Segment B of Study 3001

	Ciclopirox once weekly. N=136	Ciclopirox once every second week. N=145	Vehicle N=140
Number (%) of patients with at least one skin and appendages disorder	5 (3.7%)	13 (9.0%)	7 (5.0%)
P-values versus vehicle	0.81	0.28	-

Reviewer's Conclusions (which may be conveyed to the sponsor):

1. Treatment of seborrhoeic dermatitis

In this review, Studies 204 and 3001 (Segment A), are considered as confirmative for supporting the claim that at least one of the regimens of Ciclopirox 1% is safe and effective in the treatment of seborrhoeic dermatitis. As Study 204 was completed before the guidance meeting with the FDA and did not have Investigator's Global Evaluation of "Status" at baseline, the Reviewer's primary efficacy variable in Study 204 is different from that in Study 3001.

Study 204

In Study 204, the primary efficacy variable is the proportion of patients classified as "Clear or almost clear" and the secondary efficacy variable is the sum of the scores of itching, scaling, and inflammation. The primary efficacy results of Study 204 fail to support the claim that at least one of the three Ciclopirox 1% regimens (once weekly, twice weekly, or three times weekly) is statistically significantly better than vehicle. P-values in the three comparisons versus vehicle are greater than 0.1 even without adjustment for multiple comparisons.

The secondary efficacy analysis in Study 204 also fails to support the claim that at least one of the three Ciclopirox 1% regimens (once weekly, twice weekly, or three time weekly) is statistically significantly better than vehicle. The smallest p-value in the three comparisons is 0.046 which is greater than the significance level of 0.0167 required in the Holm adjustment procedure for three multiple comparisons.

Study 3001, Segment A

In Segment A of Study 3001, the primary efficacy variable is the responder rate. The primary efficacy analysis shows that both Ciclopirox twice weekly and Ciclopirox once weekly are statistically significantly better than vehicle ($p \leq 0.0007$). In this case the overall Type 1 error is preserved at the 0.05 level. Secondary efficacy analysis supports the results of the primary efficacy analysis.

Relative the responder rate, the subgroup efficacy analysis shows that in younger patients (≤38 years), both Ciclopirox once weekly and Ciclopirox twice weekly were statistically significantly better than vehicle ($p \leq 0.004$). In older patients (>38 years), both Ciclopirox twice weekly and Ciclopirox once weekly groups were only numerically better than vehicle ($p > 0.07$). In males, both Ciclopirox once weekly and Ciclopirox twice weekly were statistically significantly better than vehicle ($p \leq 0.003$). In females, Ciclopirox twice weekly was statistically significantly better than vehicle ($p = 0.007$) and Ciclopirox once weekly was only numerically better than vehicle ($p = 0.2$).

All randomized 949 patients of Segment A were included in the safety population. There was no statistically significant difference in the comparisons of Ciclopirox twice weekly or Ciclopirox once weekly versus vehicle relative to the proportion of patients with at least one adverse event or skin and appendages disorders ($p \geq 0.5$).

2. Prophylaxis of seborrhoeic dermatitis

Segment B of Study 3001 is used in this review as a confirmative study to support the claim that at least one of the Ciclopirox 1% regimens (once weekly or once every second week) is safe and effective in the prophylaxis of seborrhoeic dermatitis. The primary efficacy variable in the Segment B of Study 3001 is the proportion of patients with relapse of seborrhoeic dermatitis. Primary efficacy analysis of Segment B of Study 3001, adjusted for multiplicity, shows that both active treatment groups are statistically significantly better than the vehicle group ($p < 0.015$).

Subgroup efficacy analysis in Segment B of Study 3001 shows that in males, both Ciclopirox once weekly and Ciclopirox once every second week were statistically significantly better than vehicle ($p<0.013$). In females, Ciclopirox once weekly group was statistically significantly better than vehicle ($p=0.008$) and Ciclopirox once every second week was only numerically better than vehicle ($p=0.7$).

In younger patients (≤ 38 years), Ciclopirox once weekly group was statistically significantly better than vehicle relative ($p=0.018$) and Ciclopirox once every second week was only numerically better than vehicle ($p=0.1$). The same pattern was true in older patients (>38 years): Ciclopirox once weekly group was statistically significantly better than vehicle ($p=0.006$) and Ciclopirox once every second week was only numerically better than vehicle ($p=0.15$).

All randomized 428 patients of Segment B were included in safety population. There was no statistically significant difference in the comparisons of Ciclopirox twice weekly or Ciclopirox once weekly versus vehicle relative to the proportion of patients with at least one adverse event or skin and appendages disorders ($p \geq 0.1$).

Overall Conclusions:

In the Phase 2 Study 204, both primary and secondary efficacy analyses fail to support the claim that at least one of the Ciclopirox 1% regimens (once weekly, twice weekly, or three times weekly) is statistically significantly better than vehicle in the treatment of seborrhoeic dermatitis of the scalp. In Segment A of the Phase 3 Study 3001, efficacy results support the claim that each of the regimens of Ciclopirox 1% (once weekly and twice weekly) is statistically significantly better than vehicle in the treatment of seborrhoeic dermatitis of the scalp. In Segment B of Study 3001, efficacy results support the claim that each of the prophylaxis regimens of Ciclopirox 1% (once weekly and once every second week) is statistically significantly better than placebo in the prophylaxis of seborrhoeic dermatitis of the scalp. This is a matter of the clinical judgement of the reviewing medical division to

decide whether Ciclopirox 1% shampoo should be approved given one failed and one successful study.

/S/ 4.10.00

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

/S/ 4/11/00

Concur: Mohamed Al-Osh, Ph.D.
Acting Team Leader, Biometrics III

cc:
Archival NDA 21-159
HFD-540
HFD-540/Mrs. Lutwak
HFD-540/Dr. Wilkin
HFD-540/Dr. Okun
HFD-540/Dr. Huene
HFD-725/Dr. Huque
HFD-725/Dr. Al-Osh
HFD-725/Dr. Freidlin
HFD-344/Dr. Carreras
Chron.(HFD-725)
This review contains 17 pages.
Wordfile\Loprox\n21159_4\04-11-00

STATISTICAL/CLINICAL REVIEW AND EVALUATION.

ADDEMDUM

NDA:	21-159 JUN 12 2000
Applicant:	Medicis
Name of Drug:	Loprox (ciclopirox) Shampoo 1%
Documents Reviewed:	Volumes1.1 1.3-1.80 dated September 01, 1999
Type of Report:	NDA review
Indication:	Topical treatment and prevention of recurrence of seborrhoeic dermatitis of the scalp
Medical officer:	Phyllis Huene, MD (HFD-540)

Introduction

This Addendum addresses the Medical Team Leader request for a subgroup efficacy analysis in pivotal studies comparing geriatric patients (age 65 years and older) with patients younger than 65 years. Study # 204 had only one geriatric patient in the twice-daily group, three (3) geriatric patients in the once daily group and two (2) geriatric patients in the vehicle group. Due to the very small numbers, subgroup analysis for the geriatric patients in Study # 204 is not possible.

This Addendum presents subgroup analysis for geriatric patients in Study 3001. The primary efficacy variable in Study 3001 is the responder rate. The definition of responder is based on the Investigator's Global evaluation of the "status of seborrhoeic dermatitis" and inflammation /scaling scores at individual endpoint. The responder is defined as a patient with:
score = 0 or
score = 1 if baseline was $\geq$ 3 points to be met simultaneously for "status", inflammation, and scaling scores at individual endpoint.

Subgroup efficacy analysis for Segment A of Study 3001 is shown in Table 1 by age group. Table 1 shows responder rate in Study 3001 and nominal p-values (not adjusted for two multiple comparisons.

Table 1. Primary efficacy analysis for Segment A of Study 3001 by age group.
Responder rate in patients age < 65 and age ≥ 65 years old.

		Ciclopirox 2x	Ciclopirox 1x	Vehicle
Age < 65	Total number of patients	332	337	169
	Number (%) of responders	202 (60.8%)	149 (44.2 %)	50 (29.6 %)
	p-value* versus vehicle	0.001	0.0015	-
Age ≥ 65	Total number of patients	44	39	21
	Number (%) of responders	18 (40.9 %)	22 (56.4 %)	10 (47.6 %)
	p-value* versus vehicle	0.61	0.52	-

As is seen from Table 1, in the subgroup of geriatric patients (age 65 years or older), responder rates in the twice daily, once daily and vehicle groups were 40.9%, 56.4% and 47.6%, respectively. There is no dose response in these data. These results may be due to small number of patients. This study was not powered for subgroup analysis.

Reviewer's Conclusions:

Subgroup efficacy analysis of the pivotal Study 3001 shows that in the subgroup of geriatric patients (age 65 years or older), responder rates in the twice daily, once daily, and vehicle groups were 40.9%, 56.4% and 47.6%, respectively. There is no dose response in these data. These results may be due to small number of patients. This study was not powered for subgroup analysis.

Study # 204 had only one geriatric patient in the twice daily group, three (3) geriatric patients in the once daily group and two (2) geriatric patients in the vehicle group. Due to the very small number of geriatric patients, efficacy subgroup analysis for geriatric patients in Study # 204 is not possible.

Therefore, efficacy results in the geriatric subgroup in this submission are not conclusive due to small number of patients. This conclusion should be reflected in the label.

/S/ 6.12.2000

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

/S/ 6/12/00

Concur: Mohamed Al-Osh, Ph.D.
Acting Team Leader, Biometrics III

cc:
Archival NDA 21-159
HFD-540
HFD-540/Mrs. Lutwak
HFD-540/Dr. Wilkin
HFD-540/Dr. Okun
HFD-540/Dr. Huene
HFD-725/Dr. Huque
HFD-725/Dr. Al-Osh
HFD-725/Dr. Freidlin
Chron. (HFD-725)
This review contains 3 pages.
Wordfile\Loprox\Addendum_2\06-12-00

STATISTICAL REVIEW AND EVALUATION

IND: [redacted]

Applicant: Medicis

Name of Drug: Loprox (ciclopirox) Shampoo 1%

Documents Reviewed: Briefing Document dated March 28, 2001

Type of Report: Sponsor's response review

Indication: Topical treatment of seborrheic dermatitis of the scalp

Medical officer: Phyllis Huene, MD (HFD-540)

Statistical Reviewer: Valeria Freidlin, Ph.D. (HFD-725)

Introduction

As a response to the September 2000 NA letter for NDA 21-159, the sponsor submitted [redacted] with a Phase 3 Protocol 14262 to compare 1% Ciclopirox shampoo (Loprox) and vehicle used twice a week in the treatment of seborrhoeic dermatitis of the scalp. In February, 2001, this reviewer made some comments on the Protocol 14262. This submission is the sponsor's response on the Division's comments. In this review, for brevity, the term Loprox will be used instead of 1.0% Ciclopirox shampoo.

Design

It will be a randomized, multicenter, double-blind, parallel group, vehicle controlled, Phase 3 study to compare the effects of a 4-week treatment of Loprox with the effects of vehicle. Patients will use the study treatment twice a week. The study will enroll 400 patients in 15 centers in the US. The patients will be randomized at the 1:1 ratio to the two treatment arms: vehicle and Loprox shampoo. Study population will include subjects of either gender aged greater than 18 years with the diagnosis of stable or exacerbating seborrhoeic dermatitis of the scalp as evidenced at screening and baseline by:
Score "status of seborrheic dermatitis" ≥ 2 and
Score "inflammation" ≥ 2 and
Score "scaling" ≥ 2.
(In the 6-step scale, the score ≥ 2 is "mild" or worse).

Efficacy measurements:

- Percentage of area affected.
- Percentage of scalp affected
- Localization of the disease.

Patients also will be evaluated with the following 6-point scores:
Score "status of seborrheic dermatitis" (global evaluation)
Score "inflammation"
Score "scaling"
Score "itching".
Each score will range from 0 = none to 5 = severe.

The Primary Efficacy variable will be:

"Effectively treated" = 0, or
= 1 if baseline score was ≥ 3.
This must be fulfilled for Status, and Scaling, and for Inflammation.

Other efficacy variables:

- **Cleared** = score 0. This must be fulfilled for Status, and Scaling, and for Inflammation.
- **Improved 1** = Improvement from baseline by ≥ 2 points. This must be fulfilled for Status, and Scaling, and for Inflammation.
- **Improved 2** = score ≤ 1 or
Improvement from baseline by ≥ 3 points. This must be fulfilled for Status.
- **Scaling response**
- **Inflammation response**
- **Itching response**
- **Sumscore (of inflammation, scaling and itching).**

Sample size

A total of 400 patient will be randomized. With 200 patients per treatment arm, it can be expected that at least 380 patients (190 per arm) will be valid for the primary efficacy analysis (response rate for effectively treated in the ITT population). With n=190, the power is at least 81% to detect a treatment difference of 15% points and the power is at least 97% to detect the difference of 20 points relative to the primary efficacy variable, Effective Treatment. The vehicle and Loprox are expected to have success rates of 27% and 52%, respectively.

Concur: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:
Archival
HFD-540
HFD-540/Mrs. Lutwak
HFD-540/Dr. Walker
HFD-540/Dr. Wilkin
HFD-540/Dr. Huene
HFD-725/Dr. Huque
HFD-725/Dr. Al-Osh
HFD-725/Dr. Freidlin
HFD-700/Dr. Anello
Chron. (HFD-725)
This review contains 4 pages.
Wordfile\Loprox\Loprox2 24\04-24-01

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Valeria Freidlin
5/1/01 03:15:28 PM
BIOMETRICS

Mohamed Alosh
5/1/01 04:34:48 PM
BIOMETRICS
Concur with review

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL/CLINICAL REVIEW AND EVALUATION.

IND:

Applicant: Medicis

Name of Drug: Loprox (ciclopirox) Shampoo 1%

Documents Reviewed: Briefing Document dated January 02, 2001

Type of Report: IND review

Indication: Topical treatment of seborrheic dermatitis of the scalp

Medical officer: Phyllis Huene, MD (HFD-540)

Introduction

As a response to the September 2000 NA letter for NDA 21-159, the sponsor submitted a Phase 3 Protocol #14262 to compare 1% Ciclopirox shampoo (Loprox) and vehicle used twice a week in the treatment of seborrhoeic dermatitis of the scalp. In this review, for brevity, the term Loprox will be used instead of 1.0% Ciclopirox shampoo.

Design

It will be a randomized, multicenter, double-blind, parallel group, vehicle controlled, Phase 3 study to compare the effects of a 4-week treatment of Loprox with the effects of vehicle. Patients will use the study treatment twice a week. The study will enroll 400 patients in 15 centers in the US. The patients will be randomized at the 1:1 ratio to the two treatment arms: vehicle and Loprox shampoo. Study population will include subjects of either gender aged greater than 18 years with the diagnosis of stable or exacerbating seborrhoeic dermatitis of the scalp as evidenced at screening and baseline by:
Score "status of seborrheic dermatitis" $\geq$2 and
Score "inflammation" $\geq$2 and
Score "scaling" $\geq$2.
(Score $\geq$2 is "mild" or worse).

Efficacy measurements

- Patients will be evaluated with the following 6-point scores:
  Score "status of seborrheic dermatitis" (global evaluation)
  Score "inflammation"
  Score "scaling"
  Score "itching".
  Each score will range from 0 = none to 5 = severe.

- Percentage of area affected.
- Percentage of scalp affected
- Localization of the disease.

The Primary Efficacy variable will be:

"Effectively treated" = 0, or
= 1 if baseline score was ≥ 3.
This must be fulfilled for Status, and Scaling, and for Inflammation.

Other efficacy variables:

- **Cleared** = score 0. This must be fulfilled for Status, and Scaling, and for Inflammation.

- **Improved 1** = Improvement from baseline by ≥2 points. This must be fulfilled for Status, and Scaling, and for Inflammation.

- **Improved 2** = score ≤ 1 or
Improvement from baseline by ≥3 points. This must be fulfilled for Status.

- **Scaling response**
- **Inflammation response**
- **Itching response**
- **Sumscore (of inflammation, scaling and itching).**

Sample size

A total of 400 patient will be randomized. With 200 patients per treatment arm, it can be expected that at least 380 patients (190 per arm) will be valid for the primary efficacy analysis (response rate for effectively treated in the ITT population). With n=190, the power is at least 81% to detect a treatment difference of 15 points and the power is at least 97% to detect the difference of 20 points. The vehicle and Loprox are expected to have success rates of 27% and 52%, respectively.

Study populations

ITT is defined as all randomized patients who received at least one dose of study treatment and either had a rating on the primary efficacy variable or dropped due to lack of efficacy.

Per Protocol population is defined as ITT patients who had a rating on the primary efficacy variable at the end of treatment and had no record of major protocol violations. There is a list of major violations in the protocol.

Statistical analysis

The primary efficacy analysis will be based on the response rates in the category "effectively treated" in the ITT population. The response rates will be compared with the CMH test for general association adjusted for center.

Reviewer's Comments:

1. The Division recommends to define the ITT population as every patient who was dispensed the study drug (active or vehicle). If a patient did not have a post baseline rating of the primary efficacy variable, then the baseline rating should be carried forward.
2. Secondary endpoints Improved 1 and Improved 2 are not defined well and do not make up regressing subsets.
3. According to page 31, there will be seven secondary efficacy variables. If the sponsor plans to show the results of the secondary efficacy variables in the label, then the number of the secondary efficacy variables should be reduced. Otherwise, a p-value adjustment for multiple comparisons will be required.
4. Statistical methods for the secondary efficacy variables should be pre-specified in the protocol. If an analysis of variance is planned then a precise model should be pre-specified in the protocol.
5. Details about randomization and patient's treatment allocation should be done prior to the initiation of the trial. A randomization list should be included in the protocol.
6. Primary efficacy subgroup analysis (in age, race, and gender subgroups) will be needed.
7. Given the expected response rates, the sample size calculations are correct.

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

Concur: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:
Archival
HFD-540
HFD-540/Mrs. Lutwak
HFD-540/Dr. Walker
HFD-540/Dr. Wilkin
HFD-540/Dr. Huene
HFD-725/Dr. Huque
HFD-725/Dr. Al-Osh
HFD-725/Dr. Freidlin
HFD-700/Dr. Anello
Chron. (HFD-725)
This review contains 4 pages.
Wordfile\Loprox\Loprox2 02-7-01

/s/

Valeria Freidlin
2/9/01 10:47:04 AM
BIOMETRICS

please sign

Mohamed Alosh
2/9/01 11:35:13 AM
BIOMETRICS
Concur with review

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL/CLINICAL REVIEW AND EVALUATION.

IND: —

Applicant: Medicis

Name of Drug: Loprox (ciclopirox) Shampoo 1%

Documents Reviewed: Briefing Document dated January 02, 2001

Type of Report: IND review

Indication: Topical treatment of seborrheic dermatitis of the scalp

Medical officer: Phyllis Huene, MD (HFD-540)

Introduction

As a response to the September 2000 NA letter for NDA 21-159, the sponsor submitted a Phase 3 Protocol #14262 to compare 1% Ciclopirox shampoo (Loprox) and vehicle used twice a week in the treatment of seborrhoeic dermatitis of the scalp. In this review, for brevity, the term Loprox will be used instead of 1.0% Ciclopirox shampoo.

Design

It will be a randomized, multicenter, double-blind, parallel group, vehicle controlled, Phase 3 study to compare the effects of a 4-week treatment of Loprox with the effects of vehicle. Patients will use the study treatment twice a week. The study will enroll 400 patients in 15 centers in the US. The patients will be randomized at the 1:1 ratio to the two treatment arms: vehicle and Loprox shampoo. Study population will include subjects of either gender aged greater than 18 years with the diagnosis of stable or exacerbating seborrhoeic dermatitis of the scalp as evidenced at screening and baseline by:
Score "status of seborrheic dermatitis" $\geq$2 and
Score "inflammation" $\geq$2 and
Score "scaling" $\geq$2.
(Score $\geq$2 is "mild" or worse).

Efficacy measurements

- Patients will be evaluated with the following 6-point scores:
  Score "status of seborrheic dermatitis" (global evaluation)
  Score "inflammation"
  Score "scaling"
  Score "itching".
  Each score will range from 0 = none to 5 = severe.

- Percentage of area affected.
- Percentage of scalp affected
- Localization of the disease.

The Primary Efficacy variable will be:

"Effectively treated" = 0, or
= 1 if baseline score was ≥ 3.
This must be fulfilled for Status, and Scaling, and for Inflammation.

Other efficacy variables:

- **Cleared** = score 0. This must be fulfilled for Status, and Scaling, and for Inflammation.
- **Improved 1** = Improvement from baseline by ≥2 points. This must be fulfilled for Status, and Scaling, and for Inflammation.
- **Improved 2** = score ≤ 1 or
Improvement from baseline by ≥3 points. This must be fulfilled for Status.
- **Scaling response**
- **Inflammation response**
- **Itching response**
- **Sumscore (of inflammation, scaling and itching).**

Sample size

A total of 400 patient will be randomized. With 200 patients per treatment arm, it can be expected that at least 380 patients (190 per arm) will be valid for the primary efficacy analysis (response rate for effectively treated in the ITT population). With n=190, the power is at least 81% to detect a treatment difference of 15 points and the power is at least 97% to detect the difference of 20 points. The vehicle and Loprox are expected to have success rates of 27% and 52%, respectively.

Study populations

ITT is defined as all randomized patients who received at least one dose of study treatment and either had a rating on the primary efficacy variable or dropped due to lack of efficacy.

Per Protocol population is defined as ITT patients who had a rating on the primary efficacy variable at the end of treatment and had no record of major protocol violations. There is a list of major violations in the protocol.

Statistical analysis

The primary efficacy analysis will be based on the response rates in the category "effectively treated" in the ITT population. The response rates will be compared with the CMH test for general association adjusted for center.

Reviewer's Comments:

1. The Division recommends to define the ITT population as every patient who was dispensed the study drug (active or vehicle). If a patient did not have a post baseline rating of the primary efficacy variable, then the baseline rating should be carried forward.
2. Secondary endpoints Improved 1 and Improved 2 are not defined well and do not make up regressing subsets.
3. According to page 31, there will be seven secondary efficacy variables. If the sponsor plans to show the results of the secondary efficacy variables in the label, then the number of the secondary efficacy variables should be reduced. Otherwise, a p-value adjustment for multiple comparisons will be required.
4. Statistical methods for the secondary efficacy variables should be pre-specified in the protocol. If an analysis of variance is planned then a precise model should be pre-specified in the protocol.
5. Details about randomization and patient's treatment allocation should be done prior to the initiation of the trial. A randomization list should be included in the protocol.
6. Primary efficacy subgroup analysis (in age, race, and gender subgroups) will be needed.
7. Given the expected response rates, the sample size calculations are correct.

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

Concur: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:
Archival
HFD-540
HFD-540/Mrs. Lutwak
HFD-540/Dr. Walker
HFD-540/Dr. Wilkin
HFD-540/Dr. Huene
HFD-725/Dr. Huque
HFD-725/Dr. Al-Osh
HFD-725/Dr. Freidlin
HFD-700/Dr. Anello
Chron. (HFD-725)
This review contains 4 pages.
Wordfile\Loprox\Loprox2

APPEARS THIS WAY
ON ORIGINAL

/s/

Valeria Freidlin
2/9/01 10:47:04 AM
BIOMETRICS -

please sign

Mohamed Alosh
2/9/01 11:35:13 AM
BIOMETRICS
Concur with review

APPEARS THIS WAY
ON ORIGINAL