CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-749

STATISTICAL REVIEW(S)

JUL 23 1997

Statistical Review and Evaluation

NDA/ Drug Class: 20-749

Name of Drug: Lamisil® (terbinafine hydrochloride) Solution, 1%.

Applicant: Sandoz Pharamaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

Type of Report: Clinical/Statistical

Indication: Treatment of Tinea Versicolor (Pityriasis Versicolor) due to Pityrosporum species, and topical treatment of Tinea Pedis, Tinea Corporis and Tinea Cruris caused by Trichophyton Rubrum, Epidermophytom Floccosum, or Trichophyton Mentagrophytes.

Documents Reviewed: Volumes 1.1, 1.81 through 1.121 (Statistical Data), dated 17 rOctober 1996, and diskettes containing SAS data sets from the sponsor.

Medical Officer: Dr. E. Toombs (HFD-540)

Introduction:

According to the sponsor: "Lamisil® Solution 1% is the second formulation of terbinafine hydrochloride that was developed by Sandoz. Lamisil (terbinafine hydrochloride) Cream 1% was approved on December 30, 1992 (NDA 20-192) for the treatment of tinea pedis and tinea corporis/cruris. In addition, Lamisil . . . Tablets was approved on May 10, 1996 (NDA 20-539)."

Continuing: "Lamisil 1% topical solution is a new galenical formulation of a previously approved topical dosage form of terbinafine hydrochloride (Lamisil 1% cream; NDA 20-192) which has been shown to be highly effective and safe. . . . In placebo-controlled, pivotal clinical studies evaluating Lamisil 1% cream, conversion from positive to negative mycology was achieved in 85% of subjects infected with T. rubrum, in 80% of subjects with T. mentagrophytes, and in 79% of subjects with E. floccosum. In early clinical trials, Lamisil 1% solution had effectiveness similar to that of Lamisil 1% cream in tinea pedis and tinea corporis/cruris."

"Lamisil® 1% Solution will provide the physician with an additional treatment option and has an advantage in treating large surface areas of the body, hands, and face where the cream would be inconvenient, messy, or otherwise unacceptable. Thus it will be better suited than the cream for patients with widespread tinea corporis/cruris and pityriasis versicolor."

Methods

The sponsor included the results of nine studies, conducted in the U.S. and Europe, to support the claim of efficacy and safety of Lamisil (terbinafine) 1% solution in the treatment of the three indications:

i. Tinea Versicolor (Pityriasis Versicolor)
ii. Tinea Pedis
iii. Tinea Corporis/Tinea Cruris.

Eight of the studies were vehicle controlled and one was active controlled (Clotrimazole solution).

The designs used in the studies are summarized in the following table:

Table 1. Phase III Clinical Studies
Tinea Versicolor/Tinea Pedis/Tinea Corporis-Tinea Cruris

Protocol no	US vs non US	design	objective	duration of study	No. enrolled
Tinea Versicolor (Pityriasis Versicolor)					
SFF 353	US	multicenter, double blind, randomized, parallel-group	safety/efficacy vs vehicle twice daily for treatment of tinea versicolor (pityriasis versicolor)	1-week treatment with a 7-week untreated follow-up	LAM. 1% 103 Veh 49
SFF 305	non US				LAM. 1% 79 Veh 36
Tinea Pedis					
SFF 351	US	multicenter, double blind, randomized, parallel-group	safety/efficacy vs vehicle twice daily for treatment of tinea pedis.	1-week treatment with a 7-week untreated follow-up	LAM. 1% 104 Veh 49
SFF 301	Non-US	multicenter, double blind, randomized, parallel-group	safety/efficacy vs vehicle once daily for treatment of tinea pedis.	1-week treatment with a 7-week untreated follow-up	LAM. 1% 115 Veh 57
SFF 309	Non-US	multicenter, double blind, randomized, parallel-group	safety/efficacy vs Clotrimazole twice daily for treatment of tinea pedis.	1-week treatment for Lamisil (with a 3-week PBO) vs 4-week Clotrimazole. Both have further 3-week untreated follow-up.	LAM. 1% 348 Veh 351
SFF 104	US	multicenter, double blind, randomized, parallel-group	safety/efficacy vs vehicle once daily for treatment of tinea pedis.	2-week treatment with a 4-week untreated follow-up	LAM. 1% 43 Veh 43

Tinea Corporis / Cruris						
SFF 303	Non-US	multicenter, double blind, randomized, parallel-group	safety/efficacy vs vehicle once daily for treatment of tinea corporis/cruris.	1-week treatment with a 7-week untreated follow-up	LAM. 1% 102	Veh 49
SFF 105	US	multicenter, double blind, randomized, parallel-group	safety/efficacy vs vehicle once daily for treatment of tinea corporis/cruris.	1-week treatment with a 3-week untreated follow-up	LAM. 1% 32	Veh 34
SFF 108	Non-US				LAM. 1% 36	Veh 36

The three 100-series studies (SFF104, SFF105, and SFF108), were conducted earlier, with some significant differences in variables between each of them and the six 300-series studies. The 100-series studies were considered to be supporting, and SAS data sets for them were not supplied by the sponsor, nor were they pooled into the integrated summary of safety.

For the six 300-series studies, except for the differences noted above, protocols were similar. Patient visits were recorded at baseline, the end of treatment, i.e., after the first week (approximately day 7), at the end of second week, usually the fourth week, and at the end of the study (nominally the 8th week, roughly day 56).

Three populations were defined for the analysis. "The safety population includes any subject, who is randomized, receives at least one dose of the study drug, and has at least one non-missing post-baseline assessment." The division definition of (modified) intent-to-treat is all patients who are randomized to treatment, and have the infection confirmed by microscopy and culture (except in the tinea versicolor studies). The sponsor's definition of intent-to-treat further limits this to cases with a clinical signs and symptoms score greater than two and requires at least one non-missing post-baseline efficacy assessment. According to the sponsor, "a valid population is created in each study by excluding patients not compliant with the protocol to the extent that treatment effectiveness might have been compromised. Subjects could be excluded from the valid population because of violation of certain inclusion/exclusion criteria, premature discontinuation from the study, not applying study medication according to protocol requirements, etc." The Medical Officer agreed with the sponsor's definition of valid population.

"Data concerning efficacy are collected by appropriate case report forms in three categories:

(a) Mycology, including microscopy for p. versicolor studies and both microscopy and culture for t. pedis and t. corporis/cruris studies.
(b) Clinical assessment, including severity scores for clinical signs and symptoms for all studies.
(c) Overall assessment of efficacy by investigator for all studies, and by subject for U.S. Studies SFF353 and SFF351."

In studies SFF 353 and SFF 305, the individual signs and symptoms scores (or severity scores) were recorded as the severity of erythema, desquamation, or pruritus. In the four remaining studies, variables for pustules, incrustation, and vesiculation were added. All six of these possible severity scores were each evaluated on a 4-point scale:

0 = absent 2 = moderate
1 = mild 3 = severe.

For each study the total signs and symptoms score was defined as the sum of the scores of the individual signs and symptoms severity scales. So for study SFF 353 and SFF 305 the total signs and symptoms score was the sum of three severity scores, while in the remaining 300-series studies it was the sum of six such scores.

For the 300-series studies, the investigator overall assessments are evaluated on a five-point scale:

1 = very good 4 = poor
2 = good 5 = very poor
3 = moderate

In SFF 351 and SFF 353 the same scale was used by the patient to give an overall assessment of treatment.

The sponsor proposes to use the binary response "effective treatment," defined as negative mycology and total signs and symptoms score ≤ 1 in the tinea versicolor (pityriasis versicolor) studies SFF353 and SFF305, and ≤ 2 in the remaining 300-series studies (SFF 301, SFF303, SFF309, SFF351), as the primary response. Note that for the treatment to be "effective" in the remaining 300-series studies, a further requirement was that the sum of severity scores for pustules, incrustation, and vesiculation must be zero. Secondary response variables included the following:

"complete cure" "negative mycology"
"clinical cure" "total signs and symptoms scores"
"negative microscopy" "overall assessment of efficacy"
"negative culture (except for the tinea versicolor studies)"

"Complete cure" was defined as a binary response indicating where mycology measures were negative and that the total signs and symptoms score was zero. "Clinical cure" was defined as a total signs and symptoms score of zero. The Medical Officer showed some preference for the sponsor defined "effective treatment" as a reasonable primary endpoint, but agreed that complete cure would do as well. Hence both are used in the 300-series studies in this report. For completeness in comparison with earlier studies mycological cure is included as well.

As an aside, as explained in some detail in their reports (e.g., volume 81, pages 10-221 to 10-222), the nominal weeks of evaluation have been recoded to time points closer to the original times point than was the original nominal week. For example, the week 2 measurement is defined to occur between the 11th and 21st study day in all studies.

Further details about the individual studies appear in the discussion of that particular study.

I. Tinea Versicolor (Pityriasis Versicolor)

A. Study SFF 353:

The objective of this study was to evaluate the safety, efficacy and duration of therapeutic effect of Lamisil® (terbinafine) 1% solution versus vehicle solution applied twice daily in patients with tinea versicolor (pityriasis versicolor). Subjects were randomly assigned to apply Lamisil 1% solution or its vehicle twice daily, in the morning and evening, for one week. This was followed by a seven-week follow-up period. The study was conducted at 10 centers (investigators) in the United States.

1. Patient Demographics:

The following table 2. summarizes the demographics of the randomized subjects.

Table 2. SFF353 Patient Demographics

		Lamisil	Vehicle
Age			
Mean (Std Dev)		33.5 (11.4)	33.4 (10.8)
Range			
Sex	M	51	27
	F	52	22
Race	White	84	39
	Black	15	8
	Oriental	1	0
	Other	3	2
Total patient no		103	49

As indicated by an ANOVA (not displayed) with investigator, treatment group, and interactions as factors, there were no statistically significant differences in age for any factor, including center (p-value drug:$p \leq 0.8269$, center $p \leq 0.2744$, interaction $p \leq 0.1922$). Cochrane-Mantel-Haenzsel (CMH) tests, also not displayed here, stratified on center, of the association between sex and treatment were not statistically significant ($p \leq 0.496$). In particular, there is no evidence to reject the hypothesis that gender is homogeneous over treatment. Similarly, when race was dichotomized into "white" and "non-white", again there is no evidence to reject the hypothesis that race was homogeneous over treatment $p \leq 0.627$). Corresponding loglinear models, also not displayed here, showed no significant main effects or interactions for gender, confirming the results for the CMH tests. There were significant effects for dichotomized race and its interaction with center. But these do not have statistically significant interactions with drug, and hence can probably be ignored.

2. Efficacy Assessments:

The following tables display the complete cure as well as the sponsor defined effective treatment, and the mycological cure (in this case negative microscopy). The p-value is the p-value of the Cochrane-Mantel-Haenszel (CMH) p-value of treatment mean differences over investigators using integer (trend) scores. One possible problem with the printed p-values is that it is possible that the tables are too sparse for the asymptotic approximation to the CMH statistics to apply. This was evaluated using the Mantel-Fleiss (1980) criterion. While some tables were too sparse for the asymptotic approximations to the distribution to be extremely close, these were always early in the study. For convenience the asymptotic p-values are reported. When the result is statistically significant, the asymptotic approximation was almost invariably applicable.

Recall that the division definition of (modified) intent-to-treat is all subjects whose infection is confirmed by microscopy (For the tinea versicolor studies this is the only mycology measurement, i.e. culture was not performed). The sponsor's definition is all such patients, restricted to those whose total signs and symptoms score is greater than or equal to one. The following tables, table 3 and 4, display key variables for each definition of intent-to-treat.

Table 3. Study SFF353
Division ITT

Response/ Treatment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	4 Cure/n	%	8 Cure/n	%	EOS(LOCF) Cure/n	%	18 Cure/n	%
Mycological Cure														
Lamisil	0/103	0%	57/96	59.4%	70/91	76.9%	73/86	84.9%	69/85	81.2%	76/103	73.8%	2/3	66.7%
Placebo	0/49	0%	26/46	56.5%	27/46	58.7%	23/44	52.3%	14/43	32.6%	14/49	28.6%	.	.
p-value	NA		0.642		0.040		≤0.001		≤0.001		≤0.001		NA	
Complete Cure														
Lamisil	0/103	0%	26/96	27.1%	44/91	48.4%	60/86	69.8%	61/85	71.8%	64/103	62.1%	2/3	66.7%
Placebo	0/49	0%	6/46	13.0%	20/46	43.5%	15/44	34.1%	12/43	27.9%	12/49	24.5%	.	.
p-value	NA		0.064		0.778		≤0.001		≤0.001		≤0.001		NA	
Effective Treatment														
Lamisil	0/103	0%	46/96	47.9%	61/91	67.0%	69/86	80.2%	69/85	81.2%	75/103	72.8%	2/3	66.7%
Placebo	0/49	0%	14/46	30.4%	23/46	50.0%	20/44	45.5%	13/43	30.2%	13/49	26.5%	.	.
p-value	NA		0.041		0.099		≤0.001		≤0.001		≤0.001		NA	

By the 4th week each of mycological cure, complete cure, and effective treatment are statistically significantly better for the Lamisil (terbinafine) 1% solution than the corresponding vehicle (placebo) ($p \leq 0.001$). These differences remain at week 8 and at the end of study, EOS, using the last-observation-carried-forward technology. Under reasonable assumptions on the tests, this LOCF technology should result in conservative tests.

The following table 4 displays this reviewer's implementation of the sponsor's definition of intent-to-treat. Note that it does differ in a few places from that supplied by the sponsor. Presumably this reflects slight differences in the data sets used to provide the reports. In no case are these differences more than one or two subjects, and never have an impact on conclusions.

Table 4. Study SFF353
Sponsor ITT

Response/ Treatment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	4 Cure/n	%	8 Cure/n	%	EOS (LOCF) Cure/n	%	18 Cure/n	%
Mycological Cure														
Lamisil	0/97	0%	57/96	59.4%	70/91	76.9%	73/86	84.9%	69/85	81.2%	76/97	78.4%	2/3	66.7%
Placebo	0/47	0%	26/46	56.5%	27/45	60.0%	23/44	52.3%	14/43	32.6%	14/47	29.8%	.	.
p-value	NA		0.642		0.060		≤0.001		≤0.001		≤0.001		NA	
Complete Cure														
Lamisil	0/97	0%	26/96	27.1%	44/91	48.4%	60/86	69.8%	61/85	71.8%	64/97	66.0%	2/3	66.7%
Placebo	0/47	0%	6/46	13.0%	20/45	44.4%	15/44	34.1%	12/43	27.9%	12/47	25.5%	.	.
p-value	NA		0.064		0.908		≤0.001		≤0.001		≤0.001		NA	
Effective Treatment														
Lamisil	0/97	0%	46/96	47.9%	61/91	67.0%	69/86	80.2%	69/85	81.2%	75/97	77.3%	2/3	66.7%
Placebo	0/47	0%	14/46	30.4%	23/45	51.1%	20/44	45.5%	13/43	30.2%	13/47	27.7%	.	.
p-value	NA		0.041		0.140		≤0.001		≤0.001		≤0.001		NA	

Again, by the 4th week each of mycological cure, complete cure, and effective treatment are statistically significantly better for the Lamisil (terbinafine) 1% solution than the corresponding vehicle (placebo) ($p \leq 0.001$). These differences remain at week 8 and at the end of study, EOS, using the last-observation-carried-forward technology.

Although not displayed here, the decrease from baseline in the total signs and symptoms scores showed statistically significant differences in favor of Lamisil from the 4th week on. Further, both the physician's and subjects assessments showed statistically significant differences in favor of Lamisil 1% solution ($p \leq 0.001$).

3. Subset Analysis

The following table 5 summarizes the analysis for each response variable, at each adjusted week. When the test statistic is arguably statistically significant, in favor of Lamisil solution at the 0.10 level the actual numerical significance level is printed, otherwise a '-' is printed when the statistic is defined and a 'N' when the statistic is undefined. The 0.10 level was chosen instead of the more usual 0.05 level, to adjust for the reduced sample size and limited discrimination due to the binary response coding.

Actually, some of the cells in this table are too sparse for the asymptotic distribution of the Mantel-Haenszel statistic to be accurate. In particular a number of

times the Mantel-Fleiss criterion was violated. Still, most of these appear at the end of treatment or early in the follow-up period. These are the time points of least interest in assessing the exact p-value. For this reason, and of course, convenience, the asymptotic p-values as printed by SAS were reported here.

Table 5. Summary of Subset Analyses SFF353

	Complete Cure Week					Effective Treatment Week				
	1	2	4	8	LOCF	1	2	4	8	LOCF
Sex Female	-	-	0.027	≤0.001	≤0.001	-	-	0.044	≤0.001	≤0.001
Male	-	-	0.004	0.015	0.024	-	0.074	≤0.001	≤0.001	≤0.001
Age 14-25	-	-	0.023	0.002	0.007	-	-	0.009	0.002	≤0.001
26-67	0.062	-	0.002	≤0.001	≤0.001	-	-	0.002	≤0.001	≤0.001
Race Caucasian	0.075	-	≤0.001	≤0.001	≤0.001	0.072	-	≤0.001	≤0.001	≤0.001
Other	-	-	0.090	-	0.065	-	0.044	0.072	0.053	0.018

- denotes not statistically significant at a .10 level, i.e. p>.10
N denotes statistic not defined, or too few degrees of freedom

	Mycological Cure Week				
	1	2	4	8	LOCF
Sex Female	-	-	0.070	≤0.001	≤0.001
Male	-	0.003	0.002	≤0.001	≤0.001
Age 14-25	-	0.099	0.004	0.002	≤0.001
26-67	-	-	0.006	≤0.001	≤0.001
Race Caucasian	-	-	≤0.001	≤0.001	≤0.001
Other	-	0.074	0.011	-	0.046

- denotes not statistically significant at a .10 level, i.e. p>.10

Note that results at the EOS, end-of-study, are consistent across gender, age groups, and even dichotomized race. For all of them there are statistically significant differences favoring the Lamisil 1% solution treatment group ($p \leq 0.046$ over all subgroups and variables). This seems to confirm that the statistically significant results remain essentially invariant across these demographic groups.

B. Study SFF 305:

The objective of this study was to evaluate the safety, efficacy and duration of therapeutic effect of Lamisil® (terbinafine) 1% solution versus vehicle solution applied twice daily in patients with tinea versicolor (pityriasis versicolor). Subjects were randomly assigned to apply Lamisil 1% solution or its vehicle twice daily, in the morning and evening, for one week. This was followed by a seven-week follow-up period. The study was conducted at 22 centers (investigators) in the Netherlands and Belgium.

1. Patient Demographics:

The following table 6. summarizes the demographics of the subjects.

Table 6. SFF 305 Patient Demographics

		Lamisil	Vehicle
Age			
	Mean (Std Dev)	34.2 (12.6)	32.5 (11.0)
	Range		
Sex	M	39	20
	F	40	16
Race	White	71	33
	Black	4	0
	Oriental	4	2
	Other	0	1
Total patient no		79	36

As in the preceding study, an ANOVA (not displayed) with terms for investigator, treatment group, and interactions, indicated that there were no statistically significant differences in age for any factor, including center (p-value drug:$p \leq 0.2446$, center $p \leq 0.4520$, interaction $p \leq 0.9327$). Cochrane-Mantel-Haenzsel (CMH) tests, also not displayed here, stratified on center, of the association between sex and treatment were not statistically significant ($p \leq 0.329$). In particular, there is no evidence to reject the hypothesis that gender is homogeneous over treatment. Corresponding loglinear models, also not displayed here, showed no significant main effects or interactions for gender or race, confirming the results for the CMH tests. However, there were too few cases in the vehicle group to make any race comparisons very relevant.

2. Efficacy Assessments

The following tables 7. and 8. display the complete cure (complete cure) as well as the sponsor defined effective treatment and mycological cure. The p-value displayed is the p-value of the Cochrane-Mantel-Haenszel (CMH) test of treatment mean differences stratified over investigators, using integer (trend) scores.

Table 7. Study SFF305
Division ITT

Response/ Treatment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	4 Cure/n	%	8 Cure/n	%	LOCF Cure/n	%	18 Cure/n	%
Mycological Cure														
Lamisil	0/79	0%	26/69	37.7%	47/67	70.1%	50/63	79.4%	49/61	80.3%	60/79	75.9%	2/2	100.0%
Placebo	0/36	0%	9/34	26.5%	14/33	42.4%	13/33	39.4%	11/29	37.9%	15/36	41.7%	3/5	60.0%
p-value	NA		0.179		0.003		≤0.001		≤0.001		≤0.001		NA	
Complete Cure														
Lamisil	0/75	0%	7/69	10.1%	18/67	26.9%	26/63	41.3%	31/61	50.8%	34/76	44.7%	2/2	100.0%
Placebo	0/35	0%	3/34	8.8%	7/33	21.2%	8/33	24.2%	6/29	20.7%	9/36	25.0%	3/5	60.0%
p-value	NA		0.707		0.377		0.026		0.002		0.018		NA	
Effective Treatment														
Lamisil	0/75	0%	20/69	29.0%	37/67	55.2%	43/63	68.3%	43/61	70.5%	53/78	67.9%	2/2	100.0%
Placebo	0/35	0%	5/34	14.7%	10/33	30.3%	10/33	30.3%	7/29	24.1%	10/36	27.8%	3/5	60.0%
p-value	NA		0.094		0.003		≤0.001		≤0.001		≤0.001		NA	

By the 2nd week after treatment mycological cure and effective treatment are statistically significantly better for the Lamisil (terbinafine) 1% solution than the corresponding vehicle (placebo) ($p \leq 0.003$). By week 4, the same conclusion holds for the complete cure ($p \leq 0.026$). By week 8 and at the end of study, EOS, using the last-observation-carried-forward technology, these differences are virtually all highly statistically significant. Recall that under reasonable assumptions on the tests, the LOCF technology should result in conservative tests.

The following table, table 8, displays this reviewer's implementation of the sponsor's definition of intent-to-treat. Again note that it does differ in a few places from that supplied by the sponsor. Presumably this reflects slight differences in the data sets used to provide the reports. In no case are these differences more than one or two subjects, and never have an impact on conclusions.

Table 8. Study SFF305
Sponsor ITT

Response/ Treat-ment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	4 Cure/n	%	8 Cure/n	%	LOCF Cure/n	%	18 Cure/n	%
Mycological Cure														
Lamisil	0/76	0%	26/68	38.2%	47/66	71.2%	49/62	79.0%	49/60	81.7%	60/76	78.9%	2/2	100.0%
Placebo	0/34	0%	9/33	27.3%	14/32	43.8%	12/32	37.5%	11/28	39.3%	15/34	44.1%	3/5	60.0%
p-value	NA		0.198		0.005		≤0.001		≤0.001		≤0.001		NA	
Complete Cure														
Lamisil	0/73	0%	7/68	10.3%	18/66	27.3%	26/62	41.9%	31/60	51.7%	34/73	46.6%	2/2	100.0%
Placebo	0/34	0%	3/33	9.1%	7/32	21.9%	8/32	25.0%	6/28	21.4%	9/34	26.5%	3/5	60.0%
p-value	NA		0.707		0.377		0.029		0.003		0.020		NA	
Effective Treatment														
Lamisil	0/73	0%	20/68	29.4%	37/66	56.1%	43/62	69.4%	43/60	71.7%	53/75	70.7%	2/2	100.0%
Placebo	0/34	0%	5/33	15.2%	10/32	31.3%	10/32	31.3%	7/28	25.0%	10/34	29.4%	3/5	60.0%
p-value	NA		0.130		0.008		≤0.001		≤0.001		≤0.001		NA	

Results are virtually identical for the sponsor's definition of ITT. By the 2nd week after treatment mycological cure and effective treatment are statistically significantly better for the Lamisil (terbinafine) 1% solution than the corresponding vehicle (placebo) ($p \leq 0.008$). By week 4, the same conclusion holds for the complete cure ($p \leq 0.029$). By week 8 and at the end of study, EOS, using the last-observation-carried-forward technology, these differences are virtually all highly statistically significant.

Although not displayed here, the decrease in total signs and symptoms scores showed statistically significant differences in favor of Lamisil from the 8th week and at the end of the study ($p \leq 0.037$ and $p \leq 0.045$, respectively). Further, both the physician's assessment at the end of the study showed a statistically significant difference in favor of Lamisil 1% solution ($p \leq 0.001$).

3. Subset Analysis

The following table, table 9., summarizes the analysis for each response variable, at each adjusted week. When the test statistic is arguably statistically significant, in favor of Lamisil solution at the 0.10 level the actual numerical significance level is printed, otherwise a '-' is printed when the statistic is defined and a 'N' when the statistic is undefined. The 0.10 level was chosen instead of the more usual 0.05 level, to adjust for the reduced sample size and limited discrimination due to the binary response coding.

Actually, some of these tables are too sparse for the asymptotic distribution of the Mantel-Haenszel statistic to be accurate. In particular a number of times the Mantel-Fleiss criterion was violated. Still, most of these appear at the end of treatment or early in the follow-up period. These are the time points of least interest in assessing the exact p-value. For this reason, and of course, convenience, the asymptotic p-values as printed by

SAS were reported here.

Table 9. Summary of Subset Analyses SFF305

	Complete Cure Week					Effective Treatment Week				
	1	2	4	8	LOCF	1	2	4	8	LOCF
Sex Female	-	-	0.019	0.011	0.055	0.031	0.009	0.002	≤0.001	≤0.001
Male	-	-	-	0.047	0.082	-	-	0.009	0.056	0.066
Age 15-25	-	-	-	-	-	-	-	0.057	-	-
26-72	-	-	0.045	0.001	0.009	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001
Race Caucasian	-	-	0.020	0.003	0.031	-	≤0.001	≤0.001	≤0.001	≤0.001
Other	N	N	N	N	N	N	N	N	N	N

- denotes not statistically significant at a .10 level, i.e. p>.10
N denotes statistic not defined, or too few degrees of freedom

	Mycological Cure Week				
	1	2	4	8	LOCF
Sex Female	0.097	0.084	0.009	0.010	0.002
Male	-	-	0.001	0.017	0.038
Age 15-25	-	-	0.006	-	-
26-72	-	0.031	0.003	≤0.001	≤0.001
Race Caucasian	-	0.003	≤0.001	≤0.001	≤0.001
Other	-	N	-	N	N

- denotes not statistically significant at a .10 level, i.e. p>.10
N denotes statistic not defined, or too few degrees of freedom

Note that results at the EOS, end-of-study, are consistent across gender as well as for the older age subgroup and the Caucasian subgroup. The subgroups for non Caucasians and for younger patients are too sparse to draw any conclusions. Even for these more sparse numerical groups trends favoring Lamisil 1% solution over its vehicle are apparent, though not displayed here.

C. Conclusions:

Using either endpoint, complete cure or effective treatment, both studies of tinea versicolor (pityriasis versicolor) showed statistically significant differences between Lamisil 1% solution and its vehicle at the end of the study ($p \leq 0.001$ for both studies and indications). These differences were apparent by week 4 of the study and increased in magnitude thereafter.

II. Tinea Pedis

A. Study SFF 351:

The objective of this study was to evaluate the safety, efficacy and duration of therapeutic effect of Lamisil® (terbinafine) 1% solution versus vehicle solution applied twice daily in patients with interdigital tinea pedis (Athlete's foot). Subjects were randomly assigned to apply Lamisil 1% solution or its vehicle twice daily, in the morning and evening, for one week. This was followed by a seven-week follow-up period. The study was conducted at 10 centers (investigators) in the United States.

1. Patient Demographics:

The following table 10. summarizes the demographics of the subjects.

Table 10. SFF 351 Patient Demographics

		Lamisil	Vehicle
Age			
Mean (Std Dev)		41.3 (17.0)	44.0 (18.4)
Range			
Sex	M	51	27
	F	52	22
Race	White	84	39
	Black	15	8
	Oriental	1	0
	Other	3	2
Total patient no		103	49

As indicated by an ANOVA with treatment group, investigator, and interactions as factors, there were no statistically significant differences in age for the latter two factors. The effect of treatment group (i.e. drug) was close to statistical significance ($p \leq 0.0938$), with the Lamisil group being approximately 7 years younger (by difference in least squares means) or 3 years younger (by difference in means). The effects for center and interaction were clearly nonsignificant ($p \leq 0.6195$ and $p \leq 0.1767$, respectively). One might expect younger patients to respond better, and this may tend to reduce the impact of significant results in this trial.

Cochrane-Mantel-Haenzsel (CMH) tests, also not displayed here, stratified on center, of the association between sex and treatment were not statistically significant ($p \leq 0.652$). In particular, there is no evidence to reject the hypothesis that gender is homogeneous over treatment. Similarly, when race was dichotomized into "white" and "non-white", again there is no evidence to reject the hypothesis that race was homogeneous over treatment ($p \leq 0.263$). These results were essentially verified by the corresponding log-linear models.

2. Efficacy Assessments

The following tables 11. and 12. display the complete cure as well as the sponsor defined effective treatment, the global response, the total signs and symptoms scores, and the patient assessment of treatment response. The p-value is the p-value of the Cochrane-Mantel-Haenszel (CMH) test of treatment mean differences stratified over investigators using integer (trend) scores.

Table 11. Study SFF351
Division ITT

Response/ Treatment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	4 Cure/n	%	6 Cure/n	%	8 Cure/n	%	EOS(LOCF) Cure/n	%
Mycological Cure														
Lamisil	0/67	0%	27/63	42.9%	37/63	58.7%	47/59	79.7%	48/56	85.7%	49/56	87.5%	55/67	82.1%
Placebo	0/35	0%	5/34	14.7%	4/32	12.5%	5/31	16.1%	3/28	10.7%	5/28	17.9%	6/35	17.1%
p-value	NA		0.004		≤0.001		≤0.001		≤0.001		≤0.001		≤0.001	
Complete Cure														
Lamisil	0/64	0%	1/63	1.6%	1/63	1.6%	1/59	1.7%	10/56	17.9%	11/56	19.6%	12/63	19.0%
Placebo	0/34	0%	0/34	0%	0/32	0%	0/32	0%	1/28	3.6%	2/28	7.1%	2/35	5.7%
p-value	NA		0.500		0.527		0.922		0.018		0.015		0.005	
Effective Treatment														
Lamisil	0/64	0%	11/63	17.5%	10/63	15.9%	26/59	44.1%	33/56	58.9%	33/56	58.9%	38/63	60.3%
Placebo	0/34	0%	0/34	0%	3/32	9.4%	4/31	12.9%	3/28	10.7%	3/28	10.7%	3/35	8.6%
p-value	NA		0.023		0.221		0.003		≤0.001		≤0.001		≤0.001	

By the end of the one-week treatment period, the mycological cure rate is statistically significantly better for the Lamisil (terbinafine) 1% solution than the corresponding vehicle (placebo) ($p \leq 0.004$). By week 4, the same conclusion holds for effective treatment ($p \leq 0.003$). By week 6, the same conclusion holds for complete cure ($p \leq 0.018$). By week 8 and at the end of study, EOS, using the last-observation-carried-forward technology, these differences are all highly statistically significant ($p \leq 0.001$, 0.005, and 0.001 respectively). Again under reasonable assumptions on the tests, the LOCF technology should result in conservative tests.

The following table 12. displays this reviewer's implementation of the sponsor's definition of intent-to-treat. Again note that it does differ in a few places from that supplied by the sponsor. Presumably this reflects slight differences in the data sets used to provide the reports. In no case are these differences more than one or two subjects, and never have an impact on conclusions.

Table 12. Study SFF351
Sponsor ITT

Response/ Treatment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	4 Cure/n	%	6 Cure/n	%	8 Cure/n	%	EOS(LOCF) Cure/n	%
Mycological Cure														
Lamisil	0/58	0%	24/56	42.9%	35/57	61.4%	43/55	78.2%	46/53	86.8%	47/54	87.0%	51/58	87.9%
Placebo	0/27	0%	3/27	11.1%	2/24	8.3%	3/23	13.0%	2/22	9.1%	3/22	13.6%	4/27	14.8%
p-value	NA		0.004		≤0.001		≤0.001		≤0.001		≤0.001		≤0.001	
Complete Cure														
Lamisil	0/58	0%	1/56	1.8%	1/57	1.8%	1/55	1.8%	10/53	18.9%	11/54	20.4%	12/58	20.7%
Placebo	0/28	0%	0/28	0%	0/24	0%	0/23	0%	0/22	0%	0/22	0%	0/27	0%
p-value	NA		0.500		0.584		0.500		0.023		0.021		0.007	
Effective Treatment														
Lamisil	0/56	0%	10/56	17.9%	9/57	15.8%	24/55	43.6%	32/53	60.4%	35/54	64.8%	38/58	65.5%
Placebo	0/26	0%	0/27	0.0%	1/24	4.2%	3/23	13.0%	2/22	9.1%	1/22	4.5%	1/27	3.7%
p-value	NA		0.029		0.132		0.012		≤0.001		≤0.001		≤0.001	

By the end of the one-week treatment period, the mycological cure rate is statistically significantly better for the Lamisil (terbinafine) 1% solution than the corresponding vehicle (placebo) ($p \leq 0.004$). By week 4, the same conclusion holds for effective treatment ($p \leq 0.012$). By week 6, the same conclusion holds for complete cure ($p \leq 0.023$). By week 8 and at the end of study, EOS, using the last-observation-carried-forward technology, these differences are virtually all reasonably statistically significant. Again, under reasonable assumptions on the tests, the LOCF technology should result in conservative tests.

3. Subset Analysis

The following table summarizes the analysis for each response variable, at each adjusted week. When the test statistic is arguably statistically significant, in favor of Lamisil solution at the 0.10 level the actual numerical significance level is printed, otherwise a '-' is printed when the statistic is defined and a 'N' when the statistic is undefined. The 0.10 level was chosen instead of the more usual 0.05 level, to adjust for the reduced sample size and limited discrimination due to the binary response coding.

Table 13. Summary of Subset Analyses SFF351

	Complete Cure Week					Effective Treatment Week				
	1	2	4	8	EOS(LOCF)	1	2	4	8	EOS(LOCF)
Sex Female	N	N	N	-	-	-	-	-	0.036	0.012
Male	-	-	-	0.060	0.043	N	-	0.009	≤0.001	≤0.001
Age 15-25	N	N	N	-	-	N	N	N	0.083	0.083
26-72	N	-	-	0.052	0.021	0.025	-	0.007	≤0.001	≤0.001
Race Caucasian	N	N	-	0.013	0.003	0.031	-	≤0.001	≤0.001	≤0.001
Other	N	N	N	-	-	-	-	-	0.084	0.064

- denotes not statistically significant at a .10 level, i.e. p>.10
N denotes statistic not defined, or too few degrees of freedom

	Mycological Cure Week				
	1	2	4	8	EOS(LOCF)
Sex Female	-	0.018	0.045	0.007	0.005
Male	0.004	0.002	≤0.001	≤0.001	≤0.001
Age 15-25	-	-	0.083	0.083	0.083
26-72	0.005	≤0.001	≤0.001	≤0.001	≤0.001
Race Caucasian	0.011	≤0.001	≤0.001	≤0.001	≤0.001
Other	-	0.037	-	0.012	0.028

- denotes not statistically significant at a .10 level, i.e. p>.10

Note that results for effective treatment and mycological cure are fairly consistent. At the end-of-study (EOS) tests of differences between treatment groups are all statistically significant or close (i.e. p≤0.10) for each gender, race group, or age subgroup. The number of complete cures is too small for the consistent p-values in the subgroups. However, numerically the results are consistent with the main tables (table 11 above).

B. Study SFF 301:

The objective of this study was to evaluate the safety, efficacy and duration of therapeutic effect of Lamisil® (terbinafine) 1% solution versus vehicle solution applied twice daily in patients with tinea pedis. Subjects were randomly assigned to apply Lamisil 1% solution or its vehicle twice daily, in the morning and evening, for seven days. This was followed by a seven-week follow-up period. The study was conducted at 19 centers (investigators) in Denmark (12), the United Kingdom (4), France (2), and Iceland (1).

1. Patient Demographics:

The following table 14. summarizes the demographics of the subjects.

Table 14. Patient Demographics

		Lamisil	Vehicle
Age			
Mean (Std Dev)		40.6 (16.3)	39.6 (15.2)
Range			
Sex	M	55	33
	F	21	7
Race	White	74	40
	Oriental	1	0
	Other	1	0
Total patient no		76	40

As indicated by a separate ANOVA, with factors for investigator, treatment group, and interactions as factors, there were no statistically significant differences in age for any factor, including center (p-value drug:$p \leq 0.2279$, center $p \leq 0.2638$, interaction $p \leq 0.9603$). Cochrane-Mantel-Haenzsel (CMH) tests, also not displayed here, stratified on center, of the association between sex and treatment were not statistically significant ($p \leq 0.181$). In particular, there is no evidence to reject the hypothesis that gender is homogeneous over treatment. Only two subjects were non-Caucasians, and both were assigned to Lamisil. So stratification based on race is not reasonable. Corresponding loglinear models, also not displayed here, showed no significant main effects or interactions with gender, confirming the results for the CMH tests.

2. Efficacy Assessments

The following tables 15. and 16. display the complete cure as well as the sponsor defined effective treatment, the global response, the total signs and symptoms scores, and the patient assessment of treatment response. The p-value is the p-value of the Cochrane-Mantel-Haenszel (CMH) test of treatment mean differences over investigators using integer (trend) scores.

Table 15. Study SFF301
Division ITT

Response/ Treatment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	8 Cure/n	%	EOS (LOCF) Cure/n	%	18 Cure/n	%
Mycology												
Lamisil	0/74	0%	38/72	52.8%	38/72	52.8%	51/54	94.4%	63/75	84.0%	5/6	83.3%
Placebo	0/41	0%	5/39	12.8%	6/34	17.6%	8/34	23.5%	11/41	26.8%	0/3	0%
p-value	NA		≤0.001		≤0.001		≤0.001		≤0.001		0.317	
Complete Cure												
Lamisil	0/74	0%	2/71	2.9%	10/70	14.3%	29/54	53.7%	35/74	47.3%	3/7	42.9%
Placebo	0/40	0%	0/39	0%	1/34	2.9%	2/34	5.9%	3/41	7.3%	0/3	0%
p-value	NA		0.251		0.074		≤0.001		≤0.001		0.317	
Effective Treatment												
Lamisil	0/74	0%	16/71	22.5%	21/70	30.0%	44/54	81.5%	55/75	73.3%	5/7	71.4%
Placebo	0/40	0%	2/39	5.1%	2/34	5.9%	7/34	20.6%	9/41	22.0%	0/3	0%
p-value	NA		0.030		0.004		≤0.001		≤0.001		0.317	

By the end of treatment there are statistically significant differences between Lamisil 1% solution and its vehicle in terms of mycological cure and effective treatment ($p \leq 0.001$ and $p \leq 0.03$, respectively). By week 8, and at the end-of-study (LOCF) differences between Lamisil 1% solution and its vehicle for all three responses are highly statistically significant ($p \leq 0.001$).

The following table 16. displays this reviewer's implementation of the sponsor's definition of intent-to-treat. Again it differs ever so slightly from that provided by the sponsor.

Table 16. Study SFF301
Sponsor ITT

Response/ Treatment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	8 Cure/n	%	LOCF Cure/n	%	18 Cure/n	%
Mycology												
Lamisil	0/69	0%	34/68	50.0%	37/66	56.1%	49/52	94.2%	60/70	85.7%	5/7	71.4%
Placebo	0/39	0%	5/37	13.5%	6/32	18.8%	8/32	25.0%	11/39	28.2%	0/3	0%
p-value	NA		0.002		≤0.001		≤0.001		≤0.001		0.317	
Complete Cure												
Lamisil	0/69	0%	2/67	3.0%	10/66	15.2%	29/52	55.8%	35/69	50.7%	3/7	42.9%
Placebo	0/38	0%	0/37	0%	1/32	3.1%	2/32	6.3%	3/39	7.7%	0/3	0%
p-value	NA		0.255		0.083		≤0.001		≤0.001		0.317	
Effective Treatment												
Lamisil	0/69	0%	14/67	20.9%	20/66	30.3%	43/52	82.7%	53/70	75.7%	5/7	71.4%
Placebo	0/38	0%	2/37	5.4%	2/32	6.3%	7/32	21.9%	9/39	23.1%	0/3	0%
p-value	NA		0.047		0.004		≤0.001		≤0.001		0.317	

Results are virtually identical for the sponsor's definition of ITT. By the end of treatment there are statistically significant differences between Lamisil 1% solution and its vehicle in terms of mycological cure and effective treatment ($p \leq 0.001$ and $p \leq 0.03$, respectively). By week 8, and at the end-of-study (LOCF) differences between Lamisil 1% solution and its vehicle for all three responses are highly statistically significant ($p \leq 0.001$).

3. Subset Analysis

The following table 17. summarizes the analysis for each response variable, at each adjusted week. When the test statistic is arguably statistically significant, in favor of Lamisil solution at the 0.10 level the actual numerical significance level is printed, otherwise a '-' is printed when the statistic is defined and a 'N' when the statistic is undefined. The 0.10 level was chosen instead of the more usual 0.05 level, to adjust for the reduced sample size and limited discrimination due to the binary response coding.

Table 17. Summary of Subset Analyses
SFF301

	Complete Cure Week				Effective Treatment Week			
	1	2	8	LOCF	1	2	8	LOCF
Sex Female	-	-	0.014	0.009	-	-	-	0.034
Male	-	0.098	0.002	≤0.001	0.067	0.011	≤0.001	≤0.001
Age 15-25	-	-	0.043	0.059	-	-	0.066	-
26-72	-	-	≤0.001	≤0.001	0.034	0.007	≤0.001	≤0.001
Race Caucasian	-	0.096	≤0.001	≤0.001	0.039	0.005	≤0.001	≤0.001
Other	N	N	N	-	N	N	N	-

- denotes not statistically significant at a .10 level, i.e. p>.10
N denotes statistic not defined, or too few degrees of freedom

	Mycological Cure Week			
	1	2	8	LOCF
Sex Female	-	-	0.014	0.009
Male	0.001	0.002	≤0.001	≤0.001
Age 15-25	-	-	0.066	0.080
26-72	0.003	0.002	≤0.001	≤0.001
Race Caucasian	≤0.001	≤0.001	≤0.001	≤0.001
Other	-	-	-	-

- denotes not statistically significant at a .10 level, i.e. p>.10

Note that results for effective treatment and mycological cure are fairly consistent. At the end-of-study (EOS) tests of differences between treatment groups are all statistically significant or close (i.e. $p \leq 0.10$) for each gender, race group, or age subgroup. The number of complete cures is too small for the consistent p-values in the subgroups. However, numerically the results are consistent with the main tables (table 11 above). That is, at the end of study (EOS), among non-Caucasian patients 66.7% of the Lamisil group had complete cure versus 0% for the vehicle group.

C. Study SFF 309:

The objective of this study was to evaluate the safety, efficacy and duration of therapeutic effect of Lamisil® (terbinafine) 1% solution applied for one week versus clotrimazole 1% solution for four weeks in patients with interdigital tinea pedis. Subjects were randomly assigned to apply one of the two solutions twice daily. Those subjects assigned to the Lamisil 1% solution applied the solution for one week, followed by three weeks of vehicle. These four week periods were followed by a four week untreated follow-up period. The study was conducted at a total of 40 centers (investigators) in Germany (35) and the Czech Republic (5).

1. Patient Demographics:

The following table 18. summarizes the demographics of the subjects.

Table 18. Patient Demographics

		Lamisil	Clotrimazole
Age			
	Mean (Std Dev)	48.1 (16.4)	48.5 (16.4)
	Range		
Sex	M	147	150
	F	70	68
Race	White	214	213
	Black	1	0
	Oriental	2	3
	Other	0	2
Total patient no		217	218

As indicated by an ANOVA (not displayed) with investigator, treatment group, and interactions as factors, there were no statistically significant differences in age for treatment group or interaction ($p \leq 0.7796$ and $p \leq 0.9276$, respectively). There were statistically significant age differences across centers ($p \leq 0.0009$). However, there were 40 centers, and the F-ratio for testing investigator effects was less than 2.0, so these effects may be of less real impact than suggested by the small p-value. Further, interactions with drug were not significant ($p \leq 0.9276$), so it seems the imbalance in age is roughly balanced across treatments, and, again should be ignorable.

Cochrane-Mantel-Haenzsel (CMH) tests, also not displayed here, stratified on center,

of the association between sex and treatment were not statistically significant (p≤0.624). This is corroborated by the results of the corresponding loglinear model. Note that there are too few non-Caucasian patients to make any conclusions about race subgroups.

2. Efficacy Assessments

The following tables 19. and 20. display the complete cure as well as the sponsor defined effective treatment, the global response, the total signs and symptoms scores, and the patient assessment of treatment response. The p-value is the p-value of the Cochrane-Mantel-Haenszel (CMH) test of treatment mean differences over investigators using integer (trend) scores.

Table 19. Study SFF309
Division ITT

Response/ Treatment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	4 Cure/n	%	8 Cure/n	%	LOCF Cure/n	%	18 Cure/n	%
Mycology														
Lamisil	0/217	0%	87/203	42.9%	124/204	60.8%	169/196	86.2%	166/177	93.8%	196/217	89.9%	16/16	100%
Clotrimazole	0/217	0%	87/204	42.6%	124/205	60.5%	168/198	84.8%	167/181	92.3%	193/217	88.9%	12/13	90.9%
p-value	NA		0.748		0.934		0.524		0.363		0.719		0.157	
Lamisil	0/217	0%	1/202	0.5%	19/204	9.3%	85/196	43.4%	96/175	54.9%	114/213	53.5%	12/16	75.0%
Clotrimazole	0/217	0%	3/203	1.5%	22/203	10.8%	84/198	42.4%	108/181	59.7%	122/215	56.7%	8/13	61.5%
p-value	NA		0.233		0.190		0.855		0.500		0.464		0.576	
Lamisil	0/217	0%	30/202	14.9%	86/204	42.0%	153/196	78.1%	149/175	85.1%	178/217	82.0%	15/16	93.8%
Clotrimazole	0/217	0%	26/203	12.8%	89/203	43.5%	155/198	78.3%	153/181	84.5%	173/215	80.5%	11/13	84.6%
p-value	NA		0.942		0.668		0.816		0.649		0.762		0.576	

Note that none of the differences are statistically significant at any endpoint. For comparison, the following table 20. displays this reviewer's implementation of the sponsor's definition of intent-to-treat.

Table 20. Study SFF309
Sponsor ITT

Response/ Treatment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	4 Cure/n	%	8 Cure/n	%	Locf Cure/n	%	18 Cure/n	%
Mycology														
Lamisil	0/212	0%	87/201	43.3%	123/202	60.9%	167/194	86.1%	164/175	93.7%	194/212	91.5%	16/16	100%
Clotrimazole	0/207	0%	84/199	42.2%	122/201	60.7%	164/194	84.5%	164/178	92.1%	188/207	90.8%	10/11	90.9%
p-value	NA		0.576		0.941		0.478		0.267		0.572		0.576	
Lamisil	0/211	0%	1/200	0.5%	19/202	9.4%	85/194	42.7	96/173	53.8%	114/207	55.1%	12/16	75.0%
Clotrimazole	0/207	0%	3/198	1.5%	22/199	11.1%	82/194	42.3%	107/178	59.6%	120/205	58.5%	6/11	54.5%
p-value	NA		0.242		0.185		0.750		0.598		0.501		0.576	
Lamisil	0/211	0%	30/200	15.0%	86/202	42.6%	152/194	78.4%	148/173	85.5%	177/211	83.9%	15/16	93.8%
Clotrimazole	0/207	0%	28/198	13.1%	87/199	43.7%	153/194	78.9%	152/178	85.4%	170/205	82.9%	9/11	81.8%
p-value	NA		0.997		0.819		0.901		0.650		0.694		0.576	

Again no differences are close to statistical significance. However this is not sufficient to conclude that these treatments are essentially equivalent. One derivation is based on the following procedure:

i. Calculate the 95% confidence interval for the difference, computed by subtracting the active reference drug mean from the test drug mean.

ii. The test and reference drug are said to be equivalent if the 95% confidence interval (LL,UL) includes zero and the lower limit , LL, is not less than -0.2 times the reference drug mean. That is, the lower limit, LL, should not be more than 20% worse than the active control mean.

This procedure seems to have some problems (e.g., it is apparently not reflexive) but it apparently has been used in a number of NDA's at the FDA.

Statistical Note:

In the following the estimators of difference are derived assuming the number of patients assigned to each treatment is fixed within center. Then for each of the response variables above, the "natural distribution" of the within drug response is a product binomial (over centers). The estimator of the proportion of successes was that derived to be most efficient when the proportions of successes are the same across centers. However, the observed within center proportion is used to derive the estimate of variance.

Table 21. Study SFF309
Analyses of Equivalence

Week	Test Drug Proportion	Reference Proportion	(n_T, n_R)	Difference	95% CI for diff (Lower,Upper)	-2*Ref Prop	Equivalent?
Mycological Cure							
1	0.429	0.426	(203,204)	0.002	(-.083,0.087)	-.085	equivalent
2	0.608	0.605	(204,205)	0.003	(-.084,0.089)	-.121	equivalent
4	0.862	0.848	(196,198)	0.014	(-.049,0.077)	-.170	equivalent
8	0.938	0.923	(177,181)	0.015	(-.028,0.058)	-.185	equivalent
EOS	0.899	0.889	(218,217)	0.010	(-.040,0.060)	-.178	equivalent
Complete Cure							
1	0.005	0.015	(202,203)	-.010	(-.028,0.008)	-.003	
2	0.093	0.108	(204,204)	-.015	(-.062,0.033)	-.022	
4	0.434	0.424	(196,198)	0.009	(-.072,0.091)	-.085	equivalent
8	0.549	0.597	(175,181)	-.048	(-.134,0.037)	-.119	
EOS	0.528	0.565	(216,216)	-.037	(-.117,0.043)	-.113	
Effective Treatment							
1	0.149	0.128	(202,203)	0.020	(-.040,0.081)	-.026	
2	0.422	0.436	(204,204)	-.015	(-.101,0.072)	-.087	
4	0.781	0.783	(196,198)	-.002	(-.076,0.072)	-.157	equivalent
8	0.851	0.845	(175,181)	0.006	(-.057,0.069)	-.169	equivalent
EOS	0.815	0.806	(216,216)	0.009	(-.056,0.074)	-.161	equivalent

Using these criteria, at all time points, mycological cure rates for Lamisil 1% solution are equivalent to those for Clotrimazole. At weeks 4, 8, and at EOS rates of effective treatment for Lamisil 1% solution are equivalent to those for Clotrimazole.

3. Subset Analysis

As could be expected, the tables for separate analyses by sex showed the same lack of statistical significance as the main tables. However the relevance of these tables is debatable, and hence they were not displayed. Note that there were too few non-Caucausian patients to make any breakdown by race meaningful.

D. Study SFF 104:

The objective of this study was to evaluate the efficacy and tolerability of Lamisil® (terbinafine) 1% solution versus vehicle solution applied once daily for two weeks in patients with tinea pedis. This was succeeded by a four week follow-up period. The study was conducted at four centers (investigators) in the United States. Of 36 subjects in the (modified) intent-to-treat population randomized to Lamisil 1% solution, 27 were male and 9 were female, with a mean age of 37, and an age range of 9 to 76. Of 39 subjects randomized to vehicle, 26 were male and 13 were female, with a mean age of 41, and an age range of

Note that two of the investigators in this study also were in the SFF 351 study. Note that deletion of their centers from the SFF 351 study had no impact upon conclusions, and hence those centers were left in the SFF 351 study.

Efficacy Assessments

The following table 22. displays the mycological cure, effective treatment, and complete cure. The p-value is the significance level of the Fisher-exact test of homogeneity over treatments. Note that this test ignores stratification on center and hence is theoretically quite likely to be anti-conservative. However, comparisons to CMH p-values indicate this anti-conservativeness is slight.

Table 22. Study SFF104
Sponsor ITT

Response/ Treatment	Baseline Cure/n	%	Week 2 Cure/n	%	6 Cure/n	%	EOS(LOCF) Cure/n	%
Mycological Cure								
Lamisil	0/36	0%	28/36	78%	36/36	100%	36/36	100%
Placebo	0/39	0%	8/39	21%	8/36	22%	9/39	23%
p-value	NA		≤0.001		≤0.001		≤0.001	
Complete Cure								
Lamisil	0/36	0%	18/36	50%	10/36	28%	10/36	28%
Placebo	0/39	0%	5/39	13%	0/39	0%	0/32	0%
p-value	NA		0.005		0.003		0.003	
Effective Treatment								
Lamisil	0/36	0%	18/36	50%	31/36	86%	31/36	86%
Placebo	0/39	0%	5/39	13%	6/36	17%	6/39	15%
p-value	NA		≤0.001		≤0.001		≤0.001	

Note that for both mycological cure and effective treatment, statistically significant differences appeared by week two ($p \leq 0.001$). Results are similar for complete cure ($p \leq 0.005$). All three endpoints remain statistically significant through the study, to the EOS (end-of-study) time point ($p \leq 0.001$, $p \leq 0.003$, and $p \leq 0.001$, respectively).

E. Conclusions:

For tinea pedis, using either endpoint, study SFF 351 showed statistically significant differences between Lamisil 1% solution and its vehicle at the end of the study ($p \leq 0.001$ for both indications). Note that under the dosage schedule used, Clotrimazole has been accepted as an effective treatment. In SFF 309, effective treatment tended to favor Lamisil over Clotrimazole, while complete cure tended to favor Clotrimazole over Lamisil. But these tendencies were not statistically significant. In fact, at the end of the study, or by week 4, using the definition of equivalence on page 22 of this report, these treatments were shown to be equivalent in terms of effective treatment. Equivalence was not shown for complete treatment, but there was no statistically significant difference between treatments. Both of these Lamisil treatments were twice daily for one week, although in SFF 309 the Lamisil treatment is followed by a three week course of treatment using vehicle.

Study SFF 301 followed a once daily dosing schedule for one week, but otherwise was similar to SFF351. Again, at the end of the study both complete cure and effective treatment showed statistical significance ($p \leq 0.005$ and $p \leq .001$, respectively). It seems to this reviewer that efficacy under a single dosing schedule could be used to imply efficacy under a twice daily dosing schedule, particularly if the results are used as verification, not origination. Thus, it is this reviewer's opinion that these studies combine to show efficacy of Lamisil 1% solution in the treatment of tinea pedis when used twice daily for one week.

III. Tinea Corporis

A. Study SFF 303:

The objective of this study was to evaluate the efficacy and safety of Lamisil® (terbinafine) 1% solution versus vehicle solution applied once daily in patients with tinea corporis/cruris. Subjects were randomly assigned to apply Lamisil 1% solution or its vehicle once daily for seven days. This was followed by a seven-week follow-up period with assessments at week 1, 2, 4, and 8. The study was conducted at 20 centers (investigators) in France (12), Norway (5), and Switzerland (3).

1. Patient Demographics:

The following table 23. summarizes the demographics of the subjects.

Table 23. SFF303 Patient Demographics

		Lamisil	Vehicle
Age			
Mean (Std Dev)		43.7 (17.6)	44.7 (16.2)
Range			
Sex	M	65	29
	F	14	10
Race	White	69	33
	Black	4	1
	Oriental	5	4
	Other	1	1
Total patient no		79	39

Again, for the ANOVA of age as response, with investigator, treatment group, and interactions as factors, there were no statistically significant differences for any factor (p-value drug:$p \leq 0.6579$, center $p \leq 0.9188$, interaction $p \leq 0.7459$). Cochrane-Mantel-Haenzsel (CMH) tests, also not displayed here, stratified on center, of the association between sex or dichotomized race with treatment were not statistically significant ($p \leq 0.447$ and $p \leq 0.522$, respectively). These results were supported by the corresponding loglinear models.

2. Efficacy Assessments:

The following tables 24. and 25. display the complete cure as well as the sponsor defined effective treatment, the global response, the total signs and symptoms scores, and the patient assessment of treatment response. The p-value is the p-value of the Cochrane-Mantel-Haenszel (CMH) test of treatment mean differences over investigators using integer (trend) scores.

Table 24. Study SFF303
Division ITT

Response/ Treat-ment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	4 Cure/n	%	8 Cure/n	%	LOCF Cure/n	%	18 Cure/n	%
Mycology														
Lamisil	0/78	0%	57/74	77.0%	56/66	84.8%	44/55	80.0%	38/42	90.5%	64/78	82.1%	6/7	85.7%
Placebo	0/40	0%	5/39	12.8%	10/32	31.3%	8/19	42.1%	6/14	42.9%	12/40	30.0%	.	.
p-value	NA		≤0.001		≤0.001		0.053		0.004		≤0.001		NA	
Complete Cure														
Lamisil	0/78	0%	4/74	5.4%	17/65	25.8%	31/55	56.4%	30/42	71.4%	40/74	54.1%	3/7	42.9%
Placebo	0/40	0%	0/39	0%	1/32	3.2%	2/19	10.5%	1/14	7.1%	2/39	5.1%	.	.
p-value	NA		0.112		0.014		0.007		0.010		≤0.001		NA	
Effective Treatment														
Lamisil	0/78	0%	28/74	37.8%	46/66	69.7%	38/55	69.1%	35/42	83.3%	54/77	70.1%	5/7	71.4%
Placebo	0/40	0%	0/39	0%	3/32	9.4%	4/19	21.1%	5/14	35.7%	6/39	15.4%	.	.
p-value	NA		≤0.001		≤0.001		0.010		0.006		≤0.001		NA	

By the end of treatment, week 1, both mycological cure and effective treatment displayed statistically significant differences in favor of Lamisil (terbinafine) 1% solution over its vehicle ($p \leq 0.001$). By week 2, the difference between treatment groups was statistically significant for complete cure ($p \leq 0.014$). These differences remain at all succeeding weeks up to the end of study, EOS, using the last-observation-carried-forward technology.

The following table 25. displays this reviewer's implementation of the sponsor's definition of intent-to-treat. Note that it does differ in a few places from that supplied by the sponsor. Presumably this reflects slight differences in the data sets used to provide the reports. In no case are these differences more than one or two subjects, and never have an impact on conclusions.

Table 25. Study SFF303
Sponsor ITT

Response/ Treat-ment	Baseline # Cure/n	%	Week 1 Cure/n	%	2 Cure/n	%	4 Cure/n	%	8 Cure/n	%	LOCF Cure/n	%	18 Cure/n	%
Mycology														
Lamisil	0/72	0%	54/69	78.3%	53/63	84.1%	41/51	80.4%	35/38	92.1%	61/72	82.1%	6/7	85.7%
Placebo	0/37	0%	4/36	11.1%	9/30	30.0%	5/16	31.3%	5/12	41.7%	10/37	27.0%	.	.
p-value	NA		≤0.001		≤0.001		0.010		0.006		≤0.001		NA	
Complete Cure														
Lamisil	0/72	0%	4/69	5.8%	16/63	25.4%	29/51	56.9%	28/38	73.7%	38/68	55.9%	3/7	42.9%
Placebo	0/37	0%	0/36	0%	1/30	3.3%	1/16	6.3%	1/12	8.3%	1/36	2.8%	.	.
p-value	NA		0.102		0.022		0.008		0.014		≤0.001		NA	
Effective Treatment														
Lamisil	0/72	0%	26/69	37.7%	44/63	69.8%	36/51	70.6%	33/38	86.8%	52/71	73.2%	5/7	71.4%
Placebo	0/37	0%	0/36	0%	3/30	10.0%	3/16	18.8%	4/12	33.3%	4/36	11.1%	.	.
p-value	NA		≤0.001		≤0.001		0.007		0.008		≤0.001		NA	

By the end of treatment, week 1, both mycological cure and effective treatment displayed statistically significant differences in favor of Lamisil (terbinafine) 1% solution over its vehicle ($p \leq 0.001$). By week 2, the difference between treatment groups was statistically significant for complete cure ($p \leq 0.022$). These differences remain at all succeeding weeks up to the end of study, EOS, using the last-observation-carried-forward technology.

By the end of the study, though not displayed here, the reduction in total signs and symptoms was statistically significantly better for the Lamisil group over its vehicle ($p \leq 0.001$).

3. Subset Analysis

The following table 26. summarizes the analysis for each response variable, at each adjusted week. When the test statistic is arguably statistically significant, in favor of Lamisil solution at the 0.10 level the actual numerical significance level is printed, otherwise a '-' is printed when the statistic is defined and a 'N' when the statistic is undefined. The 0.10 level was chosen instead of the more usual 0.05 level, to adjust for the reduced sample size and limited discrimination due to the binary response coding.

Table 26. Summary of Subset Analyses SFF303

	Complete Cure Week 1	2	4	8	LOCF	Effective Treatment Week 1	2	4	8	LOCF
Sex Female	N	-	-	0.083	0.025	0.072	0.074	-	N	-
Male	0.089	0.047	0.014	0.011	≤0.001	≤0.001	≤0.001	0.007	0.002	≤0.001
Age 15-25	-	0.085	0.025	0.046	0.001	0.021	0.004	0.013	0.046	≤0.001
26-59	-	-	-	-	0.022	0.019	0.002	-	-	0.008
60-72	N	N	0.063	0.083	0.026	0.025	0.008	0.063	0.025	0.023
Race Caucasian	-	0.028	0.008	0.002	≤0.001	≤0.001	≤0.001	0.003	0.011	≤0.001
Other	-	-	N	N	-	-	-	N	N	-

- denotes not statistically significant at a .10 level, i.e. p>.10
N denotes statistic not defined, or too few degrees of freedom

	Mycological Cure Week 1	2	4	8	LOCF
Sex Female	0.005	-	-	-	-
Male	≤0.001	≤0.001	0.013	0.003	≤0.001
Age 15-25	0.003	-	0.025	N	0.023
26-59	≤0.001	0.003	-	-	≤0.001
60-72	0.010	0.038	-	0.025	0.023
Race Caucasian	≤0.001	≤0.001	0.022	0.008	≤0.001
Other	-	-	N	N	-

- denotes not statistically significant at a .10 level, i.e. p>.10
N denotes statistic not defined, or too few degrees of freedom

Note that results for effective treatment and mycological cure are fairly consistent. At the end-of-study (EOS) tests of differences between treatment groups are all statistically significant or close (i.e. p≤0.10) for each gender, race group, or age subgroup. The number of complete cures is too small for the consistent p-values in the subgroups. However, numerically the results are consistent with the main tables (table 11 above).

B. Study SFF 105:

The objective of this study was to evaluate the efficacy and safety of Lamisil® (terbinafine) 1% solution versus vehicle solution applied once daily for one week in patients with tinea corporis/cruris. This was succeeded by follow-up assessments at weeks 2 and 4. The study was conducted at three centers (investigators) in the United States. Sixty-six subjects were randomized, but only 52 of them had confirmed mycology at baseline. Of 26 subjects in the (modified) intent-to-treat population randomized to Lamisil 1% solution, 17 were male and 9 were female, with a mean age of 41, and an age range of

Of 26 subjects randomized to vehicle, 18 were male and 8 were female, with a mean age of 44, and an age range of

Note that the three centers in this study were also centers in the SFF 351 tinea pedis study. Tinea Pedis is, of course, a different indication, but deletion of these centers had no impact upon any conclusions in that study. Note that within an indication one of the assumptions is that studies are independent, certainly violated if the same centers are used in both studies. However, even here, deletion of these three centers from the SFF 351 study has no impact upon any conclusions, so even if these studies were for the same indication this, possible difficulty is moot.

Efficacy Assessments

The following table 27. displays the mycological cure, effective treatment, and complete cure. The p-value is the significance level of the Fisher-exact test of homogeneity over treatments. Note that this test ignores stratification on center and theoretically should be anti-conservative. However, comparisons with corresponding CMH p-values indicate this anti-conservativeness is slight.

Table 27. Study SFF105
Sponsor ITT

Response/			Week					
	Baseline		1		4		EOS (LOCF)	
Treat-ment	Cure/n	%	Cure/n	%	Cure/n	%	Cure/n	%
Mycological Cure								
Lamisil	0/26	0%	10/26	38%	18/23	78%	18/26	69%
Placebo	0/26	0%	6/26	23%	5/16	31%	6/26	23%
p-value	NA		0.368		0.007		0.002	
Complete Cure								
Lamisil	0/26	0%	1/26	4%	10/23	43%	10/26	38%
Placebo	0/26	0%	0/26	0%	2/23	9%	2/26	8%
p-value	NA		1.00		0.008		0.009	
Effective Treatment								
Lamisil	0/26	0%	5/26	19%	17/23	74%	17/26	65%
Placebo	0/26	0%	2/26	8%	2/16	13%	2/26	8%
p-value	NA		0.419		≤0.001		≤0.001	

Note that for both mycological cure, complete cure, and effective treatment, statistically significant differences appeared by week four after treatment ($p \leq 0.007$, $p \leq 0.008$, and $p \leq 0.001$ respectively). Results remain statistically significant at the end of the study. ($p \leq 0.002$, $p \leq 0.009$, and $p \leq 0.001$ respectively).

There was no breakdown by gender, age group, or race of any response variable in the sponsor's report.

C. Study SFF 108:

The objective of this study was to evaluate the efficacy and tolerability of Lamisil® (terbinafine) 1% solution versus vehicle solution in patients with tinea corporis/cruris. The study medication was to be applied once a day for seven days, with follow-up at weeks 2 and 4, post-treatment. The study was conducted at three centers in Brazil. Of 35 subjects in the (modified) intent-to-treat population randomized to Lamisil 1% solution, 26 were male and 9 were female, with a mean age of 32, and an age range of 5 to 76. Of 35 subjects randomized to vehicle, 23 were male and 12 were female, with a mean age of 37, and an age range of

Efficacy Assessments

The following table 28. displays the mycological cure, effective treatment, and complete cure. The p-value is the significance level of the Fisher-exact test of homogeneity over treatments.

Table 28. Study SFF108
Sponsor ITT

Response/			Week					
	Baseline		1		4		EOS(LOCF)	
Treat-ment	Cure/n	%	Cure/n	%	Cure/n	%	Cure/n	%
Mycological Cure								
Lamisil	0/34	0%	15/32	47%	21/27	78%	25/33	76%
Placebo	0/36	0%	5/34	15%	9/32	28%	10/35	29%
p-value	NA		0.010		≤0.001		≤0.001	
Complete Cure								
Lamisil	0/34	0%	9/34	26%	14/27	52%	14/34	41%
Placebo	0/36	0%	2/35	6%	2/34	6%	2/35	6%
p-value	NA		0.023		≤0.001		≤0.001	
Effective Treatment								
Lamisil	0/34	0%	9/33	27%	20/27	74%	22/34	65%
Placebo	0/36	0%	2/35	6%	7/33	21%	7/35	20%
p-value	NA		0.021		≤0.001		≤0.001	

Note that for each of mycological cure, complete cure, and effective treatment, statistically significant differences appeared by the end of treatment ($p \leq 0.001$).

There was no breakdown by gender, age group, or race of any response variable in the sponsor's report.

D. Conclusions:

For tinea corporis/cruris, all three studies, SFF 303, SFF 105, and SFF 108 show a statistically significant difference between Lamisil and its vehicle at the end of treatment (p-value of at most $p \leq 0.009$ in all three studies for all three endpoints). Since SFF 105 was a U.S. study, it is this reviewer's opinion it can be combined with the results of the other two studies to justify the claim of efficacy for a one week, once daily course of treatment.

Safety Data (Adverse Events)

The sponsor only included machine readable data for the 300-series studies. These were grouped into three similar groups for tabulation of the results. SFF 353 was a vehicle controlled U.S. study for one week with twice daily doses of Lamisil solution for the treatment of tinea versicolor (i.e., P. Versicolor). SFF 351 was a similarly organized vehicle controlled study in the U.S. for one week involving twice daily doses of Lamisil 1% solution for interdigital tinea pedis. Due to the similarity of their organization, the adverse events for these studies were pooled.

Similarly, SFF 305 was a vehicle controlled non-US study of the effect of a one week treatment with Lamisil 1% solution on tinea versicolor (P. Versicolor). SFF 309 was a somewhat similar study of a 1 week Lamisil 1% treatment, followed by 3 weeks vehicle, versus 4 weeks of Clotrimazole. For each patient, each study runs for eight weeks. Strictly speaking the SFF 309 Lamisil treatment is not quite analogous to the SFF 305 Lamisil treatments but for simplicity was pooled with these studies.

Finally, SFF 303 was a non-U.S. study of a one week Lamisil 1% solution versus vehicle for the treatment of tinea corporis/cruris. SFF 301 was a similarly structured study for tinea pedis. The studies above all ran for eight weeks.

A. SFF 353 & SFF 351

For each subject, the severity of that subject's most severe adverse event is tabulated in table 29 below. The CMH p-value corresponds to the test of equal treatment means assuming integer (trend) scores. Note that the Lamisil 1% solution and placebo (vehicle) profiles (i.e. row percents) are almost identical. This suggests that the incidence of severe events is almost identical for the treatment and the vehicle.

Table 29. SFF 353 & SFF 351
Severity of Subjects Most Severe Adverse Event
U.S. Studies, Lamisil Applied BID
All adverse events

Treatment	Severity								Total
	No event		Mild		Moderate		Severe		n
	n	%	n	%	n	%	n	%	
Lamisil	181	87.4	19	9.2	6	2.9	1	0.5	207
Placebo	88	89.8	9	9.2	1	1.0	.	.	98
CMH row means differ p-value	0.382								

One patient in the Lamisil treatment group experienced severe adverse events, namely hyperglycemia, hypertension, and photophobia. The investigator assessed these as not being related to treatment.

The following table, table 30, is restricted to adverse events that the investigator's rated as at least possibly related to treatment. As before, the counts show no statistically significant differences across treatments.

Table 30. SFF 353 & SFF 351
Severity of Subjects Most Severe Adverse Event
U.S. Studies, Lamisil Applied BID
Adverse events at least possibly associated with drug

Treatment	No event		Severity Mild		Moderate		Total n
	n	%	n	%	n	%	
Lamisil	200	96.7	4	1.9	3	1.4	207
Placebo	95	96.9	3	3.1	.	.	98
CMH row means differ p-value	0.656						

The three moderate adverse events in the Lamisil 1% treatment group were one patient who had an application site reaction, one patient who experience pruritus, and one patient with skin exfoliation. Still, there is no evidence to suggest that the profiles of these treatment groups differ.

Table 31. below summarizes the adverse events identified by the sponsor in the two trials. The listing is by the number of subjects, as well as by the number of times that event was reported. Note that it is evident that none of these counts would show statistically significant differences across treatments.

Table 31. SFF 353 & SFF 351
U.S. Studies, Lamisil Applied BID
All adverse events

Body System	Adverse Event	Lamisil Solution # indiv	Vehicle # indiv	Lamisil Solution # event	Vehicle # event
Application Site Disorders	Application Site Reaction	4	1	4	1
Body As A Whole - General Disorders	Accidental Trauma	1	.	1	.
	Infection Bacterial	1	.	1	.
	Infection Viral	1	.	1	.
	Influenza-Like Symptoms	.	1	.	1
Cardiovascular Disorders, General	Hypertension	1	.	1	.

Table 31. (cont.) SFF 353 & SFF 351
All adverse events

Body System	Adverse Event	Lamisil Solution # indiv	Vehicle # indiv	Lamisil Solution # event	Vehicle # event
Central And Peripheral Nervous Syst. Disorders	Headache	4	1	4	1
Hearing And Vestibular Disorders	Ear Disorder NOS	1	.	1	.
Metabolic And Nutritional Disorders	Hyperglycaemia	1	.	2	.
Musculo-Skeletal System Disorders	Back Pain	1	.	1	.
	Myopathy	1	.	1	.
Respiratory System Disorders	Bronchitis	1	.	1	.
	Coughing	2	.	2	.
	Pharyngitis	1	1	1	1
	Pneumonia	1	.	1	.
	Rhinitis	1	.	1	.
	Sinusitis	3	1	3	1
	Upper Resp Tract Infection	4	.	5	.
Skin And Appendages Disorders	Bullous Eruption	1	.	1	.
	Dermatitis Contact	1	.	1	.
	Eczema	1	1	1	1
	Herpes Simplex	1	.	1	.
	Onychomycosis	.	1	.	1
	Pruritus	1	.	1	.
	Rash	1	.	1	.
	Rash Maculo-Papular	1	.	1	.
	Seborrhoea	1	.	1	.
Skin And Appendages Disorders	Skin Disorder	.	3	.	3
	Skin Dry	.	1	.	1
	Skin Exfoliation	1	.	1	.
Urinary System Disorders	Urethral Disorder	1	.	1	.
	Urinary Tract Infection	1	.	1	.
Vision Disorders	Photophobia	1	.	1	.
Total/Overall n		41/207	11/98	43	11

Note that it is evident that none of these counts would show statistically significant differences across treatments.

B. SFF 305 & SFF 309

Again, for each subject, the severity of that subject's most severe adverse event is recorded in the following table, table 32. The CMH p-value corresponds to the test of equal treatment means assuming integer (trend) scores.

Table 32. SFF 305, & SFF 309
Severity of Subjects Most Severe Adverse Event
non-U.S. Studies, Lamisil Applied BID
All adverse events

Treatment	Severity								Total
	No event		Mild		Moderate		Severe		n
	n	%	n	%	n	%	n	%	
Lamisil	328	77.0	59	13.9	28	6.6	11	2.6	426
Clotrimazole	299	85.2	30	8.6	19	5.4	3	0.8	351
Placebo	20	55.6	12	33.3	4	11.1	.	.	36
CMH row means differ p-value	0.421								

Again there is no particularly statistically significant evidence that one should reject the hypothesis that row means are equal ($p \leq 0.421$).

The following table, table 33., is restricted to adverse events that the investigator's rated as at least possibly related to treatment. Again, the response profiles for the vehicle (placebo) group does seem to have a higher mean than the others. However, the counts show no statistically significant differences across treatments.

Table 33. SFF 305 & SFF 309
Severity of Subjects Most Severe Adverse Event
non-U.S. Studies, Lamisil Applied BID
Adverse events at least possibly associated with drug

Treatment	Severity								Total
	No event		Mild		Moderate		Severe		n
	n	%	n	%	n	%	n	%	
Lamisil	397	93.2	16	3.8	8	1.9	5	1.2	426
Clotrimazole	336	95.7	6	1.7	8	2.3	1	0.3	352
Placebo	35	89.7	3	7.7	1	2.6	.	.	36
CMH row means differ p-value	0.824								

Tables 34. below summarize the adverse events identified by the sponsor in the trials. Note that it is evident that none of these counts would show statistically significant differences across treatments.

Table 34. SFF 305 & SFF 309 non-U.S. Studies, Lamisil Applied BID All adverse events

Body System	Adverse Event	Lamisil # indiv	Clotri-mazole # indiv	Vehicle # indiv	Lamisil # event	Clotri-mazole # event	Vehicle # event
Application Site Disorders	Application Site Reaction	5	3	.	5	3	.
	Dermatitis Contact	.	1	.	.	1	.
Body As A Whole - General Disorders	Accidental Trauma	1	2	.	1	2	.
	Condition Aggravated	15	7	2	19	8	2
	Fever	1	.	1	1	.	1
	Headache	1	.	.	1	.	.
	Infection	3	.	.	3	.	.
	Infection Viral	4	.	.	4	.	.
	Influenza-Like Symptoms	2	3	.	2	3	.
	Oedema	1	.	.	1	.	.
	Pain	1	.	1	1	.	1
Cardiovascular Disorders, General	Hypertension	1	.	.	1	.	.
Central And Peripheral Nervous Syst. Disorders	Headache	1	.	1	1	.	1
	Migraine	1	.	.	1	.	.
	Paraesthesia	1	.	.	1	.	.
Gastro-Intestinal System Disorders	Abdominal Pain	1	.	.	1	.	.
Metabolic And Nutritional Disorders	Gout	1	.	.	1	.	.
Musculo-Skeletal System Disorders	Arthritis	.	1	.	.	2	.
	Myalgia	2	.	.	2	.	.
Psychiatric Disorders	Depression	1	.	.	1	.	.
Reproductive Disorders, Female	Moniliasis	.	1	.	.	1	.
	Tumor Benign	1	.	.	1	.	.

Table 34. (cont.) SFF 305 & SFF 309 non-U.S. Studies, Lamisil Applied BID All adverse events

Body System	Adverse Event	Lamisil # indiv	Clotri-mazole # indiv	Vehicle # indiv	Lamisil # event	Clotri-mazole # event	Vehicle # event
Respiratory System Disorders	Bronchitis	.	1	.	.	1	.
	Bronchospasm	.	.	1	.	.	1
	Coughing	.	.	2	.	.	2
	Hyperventilation	1	.	1	1	.	1
	Pneumonia	.	.	1	.	.	1
	Pulmonary Disorder	2	.	.	2	.	.
Respiratory System Disorders	Sinusitis	1	.	.	1	.	.
	Upper Resp Tract Infection	1	.	.	1	.	.
Skin And Appendages Disorders	Abscess	1	.	.	1	.	.
	Bullous Eruption	1	.	.	1	.	.
	Eczema	3	3	1	3	3	1
	Folliculitis	1	.	.	1	.	.
	Herpes Simplex	1	.	.	1	.	.
	Pruritus	16	12	5	16	12	6
	Rash Erythematous	14	15	4	15	16	4
	Rash Maculo-Papular	4	2	.	4	2	.
	Rash Pustular	1	1	.	1	1	.
	Rhagades	7	1	.	7	1	.
	Skin Depigmentation	2	.	1	2	.	1
	Skin Disorder	11	3	1	11	3	1
	Skin Dry	1	2	.	1	2	.
	Skin Exfoliation	27	19	8	27	19	8
Overall/ Total n		139/ 426	77/ 351	30/ 36	144	80	31

Overall, there seems to be little difference in adverse event rates. If anything, rates for Lamisil fall below those for vehicle.

Three patients had serious adverse events, all in the Lamisil treatment group. One patient had an abscess in their skin, one had a tumor in her reproductive organs, and one had a pulmonary disorder. None of these were classified as clearly related to treatment.

C. SFF 301 & SFF 303

Again, for each subject, the severity of that subject's most severe adverse event is tabulated in table 35, below. The CMH p-value corresponds to the test of equal treatment means assuming integer (trend) scores.

Table 35. SFF 301 & SFF 303
Severity of Subject's Most Severe Adverse Event
European study, Lamisil Applied QD
All adverse events

Treatment	Severity: No event n	No event %	Mild n	Mild %	Moderate n	Moderate %	Severe n	Severe %	Total n
Lamisil	159	73.3	25	11.5	22	10.1	11	5.1	217
Placebo	53	50.0	20	18.9	20	18.9	13	12.3	106

CMH row means differ p-value 0.001

Note that the test of different means is highly statistically significant. From the profiles it is clear that most of this difference is due to a higher mean severity score in the vehicle (placebo) group.

The following table, table 36, is restricted to adverse events that the investigator's rated as at least possibly related to treatment. Again, the response profiles for the vehicle (placebo) group does seem to have a higher mean than the others. This difference is statistically significant ($p \leq 0.020$).

Table 36. SFF 301 & SFF 303
Severity of Subject's Most Severe Adverse Event
European study, Lamisil Applied QD
Adverse events at least possibly associated with drug

Treatment	Severity: No event n	No event %	Mild n	Mild %	Moderate n	Moderate %	Severe n	Severe %	Total n
Lamisil	197	90.1	8	3.7	8	3.7	4	1.8	217
Placebo	85	80.2	8	7.6	9	8.5	4	3.7	106

CMH row means differ p-value 0.020

Table 37. below summarizes the adverse events identified by the sponsor in the trials.

Table 37. SFF 301 & SFF 303
European studies, Lamisil Applied QD
All adverse events

Body System	Adverse Event	Lamisil # indiv	Vehicle # indiv	Lamisil # event	Vehicle # event
Application Site Disorders	Application Site Reaction	1	2	1	2
Body As A Whole - General Disorders	Accidental Trauma	1	.	1	.
	Allergic Reaction	.	1	.	1
	Back Pain	1	.	1	.
	Condition Aggravated	5	5	5	5
	Infection	1	.	1	.
	Infection Bacterial	.	1	.	1
	Infection Fungal	1	1	1	1
	Infection Viral	1	.	1	.
Liver And Biliary System Disorders	Hepatitis Cholestatic	.	1	.	1
Reproductive Disorders, Male	Balanoposthitis	1	.	1	.
Respiratory System Disorders	Bronchitis	1	.	1	.
	Sinusitis	1	.	1	.
Skin And Appendages Disorders	Folliculitis	1	3	1	3
	Pigmentation Abnormal	11	1	12	1
	Pruritus	14	22	17	26
	Rash	1	.	1	.
	Rash Erythematous	15	21	16	23
	Rash Maculo-Papular	8	9	8	10
	Rash Papular	.	1	.	1
	Rash Pustular	6	12	7	14
	Rhagades	2	3	2	3
	Skin Depigmentation	1	.	1	.
	Skin Disorder	10	16	12	19
	Skin Dry	.	1	.	1
	Skin Exfoliation	14	21	15	23
	Urticaria	1	.	1	.

Table 37. SFF 301 & SFF 303
European studies, Lamisil Applied QD
All adverse events

Body System	Adverse Event	Lamisil # indiv	Vehicle # indiv	Lamisil # event	Vehicle # event
Urinary System Disorders	Pyelonephritis	1	.	1	.
Vision Disorders	Miosis	1	.	1	.
Overall		100/217	121/106	109	135

Overall, with one exception, the adverse event rates for Lamisil seldom exceed those for the vehicle. The one exception is that It would appear that Lamisil 1% solution was associated with an usually high incidence of abnormal pigmentation or depigmentation.

One patient had a serious adverse event, cholestatic hepatitis, apparently not related to treatment.

D. Drop-Outs

The following table 38 tabulates the reasons for the drop-outs in the tinea versicolor studies:

Table 38. SFF 353 & SFF 305

SFF 353	Reason For Discontinuation							
	Withdrew consent		Treatment Failure		Did not return		Other	
	n	%	n	%	n	%	n	%
Lamisil	2	13.3	2	13.3	10	66.7	1	6.7
Placebo	.	.	2	33.3	4	66.7	.	.

SFF 305	Reason For Discontinuation			
	Withdrew consent		Did not return	
	n	%	n	%
Lamisil	1	33.3	2	66.7
Placebo	1	100.0	.	.

The number of drop-outs is small, perhaps too small to make statistical tests relevant. Considering the initial imbalance in treatment allocation (2:1) in these studies, there seems to be no particular evidence of differences in drop out rates.
The following table 39 tabulates the reasons for the drop-outs in the tinea pedis studies:

Table 39. SFF 351, SFF 301 & SFF 309

SFF 351 Reason For Discontinuation

	Withdrew consent		Protocol violation		Treatment Failure		Did not return		Other	
	n	%	n	%	n	%	n	%	n	%
Lamisil	1	4.3	1	4.3	5	21.7	2	8.7	14	60.9
Placebo	.	.	1	9.1	4	36.4	2	18.2	4	36.4

SFF 301 Reason For Discontinuation

	Withdrew consent		Protocol violation		Treatment Failure		Did not return		Other	
	n	%	n	%	n	%	n	%	n	%
Lamisil	.	.	2	20.0	1	10.0	5	50.0	2	20.0
Placebo	1	16.7	1	16.7	2	33.3	2	33.3	.	.

SFF 309 Reason For Discontinuation

	Treatment Success		Adverse Event		Withdrew consent		Protocol violation		Treatment Failure		Did not return		Other	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Lamisil	1	2.7	.	.	2	5.4	2	5.4	1	2.7	27	73.0	4	10.8
Clotri-mazole	.	.	1	3.6	4	14.3	3	10.7	1	3.6	19	67.9	.	.

Again, the number of drop-outs is small, perhaps too small to make statistical tests relevant. Considering the initial imbalance in treatment allocation (2:1) in the SFF 351 and SFF 301 studies, versus equal balance (1:1) in the SFF 309 study, again there seems to be no particular evidence of differences in drop out rates.

The following table 40 tabulates the reasons for the drop-outs in the single 300-series tinea corporis/cruris study:

Table 40. SFF 303

SFF 303 Reason For Discontinuation

	Adverse Event		Protocol violation		Treatment Failure		Did not return		Other	
	n	%	n	%	n	%	n	%	n	%
Lamisil	2	6.5	4	12.9	10	32.3	10	32.3	5	16.1
Placebo	2	6.9	1	3.4	24	82.8	2	6.9	.	.

Considering the initial imbalance in treatment allocation (2:1) in this study, there is clear evidence of a much greater proportion of treatment failures in the vehicle group than in the Lamisil. However, none of these observations impact on final conclusions about the relative efficacy of Lamisil 1% solution and its vehicle.

Conclusions (Which may be conveyed to the Sponsor):

1. The sponsor provided nine studies to support the claim of efficacy of Lamisil® Solution 1% (terbinafine hydrochloride solution). All studies were multicenter, double-blind, randomized, parallel group studies. All save one, were vehicle controlled. Three indications are claimed, and the design of the studies vary in critical ways across the studies:

Table 41. Phase III Clinical Studies

Protocol no	US vs non US	design
Tinea Versicolor (Pityriasis Versicolor)		
SFF 353	US	1-week, twice daily treatment, with a 7-week untreated follow-up
SFF 305	non US	
Tinea Pedis		
SFF 351	US	1-week, twice daily treatment, with a 7-week untreated follow-up
SFF 301	Non- US	1-week, once daily treatment, with a 7-week untreated follow-up
SFF 309	Non-US	1-week, twice daily, treatment for Lamisil (with a 3- week PBO) vs 4-week Clotrimazole. Both have further 3- week untreated follow-up.
SFF 104	US	2-week, once daily treatment, with a 4-week untreated follow-up
Tinea Corporis / Cruris		
SFF 303	Non-US	1-week, once daily treatment with a 7-week untreated follow-up
SFF 105	US	1-week, once daily treatment with a 3-week untreated follow-up
SFF 108	Non- US	

2. This review used the proposed Division V definition of a modified intent-to-treat (MITT) population, based on every subject who was dispensed a study treatment who additionally had a baseline positive dermatophyte mycology.

3. Complete cure was defined as a negative mycology and a total signs and symptoms score of zero. The Medical Officer showed some preference for the sponsor's defined effective treatment (see page 3 of this report for a definition), but agreed that complete cure was useful. It is this reviewer's opinion that the endpoint "complete cure" seems more consistent with the primary endpoints used in other recent NDA's. By the end of the study, using either effective treatment or complete cure, all of the vehicle controlled studies showed highly statistically significant differences in favor of Lamisil.

4. Using either endpoint, both studies of tinea versicolor (pityriasis versicolor), SFF 353 and SFF 305, showed statistically significant differences between the one week, twice daily course of treatment of Lamisil 1% solution and its vehicle at the end of the study

($p \leq 0.001$ for both studies and indications). These differences were apparent by week 4 of the study and increased in magnitude thereafter.

5. For tinea corporis/cruris, all three studies, SFF 303, SFF 105, and SFF 108 showed a statistically significant difference between Lamisil and its vehicle at the end of treatment (p-value of no more than $p \leq 0.009$ in all studies for both endpoints). Since SFF 105 was a U.S. study, it is this reviewer's opinion it can be combined with the results of the other two studies to justify the claim of efficacy for a one week, once daily course of treatment.

6. For tinea pedis, using either endpoint, study SFF 351 showed statistically significant differences between Lamisil 1% solution and its vehicle at the end of the study ($p \leq 0.001$ for both indications). Note that under the dosage schedule used, Clotrimazole has been accepted as an effective treatment. In SFF 309, effective treatment tended to favor Lamisil over Clotrimazole, while complete cure tended to favor Clotrimazole over Lamisil. However, at the end of the study, or by week 4, using the definition of equivalence on page 22 of this report, these treatments were shown to be equivalent in terms of effective treatment. Equivalence was not shown for complete treatment, but there was no statistically significant difference between treatments. Both of these Lamisil treatments were twice daily for one week, although in SFF 309 the Lamisil treatment is followed by a three week course of treatment using vehicle. Study SFF 301 followed a once daily dosing schedule for one week, but otherwise was similar to SFF351. Again, at the end of the study both complete cure and effective treatment showed statistical significance ($p \leq 0.005$ and $p \leq .001$, respectively). It seems to this reviewer that efficacy under a single dosing schedule could be used to imply efficacy under a twice daily dosing schedule, particularly if the results are used as verification, not origination. Thus, it is this reviewer's opinion that these studies combine to show efficacy of Lamisil 1% solution in the treatment of tinea pedis when used twice daily for one week.

7. The sponsor wants to claim a once daily dose for both tinea pedis and tinea corporis/cruris. The current requirement has been interpreted as requiring two independent, well-controlled trials for each indication. At least one of these studies is supposed to be conducted in the U.S. or Canada. By using one of the studies, SFF 105, that the sponsor labels as non-pivotal it is this reviewer's opinion that the once daily dose has been shown to effective for tinea corporis/cruris. However, no such claim seems to be justified for tinea pedis. To justify a once a day, one week course of treatment for tinea pedis it is this reviewer's opinion that the sponsor would need to run one more clinical trial, conducted in the U.S. Otherwise it is this reviewer's opinion that the sponsor has not provided sufficient studies to justify the claim for a once a day course of treatment.

8. Note that overall, the proportion of adverse events was lower for the treatment group than the vehicle group. There were some signs that Lamisil treatment may be associated with abnormal skin pigmentation but these were not verified in the U.S. studies.

9. Thus, it is this reviewer's opinion that the sponsor has demonstrated that Lamisil Solution, 1%, is statistically significantly more effective than, and at least as safe as, its

vehicle when used twice daily in a one week course of treatment for tinea versicolor (pityriasis versicolor) or tinea pedis. Further, when used once daily in a one week course of treatment for tinea corporis/cruris it is significantly more effective than, and at least as safe as, its vehicle.

28 July 1997

Steve Thomson
Mathematical Statistician, Biometrics V

July 28, 97

concur: R. Srinivasan, Ph.D.
Team Leader, Biometrics V

cc:
Archival NDA: 20-749
HFD-540/Division File
HFD-540/Dr. Wilkin
HFD-540/Dr. Toombs
HFD-540/Mr. Cross
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-725/Mr. Thomson
HFD-340/Dr. Lepay
This review has 45 pages.
Chron.

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OCT 16 ...

Statistical Review and Evaluation
(Addendum)

NDA/ Drug Class: 20-749

Name of Drug: Lamisil® (terbinafine hydrochloride) Solution, 1%.

Applicant: Sandoz Pharamaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936

Type of Report: Clinical/Statistical

Indication: Treatment of Tinea Versicolor (Pityriasis Versicolor) due to Pityrosporum species, and topical treatment of Tinea Pedis, Tinea Corporis and Tinea Cruris caused by Trichophyton Rubrum, Epidermophytom Floccosum, or Trichophyton Mentagrophytes.

Medical Officer: Dr. E. Toombs (HFD-540)

Introduction:

For the construction of the label, it was decided to depend upon four studies among the eight "key" studies originally specified by the sponsor (though data sets were only provided for six of the putative "key" studies). After generating the efficacy tables in for the label, it was discovered that there were discrepancies in several of the applicant's data sets associated with these studies. These discrepancies were not of statistical significance in the sense that they would have had no impact upon statistical significance levels (i.e., <0.001 significance level would have remained <0.001). However, exact counts of subjects in various categories were occasionally slightly discrepant.

Due to differences in design, only four of the nine studies labeled "key" by the sponsor were used to generate the label. The designs used in the studies are summarized in the following table, Table 1:

Table 1. Phase III Clinical Studies
Tinea Versicolor/Tinea Pedis/Tinea Corporis-Tinea Cruris

Protocol no	US vs non US	design	objective	duration of study	No. enrolled
Tinea Versicolor (Pityriasis Versicolor)					
SFF 353	US	multicenter, double blind, randomized, parallel-group	safety/efficacy vs vehicle twice daily for treatment of tinea versicolor (pityriasis versicolor)	1-week treatment with a 7-week untreated follow-up	LAM. 1% 103 Veh 49
SFF 305	non US				LAM. 1% 79 Veh 36
Tinea Pedis					
SFF 351	US	multicenter, double blind, randomized, parallel-group	safety/efficacy vs vehicle twice daily for treatment of tinea pedis.	1-week treatment with a 7-week untreated follow-up	LAM. 1% 104 Veh 49
Tinea Corporis / Cruris					
SFF 303	Non-US	multicenter, double blind, randomized, parallel-group	safety/efficacy vs vehicle once daily for treatment of tinea corporis/cruris.	1-week treatment with a 7-week untreated follow-up	LAM. 1% 102 Veh 49

In studies SFF 353 and SFF 305, individual signs and symptoms scores (or severity scores) were recorded as the severity of erythema, desquamation, or pruritus. In the other two, variables for pustules, incrustation, and vesiculation were also recorded. All six of these possible severity scores were each evaluated on a 4-point scale:

0 = absent 2 = moderate
1 = mild 3 = severe.

For each study the total signs and symptoms score was defined as the sum of the scores of the individual signs and symptoms severity scales. So for study SFF 353 and SFF 305 the total signs and symptoms score was the sum of three severity scores, while in the remaining studies it was the sum of six such scores.

The sponsor defined the binary response variable "effective treatment," with a value of "yes," when a case has negative mycology and a total signs and symptoms score ≤ 1 (in the tinea versicolor studies SFF 353 and SFF 305, and ≤ 2 in the SFF 303 and SFF 351 studies). In the last two studies a further criterion for the effective treatment to be "yes" was that the sum of severity scores for pustules, incrustation, and vesiculation must be zero. The variable "effective treatment" is evaluated as a "no," if the case has positive mycology or a total signs and symptoms score exceeding the study dependent bound, noted above. "Complete cure" was defined similarly as a binary response with "yes," indicating where mycology measures were negative and the total signs and symptoms score was zero. Otherwise, if both mycology and total signs and symptoms are defined, the value of "complete cure" is "no." The primary endpoints used in the statistical report

were "effective treatment," "complete cure," and whether or not the mycology was negative.

Note, by definition, the total number of cases with an effective treatment score, i.e., either "yes," or "no," has to be the same as the corresponding total number of cases with either "complete cure" score. Note these totals would be the denominator in any tabulation of the proportion of say "yes" responses for either variable. Further, both of these totals have to be less than or equal to the number of cases having a mycological cure score, either positive or negative, as well as less than or equal to the number of cases with a total signs and symptoms score.

In updating the tables for the label, it was discovered that these relations among the response variables did not hold for some cases in several of the data sets supplied by the sponsor, either in the populations used in the sponsor's analyses or in the populations used in this reviewer's analyses. Since the number of cases involving such data were small, particularly in the sponsor's analyses, and would have had no substantial impact upon conclusions, it was decided not to request corrected data sets. Further since the number of such cases was smaller in the population used in the sponsor's analyses, it was decided to use the sponsor's numbers to generate the tables of the percentages of mycological cure, effective treatment, and complete cure used in the label.

Conclusions (Which may be conveyed to the Sponsor):

1. The sponsor defined the binary response variable "effective treatment," with a value of "yes," when a case has negative mycology and a total signs and symptoms score ≤ 1 (in the tinea versicolor studies SFF 353 and SFF 305, and ≤2 in the SFF 303 and SFF 351 studies). In the last two studies a further criterion for the effective treatment to be "yes" was that the sum of severity scores for pustules, incrustation, and vesiculation must be zero. The variable "effective treatment" is evaluated as a "no" if the case has positive mycology or a total signs and symptoms score exceeding the study dependent bound, noted above. "Complete cure" was defined similarly as a binary response with "yes," indicating where mycology measures were negative and the total signs and symptoms score was zero. Otherwise, if both mycology and total signs and symptoms are defined, the value of "complete cure" is "no." The primary endpoints used in the statistical report were "effective treatment," "complete cure," and whether or not the mycology was negative.

2. Note, by definition, the total number of cases with an effective treatment score, i.e., either "yes," or "no," has to be the same as the corresponding total number of cases with either "complete cure" score. These totals would be the denominators in any tabulation of the proportion of say "yes" responses for either variable. Further, both of these totals have to be less than or equal to the number of cases having a mycological cure score, either positive or negative, as well as less than or equal to the number of cases with a defined total signs and symptoms score.

3. In updating the tables for the label, it was discovered that these relations among the response variables did not hold for some cases in several of the data sets supplied by the sponsor, either in the populations used in the sponsor's analyses or in the populations used in this reviewer's analyses. Since the number of cases involving such data were small, particularly in the sponsor's analyses, and would have had no substantial impact upon conclusions, it was decided not to request corrected data sets. Further since the number of such cases was smaller in the population used in the sponsor's analyses, it was decided to use the sponsor's numbers to generate the tables of the percentages of mycological cure, effective treatment, and complete cure used in the label.

10/16/97

Steve Thomson
Mathematical Statistician, Biometrics V

Oct 16, 97

concur: R. Srinivasan, Ph.D.
Team Leader, Biometrics V

cc:
Archival NDA: 20-749 Addendum
HFD-540/Division File
HFD-540/Dr. Wilkin
HFD-540/Dr. Toombs
HFD-540/Mr. Cross
HFD-725/Dr. Anello
HFD-725/Dr. Srinivasan
HFD-725/Mr. Thomson
HFD-340/Dr. Lepay
This addendum has 5 pages, including this signature page.
Chron.

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