Study Procedures

Eligible study patients were treated on an outpatient basis. The diagnosis of tinea pedis was made presumptively by a KOH wet mount positive for dermatophyte for entry. The culture taken at Baseline was to be positive to confirm the diagnosis and for the patient to continue in the study. A target lesion was identified on one of the feet and scored at the Baseline visit for clinical signs and symptoms, including fissuring, erythema, maceration, vesicles, desquamation, exudation, pruritus and burning/stinging, and then compared to this score at each of the subsequent six visits.

Formulation (The same approved formulation was used in each study.)

Name:	SF 86-327 (Terbinafine)
Chemical Name:	(E)-N-(6,6-Dimethyl-2-hepten-4-inyl)-N-methyl-1-naphthalenemethanamine hydrochloride
Formulation:	1% SF 86-327 by weight in a cream base containing benzyl alcohol, cetyl palmitate, cetyl alcohol, isopropyl myristate, and deionized, filtered water

Study Evaluations

The response to treatment was evaluated by mycological and clinical assessment of the target lesion at each follow-up visit. Global clinical assessments of all lesions were compared to baseline assessments at each follow-up visit.

Effectiveness Parameters

1) Clinical Signs and Symptoms of the Target Lesion

Response to treatment was measured by the following clinical signs and symptoms of the disease and was scored in reference to the 'target lesion' at each study visit as follows:

Signs: fissuring, erythema, maceration, vesiculation, exudation, desquamation

Symptoms: pruritus and burning/stinging

Scoring:

0 = none	complete absence of any signs or symptoms
1 = mild	obvious but minimal involvement
2 = moderate	something that is easily noted
3 = severe	quite marked

2) Physician's Assessment of Overall Disease Severity of all lesions on the feet **(Baseline, Days 8, 15 and 29 and Weeks 6, 9 and 12).** The overall severity of all lesions on the feet was assessed according to the scoring system described above.

3) Physician's Rating Of Global Clinical Response to Treatment of All Treated Lesions on the Feet Including the Target Lesion (Day 29 and Weeks 6 and 12). The global clinical response to treatment of all treated lesions will be rated as follows:

Clinical Cure:	Complete improvement from Baseline
Marked Improvement:	Approximately 75% or more improvement, but less than complete improvement

Moderate Improvement:	Approximately 50% or more improvement, but less than 75 % improvement
Slight Improvement:	Less than 50% improvement
No Change:	No detectable improvement
Exacerbation	Increase in overall severity of the condition

4) Patient evaluation: Overall Assessments of Therapy and Tolerability by Patient Opinion(Day 29 and Weeks 6 and 12).

The patient was asked to rate the overall efficacy of treatment and to overall tolerability of treatment according to the following scale:

0 = poor 1 = fair 2 = good 3 = very good or 4 = excellent

5) Efficacy

Conversion to negative mycology (KOH/culture results) of the target lesion was the primary response variable to compare efficacy of terbinafine between the two treatment regimens. In addition, clinical signs and symptoms were considered.

Effective Therapy:

Complete Cure:	KOH and culture are negative, no residual signs and symptoms
Mycological Cure:	KOH and culture are negative, mild (score of 1) residual erythema and/or maceration and/or scaling and/or pruritus/ and/or fissures (total sum of scores of 2 or less).
Ineffective Therapy:	All other responses to therapy.

Delayed exclusions were patients with positive microscopy that was not subsequently confirmed by mycological culture, and those whose culture demonstrated the presence of other pathogens.

8.1 Indication # 1 Tinea Pedis (interdigital type)

8.1.1 Reviewer's Trial #1 Sponsor's Protocol # 2-1 (Study Code: SAN 2506-01) (Study dates: 07-11-90 to 01-10-91)

Title: "A Double-Blind, Parallel, Multicenter Trial Comparing the Efficacy and Safety of 1% Terbinafine Cream with Placebo Cream in the Treatment of Tinea Pedis (Interdigital Type) Athlete's Foot"

8.1.1.1 Objective/Rationale

The objective of this study is to compare the efficacy and safety of one week treatment of 1% terbinafine cream to placebo over a six week period in the treatment of tinea pedis (interdigital).

8.1.1.2 Design

This study was a stratified, multicenter, parallel-group, double-blind clinical trial.

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

Table 1. Patient Disposition

Pt. Population	Terbinafine	Vehicle	Total
Entered	38	39	77
Delayed excel.	4	4	8
Dropouts	1	1	2
Evaluable cases	33	34	67

Table 2. Demographics

Pt. Population	Terbinafine	Vehicle	Total
male/female	26/7	31/3	57/10
age (min/max) yrs.	19/72	14/74	14/74
age (mean) yrs.	43.1	43	43.1
Eval. For efficacy	33	34	67

Racial Distribution

Fifty-one (76%) of evaluable patients were Caucasian, with 14 (21%) Black, and 2 (3%) Hispanic.

Infecting organisms

The infecting organisms were T. rubrum (79%), T. mentagrophytes (3%), E. floccosum (9%), and T. tonsurans (3%).

8.1.1.4.2 Efficacy endpoint outcomes

Efficacy endpoints were as follows:

1) Mycological Cure defined as KOH, culture negative, and signs <=2.
2) Complete Cure defined as KOH and culture negative with no residual signs and symptoms.

For Mycological Cure at the end of one week treatment, statistical review demonstrated that statistical significance over vehicle occurred by Week-2 ($p \leq 0.004$) and by Week-6 ($p \leq 0.001$).

Statistical significance was demonstrated for Complete Cure at the end of one week treatment with terbinafine at Week-2 ($p \leq 0.035$) and by Week-6 ($p \leq 0.006$)

8.1.1.4.3 Safety outcomes

There were 77 patients included in the safety analysis. In the terbinafine treatment group there were 38 (49%) and 39 (51%) evaluated for safety in the vehicle group.

Table 3. Disposition/Adverse Events

Pt. Population	Terbinafine	Vehicle	Total
Discontinued safety	0	0	0
Discont. Ineffect. Tmt.	0	4	4
Subj. With Adverse Events	5	5	10

Table 4. Adverse Events

System/Event	Terbinafine	Vehicle
Skin		
Cracking skin/toes	1 (3%)	0 (0%)
Itching	1 (3%)	0 (0%)
Stinging right foot	1 (3%)	0 (0%)
Tenderness below target site	0 (0%)	1 (3%)
Respiratory		
Cough	0 (0%)	1 (3%)
Nasal congestion	0 (0%)	1 (3%)
URI	2 (5%)	0 (0%)
Body As a Whole		
Back pain	0 (0%)	1 (3%)
Musuloskeletal		
Fractured right finger	0 (0%)	1 (3%)
Sprained left ankle	1 (3%)	0 (0%)
Totals		
Total with event	5 (13%)	5 (13%)
Total enrolled	38	39

Skin related adverse events follow. No patient withdrew from the study because of these

reported events.

Table 5. Adverse Reactions

Skin	Terbinafine	Vehicle
Cracking skin/toes	1 (3%)	0
Itching	1 (3%)	0
Stinging foot	1 (3%)	0
Tenderness	0	1 (3%)
Total Patients enrolled	38	39

8.1.1.5 Conclusions Regarding Efficacy Data and Safety

Final Treatment Visit (FTV), also known as End of Therapy (EOT) plus two weeks (FTV + 2 weeks) is the Proof of Cure (POC) time point. This visit is considered the primary efficacy endpoint for proof of treatment success. Therefore, Study 2-1, supports the sponsor's efficacy claim for twice daily applications for one week with terbinafine HCL cream, 1% in treatment of interdigital tinea pedis.

There were three adverse events reported which appeared to be drug related. The AEs were cracking skin/toes, itching, and stinging right foot of moderate to mild severity assessments. There were no reported withdrawals due to adverse events. Terbinafine HCl cream, 1% appears to be well tolerated.

It should be noted that the study was open to patients 5 years of age or older; however, the youngest patient enrolled was 19 years of age.

8.1.2 Reviewer's Trial #2 (interdigital) Sponsor's Protocol # 2-2 (Study Code: SAN 2506-02)

(Study dates: August 22, 1990 to December 21, 1990)

Title: "A Double-Blind, Parallel, Multicenter Trial Comparing the Efficacy and Safety of 1% Terbinafine Cream with Placebo Cream in the Treatment of Tinea Pedis Athlete's Foot (Interdigital Type)"

8.1.2.1 Objective/Rationale

The objective of this study is to compare the efficacy and safety of one week treatment of 1% terbinafine cream to placebo over a six week period in the treatment of tinea pedis (interdigital).

8.1.2.2 Design

This study was a stratified, multicenter, parallel-group, double-blind clinical trial.

8.1.2.4 Results

8.1.2.4.1 Populations enrolled/analyzed

Table 6. Disposition

Pt. Population	Terbinafine	Vehicle	Total
Entered	56	54	110
Delayed excel.	6	7	13
Dropouts	3	2	5
Evaluable cases	47	45	92

Table 7. Demographics

Pt. Population	Terbinafine	Vehicle	Total
male/female	33/14	36/9	69/23
age (min/max) yrs.	15/74	9/74	9/74
age (mean) yrs.	40.9	36.4	38.7
Eval. For efficacy	47	45	92

Racial Distribution

Of the evaluable patients, 23 (49%) patients were Caucasian, 18 (38%) Hispanic 14 (21%) , and 10 (11%) Black.

Infecting Organisms

The majority of the patients were infected with T. rubrum (68%). Other infecting organisms were T. mentagrophytes (23%) and E. floccosum (9%).

8.1.2.4.2 Efficacy endpoint outcomes

Efficacy endpoints were as follows:

1) Mycological Cure defined as KOH, culture negative, and signs <=2.
2) Complete Cure defined as KOH and culture negative with no residual signs and symptoms.

For Mycological Cure at the end of one week treatment, statistical review concluded that significance over vehicle was demonstrated by Week-4 ($p \leq 0.002$) and by Week-6 ($p \leq 0.001$).

Statistical significance was demonstrated for Complete Cure at the end of one week treatment with terbinafine at Week-4 ($p \leq 0.006$) and by Week-6 ($p \leq 0.001$)

8.1.2.4.3 Safety outcomes

There were 77 patients included in the safety analysis. In the terbinafine treatment group there were 38 (49%) and 39 (51%) evaluated for safety in the vehicle group.

Table 8. Disposition/Adverse Events

Pt. Population	Terbinafine	Vehicle	Total
Discontinued safety	0	0	0
Discont. Ineffect. Tmt.	2	6	8
Subj. With Adverse Events	1	2	3

Table 9. Adverse Events

	Terbinafine	Vehicle
Body As A Whole		
Headache	1 (2%)	0 (0%)
Migraine headache	0 (0%)	1 (2%)
Respiratory		
Common cold	0 (0%)	1 (2%)
Totals		
Number with an event	1 (2%)	2 (4%)
Total receiving treatment	56	54

8.1.2.5 Conclusions Regarding Efficacy Data and Safety

Study 2-2 supports the sponsor's efficacy claim for twice daily applications for one week with terbinafine HCL cream, 1% in treatment of interdigital tinea pedis.

There were no adverse events reported which appeared to be drug related. There were no reported withdrawals from the study due to adverse events.

It should be noted that the study was open to patients 5 years of age or older; however, the youngest patients enrolled were two 15 year old patients with exposure to active drug.

8.1.3 Reviewer's Trial # 3 **Sponsor's Protocol # SAN 2508-01**

Study Dates: The study began on 07-29-91 and the last patient completed the study on 03-16-92.

Title: "A Double-Blind, Parallel, Multicenter Trial Comparing the Efficacy and Safety of 1% Terbinafine Cream with 1% Clotrimazole Cream the in the Treatment of Tinea Pedis (Interdigital Type) Athlete's Foot"

8.1.3.1 Objective/Rationale

The specific objectives of this study were multiple comparisons of the efficacy and safety as follows:

1) One week application of 1% terbinafine cream b.i.d. with four weeks application of 1% terbinafine cream b.i.d.
2) One week application of 1% terbinafine cream b.i.d. with one week application of 1% clotrimazole cream b.i.d.
3) One week application of 1% terbinafine cream b.i.d. with four weeks application of 1% clotrimazole cream b.i.d.
4) One week application of 1% clotrimazole cream b.i.d. with four weeks application of 1% clotrimazole cream b.i.d.

8.1.3.2 Design

This was a comparative superiority study and not vehicle-controlled. This study was a stratified, multicenter, parallel-group, double-blind clinical trial. The study was double-blind within two strata of one-week application and four-week application of terbinafine 1% cream in the study of interdigital tinea pedis.

Patients were randomly assigned to one of four of the following treatment groups:

1% terbinafine cream b.i.d. for a period of one week
1% terbinafine cream b.i.d. for a period of four weeks
1% clotrimazole cream b.i.d. for a period of one week
1% clotrimazole cream b.i.d. for a period of four weeks

Patients applied the study medication either twice daily for one week with evaluation at Day 8 at the end of treatment, and at follow-up visits Days 15 and 29, and Weeks 6, 9 and 12; or twice daily for four weeks and returned for evaluation at Days 8 and 15 during treatment, at Day 29 at the end of treatment and at follow-up visits at Weeks 6, 9 and 12. The purpose of the lengthy follow-up period was to evaluate the duration of maintenance of clearing of target lesions.

Formulations

1) Study Drug SF 86-327 (Terbinafine)
2) Comparative Drug
   Name: clotrimazole
   Formulation: 1% clotrimazole USP by weight in a cream base containing benzyl alcohol, cetearyl alcohol, polysorbate, sorbitan monostearate and deionized, filtered water.

8.1.3.3.1 Population

Two hundred eighteen patients were enrolled in this eight center, double-blind, randomized, parallel-group study of the use of terbinafine 1% cream twice daily compared to clotrimazole 1% cream twice daily. The study was conducted in the United States.

8.1.3.4 Results

8.1.3.4.1 Populations enrolled/analyzed

Table 10. Demographics:

	Terbinafine		Clotrimazole		Total
	1 Week	4 Weeks	1 Week	4 Weeks	
Male/Female	36/11	34/12	39/11	37/13	146/47
Age (mean) yrs.	40.2	37.3	34.8	39.8	38.0

Table 11. Disposition

	Terbinafine		Clotrimazole		Total
	1 Week	4 Weeks	1 Week	4 Weeks	
Total Entered	54	55	53	56	218
Delayed Exclusion	6	8	3	5	22
Admitted/NoFUP	1	1	0	1	3
Evaluable Cases	47	46	50	50	193
Discontinued safety	0	0	0	0	0
Discontinued Ineffect. Tmt	2	1	8	1	12
Subjects with ADR	17	17	11	13	58

Infecting organisms at baseline were:

Trichophyton rubrum	82%
Trichophyton mentagrophyton	14%
Epidermophyton floccosum	4%

8.1.3.4.2 Efficacy Endpoint Outcome

Statistical significance was shown by week 9 for mycological cure for the one week terbinafine 1% cream treatment group as compared to the one week clotrimazole 1% cream treatment group ($p=0.001$ at 9 weeks, $p \leq 0.017$ at 12 weeks, and $p \leq 0.003$ at the end of study, LOCF). No other differences were statistically significant.

For complete cure, there were no statistically significant difference between one week terbinafine 1% cream treatment group as compared to the any of the other clotrimazole 1% cream treatment groups (one week and four weeks) at any time points. All treatment groups showed some improvement.

8.1.1.4.3 Safety Outcomes

Table: 12 (Sponsor's Table 22 B)

Drug related adverse events were as follows:

Drug-Related Adverse Events Treatment Group				
System/Event	**Terbinafine**		**Clotrimazole**	
	1 Week	4 Weeks	1 Week	4 Weeks
Skin				
Burning	0 (0%)	1 (2%)	3 (6%)	0 (0%)
Itching	0 (0%)	2 (4%)	2 (4%)	1 (2%)
Pruritus	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Digestive				
Metallic taste in mouth	1 (2%)	0 (0%)	0 (0%)	0 (0%)

Tables 22 B (Vol. 14, pgs. 14 073 & 14 074) and Table 22 A (Vol. 14, pg. 14 075) were extracted from the sponsor's submission.)

Table 13.

(Table 22A)
ADVERSE EVENTS
(Page 1 of 2)

System/Event	Treatment Group: Terbinafine One week		Clotrimazole	
	1 week	4 weeks	1 week	4 weeks
Skin				
Blisters	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Burning	0 (0%)	1 (2%)	3 (6%)	0 (0%)
Burning (thigh)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Herpes simplex L buttocks	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Ingrown toenail	0 (0%)	0 (0%)	2 (4%)	0 (0%)
Itching	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Pain (toe area)	0 (0%)	1 (2%)	1 (2%)	0 (0%)
Pruritus	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Soreness	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Digestive				
Food poisoning	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Gingivitis	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Metallic taste in mouth	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Reflux	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Stomach upset	1 (2%)	1 (2%)	0 (0%)	0 (0%)
Respiratory				
Allergies	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Cold/Sinus/Nasal congestion	4 (7%)	0 (0%)	2 (4%)	1 (2%)
Cough	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Laryngoscopy	0 (2%)	0 (0%)	0 (0%)	1 (2%)
Laryngopharyngitis	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Microlaryngoplasty with laser	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Pneumonia	1 (2%)	1 (2%)	0 (0%)	0 (0%)
Rhinorrhea	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Sinus infection	0 (0%)	1 (2%)	0 (0)	0 (0%)
Sore throat	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Strep throat	0 (2%)	0 (0%)	0 (0%)	1 (2%)
URI	3 (2%)	2 (4%)	1 (2%)	3 (5%)

Table 13.

(Table 22A)
ADVERSE EVENTS
(Page 2 of 2)

System/Event	Treatment Group: Terbinafine One week		Clotrimazole	
	1 week	4 weeks	1 week	4 weeks
Body As a Whole				
Excisional biopsy	0 (2%)	1 (2%)	0 (0%)	0 (0%)
Influenza	4 (7%)	6 (11%)	0 (0%)	1 (2%)
Musculoskeletal				
Arthritis	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Back pain	2 (4%)	0 (0%)	1 (2%)	0 (0%)
Foot pain	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Fractured (L) clavicle	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Fractured (L) fibula	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Shoulder out of join	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Sprained wrist	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Swollen foot	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Swollen thigh	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Urogenital				
Burning on urination	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Lanced hemorrhoid	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Prostatitis	0 (0%)	0 (0%)	1 (2%)	0 (0%)
UTI	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Special Senses				
Loss of perep. vision (R) eye	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Nervous System				
Headache	2 (4%)	0 (0%)	0 (0%)	0 (0%)
Seizure	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Syncopal episode	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Disorientation	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Total with event	17 (31%)	17 (31%)	11 (21%)	13 (23%)
Total enrolled	54	55	53	56

8.1.4.5 Conclusions Regarding Efficacy Data and Safety

Study SAN 2508-01 is suggestive of the efficacy of one week of terbinafine treatment for interdigital tinea pedis. However, since statistical significance is not apparent until week 9 for mycological cure of one week terbinafine 1% cream treatment as compared to the one week clotrimazole 1% cream treatment, the clinical relevance is unclear. It would be unreasonable to claim superiority based on one study for mycological cure at nine weeks. An OTC consumer may not perceive a clinical benefit as useful if they must wait 8 weeks. There was no placebo (vehicle) group in this study. A second independent multicenter study of similar design was not submitted in support of the superiority over comparator claim.

One adverse reaction of interest; however unexplained, is the metallic taste in the mouth reported in patient # 354, a 55 year old female. Metallic taste has been reported with oral administration of terbinafine.

From the line listings, Appendix 1A (Vol. 15), there were 9 pediatric patients enrolled in terbinafine treatment groups. The ages and number of pediatric patients enrolled were: three 12 year old, three 14 year old, two 15 year old, and one 17 year old.. There were two enrolled in the 4 week terbinafine treatment group. There were only two adverse events listed among these pediatric patients enrolled (a sore throat in pt. #227 and an upset stomach in pt.# 129). Therefore an inference could be made that these pediatric patients tolerated the treatment well.

8.1.4 Reviewer's Trial #4 (Tinea Pedis, interdigital type) Sponsor's Study# SF0040

Dates: The start date was August 13, 1991 and the last patient completed the study on October 5, 1992 conducted in the United Kingdom.

Title: "A Double-Blind, Randomized, Parallel Group Study to Compare Lamisil ® (Terbinafine) 1% Cream Given for One Week with Canesten® (Clotrimazole) 1% Cream Given for Four Weeks in Tinea Pedis (Athlete's Foot Type)."

8.1.4.1 Objective/Rationale

The objective of the study is to compare the safety and efficacy Lamisil® 1% cream, applied twice daily, for one week with clotrimazole 1% cream, applied twice daily, for four weeks in the treatment of tinea pedis (athlete's foot type).

8.1.2.2 Design

The design is problematic. Vehicle was applied for three weeks following one week application of terbinafine cream. The sponsor acknowledges that vehicle cream (placebo cream) applied for three weeks following the application of the active substance may have helped maintained the levels of the active substance in the stratum corneum by acting as a chemical occlusive dressing. Therefore, this study was primarily reviewed for safety.

Study Plan

The study period was six weeks. Four weeks of treatment and a follow-up period of two weeks.

	Week 1	Week 2	Week 3	Week 4
Lamisil	1 active Lamisil tube	1 placebo Lamisil tube	1 placebo Lamisil tube	1 placebo Lamisil tube
Canesten	1 active Canesten tube	1 active Canesten tube	1 active Canesten tube	1 active Canesten tube

Although is a tinea pedis study, fungal lesions occurring elsewhere on the body could be treated.

Patient population

A total of 256 patients entered the study. One-hundred-thirty-one patients were randomized to Lamisil cream group and 125 to Canesten treatment group. A total of 211 patients were evaluable.

Table 14. Demographics (All randomized patients)

	Total	Lamisil	Canesten
Male/Female	190/96	95/36	95/30
Age (min/max)	12/81	12/81	12/74

Ninety-three percent of the patients in the Lamisil group were Caucasian and 7% were Asian.

8.1.2.4 Results

Table 15. Disposition

	Total	Lamisil	Canesten
Total entered	256	131	125
Withdrawals	45	24	21
Total evaluated	211	107	104

Infecting organisms at entry were:

T. rubrum	64%
T. mentragrophytes	29%
E. flocossum	7%

8.1.4.4.2 Efficacy Endpoint Outcomes

The study design is problematic in support of this application. There was no vehicle control group. The study was reviewed for safety. The sponsor's statistical analysis for this study was not validated.