c. Study No. 2-2: Tinea Pedis

The following table presents both a count of adverse events and a count of the individuals experiencing adverse events, at least according to the data provided by the sponsor:

Table 23. Study 2-2 Adverse Events

---------- Protocol Number=SAN 2506-02 ----------

Adverse Events	Severity	Terbinafine n indiv	Vehicle n indiv	Terbinafine n event	Vehicle n event
Common Cold	Moderate	.	1	.	1
Headache	Mild	1	.	2	.
Migraine Headache	Moderate	.	1	.	2
Overall		1	2	2	3

As above, it is apparent that no treatment related differences are statistically significant.

APPEARS THIS WAY
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d. Study No. 2508-01: Tinea Pedis

The following table is also both a count of adverse events and a count of the individuals experiencing adverse events, at least according to the data provided by the sponsor:

Table 24. Study 2508-01 Adverse Events

Adverse Events	Severity	1 wk Clot. n indiv	4 wk Clot. n indiv	1 wk Terb. n indiv	4 wk Terb. n indiv	1 wk Clot. n event	4 wk Clot. n event	1 wk Terb. n event	4 wk Terb. n event
"food Poisoning"	Moderate	.	.	.	1	.	.	.	1
Arthritis Pain	Moderate	.	.	1	.	.	.	1	.
Avulsion Of Ingrown Toenail	Moderate	1	.	.	.	1	.	.	.
Back Pain	Mild	.	.	2	.	.	.	2	.
Burn Right Thigh	Mild	.	1	.	.	.	1	.	.
Burning	Severe	1	.	.	.	1	.	.	.
Burning On Urination	Mild	.	.	1	.	.	.	1	.
Burning Upon Application	Severe	1	.	.	.	1	.	.	.
Burning-minor Itching	Severe	.	.	.	1	.	.	.	1
Cold	Mild	2	1	1	2	3	2	2	2
	Moderate	.	.	.	1	.	.	.	1
Cold & Runny Nose	Mild	.	.	.	1	.	.	.	1
Cold-sinus	Mild	.	.	1	.	.	.	1	.
Cold/allergies	Mild	.	1	.	.	.	1	.	.
Congestion	Mild	.	.	1	.	.	.	1	.
Cough	Mild	.	.	1	.	.	.	1	.
Disorientation	Moderate	.	1	.	.	.	1	.	.
Elev. Itch Both Feet Aff. Area	Severe	.	.	1	.	.	.	1	.
Excisional Biopsy	Moderate	.	.	.	1	.	.	.	1
Flu	Mild	.	.	.	2	.	.	.	2
	Moderate	.	1	1	1	.	1	1	1
	Severe	.	.	1	1	.	.	1	1
Flu & Cold	Moderate	.	.	.	1	.	.	.	1

Table 24. (Cont.) Study 2508-01 Adverse Events

Flu Symptoms	Mild	.	.	.	1	.	.	.	1
	Moderate	.	.	1	.	.	.	1	.
Fractured Left Fibula	Moderate	.	.	1	.	.	.	2	.
Frx (l) Clavicle	Moderate	.	.	1	.	.	.	1	.
Gingivitis	Moderate	.	.	1	.	.	.	1	.
Head Cold	Mild	.	.	.	1	.	.	.	1
Headache	Mild	.	.	1	.	.	.	1	.
	Moderate	.	.	1	.	.	.	1	.
Herpes Simplex Left Buttocks	Mild	.	.	1	.	.	.	3	.
Influenza/pneumonia	Moderate	.	.	1	.	.	.	1	.
Ingrown Left Large Toenail	Moderate	1	.	.	.	1	.	.	.
Itch Instep Both Feet,blisters	Severe	.	1	.	.	.	2	.	.
Itch/pain 1st Web Toe Space	Moderate	.	.	.	1	.	.	.	1
Itching	Mild	1	.	.	.	1	.	.	.
Itching, Burning	Moderate	1	.	.	.	1	.	.	.
Lanced-inflammed Hemorrhoid	Moderate	.	1	.	.	.	1	.	.
Laryngopharyngitis	Severe	.	.	1	.	.	.	1	.
Laryngoscopy	Severe	.	1	.	.	.	1	.	.
Loss Of Perep. Vision (r) Eye.	Moderate	.	.	.	1	.	.	.	1
Lower Back Pain	Moderate	1	.	.	.	1	.	.	.
Metallic Taste In Mouth	Mild	.	.	1	.	.	.	1	.
Microlaryngoplasty With Laser	Severe	.	.	1	.	.	.	1	.
Nasal Congestion	Severe	.	.	1	.	.	.	2	.
Pain Left Great Toe	Mild	1	.	.	.	1	.	.	.
Prostatitis	Moderate	1	.	.	.	1	.	.	.

Table 24. (Cont.) Study 2508-01 Adverse Events

Pruritus Upon Application	Severe	.	.	.	1	.	.	.	1
Reflux	Moderate	.	1	.	.	.	1	.	.
Rhinorrhea	Moderate	1	.	.	.	1	.	.	.
Right Ball Of Foot Pain	Mild	.	.	.	1	.	.	.	1
Right Lower Lobe Pneumonia	Moderate	.	.	.	1	.	.	.	2
Seizure	Moderate	1	.	.	.	1	.	.	.
Severe Pruritus	Severe	.	.	.	1	.	.	.	1
Shoulder Out Of Joint	Mild	.	.	.	1	.	.	.	1
Sinus Infection	Moderate	.	.	.	1	.	.	.	1
Sore Throat	Moderate	.	.	1	.	.	.	1	.
Soreness	Severe	1	.	.	.	2	.	.	.
Sprained (l) Wrist	Moderate	.	1	.	.	.	1	.	.
Stomach Distress	Moderate	.	.	1	.	.	.	1	.
Strep Throat	Moderate	.	1	.	.	.	1	.	.
Swollen L Foot	Moderate	.	1	.	.	.	1	.	.
Syncopal Episode	Mild	.	1	.	.	.	1	.	.
Upper Respiratory Disease	Mild	.	1	.	.	.	1	.	.
Upper Respiratory Illness	Mild	.	.	1	.	.	.	2	.
Upper Respiratory Infection	Moderate	.	1	1	.	.	1	1	.
Upset Stomach	Mild	.	.	.	1	.	.	.	1
Uri	Mild	1	1	1	2	2	4	2	3
	Moderate	.	.	1	.	.	.	1	.
Uti	Moderate	.	.	.	1	.	.	.	1
Overall		15	16	29	26	18	21	36	28

Again, it is apparent that no treatment related differences would be statistically significant.

e. Study No. SF 0040: Tinea Pedis

The following table provides both a count of adverse events and a count of the individuals experiencing adverse events, at least according to the data provided by the sponsor:

Table 25. Study SF 0040 Adverse Events

Adverse Event	Severity	Clot. n indiv	Terb. n indiv	Clot. n event	Terb. n event
Abdominal Pain	Moderate	.	1	.	1
Acneiform	Mild	1	.	1	.
Acute Coryza	Mild	1	.	1	.
Alvedar Abcess	Moderate	1	.	1	.
Anal Fissure	Moderate	.	1	.	1
Angina	Mild	1	.	1	.
Cellulitis Rt Foot	Moderate	.	1	.	1
Chest Pain	Moderate	.	1	.	1
Cold	Mild	1	.	1	.
Cold Feet	Mild	1	.	1	.
Contact Eczema Earlobes	Mild	.	1	.	1
Coryza	Moderate	1	.	1	.
Diarrhoea	Mild	1	.	1	.
	Moderate	1	.	1	.
Eczema	Mild	.	1	.	1
Erythema	Severe	.	1	.	1
Erythema/swelling Of Skin	Severe	1	.	1	.
Fissures In Toe Cleft	Moderate	.	1	.	1
Generalised Allergic Rash	Moderate	.	1	.	1
Increased Itch	Mild	1	.	1	.
Increased Pruritis	Mild	1	.	1	.
Increasing Itch	Severe	.	1	.	1

Table 25. (Cont.) Study SF 0040 Adverse Events

Infected Foot	Moderate	1	.	1	.
Intense Irrit Apply Cream	Moderate	1	.	1	.
Irritation Of Eyes	Severe	1	.	1	.
Itching	Mild	.	1	.	2
	Moderate	.	1	.	1
Itching At Site	Moderate	1	.	1	.
Itching+soreness	Moderate	.	1	.	1
Macular Rash	Moderate	.	1	.	1
Mild Vertigo	Mild	.	1	.	1
Nausea	Moderate	1	.	1	.
Neurological Migraine	Severe	1	.	1	.
Pain & Itching At Target	Moderate	1	.	1	.
Pain Due To Cracking Skin	Mild	.	1	.	1
Pain+cracking Between Toe	Moderate	1	.	1	.
Painful Stinging & Cracks	Mild	1	.	1	.
Papular Urticaria Hands	Moderate	.	1	.	1
Pulled Muscle In Neck	Moderate	1	.	1	.
Red Rash	Mild	.	1	.	1
Slight Redness/itchy	Mild	.	1	.	1
Soreness	Severe	.	1	.	1
Vaginal Thrush	Moderate	.	1	.	1
Overall		22	21	22	22

Overall, it is apparent that no treatment related differences would be statistically significant.

f. Study No. 3-1: Tinea Cruris/Corporis

The following table provides both a count of adverse events and a count of the individuals experiencing adverse events, at least according to the data provided by the sponsor:

Table 26. Study 3-1 Adverse Events

Adverse Event	Severity	Terb. n indiv	Veh. n indiv	Terb. n event	Veh. n event
Headache	Mild	.	1	.	1
Sinusitis	Moderate	1	.	2	.
Overall		1	1	2	1

Overall, it is apparent that no treatment related differences are statistically significant.

g. Study No. 3-2: Tinea Cruris/Corporis

As with the preceding tables of adverse events, the following table presents both a count of adverse events and a count of the individuals experiencing adverse events, at least according to the data provided by the sponsor:

Table 27. Study 3-2 Adverse Events

Adverse Event	Severity	Terb. n indiv	Veh. n indiv	Terb. n event	Veh. n event
Death(cause=Asthma)	Severe	1	.	1	.
Pruritus	Severe	.	1	.	1
Vesicules	Mild	.	1	.	1
Overall		1	2	1	2

Overall, it is apparent that no treatment related differences are statistically significant.

h. Study 2509-01: Tinea Pedis: Safety analysis (by the sponsor).

Again, this involved a two week BID course of treatment. "Four of the 107 safety evaluable patients (4%) reported adverse events, two in each group. However, only one of these patients reported an adverse event that was possibly related to the test medication. This was a vehicle treated patient who reported mild burning on the bottom of the feet.

"No differences (p=0.362) in the two groups were noted with respect to tolerability (as rated by patients) at the end of treatment (Week 2). Eighty-five percent of the Lamisil group indicated that tolerability was either excellent or very good as compared to 84% for the vehicle group."

i. Study 2509-02: Tinea Pedis: Safety analysis (by the sponsor).

"A total of 35 of the 118 safety evaluable patients admitted to this study (30%) reported adverse events, 15 in the Lamisil-treated group (25%) and 20 in the vehicle group (34%). However, only 6 of these 35 patients (17%) reported adverse events that were possibly or probably related to the test medication. Of these 6 patients, 4 were in the Lamisil treated group (67%) and 2 were in the vehicle group (33%).

"No differences (p=0.652) in the two treatment groups were noted with respect to tolerability (as rated by patients) at the end of treatment (Week 2). Eighty-five percent of the Lamisil group indicated that tolerability was either excellent or very good as compared to 81% for the vehicle group. No patients discontinued because of an adverse event."

5. Learning Comprehension Study.

According to the sponsor, "the purpose of this study was to measure consumer comprehension of the carton label and educational brochure, particularly the dosing instructions which are dependent on the part of the foot affected." The method of the study was to display the Lamisil® AT™ cream and a supporting educational brochure. Then consumers were interviewed about what the product was for, conditions of use, etc. Some 507 interviews were conducted in various shopping malls displaying a wide geographic variation.

Non-native speakers whose English was not "well" were excluded, as were any subjects with special knowledge related to the product or interviewing process. The limitation to shopping malls suggests to this reviewer that it would be quite likely that the population from which subjects were drawn displays a much smaller proportion of people in poverty or minorities than would be typical of the general population in that geographic region. Similarly, one might guess that people willing to serve in such a study would likely be on average somewhat older than the population of potential Lamisil users. Presumably these exclusions and limitations

would reduce to some degree the proportion of patients who seem to understand the Lamisil label and brochure.

According to the sponsor's report: "virtually all respondents (94%-100%) correctly cited one or more conditions that Lamisil® AT™ cream treats." "The majority of respondents (78%-97%) rated the information contained in the Lamisil® AT™ cream carton label as "extremely" or "very" understandable. Low Literacy respondents were less apt than others to rate the information as "extremely" or "very" understandable (78% vs. 92%-97%)."

"After reading the Lamisil® AT™ cream carton label (but before exposure to the educational brochure), the vast majority of consumers, even those categorized as "Low Literacy", correctly indicated that the cream was to be used twice a day or as directed by a doctor to treat athlete's foot on specific areas of the foot" (72%-94%)." "The majority of respondents (78%-97%) rated the information contained in the Lamisil® AT™ cream carton label as "extremely" or "very" understandable. Low Literacy respondents were less apt than others to rate the information as "extremely" or "very" understandable (78% vs. 92%-97%)." After exposure to the label, 81%-86% correctly responded that treatment should be for one week or as directed by a doctor for athlete's foot between the toes. Similarly, for athlete's foot on the bottom or side of the foot, 85%-93% correctly responded that treatment should be for two weeks or as directed by a doctor.

This reviewer would claim no particular expertise in evaluating such studies, but personally would suggest that these proportions seem to indicate a fair degree of understanding of the label. Of course, due to the method of subject selection, one would expect that the proportions responding correctly would be somewhat lower among the population of potential patients than among these patients.

Conclusions (Which may be conveyed to the Sponsor):

1. The sponsor provided the results from nine studies to support the claim of efficacy and safety for the use of terbinafine hydrochloride 1% cream in the treatment of i) interdigital tinea pedis (BID one week), ii) tinea cruris/corporis (QID one week). In addition, to extend the results to most types of tinea pedis, statistical reports of two studies of the efficacy and safety of terbinafine hydrochloride cream for the treatment of iii) plantar type tine pedis (BID two weeks), were briefly reviewed.

2. As would be expected with a product that had previously been approved for prescription use, all relevant vehicle controlled studies showed statistically significant differences between terbinafine hydrochloride cream and vehicle (at the end-of-study for effective treatment: $p \leq 0.001$ for most studies).

3. Ignoring study and center (which should result in a somewhat anticonservative tests) one can compare the frequencies of subjects with adverse events between vehicle and terbinafine hydrochloride groups using Fisher's exact test. Still, they may be indicative, and hence helpful. For mild adverse events, the proportions reported by the sponsor pooling the nine data sets were 6.4% in the terbinafine hydrochloride cream group and 2.4% in the vehicle group ($p \leq 0.029$). For moderate adverse events, the proportions were 6.2% in the terbinafine group and 1.9% in the vehicle group ($p \leq 0.015$). For severe adverse events, the proportions were 2.2% in the terbinafine group and 0.5% in the vehicle group ($p \leq 0.126$). Descriptively, the proportion of adverse events in each body system seems to be higher with the terbinafine cream than with its vehicle.

5. Assuming we can pool cases with different levels of severity in adverse events, and ignoring the presumably slight duplication of subjects that such pooling entails, we can compare the 17% incidence of adverse events in the terbinafine group with the 5% incidence in the vehicle group ($p \leq 0.000003$). Even with a few extra subjects in the adverse event group, and even with considerable inflation of the p-value due to the clustering of responses within studies, this is presumably statistically significant. Whether or not this apparent difference in adverse events between vehicle and terbinafine cream is of any medical importance is a matter for the clinical judgement of the Medical Officer. Note that much of the difference seems to be related to a higher rate of infections among the terbinafine group (see page 19, table 20 of this report, originally sponsor's table 10).

6. It was noted by the Medical Officer that the range of dosages and periods of use observed in the 2265 patients involved in the development of the drug will quite likely be more typical of the use of an OTC drug, than the 550 patients in the nine efficacy studies provided by the sponsor. This reviewer considers that to be a very astute observation, and also would have preferred a more detailed analysis of adverse events based on the 2265 patients. However, terbinafine hydrochloride cream 1% has been accepted as safe for prescription use, with a learned intermediary.

7. The sponsor also provided the results from a label comprehension study. After exposure to the label, 81%-86% correctly responded that treatment should be for one week or as directed by a doctor for athlete's foot between the toes. Similarly, for athlete's foot on the

bottom or side of the foot, 85%-93% correctly responded that treatment should be for two weeks or as directed by a doctor. This reviewer would claim no particular expertise in evaluating such studies, but personally would suggest that these proportions seem to indicate a fair degree of understanding of the label. The only caveat would be that this reviewer would expect that due to the methods of subject selection, one would expect that the proportions responding correctly would be somewhat lower among the population of potential patients than among the population of subjects at shopping malls.

6. Thus, it is this reviewer's opinion that the sponsor has demonstrated statistically significant differences between the one week, once a day course of treatment with terbinafine hydrochloride 1% cream with the corresponding vehicle cream in the treatment for tinea cruris/corporis. Further, there seem to be statistically significant differences between the a one week, twice a day course of treatment with Lamisil versus vehicle cream in the treatment for interdigital tinea pedis. Also, it is this reviewer's opinion that the sponsor has demonstrated statistically significant differences between the two week, twice a day course of treatment with terbinafine 1% cream with the corresponding vehicle cream in the treatment for plantar type tinea pedis. Although there seems to be a statistically significantly higher rate of adverse events associated with the use of the active cream versus its vehicle, and this difference seems to be associated with most body systems, analyzing the implications of that observation is beyond the expertise of this reviewer. Thus, this reviewer sees no particular statistical objection to the sponsor's request.

/S/ 01/06/99

Steve Thomson
Mathematical Statistician, Biometrics III

01/06/'99

concur: **R. Srinivasan, Ph.D.**
Team Leader, Biometrics III

cc:
Archival NDA: 20-980
HFD-540/Division File
HFD-540/Dr. Wilkin
HFD-540/Dr. Vaughan
HFD-540/Mr. Cross
HFD-725/Dr. Anello
HFD-725/Dr. Srinivasan
HFD-725/Mr. Thomson
HFD-340/Dr. Lepay
This review has 33 pages.
Chron.

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