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RESEARCH**

APPLICATION NUMBER:

21-738

MEDICAL REVIEW

Team Leader Memo for NDA 21-738
Extina (ketoconazole, USP) Foam, 2%

Letter date: 12/11/06

CDER Stamp date: 12/12/06

PDUFA goal date: 6/12/06

Applicant: Connetics Corporation

Indication sought: topical treatment of seborrheic dermatitis

Primary Medical Reviewer: Brenda Carr, MD

Project Manager: Melinda Bauerlien

The applicant has requested approval for Extinal (ketoconazole) Foam, 2% for the topical treatment of seborrheic dermatitis in immunocompetent patients 12 years of age and older.

Regulatory Background

The applicant's initial submission (letter date January 23, 2004) was not approved (letter date November 23, 2004), as the applicant's product did not demonstrate superiority to its vehicle, although it was non-inferior to the listed drug, Nizoral cream. The applicant was informed that they would need to submit another pivotal study demonstrating superiority of their product to its vehicle and non-inferiority to a listed drug. In the resubmission, the applicant chose Teva ketoconazole cream, as Nizoral cream was no longer marketed.

The applicant pursued approval of their product under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, with Nizoral (ketoconazole) Cream, 2% and ketoconazole cream, 2% (manufactured by Teva) as the listed drugs in their submission and resubmission, respectively. To construct a clinical bridge to the Agency's findings of safety for the listed drugs the applicant conducted a comparative pharmacokinetic study with Extina Foam, Nizoral Cream, and oral ketoconazole; the applicant also conducted comparative clinical trials.

Efficacy

The applicant conducted a single four-arm pivotal trial comparing Extina Foam, vehicle foam, ketoconazole 2% cream (Teva), and vehicle cream used twice daily for four weeks in 1,162 subjects with mild to severe seborrheic dermatitis. The reader is referred to the excellent reviews by Dr. Kathleen Fritsch (biostatistics) and Dr. Brenda Carr (clinical) for a thorough discussion of the trials and results. Both reviewers found that the applicant convincingly demonstrated that the applicant's product, Extina Foam, is superior to vehicle and non-inferior to ketoconazole 2% cream (Teva) for the treatment of mild to severe seborrheic dermatitis, the two comparisons providing replication.

Safety

The reader is referred to the clinical review by Dr. Brenda Carr for a full discussion of the safety database. The safety population included 672 subjects with seborrheic dermatitis who were treated with Extina Foam. There were no deaths or serious adverse events

attributed to study drug. The most common treatment-related adverse events occurred at the application site (application site burning and application site reaction) and were similar for Extina Foam and vehicle foam. Topical safety studies in the resubmission (phototoxicity and photoallergenicity) demonstrated an irradiation-independent contact dermatitis, which confirmed the contact sensitization signal identified in the contact sensitization studies reviewed in the original submission. The application site reactions and potential for contact sensitization are adequately addressed in labeling.

Chemistry

The reader is referred to the review by Dr. Jane Chang for full discussion of the chemistry, manufacturing and control issues.

~~_____~~ The applicant has agreed to acceptance criteria for ~~_____~~, and although not a phase 4 commitment, ~~_____~~.

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Post-marketing Commitments

The applicant has been requested to conduct a clinical study to assess the long-term safety of their product, and their agreement is anticipated.

Conclusion

In a single, robust pivotal trial, and in combination with supportive studies, the applicant has demonstrated the safety and efficacy of Extina Foam applied twice daily for four weeks for the treatment of mild to severe seborrheic dermatitis in immunocompetent adults and children twelve years and older. I concur with the recommendations of the multi-disciplinary review team for approval for marketing.

Jill Lindstrom, MD

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/s/

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CLINICAL REVIEW of NDA 21-738

Application Type 505(b)(2)
Submission Number 000
Submission Code BZ

Letter Date December 11, 2006
Stamp Date December 12, 2006
PDUFA Goal Date June 12, 2007

Reviewer Name Brenda Carr, M.D.
Review Completion Date May 14, 2007

Established Name ketoconazole 2%
(Proposed) Trade Name Extina
Therapeutic Class antifungal
Applicant Connetics Corporation

Priority Designation P

Formulation foam
Dosing Regimen twice daily for four weeks
Indication seborrheic dermatitis
Intended Population 12 years and older

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Clinical Review
Brenda Carr, M.D.
NDA 21-738 N-000
Extina (ketoconazole foam)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This resubmission proposes marketing of a foam formulation of ketoconazole 2% for “the topical treatment of seborrheic dermatitis in patients 12 years of age and older.” Ketoconazole is currently marketed in tablet, cream, gel and shampoo formulations. Thus, the applicant’s product represents a new dosage form. The proposed dosing regimen is twice daily for four weeks, and the proposed trade name is Extina®. The applicant’s product is not marketed in any country.

The application was originally submitted in January 2004 (correspondence date January 23; receipt date January 26) and included data from one Phase 3 trial, Study KFD.C.002. The application was not approved on November 23, 2004. Per the action letter, the stated deficiency was:

“The data from study KFD.C.002 do not support the conclusion that ketoconazole foam, 2%, is effective for the treatment of seborrheic dermatitis. Study KFD.C.002 was designed to evaluate whether ketoconazole foam was superior to its vehicle and non-inferior to the active comparator. However, superiority was not demonstrated for the primary efficacy parameter that was defined prospectively. Because this deficiency cannot be addressed with additional analyses of study KFD.C.002, 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.”

The resubmission provided the results from a new, four-arm Phase 3 study, in which the sponsor demonstrated that their product is safe and effective for the treatment of seborrheic dermatitis in patients 12 years and older under the proposed conditions of use of twice daily for four weeks.

From a clinical perspective, it is recommended that the application be approved.

05(b)(2)

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no recommendations for any specific risk management activities.

1.2.2 Required Phase 4 Commitments

The applicant should conduct a study in which the long-term safety of their product is assessed, as per the ICH E1A guidelines.

Protocol Submission: by December 28, 2007
Study Start: by June 2, 2008
Final Report Submission: by June 30, 2011

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

For the resubmission, the applicant conducted one adequate and well-controlled, pivotal Phase 3 study, KFD.C.005, in which their ketoconazole 2% foam was compared to its vehicle and to ketoconazole 2% cream in treatment of mild to severe seborrheic dermatitis.

A total of 1,162 subjects were randomized in the study (4:4:2:1): 427 subjects to ketoconazole foam, 420 subjects to vehicle foam, 210 subjects to ketoconazole cream, and 105 subjects to vehicle cream. Subjects were treated with study product twice daily for four weeks (even if lesions cleared). Primary efficacy was assessed by "Treatment success", defined as the proportion of subjects who had an Investigator's Global Assessment of 0 or 1 at Week 4 (end of treatment). Subjects with a baseline score of 2 had to have a final score of 0 to be judged a success.

1.3.2 Efficacy

The primary analyses consisted of demonstration of the superiority of ketoconazole foam over vehicle foam and the non-inferiority of ketoconazole foam to ketoconazole cream. The results of the sponsor's primary analyses results are presented in the following table:

Sponsor Table 14.2.3: Treatment Success at Week 4

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
Treatment Success	239 (56%)	176 (42%)	118 (56%)	33 (31%)
p-value		<.0001		
Lower Confidence Limit			-8.42%	

The applicant adequately demonstrated that their product, ketoconazole foam, 2%, was statistically superior to its vehicle and non-inferior to the active comparator, ketoconazole cream, 2%, in the treatment of mild to severe seborrheic dermatitis. Ketoconazole foam was statistically superior to its vehicle in the treatment of the erythema, scaling and induration of seborrheic dermatitis (secondary endpoints), although the reviewer does not consider induration to be a classic sign of seborrheic dermatitis.

1.3.3 Safety

The safety database consists of the combined safety data from three clinical studies conducted for the evaluation of the applicant's product in the treatment of seborrheic dermatitis: a bioavailability study, and the two Phase 3 studies (KFD.C.002 and KFD.C.005). When all three studies are considered, a total of 672 subjects were treated with the applicant's product twice daily for four weeks.

The most common adverse events in the safety population were "Application site burning" (10% of subjects in the ketoconazole foam group) and "Application site reaction NOS" (4%). "Application site reaction" was the third most common event (3%). The most common treatment-related adverse event in the safety population for ketoconazole foam treated subjects was "application site burning": 67 (10%) in the ketoconazole foam group [49 (10%) in the vehicle foam group, 4 (1%) in the ketoconazole cream group, and 2 (1%) in the vehicle cream group]. The second most common treatment-related adverse event in the safety population for this group was "application site reaction NOS": 24 (4%) in the ketoconazole foam group [8 (2%) in the vehicle foam group, 5 (1%) in the ketoconazole cream group, and 1 (1%) in the vehicle cream group]. Other treatment-related adverse events that occurred at $\geq 1\%$ in the ketoconazole foam group were:

- application site reaction in 17 subjects (3%) [16 (3%) in the vehicle foam group, 3 (1%) in the ketoconazole cream group, and 1 (1%) in the vehicle cream group],
- application site pruritus in 5 subjects (1%) [4 (1%) in the vehicle foam group, 2 (<1%) in the ketoconazole cream group, and 2 (1%) in the vehicle cream group], and
- application site erythema in 4 subjects (1%).

As was the case for the total safety population, "Application site burning" was the most common adverse event in the sub-group analyses, and this event was generally reported at the same rate as in the total safety population, i.e. approximately 10%.

An adequate number of subjects were exposed to the applicant's product to characterize its safety in the short-term (4 weeks). Doses and durations of exposure were adequate to assess the safety of the product for its intended use. Topical safety was adequately evaluated by clinical assessments at each study visit in the pivotal trial and by the conduct of formal dermal safety studies. Long-term safety has not been evaluated.

1.3.4 Dosing Regimen and Administration

The applicant did not conduct dose-ranging studies.

1.3.5 Drug-Drug Interactions

The applicant did not conduct drug interaction studies.

1.3.6 Special Populations

There are no special dosing recommendations for demographics based on the clinical trial

data. The product has not been adequately evaluated in the pediatric population (44 subjects between 12 < 18 years) or in pregnant (no pregnancies were reported in any study) or lactating women. There were 107 subjects > 65 years in the applicant's safety database, permitting some assessment of tolerance of ketoconazole foam by the elderly.

Sub-group analyses were performed on the primary endpoint for age, gender, race, and baseline Investigator's Global Assessment. Treatment success rates in the sub-group analyses for age, gender and race were similar to the success rate from the primary analysis for the comparison between Ketoconazole foam and its vehicle.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The applicant has developed a ketoconazole foam product, which represents a new dosage form. The product is proposed for "the topical treatment of seborrheic dermatitis in patients 12 years of age and older." The proposed dosing regimen is twice daily for four weeks. The proposed trade name is Extina®.

2.2 Currently Available Treatment for Indications

Seborrheic dermatitis is a common inflammatory skin disease that may affect the scalp, ears, face and/or trunk. Particular sites of involvement on the face include the nasal creases, eyebrows and inter-brow region. On the trunk, sites of involvement may include the pre-sternal region, axillae and groin. The condition is characterized by somewhat oily scale overlying erythematous skin. Pruritus may be associated. Although the etiology of seborrheic dermatitis is not entirely understood, it is thought that *Malassezia furfur* (known also as *Pityrosporum ovale*) plays some role in its pathogenesis. Per the package inserts for approved ketoconazole 2% cream formulations, "~~_____~~

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Ketoconazole cream and gel formulations are currently marketed for treatment of seborrheic dermatitis. Other available treatments include topical corticosteroids, sulfur-containing products and selenium sulfide products.

2.3 Availability of Proposed Active Ingredient in the United States

Ketoconazole is currently available by prescription in tablet (200 mg), cream, gel and shampoo dosage forms (all three formulations are 2%). A 1% shampoo formulation is approved for over-the-counter marketing for "control of flaking, scaling, and itching associated with dandruff" (per the approval letter).

2.4 Important Issues With Pharmacologically Related Products

There are two classes of azole antifungal agents: the imidazoles and the triazoles (ketoconazole is an imidazole). Most azoles under current development are reportedly of the triazole class primarily because:

- Systemic triazoles are metabolized more slowly.
- Systemic triazoles are said to have less effect on sterol synthesis in humans as compared to the imidazoles.¹

The most common adverse reaction reported for systemically-administered-azoles is gastrointestinal upset. Nausea and vomiting have been reported. All systemically-administered

azoles have reportedly been shown to cause liver enzyme abnormalities, and the potential for hepatotoxicity may be a significant concern.^{2,3}

2.5 Presubmission Regulatory Activity

The product was developed under IND 63,153. The application was originally submitted in January 2004 (correspondence date January 23; receipt date January 26). The submission included data from one Phase 3 trial, Study KFD.C.002. The application was not approved on November 23, 2004. Per the action letter, the stated deficiency was:

"The data from study KFD.C.002 do not support the conclusion that ketoconazole foam, 2%, is effective for the treatment of seborrheic dermatitis. Study KFD.C.002 was designed to evaluate whether ketoconazole foam was superior to its vehicle and non-inferior to the active comparator. However, superiority was not demonstrated for the primary efficacy parameter that was defined prospectively. Because this deficiency cannot be addressed with additional analyses of study KFD.C.002, 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."

Although not the basis for the not-approvable action, the letter also advised that the resubmission should present plans for a long-term open label safety study as per ICH E1A guidance. Additionally, the action letter advised that the resubmission address 12 chemistry issues (none of which were the basis for not-approvable action).

The failed Phase 3 study was discussed at a "post-NA" meeting held on February 7, 2005. The meeting minutes included the following:

"The Agency noted that demonstrating superiority to vehicle is a key objective for establishing efficacy in a 505(b)2 submission. The two efficacy comparisons, test product versus vehicle and test product versus reference listed drug, provide separate pieces of efficacy evidence for a single-trial 505(b)(2) submission. The Agency noted that the sponsor elected not to conduct a Phase 2 trial to estimate treatment and vehicle effects before proceeding to the Phase 3 trial, instead relying on historical data for ketoconazole cream to power the study. Since Study KFD.C.002 was the only study conducted comparing Extina to its vehicle, the sponsor has no additional data on the relative effects of Extina and the foam vehicle. Although the sponsor did allocate the treatments in a 3:1 ratio for Extina and vehicle, the protocol indicates that the sponsor considered this sample size allocation to have adequate power."

The design of the new Phase 3 trial was discussed at a guidance meeting held May 23, 2005. The Division also advised the applicant at this meeting that the long-term safety study "could be submitted as a post-marketing commitment."

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3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The resubmission did not include a CMC section; however, CMC information to address the additional issues included in the action letter was submitted as an amendment to the original submission. ~~_____~~

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~~_____~~ From the CMC review of the original submission:

"The (applicant's) provided explanation was that ~~_____~~

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~~_____~~ The limited studies reported to date indicate that absorbance at ~~_____~~ of the solution, ~~_____~~

~~_____~~ Consequently, a test for absorbance has been included in the product specification, and an acceptance criterion of ~~_____~~ absorbance unit [AU] has been established based on analysis of limited data. Another test missing in the specification is a determination of spray rate, which would assure dispensation of a uniform amount of foam from the can. The sponsor will include this test in the product specification in order to comply with USP <601> for pressurized topical aerosols. An acceptance criterion will be set when sufficient data become available (from ~~_____~~ commercial lots or within one year of NDA approval)."

Based on review of the amendment submitted to address the CMC issues listed in the not-approvable letter, the CMC reviewer does not consider that the applicant has provided acceptable qualification at the proposed acceptance criterion of NMT ~~_____~~ absorbance units for absorbance at ~~_____~~ and proposes that the acceptance criterion be ~~_____~~ until data is available to support ~~_____~~

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Also, please see the chemistry review.

3.2 Animal Pharmacology/Toxicology

No additional non-clinical studies were required for the resubmission and none were provided. There are no pharmacology/toxicology issues pertaining to the resubmission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of the clinical data were trials conducted by the applicant.

4.2 Tables of Clinical Studies

The resubmission provided for three clinical study reports:

Study #/ Study Type	# of Subjects/ Population	Study Design/ Duration	Objectives
KFD.C.005/ Phase 3	1162/ subjects with mild to severe seborrheic dermatitis	randomized, double-blind, double-dummy, vehicle- and active- controlled/ 4 weeks	efficacy and safety of ketoconazole foam vs vehicle foam vs ketoconazole cream vs vehicle cream
KFD.C.006/ phototoxicity	36/ healthy volunteers	randomized, evaluator-blind, patch-site testing, vehicle- controlled/single, 24-hour application	to evaluate the phototoxic potential of ketoconazole foam using product near the end of its proposed 24-month expiry
KFD.C.007/ photoallergenicity	56/ healthy volunteers	randomized, evaluator-blind, patch-site testing, vehicle- controlled/6 weeks	to evaluate the photollergenic potential of ketoconazole foam using product near the end of its proposed 24-month expiry

4.3 Review Strategy

The review of efficacy was based on the new Phase 3 study, KFD.C.005.

4.4 Data Quality and Integrity

Division of Scientific Investigations inspections were not requested. The applicant's analyses were reviewed, and independent analyses of their data were performed by the biostatistics reviewer.

4.5 Compliance with Good Clinical Practices

The sponsor attested that the submitted studies were conducted in compliance with FDA and ICH Good Clinical Practice regulations/guidelines.

4.6 Financial Disclosures

The sponsor certified that they had not entered into any financial arrangement with the clinical investigators for the new study.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

In the original submission, the sponsor provided the results of a comparative bioavailability of Ketoconazole Foam, 2%, versus Nizoral (ketoconazole) 2% Cream in subjects with moderate to severe seborrheic dermatitis, study KFD.C.003. Per the Medical Officer's review of the original submission, the results of the study included that,

"Absorption of ketoconazole was higher with Ketoconazole Foam than with Nizoral Cream. All subjects treated with Ketoconazole Foam had measurable serum levels of ketoconazole; 75% (8/12) had levels greater than 6 ng/mL and 50% (6/12) had levels greater than 5 ng/mL. The maximal level which was observed in one subject was 11.1 ng/mL. In the Nizoral Cream group, 6 subjects had measurable levels of ketoconazole; the maximal level observed was 4.3 ng/mL."

From review of the applicant's data the Clinical Pharmacology/Biopharmaceutics Reviewer concluded:

"Overall, absorption of ketoconazole in subjects treated with Ketoconazole Foam was higher than in subjects treated with Nizoral Cream. Detailed PK analysis and estimation of PK parameters were not performed for this study following application of Ketoconazole Foam as only a single blood sample was collected from subjects at study visit. There appeared to be no correlation between amounts of study drug applied, extent of seborrheic dermatitis, or severity of disease and absorption of ketoconazole. The resulting increased absorption of the foam product as compared to the cream may be due to differences in the vehicle. Ketoconazole levels from Extina foam are significantly lower than levels measured following oral administration of ketoconazole. Oral administration of ketoconazole results in blood concentrations of ketoconazole of 3.5 µg/mL (or 3500 ng/mL) within 1 to 2 hours following a single 200 mg dose (Nizoral Tablets PI, 1998). Mean trough concentrations of ketoconazole achieved with multiple oral doses of 400, 800 and 1200 mg/day were 3.21, 4.42 and 6.38 µg/mL, respectively. These levels are approximately 300 to 600 fold higher than the maximum level attained with topical administration of Ketoconazole Foam."

Comment: The applicant did not conduct a comparative bioavailability with the new ketoconazole cream comparator, Teva.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is the topical treatment of seborrheic dermatitis in patients 12 years and older.

6.1.1 Methods

The efficacy data was provided by the new Phase 3 study, KFD.C.005.

6.1.2 General Discussion of Endpoints

In Section 9.2 of the study report, the sponsor states that the endpoints and four-week treatment duration were “identical” to those in the original Phase 3, pivotal study, KFD.C.002.

6.1.3 Study Design

Study KFD.C.005: A Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of Ketoconazole Foam, 2%, versus Teva® (ketoconazole) 2% Cream in the Treatment of Seborrheic Dermatitis.

Study design: This was a multi-center (24 investigators/study sites), randomized, double-blind, vehicle- and active-controlled study.

Study Initiation: September 28, 2005

Study Completion: July 10, 2006

Objectives: to evaluate the safety and efficacy of Ketoconazole Foam 2% by demonstrating superior efficacy to vehicle foam and non-inferiority (margin =-10%) to the listed drug Ketoconazole Cream 2% (Teva®) in subjects 12 years and older with mild to severe seborrheic dermatitis with applications of study products twice daily for 4 weeks. Subjects were randomized to one of four treatment groups: Ketoconazole 2% Foam, vehicle foam, Ketoconazole 2% Cream, and vehicle cream (4:4:2:1). Randomization was 3:13:1 in the previous trial.

Comment: *Nizoral cream was the active comparator in the original study; however, marketing of Nizoral was discontinued, and the product was not available when study KFD.C.005 was undertaken. Nizoral cream was not discontinued for safety reasons. Teva Cream was the ketoconazole product chosen as the active comparator for the new study.*

Main Inclusion Criteria:

1. Male or female subjects 12 years of age or older, in good general health.
2. Seborrheic dermatitis with an Investigator’s Static Global Assessment (ISGA) score of 2, 3, or 4 at baseline.
3. A discrete, evaluable target area of at least 5 cm² with a score of 2, 3, or 4 for erythema and scaling and at 1, 2, 3, or 4 for induration.

Comment: *The remaining three Inclusion Criteria pertained to ability to follow or understand study procedures, informed consent and HIPAA authorization form (use and disclosure of identifiable health information).*

Exclusion Criteria:

1. Use of systemic antifungal, corticosteroid, or other immunosuppressive therapies, or systemic retinoids, within the four weeks prior to the baseline visit.
2. Use of topical antifungal or corticosteroid therapy to the scalp, face or chest within two weeks before the Baseline Visit.
3. Use of other topical preparations with suggested therapeutic benefit in the treatment of seborrheic dermatitis, within two weeks prior to the baseline (e.g., shampoos containing zinc pyrithione or other zinc preparations, selenium sulfide, tars, salicylic acid, sulfacetamide, benzoyl peroxide, calcipotriene, retinoids, tacrolimus, pimecrolimus)
4. Use of any investigational therapy within eight weeks before the Baseline Visit
5. Concomitant skin disease regardless of location consistent with a diagnosis of contact dermatitis, tinea capitis, tinea corporis, and tinea faciei, impetigo, psoriasis, atopic dermatitis, dermatophytosis, impetigo, rosacea, or pityriasis versicolor, or autoimmune diseases such as systemic or discoid lupus erythematosus or dermatomyositis
6. HIV infection, other immunocompromised states (except diabetes), zinc deficiency, or Parkinson's disease.
7. Pregnant women, women who were breast feeding, or women of childbearing potential who were not practicing an acceptable form of birth control (abstinence, birth control pill/patch, barrier with spermicidal jelly, IUD, etc.), as determined by the investigator. Acceptable contraception was to be used during the entire study.
8. Current drug or alcohol use.
9. Any other condition which, in the judgment of the investigator, would put the subject at unacceptable risk for participation in the study
10. Known allergy to ketoconazole or to any component of the investigational formulations.
11. Previous participation in a clinical trial involving Ketoconazole Foam 2%, irrespective of treatment received.

The primary objective of the study was to demonstrate superiority of ketoconazole foam to the vehicle foam based on the proportion of patients who had an Investigator's Static Global Assessment of clear (0) or almost clear (1), at Week 4, and a minimum improvement in the ISGA score of two grades from baseline. If superiority of ketoconazole foam to the vehicle foam was established, the non-inferiority of ketoconazole foam, 2% to ketoconazole 2% cream was tested.

Study products were applied twice daily for four weeks (even if lesions cleared). The dose was the amount of product necessary to cover all lesions on the face, scalp, and chest. New sites of involvement that appeared during the treatment period were also treated. Subjects were dispensed three 100 g cans of ketoconazole foam or vehicle foam or four 60 g tubes of ketoconazole cream or vehicle cream.

Comment: The applicant proposes to dispense their product in 50 g and 100 g containers.

The **primary efficacy variable** was the proportion of subjects who had an Investigator's Static Global Assessment of 0 or 1 at Week 4 (end of treatment). Subjects with a baseline score of 2 had to have a final score of 0 to be judged a success.

In Section 9.7.4.2 of the study report, the sponsor stated that a Principal Secondary endpoint was included "(p)er FDA request." This endpoint was defined as the proportion of subjects who at Week 4 had a score of 0 or 1 for the ISGA, erythema at the target area and scaling at the target area. Subjects with a baseline score of 2 for any parameter must have improved to a score of 0 for that parameter to be considered a success.

Seborrheic Dermatitis Grading Scale

Score	Scaling	Erythema	Induration	Pruritus
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

Investigator's Global Assessment

Score	Description
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

6.1.4 Efficacy Findings

A total of 1,162 subjects were randomized in the study (4:4:2:1): 427 subjects to Ketoconazole Foam, 420 subjects to Vehicle Foam, 210 subjects to Ketoconazole Cream, and 105 subjects to Vehicle Cream. Demographic information and baseline disease severity are presented in the following tables:

Taken from Sponsor Table 14.1.5: Demographic Information

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
Age				
n	426	418	210	105
mean	44.3 (18.0)	45.8 (18.0)	44.6 (18.0)	47.1 (18.0)
median	44.0	44.0	44.0	47.0
min., max.	(12.0, 86.0)	(12.0, 91.0)	(12.0, 84.0)	(13.0, 86.0)
Age Category				
12<18 years	28 (7%)	26 (6%)	9 (4%)	4 (4%)
18<65 years	336 (79%)	322 (77%)	165 (79%)	82 (78%)
≥65 years	62 (15%)	70 (17%)	36 (17%)	19 (18%)

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missing	1 (0%)	2 (0%)	0 (0%)	0 (0%)
Gender				
Male	223 (52%)	213 (52%)	118 (56%)	50 (48%)
Female	203 (48%)	205 (49%)	92 (44%)	55 (52%)
Missing	1 (0%)	2 (0%)	0 (0%)	0 (0%)
Race				
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 (0%)	2 (0%)	0 (0%)	0 (0%)

Sponsor Tables 14.1.6 & 14.1.7 Baseline Disease Characteristics

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
% BSA*				
n	426	418	210	104
mean	2.9 (2.1)	2.8 (2.2)	3.0 (2.1)	2.9 (2.4)
median	2.0	2.0	2.0	2.0
min., max.	(0.1, 12.0)	(0.1, 15.0)	(0.1, 10.0)	(0.1, 15.0)
Investigator's Global Score				
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 (0%)	2 (0%)	0 (0%)	0 (0%)
Pruritus Severity				
No itching	30 (7%)	31 (7%)	19 (9%)	12 (11%)
Minimal	60 (14%)	62 (15%)	34 (16%)	11 (10%)
Mild	164 (38%)	144 (34%)	80 (38%)	33 (31%)
Moderate	150 (35%)	148 (35%)	62 (30%)	45 (43%)
Severe	22 (5%)	33 (8%)	15 (7%)	4 (4%)
Missing	1 (0%)	2 (0%)	0 (0%)	0 (0%)

*body surface area

Most subjects were Caucasian, 18 < 65 years in age, with mild baseline disease severity with associated mild to moderate pruritus.

Primary Analysis:

Primary efficacy was assessed by "Treatment success", defined as the proportion of subjects who had an Investigator's Global Assessment of 0 or 1 at Week 4 (end of treatment). Subjects with a baseline score of 2 had to have a final score of 0 to be judged a success. The primary analyses consisted of the superiority of ketoconazole foam compared to foam vehicle and the non-inferiority of ketoconazole foam compared to ketoconazole cream. The results of the sponsor's primary analyses results are presented in the following table:

Sponsor Table 14.2.3: Treatment Success at Week 4

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
Treatment Success	239 (56%)	176 (42%)	118 (56%)	33 (31%)
p-value		<.0001		
Lower Confidence Limit			-8.42%	

Comment: The statistical reviewer agrees with the results of the applicant's primary analyses. From the statistical review:

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%)

The applicant adequately demonstrated that their product, ketoconazole foam, 2%, is statistically superior to its vehicle and non-inferior to the active comparator, ketoconazole cream, 2%, in the treatment of mild to severe seborrheic dermatitis. However, although the applicant is not making any claims that the vehicle contributes to efficacy, at 42%, the results for subjects who received vehicle treatment are notable.

Secondary Analyses

The sponsor stated that a "Principal Secondary endpoint" was the proportion of subjects who at Week 4 had a score of 0 or 1 for the Investigator's Global Assessment, erythema at the target area and scaling at the target area. Subjects with a baseline score of 2 for any parameter must have improved to a score of 0 for that parameter to be considered a success. The results of this principal secondary analysis are presented in the following table, as "Modified Treatment Success":

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Sponsor Table 31: “Modified Treatment Success”* at Week 4

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
“Modified” Treatment Success	214 (50%)	140 (33%)	103 (49%)	25 (24%)
p-value		<.0001	0.7435	

* the proportion of subjects who at Week 4 had a score of 0 or 1 for the Investigator’s Global Assessment, erythema at the target area and scaling at the target area; subjects with a baseline score of 2 for any parameter must have improved to a score of 0 for that parameter to be considered a success.

Other specified secondary analyses considered subjects who had a score of 0 or 1 for erythema, scaling or induration at Week 4, and these outcomes are presented in the following three tables:

Sponsor Table 14.2.19: Erythema Success at at the Target Area at Week 4

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
Erythema Success	263 (62%)	212 (50%)	129 (61%)	41 (39%)
p-value		.0008	0.9331	

Sponsor Table 14.22: Scaling Success at the Target Area at Week 4

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
Scaling Success	271 (63%)	204 (49%)	131 (62%)	39 (37%)
p-value		<.0001	0.7796	

Sponsor Table 38: Subjects with Induration at the Target Area at Week 4

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
Induration Success	180 (42%)	133 (32%)	90 (43%)	26 (25%)
p-value		.0007	0.89881	

Comment: Ketoconazole foam was statistically superior to its vehicle in the treatment of the erythema, scaling and induration of seborrheic dermatitis, although the reviewer does not consider induration to be a classic sign of seborrheic dermatitis.

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From Section 1.3 of the statistical review:

Table 2 – 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%) 0.0008 ¹	129 (61%) -7.9% ²	41 (39%)
Scaling	271 (63%)	204 (49%) <0.0001 ¹	131 (62%) -6.9% ²	39 (37%)
Induration	180 (42%)	133 (32%) 0.0007 ¹	90 (43%) -8.9% ²	26 (25%)
ISGA/Ery/Scal	214 (50%)	140 (33%) <0.0001 ¹	103 (49%) -7.2% ²	25 (24%)

¹ p-value for ketoconazole foam versus vehicle foam

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

“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 defined 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 applicant also conducted numerous “additional evaluations,” and these were analyzed only in the intent-to-treat population, with no statistical inferences made. These evaluations included pruritus and outcomes for signs at Week 2. The reviewer considers these analyses to be exploratory and will not further discuss them further.

Sub-group Analyses

Sub-group analyses were performed on the primary endpoint for age, gender, race, and baseline ISGA.

From Sponsor Table 14.2.7: Treatment Success at Week 4 by Age

	Ketoconazole foam n=427	Vehicle foam n=420	Ketoconazole cream n=210	Vehicle cream n= 105
Age Category	n (% success)	n (% success)	n (% success)	n (% success)
12<18 years	14/28 (50%)	13/26 (50%)	5/9 (56%)	0/4 (0%)
18<65 years	186/336 (55%)	137/322 (43%)	93/165 (56%)	27/82 (33%)
≥65 years	39/62 (63%)	26/70 (37%)	20/36 (56%)	6/19 (32%)

Comment: *For the ketoconazole foam arm, rates of treatment success trended towards progressive increase with increase in age, with the highest rate and greatest treatment effect*

being in subjects ≥ 65 years. These rates were generally similar to that in the primary analysis (56%). For subjects $12 < 18$ years, vehicle foam was as effective as the ketoconazole foam.

From Sponsor Table 14.2.8: Treatment Success at Week 4 by Gender

	Ketoconazole foam n=427	Vehicle foam n=420	Ketoconazole cream n=210	Vehicle cream n= 105
Gender	n (% success)	n (% success)	n (% success)	n (% success)
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%)

Comment: Although somewhat higher in males, outcomes in the ketoconazole foam group were similar for males and females, and the rates for both foam groups were similar to that in the primary analysis.

From Sponsor Table 14.2.9: Treatment Success at Week 4 by Race

	Ketoconazole foam n=427	Vehicle foam n=420	Ketoconazole cream n=210	Vehicle cream n= 105
Race	n (% success)	n (% success)	n (% success)	n (% success)
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%)

Comment: Outcomes were generally similar to the primary analysis for all races in the ketoconazole foam group. Rates were highest for Hispanics and lowest for "other" (included Asians).

From Sponsor Table 14.2.10: Treatment Success at Week 4 by Baseline Investigator's Global Assessment

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
Investigator's Global Score	n (% success)	n (% success)	n (% success)	n (% success)
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%)

Comment: Treatment success rates were higher for ketoconazole foam compared to its vehicle for mild, moderate and severe baseline global assessment. However, success rates for severe baseline disease were similar between applicant's product and its vehicle.

6.1.5 Clinical Microbiology

Although the product is an antifungal, the proposed indication is not an infectious process, and the sponsor is not seeking an antimicrobial claim.

6.1.6 Efficacy Conclusions

The applicant conducted one adequate and well-controlled, pivotal Phase 3 study, KFD.C.005, in which their ketoconazole 2% foam was compared to its vehicle and to ketoconazole 2% cream in the treatment of mild to severe seborrheic dermatitis. Subjects were treated with study product twice daily for four weeks.

Primary efficacy was assessed by "Treatment success", defined as the proportion of subjects who had an Investigator's Global Assessment of 0 or 1 at Week 4 (end of treatment). Subjects with a baseline score of 2 had to have a final score of 0 to be judged a success. The primary analyses consisted of the demonstration of superiority of ketoconazole foam compared to foam vehicle and the non-inferiority of ketoconazole foam compared to ketoconazole cream.

The applicant adequately demonstrated that their product, ketoconazole foam, 2%, is statistically superior to its vehicle and non-inferior to the active comparator, ketoconazole cream, 2%, in the treatment of mild to severe seborrheic dermatitis. Specifically, "Treatment success" outcomes at Week 4 were: 56% in the ketoconazole foam group, 42% in the vehicle foam group, 56% in the ketoconazole cream group, and 31% in the vehicle cream group.

Ketoconazole foam was statistically superior to its vehicle in the treatment of the erythema, scaling and induration of seborrheic dermatitis (secondary endpoints), although the reviewer does not consider induration to be a classic sign of seborrheic dermatitis.

Sub-group analyses were performed on the primary endpoint for age, gender, race, and baseline Investigator's Global Assessment. Treatment success rates in the sub-group analyses for age, gender, race were similar to the success rate from the primary analysis for ketoconazole-treated subjects.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The integrated summary of safety combined the safety results from three clinical studies conducted for the evaluation of the applicant's product in the treatment of seborrheic dermatitis: the bioavailability study KFD.C.003, and the Phase 3 studies KFD.C.002 and KFD.C.005. When all three studies are considered, a total of 672 subjects were treated with study product twice-daily for four weeks. Nizoral cream was the active comparator in studies KFD.C.003 and KFD.C.002, and Teva (ketoconazole) 2% cream was the active comparator study in KFD.C.005. For the integrated safety summary, "ketoconazole cream" refers to both Nizoral cream and Teva cream. The applicant did not make comparisons to the vehicle cream group in the integrated summary.

7.1.1 Deaths

There were no deaths in the clinical development program.

7.1.2 Other Serious Adverse Events

Four serious adverse events were reported for the safety population, and all occurred in the new study, KFD.C.005:

Subject 520-0012 (ketoconazole foam); Event: diverticulitis

A 58-year-old Caucasian male used study drug from October 12, 2005 through _____ at which point treatment was interrupted due to hospitalization for diverticulitis. Study drug was resumed on November 10, 2005 (discharged from hospital or _____). The investigator considered the event not related to study drug.

b(6)

Subject 510-0287 (ketoconazole cream); Event: right coronary artery occlusion

A 67-year-old Caucasian male was enrolled on November 22, 2005 and completed study treatment on December 19, 2005. He was admitted to the hospital on _____ with pleural effusions, heart failure, exertional shortness of breath, chest tightness and pedal edema. Study treatment was discontinued on _____ and resumed on December 8. He underwent cardiac catheterization on _____ and was found to have stenosis of the right coronary artery (among other findings). He underwent stent placement on the same day and was discharged from the hospital or _____. The investigator considered the event not related to study drug.

b(6)

Subject 517-0768 (vehicle foam); Event: congestive heart failure

A 41-year old black male was enrolled on December 15, 2005. Study treatment was discontinued on December 29, 2005 after he developed symptoms of congestive heart failure. He was admitted to the hospital on _____ with edema of the lower extremities, chest pain, substernal pressure and dyspnea. He was discharged on _____ and study treatment was resumed on January 7, 2006. The subject completed the study (and study treatment) on January 12, 2006. The investigator considered the event not related to study drug.

b(6)

Subject 516-0798 (ketoconazole foam); Event: cerebrovascular accident

A 75-year-old Caucasian male enrolled in the study on January 11, 2006. On January 24, 2006 he fell, developed left arm weakness and inability to walk without stumbling. Study treatment was discontinued the same day. CT scan revealed a stroke. He resumed study treatment on January 31, 2006 and completed treatment on February 1, 2006. The investigator considered the event probably not related to study drug.

7.1.3 Dropouts and Other Significant Adverse Events

Overall profile of dropouts

Discontinuations from study KFD.C.005 and from the safety population are presented in the following tables.

From Sponsor Tables 14.1.4 and 1.2.1.3: Reason for Study Drug Discontinuation in study KFD.C.005

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
Completed Study	410 (96%)	404 (96%)	198 (94%)	100 (95%)
Discontinued	17 (4%)	16 (4%)	12 (6%)	5 (5%)
Reason for Discontinuation				
Adverse Experience	3 (1%)	6 (1%)	4 (2%)	1 (1%)
Non-compliance	3 (1%)	2 (0%)	1 (0%)	0 (0%)
Subject Withdrew	4 (1%)	8 (2%)	3 (1%)	3 (3%)
Lost to Follow-up	7 (2%)	0 (0%)	2 (1%)	0 (0%)
Failed Enrollment Criteria	0 (0%)	0 (0%)	1 (0%)	0 (0%)
Early Termination*	0 (0%)	0 (0%)	1 (0%)	0 (0%)
Incarceration	0 (0%)	0 (0%)	0 (0%)	1 (0%)

*Site inadvertently conducted Visit 3 instead of Visit 2

Comment: Rates and reasons for discontinuation were generally similar between treatment groups.

Sponsor Tables 5: Subject Withdrawals for Safety Population

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	672	497	455	181
Withdrawn	30 (5%)	16 (3%)	27 (6%)	8 (4%)
Withdrawn Adverse Experience	3 (<1%)	8 (2%)	8 (2%)	2 (1%)

Comment: Rates for withdrawal from the safety population were generally similar between treatment groups.

7.1.3.2 Adverse events associated with dropouts

Per Table 16.2.1.3, the adverse events associated with discontinued subjects in study KFD.C.005 were:

- ketoconazole foam group: “burning irritation on face-target area”, “abdominal pain” and “burning at study drug application site”

- vehicle foam group: “stinging upon application”, “numbness sensation of tongue”, “scalp itching”, “contact dermatitis at application site”, “stinging (application sites)”, and “scalp burning after application.”
- ketoconazole cream group: “application site reaction right ear with erosions”, “rash around eyes”, “allergic reaction” and “headaches”
- vehicle cream group: “burning at application site”

Comment: The distribution of adverse events suggests that the sponsor’s vehicle may contribute to irritancy.

Regarding the total safety population, all discontinuations for adverse events for ketoconazole foam-treated subjects occurred in study KFD.C.005 and are described above.

7.1.3.3 Other significant adverse events

Non-serious adverse events that resulted in study drug interruption or discontinuation in study KFD.C.005 occurred in:

- 5 of 427 (1%) subjects in the ketoconazole foam group,
- 9 of 420 (2%) subjects in the vehicle foam group,
- 6 of 210 (3%) of subjects in the ketoconazole cream group, and
- 1 of 105 (1%) in the vehicle cream group.

Most of these non-serious adverse events were application site reactions. Seven subjects experienced non-serious adverse events that resulted in study drug interruption or discontinuation and that were not common application site reactions:

- Subject 511-0776 (ketoconazole foam): abdominal pain and rhinorrhea
- Subject 507-0948 (vehicle foam): numbness of tongue and tingling of lips
- Subject 519-0035 (vehicle foam): angina pectoris
- Subject 502-0314 (ketoconazole cream): pityriasis rosea
- Subject 523-0187 (ketoconazole cream): headaches, burning and watering of eyes
- Subject 502-0872 (ketoconazole cream): application site reaction, erosions, infection of the ears
- Subject 511-0773 (vehicle cream): itching, stinging, burning at the application site

7.1.4 Other Search Strategies

No other search strategies were undertaken.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Subjects were evaluated at baseline and weeks 2 and 4 and were queried for adverse events and use of concomitant medications at each return visit.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor used the MedDRA dictionary and grouped preferred terms under appropriate system organ classes.

7.1.5.3 Incidence of common adverse events

See Section 7.1.5.4

7.1.5.4 Common adverse event tables

From Sponsor Tables 14.3.1.2 & 14.3.1.3 Adverse Experiences by $\geq 1\%$ in Study KFD.C.005 Classified by MedDRA Preferred Terms in Descending Order of Frequency

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
# of Subjects with an Adverse Experience	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%)
Upper respiratory infection	6 (1%)	4 (1%)	1 (<1%)	0 (0%)
Headache	5 (1%)	3 (1%)	1 (<1%)	1 (1%)
Nasopharyngitis	3 (1%)	5 (1%)	2 (1%)	0 (0%)
Application site erythema	3 (1%)	0 (0%)	4 (2%)	0 (0%)
Influenza	3 (1%)	2 (<1%)	2 (1%)	0 (0%)

Comment: All "Application site burning" and "Application site reaction" were considered treatment-related (per Table 14.3.1.4). The rate for "Application site burning" in the new trial is exactly the same as reported in the previous trial for all treatment groups except vehicle (per the Medical Officer's review of the original submission). The rates were similar between the ketoconazole foam and vehicle foam groups for application site burning and application site reaction, suggesting that these events may be attributable to some ingredient(s) in the vehicle rather than the active ingredient. This possibility is further supported by the low incidences of these two events in the ketoconazole cream and vehicle cream groups.

From Sponsor Tables 3 in Summary of Clinical Safety: Adverse Experiences by $\geq 1\%$ in Ketoconazole Foam Group in the Safety Population Classified by MedDRA Preferred Terms in Descending Order of Frequency

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	672	497	455	181
# of Subjects with an Adverse Experience	188 (28%)	122 (25%)	88 (19%)	29 (16%)
Application site burning	67 (10%)	49 (10%)	4 (1%)	2 (1%)
Application site reaction NOS	24 (4%)	8 (2%)	5 (1%)	1 (1%)
Application site reaction	17 (3%)	16 (3%)	3 (1%)	1 (1%)
Nasopharyngitis	10 (1%)	9 (2%)	8 (2%)	1 (1%)
Headache NOS	8 (1%)	0 (0%)	6 (1%)	2 (1%)
Application site pruritus	5 (1%)	4 (1%)	3 (1%)	2 (1%)
Upper respiratory infection	6 (1%)	4 (1%)	1 (<1%)	0 (0%)
Headache	5 (1%)	3 (1%)	1 (<1%)	1 (1%)
Application site erythema	4 (1%)	1 (<1%)	5 (1%)	0 (0%)

Comment: Similar to study KFD.C.005, the most common adverse events in the safety population were "Application site burning" and "Application site reaction NOS." "Application site reaction was the third most common event.

7.1.5.5 Identifying common and drug-related adverse events

The most common treatment-related adverse event in the safety population for ketoconazole foam treated subjects was application site burning: 67 (10%) in the ketoconazole foam group [49 (10%) in the vehicle foam group, 4 (1%) in the ketoconazole cream group, and 2 (1%) in the vehicle cream group]. The second most common treatment-related adverse event in the safety population for this group was application site reaction NOS: 24 (4%) in the ketoconazole foam group [8 (2%) in the vehicle foam group, 5 (1%) in the ketoconazole cream group, and 1 (1%) in the vehicle cream group]. Other treatment-related adverse events that occurred at $\geq 1\%$ in the ketoconazole foam group were:

- application site reaction in 17 subjects (3%) [16 (3%) in the vehicle foam group, 3 (1%) in the ketoconazole cream group, and 1 (1%) in the vehicle cream group],
- application site pruritus in 5 subjects (1%) [4 (1%) in the vehicle foam group, 2 (<1%) in the ketoconazole cream group, and 2 (1%) in the vehicle cream group], and
- application site erythema in 4 subjects (1%).

7.1.5.6 Additional analyses and explorations

Adverse events were analyzed by the sub-groups of age, race and gender. The discussion of adverse events for these sub-groups below is presented for the ketoconazole foam and vehicle foam groups.

Age

Age groups were categorized as follows: 12 to < 18 years (44 subjects), 18 to < 65 years (520 subjects), and \geq 65 years (107 subjects). "Application site burning" was the most common adverse event for adult subjects, and the rates were similar between the ketoconazole foam and vehicle foam groups and similar to this event in the total safety population (i.e. approximately 10% for both treatment groups). For subjects 12 to < 18 years, the rates of this event were lower than for the safety population for both treatment groups: 2 of 44 subjects (5%) in the ketoconazole foam group and 1 of 31 (3%) subjects in the vehicle foam group. Headache was the only other event reported for more than one ketoconazole-foam-treated subject in the category of "12 to < 18 years", and this event was reported for 2 subjects (5%). "Application site reaction" (NOS for subjects \geq 65 years) was the second most common adverse event for adult subjects in the ketoconazole foam group.

Race

Races were categorized as follows: Caucasian, Black, Hispanic, and Other. "Application site burning" was the most common adverse event for Caucasian, Black and Hispanic subjects. This event was reported for 1 of 16 "Other" subjects (6%).

For Caucasians, "Application site burning" was reported for 53 of 500 subjects (11%) in the ketoconazole foam group and 34 of 363 subjects (9%) in the vehicle foam group (and similar to overall adverse events). "Application site reaction NOS" was the second most common adverse event for Caucasian subjects, occurring in 21 subjects (4%) in the ketoconazole foam group and 7 subjects (2%) in the vehicle foam group.

For Black subjects, "Application site burning" was reported for 6 of 108 subjects (6%) in the ketoconazole foam group and 11 of 79 subjects (14%) in the vehicle foam group. Thus, in contrast to the overall safety population, for Black subjects "Application site burning" was reported more commonly in the vehicle foam group and at a lower rate in the ketoconazole foam group (as compared to this event in the total safety population). "Nasopharyngitis" was the second most common adverse event for Black subjects, occurring in 5 subjects (5%) in the ketoconazole foam group and no subjects (0%) in the vehicle foam group.

For Hispanic subjects, "Application site burning" was reported for 7 of 47 subjects (15%) in the ketoconazole foam group and 1 of 32 subjects (3%) in the vehicle foam group. Thus, in contrast to the overall safety population, for Hispanic subjects the rates of "Application site burning" were dissimilar between the ketoconazole foam and the vehicle foam groups and slightly higher in the ketoconazole foam group (as compared to this event in the total safety population). "Pharyngolaryngeal pain" was the second most common adverse event for Hispanic subjects, occurring in 2 subjects (4%) in the ketoconazole foam group and no subjects (0%) in the vehicle foam group.

No event was reported for more than one ketoconazole-foam-treated subject in the "Other" category.

Gender

“Application site burning” was the most common adverse event for both genders: 35 of 355 males (10%) in the ketoconazole foam group and 23 of 254 (9%) in the vehicle foam group; 32 of 316 females (10%) in the ketoconazole foam group and 25 of 241 (10%) in the vehicle foam group. “Application site reaction NOS” was the second most common adverse event for both genders: 13 males (4%) in the ketoconazole foam group and 5 (2%) in the vehicle foam group; 11 females (3%) in the ketoconazole foam group and 3 (1%) in the vehicle foam group.

Comment: As was the case for the total safety population, “Application site burning” was the most common adverse events in the sub-group analyses, and this event was generally reported at the same rate as in the total safety population, i.e. approximately 10%.

7.1.6 Less Common Adverse Events

With the exception of burning, “application site reaction” and erythema, all treatment site reactions reported in subjects treated with ketoconazole foam in study KFD.C.005 occurred at a rate of < 1%. These application site reactions were: dryness, paresthesias, pruritus, and warmth (sponsor Table 14.3.1.4). See Section 7.1.5 of less common adverse events that occurred in total safety population.

7.1.7 Laboratory Findings

Urine pregnancy testing was the only laboratory data collected in this study KFD.C.005. Hematology and chemistry testing were done in the first Phase 3 study KFD.C.002. The Medical Officer who reviewed those data concluded that, “There were no laboratory abnormalities in the Ketoconazole Foam group that appeared to be drug-related; either the only abnormality was at baseline, or the week 4 value was comparable to the baseline value.”

7.1.8 Vital Signs

Vital signs were only measured at the baseline visit.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not done in this study.

7.1.10 Immunogenicity

This section is not applicable.

7.1.11 Human Carcinogenicity

Controlled trials were not of sufficient duration to permit assessment of carcinogenicity.

7.1.12 Special Safety Studies

The results of a contact sensitization, KFD.C.004, were provided in the original submission (irritation was also assessed in this study). The resubmission provided for the results from a phototoxicity study and a photoallergenicity study. Regarding the contact sensitization study, the Medical Officer who reviewed the original submission had the following comments:

"Results in the challenge phase were reported as consistent with contact sensitization to both the active foam and the vehicle in 9 patients, or about 5%. It appears to this reviewer that the number of patients developing sensitization may have been underreported. The first criterion used to determine sensitization, namely, that the patch site had to show a reaction of Grade 3 (erythema with marked edema) or Grade 4 (erythema with edema and blistering) at the initial reading (patch removal), is too stringent, and may have caused instances of sensitization to be overlooked. Also, the third criterion was that the reaction had to be reproducible on re-challenge, and yet perusal of the individual data listings shows that an additional 16 subjects who met the first two criteria for sensitization (Grade 3 or 4 reaction at the initial reading, persistence of the reaction 24 hours later) did not have a re-challenge and so were not recorded as possible sensitization. If these 16 subjects are included as being sensitized, the incidence of sensitization is about 13%."

Regarding this study, the Medical Officer concluded that:

"Under the exaggerated exposure conditions of the induction phase, Ketoconazole Foam and the vehicle foam showed a higher level of irritation than the negative control, and a level of irritation roughly comparable to the positive control, 0.2% sodium lauryl sulfate cream, but had a generally low level of irritation overall. Ketoconazole foam was associated with a grade 3 reaction (erythema with marked edema) in 7%, and a grade 4 reaction (erythema with edema and blistering) in 2%. The remainder of the subjects showed no or mild irritation. The incidence of sensitization may have been underreported in the sensitization study, due to overly stringent criteria used to determine sensitization."

KFD.C.006: "An Evaluation of the Phototoxic Potential of Ketoconazole Foam, 2% in Healthy Volunteers"

Objective: to evaluate the phototoxic potential of ketoconazole foam, 2%, using product near the end of its proposed 24 month expiry period

Comment: *Per Section 9.2 of the study report, the ketoconazole and vehicle foams were near the end of their expiry to "maximize any effects that might be attribute"*

b(4)

Methodology: This was a randomized, evaluator-blinded study in which three sets of patches were applied to naïve sites on the backs of subjects for one 24-hour application period. Each of the three sets consisted of three patches: one patch containing ketoconazole foam 2%, one patch containing vehicle foam, and one blank patch. Eighty µL of study product was applied under 4 cm² occlusive patches (20µL/cm²). One set of test sites was exposed to UVB and UVA radiation, and one set test sites was exposed to UVA, UVB and visible light. The third set of test

sites served as non-irradiated controls. Follow-up visits were at 1, 24, 48 and 72 hours after removal of patches and treatment sites were visually evaluated at each of those time points. The total study duration was 5 days (plus a 2-day screening period).

The phototoxic potential of the test agents was assessed by within subject comparisons of the irradiated sites to the non-irradiated sites and by comparing the sites to which test products had been applied to the blank sites. The phototoxic potential in the visible light range was assessed by comparing the test sites irradiated with UV plus visible light to the test sites irradiated with UV only.

Inflammatory responses or superficial effects were scored according to the following scales:

Erythema Scale

- 0 No visible reaction and/or erythema
- 0.5 Slight, confluent or patchy erythema
- 1 Mild erythema (pink)
- 2 Moderate erythema (definite redness)
- 3 Strong erythema (very intense redness)

Local Skin Reaction Grading Scale

- E= Edema-swelling, spongy feeling when palpated
- P= Papule-red, solid, elevation
- V= Vesicle-small elevation containing fluid
- B= Bullous reaction-fluid-filled lesion (blister)
- S= Spreading-evidence of the reaction beyond the irradiated area
- W=Weeping-result of a vesicular or bullous reaction-serous exudate
- I= Induration-solid, elevated, hardened, thickened skin
- ~ Response occurs \leq 25% of test site

Superficial Effects Grading Scale

- g= Glazing
- y= Peeling
- c= Scab, dried film of serous exudate of vesicular or bullous reaction
- d= Hyperpigmentation (reddish-brown discoloration of test site)
- h= Hypopigmentation (loss of visible pigmentation at test site)
- f= Fissuring- grooves in the superficial layers of the skin

Scores represented the presence of clinically significant effects (i.e. involving at least 25% of the test site). Erythema that was barely perceptible, minimal or involving less than 25% of the test site and reactions that were scored as 0.5 were not considered to be significant. Subjects with an erythema response of moderate (Grade 2) or greater to the test foams were categorized by the following criteria:

1. **potential phototoxicity:** moderate or greater erythema to UV only and UV plus visible light with no significant, consistent reactions at non-irradiated sites
2. **potential phototoxicity to visible light:** moderate or greater erythema only to UV plus visible light with no significant, consistent reactions at non-irradiated sites or UV irradiated sites
3. **irritant contact dermatitis:** moderate or greater erythema to any of the non-irradiated sites, as well as irradiated test sites with significant, consistent reactions to all other light exposures

4. **inconclusive response:** moderate or greater erythema to UV only with no significant, consistent reactions at UV plus visible light and/or non-irradiated sites

The sponsor selected an irradiation source that would cover the visible spectrum _____ and a filter that would peak in the green light range _____. Section 3 of the protocol states that the exposure dose was to be calculated to simulate the approximate exposure a person would receive to this portion of the visible spectrum on an average day (approximately 15 Joules/cm²).

b(4)

Number of subjects: 30 evaluable planned; 36 enrolled and completed the study

Demographics: male and female; 19-63 years of age; 35 Caucasian, and 1 Hispanic; Fitzpatrick skin types I (1 subject), II (12 subjects), or III (23 subjects).

Comment: Enrollment appears to have been heavily biased towards type III skin, the least "vulnerable" skin type usually enrolled in this type of study.

Results:

No subjects showed strong reactions (Grade 3) to any test article.

From Tables 14.3.5.1 A-I, the reviewer considers that reactions for 5 subjects (17%) met the sponsor's definition for potential phototoxicity: 2 subjects for the ketoconazole sites, (#'s 24, 26), 4 subjects for the vehicle sites (#'s 21, 26, 30, and 33), and one subject at the blank site (#28). Subject #26 reacted to UV + visible light exposure at both the ketoconazole and vehicle sites.

Four subjects had inconclusive responses as their reactions were only with the UV radiation, and the sponsor's product absorbs at _____ in the visible range (#'s 3, 18, 20 and 32 at ketoconazole sites and #'s 3 and 33 at vehicle sites). (Subject #33 also manifested "potential phototoxicity" at the vehicle site exposed to UV + visible light, as described above). A fifth subject (#4) was considered to have experienced a contact dermatitis, having reacted at non-irradiated and irradiated ketoconazole and vehicle sites.

b(4)

Potential phototoxicity to visible light was observed in three subjects: one subject had a reaction to vehicle foam only, one subject had a reaction to ketoconazole foam only, and one subject had a reaction to both ketoconazole foam and vehicle foam. Irritant contact dermatitis was observed in one subject to ketoconazole foam and vehicle foam. Inconclusive responses were observed in four subjects.

Conclusion: Under conditions of the study, there was no conclusive evidence to suggest that the applicant's product has significant potential to cause phototoxicity.

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On Original

KFD.C.007: “An Evaluation of the Photoallergy Potential of Ketoconazole Foam, 2% in Healthy Volunteers”

Objective: to evaluate the photoallergy potential of ketoconazole foam, 2%, using product near the end of its proposed 24 month expiry period

Methodology: This was a randomized, evaluator-blinded study and consisted of the following phases: screening, induction, rest, and challenge. Subjects' MED's were determined during the screening period. The induction period consisted of six 24-hour applications of duplicate patches to sites on the back over three weeks, and 2.0 MED exposure of broad spectrum UVB to each site after each patch was removed. Two of these sites one (1 ketoconazole foam, 2%, 1 vehicle foam) were also irradiated with 15 Joules/cm² of visible light. The rest period was approximately 10-17 days. The challenge phase consisted of a single 24-hour application of 3 sets of patches (9 total) to naïve sites on the backs of subjects. Each set consisted of 3 patches: 1 active, 1 vehicle and 1 blank. One set of test sites was exposed to UVB and UVA radiation (UV only) for evaluation of photoallergy potential. The second set of test sites was exposed to UVB and UVA radiation plus visible light (UV plus visible light) for evaluation of photoallergy potential with visible light. The third set of test sites was used as non-irradiated controls. Challenge Phase follow-up evaluations were at 1, 24, 48, and 72 hours after patch removal. Subjects with an erythema response of moderate (2) or greater to the test foams were categorized by the following criteria:

1. **potential photoallergenicity:** moderate or greater erythema to UV only and UV plus visible light during the challenge phase with persistent reactions observed at each visit or reactions consistent with an allergic response (i.e. reactions that do not resolve within 24 hours and likely to include edematous erythema with localized spreading). In addition, there are no significant, consistent reactions at non-irradiated sites.
2. **potential photoallergenicity to visible light:** moderate or greater erythema to UV plus visible light during the challenge phase with persistent reactions observed at each visit or reactions consistent with an allergic response (i.e. reactions that do not resolve within 24 hours and likely to include edematous erythema with localized spreading). In addition, there are no significant, consistent reactions at non-irradiated sites.
3. **contact dermatitis:** moderate or greater erythema to any of the non-irradiated sites, as well as irradiated test sites with significant, consistent reactions to all other light exposures. Irritant and allergic contact dermatitis were further defined:
 - **irritant contact dermatitis:** moderate or greater erythema to ketoconazole foam or vehicle foam during the challenge phase and moderate or greater erythema reactions throughout the induction phase. Also, reactions resolved during the challenge phase within 24 hours.
 - **allergic contact dermatitis:** moderate or greater erythema to ketoconazole foam or vehicle foam during the challenge phase with persistent reactions observed at each visit or reactions consistent with an allergic response (i.e. reactions that do not resolve within 24 hours and likely to include edematous erythema with localized spreading).

4. **inconclusive response:** moderate or greater erythema to UV only with no significant, consistent reactions at UV plus visible light and/or non-irradiated sites

Skin assessments were according to the same scales described in the phototoxicity study, e.g. erythema, local skin reactions.

Comment: The protocol stated that phototesting would be conducted with UVB and UVA (\pm visible light), and the body of the study report describes that such testing was done. However, the data presentations in Section 14.3.5 of the study report describe that testing was conducted with UVB only (\pm visible light). Thus, it is not clear that UVA wavelengths were used in the study. However, the reviewer does not consider this to have compromised the study, since the product absorbs only in the visible light range ~~_____~~

b(4)

Number of subjects: 62 planned; 56 enrolled; 53 completed the challenge phase (per Section 12 of the study report: one subject discontinued during induction due to a strong reaction; two subjects discontinued due to non-compliance)

Demographics: male and female; 19-63 years of age; Caucasian, Hispanic and Other; Fitzpatrick skin types I (4 subjects), II (18 subjects), or III (34 subjects)

Results: Of the 53 subjects, 17 (32%) had moderate or greater erythema reactions to ketoconazole foam or vehicle foam. Three subjects were considered to have had “**potential photoallergenicity**” to UV only and UV plus visible light to both the active and vehicle foams. One of these 3 subjects (#10) was discontinued during induction because of strong reactions to both test products. As this subject was not challenged, the subject was conservatively classified as having “**potential photoallergenicity.**”

One subject was considered to have “**potential photoallergenicity**” to only the ketoconazole foam and only when tested with UV plus visible light (i.e. this subject did not have a significant reaction with exposure to only UV).

Nine subjects (17%) were considered to have had an allergic contact dermatitis (this count includes subject #10 who was discontinued during induction), having shown significant reactions at both irradiated and at non-irradiated ketoconazole sites during the challenge period.

No subjects were rechallenged.

Conclusions: Under the exaggerated conditions of the study, ketoconazole foam was demonstrated to have some potential to cause allergic contact dermatitis. The Medical Officer who reviewed the contact sensitization study provided in the original submission, concluded that **the applicant’s reported rate** of sensitization (2%) might have reflect underreporting from the criteria applied for determination of sensitization and that a more conservative interpretation of the data could put the rate at 13%. The rate of 13% would be similar to the 17% in the photoallergenicity study. Thus, it appears that **the applicant’s product has the potential to be a contact sensitizer.**

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Ketoconazole is not in a class with a history of abuse or withdrawal phenomena. There would appear to be limited potential for abuse of this product and no apparent withdrawal symptoms.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well controlled studies in pregnant women. Per the Summary of Clinical Safety, "No pregnancies occurred in any of the subjects during the studies."

7.1.15 Assessment of Effect on Growth

The protocol for the pivotal Phase 3 study allowed for enrollment of subjects 12 years and older. Assessment of the effect of the product on growth was not done.

7.1.16 Overdose Experience

There has been no overdose experience reported with ketoconazole foam.

7.1.17 Postmarketing Experience

Ketoconazole 2% foam is not marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

See Sections 6.1.3 and 6.1.4 for study KFD.C.005 (the new Phase 3 study). See Section 7.2.1.2 (below) for patient enumeration for total safety population.

7.2.1.2 Demographics

See Section 6.1.4 for demographics of the population for study KFD.C.005.

Taken from Sponsor Table 2: Demographic Information for the Safety Population

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	672	497	455	181
Age n	671	495	455	181
mean	44.9 (18.1)	45.5 (18.1)	44.7 (17.4)	46.4 (17.6)

median min., max.	445.0 (12.0, 86.0)	44.0 (12.0, 91.0)	44.0 (12.0, 84.0)	46.0 (12.0, 86.0)
Age Category				
12<18 years	44 (7%)	31 (6%)	23 (5%)	7 (4%)
18<65 years	520 (77%)	383 (77%)	357 (78%)	145 (80%)
≥65 years	107 (16%)	81 (16%)	75 (16%)	29 (16%)
missing	1 (<1%)	2 (<1%)	0 (0%)	0 (0%)
Gender				
Male	355 (53%)	254 (51%)	258 (57%)	82 (45%)
Female	316 (47%)	241 (48%)	197 (43%)	99 (55%)
Missing	1 (<1%)	2 (<1%)	0 (0%)	0 (0%)
Race				
Caucasian	500 (74%)	363 (73%)	348 (76%)	127 (70%)
Black	108 (16%)	79 (16%)	64 (14%)	35 (19%)
Hispanic	47 (7%)	32 (6%)	27 (6%)	15 (8%)
Other	16 (2%)	21 (4%)	16 (4%)	4 (2%)
Missing	1 (<1%)	2 (<1%)	0 (0%)	0 (0%)

7.2.1.3 Extent of exposure (dose/duration)

Subjects were dispensed three 100 gm cans of ketoconazole foam or vehicle foam for the four-week treatment period.

Sponsor Table 14.3.1.1: Study Drug Exposure in Study KFD.C.005

	Ketoconazole foam	Vehicle foam	Ketoconazole cream	Vehicle cream
# of subjects	427	420	210	105
Days on Therapy				
n	427	420	210	105
mean	28.6 (5.2)	28.3 (4.5)	27.8 (5.4)	27.9 (5.2)
median	29.0	29.0	2.9	29.0
min., max.	(1, 55)	(1, 42)	(1, 43)	(1, 34)
Therapy Usage (g)				
n	414	418	207	103
mean	79.17 (56.27)	81.20 (58.11)	49.96 (43.21)	59.00 (51.92)
median	67.20	69.9.0	33.20	46.90
min., max.	(1.3, 308.3)	(0.3, 453.7)	(0.0, 217.2)	(2.0, 225.15)
Daily Mean Usage (g)				
n	414	418	207	103
mean	2.83 (2.76)	2.85 (1.99)	1.70 (1.55)	2.24 (2.02)
median	2.30	2.40	1.20	1.70
min., max.	(0.1, 42.1)	(0.1, 16.2)	(0.0, 7.8)	(0.1, 10.9)

Comment: The sponsor proposes to dispense the product in 50 g and 100 g cans. The utility of the 50 g can is not clear, given the mean usage over the four-week treatment period in the Phase 3 study (above) of 79.17 g.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 *Other studies*

The sponsor's initial Phase 3 study also contributed to the safety database.

7.2.2.2 *Postmarketing experience*

The applicant's product is not marketed.

7.2.2.3 *Literature*

Per the Section 2.7.4.6 of the Summary of Clinical Safety, the applicant "conducted a thorough review of publicly available literature on the use of ketoconazole, 2.0% to meet FDA's request for worldwide post-marketing safety data on all ketoconazole products."

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects was exposed to the applicant's product to characterize its safety in the short-term (4 weeks). Doses and durations of exposure were adequate to assess the safety of the product for its intended use. The designs of the Phase 3 studies were adequate to assess the safety of the product for its intended use. Topical safety was adequately assessed in the development program both in the Phase 3 and the Phase 1 dermal safety studies. There was adequate experience with the drugs in regard to overall numbers of subjects exposed and durations of exposures. Long-term safety has not been evaluated.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This section is not applicable.

7.2.5 Adequacy of Routine Clinical Testing

See Sections 7.1.7, 7.1.8 and 7.1.9.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The applicant did not conduct drug-drug interaction assessment.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The assessment of local and systemic tolerance have been previously discussed. See Section 7.2.3. There are no recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

See Sections 6 and 7.

7.2.9 Additional Submissions, Including Safety Update

The applicant advised the project manager that they had no new safety information to report; however, formal submission of the safety update was pending as of May 14, 2007.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most common treatment-related adverse event in the safety population for ketoconazole foam treated subjects was application site burning: 67 (10%) in the ketoconazole foam group [49 (10%) in the vehicle foam group, 4 (1%) in the ketoconazole cream group, and 2 (1%) in the vehicle cream group]. The second most common treatment-related adverse event in the safety population for this group was application site reaction NOS: 24 (4%) in the ketoconazole foam group [8 (2%) in the vehicle foam group, 5 (1%) in the ketoconazole cream group, and 1 (1%) in the vehicle cream group]. Other treatment-related adverse events that occurred at $\geq 1\%$ in the ketoconazole foam group were:

- application site reaction in 17 subjects (3%) [16 (3%) in the vehicle foam group, 3 (1%) in the ketoconazole cream group, and 1 (1%) in the vehicle cream group],
- application site pruritus in 5 subjects (1%) [4 (1%) in the vehicle foam group, 2 (<1%) in the ketoconazole cream group, and 2 (1%) in the vehicle cream group], and
- application site erythema in 4 subjects (1%).

The applicant's product appears to have some potential to act a contact sensitizer.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

As both Phase 3 studies were of identical design, the applicant reasonably integrated the safety data from the Phase 3 studies. The applicant's approach to pooling was acceptable.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

These explorations were not done.

7.4.2.2 Explorations for time dependency for adverse findings

These explorations were not done.

7.4.2.3 Explorations for drug-demographic interactions

See Section 7.1.5.6 for sub-group analyses.

7.4.2.4 Explorations for drug-disease interactions

These explorations were not done.

7.4.2.5 Explorations for drug-drug interactions

These explorations were not done.

7.4.3 Causality Determination

Treatment-related adverse events were generally similar between the ketoconazole and the vehicle foam groups. Treatment-related adverse events were generally higher in the ketoconazole foam group compared to the ketoconazole cream group. Treatment-related adverse events were generally similar between the ketoconazole and the vehicle cream groups. In the reviewer's opinion, this all suggests that the drug substance, ketoconazole, has low potential for irritancy, and that irritancy of the sponsor's product may be attributable to the vehicle. See Section 7.1.5.5.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The applicant did not conduct dose-ranging studies.

8.2 Drug-Drug Interactions

The applicant did not conduct drug interaction studies.

8.3 Special Populations

There are no special dosing recommendations for demographics based on the clinical trial data. The product has not been adequately evaluated in the pediatric population (44 subjects between 12 < 18 years) or in pregnant (no pregnancies were reported in any study) or lactating women. There were 107 subjects > 65 years in the applicant's safety database, permitting some assessment of tolerance of ketoconazole foam by the elderly.

8.4 Pediatrics

A request for a waiver of pediatric studies in children younger than 12 years of age was provided in of Module 1, Volume 1, Section 1.9.1. The stated reason for the request was, "The waiving of pediatric studies is based on agreements with the Food and Drug Administration, Division of Dermatologic & Dental Drug Products." The applicant further states that agreement on this matter was reached at both the Pre-IND/End-of-Phase 2 meetings and at the Pre-NDA meeting.

Review of the minutes for the Pre-IND/End-of-Phase 2 meeting reveals the applicant's rationale for requesting the waiver to be embedded in one their questions:

"Does the FDA agree that it is appropriate to request a waiver for pediatric studies on neonates, infants and children, because seborrheic dermatitis is not prevalent in these subsets of the pediatric population, and because ketoconazole would not represent a substantive therapeutic benefit as a treatment for seborrheic dermatitis...for that portion of the pediatric population."

The Agency responded: "It is required that the Sponsor provide a rational for exclusion of children less than 12 years of age and request a waiver, which appears to be appropriate for this condition."

Also at the Pre-IND/End-of-Phase 2 meeting, the agency requested that subjects 12-17 be enrolled in the applicant's comparative bioavailability study, KFD.C.003. Per the Medical Officer's review of the original submission, the comparative bioavailability study was designed to enroll subjects 12 years and older. However, per the review, the age range of enrolled subjects was said to be 25 to 76 years (no explanation was found regarding the lack of pediatric subjects in this study).

From the minutes of the Pre-NDA meeting (May 30, 2003), the applicant posed the following question:

"Does the Agency agree with Connetics' understanding that inclusion of subjects less than 12 years of age in the clinical studies is not a requirement for approval of Ketoconazole Foam, 2%, for seborrheic dermatitis?"

The Agency responded: "The inclusion of subjects younger than 12 is not required."

For subjects between the ages of 12 and 18 years, application site burning and headache were the only events reported by > one subject in the ketoconazole foam group (two subjects for each event).

8.5 Advisory Committee Meeting

This section is not applicable.

8.6 Literature Review

See Section 7.2.2.3.

8.7 Postmarketing Risk Management Plan

There are no recommendations for a specific post-marketing risk management plan.

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor has demonstrated that their product is safe and effective for the treatment of seborrheic dermatitis in patients 12 years and older under the proposed conditions of use of twice daily for four weeks.

Efficacy

The applicant conducted one adequate and well-controlled, pivotal Phase 3 study, KFD.C.005, in which their ketoconazole 2% foam was compared to its vehicle and to ketoconazole 2% cream in treatment of mild to severe seborrheic dermatitis. Subjects were treated with study product twice daily for four weeks.

Primary efficacy was assessed by "Treatment success", defined as the proportion of subjects who had an Investigator's Global Assessment of 0 or 1 at Week 4 (end of treatment). Subjects with a baseline score of 2 had to have a final score of 0 to be judged a success. The primary analyses consisted of the demonstration of superiority of ketoconazole foam compared to foam vehicle and the non-inferiority of ketoconazole foam compared to ketoconazole cream.

The applicant adequately demonstrated that their product, ketoconazole foam, 2%, is statistically superior to its vehicle and non-inferior to the active comparator, ketoconazole cream, 2%, in the treatment of mild to moderate seborrheic dermatitis. Specifically, "Treatment success" outcomes at Week 4 were: 56% in the ketoconazole foam group, 42% in the vehicle foam group, 56% in the ketoconazole cream group, and 31% in the vehicle cream group. Ketoconazole foam was statistically superior to its vehicle in the treatment of the erythema, scaling and induration of seborrheic dermatitis (secondary endpoints), although the reviewer does not consider induration to be a classic sign of seborrheic dermatitis.

Sub-group analyses were performed on the primary endpoint for age, gender, race, and baseline Investigator's Global Assessment. Treatment success rates in the sub-group analyses for age, gender and race were similar to the success rate from the primary analysis for the comparison between Ketoconazole foam and its vehicle.

Safety

The most common adverse events in the safety population were "Application site burning" (10% of subjects in the ketoconazole foam group) and "Application site reaction NOS" (4%)

“Application site reaction” was the third most common event (3%). The most common treatment-related adverse event in the safety population for ketoconazole foam treated subjects was “application site burning”: 67 (10%) in the ketoconazole foam group [49 (10%) in the vehicle foam group, 4 (1%) in the ketoconazole cream group, and 2 (1%) in the vehicle cream group]. The second most common treatment-related adverse event in the safety population for this group was “application site reaction NOS”: 24 (4%) in the ketoconazole foam group [8 (2%) in the vehicle foam group, 5 (1%) in the ketoconazole cream group, and 1 (1%) in the vehicle cream group]. Other treatment-related adverse events that occurred at $\geq 1\%$ in the ketoconazole foam group were:

- application site reaction in 17 subjects (3%) [16 (3%) in the vehicle foam group, 3 (1%) in the ketoconazole cream group, and 1 (1%) in the vehicle cream group],
- application site pruritus in 5 subjects (1%) [4 (1%) in the vehicle foam group, 2 (<1%) in the ketoconazole cream group, and 2 (1%) in the vehicle cream group], and
- application site erythema in 4 subjects (1%).

As was the case for the total safety population, “Application site burning” was the most common adverse events in the sub-group analyses, and this event was generally reported at the same rate as in the total safety population, i.e. approximately 10%.

An adequate number of subjects were exposed to the applicant’s product to characterize its safety in the short-term (4 weeks). Doses and durations of exposure were adequate to assess the safety of the product for its intended use. Topical safety was adequately evaluated by clinical assessments at each study visit in the pivotal trial and by the conduct of formal dermal safety studies. Long-term safety has not been evaluated.

9.2 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that the application be approved.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no recommendations for any specific risk management activities.

9.3.2 Required Phase 4 Commitments

The applicant should conduct a study in which the long-term safety of their product is assessed, as per the ICH E1A guidelines.

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9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

To be entered as an addendum.

9.5 Comments to Applicant

None

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10 APPENDICES

None

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On Original

Clinical Review
Brenda Carr, M.D.
NDA 21-738 N-000
Extina (ketoconazole foam)

REFERENCES

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- ² Sheppard D and Lampiris HW. Antifungal Agents. In: Katzung BG, editor. *Basic & Clinical Pharmacology*. New York: Lange Medical Books/McGraw-Hill; 2001: 817-821.
- ³ Bodey GP. Azole Antifungal Agents. *Clinical Infectious Diseases* 119;14(Suppl 1):S161-9.

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/s/

Brenda Carr
6/7/2007 11:55:43 AM
MEDICAL OFFICER

Jill Lindstrom
6/7/2007 02:46:11 PM
MEDICAL OFFICER
The UV absorbance study (p42) is not a Phase 4 commitment

Susan Walker
6/11/2007 12:38:24 PM
DIRECTOR

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Clinical Review of Teleconference Request

Subject: Extina Clin/Stat teleconference

Drug: Extina (Ketoconazole Foam 2%)

Indication: Seborrheic dermatitis

Applications: NDA 21-738; IND 63,153

Date of teleconference: February 13, 2006

Date of teleconference pre-meeting: February 6, 2006

Category: Post-Action

Clinical reviewer: Phyllis Huene, M.D.

Team Leader: Markham Luke, M.D.

Project Manager: Felecia Curtis

The sponsor wishes to discuss in this meeting the Agency fax of December 28, 2005, in which the following clinical comments were made on the Phase 3 study KFD.C.005:

- 1) The primary efficacy variable should be a score of 0 for erythema, scaling, and the General Assessment, or a score of 1 for each parameter if the baseline score were 3 or greater.
- 2) Induration is not a feature of seborrheic dermatitis and should be deleted from the scoring scales.

The sponsor makes the following arguments in this regard.

- a) The Division's comments are too late to be implemented in the ongoing study, which was initiated in September, 2005, with more than half the planned 1100 subjects enrolled as of January 2006.
- b) Study KFD.C.005 was submitted to the Division in April 2005 in an information package for a Type C meeting, and the stated purpose of the meeting was to obtain Agency agreement on the design of the study. While the Division offered comments on other aspects of the study design, the sponsor did not receive guidance on changing the definition of the primary outcome measure, or excluding induration from the rating scales.
- c) This request appears to conflict with the Guidance offered by the Division in the Post-Action meeting of March 9, 2005, in which the Division recommended that we repeat the original Phase 3 study but did not recommend any changes to that study design.
- d) When the original Phase 3 study KFD.C.002 is analyzed using the primary outcome measure now proposed by the Division, Extina demonstrates superiority over the vehicle foam and non-inferiority to Nizoral. This was considered by the Division to be a post-hoc analysis, and therefore not of substantial regulatory utility.

- e) Induration is an inherent part of the General Assessment scale currently used by the investigators and is an inclusion criterion. The subjects already enrolled have demonstrated indurated disease, as judged by the study's 26 investigator dermatologists. Indurated papules and plaques are a result of the spongiosis, papillary dermal edema, and epidermal hyperplasia. Although severe seborrheic dermatitis can be present without significant induration, induration is often a clinically significant feature.

The sponsor wishes to discuss the following proposals (as summarized by this reviewer):

- 1) Because the Division is now requesting that the identical endpoint definition applied post hoc in KFD.C.002 be used in the primary efficacy analysis of KFD.C.005, the sponsor requests that the Division reconsider the regulatory value of the post hoc analysis of KFD.C.002, and reopen review of the original NDA.
- 2) Should the Division agree that the analysis in the original NDA demonstrates that Extina is superior to its vehicle and non-inferior to the reference listed drug, and if the Division agrees that this reassessment establishes adequate evidence of safety and efficacy consistent with the Division's current preferred definition of the primary outcome measure, the sponsor requests that the Division consider approval of NDA 21-738 based on the contents of the original NDA.
- 3) If the NDA were approved based on this re-analysis, KFD.C.005 would be amended to make safety the primary objective of the study, and would complete the study as a post-approval commitment to provide additional safety data.
- 4) If the Division does not agree that the analysis in the original NDA provides a sufficient basis for approval, the sponsor proposes that the present study be completed as per the protocol, and the analysis of the outcome measure as defined by the Division be provided as a principal secondary endpoint. Induration would not be removed as an inclusion criterion or as a component of the disease assessment.

Reviewer's evaluation: The Agency comments in the facsimile of December 28, 2005 are the current Agency recommendations for the conduct of studies in seborrheic dermatitis, and have been conveyed to other sponsors in the review of similar protocols. However, in instances where a sponsor has conducted the study but has not precisely followed the Agency recommendations for the scoring scale or the primary efficacy variable, and these are felt by the Agency to be reasonable assessments, the Agency has accepted the sponsor's methodology.

This reviewer agrees with the sponsor that it is unreasonable to ask the sponsor to change the protocol at this point when more than half of the anticipated patients have already been enrolled.

This reviewer recommends that the sponsor's fourth proposal be accepted, that is, that the present study be completed per protocol, and the analysis of the outcome measure as defined by the Agency be provided as a secondary endpoint.

Information to be conveyed to the sponsor: Reference is made to your communication of January 16, 2006, in which you request a teleconference to discuss the comments in the Agency communication of December 28, 2005.

The clinical comments which were conveyed to you were made in the belief that the study had not already been initiated. While our comments reflect the Division's preferred study design for seborrheic dermatitis, we acknowledge that there is more than one acceptable definition of the primary endpoint. We therefore agree with the fourth proposal in your communication, namely, that the present study be completed as per protocol.

It appears that the scheduled teleconference on February 13, 2006 is no longer needed, unless you would like to retain this for further discussion.

Phyllis A. Huene, M.D.

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/s/

Phyllis Huene
2/6/2006 02:46:34 PM
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Markham Luke
2/6/2006 03:25:41 PM
MEDICAL OFFICER
Comments to be conveyed

Stanka Kukich
2/7/2006 12:05:51 PM
MEDICAL OFFICER

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Team Leader Summary
NDA 21-738 TRADENAME (ketoconazole) Foam, 2%

November 18, 2004

Sponsor: Connetics Corporation

Indication: Topical treatment of seborrheic dermatitis

PDUFA Due Date: November 26, 2004

The Clinical Team Leader concurs with the Primary Medical Reviewer, Dr. Phyllis Huene, regarding her conclusion that this application is Not Approvable, as the one clinical study submitted failed to statistically demonstrate superiority of the product over its own vehicle for the indication of the topical treatment of seborrheic dermatitis.

Biostatistical Evaluation of Efficacy

The Primary Biostatistics Reviewer, Dr. Kathleen Fritsch indicates that "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." Non-inferiority of the foam to another active is insufficient evidence of efficacy when in the same study there is a failure to demonstrate superiority of the foam active to its own vehicle.

As Dr. Fritsch states, "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))."

Of note, the study failure could possibly be attributed to the uneven randomization of the arms, as subjects were randomized in a 3:1:3:1 ratio to ketoconazole foam, vehicle foam, ketoconazole cream, and vehicle cream, respectively. Dr. Fritsch indicates that "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."

Dr. Fritsch concludes that "an additional study is needed to demonstrate the statistical superiority of ketoconazole foam to its vehicle." A caveat to this study requirement is needed in that the ketoconazole foam should also be non-inferior to the active comparator ketoconazole cream in the same study. Failure to demonstrate superiority of the ketoconazole foam to its own vehicle in Study KFD.C.002 does not allow a conclusion that some efficacy was demonstrated in the non-inferiority comparison of the ketoconazole foam with ketoconazole cream. An additional 3 or 4 armed study is needed.

Of note, the high success rate (>40%) of the foam vehicle may suggest that the vehicle itself may have some contribution to efficacy. A Phase 2 study may have been able to reveal this potential and guided the design of the pivotal Phase 3 study had such a

study been done. Results from the submitted study KFD.C.002 could be used to help power the future study.

Clinical Safety Evaluation

Of note a long-term safety evaluation with this product has not been initiated by the Applicant (as per ICH E1A). Such an evaluation could be part of a post-marketing commitment may not be needed prior to approval based on current assessment of this product.

CMC Concerns

Several concerns are raised by the CMC reviewer, Dr. Allan Fenselau, regarding the integrity of the drug product. These concerns have not been adequately addressed by the Applicant despite ample communication on the part of the Agency.

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This issue is not viewed as an Approvability issue as the

However, the Applicant should provided the needed

b(4)

Similarly,

However, the Applicant should attempt to re-evaluate whether it has the best container for this formulation.

Conclusion

It is recommended that NDA 21-738 not be approved. It is recommended that the Applicant conduct an additional clinical study to demonstrate that its product is superior to its own vehicle and non-inferior to the active comparator.

Further, it is recommended that the Applicant include a long-term safety evaluation of their product as per ICH E1A.

Finally, the Applicant should address CMC concerns as recommended by the CMC review.

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

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/s/

Markham Luke

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TL Summary. See also primary Biostat, Clinical and CMC
reviews.

Stanka Kukich

11/23/04 10:33:10 AM

MEDICAL OFFICER

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Correspondence date: January 26, 2004
CDER Stamp date: January 28, 2004

MEDICAL OFFICER'S REVIEW OF NDA 21-738
ORIGINAL SUBMISSION

DATE: September 9, 2004

SPONSOR: Connectics Corporation

DRUG: Ketoconazole Foam 2%

PROPOSED TRADE NAME: Extina

INDICATION: Seborrhic dermatitis

PROPOSED LABELING INDICATION: For the topical treatment of seborrhic dermatitis.

RELATED APPLICATIONS: IND 63,153

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Executive summary

- 1) Recommendations on approvability: The application is not approvable for Ketoconazole Foam 2% for the indication "for the topical treatment of seborrheic dermatitis." Effectiveness has not been demonstrated, because Ketoconazole Foam has not been shown to be superior to its vehicle.
- 2) Summary of clinical findings.
 - A. Overview of clinical trials.

This is a 505(b)(2) application. The following clinical studies have been submitted in support of the application.

Overview of clinical studies		
Study #	Design	# pts
KFD.C.004	Contact sensitization	192
KFD.C.003	Pharmacokinetic	21
KFD.C.002	Phase 3 safety and efficacy	619

B. Efficacy.

Study 002 has been submitted as the sole pivotal study for a demonstration of safety and efficacy. This was a double blind, multicenter, randomized comparison of Ketoconazole Foam 2% with Nizoral (ketoconazole) Cream 2%, and with the cream and foam vehicles, in the treatment of patients with mild to severe seborrheic dermatitis. Applications were made twice daily for four weeks.

The pertinent efficacy parameters were scoring of erythema and scaling at a target lesion, and an Investigator's Static Global Assessment (ISGA). The predesignated primary efficacy variable was the proportion of patients with an ISGA score of 1 or 0 at the end of treatment.

Analysis of the results showed that Ketoconazole Foam was non-inferior to Nizoral Cream, but that Ketoconazole Foam was not superior to its vehicle. Because it is necessary for a demonstration of effectiveness that the product is shown to be superior to its vehicle, the conclusion is that the effectiveness has not been established. Our biostatistician is in agreement with this analysis and conclusion.

C. Safety.

Adverse events in Study 002 were local cutaneous burning, stinging, itching, or tingling in approximately 15% of patients with both Ketoconazole Foam and its vehicle. Laboratory tests, including hemograms and clinical chemistries, showed no drug-related changes.

The incidence of sensitization may have been underreported in the sensitization study (#004), due to the stringency of the criteria for the occurrence of sensitization.

D. Requirements for approval.

For approval of Ketoconazole Foam for the treatment of seborrheic dermatitis, the following are recommended.

1. A controlled clinical trial which compares Ketoconazole Foam to the foam vehicle, with results that show that the active foam is superior to its vehicle. The sponsor should submit the protocol for our review, preferably as a Special Protocol Assessment request, prior to initiation of the study.
2. A long term open label safety study.

Labeling indication, dosage and administration

These sections of the proposed labeling are as follows.

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Request for pediatric waiver

The sponsor has requested a waiver of pediatric studies for seborrheic dermatitis in children under 12 years of age. The reason given is that such a waiver is based on agreements with the FDA, namely, that in the End of Phase 2 meeting and the pre-NDA meeting, the Division concurred that the inclusion of subjects younger than 12 was not required.

Reviewer's evaluation: The Agency stated in the Pre-IND/End of Phase 2 meeting that the sponsor should provide a rationale for exclusion of children less than 12 years of age, and request a waiver, which appears to be appropriate. When queried by the sponsor in the pre-NDA teleconference, the Agency stated that the inclusion of subjects younger than 12 is not required. However, the sponsor needs to provide the rationale for a request for a pediatric waiver in this age group, presumably based on the lack of occurrence of seborrheic dermatitis in

subjects less than 12 years.

Financial disclosure

The sponsor has provided the following statement:

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

Listed are the investigators for the phase 1 irritation and sensitization study (KFD.C.004) and the Phase 3 study (KFD.C.002), with the exception of _____ received \$38,000 in a study specific payment and \$55,000 as an honorarium from the sponsor.

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Guidance meeting

A Guidance meeting was held on April 9, 2001. At that time the sponsor had proposed _____

b(4)

_____ The clinical comments relevant to a sole indication of seborrheic dermatitis are summarized by this reviewer as follows.

- 1) In regard to topical safety studies, the Agency recommended that irritation and sensitization studies be performed, noting that it is unclear what the irritation potential of _____ will be in combination with the other listed excipients. The presence of ethyl alcohol may enhance irritation potential.

b(4)

The Agency stated that the new formulation of ketoconazole foam is substantially different from the reference listed product. The final concentration of ketoconazole (minus any volatile excipients including ethyl alcohol) appears to be greater than _____

b(4)

- 2) In comments on the proposed clinical plan, the Agency said that due to differences in formulation of the foam product and the cream product, it is expected that some clinical differences in safety and efficacy may result in the need for clinical studies to be conducted to compare the two products. Such studies should compare the efficacy of the proposed product with the reference listed drug, and demonstrate non-inferiority. A foam vehicle comparator arm is recommended, and a demonstration of superiority

over the vehicle will be needed.

Pre-IND/End of Phase 2 meeting

A Pre-IND/End of Phase 2 meeting was held on July 30, 2001. The salient part of the clinical portion of the meeting minutes is summarized by this reviewer as follows, according to each topic under discussion, as designated below.

- 1) Regulatory pathway: The Agency agreed that a 505(b)(2) application seems to be an appropriate regulatory pathway, given that the sponsor will conduct studies that will support changes made to the Reference Listed Drug.
- 2) Clinical study design: In response to the sponsor's question concerning the design of the clinical study, the Agency replied that commitments regarding specific Phase 3 protocols will be given once the formal protocols are submitted and reviewed. The Agency said that the study should be powered to show that ketoconazole foam 2% is not inferior to the active comparator (non-inferiority design) using the following criteria for non-inferiority: two-sided 95% confidence interval, or one-sided 97.5% confidence interval to show noninferiority of 10%.
- 3) Safety database: The sponsor inquired about the adequacy of the safety database at the conclusion of the clinical studies. The safety parameters will consist of blood pressure, pulse and adverse events in all 360 patients, 120 of whom will be on ketoconazole foam; CBC and liver function tests in 180 patients, 60 of whom will be on ketoconazole foam, and, in the bioavailability study, blood pressure, pulse, and adverse events in an additional 60 patients on ketoconazole foam.

The Agency stated that without knowledge of the results of the PK studies, it is difficult to state if this safety monitoring is sufficient to support adequate evidence of safety. If the PK studies reveal that there is little to no absorption of the product in patients with seborrheic dermatitis, this monitoring may be sufficient. If there is evidence of absorption, it may be necessary to perform more extensive safety testing.

- 4) Dermal safety studies: In regard to phototoxicity and photosensitization studies, the Agency stated that these studies may be waived if there is no drug product absorption in the ~~_____~~ nM spectrum. The sponsor was requested to provide a point estimate of absorption at ~~_____~~ nM so that this determination may be made.

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The sponsor stated that they believed that the dermal safety of ketoconazole and the safety of the foam formulation have been demonstrated in clinical studies previously submitted to the FDA, and that they do not plan to conduct additional human dermal irritation/sensitization studies on ketoconazole foam, 2%. The Agency stated that we do not concur with this plan, and that the new formulation of ketoconazole foam, 2%, is substantially different from the proposed RLD. The presence of ethyl alcohol may enhance irritation potential. The Agency recommended that the sponsor perform human dermal irritation/sensitization studies on the to-be-marketed formulation of ketoconazole foam 2%.

- 5) Pediatric studies: In response to the sponsor's question concerning the need for pediatric studies, the Agency stated that the sponsor should provide a rationale for exclusion of children less than 12 years of age, and request a waiver, which appears to be appropriate for this indication.

In response to the sponsor's question as to whether their clinical study plan fulfills the current pediatric study requirements for the population between 12 and 17 years old, the Agency stated that it appears that the PK portion of the study does not include this pediatric subset. While there may not be great differences in the absorption of ketoconazole foam in this population as compared with older adults, this is not known, and children 12-17 years old should be included in the PK portion of the study.

The Agency said that it is also important to have sufficient numbers of patients in these age groups (12-17 years) equally divided between the different arms of the study. Although literature may support equivalent disease process response, there may be differences in the safety profile. The sponsor was requested to ensure that there are adequate numbers of patients in the age ranges of 12-17 years and greater than 65 years.

- 6) Concurrent performance of PK and clinical studies: In response to the sponsor's question as to whether the two proposed clinical studies may be conducted concurrently, the Agency stated that, while they may be conducted concurrently, the PK study may reveal information that would alter requirements for the pivotal Phase 3 study (i.e., number of patients needed, safety monitoring). It might be a better use of the sponsor's resources to determine this information first, so that the number of patients and the safety monitoring required for Phase 3 studies might be minimized if the PK study supports this.

- 7) Additional Agency comments.

- a. Regarding the seborrheic dermatitis rating scale: The Agency stated "The difference between a score of 1 and 2 may be difficult to differentiate clinically. Patients who have a baseline score of 2 should improve to a score of 0 to be considered a success, those with a baseline of 3 should go to a

score of 1 or 0, those with a baseline score of 3 or 4 should improve to a 1 or 0 to be considered a success."

- b. Regarding drug administration procedures in the proposed study as described in the briefing package: The Agency stated "It may be more appropriate for the patient to have written instructions to follow for application of the study treatment rather than instruction by a nurse/coordinator. This would more closely replicate use conditions, and would improve the blind because the nurse/coordinator would not have to know what product was being used."
- c. Regarding primary efficacy endpoints: The Agency stated "The Investigator's Global assessment should take into account a patient's global condition at one point in time. To limit this evaluation to one target area in one geographical area of the body would not have much clinical significance and is not recommended."
- d. Regarding secondary efficacy endpoints: The Agency made comments on changes in pruritus scores, the subject's global assessment, and a quality of life index.

Clinical/Biostatistical teleconference of August 20, 2001

This teleconference was in response to a meeting request by the sponsor, and the discussion was based on the sponsor's briefing package. The verbatim clinical portion of the meeting minutes is as follows.

Agency: A non-inferiority margin (absolute) of 10% is appropriate. The Agency agrees that if the Sponsor can achieve an absolute margin of 10% to the listed drug in its studies, then the Sponsor will have demonstrated non-inferiority. If the results of the studies fail to meet a 10% non-inferiority margin despite adequate sample size and protocol design, the Sponsor should address this in its NDA submission which will be reviewed by Agency.

Sponsor: The Sponsor stated that it will evaluate its results from a separate PK study to assist in determining sample size for the Bioequivalence study.

Agency: Agency agreed that this could be appropriate, as no data from Phase 2 studies regarding rate of efficacy of the proposed product were currently available."

Facsimile of February 11, 2002

The clinical comments and recommendations in the review of the original submission of IND 63,153, made by Lisa Mathis, M.D., were conveyed to the sponsor on 2/11/02. This submission provided for Protocol KFD.C.001, an open label bioavailability study of Ketoconazole foam and Nizoral cream in the treatment of moderate to severe seborrheic dermatitis.

The Agency comments were as follows.

- 1) It is strongly recommended that the person responsible for monitoring the safety of a drug have adequate training to assess the health effects of the drug on patients enrolled in the study. It is preferable that a Physician (M.D. or D.O.) holds this position.
- 2) PIs and IRB information must be submitted prior to initiation of this study.
- 3) Please ensure that there are adequate numbers of patients in the age ranges of 12-17 years and greater than 65 years. It may be helpful to stratify subjects by age.
- 4) The Sponsor may wish to exclude patients with this condition in their groin and armpits so that they do not have to endure 4 weeks without treatment.
- 5) The PK data obtained from this study should be obtained under conditions that reflect future clinical use. If patients will be using this medication in the groin and/or axilla, it is recommended that the study subjects also be allowed to use the products in these areas of the body.
- 6) It would be prudent to monitor serum chemistries and hepatic function in patients enrolled in this study. Please note that if the PK study demonstrates that there are detectable serum levels of ketoconazole, these tests may also be requested for Phase 3 trials.
- 7) It is recommended that the most sensitive pregnancy test be used to assess for pregnancy.
- 8) Initial application should be at home, not clinic, unless difficulties in subjects' application technique are anticipated that would necessitate in product labeling special instructions to apply first dose in clinic.
- 9) The Sponsor will use results from the Phase 2 PK study to determine the number of patients required for Phase 3 stud(ies). As discussed in the teleconference 8/20/01, the stud(ies) should be powered to show that ketoconazole foam is not inferior to the active comparator (non-inferiority design) using the following criteria for non-inferiority: two-sided 95% confidence interval (CI), or one-sided 97.5% confidence interval to show non-inferiority of 10%.
- 10) It appears that the future clinical study plans include a study that compares ketoconazole foam, 2%, against ketoconazole cream, 2%, as well as placebo. The planned analysis appears to compare primary efficacy versus placebo as well as non-inferiority to the listed drug. Please submit all protocols to the Division to obtain

concurrence on clinical study and statistical analysis plan."

Facsimile of February 15, 2002

This facsimile conveyed the comments from the clinical review of amendment 003 to IND 63,153. This amendment provided a protocol for an open label bioavailability and efficacy study on Ketoconazole foam and Nizoral cream.

The Agency comments were as follows.

- "1. The Sponsor must provide the name of the IRB and primary investigator to the FDA.
2. Please ensure that there are adequate numbers of patients in the age ranges of 12-17 years and greater than 65 years. It may be helpful to stratify subjects by age.
3. Patients with seborrheic dermatitis in the axilla and groin are not allowed to use study medication in these sites, and the exclusion criteria prevent them from using other treatments as well. There may be ethical concerns of enrolling patients and not treating the condition of interest.
4. All of a patient's lesions (including non-scalp lesions) should be treated and assessed.
5. Also, unless there is a reason why patients should not use this product in these areas, they should be included in the PK study so that true use conditions are represented in the results.
6. It would be prudent to monitor serum chemistries and hepatic function in patients enrolled in this study. Please note that if the PK study demonstrates that there are detectable serum levels of ketoconazole, these tests may also be requested for Phase 3 trials.
7. If a nurse is required to observe the initial application, data regarding whether the patient was able to properly administer the medication, or whether they needed correction should be collected and provided to the Agency.
8. The Sponsor will use results from the Phase 2 PK study to determine the number of patients required for Phase 3 stud(ies). As discussed in the August 20, 2001 teleconference, the stud(ies) should be powered to show that ketoconazole foam is not inferior to the active comparator (non-inferiority design) using the following criteria for non-inferiority: two-sided 95% confidence interval (CI), or one sided 97.5% confidence interval to show non-inferiority of 10%."

Facsimile of March 7, 2002

This facsimile conveyed the comments from the clinical review of amendment 004 to IND 63,153, done by Lisa Mathis, M.D. As described in the medical officer's review, this amendment provided a protocol for Study KFD.C.002, a Phase 3 comparison of the safety and efficacy of Ketoconazole foam and Nizoral cream. The four treatment arms were to be Ketoconazole foam, the foam vehicle, Nizoral cream, and the cream vehicle. The grading scales for erythema, scaling, induration, and pruritus, and for the investigator's global assessment, were the same as in the final study report for Study KFD.C.002 in this NDA. Grading of clinical signs was to be done at a target lesion selected at baseline. The primary efficacy variable was to be the proportion of patients that had an Investigator's Static Global Assessment score of 0 or 1 at week 4 (or end of treatment) in the sum of individual scores [sic] of signs of seborrheic dermatitis (erythema, scaling, and induration) at the target lesion. Patients with a baseline score of 2 had to have a score of 0 to be considered a success.

The Agency comments were as follows.

1. There should be adequate numbers of patients in the age ranges of 12-17 years and greater than 65 years. These subjects should be stratified by age.
2. Because this is a Phase 3 study, patients should not be excluded based on 10% or less body surface area involvement.
3. The patients in this study are to use a restricted amount of medication that is not based on the extent and natural history of the seborrheic dermatitis in the effected patients. The Sponsor should design this Phase 3 study to reflect actual clinical use conditions, or provide scientific rationale for using the proposed study design.
4. Subjects in this study are not allowed to use concomitant medications for the treatment of seborrheic dermatitis, and are limited to 50 grams of study medication per week. The denial of treatment to patients having involved skin in the axilla and groin that may cause discomfort is problematic, and may result in an inability to determine the efficacy of the product. One possible solution is to have the study mimic real use conditions where patients are allowed to use as much medication as is required to treat the condition that is being treated.
5. All lesions (to include all non-facial lesions) in individual subjects should be treated and evaluated.
6. If a nurse is required to observe the initial application, data regarding whether the patient was able to properly administer the medication, or whether they needed correction should be collected and provided to the Agency.
7. If photographs are to be used in advertisement, the Agency requests that the photographs are submitted along with the NDA to

ensure that the photos are representative of the response to treatment rather than selected best case scenarios.

8. There are many secondary endpoints listed in this protocol. If the Sponsor plans to show the results of the secondary endpoints in the label, then the number of secondary endpoints should be reduced. Otherwise, a p-value adjustment for multiple comparisons will be required.
9. The change in quality of life may have little regulatory utility for this indication."

Facsimile of January 14, 2003

This facsimile conveyed the comments from the clinical review of amendment 025 to IND 63,153, done by Joseph Porres, M.D. As described in the medical officer's review, this amendment provided a protocol for Study KFD.C.003, an open label study to compare the bioavailability of ketoconazole foam and Nizoral cream. It is noted in the review that this submission was for a slightly different formulation than that in the original submission, and that in the previous study the blood levels [of ketoconazole] were less than 5 ng/mL for Nizoral cream, while for ketoconazole foam three subjects had serum levels between 5-10 ng/mL, the maximum reported level being 8 ng/mL.

The Agency comments were as follows.

- "1. The exact composition of the new ketoconazole foam, 2%, formulation should be stated in the protocol.
2. Please ensure that there are adequate numbers of patients in the age ranges of 12-17 years and greater than 65 years. It may be helpful to stratify subjects by age.
3. It would be prudent to monitor serum chemistries and hepatic function in patients enrolled in this study. Please note that if the PK study demonstrates that there are detectable levels of ketoconazole, these tests may be needed for Phase 3 trials.
4. Blood should be obtained at the time when serum levels are anticipated to be highest."

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Pre-NDA teleconference

A pre-NDA teleconference was held on May 30, 2003. The clinical portion of the meeting minutes is summarized by this reviewer as follows.

- 1) The Sponsor stated that they propose to submit a 505(b)(2) NDA, using the CTD organization. The Sponsor asked whether the Agency finds the proposed format and structure for the NDA, as provided in the briefing package, acceptable for submission.

The Agency replied that the proposed format appears to be generally appropriate. The Sponsor was referred to the Agency's further comments on CTD and on electronic vs paper submissions.

- 2) The Sponsor listed the number of copies of each module it planned to submit; the Agency said that the number of copies for clinical review appeared to be adequate.
- 3) In response to a question by the Sponsor, there was a discussion of the format preferred for electronic documents. This was followed by a listing by the Agency of all the information that should be included in the data sets.
- 4) The Sponsor had a question on the User Fee assessment; they were referred to the User Fee staff.
- 5) The Sponsor asked whether the Agency agreed with the Sponsor's understanding that inclusion of subjects less than 12 years of age in the clinical studies is not a requirement for approval of Ketoconazole Foam, 2%, for seborrheic dermatitis. The Agency stated that inclusion of subjects younger than 12 is not required.
- 6) The Sponsor asked whether the Agency agreed with the proposal to include copies of the clinical photographs for KFD.C.002 only in the archival copy and one designated review copy of Module 5 of the CTD. The Agency replied that supplying them in one module seems adequate.
- 7) An additional Agency comment was made, which stated that, as agreed at the End of Phase 2 meeting, approval via the 505(b)(2) route will be contingent on the demonstration that the active is superior to its vehicle, as well as non-inferior to the Reference Listed Product.
- 8) As an addendum, the Agency commented that the sponsor would be taking an enormous risk with an NDA submission where a clear demonstration of superiority of efficacy of the drug product vs the vehicle is lacking. The sponsor was referred to the biostatistical comments in this regard.

Response to filing letter

The Filing Communication Letter, dated April 7, 2004, had the following clinical comments.

- "1. There do not appear to be adequate numbers of patients in the 12 to 18 year age range.
2. As was stated in the pre-NDA meeting, there is risk with an NDA submission in which a clear demonstration of superiority of the drug product over the vehicle is lacking."

The sponsor's response to these comments is provided in the amendment of July 23, 2004, and is summarized by this reviewer as follows.

1. In an attempt to address the Agency's request that adolescent patients be included in the clinical studies, enrollment criteria for the comparative bioavailability study and the Phase 3 study permitted inclusion of subjects in this category. Stratification by age was not specified in the study protocols as the Agency did not provide any specific requirements regarding the exact number of adolescent subjects required for approval. The number of adolescent subjects participating in the studies directly reflects the percentage of adolescent patients typically seen at the participating centers.

The sponsor believes that the application meets the statutory requirements under Section 505(b)(2) of the Act for product approval in that the development program was consistent with the intent of the Act by only undertaking conduct of appropriate bridging studies to the RLD and not including duplicative studies to demonstrate what is already known about the drug.

It is their belief that the number of adolescent subjects included in the Phase 3 study allows for an assessment of this age subpopulation. The subgroup analysis for the adolescent population did not show major differences in success rate in the Investigator's Global Assessment nor in the safety profile from that of the adult population.

2. The protocol for the Phase 3 study was written as a non-inferiority study design consistent with requirements outlined in ICH E9, "Statistical Principles for Clinical Trials", agreements reached at the End of Phase 2 meeting, and comments received following completion of the Special Protocol Assessment. As stated in the statistical section of the study protocol, a comparison between Ketoconazole Foam and its vehicle was to be performed in order to assure the validity of the study design. This comparison primarily serves to evaluate for assay sensitivity in support of the non-inferiority claim, as opposed to supporting a claim of efficacy over placebo. This comparison assesses whether the study design is capable of detecting a treatment effect if in fact a treatment effect is present.

The results from Study KFD.C.002 demonstrated statistical superiority of Ketoconazole Foam over Vehicle Foam for every efficacy variable except the primary study endpoint. Accordingly, the sponsor believes that the totality of the data supports demonstration of assay sensitivity and non-inferiority of Ketoconazole Foam to Nizoral Cream. An independent assessment performed by Statistical Collaborative is in agreement with the sponsor.

Overview of clinical studies

The following clinical studies were submitted in support of this application.

Overview of clinical studies		
Study #	Design	# pts
KFD.C.004	Contact sensitization	192
KFD.C.003	Pharmacokinetic	21
KFD.C.002	Phase 3 safety and efficacy	619

Study KFD.C.004 (Irritation and sensitization)

This study was conducted by Karl Beutner, M.D., Solano Clinical Research, Davis, CA. The study population was 216 healthy subjects, of which 192 subjects completed the study.

The test articles were Ketoconazole foam 2%, vehicle foam, sodium lauryl sulfate 0.2% in a cream vehicle, and distilled water. For application of the foam products, a small amount of foam was released into a glass container, which was sealed and heated to 37C in a water bath to liquify the foam. The liquified foam was applied to patches for application.

During the induction phase the articles were applied under occlusive patches to the same randomly designated sites on the back, three times weekly for three weeks. The patches were left in place for 48 hours on Mondays and Wednesdays and for 72 hours on Fridays. At each patch removal the skin reactions were scored by a treatment blinded evaluator, using the following scale.

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0	no visible reaction
0.5	barely perceptible erythema
1	slight erythema
2	noticeable erythema with slight infiltration
3	erythema with marked edema
4	erythema with edema and blistering

If severe irritation (Grade 4) were observed at any site, the patch was to be dropped.

After a two week rest period, challenge patches were applied to naive sites on the back for 48 hours. Evaluation of skin reactions was made on removal of the patches, at 24 hours later, and, if indicated, at 48 hours after patch removal, using the same scale as in the induction phase. Subjects who displayed signs of sensitization were to be re-challenged with a 48 hour patch at a new skin site, with evaluations made at patch removal and 24 hours later.

Results were as follows.

Of the 216 subjects enrolled in the study, 192 subjects completed the study. Of the 24 subjects that were discontinued from the study, 11 were terminated due to non-compliance, 8 terminated due to adverse experiences, and 5 requested to withdraw early from the study. The adverse experiences were pruritus at the patch sites in 5 subjects, and unrelated intercurrent illness in 3.

Induction phase: Results during the induction phase are presented as mean irritation scores and cumulative skin reaction scores. Mean irritation scores were the sum of the skin reaction scores divided by the total number of evaluations performed. Cumulative skin reaction scores were calculated, and were then compared to the maximum potential cumulative skin reaction score, i.e., the maximum skin reaction score of 4 multiplied by the number of evaluations.

The mean irritation and cumulative irritation scores were as follows.

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	Mean irritation score	Cumulative skin reaction score	
		Cumulative score	Maximum possible cumulative score
Ketoconazole foam	0.63	1132	7184
Vehicle foam	0.56	1001	7184
Sodium lauryl sulfate	0.34	615	7184
Distilled water	0.21	380	7180

The number of subjects with each score at the end of the induction period was as follows.

Score	Water n=216	Ketoconazole foam n=216	Sodium lauryl sulfate n=216	Vehicle foam n=216
0	151 (70%)	69 (32%)	100 (46%)	80 (37%)
0.5	20 (9%)	28 (13%)	36 (17%)	30 (14%)
1	11 (5%)	40 (19%)	38 (18%)	39 (18%)
2	5 (2%)	37 (17%)	9 (4%)	25 (12%)
3	6 (3%)	16 (7%)	8 (4%)	16 (7%)
4	1 (0%)	4 (2%)	3 (1%)	4 (2%)
NA	22 (10%)	22 (10%)	22 (10%)	22 (10%)

Challenge phase: The criteria for contact sensitization included the following: 1) the patch site reached a Grade 3 or 4 reaction at the initial reading, 2) the reaction persisted at least 24 hours after patch removal, and 3) the reaction was reproducible on rechallenge.

During the challenge phase, 30 subjects had an additional evaluation at 48 hours after patch removal. Of these, 15 subjects were identified by the investigator as having reactions consistent with possible sensitization. Three of these subjects did not return for rechallenge. Twelve subjects had a rechallenge patch.

The re-challenge patch reactions for both Ketoconazole foam and the foam vehicle were deemed consistent with contact sensitization in 9 subjects. An additional 2 subjects also showed reactions

consistent with contact sensitization at the Ketoconazole foam and vehicle sites, but were considered to have been possibly incorrectly patched, with indeterminate results. In one subject sensitization could not be determined. There was no evidence of sensitization to the two control test articles.

Reviewer's evaluation of Study KFD.C.004: Results in the challenge phase were reported as consistent with contact sensitization to both the active foam and the vehicle in 9 patients, or about 5%. It appears to this reviewer that the number of patients developing sensitization may have been underreported. The first criterion used to determine sensitization, namely, that the patch site had to show a reaction of Grade 3 (erythema with marked edema) or Grade 4 (erythema with edema and blistering) at the initial reading (patch removal), is too stringent, and may have caused instances of sensitization to be overlooked. Also, the third criterion was that the reaction had to be reproducible on re-challenge, and yet perusal of the individual data listings shows that an additional 16 subjects who met the first two criteria for sensitization (Grade 3 or 4 reaction at the initial reading, persistence of the reaction 24 hours later) did not have a re-challenge and so were not recorded as possible sensitization. If these 16 subjects are included as being sensitized, the incidence of sensitization is about 13%.

Reviewer's conclusion on Phase 1 studies: Under the exaggerated exposure conditions of the induction phase, Ketoconazole Foam and the vehicle foam showed a higher level of irritation than the negative control, and a level of irritation roughly comparable to the positive control, 0.2% sodium lauryl sulfate cream, but had a generally low level of irritation overall. Ketoconazole foam was associated with a grade 3 reaction (erythema with marked edema) in 7%, and a grade 4 reaction (erythema with edema and blistering) in 2%. The remainder of the subjects showed no or mild irritation.

The incidence of sensitization may have been underreported in the sensitization study, due to overly stringent criteria used to determine sensitization.

The absorption spectrum for Ketoconazole Foam shows no absorption in the _____ nm range. A waiver of phototoxicity and photosensitivity studies has been requested, and the waiver should be granted.

b(4)

Study KFD.C.003

- 1) Study title: A Randomized, Open-Label Study to Evaluate the Comparative Bioavailability of Ketoconazole Foam, 2%, versus Nizoral (ketoconazole) 2% Cream in Subjects with Moderate to Severe Seborrheic Dermatitis.
- 2) Subject selection: The study population was males and non-pregnant females, 12 years of age or older, with moderate to severe seborrheic dermatitis of the face, scalp, and/or chest, and an

Investigator's Static Global Assessment of 3 or 4 at baseline.

- 3) Study procedures: The subjects applied 3 gm of Ketoconazole Foam or Nizoral Cream to seborrheic dermatitis lesions of the face, scalp, and chest twice daily for 4 weeks. Lesions at other sites could be treated at the investigator's discretion. Any remaining drug was to be applied to non-involved areas of the chest. The subjects were randomly assigned to the treatment groups.

Serum samples for ketoconazole levels were collected at baseline, day 15, and day 29.

- 4) Study results: 24 subjects were enrolled into the study, of which 21 completed the study. The age ranged from 25 to 76 years, and most subjects were Caucasian. The mean percent of BSA involvement was 3.1% in the Ketoconazole Foam group, and 3.3% in the Nizoral Cream group.

Absorption of ketoconazole was higher with Ketoconazole Foam than with Nizoral Cream. All subjects treated with Ketoconazole Foam had measurable serum levels of ketoconazole; 75% (8/12) had levels greater than 6 ng/mL and 50% (6/12) had levels greater than 5 ng/mL. The maximal level which was observed in one subject was 11.1 ng/mL. In the Nizoral Cream group, 6 subjects had measurable levels of ketoconazole; the maximal level observed was 4.3 ng/mL.

Ketoconazole blood levels in the two groups are summarized as follows.

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Ketoconazole blood levels (ng/mL)		
	Ketoconazole foam	Nizoral cream
Baseline		
# subjects	12	12
Mean	0.2	0.0
Range	<2.00-2.67	<2.00
Week 2		
# subjects	12	10
Mean	4.2	0.6
Range	2.32-11.10	<2.00-3.74
Week 4		
# subjects	12	9
Mean	5.1	1.5
Range	2.45-10.90	<2.00-4.25

The sponsor states that the clinical significance of the ketoconazole levels in subjects treated with Ketoconazole foam is believed to be minimal, especially when compared with blood levels after oral administration, which are 3500 ng/mL within 1 to 2 hours following a single oral 200 mg dose. In a review of therapeutic drug monitoring of systemic antifungal therapies, it was noted that mean trough concentrations of ketoconazole attained with multiple oral doses of 400, 800, and 1200 mg/day were 3.2, 4.4, and 6.4 mg/L, respectively, levels approximately 300 to 600 times higher than the maximum level attained with topical Ketoconazole foam.

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Study KFD.C.002

The investigators for this study were as follows.

William Abramovits, M.D. Dallas, TX	Dale Martin, M.D. San Diego, CA
Suzanne Bruce, M.D. Houston, TX	Robert Matheson, M.D. Portland, OR
Boni Elewski, M.D. Birmingham, AL	Amy McMichael, M.D. Winston-Salem, NC
Harold Farber, M.D. Philadelphia, PA	Ray Parker, M.D. Little Rock, AR
Shiela Friedlander, M.D. San Diego, CA	Thomas Russell, M.D. Milwaukee, WI
Toni Funicella, M.D. Austin, TX	Ronald Savin, M.D. New Haven, CT
Michael Gold, M.D. Nashville, TX	Brett Shulman, M.D. Rochester, NY
Pearl Grimes, M.D. Los Angeles, CA	Jerome Shupack, M.D. New York, NY
Terry Jones, M.D. Bryan, TX	Jeffrey Sobel, M.D. North Andover, MA
Steven Kempers, M.D. Fridly, MN	Barry Solomon, M.D. Smithtown, NY
Raymond Kuwahara, M.D. Oklahoma City, OK	Linda Stein, M.D. Detroit, MI
Craig Leonardi, M.D. St. Louis, MO	James Swinehart, M.D. Denver, CO
	Guy Webster, M.D. Philadelphia, PA

The study was conducted from June 12, 2002 to March 7, 2003.

- 1) Study title: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study of the Safety and Efficacy of Ketoconazole Foam, 2%, versus Nizoral (ketoconazole) 2% Cream in the Treatment of Seborrheic Dermatitis.
- 2) Study objectives: The primary objective was to demonstrate non-inferiority of Ketoconazole Foam, 2%, versus Nizoral (ketoconazole) 2% Cream. Additional objectives were to demonstrate

superiority of Ketoconazole Foam versus Vehicle Foam and to evaluate the safety of Ketoconazole Foam versus Nizoral Cream and Vehicle Foam in the treatment of seborrheic dermatitis.

- 3) Study design: This was a multicenter, double-blind, randomized, double-dummy, vehicle controlled comparison of the safety and effectiveness of Ketoconazole Foam and Nizoral Cream in patients with mild to severe seborrheic dermatitis, with applications twice daily for 4 weeks. The subjects were enrolled in a 3:1:3:1 ratio for Ketoconazole Foam:vehicle foam:Nizoral Cream:vehicle cream. Patients and nurse/coordinators (who provided instructions on product applications) were aware of the nature of the vehicle, but were otherwise blinded to the treatment assignments, while investigators were blinded to the treatment assignments and to the vehicle.
- 4) Inclusion criteria: Patients who met the following criteria were enrolled in the study.
 - a. Male or female subjects 12 years of age or older, in good general health.
 - b. Seborrheic dermatitis with an Investigator's Static Global Assessment score of 2 to 4 at baseline. (This corresponds to mild to severe seborrheic dermatitis.)
 - c. A discrete, evaluable target area of at least 5 cm² which is scored at 2 to 4 for erythema and scaling and at 1 to 4 for induration.
- 5) Exclusion criteria: Patients with the following conditions or circumstances were excluded from the study.
 - a. Use of systemic antifungal, corticosteroid, or other immunosuppressive therapies, or systemic retinoids, within the four weeks prior to the baseline visit.
 - b. Use of topical antifungal or corticosteroid therapy within the prior two weeks. Use of other topical preparations, including shampoos containing zinc pyrithione or other zinc preparations, selenium sulfide, tars, salicylic acid, sulfacetamide, benzoyl peroxide, calcipotriene, retinoids, tacrolimus, or other agents with suggested therapeutic benefit in the treatment of seborrheic dermatitis, within two weeks prior to the baseline visit.
 - c. Concomitant skin disease on study sites or other skin sites consistent with a diagnosis of psoriasis, atopic dermatitis, contact dermatitis, dermatophytosis, impetigo, rosacea, or pityriasis versicolor, or autoimmune diseases such as systemic or discoid lupus erythematosus or dermatomyositis, or other skin diseases which in the opinion of the investigator could put the patient at unacceptable risk for participation in the

study.

- d. Known or suspected HIV infection (testing not required), immunocompromised (except diabetes), zinc deficiency, or Parkinson's disease.
 - e. Pregnant women, women who were breast feeding, or women of childbearing potential who were not practicing an acceptable form of birth control (abstinence, birth control pill/patch, barrier with spermicidal jelly, IUD, etc.), as determined by the investigator. Acceptable contraception was to be used during the entire study.
 - f. Current drug or alcohol use.
 - g. Known allergy to ketoconazole or to any component of the investigational formulations.
- 6) Treatment regimen: The patients were randomly assigned to the test products, namely, Ketoconazole Foam, vehicle foam, Nizoral Cream, and cream vehicle in a 3:1:3:1 ratio. Applications were made twice daily for four weeks.

At the baseline visit the patients received instructions regarding the proper application of the study treatment, including instructions to apply a sufficient amount to cover all lesions. The first application was applied by the patient at the study center. The patients who received a foam treatment were instructed to dispense a small amount of foam into the cap of the foam canister. The patient was then to gently massage the foam into the affected lesions. Patients who received the cream treatment were instructed to dispense a small amount of cream onto the fingertips, and then to gently massage the cream into affected lesions.

All seborrheic dermatitis lesions on the face, scalp, and chest were to be treated with the study treatment; lesions on other body sites could be treated with study drug at the discretion of the investigator. All lesions treated with study drug were to be included in the global assessments by the investigator.

The study drug was to be applied prior to application of any powder-based (oil free) cosmetic products that the patient habitually used. The application sites were not to be washed for at least 8 hours after application.

No other concomitant topical treatment to seborrheic dermatitis lesions was permitted. The introduction of systemic drugs for other medical conditions that are known to affect seborrheic dermatitis, e.g., systemic corticosteroids, antifungals, immunosuppressive agents, etc., or of certain topical drugs, e.g., topical antifungals or corticosteroids, was not permitted during the study. The patients were discouraged from using hair products

such as mousse, hair spray, or gels during the study, as these might affect penetration of the study product onto the affected areas of the scalp.

- 7) Efficacy parameters: At baseline a discrete target area of at least 0.5 cm² was selected by the investigator to be graded for clinical signs. At baseline and days 8, 15, and 29, the target area was evaluated for erythema, scaling, and induration, an evaluation of pruritus was made, and an Investigator's Static Global Assessment (ISGA) was made. The following scales were used for the clinical signs, pruritus, and the ISGA.

Erythema	
Score	Description
0	Normal skin without erythema; may have residual hyperpigmentation
1	Faint erythema
2	Light red erythema
3	Moderate red coloration
4	Dusky to deep red coloration

Scaling	
Score	Description
0	Normal skin with rare fine scale
1	Minimal: occasional fine scales over less than 10% of the lesions
2	Mild; fine scales predominate
3	Moderate; coarse scales predominate
4	Severe; thick tenacious scales predominate

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Induration	
Score	Description
0	Normal skin without induration
1	Minimal papule or plaque elevation; approximately 0.2 mm
2	Mild plaque elevation; approximately 0.5 mm
3	Moderate papule or plaque elevation; approximately 1 mm
4	Severe papule or plaque elevation; approximately 1.5 mm

Pruritus	
Score	Description
0	No itching
1	Minimal: rarely aware of itching
2	Mild: only aware of itching at times; only present when relaxing; not present when focused on other activities
3	Moderate: often aware of itching; annoying; sometimes disturbs sleep and daytime activities
4	Severe: constant itching; distressing; frequent sleep disturbance; interferes with activities

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Investigator's Static Global Assessment	
Score	Description
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

A global assessment was also made by the patient, using the following scale.

Patient's global assessment	
Score	Description
0	No seborrheic dermatitis; my skin looks and feels normal.
1	Minimal seborrheic dermatitis; my skin has occasional fine scale, faint pink color, and the lesions can barely be felt with my fingertips
2	Mild seborrheic dermatitis; my skin has noticeable fine scale, light red color, and the lesions are easily felt with my fingertips
3	Moderate seborrheic dermatitis; my skin has coarse scale, red color, and the lesions are elevated by my visual inspection as well as felt with my fingertips
4	Severe seborrheic dermatitis; my skin has thick and adherent scale, deep red color, and the lesions are notably elevated

- 8) Primary efficacy variable. The primary efficacy variable was the proportion of patients who had an Investigator's Global Assessment of 0 or 1 at the end of treatment. Patients with a baseline score of 2 had to have a final score of 0 to be judged a success.

The sponsor also performed a post-hoc analysis of 'Effective Treatment', defined as the proportion of patients with an ISGA score of 0 or 1, and a target area score of 0 or 1 for erythema and scaling.

The secondary efficacy variable was the percent change from baseline to week 4 in the sum of the individual scores for the signs of seborrheic dermatitis, namely erythema, scaling, and induration, at the target area.

Additional analyses were:

- a) the change from baseline to week 2 and to week 4 in the individual scores for erythema, scaling, and induration at the target area.
 - b) the change in the pruritus score from baseline to week 2 and week 4.
 - c) the change in the Subject's Global Assessment from baseline to week 2 and week 4.
 - d) the proportion of patients with an Investigator's Global Assessment of 0 or 1 at week 2.
- 9) Safety evaluations. Vital signs measurements were done at baseline and at each return visit. The patients were queried for adverse events at each return visit. The following laboratory tests were done at baseline and at termination:
- CBC: WBC and differential, RBC, hemoglobin, hematocrit, platelets
 - Liver function tests: SGOT, SGPT, alkaline phosphatase, total bilirubin, direct bilirubin

Results were as follows.

- 1) Patient enrollment and disposition: 619 patients were enrolled into the study, and were randomly assigned to the treatment groups as follows: Ketoconazole Foam - 233; Nizoral Cream - 233; vehicle foam - 77, and vehicle cream - 76.

The disposition of the patients was as follows.

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Patient disposition				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
# completed	220 (94%)	221 (95%)	73 (95%)	73 (96%)
# discontinued	13 (6%)	12 (5%)	4 (5%)	3 (4%)
Reasons for discontinuation				
Adverse event	0	2 (1%)	2 (3%)	1 (1%)
Non-compliance	4 (2%)	1 (0%)	1 (1%)	0
Disease progression	0	3 (1%)	0	1 (1%)
Request to withdraw	3 (1%)	3 (1%)	0	1 (1%)
Other	6 (3%)	3 (1%)	1 (1%)	0
Lost to followup	3	1	1	
Baseline lab abnormalities	2			
Protocol violation		2		
Unrelated	1			

- 2) Demographic and baseline disease characteristics: These were as follows.

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Demographic characteristics				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Age				
Mean	45	44	44	45
Range	12-85	12-83	12-84	12-83
Age category				
< 18 years	16 (7%)	14 (6%)	5 (6%)	3 (4%)
18-65 years	178 (76%)	188 (81%)	61 (79%)	65 (86%)
> 65 years	39 (17%)	31 (13%)	11 (14%)	8 (11%)
Gender				
Male	124 (53%)	132 (57%)	41 (53%)	32 (42%)
Female	109 (47%)	101 (43%)	36 (47%)	44 (58%)
Race				
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
Other	2 (1%)	4 (2%)	0	1 (1%)
Baseline Investigator's Global Assessment				
2	152 (65%)	155 (67%)	50 (65%)	52 (68%)
3	70 (30%)	76 (33%)	26 (34%)	22 (29%)
4	11 (5%)	2 (1%)	1 (1%)	2 (3%)

- 3) Efficacy results: Primary efficacy variable. The success rates, defined as the proportion of patients that had an Investigator's Global Assessment of 0 or 1 at week 4 for those with a baseline score of 3 or 4, and a score of 0 for those with a baseline score of 2, were as follows.

Success rates				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Success rate	116 (50%)	103 (44%)	31 (40%)	20 (26%)
Lower confidence limit		-3.5%		
p value			0.1318	0.0053

The conclusion was that Ketoconazole Foam was not inferior to Nizoral Cream, but Ketoconazole Foam was not superior to its vehicle ($p=0.1318$). Nizoral Cream was superior to its vehicle ($p=0.005$).

The sponsor states that this analysis supports the observation that overall greater improvement was seen in the active treatments versus the vehicle controls, and allows for interpretation that the active treatments were effective under the conditions of the study. (For the sponsor's discussion of the significance of the lack of superiority of Ketoconazole Foam to its vehicle in the primary efficacy variable, refer to the response to the filing letter, page 14 of this review).

The sponsor performed additional analyses based on the Investigator's Static Global Assessment (ISGA), in order to "further test the consistency and robustness of the study results". These were as follows.

- a) The proportion of patients with an ISGA score of 0 (clear) at week 4.

ISGA of 0 (clear)				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
ISGA of 0	92 (39%)	77 (33%)	19 (25%)	13 (17%)
Lower confidence limit		- 2.27%		
p value			0.0177	

Ketoconazole foam was non-inferior to Nizoral cream, and was superior to vehicle foam.

- b) Effective Treatment at week 4: this was defined as the proportion of patients with an ISGA score of 0 or 1, and a target area score of 0 or 1 for each of erythema and scaling at week 4. Patients with a baseline ISGA score of 2, or a target area erythema or scaling score of 2, were required to have a score of 0 at week 4 to be considered an Effective Treatment.

The sponsor states that Effective Treatment, as defined, was used to establish the efficacy of a recently approved topical product for seborrheic dermatitis.

Effective Treatment				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Effective Treatment	91 (39%)	76 (33%)	20 (26%)	15 (20%)
Lower confidence limit		- 2.25%		
p value			0.0300	

Ketoconazole foam was non-inferior to Nizoral cream, and was superior to vehicle foam.

- 4) Efficacy results: Secondary efficacy variables. (Statistical analyses were not performed by the sponsor on most of these variables.)
- a) The mean percent change from baseline in the sum of the individual scores for erythema, scaling, and induration at the target area.

Percent change in sum of individual sign/symptom scores				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Mean percent change	- 66.2	- 61.6	- 53.8	- 48.7
p value			0.0136	

- b) The mean change from baseline in the individual scores for erythema, scaling, and induration at the target area, and pruritus.

Erythema				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Mean change	- 1.5	- 1.4	- 1.2	- 1.1

Scaling				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Mean change	- 1.6	- 1.4	- 1.4	- 1.1

Induration				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Mean change	- 1.2	- 1.2	- 1.0	- 1.0

Pruritus				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Mean change	- 1.5	- 1.3	- 1.5	- 1.2

c) The mean change from baseline in the patient's global assessment scores.

Patient Global Assessment				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Mean change	- 1.5	- 1.3	- 1.4	- 1.0

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- d) The proportion of patients with an Investigator's Static Global Assessment score of 0 or 1 at week 1 and 2.

Investigator's Global Assessment score of 0 or 1				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Week 1	108 (46%)	109 (47%)	29 (38%)	32 (42%)
Week 2	154 (66%)	146 (63%)	37 (48%)	41 (54%)

- 5) Efficacy analysis of Success Rate by subgroups of gender, race, and age. Success Rate was defined as the proportion of patients who had an Investigator's Global Assessment of 0 or 1 at week 4, with those patients having a baseline score of 2 required to have a final score of 0.

Success rate by gender				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Male				
# pts	124	132	41	32
Success rate	62 (50%)	61 (46%)	18 (44%)	12 (38%)
Female				
# pts	109	101	36	44
Success rate	54 (50%)	42 (42%)	13 (36%)	8 (18%)

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Success rate by race				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Caucasian				
# pts	179	187	64	52
Success rate	87 (49%)	87 (47%)	25 (39%)	18 (35%)
Black				
# pts	37	28	10	16
Success rate	22 (59%)	10 (36%)	4 (40%)	2 (13%)
Hispanic				
# pts	13	12	3	7
Success rate	6 (46%)	6 (50%)	2 (67%)	0

Success rate by age				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
# patients	233	233	77	76
Under 18				
# pts	16	14	5	3
Success rate	5 (31%)	5 (36%)	1 (20%)	0
18-65				
# pts	178	188	61	65
Success rate	94 (53%)	87 (46%)	27 (44%)	16 (25%)
Over 65				
# pts	39	31	11	8
Success rate	17 (44%)	11 (35%)	3 (27%)	4 (50%)

6) Safety evaluation.

- a. Adverse events. The sponsor lists cutaneous adverse events separately for those occurring at the application site and for those specified as 'Skin disorders'; the distinction is not readily apparent. The sponsor's tabulations of treatment-

emergent cutaneous adverse experiences classified by MedDRA preferred terms are as follows.

- 1) The adverse events classified as application site reactions were listed as follows.

Application site reactions MedDRA Preferred terms Sponsor's presentation				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
Burning	23 (10%)	2 (1%)	8 (10%)	-
Desquamation	-	-	1 (1%)	-
Dryness	1 (0%)	-	1 (1%)	-
Erythema	1 (0%)	1 (0%)	1 (1%)	-
Hyperaesthesia	-	-	-	1 (1%)
Irritation	1 (0%)	1 (0%)	1 (1%)	-
Pruritus	4 (2%)	2 (1%)	1 (1%)	2 (3%)
Rash	-	-	-	1 (1%)
Reaction NOS	21 (9%)	3 (1%)	8 (10%)	1 (1%)
Swelling	-	1 (0%)	-	-

- 2) The adverse events which were listed under 'Skin disorders' were as follows.

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'Skin Disorders' MedDRA preferred terms Sponsor's presentation				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
Dermatitis NOS	-	-	1 (1%)	-
Allergic dermatitis	1 (0%)	-	-	-
Contact dermatitis	1 (0%)	2 (1%)	-	-
Exfoliative dermatitis NOS	1 (0%)	-	-	-
Exacerbation of eczema	1 (0%)	-	-	1 (1%)
Seborrheic dermatitis	-	3 (1%)	1 (1%)	2 (3%)
Erythema	1 (0%)	-	-	-
Pruritus NOS	1 (0%)	-	1 (1%)	1 (1%)
Rash NOS	-	-	1 (1%)	-
Vesicular rash	-	1 (0%)	-	-
Burning	1 (0%)	-	-	-
Hypertrophy	1 (0%)	-	-	-
Inflammation NOS	1 (0%)	-	-	-
Swelling	1 (0%)	-	-	-

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This reviewer has tabulated below all cutaneous adverse events (except those which were obviously not drug-related) by the verbatim terms in the patient line listings, as follows.

Cutaneous adverse events Verbatim terms Reviewer's tabulation				
	Ketoconazole foam n=233	Nizoral cream n=233	Vehicle foam n=77	Vehicle cream n=76
Burning/stinging/ itching/tingling	36 (15%)	5 (2%)	13 (17%)	3 (4%)
Worsening of seborrheic dermatitis		3 (1.3%)		3 (4%)
Application site erythema	1	1	1	
Facial burning, itching, leathery, erythema, peeling, swelling	1			
Dryness, itching	1			
Generalized contact dermatitis	1			
Application site irritation	1	1	1	
Eye irritation	1			
Vesicular rash-palms		1		
Application site swelling		1		
Facial rash			1	
Application site scaling			1	
Application site oily scalp				1
Allergic dermatitis hairline				1

Most of the cutaneous adverse events were mild to moderate in severity. There were two reactions which were considered to be severe; these were stinging in two patients on the vehicle foam.

Three patients were discontinued due to treatment related events at the application site; these were mild erythema and burning in one on Nizoral cream, moderate irritation and swelling in one on Nizoral cream, and moderate stinging in one on vehicle foam. Another patient with pre-existing eczema of the fingers who was on vehicle cream reported exacerbation of the eczema and was discontinued.

Application site burning and stinging in the Ketoconazole Foam group and the vehicle foam group was thought to be related to the alcohol excipients of the foam product.

b. Laboratory results. Laboratory adverse events were as follows.

Laboratory adverse events				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
Leukopenia NOS	-	1	-	-
Increased alanine aminotransferase	2 (1%)	2 (1%)	-	1 (1%)
Increased alkaline phosphatase	-	-	1 (1%)	-
Decreased hematocrit	1	2 (1%)	-	1 (1%)
Decreased hemoglobin	1	1	-	1 (1%)
Abnormal liver function NOS	1	-	-	-
Decreased platelets	1	-	-	-
Decreased RBC	1	1	-	-
Decreased WBC	-	-	1 (1%)	-

The mean laboratory values at baseline and at week 4/end of treatment, and the range of values for hemoglobin, WBC, and liver function tests were as follows.

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Hemoglobin				
Normal: Males: 13.5-18.0; Females: 11.5-15.0 g/dL				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
Baseline				
N	224	215	74	74
Mean	12.8	12.6	12.5	12.3
Range	1.0 - 17.9	1.1 - 18.9	1.3 - 17.1	1.2 - 18.1
Week 4				
N	211	215	69	69
Mean	12.6	12.3	13.6	13.2
Range	1.2 - 17.3	1.2 - 19.3	1.2 - 17.8	1.2 - 18.2

WBC				
Normal: 4.0-11.0 x 10 ⁹ /L				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
Baseline				
N	224	215	74	74
Mean	6.0	6.1	6.8	6.1
Range	0.3 - 11.8	0.4 - 12.9	0.4 - 13.5	0.6 - 10.2
Week 4				
N	211	214	69	69
Mean	6.2	6.2	6.2	5.7
Range	0.3 - 15.4	0.4 - 16.5	0.5 - 13.5	0.5 - 9.6

Total bilirubin				
Normal: < 1.4 mg/dL				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
Baseline				
N	233	227	77	74
Mean	0.6	0.6	0.5	0.6
Range	0.1 - 2.7	0.1 - 1.8	0.1 - 2.2	0.1 - 1.7
Week 4				
N	217	220	73	72
Mean	0.6	0.6	0.5	0.6
Range	0.1 - 3.4	0.1 - 1.9	0.1 - 1.5	0.1 - 1.8

Alkaline phosphatase Normal: 20-115 U/L				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
Baseline				
N	233	227	77	73
Mean	8.5	8.3	8.1	8.4
Range	3 - 43	2 - 32	3 - 29	3 - 31
Week 4				
N	217	220	72	72
Mean	8.5	8.3	8.2	8.2
Range	3 - 47	3 - 30	3 - 32	3 - 32

ALT (SGPT) Normal: < 41 U/L				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
Baseline				
N	233	227	77	74
Mean	2.9	2.5	2.5	2.9
Range	1 - 26	1 - 13	1 - 12	1 - 19
Week 4				
N	217	220	73	72
Mean	2.8	2.6	2.3	2.7
Range	1 - 22	1 - 15	1 - 6	1 - 13

AST (SGOT) Normal: < 41 U/L				
	Ketoconazole foam	Nizoral cream	Vehicle foam	Vehicle cream
Baseline				
N	233	227	77	74
Mean	2.4	2.3	2.1	2.3
Range	1 - 15	1 - 8	1 - 6	1 - 11
Week 4				
N	217	220	73	72
Mean	2.3	2.3	2.0	2.3
Range	1 - 11	1 - 15	1 - 4	1 - 9

The sponsor's review of the clinical laboratory results found no pattern of changes from baseline to week 4; there were no systematic changes and no correlation with the study drugs.

The patient data was reviewed by the sponsor for potentially clinically relevant laboratory abnormalities; these were defined as a WBC of less than $3 \times 10^9/L$ or greater than $14 \times 10^9/L$, hemoglobin less than 11 g/dL, platelets less than $100 \times 10^9/L$ or greater than $500 \times 10^9/L$, eosinophils greater than 12%, and liver function tests greater than 2.5 times the upper limit of normal (ULN). The sponsor has provided a tabulation of the baseline and week 4 values for those laboratory tests that were outside these parameters for each patient.

On review of the tabulation of the individual abnormal hematological parameters, this reviewer concludes that there were no apparent drug-related changes; either the only abnormality was at baseline, or the abnormal week 4 value was comparable to the baseline value. One patient was considered by the investigator to have a clinically significant and drug related decreased hemoglobin at week 4; this patient was in the Nizoral group, and had hemoglobin values of 11.9 at baseline and 10.3 at week 4.

On review of the tabulation of the individual abnormal liver function tests, this reviewer concludes that in all cases but one there were no apparent drug related changes; either the only abnormality was at baseline, or the week 4 value was comparable to the baseline value. The one exception that might possibly have been drug related was a patient in the Nizoral group who had an SGOT of 18 at baseline and an SGOT of 148 at week 4. None of the elevated liver function test results were considered by the investigator to be clinically significant.

Reviewer's evaluation of Study KFD.C.002

Efficacy: Ketoconazole Foam was non-inferior to Nizoral Cream, but was not superior to the foam vehicle in the analysis of the primary efficacy variable, namely, the 'success rate' at week 4, defined as the proportion of patients that had an Investigator's Static Global Assessment (ISGA) of 0 or 1 for those with a baseline score of 3 or 4, and a score of 0 for those with a baseline score of 2.

A post-hoc analysis was done of the proportion of patients with 'Effective Treatment' at week 4, defined as an ISGA score of 0 or 1, and a target area score of 0 or 1 for erythema and scaling. In this analysis Ketoconazole foam was non-inferior to Nizoral cream, and was superior to the foam vehicle. The sponsor states that Effective Treatment, as defined, was used to establish the efficacy of a recently approved topical product for seborrheic dermatitis. However, not only was the sponsor's analysis a post-hoc analysis, and as such, unacceptable for a determination of efficacy, but the assessment of clinical signs was done at a target lesion, and the sponsor had been

specifically informed at the pre-IND/EOP2 meeting that assessment of target lesions would not have much clinical significance.

The primary efficacy variable which the Agency has recently recommended for other products for seborrheic dermatitis is an Investigator's Global Assessment of 0 or 1 (Clear or Almost Clear), and a score of 0 or 1 for erythema and scaling. The score for the clinical signs is to be a global score, not a target lesion score. (It is noted that induration is not a notable feature, nor an essential feature, of seborrheic dermatitis.)

The ISGA in Study KFD.C.002 encompassed global scores for the clinical signs in each of the severity categories. It is not clear whether the category given a score of 1 corresponds to a condition of 'Almost Clear'. The description of a score of 1 is that "the majority of lesions have individual scores for erythema, scaling, and induration that averages 1." This means that there could be some individual scores greater than 1 for erythema and scaling, whereas the Agency recommendation is that there should be no scores greater than 1 in the category 'Almost Clear'.

In summary, efficacy has not been demonstrated for Ketoconazole Foam in the treatment of seborrheic dermatitis, because it has not been shown to be superior to its vehicle.

The number of patients in the 12 to 18 year age range in the study, namely 16 of 233, or 7%, is marginal for an evaluation of efficacy in this group. The number of patients over 65 years, 39 of 233, or 17%, is adequate. The Success Rate in the 12 to 18 year group was numerically lower in the Ketoconazole foam group than in the Nizoral group (31% vs 36%, respectively). The Success rate in the over 65 group was numerically higher in the Ketoconazole foam group than in the Nizoral group (44% vs 35%, respectively).

Safety: The most frequent adverse events in the Ketoconazole Foam group (and also in the foam vehicle group) were local sensations of burning, stinging, itching and tingling, which occurred in 15% of patients. Other adverse events occurred in individual patients, were not severe, and did not necessitate discontinuation.

There were no laboratory abnormalities in the Ketoconazole Foam group that appeared to be drug-related; either the only abnormality was at baseline, or the week 4 value was comparable to the baseline value.

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Safety Update

The four month Safety Update has been provided on 6/3/2004. The sponsor states that there has been no new information since the submission of the NDA. The sponsor has not conducted additional clinical or nonclinical studies with Ketoconazole Foam, 2%, and is not aware of any studies being conducted with the product. There is no new information in the literature concerning the safety of topical ketoconazole since the date of the NDA submission.

Chemistry review

The Chemistry reviewer, Alan Fenselau, had the following concerns:

1. 

b(4)

2.

b(4)

Statistical review

The statistical review was done by Dr. Kathleen Fritsch. Her conclusion was that in the pivotal study KFD.C.002, Extina (ketoconazole) foam 2% is non-inferior to Nizoral (ketoconazole) cream 2% in the treatment of seborrheic dermatitis; however, ketoconazole

foam is not statistically superior to its vehicle. Because the study failed on its primary endpoint, an additional study is needed to demonstrate the statistical superiority of ketoconazole foam to its vehicle.

Dr. Fritsch further states that "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."

Summary and evaluation: This 505(b)(2) application for Ketoconazole Foam 2% in the treatment of seborrheic dermatitis includes a sensitization study (004), a pharmacokinetic study (003) and a Phase 3 study on the safety and efficacy (002).

a) Phase 1 studies: Only a sensitization study has been performed. Reactions during the induction phase show a generally low level of irritation with Ketoconazole Foam and the foam vehicle. The level of sensitization in this study may have been underreported due to the stringency of the criteria for sensitization.

The sponsor is given a waiver of phototoxicity and photosensitization studies, as there is no absorption in the ~~0-100%~~ range.

b(4)

b) Pharmacokinetic study: This showed a higher absorption of ketoconazole with Ketoconazole Foam than with Nizoral Cream, with a maximal serum level of 11 ng/ml in the Ketoconazole Foam group and 4 ng/ml in the Nizoral group.

c) Phase 3 study: Study 002 was a double blind, multicenter, randomized comparison of Ketoconazole Foam 2%, Nizoral (ketoconazole) Cream 2%, and the cream and foam vehicles in 619 patients with mild to severe seborrheic dermatitis. Applications were made twice daily for four weeks.

Efficacy: The efficacy parameters were scoring of erythema and scaling at a target lesion, and an Investigator's Static Global Assessment (ISGA). The predesignated primary efficacy variable was the Success Rate, defined as the proportion of patients with an ISGA of 0 or 1 at the end of treatment. (This required that those with a baseline score of 3 or 4 have a final score of 0 or 1, and those with a baseline score of 2 have a final score of 0.)

The results showed that Ketoconazole Foam was non-inferior to

Nizoral Cream, but that it was not superior to the foam vehicle. The proportion of patients that attained a Success was 50% in the Ketoconazole Foam group, 44% in the Nizoral Cream group, 40% in the vehicle foam group, and 26% in the vehicle cream group. The p value for the comparison of Ketoconazole Foam with its vehicle was 0.1318. Because it was not superior to its vehicle, the effectiveness of Ketoconazole Foam has not been demonstrated.

The sponsor performed a post-hoc analysis of the proportion of patients with an ISGA of 0 or 1, and a target area score of 0 or 1 for erythema and scaling; this showed Ketoconazole Foam to be non-inferior to Nizoral Cream and superior to the foam vehicle. However, a post-hoc analysis is not acceptable.

An additional study should be performed; this should be a comparison of Ketoconazole Foam with its vehicle.

Safety: The safety parameters were recording of adverse events, and laboratory evaluations, including hemograms and clinical chemistries. Adverse events were local burning, stinging, itching, or tingling in approximately 15% on Ketoconazole Foam or the foam vehicle. There were no laboratory abnormalities in the Ketoconazole Foam group that appeared to be drug-related.

A long term safety study should be performed.

Conclusions: The application is not approvable.

Recommendations: For approval of Ketoconazole Foam for the treatment of seborrheic dermatitis, the following are recommended.

1. A controlled clinical trial which compares Ketoconazole Foam to the foam vehicle, with results that show that the active foam is superior to its vehicle. The sponsor should submit the protocol for our review, preferably as a Special Protocol Assessment request, prior to initiation of the study.

Because the number of patients in the 12 to 17 year age range in Study 002 was marginal, the sponsor should try to enroll a significant number of patients in this age range in the additional study.

2. A long term open label safety study on at least 100 patients, including a significant number with severe seborrheic dermatitis, with a duration of at least 6 months. This should include assessment of adverse events, and laboratory monitoring. It is recommended that the sponsor also submit the protocol for this study to the Agency for our review prior to initiation of the studies.

Also, in the request for a pediatric waiver, the sponsor needs to provide a clinical rationale for the waiver.

Phyllis A. Huene, M.D.

cc: HFD-540/Wilkin
HFD-540/Luke
HFD-540/Huene
HFD-540/Fenselau
HFD-540/Brown
HFD-540/Giroux

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/s/

Phyllis Huene
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MEDICAL OFFICER

Markham Luke
11/4/04 12:26:27 PM
MEDICAL OFFICER

Concur with primary Clinical Reviewer's recommendations. Please also see
Biostat review.

Stanka Kukich
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