e. Study No. 2509-02 Plantar Tinea Pedis

This study was identical in design to study 2509-01.

i. Patient Demographics:

The following table summarizes the disposition of the subjects in the study:

Table 13. Patient Enrollment

	Terbinafine	Vehicle	Total
Patients enrolled	61	61	122
Evaluable for Efficacy	48	49	97

Five patients were erroneously assigned the wrong drug. One patient received tubes of vehicle instead of the active drug to which he had been assigned. He was reallocated to the vehicle group. Four patients received tubes of both vehicle and terbinafine, and were deleted from the efficacy analysis. Seventeen patients were deleted because they did not meet the entry criteria. Four patients were lost to follow-up.

Again, though not displayed here, there were no statistically significant differences among treatments with respect to age. gender, race (white versus other), and other demographic variables.

ii. Results (taken from original statistical review):

"Effective treatment was defined as in Study 1509-01. Significant differences in effectiveness were noted between treatments at Weeks, 4, 6, and 8 and at [the LOCF] End Point. At the Week 8 visit, 65% of the Lamisil [i.e., terbinafine HCl 1% cream] group were effectively treated as compared to six percent for vehicle ($p<0.001$). In the Lamisil Using End Point Analysis (the last visit for patients with at least one follow-up-visit, [i.e., LOCF], the patients who were effectively treated were 45% and 5% respectively ($p<0.001$). In the Lamisil treated group, the percentage of patients effectively treated increased steadily over time (4% at 1 week, 13% at 2 week, 24% at 4 weeks, 48% at 6 weeks, and 65% at 8 weeks) The differences between Lamisil and vehicle were statistically significant at Weeks 4 ($p=0.05$), 6($p<0.001$), and 8 ($p<0.001$), and at [the LOCF] End Point ($p<0.001$)."

f. Efficacy Summary for Tinea Pedis

In studies 2-1 and 2-2 for interdigital tinea pedis statistically significant differences in mycological cure between the terbinafine group and vehicle were apparent at both week 6 and the end of study (i.e., last observation up to week 6) ($p<0.001$ for both studies). Observed proportions of success at these endpoints ranged from 59%-67% in the terbinafine group versus 0%-15% in the vehicle group. Similar levels of statistical significance were observed using complete cure. In studies 2-1 and 2-2, statistically significant differences in complete cure were observed at both week 6 and the end of study (i.e., last observation up to week 6) ($p<0.006$ at week 6 and $p<0.002$ at EOS, End-of-study, in study 2-1, $p<0.001$ at both time points in study 2-2). Observed proportions of success varied from 21%-38% in the terbinafine group versus 0%-3% in the vehicle group. In the 2508-01 study of terbinafine 1% cream versus clotrimazole cream mycological cure rates for the one week course of treatment were 58% at the end of 12 weeks and 51% at the End-of-study(EOS).

In studies 2509-01 and 2509-02 for plantar type tinea pedis statistically significant differences between the terbinafine group and vehicle in mycological cure were apparent at both week 8 and the end of study (i.e., last observation up to week 8) ($p<0.001$ for both studies). Observed proportions at these endpoints showed success rates of 45%-65% in the terbinafine group versus 4%-6% in the vehicle group.

4. Results for Tinea Corporis/Cruris Studies

a. Study No. 3-1

Although the sample data collection forms provided suggest this study was limited to tinea cruris, the sponsor's report indicates the study pooled patients with both conditions.

i. Patient Demographics:

The following table summarizes the disposition of the subjects in the study.

Table 14. Patient Enrollment

	Terbinafine	Vehicle	Total
Patients enrolled	40	43	83
Drop-outs	4	5	9
Delayed exclusions	2	1	3

The nine drop-outs were discontinued for reasons other than safety. The three patients categorized as delayed exclusions were dropped because the initial cultures were negative for dermatophytes.

Again, though not displayed here, there were no statistically significant differences among treatments with respect to age. gender, race (white versus other), and other demographic variables

ii. Efficacy Results:

Mycological cure is defined as negative KOH and culture with a total signs and symptoms score of two or less (plus a maximum score of "1= mild" for each of erythema, desquamation, and pruritus). Note that this latter list differs slightly from that used in protocols 2506-01 and 2506-02. As in these studies, complete cure is defined as a mycological cure with a score of "0=none" for all the signs and symptoms. The following tables give proportions of mycological and complete cures for each treatment group at each time point in the study. Note that the treatment period ended after one week. Tables are given for baseline, end of treatment (one week), week 2, end of study (week 4), and a "last observation carried forward" (LOCF) analysis. Below each table is the "p-value", significance level, of a test of within center homogeneity of cure over treatment, using a Mantel-Haenszel test.

Table 15. Study 3-1 Mycological Cure

Mycological Cure (KOH & culture negative & signs <=2)

	Visit Week														
	Baseline			1			2			4			LOCF		
	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%
Terbinafine	0	40	0.0	12	38	31.6	28	37	75.7	31	35	88.6	32	40	80.0
Vehicle	0	43	0.0	3	42	7.1	6	30	20.0	6	18	33.3	6	43	14.0
p-value		.			0.006			0.001			0.001			0.001	

Observe that even at the end of treatment, week one, nearly 32% of the terbinafine group displayed a mycological cure versus only 7% for vehicle ($p \leq 0.006$). Differences remain statistically significant at each succeeding time point ($p \leq 0.001$). Using the LOCF group, at the end of the study, 80% of the terbinafine group displayed a mycological cure versus only 14% for vehicle ($p \leq 0.001$). In this particular case, due to the drop outs in the vehicle group, it is clear that an LOCF analysis is not conservative. However the difference at the sixth week is also highly statistically significant ($p \leq 0.001$), so there is still strong evidence of statistically significant differences at the end of the study.

As before, complete cure is defined as negative KOH and culture with no residual signs and symptoms. These give the following tables (by week):

Table 16. Study 3-1 Complete Cure

Complete Cure

	Visit Week														
	Baseline			1			2			4			LOCF		
	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%
Terbinafine	0	40	0.0	6	38	15.8	15	37	40.5	26	35	74.3	26	40	65.0
Vehicle	0	43	0.0	1	42	2.4	3	30	10.0	5	18	27.8	5	43	11.6
p-value		.			0.034			0.036			0.006			0.001	

At the end of treatment, week one, roughly 16% of the terbinafine group displayed a complete cure versus only 2% for vehicle ($p \leq 0.034$). Differences remain statistically significant at each succeeding time point ($p \leq 0.036$) Using the LOCF group, at the end of the study, 65% of the terbinafine group displayed a mycological cure versus only 12% for the vehicle group ($p \leq 0.001$). As above, it is clear that the LOCF analysis is not conservative. However the difference at the sixth week is also highly statistically significant ($p \leq 0.006$). Hence, once again there is strong evidence of statistically significant differences at the end of the study.

b. Study No. 3-2

i. Patient Demographics:

The following table summarizes the disposition of the subjects in the study.

Table 17. Patient Enrollment

	Terbinafine	Vehicle	Total
Patients enrolled	36	38	74
Drop-outs	5	3	8
Delayed exclusions	1	0	1

The eight patients categorized as drop-outs were discontinued for reasons other than safety. The single patient labeled as a delayed exclusion was dropped because the initial culture was negative for dermatophytes.

Again, though not displayed here, there were no statistically significant differences among treatments with respect to age. gender, race (white versus other), and other demographic variables.

ii. Efficacy Results:

As above, mycological cure is defined as negative KOH and culture with a total signs and symptoms score of two or less (plus a maximum score of "1= mild" for each of erythema, desquamation, and pruritus).

Table 18. Study 3-2 Mycological Cure

Mycological Cure (KOH & culture negative & signs <=2)

	Visit Week														
	Baseline			1			2			4			LOCF		
	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%
Terbinafine	0	35	0.0	14	34	41.2	24	31	77.4	27	30	90.0	29	35	82.9
Vehicle	0	38	0.0	2	35	5.7	3	32	9.4	5	17	29.4	5	38	13.2
p-value		.			0.001			0.001			0.001			0.001	

Observe that even at the end of treatment, week one, 41% of the terbinafine group displayed a mycological cure versus only 6% for vehicle ($p \leq 0.001$). Differences remain statistically significant at each succeeding time point ($p \leq 0.001$). Using the LOCF group, at the end of the study, 83% of the terbinafine group displayed a mycological cure versus only 13% for vehicle ($p \leq 0.001$). Again, due to the drop outs in the vehicle group, it is apparent that the LOCF analysis is not conservative. But the difference at the sixth week is also highly statistically significant ($p \leq 0.001$), thus providing strong evidence of statistically significant differences at the end of the study. These results are almost exact duplicates of the results for the 3-1 study.

As before, complete cure is defined as negative KOH and culture with no residual signs and symptoms. These give the following tables (by week):

Table 19. Study 3-2 Complete Cure

	Visit Week														
	Baseline			1			2			4			LOCF		
	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%
Terbinafine	0	35	0.0	1	34	2.9	17	31	54.8	23	30	76.7	25	35	71.4
Vehicle	0	38	0.0	1	35	2.9	2	32	6.3	4	17	23.5	4	38	10.5
p-value		.			1.000			0.001			0.001			0.001	

At the end of treatment, week one, only one subject in each treatment group showed a complete cure. By week 2, roughly 55% of the terbinafine group displayed a complete cure versus only 6% for vehicle ($p \leq 0.001$). Differences remain statistically significant at each succeeding time point ($p \leq 0.001$) Using the LOCF group, at the end of the study, 71% of the

terbinafine group displayed a complete cure versus only 10% for the vehicle group ($p \leq 0.001$), or perhaps more appropriately: at week 4, 77% of the terbinafine group displayed a complete cure versus only 24% for the vehicle group ($p \leq 0.001$). Again, these results are almost exact duplicates of the results for the 3-1 study.

c. Efficacy Summary for Tinea Corporis/Cruris

In studies 3-1 and 3-2, pooling results from tinea corporis and cruris, there were statistically significant differences in mycological cure between the terbinafine group and vehicle were apparent at both week 4 and the end of study (i.e., last observation up to week 6) ($p<0.001$ for both studies). Observed proportions at these endpoints showed success rates of 80%-90% in the terbinafine group versus 13%-33% in the vehicle group. Similar levels of statistical significance were observed using complete cure. Statistically significant differences in complete cure were observed at both week 4 and the end of study (i.e., last observation up to week 6) ($p<0.006$ at week 4 and $p<0.001$ at EOS in the 3-1 study, $p<0.001$ at both time points in the 3-2 study.). At these time points, observed proportions of success varied from 65%-75% in the terbinafine group versus 11%-28% in the vehicle group.

4. Adverse Events

a. Overview

The following table is transcription of the sponsor's table 10 listing all adverse events by treatment and severity for the nine studies provided by the sponsor.

Table 20. Sponsor's Table of All Adverse Events by Treatment and Severity *

COSTART BODY SYSTEM	COSTART TERM	Terbinafine (N=550)				Vehicle (N=212)			Clotrimazole (N=234)		
		No sev*	Mild	Mod.	Severe	Mild	Mod.	Severe	Mild	Mod.	Severe
Body as a Whole	Allerg React.								1		
	Cellulitis									1	
	Headache		3	1		1					
	Infect		15	6			1		8	1	
	Infect Bact									1	
	Infect Fung	1									
	Infect Viral		4	5	2					1	
	Injury Accid		1	3			1		1	1	
	Pain		1	4	1	1			3	2	5
	Pain Abdo									1	
	Pain Back		2				1			1	
	Pain Chest									1	
Cardiovascular	Angina Pectoris		1								
	Migraine				1		2				
	Syncope								1		
Digestive	Diarrhea		1	1							
	Dyspepsia		1	1							
	Esophagitis									1	
	Gingivitis			1							
	Nausea			1							
	Rectal Dis									2	
	Tooth Dis			1							
Metabolic & Nutritional	Edema				1					1	
Musculoskeletal	Arthritis			1							
	Myalgia			1							
Nervous	Anxiety	1									

	Convuls									1	
	Paresthesia		2								
	Thinking Abnorm									1	
	Vertigo								1		
Respiratory	Asthma				1						
	Cough Inc.		1			1					
	Pharyngitis	2		1	1						
	Pneumonia			2							
	Resp. Distress								1		
	Rhinitis		2	1	1	1				1	
	Sinusitis		2	3							
Skin and Appendages	Acne		1								
	Derm Contact								1		
	Eczema	1							1		
	Herpes Simplex		1								
	Nail Dis	1								2	
	Pruritus		3	4	4			1	3	3	2
	Rash	1			1				2		1
	Rash Mac Pap									1	
	Rash Vesic Bull					1					1
	Skin Dis	3	2	1					1	1	
	Urticaria									1	
Special Senses	Amblyopia			1							
	Conjunctive				1						
	Taste Pervers		1								
Genitourinary	Dysuria		1								
	Infect Urin Tract	1		1							
	Monila Vagina	1								1	
	Prostat Dis									1	
Total Adverse Events		12	45	40	14	5	5	1	24	27	9
Total Patients w/ AEs		10	35	34	12	5	4	1	17	24	6
Pts with AEs/ Total pts		1.8%	6.4%	6.2%	2.2%	2.4%	1.9%	0.5%	7.3%	10.3%	2.6%

*-No indicated severity

One can compare the frequencies of subjects with adverse events using Fisher's exact test. A notable problem with this test is that it assumes all randomizations of subjects are

equally likely, that is, a subject is just as likely to be randomized to a treatment in a different study as in the study in which they appeared. Clearly this is false. The net effect is that tests will tend to be somewhat anticonservative. Still, they may be indicative, and hence helpful. For mild or moderate adverse events, there are statistically significant differences across treatments ($p \leq 0.029$ and $p \leq 0.015$, respectively). The 12 to 1 ratio of severe adverse events across levels of treatment was not statistically significant ($p \leq 0.126$).

We do not have an exact count of subjects with any adverse events in the nine studies, and in some circumstances a subject may have adverse events with different levels of severity. However, the number of such subjects is presumably small. Treating different levels of severity of adverse events as occurring in different subjects, Fisher's exact test is statistically quite significant ($p \leq 0.000003$). Even with a few extra subjects, and with inflation of p-value due to the clustering of responses within studies, this is presumably statistically significant. Note that much of the difference seems to be related to a higher rate of infections among the terbinafine group. However, these counts may be largely due to chronic infections in a few patients. Without the complete data, this question can not be completely resolved.

Whether or not the apparent difference in adverse events between vehicle and terbinafine cream is of medical importance is a matter for the clinical judgement of the Medical Officer.

According to the sponsor: "A total of 2,265 patients received terbinafine topical cream 1% during the clinical development of this drug, The following table presents the total number of patients reporting adverse reactions by the dosage regimens used":

Table 21. Sponsor's Table of Adverse Events by Dosage Regimen

Regimen	Max. No. of Exposures	Terbinafine group		
		N	No. AER (%)	No. Disc.
Up to 7 days, q.d.	7	201	4 (2.0%)	1
1 week, b.i.d.	14	94	6 (2.0%)	0
2 weeks, q.d.	14	511	9 (2.0%)	1
2 weeks, b.i.d.	28	624	9 (2.0%)	1
3 weeks, q.d.,	21	89	2 (2.0%)	1
3 weeks, b.i.d.	42	9	0 (0%)	0
4 weeks, q.d.	28	279	17 (2.0%)	2
4 weeks, b.i.d.	56	434	4 (2.0%)	0
6 weeks, q.d.	42	24	1 (2.0%)	0
		2265	52	6

"Adverse events associated with terbinafine by indication were as follows (N indicates the total number of patients studies per indication)":

Table 22. Sponsor's Table of Adverse Events by Indication.

INDICATION	TERBINAFINE	
Adverse Events	%	N
tinea pedis	3.85	675
tinea coporis/cruris	2.95	271
candidiasis	2.37	211
all "other" studies	1.17	1108
All studies	2.30	2265

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, safety in these studies was accepted as part of the original review as a prescription product. So this question may be moot.

In addition tables of adverse events for each study were generated for the data sets provided to this reviewer:

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b. Study No. 2-1: 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 23. Study 2-1 Adverse Events

---------- Protocol Number=SAN 2506-01----------

Adverse Event	Severity	Terbinafine n indiv	Vehicle n indiv	Terbinafine n event	Vehicle n event
Back Pain	Moderate	.	1	.	1
Cough	Moderate	.	1	.	1
Cracking Skin/toes	Mild	1	.	1	.
Fracture R Finger	Moderate	.	1	.	1
Itching	Moderate	1	.	1	.
Nasal Congestion	Mild	.	1	.	1
Sprain Left Ankle	Moderate	1	.	1	.
Sprained Ankle Left	Moderate	1	.	1	.
Stinging R Foot	Mild	1	.	1	.
Tenderness Bl T.site	Mild	.	1	.	1
Uri	Mild	2	.	3	.
	Moderate	1	.	1	.
Overall		8	5	9	5

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