CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-124

STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION

NDA/DRUG CLASS:	21-124/6S
NAME OF DRUG:	Lamisil (Terbinafine Hydrochloride) Solution, 1%
APPLICANT:	Novartis Consumer Health, Inc.
INDICATION(S):	Interdigital-Type Tinea Pedis, Tinea Cruris & Tinea Corporis
TYPE OF REVIEW:	Statistical
DOCUMENTS REVIEWED:	Two Studies for Tinea Pedis (301 & 351) & One for Tinea Cruris & Tinea Corporis (303), Dated 8/03/99
MEDICAL REVIEWER:	Phyllis Heune, M.D./HFD-540
STATISTICAL REVIEWER:	Shahla S. Farr, M.S./HFD-725

I. INTRODUCTION:

The sponsor has submitted this NDA for switching of terbinafine hydrochloride (HCl) solution, 1%, from RX to Over The Counter (OTC) status. Terbinafine HCl solution, 1%, (Lamisil) was approved for prescriptive use for tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corposris (ringworm) and tinea versicolor under NDA 20-749.

Table I lists the three pivotal trials:

Table I
Summary of the Pivotal Studies

Study # (# of Centers)	Study Design (Country)	Treatment Arm (n)	N	Indication	Endpoint
SFF 301 (25)	Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled (Denmark, France, Iceland & Britain)	Lamisil, qd (1 Week) (119) Placebo, qd (1 Week) (59)	178	Tinea Pedis	Mycology Clinical Overall
SFF 351 (10)	Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled (US)	Lamisil, bid (1 Week) (104) Placebo, bid (1 Week) (49)	153	Tinea Pedis	Mycology Clinical Overall
SFF 303 (18)	Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled (France, Norway & Switzerland)	Lamisil, qd (1 Week) (102) Placebo, qd (1 Week) (49)	151	Tinea Corporis/Cruris	Mycology Clinical Overall

II. REVIEW:

Objective, Design, Patient Population, Primary Endpoint Variables and Statistical Methods:

According to the sponsor, all three studies are adequate and well-controlled and follow similar study designs and subject inclusion criteria. The protocols required that each subject to have a clinical diagnosis of the study indication. In all indications, this was confirmed by positive mycology (KOH and culture). On the basis of the positive microscopic results, treatment was initiated. The mycological examinations were performed on a target lesion, which was identified at the screening visit and consistently evaluated, both mycologically and clinically, throughout the study. All visible lesions were treated. Subjects were to use the dispensed durg (Lamisil or Placebo) for one week. The lesions were evaluated at Week-8. The safety evaluations consisted of adverse event reporting throughout the studies, and an overall assessment of tolerability at the last study visit.

According to the sponsor, the primary efficacy variable was "Effective Treatment at End of Study" in the intent-to-treat (ITT) population. The ITT population included any subject who was randomized, received at least one dose of the study drug, was not Delayed Exclusion (negative or missing mycology for protocol-specific organisms), and had at least one non-missing post-baseline efficacy assessment (microscopy, culture or clinical signs and symptoms).

In this review, primary endpoint variable is based on:
a) Culture Test
b) KOH Test, and
c) Clinical Cure
at Week-8 on ***Modified Intent-to-Treat population (MITT).*** MITT population included all patients who were randomized and received drug, regardless of their use, except patients with negative Culture or negative KOH at baseline. Patients with no post-baseline data were considered "Not Cured" or "Failures".

A subject was considered "Cured" if at Week-8, he/she had:
a) Negative Culture
b) Negative KOH, and
c) Positive Clinical Cure (Clinically Cured=100% clearing of clinical signs)

Comparability of the two treatment groups was assessed using an analysis of variance (ANOVA), with treatment effect for continuous variables and the Cochran Mantel-Haenszel test for discrete variables.

For the purpose of the analysis small centers with 10 or less subjects were combined.

To investigate the differences between the age groups, the variable age was categorized between two groups: younger than 60 or 60 and older.

In order for this drug product to demonstrate efficacy, the sponsor has to demonstrate the superiority of Lamisil Solution 1% to its Vehicle in all three pivotal studies.

Tinea Pedis

Study SFF 301:

Demographics:

A total of 178 subjects from twenty-five centers were enrolled into this study, out of which 119 subjects were randomized into the Lamisil and 59 into the Placebo arm.

Thirteen (11%) subjects in the Lamisil arm and 7 (12%) in the Placebo group dropped out.

Table II summarizes the demographics of all randomized subjects.

Table II
Demographics & Baseline Characteristics
All Randomized Subjects
Study SFF 301

	Whole Population (N=178)	Lamisil (n=119)	Placebo (n=59)	P-Value
Gender:				0.2
Female	43 (24%)	32 (27%)	11 (19%)	
Male	135 (76%)	87 (73%)	48 (81%)	
Race:				0.4
White	168 (94%)	112 (94%)	56 (95%)	
Black	6 (3%)	5 (4%)	1 (2%)	
Oriental	1 (1%)	1 (1%)	0 (0%)	
Other	3 (2%)	1 (1%)	2 (3%)	
Age (Mean ± Std)	41 ± 16	41 ± 16	41 ± 16	0.9
Baseline Culture:				0.4
Positive	122 (69%)	79 (66%)	43 (73%)	
Negative	56 (31%)	40 (34%)	16 (27%)	
Baseline KOH:				0.3
Positive	175 (98%)	118 (99%)	57 (97%)	
Negative	3 (2%)	1 (1%)	2 (3%)	

As shown in Table II, no statistically significant differences were found between the two treatment arms in regards to the demographics and baseline characteristics of the subjects ($p \geq 0.2$).

Clinical Efficacy Analysis & Results:

The primary efficacy endpoints (culture & KOH results and clinical cure) were analyzed based on MITT population. This excluded subjects who had negative culture or negative KOH results at baseline. A total of 119 subjects were included in these analyses.

Table III summarizes the results of the analysis for the primary endpoint variables at different time points:

Table III
Negative Results of Culture & KOH &
Positive Clinical Cure
Modified Intent-To-Treat (MITT) Population
Study SFF 301

	Lamisil (n=78)	Placebo (n=41)	P-Value
Negative Culture:			
Week-1	74 (95%)	16 (39%)	0.001
Week-2	67 (86%)	9 (22%)	0.001
Week-8	**62 (79%)**	**11 (27%)**	**0.001**
Negative KOH:			
Week-1	39 (50%)	13 (32%)	0.6
Week-2	34 (44%)	13 (32%)	0.01
Week-8	**63 (81%)**	**13 (32%)**	**0.001**
Positive Clinical Cure:			
Week-1	3 (4%)	0 (0%)	0.2
Week-2	14 (18%)	4 (10%)	0.2
Week-8	**44 (56%)**	**3 (7%)**	**0.001**
Cure*:			
Week-8	**36 (46%)**	**2 (5%)**	**0.001**

* Cure was defined as a subject who had negative culture & KOH and was completely clinically cured.

As seen in Table III, highly significant results (p=0.001) were observed when Lamisil was compared to the Placebo arm relative to negative culture and KOH and positive clinical cure at the end of treatment period. Controlling for center did not change these highly statistically significant results.

Safety Analysis:

The safety data was available only for 106 out of 119 subjects in the Lamisil group and 52 of the 59 subjects in the Vehicle arm. Table IV summarizes the results of signs and symptoms at the end of the treatment for the whole population.

Table IV
Signs & Symptoms
@ Week-8
Whole Population
Study SFF 301

	Lamisil (n=106)*	Placebo (n=52)*	P-Value
Desquamation:			0.001
Absent	65 (61%)	12 (23%)	
Mild	33 (31%)	18 (35%)	
Moderate	8 (8%)	17 (33%)	
Severe	0 (0%)	5 (10%)	
Erythema:			0.001
Absent	97 (92%)	28 (54%)	
Mild	9 (8%)	18 (35%)	
Moderate	0 (0%)	4 (8%)	
Severe	0 (0%)	2 (4%)	
Incrustation:			0.003
Absent	99 (93%)	41 (79%)	
Mild	6 (6%)	7 (13%)	
Moderate	1 (1%)	3 (6%)	
Severe	0 (0%)	1 (2%)	
Pruritus:			0.001
Absent	101 (95%)	35 (67%)	
Mild	4 (4%)	10 (19%)	
Moderate	1 (1%)	6 (12%)	
Severe	0 (0%)	1 (2%)	
Pustules:			0.002
Absent	106 (100%)	47 (90%)	
Mild	0 (0%)	4 (8%)	
Moderate	0 (0%)	1 (2%)	
Vesiculation:			0.2
Absent	106 (100%)	51 (98%)	
Mild	0 (0%)	1 (2%)	

As seen in Table IV, at the end of treatment period, statistically significant results ($p \leq 0.003$) were observed when Lamisil was compared to the Placebo arm, relative to the signs and symptoms, indicating better or same safety profile for Lamisil. No statistically significant difference was found when Lamisil solution was compared to Placebo in regards to vesiculation severity (P=0.2).

Study SFF 351:

Demographics:

A total of 153 subjects from ten centers were enrolled into this study, of these 104 subjects were randomized into the Lamisil and 49 into the Placebo arm.

Twenty (22%) subjects in the Lamisil arm and 11 (22%) in the Placebo group dropped out.

Table V summarizes the demographics of all randomized subjects.

Table V
Demographics & Baseline Characteristics
All Randomized Subjects
Study SFF 351

	Whole Population (N=153)	Lamisil (n=104)	Placebo (n=49)	P-Value
Gender:				0.6
Female	43 (28%)	28 (27%)	15 (31%)	
Male	110 (72%)	76 (73%)	34 (69%)	
Race:				0.2
White	112 (73%)	71 (68%)	41 (84%)	
Black	33 (22%)	27 (26%)	6 (12%)	
Oriental	3 (2%)	2 (2%)	1 (2%)	
Other	5 (3%)	4 (4%)	1 (2%)	
Age (Mean ± Std)	43 ± 16	43 ± 16	43 ± 16	0.9
Baseline Culture:				0.9
Positive	87 (58%)	59 (57%)	28 (58%)	
Negative	64 (42%)	44 (43%)	20 (42%)	
Baseline KOH:				
Positive	153 (100%)	104 (100%)	49 (100%)	
Negative	0 (0%)	0 (0%)	0 (0%)	

As shown in Table V, no statistically significant differences were found between the two treatment arms in regards to the demographics and baseline characteristics of the subjects ($p \geq 0.2$).

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Clinical Efficacy Analysis & Results:

The primary efficacy endpoints (culture & KOH results and clinical cure) were analyzed based on MITT population. This excluded subjects who had negative culture or KOH results at baseline. A total of 89 subjects were included in these analyses.

Table VI summarizes the results of the analysis for the primary endpoint variables at different time points:

Table VI
Negative Results of Culture & KOH &
Positive Clinical Cure
Modified Intent-To-Treat (MITT) Population
Study SFF 351

	Lamisil (n=60)	Placebo (n=29)	P-Value
Negative Culture:			
Week-1	55 (92%)	11 (38%)	0.001
Week-2	52 (87%)	6 (21%)	0.001
Week-8	50 (85%)	5 (17%)	0.001
Negative KOH:			
Week-1	25 (42%)	7 (24%)	0.1
Week-2	37 (62%)	7 (24%)	0.001
Week-8	50 (83%)	5 (17%)	0.001
Positive Clinical Cure:	2 (3%)	1 (3%)	1.0
Week-1	1 (2%)	1 (3%)	0.6
Week-2	14 (23%)	1 (3%)	0.03
Week-8			
Cure*:			
Week-8	11 (18%)	0 (0%)	0.01

* Cure was defined as a subject who had negative culture & KOH and was completely clinically cured.

As seen in Table VI, significant results ($p \leq 0.03$) were observed when Lamisil was compared to the Placebo arm relative to negative culture & negative KOH and positive clinical cure at the end of treatment period. Controlling for center did not change these highly statistically significant results.

Safety Analysis:

The safety data was available only for 81 out of 104 subjects who had used Lamisil solution and 38 of the 49 subjects in the Vehicle arm. Table VII summarizes the results of signs and symptoms at the end of the treatment for the whole population.

Table VII
Signs & Symptoms
@ Week-8
Study SFF 351

	Lamisil (n=81)	Placebo (n=38)	P-Value
Desquamation:			0.001
Absent	30 (37%)	4 (11%)	
Mild	38 (47%)	9 (24%)	
Moderate	12 (15%)	19 (50%)	
Severe	1 (1%)	6 (16%)	
Erythema:			0.001
Absent	53 (65%)	9 (24%)	
Mild	21 (26%)	15 (39%)	
Moderate	6 (7%)	13 (34%)	
Severe	1 (1%)	1 (3%)	
Incrustation:			0.7
Absent	79 (98%)	37 (97%)	
Mild	1 (1%)	0 (0%)	
Moderate	1 (1%)	1 (3%)	
Pruritus:			0.001
Absent	69 (85%)	16 (42%)	
Mild	9 (11%)	10 (26%)	
Moderate	2 (2%)	4 (11%)	
Severe	1 (1%)	8 (21%)	
Pustules:			
Absent	81 (100%)	38 (100%)	
Vesiculation:			0.5
Absent	80 (99%)	38 (100%)	
Moderate	1 (1%)	0 (0%)	

As seen in Table VII, at the end of treatment period, statistically significant results (p=0.001) were observed, when Lamisil was compared to the Placebo arm relative to Desquamation, Erythema and Pruritus indicating better safety profile for Lamisil. No statistically significant difference was found when Lamisil solution was compared to Placebo in regards to incrustation and vesiculation severity ($P \geq 0.5$).

Tinea Corporis/Cruris

Study SFF 303:

Demographics:

A total of 151 subjects from eighteen centers were enrolled into this study, where 102 subjects were randomized into the Lamisil and 49 into the Placebo arm.

Twenty-eight (27%) subjects in the Lamisil arm and 29 (59%) in the Placebo group had missing data at the end of the trial.

Table VIII summarizes the demographics of all subjects randomized.

Table VIII
Demographics & Baseline Characteristics
All Randomized Subjects
Study SFF 303

	Whole Population (N=151)	Lamisil (n=102)	Placebo (n=49)	P-Value
Gender:				0.9
Female	31 (21%)	21 (21%)	10 (20%)	
Male	120 (79%)	81 (79%)	39 (80%)	
Race:				0.7
White	133 (88%)	90 (88%)	43 (88%)	
Black	6 (4%)	5 (5%)	1 (2%)	
Oriental	10 (7%)	6 (6%)	4 (8%)	
Other	2 (1%)	1 (1%)	1 (2%)	
Age (Mean ± Std)	44 ± 18	43 ± 18	45 ± 17	0.7
Baseline Culture:				0.3
Positive	121 (81%)	80 (78%)	41 (85%)	
Negative	29 (19%)	22 (22%)	7 (15%)	
Baseline KOH:				1
Positive	148 (98%)	100 (98%)	48 (98%)	
Negative	3 (2%)	2 (2%)	1 (2%)	

As shown in Table VIII, no statistically significant differences were found between the two treatment arms in regards to the demographics and baseline characteristics of the subjects ($p \geq 0.3$).

Clinical Efficacy Analysis & Results:

The primary efficacy endpoints (culture & KOH results and clinical cure) were analyzed based on MITT population. This excluded subjects who had negative culture or KOH results at baseline. A total of 119 subjects were included in these analyses.

Table IX summarizes the results of the analysis for the primary endpoint variables at different time points:

Table IX
Negative Results of Culture & KOH &
Positive Clinical Cure
Modified Intent-To-Treat (MITT) Population
Study SFF 303

	Lamisil (n=78)	Placebo (n=41)	P-Value
Negative Culture:			
Week-1	71 (91%)	11 (27%)	0.001
Week-2	61 (78%)	14 (34%)	0.001
Week-8	**49 (64%)**	**11 (27%)**	**0.001**
Negative KOH:			
Week-1	58 (74%)	15 (37%)	0.001
Week-2	60 (77%)	15 (37%)	0.001
Week-8	**49 (63%)**	**8 (20%)**	**0.001**
Positive Clinical Cure:	6 (8%)	0 (0%)	0.07
Week-1	19 (24%)	2 (5%)	0.008
Week-2	**43 (55%)**	**6 (15%)**	**0.001**
Week-8			
Cure*:			
Week-8	**34 (44%)**	**2 (5%)**	**0.001**

* Cure was defined as a subject who had negative culture & KOH and was completely clinically cured.

As seen in Table IX, highly statistically significant results (p=0.001) were observed when Lamisil was compared to the Placebo arm relative to negative culture and negative KOH and positive clinical cure at the end of treatment period. Controlling for center did not change these highly statistically significant results.

Safety Analysis:

The safety data was available only for 74 out of 102 subjects who had used Lamisil solution and 20 of the 49 subjects in the Vehicle arm. Table X summarizes the results of signs and symptoms at the end of the treatment for the whole population.

Table X
Signs & Symptoms
@ Week-8
Study SFF 303

	Lamisil (n=74)	Placebo (n=20)	P-Value
Desquamation:			0.007
Absent	64 (86%)	11 (55%)	
Mild	7 (9%)	7 (35%)	
Moderate	3 (4%)	2 (10%)	
Erythema:			0.06
Absent	59 (80%)	11 (55%)	
Mild	12 (16%)	5 (25%)	
Moderate	2 (3%)	3 (15%)	
Severe	1 (1%)	1 (5%)	
Incrustation:			0.05
Absent	73 (99%)	18 (90%)	
Mild	1 (1%)	2 (10%)	
Pruritus:			0.006
Absent	69 (93%)	13 (65%)	
Mild	4 (5%)	5 (25%)	
Moderate	1 (1%)	1 (5%)	
Severe	0 (0%)	1 (5%)	
Pustules:			0.2
Absent	71 (96%)	18 (90%)	
Mild	3 (4%)	1 (5%)	
Moderate	0 (0%)	1 (5%)	
Vesiculation:			0.006
Absent	74 (100%)	18 (90%)	
Moderate	0 (0%)	2 (10%)	

As seen in Table X, at the end of treatment period, statistically significant results ($p \leq 0.05$) were observed when Lamisil was compared to the Placebo arm relative to Desquamation, incrustation, Pruritus and Vesiculation indicating better safety profile for Lamisil. No statistically significant difference was found when Lamisil solution was compared to Placebo in regards to Erythema and Pustules severity ($P \geq 0.06$).

Safety Analysis of the All Three Studies Combined:

The safety data for the three studies were combined and safety analyses were performed on the pooled data. Table XI summarizes the results of signs and symptoms at the end of the treatment for the whole population.

Table XI
Signs & Symptoms
@ Week-8
For All Studies Combined

	Lamisil (n=261)	Placebo (n=110)	P-Value
Desquamation:			0.001
Absent	159 (61%)	27 (25%)	
Mild	78 (30%)	34 (31%)	
Moderate	23 (9%)	38 (35%)	
Severe	1 (<1%)	11 (10%)	
Erythema:			0.001
Absent	209 (80%)	48 (44%)	
Mild	42 (16%)	38 (35%)	
Moderate	8 (3%)	20 (18%)	
Severe	2 (1%)	4 (4%)	
Incrustation:			0.01
Absent	251 (96%)	96 (87%)	
Mild	8 (3%)	9 (8%)	
Moderate	2 (1%)	4 (4%)	
Severe	0 (0%)	1 (1%)	
Pruritus:			0.001
Absent	239 (92%)	64 (58%)	
Mild	17 (7%)	25 (23%)	
Moderate	4 (2%)	11 (10%)	
Severe	1 (<1%)	10 (9%)	
Pustules:			0.01
Absent	258 (99%)	103 (94%)	
Mild	3 (1%)	5 (5%)	
Moderate	0 (0%)	2 (2%)	
Vesiculation:			0.02
Absent	260 (100%)	107 (97%)	
Mild	0 (0%)	3 (3%)	
Moderate	1 (<1%)	0 (0%)	

As seen in Table XI, at the end of treatment period, statistically significant results ($p \leq 0.05$) were observed when Lamisil was compared to the Placebo arm relative to Desquamation, incrustation, Pruritus and Vesiculation indicating better safety profile for Lamisil.

Subset Analysis:

The three data sets were merged and subset analysis was done based on gender, age category (younger than 60, 60 and older). The highly significant results were observed in each sub-category ($p=0.001$), indicating a better safety profile for Lamisil Solution.

III. CONCLUSIONS:

The results of the analyses of efficacy of Studies SFF 301 & SFF 351 demonstrate that Lamisil Topical Solution, 1% is statistically significantly better than Placebo in the treatment of Tinea Pedis at Week-8 ($p \leq 0.03$).

The results of the analyses of efficacy of Study SFF 303 demonstrate that Lamisil Topical Solution, 1% is statistically significantly better than Placebo in the treatment of Tinea Corporis/Cruris at Week 8 ($p=0.001$).

Lamisil had better or same safety profile compared to Placebo arm relative to Desquamation, Incrustation, Pruritus, Vesiculation, Erythema and Pustules severity.

The subset analyses relative to gender and age category (<60, ≥60) also demonstrated similar statistically significant results favoring Lamisil over Placebo ($p=0.001$).

Thus, the studies SFF301 and SFF351 and SFF303 provide statistical evidence to support the sponsor's claim of efficacy and safety of Lamisil Topical Solution, 1%, in the treatment of Tinea Pedis and Tinea Corporis/Cruris.

/S/ 11/19/99

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