CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-980

STATISTICAL REVIEW(S)

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Statistical / Clinical Review and Evaluation
Prescription to Non-Prescription Classification

NDA/ Drug Class:	20-980 / 6S
Name of Drug:	Terbinafine Hydrochloride Cream, 1%
Applicant:	Novartis Pharmaceuticals Corporation 59 Route 10 East Hanover, NJ 07936-1080
Type of Report:	Clinical/Statistical For Rx to OTC Switch
Indication:	Tinea Pedis, Tinea Corporis, Tinea Cruris
Documents Reviewed:	Volumes 1.22-1.35, and diskettes containing SAS data sets from the sponsor
Medical Officer:	Dr. Brenda Vaughan (HFD-540)

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1. Introduction

According to the sponsor: "Tinea pedis, tinea corporis, and tinea cruris are common worldwide diseases caused by dermatophytes. . . . The lesions caused by these infections may occur at any site on the body or skin, and are characterized by erythema, small papular vesicles, fissures and scaling."

"Presently, the most common topical antifungals available without a prescription include clotrimazole, miconazole, tolnaftate, and undecylenic acid/undecylenate. All require twice daily administration. Treatment durations are two weeks for tinea cruris and four weeks for tinea corporis and tinea pedis."

"The nonprescription topical antifungals currently available have not been proven to demonstrate significant efficacy when applied for only one week." The sponsor sent the results of nine studies in efficacy and safety to justify the switch of Lamisil 1% cream from prescription to nonprescription use.

2. Experimental Designs

The sponsor provided the reports on nine studies of the effect of terbinafine HCl Cream, 1%, on tinea pedis, tinea corporis, and tinea cruris. The following table provides study indication. study labels, a short description, and an indication of whether or not SAS data sets were provided.

Table 1. The Nine Studies

Indication	Study No.	Description	Data set?
Tinea Pedis (interdigital)	2-1	A double-blind, parallel, U.S. multicenter trial comparing the efficacy and safety of 1% terbinafine cream and vehicle cream bid for 1 week in the treatment of tinea pedis (interdigital).	Yes
	2-2	A double-blind, parallel, U.S. multicenter trial comparing the efficacy and safety of 1% terbinafine cream and vehicle cream bid for 1 week in the treatment of tinea pedis (interdigital).	Yes
	2508-01	A double-blind, parallel, U.S. multicenter trial comparing the efficacy and safety of 1% terbinafine cream with 1% clotrimazole cream, bid for either 1 or 4 weeks, in the treatment of tinea pedis (interdigital).	Yes
	SF0040	A double-blind, parallel group study conducted in the United Kingdom to compare 1% terbinafine (Lamisil®) cream given bid for 1 week (followed by bid vehicle for 3 weeks) with 1% clotrimazole cream given bid for 4 weeks for the treatment of tinea pedis.	Yes
	SF0029	A double-blind, parallel group, uncontrolled U.K. study to investigate the safety and efficacy of 1% terbinafine cream applied qid for 1, 3, 5, or 7 days in patients with tinea pedis.	No
Tinea Corporis/ Cruris	3-1	A double-blind, parallel, multicenter trial conducted in various Caribbean states comparing the efficacy and safety of 1% terbinafine cream to vehicle cream, applied once daily for one week in the treatment of tinea corporis/cruris.	Yes
	3-2	A double-blind, parallel, multicenter trial conducted in various Caribbean states comparing the efficacy and safety of 1% terbinafine cream to vehicle cream, applied once daily for one week in the treatment of tinea corporis/cruris.	Yes
	SF2003	A general practice, single center, double-blind therapeutic trial in the U.K. of the efficacy and safety of topical SF 86-327, 1% cream applied once daily compared to vehicle during 1 week in patients with tinea corporis/cruris.	No
	SF2030	A double-blind, parallel group, multicenter study in the U.K. to investigate the safety and efficacy of terbinafine 1% cream applied once daily for one day, three days, five days, or seven days in patients with tinea corporis/cruris.	No

SAS data sets were provided for six of the studies. A number of problems are apparent in several of the studies above. Study 2508-01 is a comparison of 1% terbinafine cream with 1% clotrimazole cream. Due to regression and placebo effects, plus possibly secular effects, we would expect that some improvement over time in both treatment groups. Without a vehicle or control group, we cannot disentangle these effects from true treatment effect. However, if we assume that clotrimazole is efficacious, since, in fact, the one week course of treatment with

terbinafine cream was at several time points statistically significantly better than one week of treatment with clotrimazole, in this case, the results do suggest efficacy in the terbinafine 1% group.

Study SF0040 is similar, with the additional difficulty that the Lamisil treatment actually applied was one week of 1% terbinafine cream BID, followed by 3 weeks of vehicle. Unless we can assume the vehicle has absolutely no effect, this is not equivalent to one week of treatment with terbinafine 1% cream. Study SF0029 only compares the efficacy of various treatment periods of Lamisil cream, with no explicit vehicle or control group. So again, due to regression and placebo effects, plus possibly secular effects, we have no good reference group with which to assess efficacy. Thus this reviewer considers these studies to be of little use in assessing efficacy, and these studies are only used for assessing adverse events.

There were similar problems in study SF 2030 in the tinea corporis/cruris studies. To repeat: this study only compares the efficacy of various treatment periods of Lamisil, with no vehicle or control. So again, due to regression and placebo effects, plus possibly secular effects, we have no relevant reference group with which to assess efficacy. Again, this study was only used to assess adverse events.

The sponsor originally requested that plantar type tinea pedis remain on a prescription basis, requiring a learned intermediary, and interdigital tinea pedis on a non-prescription basis. It was felt that the same indication should not be treated both bases. Hence it was felt that this review also needed to include a reference to moccasin type tinea pedis. Thus, a statistical report assessing the efficacy of for two plantar-type (moccasin) studies was also reviewed:

Table 2. Tinea Pedis (Moccasin) Studies

Indication	Study No.	Title	Data set?
Tinea Pedis (moccasin)	2509-01	A double-blind, parallel, multicenter trial comparing the efficacy and safety of 1% terbinafine cream and vehicle cream applied twice daily for two weeks in the treatment of tinea pedis (moccasin)	No
	2509-02	A double-blind, parallel, multicenter trial comparing the efficacy and safety of 1% terbinafine cream and vehicle cream applied twice daily for two weeks in the treatment of tinea pedis (moccasin)	No

i. Primary Response Measures (Common to all studies):

In all the studies, there was a mycological assessment at screening (baseline visit 1), and at later visits. All studies used both a KOH examination and culture to determine the presence of a fungal organism. "A scale of 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe) was used to grade the various symptoms of the target lesion, including (in the majority of the studies) desquamation, erythema, exudation, fissuring, maceration, vesiculation, pruritus, and burning/stinging. Some studies included crusting and pustules in addition to, or in place of, some of the previously noted signs."

Mycological cure was defined as the occurrence of negative KOH and culture with minimal signs and symptoms (total score≤ 2 for the target lesion).

Complete cure was defined as the occurrence of negative KOH and culture with no residual signs and symptoms.

3. Efficacy Results for Tinea Pedis Studies

a. Study No. 2-1 (Protocol 2506-01)

This was a double-blind, randomized, multicenter, parallel group, vehicle controlled study of the safety and efficacy of terbinafine 1% cream, applied topically twice a day for one week in patients with interdigital tinea pedis. For inclusion in the study, patients were required to have both clinical and mycological evidence of tinea pedis. The efficacy evaluation was based on a reduction in clinical signs and symptoms, and conversion from positive to negative mycology. Efficacy was evaluated at the end of the one week of therapy, and at two, four, and six weeks.

i. Patient Demographics:

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

Table 3. Patient Enrollment

	Terbinafine	Vehicle	Total
Patients Planned	40	40	80
Patients enrolled	38	39	77
Drop-outs	1	1	2
Delayed exclusions	4	4	8
Evaluable for Efficacy	33	34	67

The two drop-outs were discontinued for reasons other than safety. The 8 patients categorized as delayed exclusions were dropped because the initial cultures were negative for dermatophytes.

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

ii. Efficacy Results:

Mycological cure is defined as negative KOH and culture with a total signs and symptoms score of two or less (plus a maximum score of "1= mild" for each of erythema,

fissuring, maceration, desquamation, and pruritus). Complete cure is defined as a mycological cure with a score of "0=none" for all the signs and symptoms. The following tables give proportions of mycological and complete cures for each treatment group at each time point in the study. Note that the treatment period ended after one week. Tables are given for baseline, end of treatment (one week), weeks 2, 4, 6, and a "last observation carried forward" (LOCF) analysis. Below each of the tables is the "p-value," significance level, of a test of within center homogeneity of cure over treatment, using a Mantel-Haenszel test.

Table 4. Study 2-1 Mycological Cure

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

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

	Visit Week														
	Baseline			1			2			4			6			LOCF		
	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%
Terbinafine	0	34	0.0	6	33	18.2	9	32	28.1	18	33	54.5	21	32	65.6	22	34	64.7
Vehicle	0	34	0.0	2	34	5.9	1	31	3.2	2	30	6.7	2	30	6.7	2	34	5.9
p-value		.			0.124			0.004			0.001			0.001			0.001	

Note that differences at the end of treatment, i.e., one week, are not statistically significant ($p \leq 0.124$). By week two, differences are statistically significant ($p \leq 0.004$). By week 6, since there were relatively few dropouts, it seems that nearly 70% of the terbinafine group displayed a mycological cure versus only 7% for vehicle ($p \leq 0.001$).

To repeat: complete cure is defined as negative KOH and culture with no residual signs and symptoms. Below each level of week is the "p-value," significance level, of a test of within center homogeneity of cure over treatment, using a Mantel-Haenszel test.

Table 5. Study 2-1 Complete Cure

Complete Cure

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

	Visit Week														
	Baseline			1			2			4			6			LOCF		
	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%
Terbinafine	0	34	0.0	3	33	9.1	4	32	12.5	7	33	21.2	7	32	21.9	8	34	23.5
Vehicle	0	34	0.0	1	34	2.9	0	31	0.0	0	30	0.0	0	30	0.0	0	34	0.0
p-value		.			0.327			0.035			0.003			0.006			0.002	

As with mycological cure, differences at the end of treatment, i.e., one week, are not statistically significant ($p \leq 0.327$). By week two, differences are statistically significant ($p \leq 0.035$). By week 6, since there were relatively few dropouts, it seems that about 22% of the terbinafine

group displayed a mycological cure versus none for vehicle ($p \leq 0.006$).

b. Study No. 2-2 (Protocol 2506-02)

The protocol for this study was identical to the preceding study 2-1.

i. Patient Demographics:

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

Table 6. Patient Enrollment

	Terbinafine	Vehicle	Total
Patients Planned	40	40	80
Patients enrolled	56	54	110
Drop-outs	3	2	5
Delayed exclusions	6	7	13
Evaluable for Efficacy	47	45	92

The five drop-outs were discontinued for reasons other than safety. The 13 patients categorized as delayed exclusions were dropped because the initial cultures were negative for dermatophytes.

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

ii. Efficacy Results:

The following tables give proportions of mycological and complete cures for each treatment group at each time point in the study. Again, the treatment period ended after one week. Tables are given for baseline, end of treatment (one week), weeks 2, 4, 6, and a "last observation carried forward" (LOCF) analysis. The last row in each table is the "p-value", significance level, of a test of within center homogeneity of cure over treatment, using a Mantel-Haenszel test.

Table 7. Study 2-2 Mycological Cure

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

Protocol Number=SAN 2506-02

	Visit Week																					
	Baseline			1			2			4			6			LOCF		
	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%
Terbinafine	0	51	0.0	5	49	10.2	13	47	27.7	22	46	47.8	30	45	66.7	30	51	58.8
Vehicle	0	48	0.0	3	46	6.5	9	45	20.0	8	45	17.8	6	39	15.4	6	48	12.5
p-value		.			0.448			0.159			0.002			0.001			0.001	

Note that differences at the end of treatment, i.e., week one, or after one week of follow-up, i.e., week two, are not statistically significant ($p \leq 0.448$ and $p \leq 0.159$). By week four, differences are statistically significant ($p \leq 0.002$). By week 6, among the evaluable patients 67% of the terbinafine group displayed a mycological cure versus only 15% for vehicle ($p \leq 0.001$).

Table 8. Study 2-2 Complete Cure

Complete Cure

Protocol Number=SAN 2506-02

	Visit Week																					
	Baseline			1			2			4			6			LOCF		
	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%
Terbinafine	0	51	0.0	1	49	2.0	4	47	8.5	11	46	23.9	17	45	37.8	17	51	33.3
Vehicle	0	48	0.0	0	46	0.0	1	45	2.2	2	45	4.4	1	39	2.6	1	48	2.1
p-value		.			0.317			0.131			0.006			0.001			0.001	

As with mycological cure, differences at the end of the first two weeks are not statistically significant ($p \leq 0.317$ and $p \leq 0.131$, respectively). By week four, differences are statistically significant ($p \leq 0.006$). By week 6, among the fully evaluable subset of patients, 37% had a complete cure versus 3% for vehicle ($p \leq 0.001$). Results for the LOCF group are similar.

c. Study No. 2508-01

This was a double-blind, randomized, multicenter trial comparing the efficacy and safety of 1% terbinafine cream with 1% clotrimazole cream applied twice daily in the treatment of tinea pedis. There were two courses of treatment: a one week treatment with evaluation at the end of treatment, Day 8, and a four week treatment with evaluation during treatment at Days 8 and 15, at Day 29 (end of treatment) and at follow-up visits at Weeks 6, 9, and 12. The sponsor reported that the purpose of the lengthy follow-up was to evaluate the duration of maintenance of clearing of target lesions. For inclusion in the study, patients were required to have both clinical and mycological evidence of tinea pedis. The efficacy evaluation was based on a reduction in clinical signs and symptoms, and conversion from positive to negative mycology.

i. Patient Demographics:

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

Table 9. Patient Enrollment

	Terbinafine 1 week	Terbinafine 4 weeks	Clotrimazole 1 week	Clotrimazole 4 weeks	Total
Patients enrolled	68	68	68	68	272
Delayed exclusions	5	5	4	4	18

The 18 patients categorized as delayed exclusions were dropped because the initial cultures were negative for dermatophytes.

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

ii. Efficacy Results:

The following tables give proportions of mycological and complete cures for each treatment group at each time point in the study. In the table one week of 1% terbinafine cream treatment is denoted "T1", while one week of 1% clotrimazole cream is denoted "C1." Similarly four weeks of treatment are denoted "T4" and "C4", respectively. Again, the treatment period ended after either one week or four weeks. Tables are given for baseline, weeks 1, 2, 4, 6, 9, and a "last observation carried forward" (LOCF) analysis. Below each table is the "p-value", significance level, of a test of within center homogeneity of response, using a Mantel-Haenszel test comparing one week of 1% terbinafine cream (i.e., "T1"), with one week or four weeks of 1% clotrimazole cream (i.e., "C1" or "C4", respectively), or four weeks of 1% terbinafine cream (i.e., "T4").

Table 10. Study 2508-01 Mycological Cure

---------- Protocol Number=SAN 2508-01 ----------

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

	Baseline			Week 1			Week 2			Week 4			Week 6		
	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%
C1	0	50	0.0	2	48	4.2	4	49	8.2	11	45	24.4	15	42	35.7
C4	0	53	0.0	1	50	2.0	5	50	10.0	15	49	30.6	21	48	43.8
T1	0	49	0.0	1	48	2.1	8	46	17.4	16	42	38.1	22	41	53.7
T4	0	50	0.0	2	48	4.2	9	47	19.1	21	45	46.7	30	43	69.8
p-values:															
T1 vs C1		.			0.623			0.142			0.208			0.107	
T1 vs C4		.			0.931			0.307			0.495			0.600	
T1 vs T4		.			0.591			0.837			0.395			0.139	

	Week 9			Week 12			LOCF		
	n cure	n	%	n cure	n	%	n cure	n	%
C1	11	41	26.8	11	37	29.7	11	50	22.0
C4	25	48	52.1	20	44	45.5	21	53	39.6
T1	29	39	74.4	22	38	57.9	25	49	51.0
T4	25	42	59.5	27	42	64.3	27	50	54.0
p-values:									
T1 vs C1		0.001			0.017			0.003	
T1 vs C4		0.053			0.455			0.254	
T1 vs T4		0.140			0.545			0.834	

Note that by week 9 there are statistically significant differences between the one week 1% terbinafine cream treatment group and the one week 1% clotrimazole cream treatment group in mycological cure ($p \leq 0.001$ at 9 weeks, $p \leq 0.017$ at 12 weeks, and $p \leq 0.003$ at the end of the study, LOCF). No other differences are statistically significant.

Table 11. Study 2508-01 Complete Cure

---------- Protocol Number=SAN 2508-01 ----------

Complete Cure

	Baseline			Week 1			Week 2			Week 4			Week 6		
	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%	n cure	n	%
C1	0	50	0.0	0	48	0.0	0	49	0.0	4	45	8.9	5	42	11.9
C4	0	53	0.0	0	50	0.0	0	50	0.0	4	49	8.2	6	48	12.5
T1	0	49	0.0	0	48	0.0	1	46	2.2	4	42	9.5	7	41	17.1
T4	0	50	0.0	0	48	0.0	1	47	2.1	5	45	11.1	10	43	23.3
p-values:															
T1 vs C1		.			.			0.289			0.949			0.527	
T1 vs C4		.			.			0.289			0.970			0.722	
T1 vs T4		.			.			0.915			0.895			0.466	

	Week 9			Week 12			LOCF		
	n cure	n	%	n cure	n	%	n cure	n	%
C1	7	41	17.1	6	37	16.2	6	50	12.0
C4	12	48	25.0	11	44	25.0	12	53	22.6
T1	12	39	30.8	9	38	23.7	10	49	20.4
T4	11	42	26.2	13	42	31.0	13	50	26.0
p-values:									
T1 vs C1		0.143			0.367			0.227	
T1 vs C4		0.773			0.728			0.767	
T1 vs T4		0.735			0.519			0.619	

Although all treatment groups showed some improvement, there are no statistically significant differences between one week of 1% terbinafine cream treatment group and any of the other treatment regimens at any time point.

d. Study No. 2509-01 Plantar Tinea Pedis

This was a double-blind, randomized, parallel group, vehicle controlled study, conducted in five centers, of the safety and efficacy of Terbinafine 1% cream, applied topically twice a day for two weeks in patients with plantar tinea pedis (moccasin type). For inclusion in the study, patients were required to have both clinical and mycological evidence of tinea pedis involving at least one third of the plantar surface of the foot. Patients were also required to have a score of at least 2 for scaling/hyperkeratosis, and a total score of at least 4, adding fissuring, erythema, and pruritus. The efficacy evaluation was based on a reduction in clinical signs and symptoms, and conversion from positive to negative mycology. Efficacy was evaluated at the end of the one week of therapy, and at two, four, and six weeks.

i. Patient Demographics:

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

Table 12. Patient Enrollment

	Terbinafine	Vehicle	Total
Patients enrolled	54	55	109
Evaluable for Efficacy	49	47	96

Twelve patients were deleted because they did not meet the entry criteria. Three were lost to follow-up.

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

ii. Results (taken from original statistical review):

"Effective treatment was defined as negative mycology (conversion of both culture and KOH from positive to negative) with either no residual signs and symptoms or with some residual signs and/or symptoms (total score of ≤ 2 based on all four observed: erythema, scaling/ hyperkeratosis, pruritus, and fissuring, but with individual scores for erythema and/or scaling and/or pruritus each with score ≤ 1). Significant differences in effectiveness were noted between treatments at Weeks, 4, 6, and 8 and at End Point [i.e., LOCF endpoint]. At the end of treatment, six percent of the patients in the Lamisil group were effectively treated as compared to seven percent for the vehicle ($p=1.000$). At the week 8 visit, 48% of the Lamisil group were effectively treated as compared to five percent for vehicle ($p<0.001$). Using End Point Analysis (the last visit for patients with at least one follow-up-visit, [i.e., LOCF], the patients who were effectively treated were 45% and 5% respectively ($p<0.001$). The differences between Lamisil and vehicle were statistically significant at Weeks 4 ($p=0.015$), 6 ($p<0.001$), and 8 ($p<0.001$), and at [LOCF] End Point ($p<0.001$).