TABLE XIV - Study SF0029: Effective Treatment

	DAY 0	DAY 8	DAY 14	DAY 28	DAY 84
1 Day	0/18	2/18 (11%)	11/18 (61%)	11/18 (61%)	11/18 (61%)
3 Day	0/18	2/18 (11%)	7/18 (39%)	14/18 (78%)	12/18 (67%)
5 Day	0/17	5/17 (29%)	6/17 (35%)	12/17 (71%)	15/17 (88%)
7 Day	0/12	4/12 (33%)	7/12 (38%)	8/12 (67%)	11/12 (92%)
p-value	---	0.26	0.54	0.75	0.18

Of note, 11 of the 65 evaluable patients had target lesions on the sole of the foot (plantar type tinea pedis) and were included in the analysis of the evaluable cohort, even though they did not meet inclusion criteria in this respect. The small numbers of these patients preclude any meaningful comparison of mycological cure rates relative to the overall study population.

Study treatment was well tolerated. Only one adverse event was recorded: a patient randomized to five days treatment developed mild pruritus on the back, which was of uncertain relationship to therapy.

Study SF2030: A double-blind, randomized, parallel group study to investigate the safety and efficacy of Lamisil® (terbinafine) 1% cream applied once daily for one day, three days, five days, or seven days in patients with tinea corporis/cruris.

The objectives and design of this uncontrolled study were similar to the preceding trial. Procedures performed at each of the study visits are summarized on the attached flowchart (Attachment 4). A total of 21 patients were recruited, which did not meet the target of 40 patients (10 per group). Of these 21, 14 patients were eligible for evaluation. Table XV shows results for mycological cure for these subjects.

TABLE XV – Study SF2030: Mycological Cure

	DAY 0	DAY 8	DAY 14	DAY 28	DAY 84
1 Day	0/4 (0%)	2/4 (50%)	3/4 (75%)	4/4 (100%)	3/4 (75%)
3 Day	0/4 (0%)	¼ (25%)	3/4 (75%)	2/4 (50%)	2/4 (50%)
5 Day	0/2 (0%)	1/2 (50%)	1/2 (50%)	1/2 (50%)	2/2 (100%)
7 Day	0/4 (0%)	4/4 (100%)	3/4 (75%)	4/4 (100%)	4/4 (100%)

Table XVI on the following page details the percentage of patients effectively treated by treatment group.

TABLE XVI – Study SF2030: Effective Treatment

	DAY 0	DAY 8	DAY 14	DAY 28	DAY 84
1 Day	0/4 (0%)	1/4 (25%)	3/4 (75%)	4/4 (100%)	3/4 (75%)
3 Day	0/4 (0%)	¼ (25%)	3/4 (75%)	1/4 (25%)	2/4 (50%)
5 Day	0/2 (0%)	1/2 (50%)	1/2 (50%)	1/2 (50%)	2/2 (100%)
7 Day	0/4 (0%)	1/4 (25%)	2/4 (50%)	3/4 (75%)	4/4 (100%)

There were no adverse events reported during this study.

Study SF2003: A general practice, multicenter, double-blind therapeutic trial of the efficacy and safety of topical SF 86-327, 1% cream applied once daily compared to vehicle during one week in patients with tinea corporis/cruris.

The design of this trial is outlined in Attachment 5. Patients were seen before treatment, at the end of the one-week treatment period, and at two follow-up visits 1 and 3 weeks after the end of treatment.

A total of 76 patients were recruited. Thirty (18 terbinafine and 12 placebo) were delayed exclusions because pretreatment cultures were negative for dermatophytes. Fifteen others (7 terbinafine and 8 placebo) were dropped from the study due to either protocol violations or loss to follow up. The remaining 31 patients form the evaluable cohort (14 terbinafine and 17 placebo). The treatment groups were comparable at baseline with respect to age and mean duration of disease prior to study entry. In the terbinafine group there were 9 males and 5 females. The placebo group comprised 13 males and 4 females. The majority of patients in both treatment groups were Caucasian. Most patients in the evaluable cohort had *Trichophyton rubrum* infections.

Mycological responses at each timepoint are shown in Table XVII. Response rates between treatment groups differed by a statistically significant margin only at the first follow up visit (Fisher's Exact test, two-tailed).

TABLE XVII – Study SF2003: Mycological Responses

	Terbinafine		Placebo		
	response	95% CI	response	95% CI	p-value
Week 1	8/14 (57%)	29%, 82%	7/17 (41%)	18%, 67%	0.48
Week 2	12/14 (86%)	57%, 98%	9/17 (53%)	28%, 77%	0.07
Week 4	12/14 (86%)	57%, 98%	10/17 (59%)	33%, 82%	0.13

The investigators evaluated six signs and symptoms: erythema, desquamation, vesiculation, pruritus, incrustation and pustules. At the start of treatment, both groups were well matched for the severity of erythema, pruritus and incrustation. Desquamation and vesiculation were less severe in the terbinafine cohort than the placebo group. The mean combined scores for these

variables are summarized in Table XVIII. No significant differences were observed between treatments with respect to changes from baseline (Mann Whitney test, two-tailed).

TABLE XVIII – Study SF2003: Mean Combined Scores for Signs and Symptoms

	Terbinafine	Placebo	p-value
Week 0	6.4	7.7	
Week 1	3.3	5.4	0.50
Week 2	1.8	4.1	0.31
Week 4	0.7	3.7	0.13

Effective therapy was defined in this study as either complete cure (microscopy and culture negative, no residual clinical signs and symptoms) or mycological cure (microscopy and culture negative, mild residual erythema and/or desquamation and/or pruritus [total score less than 2], but no other clinical signs). Treatment results are shown below in Table XIX.

TABLE XIX – Study SF2003: Treatment Results (Valid Patient Analysis)

	END TREATMENT		FOLLOW-UP			
			Week 2		Week 4	
	Terbinafine	Placebo	Terbinafine	Placebo	Terbinafine	Placebo
Complete Cure or Mycological Cure	2 (14%)	1 (6%)	7 (50%)	4 (24%)	12 (86%)	6 (35%)

No statistically significant differences between terbinafine and placebo were seen at either the end of the 1 week treatment period ($p = 0.58$, Fisher's Exact test, two-tailed; $p = 0.27$, Mantel-Haenszel chi square) or at the first follow-up visit one week later ($p = 0.15$, Fisher's Exact test, two-tailed; $p = 0.15$, Mantel-Haenszel chi square. However, at the final week 4 follow-up visit (the pre-defined primary determinant of efficacy), the difference was statistically significant ($p = 0.01$, Fisher's Exact test, two-tailed and Mantel-Haenszel chi-square). Treatment centers were statistically homogeneous with respect to efficacy results.

In addition to the valid patient analysis, an intention-to-treat analysis was done on all randomized patients with at least one assessment after the start of treatment or who terminated prematurely before the week 1 evaluation. Seventy-three (73) patients were thus included Results for the overall effectiveness evaluation are summarized in Table XX. This analysis was consistent with the valid patient analysis. Terbinafine was significantly more effective than placebo ($p = 0.04$, Fisher's Exact test, two-tailed; $p = 0.03$, Mantel-Haenszel chi-square).

TABLE XX – Study SF2003: Treatment Results (Intention-to-Treat Analysis)

	ENDPOINT	
	Terbinafine	Placebo
Effective Treatment 95% CI	24 (63%) [47%-77%]	13 (37%) [20%-52%]
Failure 95% CI	14 [20%-51%]	22 [45%-77%]

In the investigators assessments (n=73), the overall tolerance was considered good or very good for 100% of both the terbinafine and placebo-treated patients. No adverse events were reported during the trial.

Reviewer's Comments (Clinical Trials):

- The safety and efficacy of Lamisil® 1% cream for the treatment of interdigital and plantar tinea pedis, tinea corporis and tinea cruris has been well established by the clinical trials supporting its approval as prescription product. However, the proposed OTC labeling makes the claim that Lamisil, in the context of the recommended one or two-week courses of treatment, "cures" these conditions. Further discussion of this issue is warranted. Studies 2508-01 and SF0040 appear to support this contention, at least for the interdigital form of tinea pedis. Data from the initial trials should be scrutinized from the perspective of rates of successful outcomes (mycological cure plus clinical cure) at the pre-defined points of cure for each of these clinical conditions following a one or two-week treatment course, as appropriate.
- Comparative marketing claims relative to other OTC topical antifungal products (either individually or as a class) are not supported by the new data presented in this NDA. These trials involved small numbers of patients and were not designed as comparative time-to-event studies. Survival curves could be constructed with data from the positively controlled new trials, but these would be post-hoc analyses and useful only for exploratory purposes.

LAMISIL LABELING COMPREHENSION STUDY:[9]

Based on efficacy data in patients with the interdigital and the plantar forms of tinea pedis, different durations of treatment are needed depending on the anatomic location of the infection. The sponsor has therefore proposed a bifurcated OTC label with respect to the directions for this indication. This labeling comprehension study[10] was designed primarily to support the contention that based on a prototype carton label and educational brochure, which include both textual and graphical information, the consumer can differentiate the two forms of disease and treat the foot for the appropriate length of time.

Five-hundred seven (507) personal interviews were conducted in facilities located in 24 geographically diverse shopping malls in the US.[11] Four adult populations, age 18 years or older, were included (quotas were established so that the respondents in each group were approximately balanced for gender):

- a general cohort who may or may not have had either form of tinea pedis in the preceding two years (n = 106)
- a group who reported experiencing interdigital disease and not plantar disease in the preceding two years (n = 145)
- a group who reported experiencing plantar disease in the preceding two years; they may or may not have also reported the interdigital type during this period (n = 144)
- low literacy respondents. These were individuals scoring 39 or below on the reading subtest of the Wide Range Achievement Test (3rd Edition, 1993). This is a

[9] Please refer also to the DDMAC review of this study.
[10] This study was designed, supervised and implemented by
[11] Of the 507 respondents, 151 (33%) were subsequently contacted for auditing purposes. No discrepancies in interviewing procedures were reported.

screening test intended for ages 5-74 years old. The test involves recognizing & naming letters, pronouncing words out of context. The mean score is 100 and the standard deviation is 15 (n = 112).

Exclusions were:

- individuals whose primary language at home was not English and who did not speak English either "very well" or "well"
- individuals who themselves or who have an immediate family member knowledgeable about research methods or the topic of this study, e.g., employees of a market research company or pharmaceutical firm, heath care professionals.
- individuals who may have participated in a market research study in the preceding three months (other than a public opinion poll).

Selected demographic characteristics of the study population are presented in percentages in Table XXI (base: total respondents). With respect to athlete's foot sufferers, the mean number of episodes suffered was comparable between the interdigital only group and the plantar group (3.3 and 3.4, respectively).

TABLE XXI - Demographics

	ATHLETE'S FOOT SUFFERERS			
AGE	**Interdigital Only**	**Plantar Type**	**General Population**	**Low Literacy**
18-34	52	57	38	51
35-54	36	29	32	30
55 or older	12	14	30	20

	ATHLETE'S FOOT SUFFERERS			
GENDER	**Interdigital Only**	**Plantar Type**	**General Population**	**Low Literacy**
Men	48	53	51	49
Women	52	47	49	51

	ATHLETE'S FOOT SUFFERERS			
ETHNICITY	**Interdigital Only**	**Plantar Type**	**General Population**	**Low Literacy**
Negro	22	26	19	23
Asian	1	3	5	2
Caucasian	64	61	68	60
Hispanic	11	8	6	10
Other	1	1	3	2
Refused/No Answer	--	1	--	4

(table continued on next page)

TABLE XXI (continued)- Demographics

EDUCATION	ATHLETE'S FOOT SUFFERERS			
	Interdigital Only	Plantar Type	General Population	Low Literacy
Eighth Grade or Less	1	3	1	5
Some High School	8	8	16	23
High School Graduate/G.E.D.	39	42	31	53
Some College	31	35	26	12
College Graduate	11	13	21	2
Postgraduate Work	10	1	6	--
Refused/No Answer	1	--	--	6

After screening for eligibility, respondents were then escorted to the interviewing facility where the WRAT3 test was administered. They were then exposed to the carton label for Lamisil®AT™ cream and with the carton label in view were questioned in the following areas:

- conditions the product treats (unaided)
- what the product does (unaided)
- overall understandability rating
- whether the package was confusing and, if so, what was confusing
- readability rating
- if the package was not rated as easy to read, why
- number of times per day the cream should be applied to particular areas of the foot (unaided)
- number of days/weeks the cream should be applied to particular areas of the foot (unaided)

The carton label was then removed from view and the respondent was exposed to and asked to read the education brochure. The carton label was then re-introduced and with both in view, the participants were asked about the following:

- how many times per day the cream should be applied to particular areas of the foot (unaided)
- how many days/weeks the cream should be applied to particular areas of the foot (unaided)
- did the respondent learn anything new about athlete's foot, and if so, what (volunteered response)

The interview closed with questions pertaining to athlete's foot episodes that the respondent may have suffered, whether he/she ever consulted a physician about their athlete's foot and demographic information.

The study found that after exposure to both the educational brochure and carton label, the majority of consumers correctly understood that the product was to be used for one week (or as directed by the doctor) with the interdigital form of athlete's foot and for two weeks (or as directed by a doctor) with the plantar form (Table XXII).

TABLE XXII – Treatment Duration versus Anatomic Location of Disease

ANATOMIC LOCATION	MEANS [95% CI]
Between the Toes Use for one week or as directed (correct)	74% (L) - 86% (G) [65%, 82%] [77%, 92%]
Bottom of the Foot Use for two weeks or as directed (correct)	80% (L) - 92% (I) [71%, 86%] [87%, 96%]
Side of the Foot Use for two weeks or as directed (correct)	80% (L) - 93% (I) [72%, 87%] [87%, 97%]

I = interdigital only cohort; P = plantar cohort; G = general population; L = low literacy

The majority of low literacy respondents (74% or greater) also correctly recalled the appropriate duration of treatment for each type of athlete's foot, although the percentages answering correctly were higher for other respondents for both forms of the disease (Table XXIII).

TABLE XXIII – Treatment Duration versus Anatomic Location of Disease (Low Literacy Respondents)

ANATOMIC LOCATION	MEANS	
	Low Literacy	Others
Between the Toes Use for one week or as directed (correct)	74%	81% - 86%
Bottom of the Foot Use for two weeks or as directed (correct)	80%	85% - 92%
Side of the Foot Use for two weeks or as directed (correct)	80%	86% - 93%

Dosing frequency was also addressed. After exposure to the carton label and the educational brochure), the great majority of consumers correctly replied that the cream was to be used twice daily or as directed by a doctor to treat athletes foot involving the specific areas: between the toes, 80%-88%; bottom of the foot, 88%-98%; side of the foot, 88%-97%. Respondents in the low literacy cohort were less likely to answer correctly than others (Table XXIV).

TABLE XXIV – Dosing Frequency versus Anatomic Location of Disease (Low Literacy Respondents)

ANATOMIC LOCATION	MEANS	
	Low Literacy	Others
Between the Toes Use for one week or as directed (correct)	80%	82% - 88%
Bottom of the Foot Use for two weeks or as directed (correct)	88%	90% - 98%
Side of the Foot Use for two weeks or as directed (correct)	88%	92% - 97%

The educational brochure appeared to increase comprehension of the correct dosing instructions with regard to both frequency and duration of application, i.e., more respondents recalled correct dosing instructions after exposure to the brochure. The differences were small (Data not reproduced here).

Although the principal objective of this study was to address bifurcated labeling in the directions for athlete's foot, additional assessments were made on the respondents awareness of the conditions that the product treats and what the cream does (unaided); the overall understandability of the information on the carton label; whether the carton label was seen as confusing; and the perceived readability of the carton label.

On an unaided basis, 90% - 100% of respondents across the four cohorts cited athlete's foot, 49% - 72% cited jock itch and 41% - 55% cited ringworm as conditions that Lamisil®AT™ treats. For each condition, the low literacy respondents had the lowest score. Volunteered comments regarding what the cream does included athlete's foot (62% - 71%), relief of jock itch (21% - 39%) and relief of ringworm (17% - 31%). In addition, 30% - 43% mentioned comments relating to general symptom relief.

Most respondents (78% - 97%) rated the information on the Lamisil®AT™ carton label as "extremely" or "very" understandable. Again, the lowest score (78%) represents low literacy respondents. However, very few in this (1%) cohort rated the information as "not very" or "not at all" understandable." Almost no one in any of the four cohorts (2% - 6%) considered the carton label of the information it presented confusing.

The majority of respondents (69% - 96%) rated the Lamisil®AT™ cream carton label as "extremely" or "very" easy to read. The lowest score (69%) again represents the low literacy respondents. However, few of these respondents (3%) however, rated the label as "not easy" or "not at all easy" to read.

Reviewer's Comments:

For consistency with other currently marketed OTC topical antifungal products, the Lamisil interdigital and plantar tinea pedis indications were collapsed into an "athlete's foot" indication and the directions were split with regard to duration of treatment versus anatomic location of disease on the foot. Within the limits of the sample size and survey construct, data from this study validate this consumer labeling approach. Findings appeared most consistent across the "interdigital only," "plantar" and "general population" cohorts. "Low literacy" respondents did less well, although scored acceptably.

The study was not intended to address other areas of labeling comprehension, so data presented on issues such as understandability and readability should be interpreted with caution.

RECOMMENDATION:

Lamisil cream 1% is an appropriate OTC product for the intermittent topical treatment of tinea pedis (athlete's foot), tinea cruris (jock itch) and tinea corporis (ringworm).

Note: Carton and tube labeling and the proposed educational brochure are the subject of a separate review document.

/S/

Steven Aurecchia, MD
2/22/99

/S/

Linda M. Katz, MD, MPH
Dep. Dir., DOTCDP 2/23/99

draft: 01/29/99
revision: 02/22/99

CC: NDA 20-980 Arch.
HFD-560
HFD-560/SAurecchia/JLipnicki/NRejali/LKatz
HFD-540

Noted, comments to CTC via email.
3/9/99

Noted DB 03/10/99

ATTACHMENT 1
Flow Chart – Study 2508

	Baseline (Day 0)	Day 8	15	29	Week 6	9	12
Clinical Diagnosis, History	X						
Patient selection criteria	X						
Informed Consent Signed	X						
KOH & Culture sampling	X	X	X	X	X	X	X
Assessments of clinical signs & symptoms	X	X	X	X	X	X	X
Investigator Global Assessment of Overall Disease Severity	X	X	X	X	X	X	X
B.I.D. cream application (one-week treatment groups)	[----------] or						
B.I.D. cream application (four-week treatment groups)	[----------|----------|----------]						
Overall Investigator and Patient Assessment		X	X	X	X	X	X
Concomitant Meds update	X	X	X	X	X	X	X
Side effects documentation	X	X	X	X	X	X	X

ATTACHMENT 2
Flow Chart – Study SF0040

WEEK: INVESTIGATION	WK -1 SCREEN	TREATMENT <---------->					FOLLOW-UP <---------->
		0 BASELINE	1	2	3	4	6
Patient History and Clinical Diagnosis		X					
Clinical Assessment		X	X	X	X	X	X
Mycology Sample	X		X	X	X	X	X
Documentation of Side Effects			X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X
Verification of Compliance			X	X	X	X	
Photography		X	X	X	X	X	X
Informed Consent		X					

ATTACHMENT 3
Flow Chart – Study SF0029

Treatment Phase

DAY:	SCREENING VISIT(V)	1	2	3	4	5	6	7	8
INVESTIGATION	(DAY - 7)	V							V
Patient History & Clinical Diagnosis		X							
Clinical Assessment		X							X
Mycology Sample	X								X
Informed Consent		X							
Once Daily Treatment		X	X	X	X	X	X	X	
Documentation of Side Effects									X
Concomitant Medication		X							X
Verification of Compliance									X
Photography		X							X

Follow-up Phase

DAY:	14 (2 weeks)	28 (1 month)	84 (3 months)
Clinical Assessment	X	X	X
Mycology Sample	X	X	X
Concomitant Medication	X	X	X
Photography	X	X	X

ATTACHMENT 4
Flow Chart – Study SF2030

Treatment Phase

DAY: / INVESTIGATION	SCREENING VISIT (V) (DAY -7)	1 V	2	3	4	5	6	7	8 V
Patient History & Clinical Diagnosis		X							
Clinical Assessment		X							X
Mycology Sample	X								X
Informed Consent		X							
Once Daily Treatment		X	X	X	X	X	X	X	
Documentation of Side Effects									X
Concomitant Medication		X							X
Verification of Compliance									X
Photography		X							X

Follow-up Phase

DAY:	14 (2 weeks)	28 (1 month)	84 (3 months)
Clinical Assessment	X	X	X
Mycology Sample	X	X	X
Concomitant Medication	X	X	X
Photography	X	X	X

ATTACHMENT 5
Flow Chart – Study SF2003

Week Number	-2	-1	0	1	2	4
	therapy free period		before therapy		follow up	
Clinical diagnosis, KOH wet mount, patient selection case history, diagnostic culture			X			
Informed consent by patient			X			
Once daily 1% cream				X		
Clinical and mycological control				X	X	X
Documentation of side effects				X		
Evaluation of therapy				X		X

APPEARS THIS WAY
ON ORIGINAL