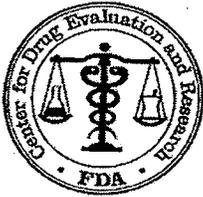


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-738

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

NDA/Serial Number: 21-738 / N-000 (AZ)
Drug Name: Extina (ketoconazole) foam 2%
Indication(s): Seborrheic dermatitis
Applicant: Connetics
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1 Executive Summary

1.1 Conclusions and Recommendations

Study 005 demonstrates that ketoconazole foam is superior to vehicle foam and non-inferior to ketoconazole cream in the treatment of seborrheic dermatitis. The Agency had previously agreed that efficacy for this 505(b)2 application could be established by demonstrating that ketoconazole foam is superior to its vehicle and non-inferior to a listed ketoconazole cream product in one study. The sponsor had also previously conducted an additional study (Study 002) which did not provide convincing evidence of efficacy on its own, as ketoconazole foam failed to demonstrate superiority to vehicle foam in Study 002. The point estimates for treatment success for the two studies are comparable even though statistical significance was only achieved in Study 005. Both studies enrolled subjects age 12 and older with mild to severe seborrheic dermatitis. Treatment success was defined as achieving a score of 0 or 1 (with at least 2 grades reduction from baseline) on an Investigator's Static Global Assessment (ISGA) at Week 4. The efficacy results for the two studies are presented in Table 1.

Table 1 – Treatment Success at Week 4 (ITT)

Study	Ketoconazole Foam	Vehicle Foam	Ketoconazole Cream	Vehicle Cream
002	N=233 116 (50%)	N=77 31 (40%) 0.1318 ¹	N=233 103 (44%) -3.5% ²	N=76 20 (26%)
005	N=427 239 (56%)	N=420 176 (42%) <0.0001 ¹	N=210 118 (56%) -8.4% ²	N=105 33 (31%)

¹ p-value for ketoconazole foam versus vehicle foam

² 97.5% lower confidence bound for ketoconazole foam versus ketoconazole cream (non-inferiority margin = -10%)

1.2 Brief Overview of Clinical Studies

The sponsor has conducted two Phase 3 studies evaluating ketoconazole foam for the treatment of seborrheic dermatitis. Subjects applied treatment twice daily for four weeks. The first study (002) was submitted as the basis for an NDA in January 2004. Since Study 002 failed to demonstrate that ketoconazole foam was superior to its vehicle, the Agency issued a non-approvable letter on November 23, 2004. Subsequently, the sponsor conducted a second study (005) which was submitted in the December 11, 2006 major amendment to this application. Both studies were 4-arm studies with the goal of demonstrating that ketoconazole foam is superior to vehicle foam and non-inferior to ketoconazole cream in the treatment of seborrheic dermatitis. Both studies were conducted in the United States. Study 002 was evaluated in the statistical review dated September 8, 2004. Study 005 is the primary basis for this review. The clinical study program for ketoconazole foam is presented in Table 2.

Table 2 – Clinical Study Program for Ketoconazole Foam

Study	Treatment Arms	No. of Subjects	Study Dates
KFD.C.002	Ketoconazole Foam	233	June 2002 – February 2003
	Vehicle Foam	77	
	Nizoral (ketoconazole) cream	233	
	Vehicle Cream	76	
KFD.C.005	Ketoconazole Foam	427	September 2005 – July 2006
	Vehicle Foam	420	
	Teva (ketoconazole) cream	210	
	Vehicle Cream	105	

1.3 Statistical Issues and Findings

Study 005 met all of its pre-specified efficacy objectives for the primary and secondary endpoints. The primary efficacy endpoint was treatment success, defined as achieving a score of 0 or 1 with at least 2 grades reduction on the ISGA. The ISGA is based on evaluations of erythema, scaling, and induration. The secondary endpoints were defined as achieving scores of 0 or 1 on the individual scores for erythema and scaling. The sponsor also proposed a modified treatment success defined as a score of 0 or 1 with at least 2 grades reduction on the ISGA, erythema, and scaling. Ketoconazole foam was superior to vehicle foam for all primary and secondary endpoints. Ketoconazole foam met the non-inferiority criterion relative to ketoconazole cream for the primary endpoint in both the ITT and per protocol population.

The study discontinuation rate was less than 5% and the reasons for study discontinuation were similar across all treatment arms. The study did not demonstrate any significant treatment by center interaction. The amount of study drug used during the study appears to be formulation dependent, as ketoconazole foam subjects used approximately twice as many grams of product as ketoconazole cream subjects used. The number of grams used by vehicle foam subjects was similar to the amount used by ketoconazole foam subjects. Most adverse events occurred at rates less than 1% for the ketoconazole foam arm with the exception of application site burning (10%) and application site reaction (4%).

2. Introduction

2.1 Overview

NDA 21-738 for Extina (ketoconazole) foam was originally submitted on January 26, 2004 as a 505(b)2 application with reference drug Nizoral (ketoconazole) cream. Ketoconazole is an anti-fungal drug that has been approved in topical dosage forms since 1985. In the original application the sponsor submitted a single 4-arm (ketoconazole foam, vehicle foam, ketoconazole cream, vehicle cream) study (KFD.C.002) with the stated goals of demonstrating that ketoconazole foam was superior to vehicle foam and non-inferior to ketoconazole cream in the treatment of seborrheic dermatitis. Although the treatment success rate for ketoconazole foam was numerically higher than for

ketoconazole cream (50% vs. 44%) and the 97.5% lower confidence bound for the treatment difference (-3.5%) was within the pre-specified non-inferiority margin of 10%, the study failed to demonstrate that ketoconazole foam was superior to its vehicle (50% vs. 40%, $p=0.132$). The study had been powered to detect a 38% treatment effect of ketoconazole foam over its vehicle and was not able to demonstrate statistical significance for the much smaller observed difference. Because the sponsor had failed to demonstrate that ketoconazole foam was superior to its vehicle, the Agency issued a non-approvable letter on November 23, 2004 stating that "results from one additional adequate and well-controlled study will need to be submitted demonstrating superiority of ketoconazole foam 2% over its vehicle and non-inferior to the active comparator."

In this submission, the sponsor has submitted a new 4-arm study (KFD.C.005) to meet the conditions of the non-approvable letter. The study is of a nearly identical design to Study 002, except the sample sizes were changed and some secondary endpoints were changed. When the sponsor conducted Study 005, Nizoral cream was no longer commercially available so the sponsor conducted the study with generic ketoconazole cream from Teva. According to the Orange Book, the Teva cream is now considered the reference listed drug for ketoconazole cream. However, it should also be noted that although Nizoral cream was indicated for tinea corporis, tinea cruris, tinea pedis, tinea versicolor, cutaneous candidiasis, and seborrheic dermatitis, some labeling for Teva ketoconazole cream lists only the tinea and candidiasis indications in its label and does not list seborrheic dermatitis as an indication. Of note, the labeling posted on FDA's Drugs@FDA website for the 4/25/2000 approval of Teva ketoconazole cream (http://www.fda.gov/cder/foi/nda/2000/75-581_Ketoconazole_prntlbl.pdf) includes the seborrheic dermatitis indication while a version of the labeling posted on NIH's DailyMed website dated 3/2005 (<http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2692>) does not.

2.2 Data Sources

This reviewer evaluated the sponsor's study reports and clinical summaries as well as the proposed labeling. The study reports were submitted on paper. The datasets used in this review are archived at \\CDSESUB1\N21738\N_000\2006-12-11\m5\53-clin-stud-rep\537-crf-ip\datasets\005.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

The sponsor has conducted two Phase 3 studies (002 and 005) to support the efficacy and safety of ketoconazole foam in the treatment of seborrheic dermatitis for this 505(b)2 application. Each of the studies had four arms (ketoconazole foam, vehicle foam, ketoconazole cream, vehicle cream) and both were designed to establish efficacy by demonstrating that ketoconazole foam was superior to vehicle foam and non-inferior to ketoconazole cream. Study 002 was originally submitted in 2004, however Study 002 failed to demonstrate that ketoconazole foam was superior to vehicle foam for the pre-specified primary endpoint. Consequently the study was unable to establish the efficacy of ketoconazole foam and the sponsor was required to conduct a second study. Refer to

the original statistical review of NDA 21-738, dated September 8, 2004, for a comprehensive review of Study 002. This review will briefly summarize the key conclusions of Study 002 and provide a full review of Study 005.

3.1.1 Study Design (Studies 002 and 005)

Studies 002 and 005 were of nearly identical design. Both studies were randomized 4-arm studies of the safety and efficacy of ketoconazole foam in the treatment of seborrheic dermatitis. The four arms are ketoconazole foam, vehicle foam, ketoconazole cream, and vehicle cream. Study 002 used Nizoral cream, while Study 005 used generic ketoconazole cream from Teva since Nizoral was no longer commercially available at the time Study 005 was conducted. Subjects applied treatment twice daily for four weeks. Subjects were evaluated at baseline, Week 2 and Week 4. (Subjects in Study 002 were also evaluated at Week 1). A nurse/coordinator handled treatment dispensation so that the primary investigator would remain blinded to the dosage form (foam or cream).

The primary efficacy endpoint was the proportion of subjects with an Investigator's Static Global Assessment (ISGA) of 0 or 1 at Week 4. Subjects with a baseline score of 2 must improve to a score of 0. The ISGA was based on the individual assessments of scaling, erythema, and induration, each graded with scores from 0 to 4. Both studies used the same definition for the primary endpoint. The scales for scaling, erythema, induration, and pruritus are presented in Table 3 and the ISGA is presented in Table 4.

Table 3 – Seborrheic Dermatitis Grading Scale

<i>Score</i>	<i>Scaling</i>	<i>Erythema</i>	<i>Induration</i>	<i>Pruritus</i>
0	Normal skin with rare fine scale	Normal skin without erythema; may have residual hyper-pigmentation	Normal skin without induration	No itching
1	Minimal; occasional fine scales over less than 10% of the lesions	Faint erythema	Minimal papule or plaque elevation; approximately 0.2 mm	Minimal: rarely aware of itching
2	Mild; fine scales predominate	Light red erythema	Mild plaque elevation; approximately 0.5 mm	Mild: only aware of itching at times; only present when relaxing; not present when focused on other activities
3	Moderate; coarse scales predominate	Moderate red coloration	Moderate papule or plaque elevation; approximately 1 mm	Moderate: often aware of itching; annoying; sometimes disturbs sleep and daytime activities
4	Severe; thick tenacious scales predominate	Dusky to deep red coloration	Severe papule or plaque elevation; approximately 1.5 mm	Severe: constant itching; distressing; frequent sleep disturbance; interferes with activities

Table 4 – Investigator’s Static Global Assessment (ISGA)

<i>Score</i>	<i>Description</i>
0	clear, except for minor residual discoloration
1	majority of lesions have individual scores for scaling, erythema, and induration that averages 1
2	majority of lesions have individual scores for scaling, erythema, and induration that averages 2
3	majority of lesions have individual scores for scaling, erythema, and induration that averages 3
4	majority of lesions have individual scores for scaling, erythema, and induration that averages 4

The superiority of ketoconazole foam to vehicle foam was assessed with a Cochran-Mantel-Haenszel test stratified by center at the two-sided significance level of 0.05. The non-inferiority of ketoconazole foam to ketoconazole cream was assessed using a 97.5% one-sided lower confidence bound (using the normal approximation to the binomial) and a non-inferiority margin of -10%.

The two studies differed slightly on the definition of the secondary endpoints. Study 002 had a single secondary endpoint which was the percent reduction in the sum of erythema, scaling, and induration scores from baseline to Week 4. Study 005 had three secondary endpoints which were defined as the proportion of subjects with scores of 0 or 1 for erythema, scaling, and induration at Week 4. The sponsor also specified one additional secondary endpoint in the statistical analysis plan of Study 005 that was not in the original protocol. This endpoint was a modified treatment success defined as a score of 0 or 1 (with at least 2 grades reduction) for the ISGA, erythema, and scaling. This endpoint was suggested by Agency reviewers during the protocol review process for consistency with other seborrheic dermatitis development programs.

The intent-to-treat (ITT) population was defined as all randomized subjects. Missing data were handled with last observation carried forward (LOCF). In Study 005, the protocol also specified sensitivity analyses for the handling of missing data. In one sensitivity analysis, the sponsor planned to impute the average response rate by treatment for subjects who did not complete the trial. In an additional sensitivity analysis, the sponsor also planned to use an iterative sequential generalized logistic model to impute missing data. The per protocol population excluded subjects with missing baseline or Week 4 efficacy assessments, subjects missing more than four sequential or eight total applications of study medication, and subjects using prohibited medications.

3.1.2 Study 002 Results

Study 002 failed to demonstrate that ketoconazole foam was superior to vehicle foam for the primary endpoint of treatment success (50% vs. 40%, $p = 0.1318$). ITT efficacy results from Study 002 are presented in Table 5. Although the lower confidence bound for the difference between ketoconazole foam and ketoconazole cream (-3.5%) was within the pre-specified non-inferiority margin of 10%, it is difficult to interpret the non-inferiority result when ketoconazole foam failed to demonstrate superiority over its vehicle. Conclusions from the per protocol population were similar (50% vs. 41% for ketoconazole foam vs. vehicle foam, $p = 0.1726$; 50% vs. 47% for ketoconazole foam vs. ketoconazole cream, LCB = -7.0%). In this study, vehicle effects are important factors in

the overall success rate, as the vehicle foam success rate in Study 002 was quite a bit higher than the vehicle cream success rate (40% vs. 26%). For a complete discussion of the results from Study 002, refer to the statistical review of the original submission. The sponsor was issued a non-approvable letter for ketoconazole foam based on the failure of the foam to demonstrate superiority to its own vehicle in Study 002.

Table 5 – Treatment Success at Week 4 (Study 002 - ITT)

Ketoconazole Foam N=233	Vehicle Foam N=77	Ketoconazole Cream N=233	Vehicle Cream N=76
116 (49.8%)	31 (40.3%) 0.1318 ¹	103 (44.2%) -3.47% ²	20 (26.3%)

¹ p-value for ketoconazole foam versus vehicle foam

² 97.5% lower confidence bound for ketoconazole foam versus ketoconazole cream

3.1.3 Subject Disposition and Demographics (Study 005)

After receiving the non-approvable letter based on the Agency's review of Study 002, the sponsor conducted Study 005. Study 005 enrolled 1162 subjects at 24 centers (427 ketoconazole foam, 420 vehicle foam, 210 ketoconazole cream, and 105 vehicle cream). The study enrolled subjects age 12 and older with mild to severe seborrheic dermatitis (ISGA score of 2 – 4 and a target area ≥ 5 cm² with a score of 2 – 4 for erythema and scaling, and 1 – 4 for induration).

Approximately 4% of subjects discontinued the study prior to Week 4. The discontinuation rates were similar for each treatment arm. The most common reasons for discontinuation from the ketoconazole foam arm were 'lost to follow-up' (2%, 7 subjects) and 'subject request to withdraw' (1%, 4 subjects). Reasons for subject discontinuations are presented in Table 6.

Table 6 – Reason for Study Discontinuation (Study 005)

	Ketoconazole Foam	Vehicle Foam	Ketoconazole Cream	Vehicle Cream
Number of Subjects	427	420	210	105
Subjects who Discontinued	17 (4%)	16 (4%)	12 (6%)	5 (5%)
Reasons for Discontinuation				
Adverse Experience	3 (1%)	6 (1%)	4 (2%)	1 (1%)
Subject Non-Compliance	3 (1%)	2 (<1%)	1 (<1%)	0 (0%)
Subject Request to Withdraw	4 (1%)	8 (2%)	3 (1%)	3 (3%)
Product/Application Issues	1	2		
Lack of Efficacy	1	2		
Adverse Event		2	1	1
Scheduling Issues	1	2	1	1
Consent Withdrawn	1		1	1
Lost to Follow-up	7 (2%)	0 (0%)	2 (1%)	0 (0%)
Other Reason ^a	0 (0%)	0 (0%)	2 (1%)	1 (1%)

^a Includes failure to meet inclusion/exclusion criteria, inadvertent termination by site, and incarceration.

Source: Vol. 8, Sec. 5.3.5.1, pg 38.

No significant differences between treatment arms were observed in demographic variables at baseline. The study enrolled similar numbers of males and females. Most of the subjects were between age 18 and 64, with about 6% of subjects below the age of 18 and about 16% of subjects 65 or older. Most of the subjects were Caucasian. Over half of the subjects had mild disease at baseline. Three subjects (from the same investigator) did not have CRFs completed at baseline and have missing demographic information.

Table 7 –Demographic and Baseline Data (Study 005)

		Ketoconazole Foam N=427	Vehicle Foam N=420	Ketoconazole Cream N=210	Vehicle Cream N=105
<i>Sex</i>	Male	223 (52%)	213 (51%)	118 (56%)	50 (48%)
	Female	203 (48%)	205 (49%)	92 (44%)	55 (52%)
	Missing	1 (<1%)	2 (<1%)	0 (0%)	0 (0%)
<i>Age (years)</i>	12 – 17	28 (7%)	26 (6%)	9 (4%)	4 (4%)
	18 – 64	336 (79%)	322 (77%)	165 (79%)	82 (78%)
	≥ 65	62 (15%)	70 (17%)	36 (17%)	19 (18%)
	Missing	1 (<1%)	2 (<1%)	0 (0%)	0 (0%)
<i>Race</i>	Caucasian	309 (72%)	299 (71%)	150 (71%)	75 (71%)
	Black	71 (17%)	69 (16%)	35 (17%)	19 (18%)
	Hispanic	34 (8%)	29 (7%)	15 (7%)	8 (8%)
	Asian	5 (1%)	13 (3%)	3 (1%)	2 (2%)
	Other	7 (2%)	8 (2%)	7 (3%)	1 (1%)
	Missing	1 (<1%)	2 (<1%)	0 (0%)	0 (0%)
<i>ISGA</i>	Mild	247 (58%)	247 (59%)	115 (55%)	65 (62%)
	Moderate	167 (39%)	158 (38%)	86 (41%)	37 (35%)
	Severe	12 (3%)	13 (3%)	9 (4%)	3 (3%)
	Missing	1 (<1%)	2 (<1%)	0 (0%)	0 (0%)

Source: Vol. 8, Sec. 5.3.5.1, pg. 42, 43

3.1.4 Primary Efficacy Endpoint

The primary efficacy endpoint was treatment success, defined as achieving an ISGA of 0 or 1 at Week 4 with at least two grades reduction from baseline. The study had two sequential hypotheses: (1) demonstrate that ketoconazole foam is superior to vehicle foam, and (2) demonstrate that ketoconazole foam is non-inferior to ketoconazole cream. For the ITT population, Study 005 demonstrated that ketoconazole foam is superior to vehicle foam (56% vs. 42%, $p < 0.0001$). Ketoconazole foam also met the pre-specified criteria for demonstrating non-inferiority to ketoconazole cream (56% vs. 56%, 97.5% lower confidence bound -8.4%, non-inferiority margin = -10%). Results from the per protocol population were consistent with the ITT population; the success rate for each treatment group was 1-2% higher for the per protocol population than the ITT population (PP: superiority p -value=0.0003, non-inferiority lower bound = -9.5%). Study 005 met the pre-specified efficacy objectives. Treatment success results for the ITT and per protocol populations are presented in Table 8.

Table 8 – Treatment Success at Week 4 (Study 005)

	Ketoconazole Foam	Vehicle Foam	Ketoconazole Cream	Vehicle Cream
ITT	N=427 239 (56%)	N=420 176 (42%) <0.0001 ¹	N=210 118 (56%) -8.4% ²	N=105 33 (31%)
PP	N=378 214 (57%)	N=376 163 (43%) 0.0003 ¹	N=188 108 (57%) -9.5% ²	N=93 31 (33%)

¹ p-value for ketoconazole foam versus vehicle foam

² 97.5% lower confidence bound for ketoconazole foam versus ketoconazole cream

The sponsor proposed two alternate ways of imputing missing data as sensitivity analyses: imputing the average response rate and using a sequential regression method. Since the dropout rate in Study 005 was fairly low (4%) and balanced across treatment arms, the sensitivity analyses led to very similar success rates (within 1-2%) and the same conclusions as the primary analysis (results not presented).

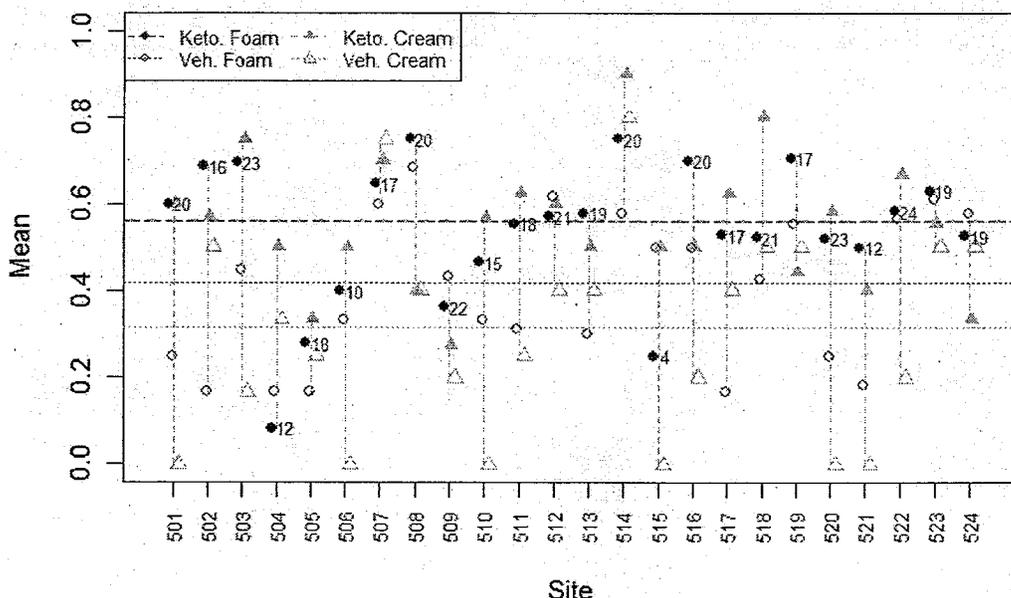
3.1.5 Efficacy by Center

Subjects were enrolled in 24 centers. For the analysis, the two smallest centers were pooled with other centers to yield 22 analysis centers. Treatment success rates by center are presented in Figure 1. The protocol stated that treatment by center interaction would be assessed with a Breslow-Day test for each comparison. The statistical analysis plan was updated to add a Gail-Simon test. The Gail-Simon test statistic is a function of the individual treatment differences, standard deviations, and whether the differences are positive or negative. The sponsor did not provide any details about how the p-values for the Gail-Simon test would be calculated and this reviewer got slightly different results. The sponsor's and reviewer's results for the Breslow-Day and Gail-Simon tests are presented in Table 9. None of the tests for interaction/non-homogeneity were significant. The conclusions of the study do not appear to be strongly influenced by any individual center.

Table 9 – Interaction/Non-Homogeneity Tests (Study 005)

	Breslow-Day p-value	Gail-Simon p- value (sponsor)	Gail-Simon p- value (reviewer)
Ketoconazole foam vs. Vehicle foam	0.5024	0.9991	0.9989
Ketoconazole foam vs. Ketoconazole cream	0.7290	0.6188	0.6023

Figure 1 – Treatment Success by Center (Study 005)



Note: Numbers represent the ketoconazole foam sample sizes. Randomization was 4:4:2:1 for ketoconazole foam : vehicle foam : ketoconazole cream : vehicle cream.

3.1.6 Secondary Efficacy Endpoints

The secondary efficacy endpoints were treatment success (0 or 1) on the individual signs (erythema, scaling, and induration). During the protocol review stage, the Agency also recommended evaluating an alternative treatment success defined as a score of 0 or 1 with at least 2 grades reduction for the ISGA, erythema, and scaling. The sponsor agreed to evaluate this definition of success as a secondary endpoint. The results of each of the secondary endpoints are consistent with the primary endpoint. For each sign and symptom, the two ketoconazole treatments had similar success rates and ketoconazole foam was superior to vehicle foam.

Table 10 – Secondary Efficacy Endpoints (Study 005)

	Ketoconazole Foam N=427	Vehicle Foam N=420	Ketoconazole Cream N=210	Vehicle Cream N=105
Erythema	263 (62%)	212 (50%)	129 (61%)	41 (39%)
Scaling	271 (63%)	204 (49%)	131 (62%)	39 (37%)
Induration	180 (42%)	133 (32%)	90 (43%)	26 (25%)
ISGA/Ery/Scal	214 (50%)	140 (33%)	103 (49%)	25 (24%)

¹ p-value for ketoconazole foam versus vehicle foam

² 97.5% lower confidence bound for ketoconazole foam versus ketoconazole cream

3.2 Evaluation of Safety

3.2.1 Extent of Exposure

The number of days in which treatment was used was similar for all four study arms (median = 29, mean = 28). However, in terms of total grams used, the foam arms had higher usage than the cream arms. Ketoconazole foam and vehicle foam had similar mean gram usage (67 vs. 70 g) which was higher than the ketoconazole cream and vehicle cream mean gram usage (33 vs. 47 g). Subjects treating with ketoconazole foam used roughly twice as many grams of drug product during the study as ketoconazole cream subjects.

3.2.2 Adverse Events

The most common adverse events observed in Study 005 were application site burning and application site reaction. These events occurred at similar rates on the two foam arms, and the rates on the foam arms were higher than on the two cream arms. Thus the reactions could be primarily due to a component of the foam vehicle. All other adverse events occurred at rates less than or equal to 1%. The most common adverse events are presented in Table 11.

Table 11 – Adverse Events Occurring in >1% of Subjects (Study 005)

	Ketoconazole Foam N=427	Vehicle Foam N=420	Ketoconazole Cream N=210	Vehicle Cream N=105
All Adverse Events	101 (24%)	96 (23%)	34 (16%)	7 (7%)
Application Site Burning	43 (10%)	41 (10%)	2 (1%)	2 (2%)
Application Site Reaction	17 (4%)	16 (4%)	3 (1%)	1 (1%)

Source: Vol. 8, Sec. 5.3.5.1, pg. 97-101.

The adverse event rates for application site burning and application site reaction were similar in Studies 002 and 005. The application site burning rate was about 10% for the foam arms and about 1% for the cream arms in both studies. The application site reaction rate was about 9% in Study 002 and 4% in Study 005 for the foam arms and 1% in both studies for the cream arms. In addition to the two Phase 3 studies (002 and 005) the sponsor also conducted a 24-subject (12 ketoconazole foam, 12 ketoconazole cream) bioavailability study (003). Subjects in Study 003 also treated their seborrheic dermatitis lesions twice daily for 4 weeks. The pooled adverse event rates for the most common adverse events (>1%) for the Phase 3 studies (002 and 005) and all 4-week studies (002, 003, 005) are presented in Table 12.

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Table 12 – Adverse Events Occurring in >1% of Subjects (Pooled 4-Week Studies)

	Ketoconazole Foam	Vehicle Foam	Ketoconazole Cream	Vehicle Cream
<i>Studies 002 & 005</i>	<i>N=660</i>	<i>N=497</i>	<i>N=443</i>	<i>N=181</i>
All Adverse Events	182 (28%)	122 (25%)	83 (19%)	29 (16%)
Application Site Burning	66 (10%)	49 (10%)	4 (1%)	2 (1%)
Application Site Reaction	38 (6%)	24 (5%)	6 (1%)	2 (1%)
<i>Studies 002,003¹ & 005</i>	<i>N=672</i>	<i>N=497</i>	<i>N=455</i>	<i>N=181</i>
All Adverse Events	188 (28%)	122 (25%)	88 (19%)	29 (16%)
Application Site Burning	67 (10%)	49 (10%)	4 (1%)	2 (1%)
Application Site Reaction	41 (6%)	24 (5%)	8 (2%)	2 (1%)

¹Study 003 is a 4-week bioavailability study in 12 ketoconazole foam and 12 ketoconazole cream subjects.
Source: Mod. 5, Vol. 8, Sec. 5.3.5.1, pg. 97-101, Mod. 2, Vol. 1, Sec. 2.7.4, pg. 6

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Comparable treatment effects were observed within the male and female subgroups, though the success rates in males were a few percent higher than in females in each arm. Among the age and race subgroups, the vast majority of subjects fall into the 18-64 age group and Caucasian race group, making it difficult to detect any age or race group patterns. However, in each subgroup success rates for ketoconazole foam were generally higher than for vehicle foam and generally similar to ketoconazole cream. Treatment success scores by age, gender, and race subgroups are presented in Table 13.

Table 13 – Treatment Success at Week 4 by Subgroup (Study 005)

		Ketoconazole Foam	Vehicle Foam	Ketoconazole Cream	Vehicle Cream
Age	12-17	14/28 (50%)	13/26 (50%)	5/9 (56%)	0/4 (0%)
	18-64	186/336 (55%)	137/322 (43%)	93/165 (56%)	27/82 (33%)
	≥65	39/62 (63%)	26/70 (37%)	20/36 (56%)	6/19 (32%)
Gender	Male	132/223 (59%)	93/213 (44%)	71/118 (60%)	18/50 (36%)
	Female	107/203 (53%)	83/205 (40%)	47/92 (51%)	15/55 (27%)
Race	Caucasian	172/309 (56%)	131/299 (44%)	81/150 (54%)	26/75 (35%)
	Black	39/71 (55%)	22/69 (32%)	20/35 (57%)	5/19 (26%)
	Hispanic	22/34 (65%)	13/29 (45%)	10/15 (67%)	1/8 (13%)
	Other	6/12 (50%)	10/21 (48%)	7/10 (70%)	1/3 (33%)

4.2 Other Special/Subgroup Populations

The treatment effects between ketoconazole foam and vehicle foam were similar in the groups with mild and moderate scores on the ISGA at baseline. The ketoconazole foam and cream success rates were similar for these groups as well. The number of subjects with severe disease at baseline was too small to draw comparisons. The success rates for

moderate subjects was higher than for mild subjects reflecting that moderate subjects could achieve scores of 0 or 1 to achieve success, while mild subjects had to achieve a score of 0. Treatment success rates by baseline ISGA scores are presented in Table 14.

Table 14 – Treatment Success at Week 4 by Baseline ISGA (Study 005)

	Ketoconazole Foam	Vehicle Foam	Ketoconazole Cream	Vehicle Cream
Mild	117/247 (47%)	84/247 (34%)	51/115 (44%)	15/65 (23%)
Moderate	116/167 (69%)	86/158 (54%)	63/86 (73%)	18/37 (49%)
Severe	6/12 (50%)	6/13 (46%)	4/9 (44%)	0/3 (0%)

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Study 005 had two objectives, (1) demonstrate that ketoconazole foam was superior to vehicle foam, and (2) demonstrate that ketoconazole foam was non-inferior to ketoconazole cream. Study 005 was conducted to fulfill the requirements of a 505(b)2 application. Study 005 was the second study evaluating ketoconazole foam conducted by the sponsor. The first study (002) was of a similar design, but Study 002 failed to demonstrate that ketoconazole foam was superior to vehicle foam ($p = 0.1318$), even though the non-inferiority criterion was technically met ($LCB = -3.5\%$). Since the sponsor was unable to demonstrate that ketoconazole foam was superior to its vehicle, the sponsor could not rely on Study 002 to demonstrate efficacy, and the Agency stated that the sponsor must conduct an additional study demonstrating that ketoconazole foam was superior to its vehicle and non-inferior to ketoconazole cream to establish efficacy. Using estimates from Study 002, the sponsor was able to adequately power Study 005 for its efficacy objectives.

The results of Studies 002 and 005 were generally consistent, with the biggest difference between the studies observed in the ketoconazole cream arm. In Study 002, ketoconazole foam trended higher than ketoconazole cream, even though the results were not statistically significant. However, in Study 005, ketoconazole foam and cream had nearly identical efficacy results. Of note, Study 002 used Nizoral cream while Study 005 used Teva ketoconazole cream since Nizoral cream was no longer available. It is not clear whether the minor difference in results is due to the change in manufacturer/formulation, or whether the differences simply reflect study-to-study variability. The results of Studies 002 and 005 are presented in Table 15. Study 005 met its pre-specified efficacy objectives.

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Table 15 – Treatment Success at Week 4

Study	Ketoconazole Foam	Vehicle Foam	Ketoconazole Cream	Vehicle Cream
002	N=233 116 (50%)	N=77 31 (40%) 0.1318 ¹	N=233 103 (44%) -3.5% ²	N=76 20 (26%)
005	N=427 239 (56%)	N=420 176 (42%) <0.0001 ¹	N=210 118 (56%) -8.4% ²	N=105 33 (31%)

¹ p-value for ketoconazole foam versus vehicle foam² 97.5% lower confidence bound for ketoconazole foam versus ketoconazole cream**5.2 Conclusions and Recommendations**

The efficacy of ketoconazole foam is supported by the demonstration of superiority to its vehicle and non-inferiority to a listed drug in Study 005. Study 005 met all pre-specified efficacy objectives. The sponsor has also conducted an earlier study that failed to demonstrate that ketoconazole foam was superior to its vehicle for the primary endpoint. The point estimates for the two studies are similar, though the earlier study was underpowered for demonstrating superiority.

Only two adverse events occurred in more than 1% of ketoconazole foam subjects: application site burning (10%) and application site reaction (4%). The rates for these two events were the same for both the ketoconazole foam and vehicle foam arms, but were higher than either of the cream arms. Similarly, the overall adverse event rates were approximately the same for both foam arms (~24%) but higher than the ketoconazole cream arm (16%).

Signatures/Distribution List

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STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

NDA/Serial Number: 21-738 / N-000
Drug Name: Extina (ketoconazole) foam, 2%
Indication(s): Seborrheic dermatitis
Applicant: Connetics
Dates: Submitted: 1/26/04
PDUFA: 11/26/04

Review Priority: Standard review

Biometrics Division: Division of Biometrics III (HFD-725)
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(HFD-540)
Clinical Team: Phyllis Huene, M.D.
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Keywords: 505 (b)(2), seborrheic dermatitis, non-inferiority

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1 Executive Summary

1.1 Conclusions and Recommendations

Extina (ketoconazole) foam 2% is not statistically superior to its vehicle in the treatment of seborrheic dermatitis; however, ketoconazole foam is non-inferior to ketoconazole cream. In Study KFD.C.002, ketoconazole foam had a slightly higher treatment success rate (achieving an ISGA score of 0 or 1 with improvement of at least 2 grades over baseline) than ketoconazole cream, (49.8% (foam) vs. 44.2% (cream)). Both the ITT and per protocol lower confidence bounds for the foam - cream difference are within the non-inferiority margin of -10% (-3.5% (ITT) and -7.0% (PP)). However, ketoconazole foam was not statistically superior to vehicle foam for the primary endpoint in either the ITT or per protocol populations (treatment success rates: 49.8% (ketoconazole foam) vs. 40.3% (vehicle foam), $p=0.1318$ (ITT)). Study 002 did demonstrate statistical significance between ketoconazole foam and its vehicle for the protocol-specified secondary endpoint, percent change in sum score of erythema, scaling, and induration ($p=0.013$). Because the study failed on the primary endpoint, however, an additional study demonstrating the statistical superiority of ketoconazole foam to its vehicle is needed to support the efficacy of ketoconazole foam.

1.2 Brief Overview of Clinical Studies

To support this 505 (b)(2) application, the sponsor conducted a single four-arm study to evaluate ketoconazole foam in the treatment of seborrheic dermatitis. Study KFD.C.002 enrolled 619 subjects in a 3:1:3:1 ratio to ketoconazole foam (233 subjects), vehicle foam (77 subjects), Nizoral (ketoconazole) cream (233 subjects), and vehicle cream (76 subjects). Subjects applied study treatment twice daily for 4 weeks. The primary efficacy endpoint was treatment success at Week 4, defined as achieving an Investigator's Static Global Assessment (ISGA) score of 0 or 1, with improvement of at least 2 grades over baseline. The study had two primary objectives: to demonstrate the superiority of ketoconazole foam to vehicle foam, and to demonstrate the non-inferiority of ketoconazole foam to ketoconazole cream with a non-inferiority margin of -10%.

1.3 Statistical Issues and Findings

The failure of Study 002 to detect a statistically significant difference between ketoconazole foam and its vehicle is a serious deficiency, as detecting a significant difference over vehicle is key to establishing the efficacy contribution of the ketoconazole. The sponsor has attempted to mitigate this problem by introducing additional analyses post hoc to support their claim that ketoconazole foam is indeed superior to its vehicle. The additional endpoints are (1) achieving an ISGA of 0 at Week 4, and (2) achieving ISGA, scaling, and erythema scores of 0 or 1, each improving by at least 2 grades at Week 4. However, these two analyses were selected from the large number of possible analyses for the data after seeing the non-significant result for the primary endpoint. Post hoc endpoints with small p-values do not provide convincing statistical evidence of a treatment effect in the absence of a significant result from the pre-specified primary endpoint, because with a large enough pool of potential endpoints it is often possible to find some which are significant due to chance alone, even in the absence of a treatment effect.

The vehicle has an important influence on the treatment success rate. Even though it was not a planned comparison, the foam vehicle is very nearly “significantly” superior to the cream vehicle (40.3% vs. 26.3%, $p=0.0701$). The foam arms had higher success rates than their corresponding cream arms (ketoconazole or vehicle). Although Study 002 demonstrates that ketoconazole foam is non-inferior to ketoconazole cream, and that ketoconazole cream is superior to its cream vehicle, the study did not have adequate power to demonstrate that ketoconazole foam is superior to its own foam vehicle. The study was powered to detect a 38% difference between ketoconazole foam and its vehicle, but the observed difference was only 9.5%. Study 002 was powered based on earlier studies of ketoconazole cream that had different endpoints. The sponsor had not conducted any prior studies involving ketoconazole foam and its vehicle.

2 Introduction

2.1 Overview

NDA 21-738/N-000 is a 505 (b)(2) application for Extina (ketoconazole) foam 2% in the treatment of seborrheic dermatitis. The reference listed drug is Nizoral (ketoconazole) cream 2%. Ketoconazole is an antifungal agent. The sponsor conducted a single four-arm study to support the safety and efficacy of ketoconazole foam in the treatment of seborrheic dermatitis. Study KFD.C.002 enrolled 619 subjects in a 3:1:3:1 ratio to ketoconazole foam (233 subjects), vehicle foam (77 subjects), Nizoral (ketoconazole) cream (233 subjects), and vehicle cream (76 subjects). Subjects applied study treatment twice daily for 4 weeks. All study centers were located in the United States.

2.2 Data Sources

The datasets for this application are archived at \\CDSESUB1\N21738\2004-04-23\crt\datasets\KFD.C.002 and \\CDSESUB1\N21738\2004-01-23\crt\datasets\KFD.C.002. The primary dataset used in this review was a_eff.xpt, which contained the efficacy data for Study 002.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study KFD.C.002 is a randomized, four-arm, multi-center study of the safety and efficacy of ketoconazole foam in the treatment of seborrheic dermatitis. The four arms of the study are ketoconazole foam 2%, Nizoral (ketoconazole) cream 2%, vehicle foam, and vehicle cream. The objectives of the study are to demonstrate the non-inferiority of ketoconazole foam to ketoconazole cream and the superiority of ketoconazole foam to vehicle foam. Subjects applied treatment twice daily to face, scalp, and chest lesions for four weeks, and were evaluated at baseline, Week 1, Week 2, and Week 4. Subjects were randomized in a 3:1:3:1 ratio to ketoconazole foam, vehicle foam, ketoconazole cream, and vehicle cream, respectively. A nurse/coordinator handled treatment dispensation so that the primary investigator would remain blind to the dosage form (foam or cream).

The primary efficacy endpoint is the proportion of subjects with an Investigator's Static Global Assessment (ISGA) of 0 or 1 at Week 4 (or end of treatment). Subjects with a baseline score of 2 must improve to a score of 0. The ISGA was based on the individual assessments of scaling, erythema, and induration, all graded with scores from 0 to 4. Refer to the Appendix (Table 12) for the complete scale for scaling, erythema, induration, and pruritus. The ISGA was defined as

- 0 = clear, except for minor residual discoloration
- 1 = majority of lesions have individual scores for scaling, erythema, and induration that averages 1
- 2 = majority of lesions have individual scores for scaling, erythema, and induration that averages 2
- 3 = majority of lesions have individual scores for scaling, erythema, and induration that averages 3
- 4 = majority of lesions have individual scores for scaling, erythema, and induration that averages 4

The sponsor's statistical analyses for the primary and secondary endpoints followed the protocol. The Cochran-Mantel-Haenszel test stratified on center was used to assess the superiority of ketoconazole foam to vehicle foam at the two-sided significance level of 0.05. The non-inferiority of ketoconazole foam to ketoconazole cream was assessed using a 97.5% one-sided lower confidence bound (using the normal approximation to the binomial) and a non-inferiority margin of -10%.

The secondary efficacy endpoint was the percent change from baseline to Week 4 in the sum of scores for erythema, scaling, and induration. If the assumption of normality was violated (from the Shapiro-Wilk test), this endpoint was to be rank-transformed. The data (or rank transform) were to be analyzed with ANOVA with terms for treatment and center (and treatment by center interaction, if significant).

The intent-to-treat (ITT) population was defined as all randomized subjects. Missing data were handled with last observation carried forward (LOCF). The per protocol population excluded subjects missing more than four sequential or eight total applications of study medication, and those using prohibited medications.

3.1.2 Subject Disposition and Demographics

Study 002 enrolled 619 subjects at 25 centers, 233 to ketoconazole foam, 233 to ketoconazole cream, 77 to vehicle foam, and 76 to vehicle cream. A total of 32 (5%) subjects discontinued early from the study. Table 1 displays the number of discontinued subjects by treatment arm. The most common reason for discontinuation was the subject's request to withdraw (7 subjects).

Table 1 – Reason for Study Discontinuation

	<i>Ketoconazole Foam</i>	<i>Ketoconazole Cream</i>	<i>Vehicle Foam</i>	<i>Vehicle Cream</i>
Number of Subjects	233	233	77	76
Subjects who Completed Study	220 (94%)	221 (95%)	73 (95%)	73 (96%)
Subjects who Discontinued	13 (6%)	12 (5%)	4 (5%)	3 (4%)
Reasons for Discontinuation				
Adverse Experience	0 (0%)	2 (1%)	2 (3%)	1 (1%)
Subject Non-Compliance	4 (2%)	1 (<1%)	1 (1%)	0 (0%)
Disease Progression	0 (0%)	3 (1%)	0 (0%)	1 (1%)
Subject Request to Withdraw	3 (1%)	3 (1%)	0 (0%)	1 (1%)
Lost to Follow-up	3 (1%)	1 (<1%)	1 (1%)	0 (0%)
Other Reason ^a	3 (1%)	2 (1%)	0 (1%)	0 (0%)

^a Includes clinical laboratory anomalies at baseline, failure to meet eligibility requirements, scheduling error, and work-related issues.

Source: Table 9, Mod. 5, Vol. 3, pg 56.

No significant differences between treatment arms were observed in demographic variables at baseline. Study 002 enrolled slightly more males than females. The study enrolled 38 (6%) pediatric subjects from ages 12 to 17, and 89 (14%) subjects over the age of 65. The majority of the subjects were Caucasian (78%), and 15% of the subjects were black. Table 2 presents the baseline demographic data.

Table 2 – Baseline Demographic Data

		<i>Ketoconazole Foam</i> N=233	<i>Ketoconazole Cream</i> N=233	<i>Vehicle Foam</i> N=77	<i>Vehicle Cream</i> N=76
<i>Sex</i>	Male	124 (53%)	132 (57%)	41 (53%)	32 (42%)
	Female	109 (47%)	101 (43%)	36 (47%)	44 (58%)
<i>Age (years)</i>	<18	16 (7%)	14 (6%)	5 (6%)	3 (4%)
	18 – 65	178 (76%)	188 (81%)	61 (79%)	65 (86%)
	> 65	39 (17%)	31 (13%)	11 (14%)	8 (11%)
<i>Race</i>	Caucasian	179 (77%)	187 (80%)	64 (83%)	52 (68%)
	Black	37 (16%)	28 (12%)	10 (13%)	16 (21%)
	Hispanic	13 (6%)	12 (5%)	3 (4%)	7 (9%)
	Asian	2 (1%)	2 (1%)	0 (0%)	0 (0%)
	Other	2 (1%)	4 (2%)	0 (0%)	1 (1%)

Source: Table 11, Mod. 5, Vol. 3, pg 59.

3.1.3 Pooling of Centers

Because Study 002 enrolled 619 subjects at 25 centers to 4 treatment arms in a 3:1:3:1 ratio, all centers enrolled relatively few subjects per treatment arm, particularly in the vehicle arms. The protocol specified that centers with fewer than 10 subjects per treatment arm would be pooled for the analyses. Since no center enrolled more than 6 subjects to a vehicle arm, all centers were pooled with at least one other center for the analysis. The 25 centers were pooled into 8 analysis centers by geographic region. The 8

analysis centers were of roughly equal size and each contained between 70 and 93 subjects (8 – 12 subjects per vehicle arm and 26 – 36 subjects per active arm). Efficacy results by center and the impact of pooling are discussed further in Section 3.1.7.2 below.

3.1.4 Primary Efficacy Endpoint

The primary efficacy endpoint was treatment success, defined as achieving a Week 4 ISGA score of 0 or 1 if the baseline ISGA was 3 or 4, or a Week 4 ISGA of 0 if the baseline ISGA was 2. Study 002 demonstrated statistically only one of the two protocol specified objectives for the primary efficacy endpoint. The two objectives for Study 002 were demonstrating the superiority of ketoconazole foam to its vehicle and demonstrating the non-inferiority of ketoconazole foam to ketoconazole cream. At Week 4, 49.8% of ketoconazole foam, 44.2% of ketoconazole cream, 40.3% of vehicle foam, and 26.3% of vehicle cream subjects achieved treatment success in the ITT population. The results from the per protocol population are similar. Table 3 presents the results from the ITT population and Table 4 presents the results from the per protocol population. For the first objective, the study fails to demonstrate the superiority of ketoconazole foam versus its vehicle with a p-value of 0.1318 in the ITT population. For the second objective, the 97.5% one-sided lower confidence bound (or lower bound of the 95% two-sided interval) for ketoconazole (foam - cream) is -3.5% for the ITT population and -7.0% for the per protocol population. Both lower bounds are within the protocol specified non-inferiority margin of -10%. In addition, ketoconazole cream is statistically superior to vehicle cream ($p=0.0053$, ITT). Thus, while the study demonstrates that ketoconazole foam is non-inferior to ketoconazole cream, it does not establish that the complete ketoconazole foam product provides benefit beyond the vehicle foam for the primary endpoint.

Table 3 – Week 4 Success Rates for ISGA=0 or 1 (Baseline ISGA=2 must have ISGA=0) (ITT)

<i>Treatment</i>	<i>Success Rate</i>	<i>Treatment</i>	<i>Success Rate</i>	
Ketoconazole Foam	116/233 (49.8%)	Ketoconazole Cream	103/233 (44.2%)	95% Conf. Int. (-3.47%, 14.63%)
Vehicle Foam	31/77 (40.3%)	Vehicle Cream	20/76 (26.3%)	
<i>p-value = 0.1318</i>		<i>p-value = 0.0053</i>		

Source: Table 15, Mod. 5, Vol. 3, pg. 66.

Table 4 – Week 4 Success Rates for ISGA=0 or 1 (Baseline ISGA=2 must have ISGA=0) (PP)

<i>Treatment</i>	<i>Success Rate</i>	<i>Treatment</i>	<i>Success Rate</i>	
Ketoconazole Foam	101/204 (49.5%)	Ketoconazole Cream	95/203 (46.8%)	95% Conf. Int. (-6.99%, 12.42%)
Vehicle Foam	28/69 (40.6%)	Vehicle Cream	19/68 (27.9%)	
<i>p-value = 0.1726</i>		<i>p-value = 0.0055</i>		

Source: Table 16, Mod. 5, Vol. 3, pg. 67.

3.1.5 Secondary Efficacy Endpoint

Ketoconazole foam is statistically superior to vehicle foam on the protocol-specified secondary endpoint of the percent change in sum score of erythema, scaling, and induration. Erythema, scaling, and induration were each evaluated on a scale from 0 to 4, so the sum score ranges from 0 to 12. Subjects were required to have a sum score of at least 5 at baseline. The distribution of the percent change from baseline to Week 4 in the sum score is skewed and the Shapiro-Wilk's test for normality is significant ($p < 0.01$). Therefore, per the protocol, the Sponsor analyzed the rank transform of the percent change variable. The p-value from the ANOVA on the percent change with terms for treatment and center for (ketoconazole - vehicle) foam is 0.013. The treatment by pooled center interaction was not included in the model because it was not significant ($p=0.9976$). The results of this analysis are presented in Table 5.

Table 5 –Sum Score of Erythema, Scaling, and Induration (ITT)

	<i>Ketoconazole Foam</i> N=233		<i>Vehicle Foam</i> N=77		p-value
	mean (sd)	median	mean (sd)	median	
Baseline	6.67 (1.55)	6	6.58 (1.21)	6	
Week 4	2.40 (2.72)	1	3.05 (2.59)	3	
Change	-4.27 (2.35)	-5	-3.53 (2.56)	-4	0.018 ^a
% Change	-66.16 (34.05)	-80.00	-53.79 (40.62)	-57.14	0.013 ^b
	<i>Ketoconazole Cream</i> N=233		<i>Vehicle Cream</i> N=76		p-value
	mean	median	mean	median	
Baseline	6.52 (1.39)	6	6.55 (1.08)	6	
Week 4	2.52 (2.40)	2	3.39 (2.48)	3	
Change	-4.00 (2.39)	-4	-3.16 (2.38)	-3	0.007 ^a
% Change	-61.58 (35.37)	-66.67	-48.68 (36.39)	-53.57	0.006 ^b

^a P-values from ANCOVA model for change from baseline to Week 4 with terms for treatment, pooled center, and baseline sum score.

^b P-values from ANOVA model for rank transformed percent change from baseline to Week 4 with terms for treatment and pooled center.

Source: Table 19, Mod. 5, Vol. 3. pg. 72 and Reviewer analysis.

Because the baseline sum scores are limited to a relatively small range (5 to 12), the percent change from baseline may be relatively unstable. Ranking does little to correct for the non-normality of the percent change, and the rank-transformed data are still highly skewed. To check the robustness of the sponsor's analysis, this reviewer also analyzed the change from baseline in the sum score, with baseline as a covariate, rather than the percent change. The results are similar to the sponsor's results, and are also presented in Table 5. The p-value for the comparison between ketoconazole and vehicle foam in this analysis is 0.018.

3.1.6 Sponsor's Post Hoc Analyses

Because Study 002 failed to demonstrate a statistically significant difference between ketoconazole foam and its vehicle for the primary endpoint, the sponsor considered some post hoc variations on the primary endpoint. The endpoints in this section were identified by the sponsor after seeing the failure on the primary endpoint. Both endpoints represent slightly stricter definitions of success than the primary endpoint, and both are nominally significant for the comparison between ketoconazole foam and its vehicle. The first endpoint counts only those subjects achieving an ISGA of 0 at Week 4 as a success. Since 16% of vehicle foam subjects achieved success under the original definition by achieving an ISGA of 1 (with baseline or 3 or 4) compared with 10% of ketoconazole foam subjects, removing these subjects from the success category allows the comparison of ketoconazole versus vehicle foam to have a larger difference and a p-value of 0.0177 when success is defined as achieving an ISGA of 0 at Week 4. The results from this analysis are presented in Table 6. The full bivariate table of baseline versus Week 4 ISGA scores is presented in Table 13 in the Appendix.

Table 6 – Week 4 Success Rates for ISGA=0 (ITT)

<i>Treatment</i>	<i>Success Rate</i>	<i>Treatment</i>	<i>Success Rate</i>	
Ketoconazole Foam	92/233 (39.5%)	Ketoconazole Cream	77/233 (33.0%)	95% Conf. Int. (-2.27%, 15.15%)
Vehicle Foam	19/77 (24.7%)	Vehicle Cream	13/76 (17.1%)	
<i>p-value</i> = 0.0177		<i>p-value</i> = 0.0083		

Note: post hoc endpoint.

Source: Table 17, Mod. 5, Vol. 3, pg. 69.

The sponsor's second proposal for modifying the primary endpoint is to require that both the individual scores for erythema and scaling must individually improve to 0 or 1 (each improving by at least 2 grades) in addition to the ISGA achieving 0 or 1 (improving by at least 2 grades). Like the previous endpoint, this modification eliminates more vehicle than active foam subjects from the success category and the p-value for this comparison is 0.0300. The results of this analysis are presented in Table 7. Section 3.1.7.1 presents further discussion regarding results based on post hoc analyses.

Table 7 – Week 4 Success Rates for ISGA=0 or 1, Erythema=0 or 1, and Scaling=0 or 1 (each must improve by at least 2 grades) (ITT)

<i>Treatment</i>	<i>Success Rate</i>	<i>Treatment</i>	<i>Success Rate</i>	
Ketoconazole Foam	91/233 (39.1%)	Ketoconazole Cream	76/233 (32.6%)	95% Conf. Int. (-2.25%, 15.13%)
Vehicle Foam	20/77 (26.0%)	Vehicle Cream	15/76 (19.7%)	
<i>p-value</i> = 0.0300		<i>p-value</i> = 0.0347		

Note: post hoc endpoint.

Source: Table 18, Mod. 5, Vol. 3, pg. 70.

3.1.7 Reviewer Analyses

3.1.7.1 Comparison of Multiple Post Hoc Endpoints

The sponsor identified two post hoc endpoints with p-values less than 0.05 to support their claim that ketoconazole has additional benefit beyond the vehicle foam. However, these endpoints are only two ways in which the data from the ISGA, scaling, and erythema scores could be analyzed, and p-values for endpoints selected in a post hoc search for significance can not be directly interpreted. To provide some context for the sponsor's post hoc endpoints, this reviewer selected six additional endpoints based on the ISGA comparing ketoconazole foam to its vehicle. The six endpoints involved various ways to dichotomize the ISGA or were analyses on the full distribution of the ISGA. Some of the endpoints are nominally significant while others are not. The p-values from these analyses are presented in Table 8. Thus, it is important keep in mind that the post hoc endpoints selected by the sponsor were chosen to provide the "most convincing" clinical and statistical evidence. P-values from post hoc tests cannot be interpreted in the same way as those from prespecified tests as the error rate is not controlled. In order to control the error rate, analyses must be specified in advance so that an appropriate adjustment for multiplicity can be applied. If the pool of possible analyses is large enough, a "significant" result due to chance alone can often be identified even in the absence of any treatment effect.

Table 8 – CMH P-values for Various Post Hoc Endpoints (ITT)

Endpoint	P-value
<i>Protocol specified primary endpoint</i>	
ISGA=0 or 1, must improve by ≥ 2 units	0.1318
<i>Sponsor's post hoc endpoints</i>	
ISGA=0	0.0177
ISGA, erythema, and scaling=0 or 1, must improve by ≥ 2 units	0.0300
<i>Other possible post hoc endpoints</i>	
ISGA ≤ 1	0.0324
ISGA ≤ 2	0.7689
Improve by ≥ 1 unit	0.1101
Improve by ≥ 2 units	0.1495
Shift in distribution (modridit scores) ^a	0.0158
Shift in distribution (table scores) ^a	0.0385

^a CMH test that row mean scores differ

Source: Reviewer analysis.

3.1.7.2 Efficacy by Center

Since Study 002 enrolled subjects on four (unequally allocated) arms at 25 centers, each center enrolled relatively few subjects per treatment arm. Due to the small sample sizes on the vehicle arms (most centers had 3 or fewer subjects per vehicle arm), the treatment with the highest success rate was not consistent across centers. For 10 of the 25 centers, the treatment with the highest success rate at that center was one of the vehicle treatments. Even after pooling, a vehicle arm had the highest treatment success estimate

in two of the eight pooled centers. However, the Breslow-Day test using the pooled centers was not significant for the comparison between the ketoconazole and vehicle foams ($p=0.7794$) or for the comparison between ketoconazole foam and ketoconazole cream ($p=0.9327$), indicating that the test was unable to detect a significant interaction for this data. Since the data were heavily pooled, tests for interaction test for more of a regional interaction effect than a true center interaction effect, and any interaction at the center level is likely obscured. Treatment success rates by pooled center are presented in Table 14 in the Appendix. That treatment with the highest success rate varied across the centers appears to reflect the fact that the success rates for ketoconazole foam, ketoconazole cream, and vehicle foam were similar.

To further assess the impact of the pooling algorithm on the primary analysis, this reviewer conducted a CMH analysis using individual centers rather than pooled centers as the strata and a chi-square test which ignores the effect of center. The results are similar to the sponsor's primary analysis with p-values of 0.1178 for the CMH analysis and 0.1467 for the chi-square analysis for the comparison of ketoconazole foam and its vehicle in the ITT population.

3.1.7.3 Treatment Success by Week

Treatment success rates improved at each visit over the four weeks of the trial. The four treatment arms were generally ranked in the order ketoconazole foam, ketoconazole cream, vehicle foam, and vehicle cream at each visit. The treatment success rates by visit are presented in Table 9.

Table 9 – Treatment Success by Week (ITT)

Week	<i>Ketoconazole Foam</i> N=233	<i>Ketoconazole Cream</i> N=233	<i>Vehicle Foam</i> N=77	<i>Vehicle Cream</i> N=76
1	36 (15.5%)	33 (14.2%)	11 (14.3%)	6 (7.9%)
2	71 (30.5%)	66 (28.3%)	16 (20.8%)	15 (19.7%)
4	116 (49.8%)	103 (44.2%)	31 (40.3%)	20 (26.3%)

Source: Reviewer analysis.

3.2 Evaluation of Safety

3.2.1 Extent of Exposure

The median number of days on treatment was the same (29 days) for all four treatment groups (means: 28.3 to 28.9). Within each dosage form, the amount of study drug used was similar for both the active and vehicle arms. Ketoconazole and vehicle foam subjects both used an average of 72.0 g of study drug during the study. Ketoconazole cream subjects used an average of 49.8 g and vehicle cream subjects used an average of 50.3 g of study drug during the study.

3.2.2 Adverse Events

Adverse event (AE) rates were similar within the same dosage form (foam or cream) and the rates were slightly higher in the foam arms than the cream arms. During the study, 178 of 619 (29%) subjects reported adverse events. The rates of adverse events were highest on the foam arms with 35% of ketoconazole foam and 34% of vehicle foam subjects reporting AEs. The percentages of subjects with AEs were lower on the cream arms with 21% of ketoconazole cream and 29% of vehicle cream subjects reporting AEs. The numbers of subjects reporting AEs for those AEs occurring in more than 3% of subjects are listed in Table 10. Application site burning and Application site reaction NOS were the most common AEs and were more common in the foam arms (9 – 10%) than the cream arms (0 – 1%).

Table 10 – Number of Subjects with Adverse Events (>3% in any arm)

	Ketoconazole Foam N=233	Ketoconazole Cream N=233	Vehicle Foam N=77	Vehicle Cream N=76
All Adverse Events	81 (35%)	49 (21%)	26 (34%)	22 (29%)
Application site burning	23 (10%)	2 (1%)	8 (10%)	0 (0%)
Application site reaction NOS	21 (9%)	3 (1%)	8 (10%)	1 (1%)
Nasopharyngitis	7 (3%)	6 (3%)	4 (5%)	1 (1%)
Headache NOS	8 (3%)	6 (3%)	0 (0%)	2 (3%)

Source: Table 54, Mod. 5, Vol. 3, pg. 158.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Treatment success rates for ketoconazole foam were similar in males and females (50%), higher in black subjects (59%) than Caucasian subjects (49%), and higher in adult subjects (53%) than in pediatric subjects (31%) or geriatric subjects (44%). Within each subgroup, ketoconazole foam had the highest success rate of the four treatments, except for within the relatively small pediatric and geriatric subgroups. The vehicle treatment arms were relatively small and the variability in the success rates on the vehicle arms across subgroups could be due to the small sample sizes. Treatment success rates for the primary-efficacy endpoint by subgroup are presented in Table 11.

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Table 11 – Week 4 Success Rates by Subgroup for ISGA=0 or 1 (Baseline ISGA=2 must have ISGA=0) (ITT)

		<i>Ketoconazole Foam</i>	<i>Ketoconazole Cream</i>	<i>Vehicle Foam</i>	<i>Vehicle Cream</i>
<i>Sex</i>	Male	62/124 (50%)	61/132 (46%)	18/41 (44%)	12/32 (38%)
	Female	54/109 (50%)	42/101 (42%)	13/36 (36%)	8/44 (18%)
<i>Race</i>	Caucasian	87/179 (49%)	87/187 (47%)	25/64 (39%)	18/52 (35%)
	Black	22/37 (59%)	10/28 (36%)	4/10 (40%)	2/16 (13%)
	Other	7/17 (41%)	6/18 (33%)	2/3 (67%)	0/8 (0%)
<i>Age (years)</i>	<18	5/16 (31%)	5/14 (36%)	1/5 (20%)	0/3 (0%)
	18 – 65	94/178 (53%)	87/188 (46%)	27/61 (44%)	16/65 (25%)
	> 65	17/39 (44%)	11/31 (35%)	3/11 (27%)	4/8 (50%)

Source: Tables 24-26, Mod. 5, Vol. 3, pg. 80-82.

4.2 Other Special/Subgroup Populations

Not Applicable.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Study 002 fails to provide convincing evidence that ketoconazole foam is superior to its vehicle. The test for the protocol-specified primary endpoint, treatment success, is not statistically significant with a p-value of 0.1318 (ITT population). In the study, 49.8% (116/233) of ketoconazole foam and 40.3% (31/77) of vehicle foam subjects achieved treatment success. Study 002 is the only study conducted by the sponsor comparing ketoconazole foam to its vehicle. At the Pre-IND Guidance Meeting held on April 9, 2001, the Agency advised the sponsor to conduct Phase 2 studies to estimate treatment effects prior to proceeding to Phase 3. However, the sponsor elected to proceed directly to Phase 3 and did not conduct any Phase 2 studies for this drug product. Therefore, the sponsor has not provided any additional information that could support that ketoconazole foam is superior to its vehicle. The sponsor used published data for ketoconazole cream to power the study. Based on these results the sponsor assumed that ketoconazole foam would have a success rate of around 73% and vehicle would have a success rate of about 35%. Since the observed treatment effect delta was only about one-fourth the anticipated delta at the planning stage, the sponsor's decision to use a 3:1 randomization ratio appears to have left the study underpowered for the ketoconazole foam versus vehicle foam comparison.

Since the study allocated more resources to the comparison between ketoconazole cream and ketoconazole foam, even though ketoconazole foam did not statistically beat its vehicle, we have confidence that the treatment success rate for ketoconazole foam is comparable to ketoconazole cream. In the study, 49.8% (116/233) of ketoconazole foam and 44.2% (103/233) of ketoconazole cream subjects achieved treatment success. Based on the 97.5% lower confidence bound for ketoconazole foam – ketoconazole cream we are confident that the success rate for ketoconazole foam is no more than 3.5% lower than the success rate for ketoconazole cream in the ITT population (7.0% for the per protocol

population), and both of these bounds lie within the non-inferiority margin of 10%. In addition, ketoconazole cream is statistically superior to the cream vehicle (44.2% vs. 26.3%, $p=0.0053$). Thus ketoconazole foam has a comparable treatment success rate to ketoconazole cream, but we do not have statistical evidence that the ketoconazole adds benefit beyond the benefit of the foam vehicle in the ketoconazole foam product.

Exploratory post hoc analyses indicate that higher proportions of successful subjects in the active arms had ISGA scores of 0 than in the vehicle arms. For example, 92/116 (79%) of successful ketoconazole foam subjects and 77/103 (75%) of successful ketoconazole cream subjects had a final score of 0 compared to 19/31 (61%) of successful vehicle foam subjects and 13/20 (65%) of successful vehicle cream subjects. Thus when only subjects who achieve a final ISGA score of 0 are counted as success, the p-value for the ketoconazole foam versus vehicle foam comparison is less than 0.05 (39.5% vs. 24.7%, $p=0.0177$). However, it is not appropriate to use an endpoint identified post hoc to claim significance when the primary analysis is non-significant, as an endpoint selected because it is the most significant of the many possible analyses can vastly overestimate the strength of evidence.

5.2 Conclusions and Recommendations

Ketoconazole foam is non-inferior to ketoconazole cream, but ketoconazole foam is not statistically superior to its vehicle in the treatment of seborrheic dermatitis. In the single study, ketoconazole foam had a slightly higher treatment success rate (achieving an ISGA score of 0 or 1 with improvement of at least 2 grades over baseline) than ketoconazole cream, (49.8% (foam) vs. 44.2% (cream) with lower confidence bound -3.5%). However, it is not possible to state with confidence that the ketoconazole adds additional benefit beyond that of the vehicle for the primary endpoint (49.8% (ketoconazole foam) vs. 40.3% (vehicle foam), $p=0.1318$). Study 002 did demonstrate statistical significance between ketoconazole foam and its vehicle for the protocol-specified secondary endpoint, percent change in sum score of erythema, scaling, and induration. Because the study failed on the primary endpoint, however, an additional study is needed to demonstrate the statistical superiority of ketoconazole foam to its vehicle.

The sponsor has provided results from two additional analyses ((1) achieving an ISGA of 0, and (2) achieving ISGA, scaling, and erythema scores of 0 or 1, each improving by at least 2-grades) that they claim provide supporting evidence that ketoconazole foam is superior to its vehicle. However, these analyses were selected after seeing the non-significant result for the primary endpoint from the large number of possible analyses that could be conducted with the data. Post hoc endpoints with small p-values do not provide convincing statistical evidence of a treatment effect in the absence of a significant result from the pre-specified primary endpoint, because with a large enough pool of potential endpoints it is often possible to find some which are significant due to chance alone, even if there is no treatment effect.

Appendix – Additional Tables

Table 12 – Seborrheic Dermatitis Grading Scale for Study KFD.C.002

<i>Score</i>	<i>Scaling</i>	<i>Erythema</i>	<i>Induration</i>	<i>Pruritus</i>
0	Normal skin with rare fine scale	Normal skin without erythema; may have residual hyperpigmentation	Normal skin without induration	No itching
1	Minimal; occasional fine scales over less than 10% of the lesions	Faint erythema	Minimal papule or plaque elevation; approximately 0.2 mm	Minimal: rarely aware of itching
2	Mild; fine scales predominate	Light red erythema	Mild plaque elevation; approximately 0.5 mm	Mild: only aware of itching at times; only present when relaxing; not present when focused on other activities
3	Moderate; coarse scales predominate	Moderate red coloration	Moderate papule or plaque elevation; approximately 1 mm	Moderate: often aware of itching; annoying; sometimes disturbs sleep and daytime activities
4	Severe; thick tenacious scales predominate	Dusky to deep red coloration	Severe papule or plaque elevation; approximately 1.5 mm	Severe: constant itching; distressing; frequent sleep disturbance; interferes with activities

Source: Appendix B, Mod. 5, Vol. 4, pg. 373.

Table 13 – Baseline by Week 4 ISGA Results (ITT)

Baseline ISGA	Week 4 ISGA					
	<i>Ketoconazole Foam</i> (N=233)			<i>Ketoconazole Cream</i> (N=233)		
	0	1	≥2	0	1	≥2
2	69 (30%)	58 (25%)	25 (11%)	57 (24%)	70 (30%)	28 (12%)
3	22 (9%)	23 (10%)	25 (11%)	20 (9%)	26 (11%)	30 (13%)
4	1 (<1%)	1 (<1%)	9 (4%)	0	0	2 (1%)
	<i>Vehicle Foam</i> (N=77)			<i>Vehicle Cream</i> (N=76)		
	0	1	≥2	0	1	≥2
2	18 (23%)	17 (22%)	15 (19%)	12 (16%)	24 (32%)	16 (21%)
3	1 (1%)	12 (16%)	13 (17%)	1 (1%)	7 (9%)	14 (18%)
4	0	0	1 (1%)	0	0	2 (3%)

Shaded cells represent a successful outcome for the primary efficacy endpoint.

Source: Reviewer Analysis.

Table 14 – Treatment Success by Pooled Center (ITT)

Pooled Center	<i>Ketoconazole Foam</i> N=233	<i>Ketoconazole Cream</i> N=233	<i>Vehicle Foam</i> N=77	<i>Vehicle Cream</i> N=76
1	17/30 (57%)	15/30 (50%)	5/11 (45%)	6/11 (55%)
2	16/30 (53%)	13/30 (43%)	5/9 (56%)	3/9 (33%)
3	12/31 (39%)	11/30 (37%)	6/11 (55%)	2/11 (18%)
4	11/27 (41%)	11/27 (41%)	2/9 (22%)	0/9 (0%)
5	24/34 (71%)	22/36 (61%)	6/12 (50%)	4/11 (36%)
6	12/27 (44%)	14/26 (54%)	3/9 (33%)	3/8 (38%)
7	12/27 (44%)	8/27 (30%)	2/8 (25%)	1/9 (11%)
8	12/27 (44%)	9/27 (33%)	2/8 (25%)	1/8 (13%)

Pooled Centers:

1 = 20, 22, 25 (New York)

5 = 6, 9, 10 (Texas)

2 = 8, 18, 21, 26 (Northeast)

6 = 12, 15, 16, 29 (Great Plains)

3 = 7, 13, 30 (South)

7 = 5, 28 (West)

4 = 11, 17, 23 (Great Lakes)

8 = 27, 31, 32 (California)

Source: Reviewer Analysis

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch

Date: 9/3/2004

Statistical Team Leader: Mohamed Alosh

cc:

Archival NDA

HFD-540/Wilkin

HFD-540/Luke

HFD-540/Huene

HFD-540/Giroux

HFD-700/Anello

HFD-700/Dubey

HFD-725/Huque

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Kathleen Fritsch
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Mohamed Alesh
9/8/04 12:59:00 PM
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Concur with review

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**Statistical Review and Evaluation
Fileability Review**

NDA: 21-738/N-000
Name of Drug: Ketoconazole Foam, 2%
Applicant: Connetics
Indication: Seborrheic Dermatitis
Fileability Meeting Date: 3/15/04
User Fee Date: 11/26/04
Statistical Reviewer: Kathleen Fritsch, Ph.D., HFD-725
Clinical Reviewer: Phyllis Huene, M.D., HFD-540
Project Manger: Lea Carrington, HFD-540

Clinical Studies: KFD.C.002 (4-arm Phase 3 trial: ketoconazole foam and cream, vehicle foam and cream)

I. ORGANIZATION AND DATA PRESENTATION	YES/NO/NA
A. Is there a comprehensive table of contents with adequate indexing and pagination?	YES
B. Are the original protocols, protocol amendments, and proposed label provided?	YES
C. Are the following tables/listings provided in each study report?	
1. Patient profile listings by center, for all enrolled patients.	YES
2. Discontinued subject tables by center (includes reason and time of loss).	YES
3. Subgroup analysis summary tables (gender, age, race, etc.)	YES
4. Adverse event listings by center and time of occurrence.	YES
D. Have the data been submitted electronically?	YES
1. Has adequate documentation of the data sets been provided?	NO
2. Do the data appear to accurately represent the data described in the study reports?	YES
3. Can the data be easily merged across studies and indications?	NA

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II. STATISTICAL METHODOLOGY	YES/NO/NA
A. Are all primary efficacy studies of appropriate design to meet basic approvability requirements within current Division policy, or to the extent agreed upon previously with the sponsor by the Division?	YES
B. For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population and per protocol population?	YES
C. Based on the summary analyses of each study,	
1. Are the analyses appropriate for the type of data collected, the study design, and the study objectives (based on protocol objectives and proposed labeling claims?)	YES
2. Are the intent-to-treat and per protocol patient analyses properly performed?	YES
3. Has missing data been appropriately handled?	YES
4. Have multiplicity issues (regarding endpoints, timepoints, or dose groups) been adequately addressed?	YES
5. If interim analyses were performed, were they planned in the protocol and appropriate significance level adjustments made?	NA
D. Were sufficient and appropriate references included for novel statistical approaches?	NA
E. Are all of the pivotal studies complete?	YES
F. Has the safety data been comprehensively and adequately summarized?	YES

III. FILEABILITY CONCLUSIONS

From a statistical perspective this submission, or indications therein, is reviewable with only minor further input from the sponsor.

Comment on submission: According to the submission, ketoconazole foam is non-inferior to ketoconazole cream, but ketoconazole foam is not statistically superior to vehicle foam for the primary endpoint.

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Information Request: The biostatistics reviewer requests the following information from the Applicant:

1. Submit an electronic analysis data set in SAS transport format for Study KFD.C.002 with (at minimum) the following variables. Adequately define any variables and codes within variables that are not immediately obvious.

Patient #

Center #

Pooled Center #

Treatment

Race

Sex

Age

Visit (provide an explanation for codes, especially those > 4)

Visit date

Extent of body involvement

Investigator's Static Global Assessment

Pruritus severity

Target area size

Lesion location

Erythema

Scaling

Induration

Subject's Global Assessment

ISGA success (ISGA=0 or 1, unless baseline=2 then ISGA=0 only)

Imputed ISGA success using LOCF (with flag identifying imputed observations)

Sum of erythema, scaling, and induration

Percent change from baseline of sum of erythema, scaling, and induration

Per protocol population status

2. Provide a more detailed description of the following variables and their codes from the datasets for Study KFD.C.002

PGSTATUS (What is pgstatus=3?)

VISIT (What are visit=9 and visit=10?)

3. Provide explanation for the following subjects in Study KFD.C.002
 - a. Subject 016-185 – why are three visits listed as Visit 1?
 - b. Subject 022-228 – why are there two Visit 4s with different efficacy assessments from the same date?

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

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

cc:
Archival NDA 21-738/N-000
HFD-540/Wilkin
HFD-540/Luke
HFD-540/Huene
HFD-540/Carrington
HFD-700/Anello
HFD-725/Huque
HFD-725/Alosch
HFD-725/Fritsch

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Mohamed Alesh
3/16/04 12:32:20 PM
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