CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-071

MICROBIOLOGY REVIEW

DIVISION OF ANTIINFECTIVE AND OPHTHALMOLOGY PRODUCTS (DAIOP)
CLINICAL MICROBIOLOGY REVIEW
CONSULTATION FOR DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (DDDP)

NDA 22-071 / SN-000 **DATE REVIEW COMPLETED: 05/20/07**

Primary Clinical Microbiology Reviewer: Harold V. Silver / DAIOP

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
e-NDA 22-071 / SN-000	09/08/06	09/08/06	11/27/06
e-NDA 22-071 / BL	03/09/07	03/09/07	03/09/07

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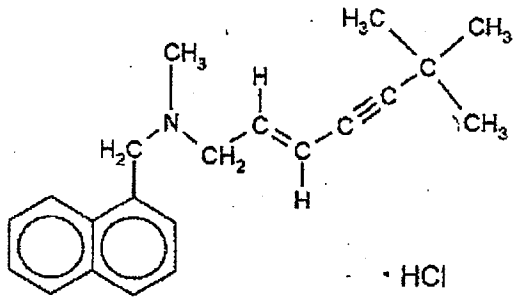
PURPOSE OF SUBMISSION:
The Applicant, Novartis Pharmaceuticals Corporation, submits e-NDA 22-071, Lamisil® (terbinafine hydrochloride) "film-coated" Tablets (called "mini-tablets"), 125 mg terbinafine base and 187.5 mg terbinafine base, a **new** pediatric formulation. The drug product is for the treatment of tinea capitis in children _____ b(4

DRUG NAME(s):
Proprietary: Lamisil® (terbinafine hydrochloride) Mini-tablets
Non-Proprietary/USAN: terbinafine (expressed as terbinafine HCl)
Codes: SFO 327 = 125 mg and 187.5 mg film-coated Tablets
Reference # 7005419 = 125 mg / 7005415 # = 187.5 mg
CAS Registry ID: *CAS-78628-80-5*

DRUG NAME, CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA and MOLECULAR WEIGHT:
Drug Name: Lamisil® (terbinafine hydrochloride) Mini-tablets
Chemical Name:
(E)-*N*-(6,6-Dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalenemethanamine hydrochloride

Structure:



terbinafine HCl

Molecular Formula: $C_{21}H_{26}ClN$ / **Molecular Weight:** 327.90

DOSAGE FORM: Film-coated tablets (called "mini-tablets")
POTENCY:
- There is 4.6875 mg of terbinafine hydrochloride in each mini-tablet (corresponding to 4.167 mg of terbinafine base).
-- Two fill sizes are proposed: 30 and 45 minitablets pe———— . corresponding to 125 mg and 187.5 mg of terbinafine base, respectively. b(4)

PHARMACOLOGICAL DRUG CATEGORY: Synthetic allylamine antifungal.

PROPOSED "INDICATION": Treatment of tinea capitis in children (———— , b(4)
PROPOSED DOSAGE AND ADMINISTRATION:
- The drug product, Lamisil® (terbinafine hydrochloride) mini-tablets is immediate-release, film-coated mini-tablets packaged in laminated aluminum "———— pouches. b(4)
- The entire content of a————s to be poured onto a spoonful of a soft food, and children (4 to 12 years of age) swallow the combination of food and mini-tablets without chewing.
- The drug product is taken once-a-day for 6 weeks based upon body weight: (< 25 kg = 125 mg terbinafine / day), 23 to 35 kg = 187.5 mg terbinafine / day, and (> 35 kg = 250 mg terbinafine / day), respectively.
- Each ———— is intended for a single dose.
- For more information, refer to **Clinical Study C2301 – Administration** in this Clinical Microbiology Review.

RELATED DOCUMENTS:
IND 57,093: Novartis Pharmaceuticals Corporation, LAMISIL (terbinafine hydrochloride tablets), for treatment of tinea capitis in children.
———— ← ¬ b(4)
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NDA 20-192: Novartis Pharmaceuticals Corporation, Lamisil (terbinafine hydrochloride) Cream, for treatment of tinea capitis in pediatric patients due to specific organisms, FDA "approval" Date: 12/30/1992.

NDA 20-539: Novartis Pharmaceuticals Corporation, Lamisil (terbinafine HCl) Tablets, for treatment of onychomycosis, FDA "approval" Date: 05/10/1996.

NDA 20-749: Novartis Consumer Health, Inc., Lamisil (terbinafine HCl) Solution 1%, Treatment of tinea versicolor, FDA "approval" Date: 10/17/1997.

NDA 20-846: Novartis Pharmaceuticals Corporation, Lamisil DermGel 1%, for treatment of tinea (pityriasis) versicolor, tinea pedis (athlete's foot), tinea corporis (ringworm) or tinea cruris jock itch) , FDA "approval" Date: 04/29/1998.

NDA 20-980: Novartis Consumer Health, Inc., and Novartis Pharmaceuticals Corporation, Lamisil (terbinafine cream) Cream 1%, for treatment of tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm) due to *Epidermophyton floccosum*, *Trichophyton mentagrophytes* and *Trichophyton rubrum*, FDA "approval" Date: 03/09/1999.

NDA 21-124: Novartis Pharmaceuticals Corporation, Lamisil (terbinafine hydrochloride) Solution 1%, for treatment of interdigital tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm), FDA "approval" Date; 03/17/2000.

DMF ——and DMF—— b(4)

REMARKS:

This is a DDDP Consult request for a Clinical Microbiology Review on Novartis Pharmaceuticals Corporation submission, e-NDA 22-071, Lamisil® (terbinafine hydrochloride "film-coated" tablets (called "mini-tablets"), 125 mg terbinafine base and 187.5 mg terbinafine base. a **new** pediatric formulation, for the treatment of tinea capitis in children ———————— b(4)

EXECUTIVE SUMMARY

NDA 22-071

(Novartis Pharmaceuticals Corporation)
Lamisil® (terbinafine hydrochloride) film-coated Tablets (mini-tablets)

INTRODUCTION

The Applicant, Novartis Pharmaceuticals Corporation, submits e-NDA 22-071, Lamisil® (terbinafine hydrochloride) "film-coated" Tablets (called "mini-tablets"), 125 mg terbinafine base and 187.5 mg terbinafine base, a **new** pediatric formulation. The drug product is for the treatment of tinea capitis in children [redacted]

Two Phase 3 clinical programs are proposed to evaluate the efficacy and safety of the terbinafine **new** pediatric formulation in children with tinea capitis. The indication being sought is: "[redacted] b(4)

The drug substance, terbinafine hydrochloride, is the same drug substance used in marketed Lamisil Tablets (NDA 20-539), Cream (NDA 20-980), and Solution (NDA 20-749).

Two Phase 3 studies were conducted to determine if terbinafine is an efficacious and safe treatment for tinea capitis in children. The dose applied in the study is expected to increase the response rate observed in earlier studies. The safety profile of this new dose is expected to be similar to the safety profile of the currently recommended dosage outside the US.

The Applicant conducted the following 2-Phase 3 (same design) pivotal studies:

1. **Study CSFO327C 2301**
   A randomized, investigator blinded, active-controlled, parallel-group study to **compare** the efficacy and safety of 6-week treatment with **terbinafine** new pediatric formulation versus 6-week treatment with **griseofulvin** pediatric suspension in children with tinea capitis.

2. **Study CSFO327C 2302**
   A randomized, investigator blinded, active-controlled, parallel-group study to **compare** the efficacy and safety of 6-week treatment with **terbinafine** new pediatric formulation versus 6-week treatment with **griseofulvin** pediatric suspension in children with tinea capitis.

Efficacy Assessments
Efficacy assessments includes:, 1) mycology, 2) clinical signs and symptoms, and 3) a global physician assessment i.e., TSSS = Total signs and symptoms score).

Mycology
Samples for KOH microscopy and for fungal culture evaluation are taken at screening, Visit 3 (Week 3, Day 22), Visit 4 (Week 6, Day 42) and at the end of study Visit 5 (Week 10, Day 70), or at early discontinuation, and are sent to a central mycology laboratory.

- **Laboratory Data**
  Laboratory samples are processed centrally through the [redacted] and [redacted] laboratories and the results are then sent electronically to Novartis. b(4)
- For more detailed instructions regarding sample collection for microscopy and culture, refer to the following **OVERALL SUMMARY OF EFFICACY RESULTS – MYCOLOGICAL EVALUATIONS** in the **EXECUTIVE SUMMARY** in this review.

BACKGROUND

Tinea capitis ("scalp ringworm") is a dermatophyte infection of the scalp hair follicles that occurs primarily in children. However, adults exposed to *Trichophyton tonsurans* infections and patients with AIDS may develop tinea capitis. The primary clinical signs associated with tinea capitis are hair loss, hair breakage, scaling, various degrees of erythema, pustules and pruritus. In addition, cervical or occipital lymphadenopathy may occur in some children.
The infection is caused by a relatively small group of dermatophytes in the genera *Trichophyton* and *Microsporum*. The predominant organisms vary geographically:

1. ***Trichophyton tonsurans*** on the **North American** continent, United Kingdom, Mexico, Central and South America
2. *Trichophyton violaceum* in Africa and the Middle East
3. *Microsporum canis* in Eastern Europe

In the United States, *Trichophyton tonsurans* replaces *Microsporum audouinii* and *Microsporum canis* as the most common cause of tinea capitis.

GENERAL NON-CLINICAL INFORMATION

MICROBIOLOGY

Description
Terbinafine HCl is a synthetic allylamine lipophilic antifungal with a broad spectrum of antifungal activity.
Mechanism of Action
Allylamines, e.g., terbinafine, inhibit ergosterol biosynthesis, an essential component of fungal cell membranes, via inhibition of squalene epoxidase enzyme. The effect finally causes fungal cell death primarily due to the increased membrane permeability mediated by the accumulation of high concentrations of squalene but not due to ergosterol deficiency.
Antimicrobial Spectrum of Activity
Terbinafine is active in vitro against the following fungi, *Malassezia furfur*, *Candida* spp., *Aspergillus* spp. *Sporothrix schenckii*, *Penicillium marneffei*, *Cryptococcus neoformans*, *Trichosporon* spp., and *Blastoschizomyces*.
- **NDA 20-539 / SN-001**
  Novartis Pharmaceuticals Corporation, Lamisil [terbinafine hydrochloride tablets (EQ 250 mg base)] Tablets, FDA "approval" date: May 10, 1996. The current FDA "approved" (01/21/2004), Package Insert Label reads as follows:
  INDICATION AND USAGE
  "LAMISIL® (terbinafine hydrochloride tablets) Tablets are indicated for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes....."
  MICROBIOLOGY
  - Terbinafine has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section: *Trichophyton mentagrophytes* and *Trichophyton rubrum*.

Fungistatic / Fungicidal Effects
Depending on the concentration of the drug and the fungal species test *in vitro*, terbinafine hydrochloride may be fungicidal. However, the clinical significance of *in vitro* data is unknown.
Drug-Drug Effect
Recent data indicate that fluconazole-resistant resistant *Candida* infections may respond to

fluconazole-terbinafine combination therapy – "synergistic effect".

Resistance

Recent literature describes fungal resistance to terbinafine, as follows: *Trichophyton rubrum*, *Aspergillus fumigatus*, *Aspergillus nidulans*, and *Saccharomyces cerevisiae*.

CHEMISTRY (synopsis)

Drug Substance

The drug substance for SFO327 film-coated tablets is terbinafine hydrochloride, the same active ingredient in marketed Lamisil Tablets, Cream, and Solution. b(4)

Drug Product

- The proposed drug product is Lamisil® (terbinafine hydrochloride "film-coated" tablets (called "mini-tablets").
- The drug product consists of SFO327 film-coated "**minitablets**" in a ——— corresponding to strengths of 125 mg (approximately 30 film coated mini-tablets) and 187.5 mg (approximately 45 film-coated mini-tablets) of terbinafine base, respectively. b(4)
- Each ——— is intended for use as a single dose.

Table 1 describes the SFO237 film-coated tablets in the ——— b(4)

Table 1* SFO327 Film-Coated Tablets in ———

Dosage form	Strength	Formulation no.
Approx. 30 off-white to yellowish, round, biconvex tablets in a ———	125 mg	7005419
Approx. 45 off-white to yellowish, round, biconvex tablets in a ———	187.5 mg	7005415

b(4)

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Module 2, Sec. 4, Subsec. 3.2.P.1, Table 1-1, Page 2.

Type of Container and Closure

The packaging used is a ——— b(4)

——— The ——— enables an easy opening of the ———

HUMAN STUDIES

Human Pharmacologic Studies

Pharmacokinetics

- Protein Binding

The following pharmacokinetic characteristics of terbinafine hydrochloride have been described in NDA 20-539, Novartis Pharmaceuticals Corporation, Lamisil (terbinafine HCl) 250 mg Tablets, for treatment of onychomycosis, FDA "approval" Date: 05/10/1996:

"Terbinafine binds strongly to plasma proteins (99%). It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum-rich skin."

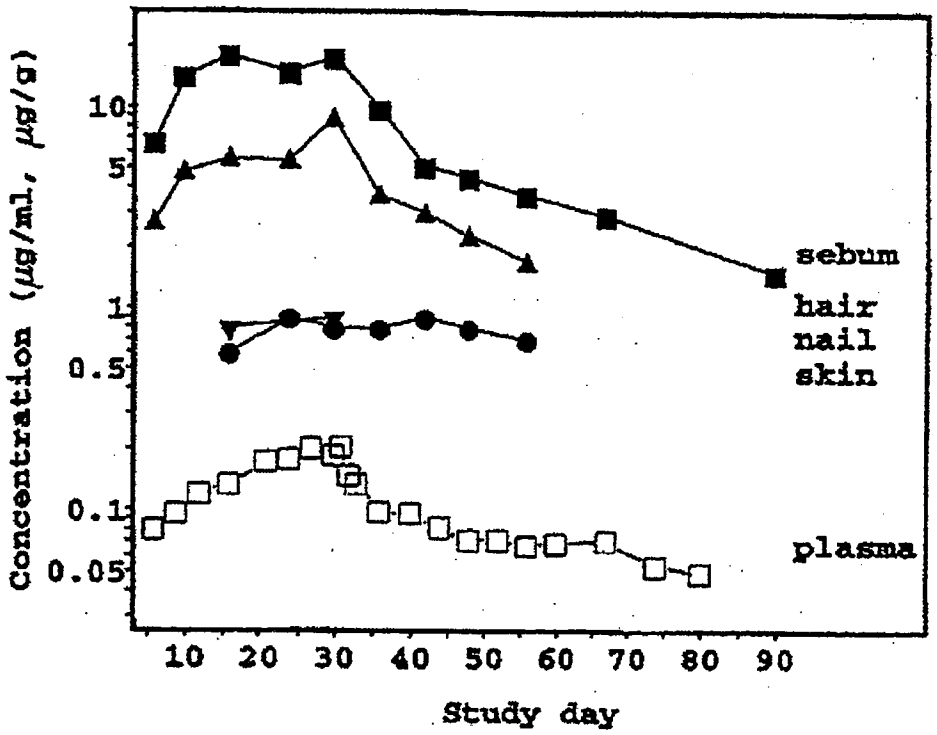
- PK Study (Appendix A)

In a PK Study [see **Appendix A** for full article], "Multiple-Dose Pharmacokinetics and Distribution in Tissue of Terbinafine and Metabolites", the pharmacokinetics of terbinafine and its inactive metabolites in plasma were characterized for 10 healthy male subjects, aged approximately 28 ± 9 years, receiving 250 mg of terbinafine orally once a day for 4 weeks and in the subsequent 8-week washout phase. The dose used in the PK study is similar to the dose used in Study C2301 and C2302. Terbinafine concentrations were also measured in sebum, hair, nail, and stratum corneum samples.

The multiple-dose pharmacokinetic study was performed to characterize the pharmacokinetics of terbinafine and its major metabolites in plasma over a typical treatment duration. An additional objective was to quantify the concentrations of terbinafine achievable at peripheral sites of clinical

Measurable concentrations of terbinafine were achieved in sebum and hair samples within the first week of administration and by week 3 In stratum corneum and nail samples.

Figure 1*: Mean Concentrations of Terbinafine in Plasma, Stratum corneum (skin), Nail, Hair, and Sebum



* Adapted from eNDA 22-071, Letter Date: 09/260/07, Module 2, Sec. 2.4, Subsec. 3.3, Page 14: Ref: Kovarik, J. M. E. A. Mueller H. Zehender, J. Denouel, H. Caplain, and L. Millerioux. Dec. 1995. Multiple-Dose Pharmacokinetics and Distribution in Tissue of Terbinafine and Metabolites. Antimicrobial Agents and Chemotherapy. *American Society for Microbiology.* **39**(12):2738-2741.

In **Figure 1**, the mean concentrations of terbinafine are shown in plasma, stratum corneum (skin), nail, hair, and sebum samples during multiple-dose administration (study days 3 to 30) and in the subsequent washout phase (study days 31 to 90). For plasma samples, only morning predose concentrations are graphed during the dosing phase. The assay quantification limits were 0.02 µg/mL for plasma samples and 0.5 µg/mL for samples from all other matrices.

Clinical Microbiology Comments

The "Multiple-Dose Pharmacokinetics and Distribution in Tissue of Terbinafine and Metabolites" PK Study [full study in **Appendix A**] and the aforementioned **Figure 1** demonstrate that terbinafine distributes extensively to peripheral body fluids and tissues. The concentrations in sebum and hair samples were several-fold higher than simultaneous concentrations in plasma samples.

Pharmacokinetic (PK) Study CSFO327C2101

The Applicant conducted 2-multiple dose pharmacokinetic studies in the target patient population, i.e. children 4 to 8 years of age with tinea capitis, were performed.
- In Study CSFO327C W352 terbinafine was given as the marketed 125-mg tablet, and
- In Study CSFO327C2101 the proposed terbinafine mini-tablets (containing 4.167 mg of terbinafine base) were administered.

The pharmacokinetic **Study CSFO327C2101** in children is described, as follows:

Study No. CSFO327C2101
Title: An open-label, multiple-dose study to evaluate the pharmacokinetics of Terbinafine Hydrochloride Minitablets in children 4-8 years of age with tinea capitis
Author: ———————————————— b(4)
Document Type: Exploratory Development Study Report, **Development Phase:** Phase 1
First Subject Dosed: 10/22/2003, **Last Subject Completed:** 12/03/2003
Document Status: Final, **Document Date:** 03/08/2006

Study Objective
- **Primary Objective**
  The primary objective was to evaluate the pharmacokinetics of terbinafine hydrochloride after a single and repeated oral doses when given as the proposed Minitablets to children 4 to 8 years of age with tinea capitis.

Investigational Plan
- **Study Population**
  1. Confirmation of suspected clinical diagnosis was made by direct microscopic examination of infected host tissue and isolation of dermatophytic pathogen culture.
  2. Tinea capitis was clinically diagnosed and confirmed by positive culture for *Trichophyton* or *Microsporum* species.

Table 2 shows the mean pharmacokinetic variables of terbinafine in plasma in children.

Table 2* **Mean Pharmacokinetic Variables of Terbinafine Base in Plasma in Children**

Dose/Day		Body weight (kg)	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (hr*ng/mL)	R	$t_{1/2,eff}$ (hr)	CL_{ss}/F (L/hr)
125mg	N	11	11	11	11	-	-	-
Day 1	**Mean**	20.3	**1.8**	**971**	**3311**	-	-	-
	SD	3.2	0.5	585	1605	-	-	-
	Min	14.3	0.5	306	1476	-	-	-
	Median	21.8	**2.0**	**770**	**3201**	-	-	-
	Max	23.6	2.0	2300	6973	-	-	-
	CV%	15.5	29.0	60	48	-	-	-
125mg	N	11	11	11	11	11	10	11
Day 42	**Mean**	20.5	**2.5**	**1118**	**6513**	**2.1**	**26.7**	**25.4**
	SD	3.1	3.2	713	4074	0.9	13.8	12.6
	Min	14.5	1.0	473	2474	0.9	7.9	8.4
	Median	22.3	**2.0**	**923**	**4975**	**1.8**	**24.3**	**25.1**
	Max	23.6	12.0	3130	14917	3.6	50.6	50.5
	CV%	15.3	130.6	64	63	44.3	51.5	49.5
187.5mg	N	4	4	4	4	-	-	-
Day 1	**Mean**	31.7	**2.0**	**1602**	**5109**	-	-	-
	SD	3.6	0.0	1010	1860	-	-	-
	Min	27.0	2.0	938	3764	-	-	-
	Median	32.1	**2.0**	**1190**	**4440**	-	-	-
	Max	35.6	2.0	3090	7791	-	-	-
	CV%	11.3	0.0	63	36	-	-	-
187.5mg	N	4	4	4	4	4	3	4
Day 42	**Mean**	31.6	**2.0**	**1575**	**8653**	**1.9**	**30.5**	**27.1**
	SD	3.8	0.0	942	4412	1.0	9.3	15.4
	Min	26.8	2.0	761	3868	0.5	20.5	13.2
	Median	32.1	**2.0**	**1315**	**8274**	**2.1**	**32.2**	**23.4**
	Max	35.5	2.0	2910	14197	2.9	39.0	48.5
	CV%	12.0	0.4	60	51	54.6	30.5	56.8
250mg	N	1	1	1	1	1	1	1
Day 1		37.7	2.0	1370	5253	-	-	-
Day 42		38.6	2.0	544	4154	0.8	-	60.2

Adapted from eNDA 22-071, Letter Date: 09/260/07, Novartis, Report SFO327C2101, Subsection 7.4.2, **Table 7-4**, on Page 37.

Clinical Microbiology Comments

In the Applicant's **Pharmacokinetic (PK) Study CSFO327C2101**, **Table 2**, for the proposed two-minitablet potencies: 125 mg terbinafine base and 187.5 terbinafine base per mini-tablet:

The steady state 125 mg terbinafine base doses at Cmax in plasma in 11 children show the following results:
- At Day 42 the plasma median at C_{max} is 0.923 µg/mL
- At Day 42 the minimum plasma median at C_{max} is 0.473 µg/mL
- At Day 42 the maximum minimum plasma median at C_{max} is 3.130 µg/mL

The steady state 175.5 mg terbinafine base dose at C_{max} in plasma in 4 children show the following results:
- At Day 42 the plasma median at C_{max} is 1.315 µg/mL
- At Day 42 the minimum plasma median at C_{max} is 0.761 µg/mL
- At Day 42 the maximum minimum plasma median at C_{max} is 2.910 µg/mL

CLINICAL STUDIES

Both pivotal clinical studies, **Study C2301** and **C2302**, have the **same study design** and are very similar (some study centers differ). Therefore, Study C2302 is not fully described. However, The microbiology (mycology) data and some clinical, on both (combined) pivotal clinical studies, Study C2301 and C2302, are discussed later in this review.

1. **Study CSFO327C 2301**
   A randomized, investigator blinded, active-controlled, parallel-group study to **compare** the efficacy and safety of 6-week treatment with **terbinafine** new pediatric formulation versus 6-week treatment with **griseofulvin** pediatric suspension in children with tinea capitis.

Microbiology Inclusion Criteria
Patients with clinical diagnosis of tinea capitis confirmed by positive KOH microscopy as determined by the central laboratory b(4)

Gender/ Age
Patients include male or female, 4 to 12 years old, with a clinical diagnosis of tinea capitis confirmed by positive KOH microscopy.

Drug Administration
Patients in both treatment arms are to take the assigned medication, according to the randomization, once daily for 6 weeks. The dose administered depends on body weight. The body weight criteria and the associated doses of both drugs are shown in **Table 3**.

Table 3[X] Study Drug Administration

Body weight	Dose
Treatment arm I – terbinafine	
< 25 kg	2 bottles (125 mg) /day
25-35 kg	3 bottles (187.5 mg) /day
> 35 kg	4 bottles (250 mg) /day
Treatment arm II – griseofulvin*	
<14 kg	1 spoon (125 mg)/day
14-23 kg	2 spoons (250 mg) /day
>23 kg	4 spoons (500 mg)/day

[X] Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Table 9-2, Page 29.
* The griseofulvin weight groups were originally <15 kg, 15-25 kg, >25 kg. They were revised in Amendment 2, per FDA's request.

Efficacy Assessments

Efficacy assessments includes: 1) mycology, 2) clinical signs and symptoms, and 3) a global physician assessment.

- **Mycology**
  Samples for **KOH microscopy** and for **fungal culture** evaluation are taken at screening, Visit 3 (Week 3, Day 22), Visit 4 (Week 6, Day 42)) and at the end of study Visit 5 (Week 10, Day 70), or at early discontinuation, and are sent to the central mycology laboratory.
- **Laboratory Data**
  Laboratory samples are processed centrally through the ——— and ——— laboratories and the results are then sent electronically to Novartis . b(4)
- For more detailed instructions regarding sample collection for microscopy and culture, refer to the following **OVERALL SUMMARY OF EFFICACY RESULTS – MYCOLOGICAL EVALUATIONS** in the **EXECUTIVE SUMMARY** in this review.

Primary Efficacy Variable(s)

The primary efficacy variable is the complete cure rate achieved at the end of follow-up (Visit5/Week 10/Day 70 after the initiation of study drug).

Database Management and Quality Control

- **Laboratory Data**
  Laboratory samples are processed centrally through the ——— and ——— laboratories and the results are sent electronically to Novartis . b(4)

- **Efficacy Evaluation**
  - **Efficacy Variables**
    Efficacy is assessed based on:
    1) Mycological results (i.e., microscopy and culture), and
    2) Total signs and symptoms score (TSSS) which comprise the sum of the scores for erythema, desquamation/scaling and papules/pustules.
    Efficacy variables are defined as follows:
    - **Complete cure** - negative microscopy, negative culture for dermatophyte, and TSSS = 0
    - **Mycological cure** - negative microscopy, and negative culture for dermatophyte
    - **Clinical cure** – TSSS = 0
  - **Primary Efficacy Analysis**
    The primary efficacy variable in the pivotal studies is the complete cure rate at the end of the study in mITT population (the ITT population, excluding those who had negative culture at baseline).

- **Secondary Efficacy Analyses**
  - The secondary efficacy variables are mycological cure and clinical cure.
  - A pooled analysis of efficacy using the data from the 2 pivotal studies is performed for the primary and secondary efficacy variables, using the same analysis plan as that used for the individual the studies.

Efficacy Evaluation

- **Analysis of Efficacy**
  - **Primary Efficacy Results**

The primary efficacy variable is the complete cure rate at end of study. The Applicant believes that in the 2 analyses, terbinafine is superior to griseofulvin.

  - **Secondary Efficacy Results**

The secondary efficacy variables are mycological cure and clinical cure. The Applicant believes that terbinafine is superior to griseofulvin in mycological cure.

Mycological cure and clinical cure rates at the end of study (EOS) for the mITT populations are shown in **Table 4** and **Table 5**, as follows:

Table 4* **Mycological Cure Rates at the End of Study (mITT Population, LOCF)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Terbinafine (N=411)	256	62.29	12.04 (3.62, 20.44)	0.003	0.005
Griseofulvin (N=197)	99	50.25			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Table 11-6, Page 48.

Mycological cure is defined as negative culture and microscopy.

Table 5* **Clinical Cure Rates at the End of Study (mITT Population, LOCF)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Terbinafine (N=411)	258	62.77	6.42 (-1.93, 14.78)	0.059	0.129
Griseofulvin (N=197)	111	56.35			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Table 11-7, Page 48.
Clinical cure is defined as TSSS = 0

- The rate of clinical cures for terbinafine is higher than that of griseofulvin.

Clinical Microbiology Comments

- In the aforementioned **Table 4** and **Table 5**, the Mycological Cure Rates and the Clinical Cure Rates at EOS for the mITT Population: terbinafine [62.29% (256/411)] & [62.77% (258/411)] are almost identical and are both greater than the griseofulvin [50.25% (99/197)] & and 56.35% (111/197)].

Comparison of Efficacy Results of all Studies
Controlled Efficacy Trials

Primary Efficacy Results

The primary efficacy variable in both studies is the Complete Cure rate at EOS in the mITT population (the ITT population, excluding those who had negative mycological culture at baseline).

Complete Cure rates at end-of-study (EOS) for the ITT and ITT populations in the 2 studies are shown in **Table 6** and **Table 7**, respectively.

Table 6* **Complete Cure Rates at EOS in the Pivotal studies (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Study C2301					
Terbinafine (N=411)	190	46.23	12.22 (4.03, 20.40)	0.001	0.004
Griseofulvin (N=197)	67	34.01			
Study C2302					
Terbinafine (N=441)	194	43.99	0.53 (-7.30, 8.36)	0.954	0.894
Griseofulvin (N=237)	103	43.46			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-16, Page 33, Source: [Study C2301, PT-Table 14.2-1.1] and [Study C2302, PT-Table 14.2-1.1]

Complete Cure is defined as negative culture and microscopy and TSSS = 0.

Table 7* **Complete Cure Rates at EOS in the Pivotal Studies (ITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Study C2301					
Terbinafine (N=503)	224	44.53	8.05 (0.62, 15.50)	0.022	0.036
Griseofulvin (N=244)	89	36.48			
Study C2302					
Terbinafine (N=537)	223	41.53	0.40 (-6.85, 7.64)	0.940	0.915
Griseofulvin (N=265)	109	41.13			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-17, Page 33, Source: [Study C2301, PT-Table 14.2-1.2] and [Study C2302, PT-Table 14.2-1.2]
Complete Cure is defined as negative culture and microscopy and TSSS = 0

Clinical Microbiology Comments

In the aforementioned **Table 6** and **Table 7**, the Clinical Cure Rates at EOS in Study C2301, for both the mITT and ITT populations; terbinafine [46.23% (190/411) & 44.53% (224/503)] are higher and close than griseofulvin [34.01% (67/197) & 36.48% (43.46% (103/237)] which are lower and close.

In the aforementioned **Table 6** and **Table 7** the Clinical Cure Rates at EOS in Study C2302, for both the mITT and ITT populations; terbinafine [43.99% (194/441) & 41.53% (223/537)] and griseofulvin [43.46% (103/237) & 41.13% (109/265)] are similar.

Secondary Efficacy Results

The secondary efficacy variables are **Mycological Cure** and **Clinical Cure**. Mycological cure and Clinical Cure rates at end-of-study (EOS) for the mITT populations are shown in the following **Table 8** and **Table 9**, respectively.

Table 8* **Mycological Cure Rates at EOS in the Pivotal Studies (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Study C2301					
Terbinafine (N=411)	256	62.29	12.04 (3.62, 20.44)	0.003	0.005
Griseofulvin (N=197)	99	50.25			
Study C2302					
Terbinafine (N=441)	268	60.77	0.85 (-6.87, 8.58)	0.892	0.828
Griseofulvin (N=237)	142	59.92			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-18, Page 34, Source: [Study C2301, PT-Table 14.2-2.1] and [Study C2302, PT-Table 14.2-2.1].

Mycological cure is defined as negative culture and microscopy.

Clinical Microbiology Comments

In the aforementioned **Table 8**, the Mycological cure Rates in Study C2301 and Study C2302 for the pooled mITT population data, terbinafine [62.29% (256/411) & 60.77% (268/441)] are similar and higher than griseofulvin [50.25% (99/197) & 59.92% (142/237)].

Table 9* **Clinical Cure Rates at EOS in the Pivotal Studies (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Study C2301					
Terbinafine (N=411)	258	62.77	6.42 (-1.93, 14.78)	0.059	0.129
Griseofulvin (N=197)	111	56.35			
Study C2302					
Terbinafine (N=441)	279	63.27	2.51 (-5.17, 10.18)	0.585	0.521
Griseofulvin (N=237)	144	60.76			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-19, Page 34, Source: [Study C2301, PT-Table 14.2-2.1] and [Study C2302, PT-Table 14.2-2.1].

Mycological cure is defined as negative culture and microscopy

Clinical Microbiology Comments

In the aforementioned **Table 9**, the Clinical Cure Rates for Study C2301 and Study C2302 in the mITT population, terbinafine [62.77% (258/411) & 63.27% (279/441)] are similar and higher than griseofulvin [56.35% (111/197) & 60.76% (144/237)].

Combined Efficacy Data

A combined data analysis for efficacy was planned prospectively and is performed using the 2 pivotal studies. The analysis is performed essentially according to the same plan as that used for the individual studies.

Table 10 presents the results of the analysis of **Complete Cure** at end-of-study (EOS) in the pooled mITT population, the primary efficacy criterion in the individual studies.

Table 10* **Complete Cure Rates at EOS in the Pooled Data (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Terbinafine (N=852)	384	45.07	5.90 (0.22, 11.58)	0.024	0.043
Griseofulvin (N=434)	170	39.17			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-20, Page 35, Source: [PT-Table 2.7.3.6-3.1].

Complete Cure is defined as negative culture and microscopy and TSSS = 0

Clinical Microbiology Comments
In the aforementioned **Table 10** the Clinical Cure Rate at EOS for the pooled mITT population data, terbinafine [45.07% (384/852)] is higher than griseofulvin [39.17% (170/434)].

Table 11 presents the results of the analysis of Mycological Cure at EOS in the pooled mITT population.

Table 11* **Mycological Cure Rates at EOS in the Pooled Data (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Terbinafine (N=852)	524	61.50	5.97 (0.27, 11.68)	0.029	0.039
Griseofulvin (N=434)	241	55.53			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-21, Page 36, Source: [PT-Table 2.7.3.6-4.1].

Complete Cure is defined as negative culture and microscopy and TSSS = 0

Clinical Microbiology Comments
In the aforementioned **Table 11**, the Mycological Cure Rate at EOS for the pooled mITT population data, terbinafine [61.50% (524/852)] is much higher than griseofulvin [55.53% (241/434).

Table 12 presents the results of the analysis of Clinical Cure at end-of-study (EOS) in the pooled mITT population.

Table 12* **Clinical Cure Rates at EOS in the Pooled Data (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Terbinafine (N=852)	537	63.03	4.27 (-1.38, 9.93)	0.091	0.136
Griseofulvin (N=434)	255	58.76			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-22, Page 36, Source: [PT-Table 2.7.3.6-5.1].

Complete Cure is defined as negative culture and microscopy and TSSS = 0

Clinical Microbiology Comments

In the aforementioned **Table 12**, the Clinical Cure Rate at EOS for the pooled mITT population data, terbinafine [63.03% (537/852)] is higher than griseofulvin [58.76% (434/434).

Comparison of Efficacy Results in Specific Subgroups

- Demographic factors

The demographic subgroups evaluated are race (Caucasian, Black, Oriental, Other), sex and age group (< 4 years, 4 to 8 years, 9 to 12 years). Country (US or non-US) subsets are also evaluated.

- Disease Factors

The pooled data and the data in the individual studies are evaluated for the dermatophyte species subgroups.

- Overall, about 50% of the 1,549 (actually 1,548) patients randomized into the 2 key studies are infected with *Trichophyton tonsurans.*
- Patients with *Trichophyton violaceum* and *Microsporum canis* infections each comprised about 15% of the population.
- Approximately 17% of patients had a negative culture at baseline.
- The remaining patients (~3%) are infected with *Microsporum audouinni, Microsporum vanbreuseghemii, Trichophyton mentagrophytes, Trichophyton rubrum,* and *Microsporum gypseum.*
- 10 patients have other infections.

- The aforementioned proportions remain similar within the terbinafine and griseofulvin treatment group
- Because the causative dermatophyte species in the US is predominantly *Trichophyton tonsurans,* the data for the US and non-US populations are discussed here along with the data for *Trichophyton.*

Table 13* shows the Primary Efficacy by Dermatophyte Species (mITT Population).

	Study 2301		Study 2302	
	Terbinafine	Griseofulvin	Terbinafine	Griseofulvin
T. Tonsurans	($N = 264$)	($N = 131$)	($N = 243$)	($N = 126$)
Success (%)	148 (56.1)	45 (34.4)	116 (47.7)	46 (36.5)
C.I. for $\delta^\dagger$	-	(11.1, 32.4)	-	(1.3, 22.3)
T. violaceum	($N = 57$)	($N = 25$)	($N = 103$)	($N = 57$)
Success (%)	16 (28.1)	8(32.0)	50 (48.5)	29(50.9)
C.I. for $\delta^\dagger$	-	(−28.5, 20.6)	-	(−19.9, 15.2)
Other	($N = 7$)	($N = 4$)	($N = 6$)	($N = 5$)
Success (%)	7 (100.0)	1 (25.0)	2 (33.3)	3 (60.0)
C.I. for $\delta^\dagger$	-	(12.9, 100.0)	-	(−100.0, 60.0)
M. canis	($N = 80$)	($N = 37$)	($N = 72$)	($N = 45$)
Success (%)	19 (23.8)	13(35.1)	22 (30.6)	23(51.1)
C.I. for $\delta^\dagger$	-	(−31.3, 8.6)	-	(−40.4, −6.8)
M. audouini	($N = 3$)	($N = 0$)	($N = 17$)	($N = 4$)
Success (%)	0 (0.0)	0 (0.0)	4 (23.5)	2 (50.0)
C.I. for $\delta^\dagger$	-	NA	-	(−94.9, 50.0)

† 95% C.I. with Yates continuity correction for δ=terbinafine - griseofulvin.

Source: Reviewer's analysis.

* Mat Soukup, Ph.D., FDA/Biometrics, Subsection 2.3, Review Analysis Table 2, Date: May 2007.

Complete Cure = negative mycology and "TSSS" = 0
Mycological Cure = negative culture and microscopy.
TSSS = "total signs and symptoms score".

Clinical Microbiology Comments

In the aforementioned FDA analysis **Table 13**, the primary efficacy (complete cure) success results for Study 2301 and Study 2302 in the mITT population are as follows:

- For *Trichophyton tonsurans*: terbinafine [56.1% (148/264) & 47.7% (116/243) are higher than griseofulvin [34.4% (45/131) & 36.5% (46/126)]. The griseofulvin success results (34.4% & 36.5%) are very close to each other.

- For *Microsporum canis*: terbinafine [23.8% (19/80) & 30.6% (22/72) are lower than griseofulvin (35.1% (13/37) & 51.1% (23/45)].
- For *Trichophyton violaceum*: terbinafine [28.1% (16/57) & 48.5% (50/103)] are lower than griseofulvin [32.0% (8/25) & 50.9% (29/57)]. The *Trichophyton violaceum* success results for Study 2301 are low as compared to the results observed in Study 2302.

Clinical Microbiology Summarization of Efficacy Results

Generally, the aforementioned data (Study 2301 and Study 2302) demonstrate (higher/greater success results for terbinafine than griseofulvin) in the treatment of tinea capitis in children, particularly in those infected with *Trichophyton tonsurans*, the most prevalent causative organism in the USA.

CLINICAL MICROBIOLOGY

MIC Expert Report

(SFO327C)

Susceptibility of Dermatophyte Isolates Obtained from a Large Worldwide Terbinafine Tinea Capitis Clinical Trial

Introduction

In the study, the antifungal susceptibility profile of a **representative** sample of (**n = 302**) baseline isolates, collected from subjects enrolled in 2 large, multinational tinea capitis clinical trials ([**CSFO327C 2301**] and [**CSFO327C 2302**]), is determined according to the modification of the Clinical and Laboratory Standards Institute (CLSI M38) method [redacted] b(4)

[redacted] Patients enrolled in the trials come from different geographical regions of the world, including **U.S.** and **non-U.S.** sites. Countries involved include **Canada, Puerto Rico, Jamaica, Colombia, Ecuador, Venezuela, Peru, Egypt, South Africa, France, Russia, and India.** As expected, *Trichophyton tonsurans* is the predominant dermatophyte isolated from patients came from the U.S. sites, while isolates form non-U.S. sites were evenly divided between *Trichophyton tonsurans*, *Microsporum canis*, and *Trichophyton violaceum*.

- **Represented Study Centers ("collected baseline isolates")**
  Protocol No. CSFO327C 2301 (Study Center(s): Total = 74 center):
  United States (44), Canada (7), Colombia (9), Egypt (3), Peru (5), Venezuela (4), and South Africa (2).
  Protocol No. CSFO327C 2302 (Study center(s): 72 Centers):
  United States (48), Ecuador (3), Egypt (4), France (4), South Africa (1), India (5), Russia (3), Brazil (2), and Guatemala (2).
  MIC Expert Report (SFO327C)
  United States, Canada, Colombia, Ecuador, Egypt, Peru, France, South Africa, Venezuela, and India, Russia, Puerto Rico, and Jamaica.
- **Clinical Microbiology Comments**
  - **Puerto Rico** and **Jamaica** clinical isolates are not represented in either Study 2301 or Study 2302.
  - Brazil and Guatemala clinical isolates are represented in Study 2303, but **not** here.
  - United States, Canada, Colombia, Ecuador, Egypt, Peru, France, South Africa, Venezuela, India, and Russia clinical isolates are represented here.
  - Some of the Clinical Microbiology MIC conclusions may be problematic. The **INDICATIONS AND USAGE** Package Insert label may be "approved" for [redacted] actually not specifying genus and species. There, the problematic differences may not be so significant. b(4)

Dermatophytes Tested Include

- *Trichophyton tonsurans*, *Trichophyton violaceum*, *Microsporum canis*, and *Microsporum audouinii*.

The distribution of isolates tested is shown below in **Table 14**.

Table 14[x] **Dermatophyte Strains from US and non-US sites**

Isolate	US	Non-US
T. tonsurans	63	62
M. canis	32	62
M. audouinii	ND*	19
T. violaceum	2	62

[x] Adapted from eNDA 22-071, Letter Date: 09/260/07, Expert Report, TD 2.7.3, SFO327C/ Lamisil® mini-tablets Table 1, Page 5.

* There are **no** *Microsporum audouinii* isolates obtained from patients enrolled in the clinical trial at US sites.

Antifungal Agent

Terbinafine powder (Lot # 3008844, Batch7A8F1) is provided by Novartis Pharma AG, Basel, Switzerland.

Dermatophyte Antifungal Susceptibility Method

The minimum inhibitory concentration (MIC) of terbinafine against each isolate is determined according to the modification of the CLSI M38A method for susceptibility testing of dermatophytes

b(4)

In order to determine whether there is a difference in susceptibility among isolates obtained from US and non-US sites, the MIC_{50} and MIC_{90} (defined as the minimum concentration that inhibits 50% and **90%** of isolates, respectively) for each group of isolates are compared, as summarized below in **Table 15**.

Table 15[**] **MIG Range, MIC_{50} and MIC_{90} Data (in µg/mL) for all Dermatophyte Isolates**

Isolate Group	Range	MIC_{50}	MIC_{90}
T. tonsurans US n=63	0.001-0.06	0.015	0.06
T. tonsurans non-US n=62	0.001-0.06	0.015	0.03
M. canis US n=32	0.004-0.25	0.03	0.25
M. canis non-US n=62	0.008-0.25	0.125	0.25
T. violaceum US n=2	0.002-0.015	0.002	N/A*
T. violaceum non-US n=62	0.001-0.125	0.002	0.03
M. audouinii non-US n=19	0.002-0.125	0.06	0.125

[**] Adapted from eNDA 22-071, Letter Date: 09/260/07, Expert Report, CTD 2.7.3, SFO327C/ Lamisil® mini-tablets Section 3, Table 2, Page 7.

* N/A = too few isolates to calculate MIC_{90}

The terbinafine MIC range for all isolates tested is 0.001 to 0.25 µg/mL. The MIC_{90} for *Microsporum canis* is identical for both US and non-US sites, while the MIC_{90} for *Trichophyton tonsurans* is within 1 dilution for US and non-US sites.

Clinical Microbiology Comments

- To determine a valid MIC_{90}, 100 isolates are required.
- "Generally, the acceptable reproducibility of the test is within one twofold dilution of the actual end point. To avoid greater variability, the dilution test must be standardized and carefully controlled....."

The MIC_{90} values of the *Trichophyton tonsurans* US and non-US isolates are very close (MIC_{90}s = 0.06 and 0.03 µg/mL). The MIC_{90} values of the *Microsporum canis* US and non-US isolates and *Microsporum audouinii* non-US isolates are identical (MIC_{90}s = 0.25 µg/mL). There appears very little variation in MIC values within the 2 clinical study dermatophyte species themselves. There are very small elevated terbinafine MICs among the 2 clinical study isolates tested from US and non US sources indicating that *Trichophyton tonsurans* and *Microsporum canis* susceptibility results from non-US sites can be compared to results from US sites.

CLINICAL MICROBIOLOGY CONCLUSIONS

Terbinafine binds strongly to plasma proteins (99%). It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum-rich skin.

The "Multiple-Dose Pharmacokinetics and Distribution in Tissue of Terbinafine and Metabolites" PK Study [full study in **Appendix A**], and aforementioned **Figure 1** demonstrate that terbinafine distributes extensively to peripheral body fluids and tissues. The concentrations in sebum and hair samples were several-fold higher than simultaneous concentrations in plasma samples.

In the Applicant's **Pharmacokinetic (PK) Study CSFO327C2101**, aforementioned **Table 2**, for the proposed two-minitablet potencies: 125 mg terbinafine base and 187.5 terbinafine base per mini-tablet:

The steady state 125 mg terbinafine base doses at Cmax in plasma in 11 children show the following results:

- At Day 42 the plasma median at C_{max} is 0.923 µg/mL
- At Day 42 the minimum plasma median at C_{max} is 0.473 µg/mL
- At Day 42 the maximum minimum plasma median at C_{max} is 3.130 µg/mL

The steady state 175.5 mg terbinafine base dose at C_{max} in plasma in 4 children show the following results:

- At Day 42 the plasma median at C_{max} is 1.315 µg/mL
- At Day 42 the minimum plasma median at C_{max} is 0.761 µg/mL
- At Day 42 the maximum minimum plasma median at C_{max} is 2.910 µg/mL

From the aforementioned **MIC Expert Report (SFO327C)**, "Susceptibility of Dermatophyte Isolates Obtained from a Large Worldwide Terbinafine", the following MIC susceptibility data, are as follows:

Table MIC Range, MIC_{50} and MIC_{90} Data (in µg/mL) for all Dermatophyte Isolates**

Isolate Group	Range	MIC_{50}	MIC_{90}
T. tonsurans US n=63	0.001-0.06	0.015	0.06
T. tonsurans non-US n=62	0.001-0.06	0.015	0.03
M. canis US n=32	0.004-0.25	0.03	0.25
M. canis non-US n=62	0.008-0.25	0.125	0.25
T. violaceum US n=2	0.002-0.015	0.002	N/A*
T. violaceum non-US n=62	0.001-0.125	0.002	0.03
M. audouinii non-US n=19	0.002-0.125	0.06	0.125

** Adapted from eNDA 22-071, Letter Date: 09/260/07, Expert Report, CTD 2.7.3, SFO327C/ Lamisil® mini-tablets Section 3, Table 2, Page 7.

* N/A = too few isolates to calculate MIC_{90}

The PK data from the aforementioned PK Study [full study in **Appendix A**] and aforementioned **Figure 1** and the PK data form the aforementioned, **Pharmacokinetic (PK) Study CSFO327C2101**, **Table 2**, indicate the concentration of terbinafine (base) achieved at the site of infection using the dosing regimen proposed by the Applicant is higher then the MIC_{90} values in the aforementioned **Table – "MIC Range, MIC_{50} and MIC_{90} Data (in µg/mL) for all Dermatophyte Isolates.***

The Clinical and Microbiology (mycology) data (Study 2301 and Study 2302) demonstrates that terbinafine is efficacious in the clinical and mycological treatment of tinea capitis in children infected with *Trichophyton tonsurans*, the most prevalent causative organism in the USA.

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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INTRODUCTION

The Applicant, Novartis Pharmaceuticals Corporation submits e-NDA 22-071, Lamisil® (terbinafine hydrochloride) "film-coated" Tablets (called "mini-tablets"), 125 mg terbinafine base and 187.5 mg terbinafine base, a **new** pediatric formulation. The drug product is for the treatment of tinea capitis in children [redacted]

Two Phase 3 clinical programs are proposed to evaluate the efficacy and safety of the terbinafine **new** pediatric formulation in children with tinea capitis. The indication being sought is: '[redacted] b(4)

Formulation Development

On 12/19/2000, the Sponsor submitted a Proposed Pediatric Study Request to IND 57, 093. On 12/28/2001, the Division issued a Written Request #1, which outlined the type of studies to be performed, age group, entry criteria, endpoints, study evaluation, drug specific safety concerns, and statistical information. Clinical investigations of terbinafine hydrochloride for the treatment of tinea capitis in the United States are conducted under IND 57,093.

The drug substance, terbinafine hydrochloride, is the same drug substance used in marketed Lamisil Tablets (NDA 20-539), Cream (NDA 20-980), and Solution (NDA 20-749).

The currently available oral dosage form of Lamisil® is an immediate release tablet containing terbinafine hydrochloride equivalent to 250 mg of terbinafine. (A 125 terbinafine mg tablet is also approved and marketed in Europe.)

Lamisil® is also marketed as a 1% cream for topical use.

The development of SFO327 125 mg terbinafine and 187.5 mg terbinafine film-coated tablets in [redacted] is life-cycle management project with the target to make a new terbinafine oral dosage form available for pediatric use.

The 2 Phase 3 studies are to confirm that terbinafine is an efficacious and safe treatment for tinea capitis in children. The dose applied in the study is expected to increase the response rate observed in earlier studies. The safety profile of this new dose is expected to be similar to the safety profile of the currently recommended dosage outside the US.

The Applicant conducted the following 2-Phase 3 (same design) pivotal studies:

1. **Study CSFO327C 2301**
   A randomized, investigator blinded, active-controlled, parallel-group study to **compare** the efficacy and safety of 6-week treatment with **terbinafine** new pediatric formulation versus 6-week treatment with **griseofulvin** pediatric suspension in children with tinea capitis.
2. **Study CSFO327C 2302**
   A randomized, investigator blinded, active-controlled, parallel-group study to **compare** the efficacy and safety of 6-week treatment with **terbinafine** new pediatric formulation versus 6-week treatment with **griseofulvin** pediatric suspension in children with tinea capitis.

Efficacy Assessments

Efficacy assessments includes:, 1) mycology, 2) clinical signs and symptoms, and 3) a global physician assessment.

Mycology
Samples for KOH microscopy and for fungal culture evaluation are taken at screening, Visit 3 (week 3), Visit 4 (week 6) and at the end of study Visit 5 (week 10), or at early discontinuation, and are sent to a central mycology laboratory.

- Laboratory Data
Laboratory samples are processed centrally through the [redacted] and [redacted] laboratories and the results are then sent electronically to Novartis . b(4

BACKGROUND

Tinea capitis ("scalp ringworm") is a dermatophyte infection of the scalp hair follicles that occurs primarily in children. However, adults exposed to *Trichophyton tonsurans* infections and patients with AIDS may develop tinea capitis. The primary clinical signs associated with tinea capitis are hair loss, hair breakage, scaling, various degrees of erythema, pustules and pruritus. In addition, cervical or occipital lymphadenopathy may occur in some children.

The infection is caused by a relatively small group of dermatophytes in the genera *Trichophyton* and *Microsporum*. The predominant organisms vary geographically, for example:
1. *Trichophyton tonsurans* in the **North American** continent, United Kingdom, Mexico, Central and South America [1]
2. *Trichophyton violaceum* in Africa and the Middle East
3. *Microsporum canis* in Eastern Europe

In the United States, *Trichophyton tonsurans* replaces *Microsporum audouinii* and *Microsporum canis* as the most common cause of tinea capitis [1].

Historically, *Microsporum audouinii* is the classic causative agent in Europe and America and *Microsporum ferrugineum* is most common in Asia. Currently, *Microsporum audouinii* and *Microsporum canis* remain prevalent in most parts of Europe, although *Trichophyton violaceum* also is common in Romania, Italy, Portugal, Spain, and the former USSR, as well as in Yugoslavia. In Africa, *Trichophyton violaceum*, *Trichophyton schoenleinii*, and *Microsporum canis* commonly are isolated. *Trichophyton violaceum* and *Microsporum canis* are prevalent agents in Asia. *Trichophyton schoenleinii* is common in Iran and Turkey, while *Microsporum canis* is common in Israel. *Epidermophyton floccosum* and *Trichophyton concentricum* do not invade scalp hair. *Trichophyton rubrum*, which is the most common dermatophyte isolated worldwide, is not a common cause of tinea capitis [1].

Dermatophytosis customarily is divided into endothrix (inside the hair shaft) and ectothrix (extending outside the hair shaft) infection based on the location of proliferation of pathogenic fungi and destruction of the hair structure [1].

Common causes of endothrix infection include *Trichophyton tonsurans*, characterized by chains of large spores and *Trichophyton schoenleinii*, characterized by hyphae with air spaces. Infected hairs break off sharply at the follicular orifice, leaving a conidia-filled stub or black dot. Suppuration and kerion formation commonly are associated with *Trichophyton tonsurans* infection [1].

In ectothrix infection, fragmentation of the mycelium into spores occurs just beneath the cuticle. In contrast to endothrix infection, destruction of the cuticle occurs. The type of infection is caused by *Trichophyton verrucosum*, *Trichophyton mentagrophytes*, and all *Microsporum* species [1].

Some dermatophytes such as *Microsporum canis* are spread from animals to humans (zoophilic), whereas others, such as *Trichophyton tonsurans* or *Trichophyton violaceum*, are spread among humans (anthropophilic).

The treatment of tinea capitis has 2 important goals

1. To remove the dermatophyte from the hair follicle to cure the symptoms of the subject, and
2. To eradicate the dermatophyte from the hair shaft to prevent relapse or epidemic spread of the infection.

The current standard of care for tinea capitis infection is oral griseofulvin

1. The Package Insert label recommends a dose of griseofulvin is 10 mg/kg/day, or 250 mg for patients weighing < 25 kg and 500 mg for those ≥ 25 kg.
2. The recommended duration of treatment is at least **4-6 weeks** in the **US** and 6-8 weeks in non-US countries, combined with topical antifungal shampoos, hair removal, and isolation of the subject from other children.

Tinea capitis is becoming a public health problem in some countries due to increased incidence and epidemic transmission. The point prevalence of tinea capitis, as defined by positive mycology in school children, varies from 0.5% (Madrid, Spain) to 13.5% (Cleveland, Ohio/US). In the US, recent studies have shown that the point prevalence of tinea capitis is 4% in inner-city African American pediatric population.

Tinea capitis is becoming a public health problem in some countries due to increased incidence and epidemic transmission. Terbinafine mini-tablets are to provide an **alternative treatment** for this condition.

GENERAL NON-CLINICAL INFORMATION

MICROBIOLOGY

Drug Product

The proposed drug produce is Lamisil® (terbinafine hydrochloride "film-coated" tablets (called "mini-tablets"). The potency is 125 mg terbinafine base and 187.5 mg terbinafine base, respectively.

Description

Terbinafine HCl is a synthetic allylamine, lipophilic antifungal with a broad spectrum of antifungal activity.

Mechanism of Action

Allylamines, e.g., terbinafine, inhibit ergosterol biosynthesis, an essential component of fungal cell membranes, via inhibition of squalene epoxidase enzyme. The effect finally causes fungal cell death primarily due to the increased membrane permeability mediated by the accumulation of high concentrations of squalene but not due to ergosterol deficiency*.

* Murray, P. R., E. J. Baron, J. H. Jorgensen, M. A. Pfaller, and R. H. Yolken. 2003. Manual of Clinical Microbiology. *American Society for Microbiology Press.* 8th ed. Vol. 2, **122**:1862-1863.

Antimicrobial Spectrum of Activity
Terbinafine is active in vitro against the following fungi: *Malassezia furfur*, *Candida* spp., *Aspergillus* spp. *Sporothrix schenckii*, *Penicillium marneffei*, *Cryptococcus neoformans*, *Trichosporon* spp., and *Blastoschizomyces*.

- **NDA 20-539 / SN-001:**
  Novartis Pharmaceuticals Corporation, Lamisil [terbinafine hydrochloride tablets (EQ 250 mg base)] Tablets, FDA "approval" date: May 10, 1996. The current FDA "approved" (01/21/2004), Package Insert Label reads as follows:

  - **INDICATION AND USAGE**
    "LAMISIL® (terbinafine hydrochloride tablets) Tablets are indicated for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes....."

  - **MICROBIOLOGY**
    Terbinafine has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:
    Trichophyton mentagrophytes
    Trichophyton rubrum

    The following *in vitro* data are available, **but their clinical significance is unknown.** *In vitro*, terbinafine exhibits satisfactory MICs against most isolates of the following microorganisms; however, the safety and efficacy of terbinafine in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:
    Candida albicans
    Epidermophyton floccosum
    Scopulariopsis brevicaulis

Fungistatic / Fungicidal Effects
Depending on the concentration of the drug and the fungal species test *in vitro*, terbinafine hydrochloride may be fungicidal. However, the clinical significance of *in vitro* data is unknown**.

- NDA 20-539: Novartis Pharmaceuticals Corporation, Lamisil (terbinafine HCl) Tablets, for treatment of onychomycosis, FDA "approval" Date: 05/10/1996. Current FDA "approved" label: 01/21/2004.
- NDA 20-749: Novartis Consumer Health, Inc., Lamisil (terbinafine HCl) Solution 1%, Treatment of tinea pedis, FDA "approval" Date: 10/17/1997, Current FDA "approved" label: 03/27/2003.
- NDA 20-846: Novartis Pharmaceuticals Corporation, Lamisil DermGel 1%, for treatment of tinea capitis in pediatric patients due to specific organisms, FDA "approval" Date: 04/29/1998, Current FDA "approved" label: 07/26/1999.

Drug-Drug Effect
Recent data indicate that fluconazole-resistant resistant *Candida* infections may respond to fluconazole-terbinafine combination therapy – "synergistic effect".

Resistance
Recent literature describes fungal resistance to terbinafine, as follows: *Trichophyton rubrum* [2,3], *Aspergillus fumigatus* [4,5], *Aspergillus nidulans* [6], and *Saccharomyces cerevisiae* [7].

DIVISION OF ANTIINFECTIVE AND OPHTHALMOLOGY PRODUCTS DAIOP)
CLINICAL MICROBIOLOGY REVIEW
CONSULTATION FOR DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (DDDP)
NDA 22-071 / SN-000 **DATE REVIEW COMPLETED: 05/20/07**

CHEMISTRY (synopsis)

Introduction

SFO327 125 mg terbinafine and 187.5 mg terbinafine "film-coated' tablets are developed as immediate release solid dosage forms for the pediatric population. They are composed of multi-particulate units, like pellets. The "mini-tablets" are film-coated, and filled into ——— Each ——— represents a dose which can be adapted by the quantity of film-coated tablets filled into the ——— b(4)

1. **Drug Substance**

   The drug substance for SFO327 film-coated tablets is terbinafine hydrochloride, the same active ingredient in marketed Lamisil Tablets, Cream, and Solution. b(4)
   - Full details on terbinafine hydrochloride are provided in NDA 20-539 for Lamisil Tablets.
   - Details of CMC information for the drug substance are referenced to NDA 20-539, FDA "approval" Date: 05/10/1996.

2. **Drug Product**

   The proposed drug produce is Lamisil® (terbinafine hydrochloride "film-coated" tablets (called "mini-tablets"). The potency is 125 mg terbinafine base and 187.5 mg terbinafine base, respectively.

   - **Description**

     SFO327 film-coated tablets in ———, are immediate release dosage forms for oral administration. b(4)
     - The drug product consists of SFO327 film-coated "**minitablets**" in a ——— corresponding to strengths of 125 mg (approximately 30 film coated mini-tablets) and 187.5 mg (approximately 45 film-coated mini-tablets) of terbinafine base, respectively.
     - Each ——— is intended for use as a single dose.
     - Each individual "mini-tablet" contains 4.6875 mg of terbinafine hydrochloride, corresponding to 4.167 mg of terbinafine base.
     - The film-coated tablets are off-white to yellowish, round, biconvex mini-tablets, having a diameter of approx. 2.1 mm.

Table 1 describes the SFO237 film-coated tables in the ——— b(4)

Table 1* **SFO327 Film-Coated Tablets in ———**

Dosage form	Strength	Formulation no.
Approx. 30 off-white to yellowish, round, biconvex tablets in a ———	125 mg	7005419
Approx. 45 off-white to yellowish, round, biconvex tablets in a ———	187.5 mg	7005415

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Module 2, Sec. 4, Subsec. 3.2.P.1, Table 1-1, Page 2.

3. **Type of Container and Closure**

   The packaging used is ——— b(4)

_____, enables an easy opening of the _____ b(4)

A schematic drawing of the _____ is presented in **Figure 1**.

Figure 1* **Schematic Drawing of _____ (dimensions in mm)** b(4)

b(4)

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Module 2, Sec. 4, Subsec. 3.2.P.3, Figure 3-1, Page 4.

HUMAN STUDIES

Human Pharmacologic Studies

Pharmacokinetics

- Protein Binding

The following pharmacokinetic characteristics of terbinafine hydrochloride have been described in NDA 20-539, Novartis Pharmaceuticals Corporation, Lamisil (terbinafine HCl) 250 mg Tablets, for treatment of onychomycosis, FDA "approval" Date: 05/10/1996:

Terbinafine binds strongly to plasma proteins (99%). It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum-rich skin. There is also evidence that terbinafine is distributed into the nail plate within the first few weeks after commencing therapy.

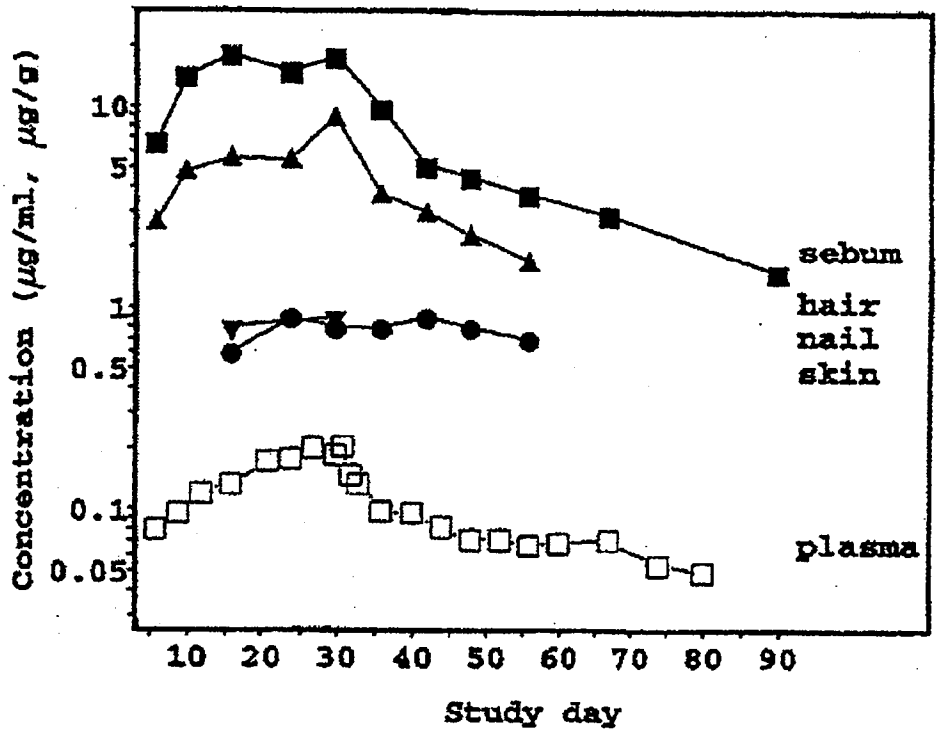
- PK Study (Appendix A)

In a PK Study [see **Appendix A** for full article], "Multiple-Dose Pharmacokinetics and Distribution in Tissue of Terbinafine and Metabolites", the pharmacokinetics of terbinafine and its inactive metabolites in plasma were characterized for 10 healthy male subjects, aged approximately 28 ± 9 years, receiving 250 mg of terbinafine orally once a day for 4 weeks and in the subsequent 8-week washout phase. The dose used in the PK study is similar to the dose used in Study C2301 and C2302. Terbinafine concentrations were also measured in sebum, hair, nail, and stratum corneum samples.

The multiple-dose pharmacokinetic study was performed to characterize the pharmacokinetics of terbinafine and its major metabolites in plasma over typical treatment duration. An additional objective was to quantify the concentrations of terbinafine achievable at peripheral sites of clinical

Measurable concentrations of terbinafine were achieved in sebum and hair samples within the first week of administration and by week 3 In stratum corneum and nail samples.

Figure 2* Mean Concentrations of Terbinafine in Plasma, Stratum corneum (skin), Nail, Hair, and Sebum



* Adapted from eNDA 22-071, Letter Date: 09/260/07, Module 2, Sec. 2.4, Subsec. 3.3, Page 14: Ref: Kovarik, J. M. E. A. Mueller H. Zehender, J. Denouel, H. Caplain, and L. Millerioux. Dec. 1995. Multiple-Dose Pharmacokinetics and Distribution in Tissue of Terbinafine and Metabolites. Antimicrobial Agents and Chemotherapy. *American Society for Microbiology*. 39(12):2738-2741.

In **Figure 2**, the mean concentrations of terbinafine are shown in plasma, stratum corneum (skin), nail, hair, and sebum samples during multiple-dose administration (study days 3 to 30) and in the subsequent washout phase (study days 31 to 90). For plasma samples, only morning predose concentrations are graphed during the dosing phase. The assay quantification limits were 0.02 µg/mL for plasma samples and 0.5 µg/mL for samples from all other matrices.

The terbinafine concentrations from peripheral matrices are compared graphically in **Figure 2**, of the tissues sampled, terbinafine concentrations were highest in sebum and hair samples. relevance in the treatment of onychomycoses and dermatomycoses.

Clinical Microbiology Conclusions

The "Multiple-Dose Pharmacokinetics and Distribution in Tissue of Terbinafine and Metabolites" PK Study [full study in **Appendix A**] and aforementioned **Figure 2** demonstrate that terbinafine distributes extensively to peripheral body fluids and tissues. The concentrations in sebum and hair samples were several-fold higher than simultaneous concentrations in plasma samples.

Pharmacokinetic (PK) Study CSFO327- C2101

Two multiple dose pharmacokinetic studies in the target patient population, i.e. children 4 to 8 years of age with tinea capitis, were performed.
- In Study CSFO327C W352 terbinafine was given as the marketed 125-mg tablet, and
- In Study CSFO327C2101 the proposed terbinafine mini-tablets (containing 4.167 mg of terbinafine base) were administered.

The pharmacokinetic **Study CSFO327C2101** in children is discussed, as follows:

Study No. CSFO327C2101
Title: An open-label, multiple-dose study to evaluate the pharmacokinetics of Terbinafine Hydrochloride Minitablets in children 4-8 years of age with tinea capitis
Author: [redacted] b(4)
Document Type: Exploratory Development Study Report
Development Phase: Phase 1
First Subject Dosed: 10/22/2003
Last Subject Completed: 12/03/2003
Document Status: Final
Document Date: 03/08/2006

Table 3 outlines the pharmacokinetic (PK) Study No. CSFO327C2101.

Table 3: **Study No. CSFO327C2101**

Title of study: An open-label, multiple-dose study to evaluate the pharmacokinetics of Terbinafine Hydrochloride Minitablets in children 4-8 years of age with tinea capitis
Investigator: [redacted] b(4)
Publication: None
Study period: first patient dosed 22-Oct-03 last patient completed 03-Dec-03

Objectives:

Primary objective

- To evaluate the pharmacokinetics of terbinafine in children 4 to 8 years of age with tinea capitis after administration of Terbinafine Hydrochloride Minitablets

Secondary objective

- To determine the safety and tolerability of Terbinafine Hydrochloride Minitablets in children 4 to 8 years of age with tinea capitis

Table 3*: (con't) Study No. CSFO327C2101

Design: This was an open-labeled, multiple-dose study, in which each patient with tinea capitis infection (regardless of causative organism - *Trichophyton* or *Microsporum*), received terbinafine hydrochloride minitablets once daily for 42 days. A total of 16 pediatric patients with tinea capitis were planned for enrollment; 16 patients were randomized and 16 completed the study.

Each patient participated in a screening, baseline and treatment period, and a study completion evaluation was performed prior to discharge from the study. Baseline laboratory evaluations occurred on Day –1 or Day 1; all results were obtained prior to dosing. Confirmation of the clinical diagnosis of tinea capitis was made by direct microscopic examination of infected host tissue treated with KOH. Patients with a positive KOH exam were allowed to enter the study. Infection with either *Trichophyton* or *Microsporum* species was confirmed by isolation of the dermatophytic pathogen on fungal culture.

Patients were treated with terbinafine hydrochloride minitablets; doses were determined based on the following weight categories:

- Patients < 25 kg received a 125 mg dose
- Patients between 25 to 35 kg received a 187.5 mg dose
- Patients > 35 kg received a 250 mg dose

Terbinafine treatment occurred for 42 days q.d. in the morning. All patients fasted for at least 1 hour following study drug administration. Patients had PK blood samples collected following the first dose of terbinafine on Day 1 up to 24 hours postdose. They were discharged from the clinic and continued study drug dosing on an out-patient basis. Patients returned to the clinic (prior to drug administration) on Day 21 and provided a predose PK blood sample; drug resupply and safety evaluations were also performed at this visit. On Day 42, patients returned to the site prior to taking their study medication. PK samples were collected from predose up to 24 hours postdose. Patients were allowed to leave the clinic following the 12-hour PK sample and returned to provide the 24-hour PK sample. Study completion evaluations were performed following the last PK sample collection.

Number of patients: Sixteen (16) patients were planned for enrollment, 16 patients were randomized and 16 patients completed the study. Distribution of patients by age was as follows: 4 years (1), 5 years (9), 6 years (1), 7 years (3) and 8 years (2).

Criteria for inclusion: Male and female patients, aged 4-8 years (inclusive), with a diagnosis of tinea capitis, but otherwise healthy.

Table 3*: (con't) Study No. CSFO327C2101

Patients confirmed the clinical diagnosis of tinea capitis by direct microscopic examination of infected host tissue and isolation of dermatophytic pathogen culture.

Tinea capitis was also confirmed by positive culture for *Trichophyton* or *Microsporum* species. Samples were obtained from patients at Screening and were sent to an independent laboratory for evaluation. Patients were entered into the study prior to obtaining the culture result. However, if a negative culture was obtained and the patient was responding to treatment (in the Investigator's opinion), the study drug treatment was continued until Day 42. All PK sampling for such patients occurred as described in the study synopsis.

Investigational drug: Terbinafine Hydrochloride Minitablets in unit dose bottles:

30 Terbinafine Hydrochloride Minitablets x one unit dose bottle = 125mg

45 Terbinafine Hydrochloride Minitablets x one unit dose bottle = 187.5mg

60 Terbinafine Hydrochloride Minitablets x one unit dose bottle = 250mg

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Drug administration: Patients received one of the following doses based on weight:

Patients < 25 kg received 125 mg q.d. (Batch X208 0803)

Patients 25 to 35 kg received 187.5 mg q.d (Batch X209 0803)

Patients > 35 kg received 250 mg q.d. (Batch X210 0803)

Duration of treatment: Study drug was administered for 42 days q.d. in the morning.

Criteria for evaluation:

Safety and tolerability assessments: Vital signs and body measurements (body height, body weight, oral body temperature, systolic and diastolic blood pressure and radial pulse rate in supine position for at least 3 minutes).

Standard clinical laboratory evaluations: Hematology (hemoglobin, hematocrit, WBC count with differential, RBC count and platelet count). Blood chemistry (Albumin, alkaline phosphatase, total bilirubin, calcium, chloride, cholesterol, creatinine, CPK, γ-GT, glucose, LDH, inorganic phosphorus, lipase, α-amylase, potassium, total protein, SGOT, SGPT, sodium, triglycerides, urea/BUN and uric acid).

Urinalysis (specific gravity, pH; semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, blood; and a microscopic examination including RBC/HPF, WBC/HPF and casts/LPF).

Visual testing: visual acuity, color vision, tonometry, and dilated fundoscopy.

Medical History, physical examination, concomitant medications / significant non-drug therapies and adverse event monitoring.

Pharmacokinetics:

Blood collection [600 µL blood per sample, Na EDTA tubes (plasma)]: Days 1 and 42 at predose, 0.5, 1, 2, 4, 6, 12 and 24 hours postdose; Day 21 at predose only.

Analysis, media and methods: Terbinafine levels in plasma, HPLC-MS method; LLOQ at 1 ng/mL.

PK parameters for terbinafine: t_{max}, C_{max}, C_{max}/Dose, C_{min}, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}24h}$/Dose CL_{ss}/F, effective $t_{½}$ from accumulation and accumulation ratio on Day 42, $t_{1/2}$ apparent elimination half-life based on apparent plasma elimination rate constant λ_z.

PK evaluations in plasma: Non-compartmental analysis. Descriptive statistics of the PK parameters include arithmetic and geometric mean, SD, CV, minimum, maximum and median. Pediatric PK data were compared to historic PK data in adults from various studies in a separate report.

Table 3*: (con't) Study No. CSFO327C2101

Pharmacokinetics:

Inter-individual variability of C_{max} and AUC_{0-24} values of terbinafine were high, which is reflected by coefficient of variation values between 36% and 64%.

In the 125 mg dose group, pharmacokinetic data were obtained for 11 patients. In the 125 mg dose group, minimum and maximum C_{max} values in individual patients varied by a factor of 7.5 and 6.6 on Days 1 and 42, respectively. In the same dose group, individual AUC_{0-24} values differed by a factor of 4.7 and 6.0 between the minimum and maximum value on Days 1 and 42, respectively. In the 187.5 mg dose group minimum and maximum C_{max} values differed by factors of 3.3 and 3.7 on Days 1 and 42, respectively. The corresponding values for AUC_{0-24} were 2.1 and 3.6.

Mean as well as median values of C_{max} and AUC_{0-24} were higher in the 187.5 mg group than in the 125 mg group, both on Day 1 and Day 42. However, on Day 42 the individual values of both parameters in the 187.5 mg dose group were within the ranges of values observed in the 125 mg dose group. After repeated administration (Day 42), mean AUC_{0-24} values were generally higher than after the first dose (Day 1), with the mean accumulation ratio being 2.1 and 1.9 for the 125 mg and 187.5 mg doses, respectively.

The only patient who received a 250 mg dose showed a lower AUC_{0-24} on Day 42 than on Day 1. This was also true for one patient in each of the other dose groups (125 mg and 187.5 mg) and is thought to reflect intra-subject variability. There was a trend to higher AUC_{0-24} with increasing dose in mg/kg on Day 1 of treatment; however, on Day 42 this trend was less visible.

Mean C_{max} values were slightly higher on Day 42 compared to Day 1 in the 125 mg dose group (ratio of mean Day 42/mean Day 1 = 1.15). In the 187.5 mg dose group mean C_{max} values were similar on Day 1 and Day 42 (ratio of mean Day 42/mean Day 1 = 0.98).

Time of maximum concentration (t_{max}) stayed constant over the dosing period with a median value of 2 hours in all dose groups. The individual values of the effective half-life of terbinafine determined from the accumulation in plasma on Day 42 as compared to Day 1 was between 7.9 and 50.6 hours. The arithmetic mean was 26.7 hours in the 125 mg dose group and 30.5 hours in the 187.5 mg dose group.

Blood samples were also collected on Day 21 before the daily dose (time = 0 hr). Eight (8) of the 16 patients had Day 42 trough concentrations which were higher than on Day 21, whereas the opposite (i.e., lower concentrations on Day 42 than on Day 21) was observed for the other 8 patients. The mean ratio of the 0-hour concentrations measured on Day 42 vs. Day 21 was close to 1, indicating that on average patients were at steady state between Days 21 and 42.

From AUC_{0-24} on Day 42, the apparent plasma clearance of terbinafine was calculated at steady state (CL_{ss}/F). The individual CL_{ss}/F values in the 125 mg and 187.5 mg dose groups ranged between 8.4 and 50.5 L/hr. The arithmetic mean was 25.4 L/hr for the 125 mg dose group and 27.1 L/hr for the 187.5 mg dose group. The patient receiving the 250 mg dose exhibited a high apparent clearance of 60.2 L/hr. Viewing a plot of CL_{ss}/F vs. body weight, a trend of increasing clearance with increasing body weight can be observed.

Table 3*: (con't) Study No. CSFO327C2101

Applicant's Conclusions:

- Terbinafine hydrochloride minitablets, administered once daily for 42 days at the weight-dependent doses used in this study (< 25 kg, 125 mg; 25-35 kg, 187.5 mg; > 35 kg, 250 mg), were safe and well-tolerated in children aged 4-8 years with tinea capitis.
- Once daily oral dosing of terbinafine in children with tinea capitis resulted in ~two-fold increase of systemic exposure to terbinafine as characterized by AUC_{0-24}, after 42 days compared to that following the first dose.
- Accumulation was similar in the 125 mg and the 187.5 mg dose groups. The mean effective half-life of terbinafine calculated from the observed accumulation was about 27 to 31 hours.
- On average, plasma concentrations of terbinafine (C_{max} and AUC_{0-24}) tended to be higher in the 187.5 mg dose group than in the 125 mg dose group.
- The apparent plasma clearance of terbinafine at steady state was similar in the 125 mg and 187.5 mg dose groups and amounted to 25 to 27 L/hr on average.
- The variables AUC_{0-24h} and apparent clearance CL_{ss}/F observed in children after daily oral doses of 125 mg and 187.5 mg were similar to those observed in adults after daily oral doses of 250 mg.
- The comparison of the results in children with data in adults revealed that children need higher doses in mg per kg body weight to reach a similar exposure (AUC_{0-24h}) to terbinafine as adults.
- With the weight classes and doses of terbinafine proposed for children (i.e., <25 kg to receive 125 mg q.d., 25-35 kg to receive 187.5 mg q.d., > 35 kg to receive 250 kg q.d.) the systemic exposure to terbinafine was shown not to exceed the exposure in adults.

Table 4 provides the definitions of some of the pharmacokinetic variables.

Table 4* **Definitions of Pharmacokinetic Variables**

Parameter	Definition
AUC_{0-24} (hr*ng/mL)	Area under the plasma concentration-time curve from time 0 up to 24 hours calculated by linear trapezoidal summation called method (1).
AUC_{0-24}/Dose (hr*ng/mL)/mg/kg	Area under the plasma concentration-time curve from time 0 up to 24 hours normalized to a dose of 1 mg per kg body weight
t_{max} (hr)	Time of maximum observed plasma concentration
C_{max} (ng/mL)	Maximum observed plasma concentration between 0 and 24 hours
C_{max} / Dose (ng/mL)/(mg/kg)	Maximum observed plasma concentration between 0 and 24 hours normalized to a dose of 1 mg per kg body weight (for publication)
C_{min} (ng/mL)	At steady state: minimum concentration between 0 and τ

Adapted from eNDA 22-071, Letter Date: 09/260/07, Novartis, Report SFO327C2101, **Table**, on Page 10.

Study Objective

- **Primary Objective**

The primary objective was to evaluate the pharmacokinetics of terbinafine hydrochloride after a single and repeated oral doses when given as the proposed Minitablets to children 4 to 8 years of age with tinea capitis.

Investigational Plan

- **Study Population**

1. Confirmation of suspected clinical diagnosis was made by direct microscopic examination of infected host tissue and isolation of dermatophytic pathogen culture.
2. Tinea capitis was clinically diagnosed and confirmed by positive culture for *Trichophyton* or *Microsporum* species.

Deviations from Investigational Plan

- **Protocol Deviations/Violations**
  - **Selection of Patients**

Dermatophyte culture specimens from 3 patients were not positive for either *Trichophyton* or *Microsporum*, as required per protocol. In 2 of these patients (5103 and 5107), the infective agent was identified as *Cladosporium* sp.; the infective agent for patient 5116 was not identified. All 3 patients had positive KOH results and completed the study.

Results

- **Results of Screening and Baseline Tests**

All patients had a positive KOH examination for dermatophyte infection at screening, as required for inclusion in the study. The results of the dermatophyte culture were obtained while the study was ongoing. Four (4) patients tested positive for *Trichophyton tonsurans* and 9 were positive for *Microsporum canis*. Specimens from 3 patients were not positive for either *Trichophyton* or *Microsporum*. In 2 of these patients (5103 and 5107), the infective agent was identified as *Cladosporium* sp.; the infective agent was not identified for patient 5116.

Table 5 shows the listing of tinea capitis infection and KOH exam results.

Table 5*: **Listing of Tinea Capitis Infection and KOH Exam Results**

Dose (mg)	Subj no	Trichophyton infection	Microsporum infection	KOH exam
125	5101	Negative	Positive	Positive
	5102	Positive	Negative	Positive
	5104	Negative	Positive	Positive
	5105	Positive	Negative	Positive
	5106	Positive	Negative	Positive
	5107	Negative	Negative	Positive
	5109	Negative	Positive	Positive
	5110	Negative	Positive	Positive
	5111	Negative	Positive	Positive
	5115	Negative	Positive	Positive
	5116	Negative	Negative	Positive
187.5	5108	Positive	Negative	Positive
	5112	Negative	Positive	Positive
	5113	Negative	Positive	Positive
	5114	Negative	Positive	Positive
250	5103	Negative	Negative	Positive

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Novartis, Report SFO327C2101, Appendix 3, Table 3.3.8, 1-1, on Pages 376 & 377.

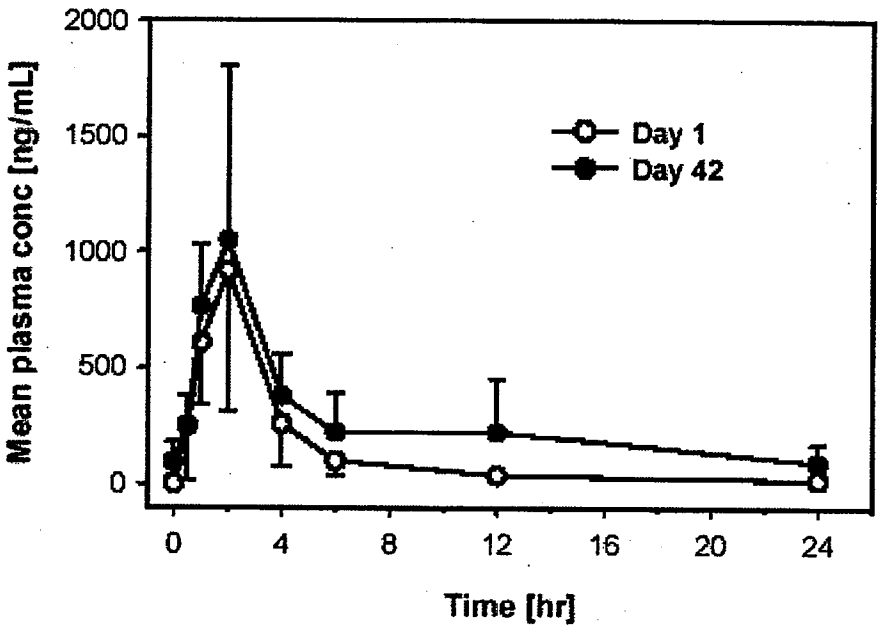
Program source: /data/devl/CSFO327C/CSFO327C2101/final/pgm_saf/t3_3_8bcl.SAS, 12:18 19JAN2004

- Pharmacokinetic Results

- Pharmacokinetic Profiles and Variables

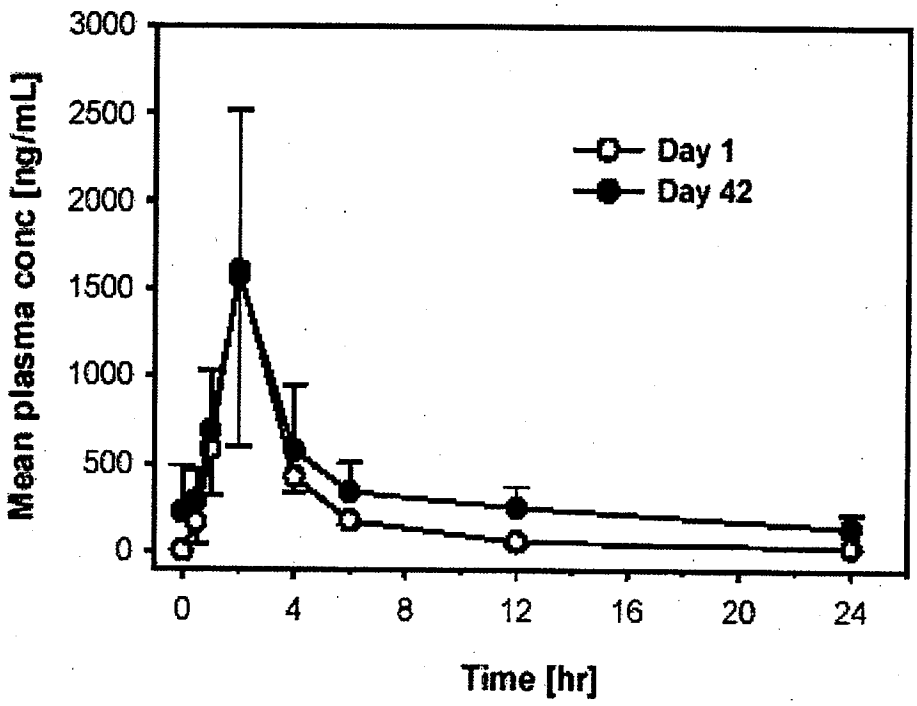
All 16 patients recruited into the study completed blood sampling as per protocol. Mean plasma concentrations are depicted in **Figure 3**, **Figure 4**, and **Figure 5**, and mean pharmacokinetic variables are given in **Table 6**.

Figure 3* Mean (+ or - SD) terbinafine plasma concentrations (ng/mL) in children (N = 11) with tinea capitis after single and repeated oral doses of 125 mg of terbinafine given once daily as minitablets



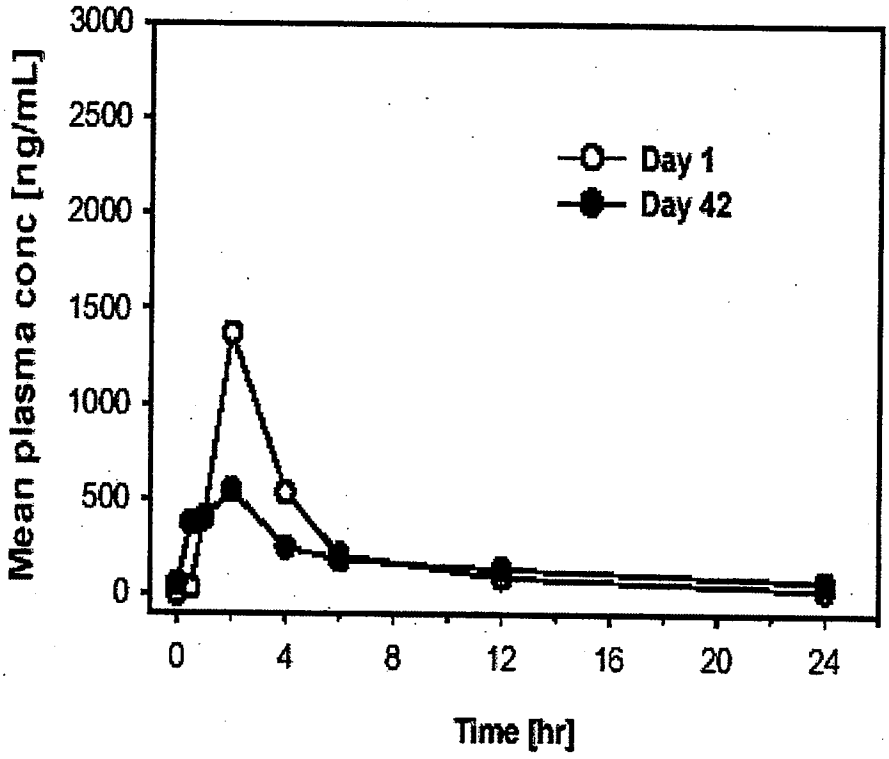
* Adapted from eNDA 22-071, Letter Date: 09/260/07, Novartis, Report SFO327C2101, Subsection 7.4.2, **Figure 7-1**, on Page 35.

Figure 4* Mean (+ or - SD) terbinafine plasma concentrations (ng/mL) in children (N = 4) with tinea capitis after single and repeated oral doses of 187.5 mg of terbinafine given once daily as minitablets



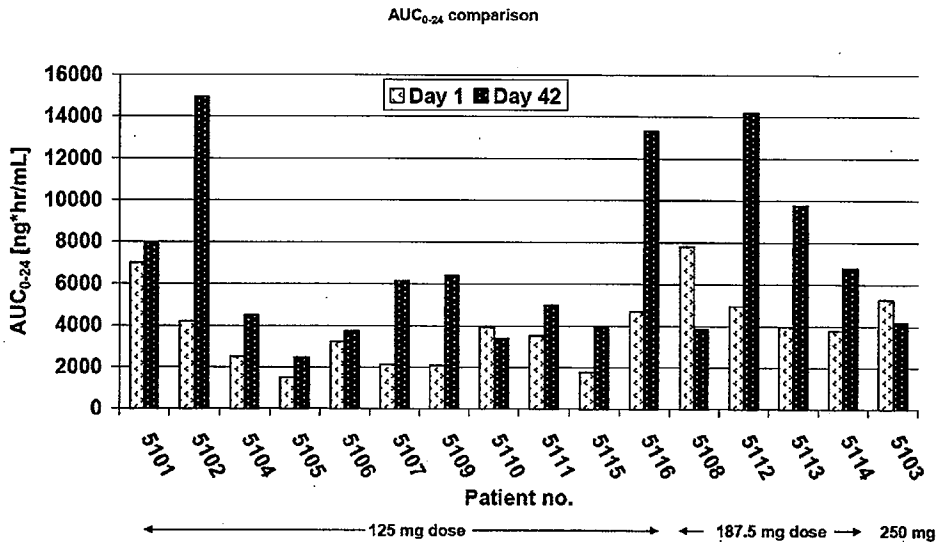
* Adapted from eNDA 22-071, Letter Date: 09/260/07, Novartis, Report SFO327C2101, Subsection 7.4.2, **Figure 7-2**, on Page 35.

Figure 5* Plasma concentrations of terbinafine (ng/mL) in one child with tinea capitis after single and repeated oral doses of 250 mg of terbinafine given once daily as minitablets



* Adapted from eNDA 22-071, Letter Date: 09/260/07, Novartis, Report SFO327C2101, Subsection 7.4.2, **Figure 7-3**, on Page 36.

Figure 6* **Comparison of AUC_{0-24} Calculated on Day 1 and 42 in Individual Patients**



* Adapted from eNDA 22-071, Letter Date: 09/260/07, Novartis, Report SFO327C2101, Subsection 7.4.2, **Figure 7-4**, on Page 38.

Clinical Microbiology Comments:

In the aforementioned **Figure 6**:

The 11 patients receiving the 125 mg dose: 92% (11/12) of the patients had a higher AUC_{0-24} on Day 42 than Day 1.

The 4 patients receiving 187.5 mg dose: 75% (3/4) of the patients had a higher AUC_{0-24} on Day 42 than Day 1.

Terbinafine activity is related to its concentration at the target site. Depending on the concentration of terbinafine, it can be fungistatic or fungicidal.

Table 6* Mean Pharmacokinetic Variables of Terbinafine Base in Plasma in Children

Dose/Day		Body weight (kg)	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (hr*ng/mL)	R	$t_{1/2.eff}$ (hr)	CL_{ss}/F (L/hr)
125mg	N	11	11	11	11	-	-	-
Day 1	**Mean**	20.3	**1.8**	**971**	**3311**	-	-	-
	SD	3.2	0.5	585	1605	-	-	-
	Min	14.3	0.5	306	1476	-	-	-
	Median	21.8	**2.0**	**770**	**3201**	-	-	-
	Max	23.6	2.0	2300	6973	-	-	-
	CV%	15.5	29.0	60	48	-	-	-
125mg	N	11	11	11	11	11	10	11
Day 42	**Mean**	20.5	**2.5**	**1118**	**6513**	**2.1**	**26.7**	**25.4**
	SD	3.1	3.2	713	4074	0.9	13.8	12.6
	Min	14.5	1.0	473	2474	0.9	7.9	8.4
	Median	22.3	**2.0**	**923**	**4975**	**1.8**	**24.3**	**25.1**
	Max	23.6	12.0	3130	14917	3.6	50.6	50.5
	CV%	15.3	130.6	64	63	44.3	51.5	49.5
187.5mg	N	4	4	4	4	-	-	-
Day 1	**Mean**	31.7	**2.0**	**1602**	**5109**	-	-	-
	SD	3.6	0.0	1010	1860	-	-	-
	Min	27.0	2.0	938	3764	-	-	-
	Median	32.1	**2.0**	**1190**	**4440**	-	-	-
	Max	35.6	2.0	3090	7791	-	-	-
	CV%	11.3	0.0	63	36	-	-	-
187.5mg	N	4	4	4	4	4	3	4
Day 42	**Mean**	31.6	**2.0**	**1575**	**8653**	**1.9**	**30.5**	**27.1**
	SD	3.8	0.0	942	4412	1.0	9.3	15.4
	Min	26.8	2.0	761	3868	0.5	20.5	13.2
	Median	32.1	**2.0**	**1315**	**8274**	**2.1**	**32.2**	**23.4**
	Max	35.5	2.0	2910	14197	2.9	39.0	48.5
	CV%	12.0	0.4	60	51	54.6	30.5	56.8
250mg	N	1	1	1	1	1	1	1
Day 1		37.7	2.0	1370	5253	-	-	-
Day 42		38.6	2.0	544	4154	0.8	-	60.2

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Novartis, Report SFO327C2101, Subsection 7.4.2, **Table 7-4**, on Page 37.

Clinical Microbiology Comments

In the Applicant's **Pharmacokinetic (PK) Study CSFO327C2101, Table 6**, for the proposed two-minitablet potencies: 125 mg terbinafine base and 187.5 terbinafine base per mini-tablet:

The steady state 125 mg terbinafine base dose at C_{max} in plasma n 11 children show the following results:
- At Day 42 the plasma median at C_{max} is 0.923 µg/mL
- At Day 42 the minimum plasma median at C_{max} is 0.473 µg/mL
- At Day 42 the maximum minimum plasma median at C_{max} is 3.130 µg/mL

The steady state 175.5 mg terbinafine base dose at C_{max} in plasma in 4 children show the following results:
- At Day 42 the plasma median at C_{max} is 1.315 µg/mL
- At Day 42 the minimum plasma median at C_{max} is 0.761 µg/mL
- At Day 42 the maximum minimum plasma median at C_{max} is 2.910 µg/mL

CLINICAL STUDIES

Novartis Pharmaceuticals Corporation, submits e-NDA 22-071, Lamisil® (terbinafine hydrochloride "film-coated" tablets (called "mini-tablets"), 125 mg terbinafine base and 187.5 mg terbinafine base, a **new** pediatric formulation. The purpose of the 2-studies is to evaluate the efficacy and safety of the terbinafine new pediatric formulation in children with tinea capitis. The indication being sought is: [redacted] b(4)

Note Both pivotal clinical studies, **Study C2301** and **C2302**, have the **same study design** and are very similar. **Study centers** may differ. Therefore, Study C2302 is not fully described. However, The microbiology (mycology) data and some clinical, on both (combined) pivotal clinical studies, Study C2301 and C2302, are discussed later in this review.

Study C2301

Applicant:
Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080,
Tel: (215) 751-3836 / FAX: 215.251.4926
- **Principal Investigator**
  Sheila Fallon-Friedlander, MD, Senior Staff, Division of Pediatric Dermatology, Children's Hospital-San Diego, San Diego, CA 92123 (Principle Investigator)
- **External Participants**
  - Contract Research Organization [redacted]
  - Central Laboratory [redacted] b(4)

Title:
A randomized, investigator blinded, active-controlled, parallel-group study comparing the efficacy and safety of 6-week treatment with terbinafine new pediatric formulation versus 6-week treatment with griseofulvin pediatric suspension in children with Tinea capitis.
Indication: Tinea capitis

DIVISION OF ANTIINFECTIVE AND OPHTHALMOLOGY PRODUCTS DAIOP)
CLINICAL MICROBIOLOGY REVIEW
CONSULTATION FOR DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (DDDP)
NDA 22-071 / SN-000 **DATE REVIEW COMPLETED: 05/20/07**

Compound/Project: SFO327C
Protocol No: CSFO327C 2301
Developmental Phase: 3
Study Initiation Date: June 23, 2004 (First patient, First visit
Study Completion Date: Mar 15, 2006 (Last patient, Last visit)
Date of Report: Jun 19, 2006
INVESTIGATIONAL PLAN

- **Study Design**
  The study is a randomized, investigator blinded, active-controlled, parallel-group study comparing the efficacy and safety of 6 weeks of treatment with terbinafine new pediatric formulation versus 6-weeks of treatment with griseofulvin pediatric suspension in children with tinea capitis.

The trials or sources of data intended to demonstrate efficacy are shown in **Table 7**.

Table 7* **Overview of Trials or Sources of Data**

Source of data	Studies	Details
dose-selection trials	W352	1 open-label, multicenter, multiple-dose study to evaluate the pharmacokinetics of terbinafine in children 4-8 years of age with Tinea capitis
	C2101	1 open-label, multiple-dose study to evaluate the pharmacokinetics of terbinafine hydrochloride mini-tablets in children 4-8 years of age with Tinea capitis
	L2306	1 randomized, open-label, multiple-dose, two-period, crossover study to evaluate the effect of food on the terbinafine New Oral Formulation (NOF) in adult healthy subjects
	T201 T202	2 phase II randomized, double-blind studies in were performed using the terbinafine tablet formulation to determine the appropriate treatment duration for Tinea capitis caused by *Trichophyton* and *Microsporum* species
controlled trials	C2301 C2302	2 large, randomized, investigator blinded, active-controlled, parallel-group phase III studies to compare the efficacy and safety of 6-weeks of treatment with terbinafine new pediatric formulation versus 6-weeks of treatment with griseofulvin pediatric suspension in children with Tinea capitis
trials used for combined efficacy analysis	C2301 C2302	Combined efficacy analysis was performed using the 2 controlled , pivotal trials.

* Adapted from eNDA 22-071, Letter Date: 09/260/07, CTD 2.7.3 Summary of Clinical Efficacy, SFO327C, Tinea capitis, Table 1-1, Page 7.

The 2-aforementioned controlled pivotal trials are used to support the efficacy claims. The treatment regimen used in the pivotal trials represents the way in which the terbinafine treatment is given in common practice. No long-term efficacy studies are included because the term for which the drug is given is covered in the pivotal studies.

Table 8 shows a summary of active controlled trials for both pivotal studies.

Table 8* **Summary of Active Controlled Trials**

Study No.	Study objective, population	Planned patients	Treatment duration	Dosage	Type of control
Controlled efficacy trials					
C2301	Randomized, investigator-blinded, parallel-group safety and efficacy study in patients 4 – 12 years of age with Tinea capitis	720 (747 enrolled)	42 days	Terbinafine mini-tablets by body weight: <25 kg - 125 mg/day, 25-35 kg - 187.5 mg/day, >35 kg - 250 mg/day	active (griseofulvin)
C2302	Randomized, investigator-blinded, parallel-group safety and efficacy study in patients 4 – 12 years of age with Tinea capitis	720 (802 enrolled)	42 days	Terbinafine mini-tablets by body weight: <25 kg - 125 mg/day, 25-35 kg - 187.5 mg/day, >35 kg - 250 mg/day	active (griseofulvin)

* Adapted from eNDA 22-071, Letter Date: 09/260/07, CTD 2.7.3 Summary of Clinical Efficacy, SFO327C, Tinea capitis, Table 1-3, Page 10.

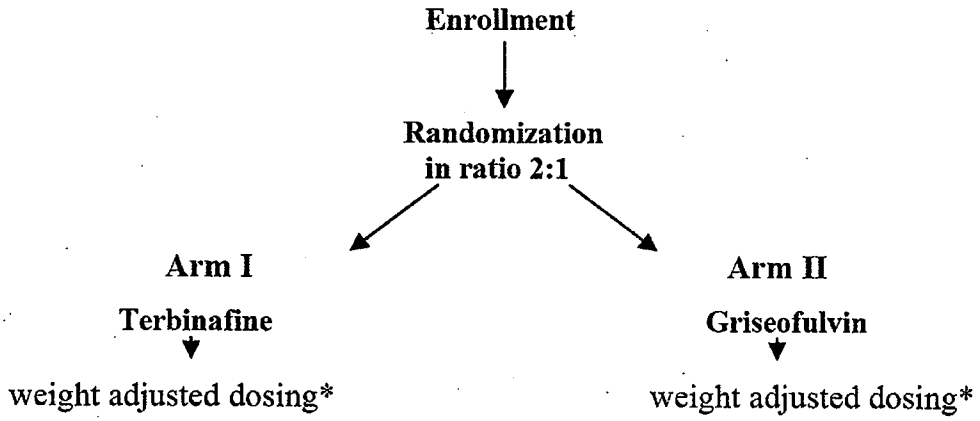
Table 9 shows the study design of Study 2301 (and Study 2302).

Table 9* **Study Design**

	Screening	Baseline	Treatment		Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Day –7 to –3	Day 1	Day 22	Day 42	Day 70
Screening/Enrollment	X				
Randomization		X			
Dosing		<----------	----------	---------->	

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Table 9-1, Page 26.
- Visits are to take place within +/- 3 days from the visit date calculated as specified in the protocol.

Figure 7* Study Schematic



* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Appendix 16, Figure 4-1, Page 12.

Study Center(s): Total / Centers = 74: US (44), Canada (7), Colombia (9), Egypt (3), Peru (5), South Africa (2), and Venezuela (4)

Study Drugs:

- **Investigational:**
  - terbinafine (as the HCl)
  - Terbinafine is supplied in bottles containing 62.5 mg/bottle of terbinafine mini-tablets (15 minitablets/bottle).
- **Reference:**
  - Griseofulvin V® microsize suspension (griseofulvin oral suspension, 125 mg/5 mL, 120 mL suspension/bottle), manufactured by Ortho Pharmaceutical Corp., USA, is used in the study. The griseofulvin suspension is supplied with a spoon to dispense 5 mL (125 mg) griseofulvin.
  - Novartis supplies both investigational products.

Study Duration / Study Endpoint Criteria:

- If a subject completes the final visit, Visit 5, the subject is considered to have completed the study.
- The study closes when a minimum of 40 randomized subjects complete the last visit (Visit 5 or early termination) of the study.

Treatment Duration: 42 days.

Microbiology Inclusion and Exclusion Criteria:

- **Microbiology Inclusion Criteria ("Acceptable")**

  Patients with clinical diagnosis of tinea capitis confirmed by positive KOH microscopy as determined by the central laboratory [redacted] b(4)

  - **Tinea capitis Diagnosis*:**
    - **Area of involvement**

      The area of involvement is recorded on a diagrammatic schema for reference purposes only. The disease is characterized as diffuse or localized, and this is recorded in the CRF.
      - Presence of any persons in your household having tinea capitis infection
      - Hair care habits

At Screening the subjects/guardian is asked to supply information regarding the subjects' hair-care habits that may affect clinical outcome.

- **Questions pertain to:**
  - number of times the subject shampoos per week,
  - typical hairstyle (braids/ponytails, loose),
  - use of hair straighteners, use of grease (pomades),

* eNDA 22-071, .2.1 Inclusion Criteria - Appendix 16.1.1-Protocol Section 5.21: Clinical Development Project: SFO327C, Study No: SFO327C 2301, Development phase: III, Date of Report: June 19, 2006, Novartis, Section, 16.1, Study No. SFO327C 2301, 7.2, Page 580 (22).

- **Microbiology Exclusion Criteria: ("Acceptable" as listed in the protocol.)**

Gender / Age:

Male or female, 4 to 12 years old, with a clinical diagnosis of tinea capitis confirmed by positive KOH microscopy.

STUDY OBJECTIVE(s)

- **Primary Objective**

To demonstrate that the efficacy of 6 weeks treatment with approximately 5-8 mg/kg terbinafine new pediatric formulation is superior to the efficacy of 6 weeks treatment with the maximum labelled dose of griseofulvin, as assessed by complete cure rates at Visit 5 (week 10), in the tinea capitis in children.

- **Secondary Objectives**

1. To assess the efficacy of 6 weeks treatment with approximately 5-8 mg/kg terbinafine new pediatric formulation as compared to 6 weeks maximum labelled dose of griseofulvin, according to the secondary outcome measures: clinical and mycological cure rates at the end of study.
2. To demonstrate that the safety of 6 weeks treatment approximately 5-8 mg/kg terbinafine new oral formulation is similar to the safety of 6 weeks treatment with maximum labelled dose of griseofulvin in tinea capitis in children.

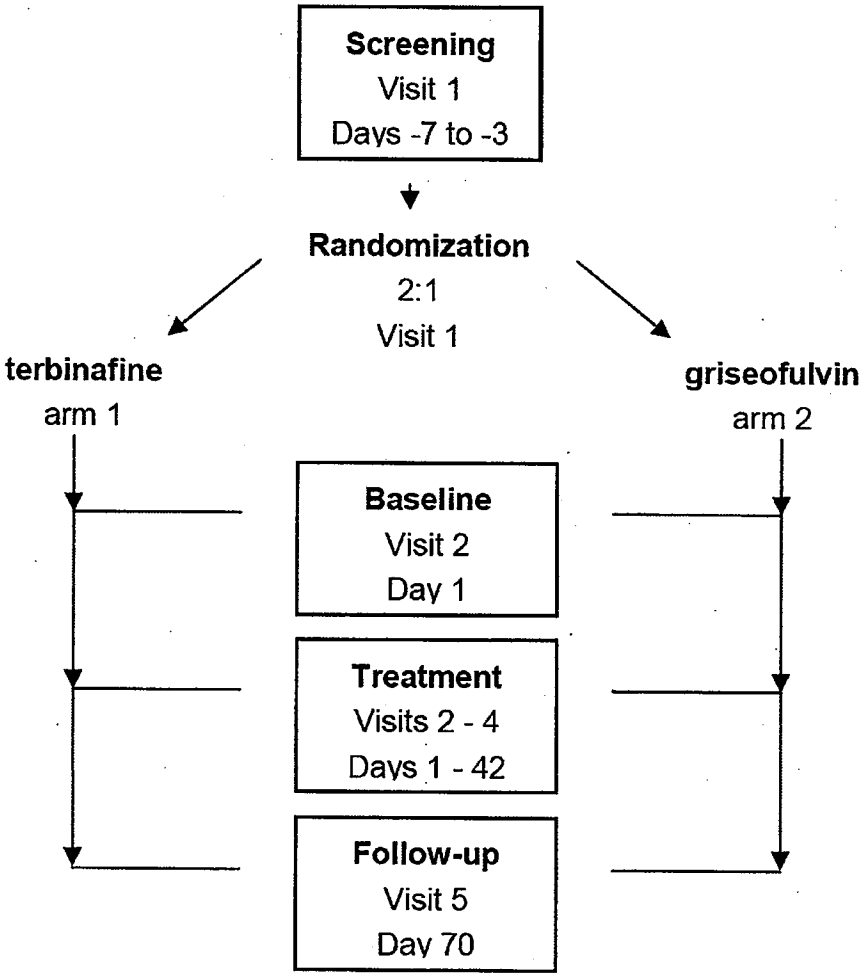
Enrollment:

- Planned: 720 (480 terbinafine, 240 griseofulvin),
- Enrolled: 747 (503 terbinafine, 244 griseofulvin)
- Analyzed: 747 (503 terbinafine, 244 griseofulvin)
- Up to 2 children per household could be enrolled in the study. Enrollment of more than 2 children from the same household required discussion with Novartis personnel prior to enrollment.

Randomization:

Patients are randomized in a 2:1 ratio to the terbinafine: griseofulvin treatment arms, as shown in **Figure 8**:

Figure 8[x] Randomization



[x] Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Table 9-2, Page 29.

Drug Administration:
Patients in both treatment arms are to take the assigned medication, according to the randomization, once daily for 6 weeks. The dose administered depends on body weight. The body weight criteria and the associated doses of both drugs are shown in **Table 10.** (The weight ranges originally specified in the protocol were slightly different from those shown. Amendment 2 modified the weight ranges, as shown, according to FDA request.)

Table 10[X] **Study Drug Administration**

Body weight	Dose
Treatment arm I – terbinafine	
< 25 kg	2 bottles (125 mg) /day
25-35 kg	3 bottles (187.5 mg) /day
> 35 kg	4 bottles (250 mg) /day
Treatment arm II – griseofulvin*	
<14 kg	1 spoon (125 mg)/day
14-23 kg	2 spoons (250 mg) /day
>23 kg	4 spoons (500 mg)/day

[X] Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Table 9-2, Page 29.
* The griseofulvin weight groups were originally <15 kg, 15-25 kg, >25 kg. They were revised in Amendment 2, per FDA's request.

The aforementioned dosing schedule provides 5-8.3 mg/kg terbinafine in Arm 1 and maximum labeled dose (10-20 mg/kg) of griseofulvin in Arm 2.

Patients take the first dose of study medication on the day of randomization (Day 1) and continue to receive the assigned treatment once daily for 6 weeks, according to the below daily dosing regimen. The dose will not change if the patient's weight changes categories during the treatment period.

Medications are to be taken either in the morning or in the evening but this is decided at the start of treatment and remain consistent during the entire duration of treatment.

For optimal absorption, griseofulvin is to be taken with food. Therefore, all patients should take the study medication with a meal.

The terbinafine bottles are to be emptied onto a tablespoon of pudding and the entire spoonful swallowed. Acidic food (e.g. orange juice and grapefruit juice) is avoided when taking study medication.

The spoon provided in the griseofulvin package is to be used to measure the griseofulvin suspension.

Other Concomitant Treatment: ("Acceptable" as listed in the protocol.)
- Use of topical antifungal therapies is not the standard of care in all countries. Therefore, and to ensure homogeneity throughout of all sites in various countries, the use of any of the listed therapies will be prohibited during the entire duration of the study.
- Systemic and topical antifungal therapies on the scalp are prohibited for the duration of the study.

VISIT SCHEDULE AND ASSESSMENTS

Patients diagnosed with tinea capitis and who have a positive KOH microscopy are enrolled into the study. Blood samples are taken and sent to the central mycology laboratory. Upon receipt of the laboratory test results and if eligibility can be confirmed based on these results, patients are randomized (Visit 2) and start study treatment as described in the protocol.

Table 11 shows the visit schedule and assessments.

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NDA 22-071 / SN-000 **DATE REVIEW COMPLETED: 05/20/07**

Table 11* **Assessment Schedule**

PROCEDURE	CATEGORY	PRE-TREATMENT	TREATMENT			POST-TREATMENT
		SCREENING	BASELINE			FOLLOW-UP
Visit label		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
		Day –7 to –3	Day 1	Day 22	Day 42	Day 70
Informed Consent/Enrollment	S/D	X				
Inclusion/Exclusion criteria	D	X				
Demography	D	X				
Medical History	D	X				
Tinea capitis diagnosis	D	X				
Prior Medication	D	X				
Concomitant Medication	D		X	X	X	X
Vital Signs	D	X	X	X	X	X
Clinical evaluation (TSSS)	D		X	X	X	X
Physical examination	D	X				
Ophthalmologic evaluations[1] - visual acuity - visual field testing - funduscopy	D		 X X X		 X X X	 X[2] X[2] X[2]
Physician's Global Assessment	D					X
Target Area designation	S	X				
Mycology -Microscopy -Culture (central laboratory)	D	 X[3] X		 X X	 X X	 X X
Laboratory evaluations: - Chemistry, Hematology - Pregnancy test[4]	D	 X X		 X X	 X X	 X[2] X[2]
Taste disturbance - Weight monitoring - Caregiver Interview - Food diary	 D D S		 X X	 X X X	 X X X	 X X X
RANDOMIZATION			X			
Dispense drug	D		X	X		
Dosing	D		←----------		----------→	
Adverse Events recording	D		←----------	As necessary	----------→	
Serious Adverse Events recording	D	←----------	As necessary		----------→	

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Table 9-3, Page 33.
[1] Baseline must be done before the first dose. / [2] In case of abnormality is detected at week 6.
[3] Performed by the central mycology laboratory. / [4] Serum pregnancy test at Screening visit only, all others are urine pregnancy tests for FOCBP.

Efficacy Assessments:

Efficacy assessments includes: 1) mycology, 2) clinical signs and symptoms, and 3) a global physician assessment.

- **Mycology**

  Samples for **KOH microscopy** and for **fungal culture** evaluation are taken at screening, Visit 3 (Week 3, Day 22), Visit 4 (Week 6, Day 42) and at the end of study Visit 5 (Week 10, Day 70), or at early discontinuation, and are sent to the central mycology laboratory.

Primary Efficacy Variable(s):

The primary efficacy variable is the complete cure rate achieved at the end of follow-up (Visit 5/Week10/ Day 70) after the initiation of study drug).

Database Management and Quality Control:

- **Laboratory Data:**

  Laboratory samples are processed centrally through the ——————— laboratories and the results are sent electronically to Novartis . b(4)

- For more detailed instructions regarding sample collection for microscopy and culture, refer to the following **OVERALL SUMMARY OF EFFICACY RESULTS – MYCOLOGICAL EVALUATIONS** in this review.

STATISTICS

- **Population Definitions:**
  - Intent-to-treat population (ITT) - all patients who are randomized and dispensed study drug. They are analyzed according to the treatment group assigned at randomization.
  - Modified ITT (mITT) - all ITT patients who have a positive culture at baseline. These patients are analyzed according to the treatment group assigned. This is the primary analysis population for efficacy.
  - Per-protocol (PP) population – all mITT patients who have no major protocol violations. The per-protocol population is used to provide confirmation of efficacy findings from the modified ITT population.
- **Efficacy Evaluation:**
  - **Efficacy Variables**

    Efficacy is assessed based on:

    3) Mycological results (i.e., microscopy and culture), and
    4) Total signs and symptoms score (TSSS) which comprise the sum of the scores for erythema, desquamation/scaling and papules/pustules.

    Efficacy variables are defined as follows:

    - **Complete cure** - negative microscopy, negative culture for dermatophyte, and TSSS = 0
    - **Mycological cure** - negative microscopy, and negative culture for dermatophyte
    - **Clinical cure** – TSSS = 0
    - **Efficacy Assessments – Mycology:** See Clinical Microbiology/Mycology later in the review.
  - **Primary Efficacy Analysis**

    The primary efficacy variable in the pivotal studies is the complete cure rate at the end of the study in mITT population (the ITT population, excluding those who had negative culture at baseline).
  - **Secondary Efficacy Analyses**
    - The secondary efficacy variables are mycological cure and clinical cure.
    - A pooled analysis of efficacy using the data from the 2 pivotal studies is performed for the primary and secondary efficacy variables, using the same analysis plan as that used for the individual the studies.

Table 12* Major Protocol Violations (ITT population)

	Terbinafine N=503 n (%)	Griseofulvin N=244 n (%)	Total N=747 n (%)
Number of patients with major protocol violations	104 (20.7)	81 (33.2)	185 (24.8)
Number of patients excluded from per-protocol population	168 (33.4)	108 (44.3)	276 (36.9)
Major protocol violations:			
KOH and/or culture result missing week 10	87 (17.3)	50 (20.5)	137 (18.3)
Less than 80% of total dose taken	53 (10.5)	46 (18.9)	99 (13.3)
Used prohibited medication	2 (0.4)	2 (0.8)	4 (0.5)

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Table 10-2, Page 44

Clinical Microbiology Comments:
In the aforementioned **Table 12**, under **Major Protocol Violations**, the number of patients with KOH and/or culture missing at Visit 5 (Week 10 / Day 70) is 17.3% (87/503).

EFFICACY EVALUATION
- **Analysis of Efficacy**
  - **Primary Efficacy Results**
    The primary efficacy variable is the complete cure rate at end of study. The Applicant believes that in the 2 analyses, terbinafine is statistically significantly superior to griseofulvin.
  - **Secondary Efficacy Results**
    The secondary efficacy variables are mycological cure and clinical cure. The Applicant believes that terbinafine is statistically significantly superior to griseofulvin in mycological cure.

    Mycological cure and clinical cure rates at the end of study (EOS) for the mITT populations are shown in **Table 13** and **Table 14**, as follows:

Table 13* Mycological Cure Rates at the End of Study (mITT Population, LOCF)

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Terbinafine (N=411)	256	62.29	12.04 (3.62, 20.44)	0.003	0.005
Griseofulvin (N=197)	99	50.25			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Table 11-6, Page 48.

Mycological cure is defined as negative culture and microscopy.

Table 14* Clinical Cure Rates at the End of Study (mITT Population, LOCF)

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Terbinafine (N=411)	258	62.77	6.42 (-1.93, 14.78)	0.059	0.129
Griseofulvin (N=197)	111	56.35			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: CSFO327C 2301, Table 11-7, Page 48.
Clinical cure is defined as TSSS = 0

Clinical Microbiology Comments:

- In the aforementioned **Table 13** and **Table 14**, the Mycological Cure Rates and the Clinical Cure Rates at EOS for the mITT Population: terbinafine [62.29% (256/411)] & [62.77% (258/411)] are almost identical and are both greater than the griseofulvin [50.25% (99/197)] & and 56.35% (111/197)].

SUMMARY OF EFFICACY RESULTS*

The 2-controlled pivotal trials are used to support the efficacy claims. The treatment regimen used in the pivotal trials represents the way in which the terbinafine treatment is given in common practice. No long-term efficacy studies are included because the term for which the drug is given is covered in the pivotal studies.

* Source: Clinical Development, Lamisil® (terbinafine) / Mini-tablets, SFO327C Tinea capitis, Tabular Listing of all Clinical Studies, Document Type: CTD Module 5.2, Document Status: Final Release Date: 08/17/06.

Table 15 shows the tabular listing of Clinical Study SFO327C 2301 and Clinical Study SFO327C 2302 / Lamisil (terbinafine) mini-tablets.

Table 15* **Reference Therapy Controlled Studies in Patients**

Ref.	Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
report: Doc. listings: Doc.	protocol:SFO327C2301 invest.: S. Fallon-Friedlander, MD, et al. Canada, Colombia, Egypt, Peru, S. Africa, US, Venezuela start: 23Jun2004 end: 15Mar2006 publ.: None	design, goal & population: Randomized, investigator-blinded, active-controlled, parallel-group study to compare the efficacy and safety of 6-week treatment with terbinafine new pediatric formulation vs. 6-week treatment with griseofulvin pediatric suspension in children with Tinea capitis evaluations: Safety and tolerability: Physical exams, vital signs, taste disturbance, ophthalmologic, AE, SAE and lab evaluations. Efficacy: Mycology, clinical signs and symptoms and global physician assessment.	total: 720 planned, 747 enrolled and analyzed, (319m, 184f) 93w, 219b, 191 other) age: 4-12y planned actual 3-12 groups: 2 (analyzed 503 terbinafine and 244 griseofulvin)	form: 62.5 mg terbinafine minitablets; griseofulvin oral suspension, 125 mg/5 ml, 120 ml suspension/bottle duration: 42 days doses: terbinafine: 5-8mg/kg/day determined by patient's body weight. <25kg: 125 mg/day, 25-35kg: 187.5 mg/day >35kg: 250 mg/day griseofulvin: <14kg 12mg/day, 14-23kg 250mg/day, >23kg 500mg/day	status: Complete report: Final dated Jun 19, 2006 general results: Safety and tolerability: Terbinafine has favorable safety profile in this populaton. Taste disturbances, weight loss, liver function abnormalities, neutropenia, ophthalmologic parameters carefully monitored with no apparent drug-related effect. Efficacy: Primary objective met. Terbinafine superior to griseofulvin with regard to complete cure. Terbinafine statistically significantly superior to griseofulvin in mycological cure, but superiority over griseofulvin in clinical cure was not statistically

Table 15* (con't) **Reference Therapy Controlled Studies in Patients**

Ref.	Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
					significant.
report: Doc. listings: Doc.	protocol:SFO327C2302 invest.: B Elewski, MD, et al. Brazil, Ecuador, Egypt, France, Guatemala, India, Russia, S. Africa start: 18Jul2004 end: 14Mar2006 publ.: None	design, goal & population: Randomized, investigator-blinded, active-controlled, parallel-group study to compare the efficacy and safety of 6-week treatment with terbinafine new pediatric formulation vs. 6-week treatment with griseofulvin pediatric suspension in children with Tinea capitis evaluations: Safety and tolerability: Physical exams, vital signs, taste disturbance, ophthalmologic, AE, SAE and lab evaluations. Efficacy: Mycology, clinical signs and symptoms and global physician assessment.	total: 720 planned, 802 enrolled and analyzed. 122w, 276b, 1 a, 138 other) age: 4-12y planned groups: 2 (analyzed 539 terbinafine and 263 griseofulvin); (346m, 191 f)	form: 62.5 mg terbinafine minitablets; griseofulvin oral suspension, 125 mg/5 ml, 120 ml suspension/bottle duration: 42 days doses: terbinafine: 5-8mg/kg/day determined by patient's body weight. <25kg: 125 mg/day. 25-35kg: 187.5 mg/day >35kg: 250 mg/day griseofulvin: <14kg 12mg/day, 14-23kg 250mg/day, >23kg 500mg/day	status: Complete report: Final dated Jun 21, 2006 general results: Safety and tolerability: Terbinafine has favorable safety profile in this populaton. Taste disturbances, weight loss, liver function abnormalities, neutropenia, ophthalmologic parameters carefully monitored with no apparent drug-related effect. Efficacy: Primary objective was not met, however, terbinafine superior to griseofulvin against T. tonsurans, the most prevalent species in USA, in complete cure and mycological cure.

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No's: CSFO327C 2301 & 2302, Clinical Development, Tabular Listing of all Clinical Studies, CTD Module 5.2, Table 8, Date: 08/17/06, Pages 22 & 23.

The primary objective of the study is to demonstrate that the efficacy of 6 weeks treatment with approximately 5 to 8 mg/kg terbinafine new pediatric formulation is superior to the efficacy of 6 weeks treatment with the maximum labelled dose of griseofulvin, as assessed by complete cure rates at Visit 5 (Week 10/Day 70), in the treatment of tinea capitis in children. The Applicant believes that this objective is accomplished.

- Terbinafine is statistically significantly superior to griseofulvin in **mycological cure**, the first of the secondary efficacy variables.
- The rate of **clinical cures** for terbinafine is slightly higher than the rate of terbinafine mycological cures, but the superiority over griseofulvin is not statistically significant.

Study C2302

Both pivotal clinical studies, Study C2301 and C2302, have the **same study design** and are very similar. Study centers may differ. Therefore, Study C2302 is not fully described. However, The microbiology (mycology) data and some clinical, on both (combined) pivotal clinical studies, Study C2301 and C2302, are discussed in this review.

Mycology

In order to confirm the clinical diagnosis, a direct microscopic examination of infected host tissue and isolation of dermatophytic pathogen on fungal culture is performed. All mycological evaluations are performed using skin scrapings taken from the target lesions.

The investigator performs the following procedures:

- Target area
  - At Visit 1, a target area is designated. The target area is used for taking samples for

microscopy and culture.

- KOH Microscopy
  Samples for microscopic evaluation are taken at Screening, Week 3 (Visit 3/Day 22), Week 6 (Visit 4/Day 42), and at the end-of-study [EOS = Week 10 (Visit 5/Day 70)} or at early discontinuation and are sent to the central mycology laboratory.
- Fungal culture
  Samples for fungal culture are taken at Screening, Week 3, Week 6 and at the end of study (Week 10) or at early discontinuation and are sent to the central mycology laboratory. Randomization of the patients occurs prior to receiving the fungal culture results.

Microscopy and culture are performed at each visit according to the Assessment schedule even if patients consider themselves to be completely sign/symptom-free. Subjects who are enrolled into the study but fungal culture result is negative at baseline may continue the study at the investigator's discretion.

MYCOLOGICAL EVALUATIONS
(NDA 22-071, Appendix 3)

Specimen Acquisition

The clinical presentation of tinea capitis is variable, ranging from a chronic non-inflammatory process with minimal alopecia to an acute infection with suppurative, boggy kerion resulting in significant alopecia and scarring. Additional features can include diffuse scaling, black dot formation, short hair stubs, pustulation, lymphadenopathy and on occasion a papulosquamous dermatophytid reaction usually restricted to the face, chest and back. The specific disease presentation observed is attributed to the dynamic of the unique fungal pathogen/host interaction. Confirmation of suspected clinical diagnosis is made by direct microscopic examination of infected host tissue and isolation of dermatophytic pathogen on fungal culture.

The investigator performs all procedure for mycological evaluation and sampling.

- **Target Area Selection**
  Specimen for *in vitro* mycological studies is obtained from the target area (selecting symptomatic areas of the scalp which demonstrate the least inflammation).
- **Target Area Preparation**
  Thoroughly clean the specimen sites with an isopropyl alcohol swab so as to remove as much contaminated debris, natural hair oils and patient applied topical moisturizers as possible. This effort should help minimize possible interference from these agents with direct microscopy and subsequent fungal pathogen isolation on culture media.

Specimen Collection

Sample for mycology tests are collected at the site and are sent to the central mycology laboratory for testing. Specimen for the KOH microscopy is prepared by the central laboratory using the sample from the "Dermapak".

Dermapak® is a designed system for the safe and convenient handling and transportation of dermatological specimens for mycological investigations.

- **Collection of Fungal Sample**
  Samples are taken from the Target Area. Use a new toothbrush (provided by the central laboratory) to remove scalpscale and hair fragments and drop them into an open Dermapak container. From the affected area, trim 3 to 4 hairs close to the scalp, pluck with sterile tweezers, and add to the Dermapak. Collect and send a generous patient specimen that will help to obtain reliable results.

- **Unacceptable Specimens**
  Long hairs and hair clippings are considered unacceptable specimens. They are most likely not infected with the fungus and possibly contain bacterial contaminants on their surfaces that could suppress the growth of the fungal pathogen.
- **Shipping**
  Inoculated Dermapaks are sealed without the use of additional tape, labeled with the identification information and returned to their zip lock bag. Re-cap the used toothbrush, label with patient identification, and include it in the same zip lock bag with the Dermapak.
  Samples should be shipped to the address noted in the mycology laboratory manual.
- **KOH Procedures**
  Specimens from the Dermapaks are used to perform the KOH by the central mycology laboratory. The result(s) is faxed to the site within 48 hours of receipt of the sample.
- **Fungal Culture**
  Specimens from Dermapaks are inoculated onto isolation medium and grown according to the SOP's of the central mycology laboratory. Plates are held 21 days before reporting no growth (negative culture results). Isolates are identified to genus and species.

Expert Report - Efficacy & Mycology

(Combined **CSFO327C 2301** and **CSFO327C 2302** studies analyses)

Clinical Microbiology

Clinical Development (terbinafine HCl mini-tablets), SFO327C, Tinea capitis

- NDA 22-071, Lamisil® Dosage Form: Minitablets, Indication: tinea capitis, **Overall Submission Table of Contents**, 3 Summary,
- NDA 22-071, Lamisil® Dosage Form: Minitablets Indication: tinea capitis, **Summary Table of Contents**, 2.73 Summary of Clinical Efficacy
- Clinical Development, terbinafine HCl mini-tablets, SFO327C, Tinea capitis, **2.7.3 Summary of** Clinical Efficacy in Children with Tinea capitis

Efficacy Assessments:
Efficacy assessments includes: 1) mycology, 2) clinical signs and symptoms, and 3) a global physician assessment.

Samples for KOH microscopy and for fungal culture evaluation are taken at screening, Visit 3 (Week 3, Day 22), Visit 4 (Week 6, Day 42) and at the end of study Visit 5 (Week 10, Day 70), or at early discontinuation, and are sent to the central mycology laboratory.

Laboratory Data:
Laboratory samples are processed centrally through the [redacted] and [redacted] laboratories and the results are sent electronically to Novartis. b(4)

Summary of Clinical Efficacy in Children with Tinea capitis

Author(s): Nyirady, J; L. A. Wraith, and B. Cai. Document type: CTD Clinical summary document, Document status: Final, Release date: 31 Aug 2006
(Novartis, CTD 2.7.3 Summary of Clinical Efficacy, SFO327C/ Tinea capitis)

Comparison and Analyses of Results Across Studies

Protocol No. CSFO327C 2301
- **Study Centers:** Total = 74 Centers
  - US (44), Canada (7), Colombia (9), Egypt (3), Peru (5), South Africa (2), and Venezuela (4)

Protocol No. CSFO327C 2302
- **Study Centers:** Total = 72 Centers
  - US (48), Egypt (4), and South Africa (1), Brazil (2), Ecuador (3), France (4), Guatemala (2), India (5), and Russia (3)

Controlled Efficacy Trials

Table 16 summarizes the baseline disease characteristics of the ITT population for the key studies.
- Study **C2301** has **more** patients with *Trichophyton tonsurans* as the infecting microorganism and fewer infected with *Trichophyton violaceum.*

The studies and groups are otherwise similar with regard to baseline disease characteristics.

Table 16* **Baseline Disease Characteristics - – Studies C2301 and C2302**

	StudyC2301		StudyC2302	
	Terbinafine (N=503)	Griseofulvin (N=244)	Terbinafine (N=537)	Griseofulvin (N=265)
Dermatophyte species - n(%)				
Negative	91 (18.1)	47 (19.3)	96 (17.9)	28 (10.6)
T. tonsurans	264 (52.5)	131 (53.7)	243 (45.3)	126 (47.5)
T. violaceum	57 (11.3)	25 (10.2)	103 (19.2)	57 (21.5)
T. mentagrophytes	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.4)
T. rubrum	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.4)
M. canis	80 (15.9)	37 (15.2)	72 (13.4)	45 (17.0)
M. gypseum	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)
M. audouinni	3 (0.6)	0 (0.0)	17 (3.2)	4 (1.5)
M. vanbreuseghemii	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.4)
Other	5 (1.0)	1 (0.4)	2 (0.4)	2 (0.8)
Total sign and symptom score (TSSS)				
Mean	2.6	2.5	2.8	2.9
SD	1.41	1.36	1.56	1.69
Median	2.0	2.0	3.0	2.0
Min – Max	0-9	0-9	0-9	0-9
Duration of present Tinea capitis infection (days)				
n	503	244	535	265
Mean	199.3	203.2	120.1	113.7
SD	372.92	329.70	236.00	238.46
Median	63.0	87.0	56.0	56.0
Min – Max	2-2880	2-1800	2-2520	1-2160
Area of involvement - n(%)				
Diffuse	249 (49.5)	126 (51.6)	267 (49.7)	126 (47.5)
Localized	254 (50.5)	118 (48.4)	270 (50.3)	139 (52.5)

* Adapted from eNDA 22-071, Letter Date: 09/260/7, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-10, Page 27 (Source: PT-Table 2.7.3.6-2.5).

Clinical Microbiology Comments:

In the aforementioned **Table 16**, for the Baseline Disease Characteristics – Study C2301 and Study C2302, the majority of dermatophyte isolates found is *Trichophyton tonsurans*: Study C2301 [Terbinafine: 52.6% (264/502) ——— & Griseofulvin: 53.7% (131/244)] and Study C2302 [Terbinafine: 45.3% (243/537 & Griseofulvin: 47.5% (126/265)]. b(5)
Microsporum canis is the second most dermatophyte isolate found in Study C2301 [Terbinafine: 15.9% (80/502) ——— and Griseofulvin: 15.2% (37/244)] and third in Study C2302 [Terbinafine: 13.4% (72/537) and Griseofulvin: 17.0% (45/265)]. b(5)

Trichophyton violaceum is the third most dermatophyte found in Study C2301 [Terbinafine: 11.4% (57/502) ——— and Griseofulvin: 10.2% (25/244)] and second in Study C2302 [Terbinafine: 19.2% 103/537) and Griseofulvin: 21.5% (57/265)]. b(5)

Table 17 summarizes the baseline disease characteristics of the **pooled** ITT population. The terbinafine and griseofulvin groups are similar at baseline with respect to baseline disease characteristics.

Table 17* Baseline Disease Characteristics – Combined Data (Studies C2301 and C2302)

	Terbinafine (N=1040)	Griseofulvin (N=509)
Dermatophyte species - n(%)		
Negative	187 (18.0)	75 (14.7)
T. tonsurans	507 (48.8)	257 (50.5)
T. violaceum	160 (15.4)	82 (16.1)
M. canis	152 (14.6)	82 (16.1)
M. audouinni	20 (1.9)	4 (0.8)
M. vanbreuseghemii	3 (0.3)	1 (0.2)
T. mentagrophytes	1 (0.1)	2 (0.4)
T. rubrum	1 (0.1)	2 (0.4)
M. gypseum	1 (0.1)	1 (0.2)
Other	7 (0.7)	3 (0.6)
Total sign and symptom score (TSSS)		
Mean	2.7	2.7
SD	1.49	1.55
Median	3.0	2.0
Min – Max	0-9	0-9
Duration of present Tinea capitis infection (days)		
n	1038	509
Mean	158.5	156.6
SD	312.36	289.05
Median	60.0	60.0
Min – Max	2-2880	1-2160
Area of involvement - n(%)		
Diffuse	516 (49.6)	252 (49.5)
Localized	524 (50.4)	257 (50.5)

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-13, Page 30 (Source: PT-Table 2.7.3.6-2.5).

Clinical Microbiology Comments:

In the aforementioned **Table 17**, for the Baseline Disease Characteristics – Combined Data (Studies C2301 and C2302), the majority of the dermatophyte isolates found is *Trichophyton tonsurans* [Terbinafine: 48.8% (507/1039) ~~48.8% (507/1040)~~ and Griseofulvin: 50.5% 257/509)].

Microsporum canis is a close second with the most dermatophyte isolates found in the 2-studies: [Terbinafine: 14.6% (152/1039) ~~14.6% (152/1040)~~ and Griseofulvin: 16.1% (82/509)].

Trichophyton violaceum is also a close second dermatophyte found in the 2-studies: [Terbinafine: 15.4 % (160/1039) ~~15.4 %(60/1040)~~ and Griseofulvin: 16.1% (82/509)]

Note: By the Clinical Microbiology Reviewer's calculations, in **Table 16**, the number 503 is actually 502. The numbers 502 are 503 is just one digit off. Likewise for **Table 17**, the number 1040 is actually 1039.The aforementioned results in a very small difference in analyses.

Comparison of Efficacy Results of all Studies

Controlled Efficacy Trials

Primary Efficacy Results

The primary efficacy variable in both studies is the Complete Cure rate at end-of study (EOS) in the mITT population (the ITT population, excluding those who had negative mycological culture at baseline).

Complete Cure rates at end-of-study (EOS) for the mITT and ITT populations in the 2 studies are shown in **Table 18** and **Table 19**, respectively.

Table 18* **Complete Cure Rates at EOS in the Pivotal studies (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Study C2301					
Terbinafine (N=411)	190	46.23	12.22 (4.03, 20.40)	0.001	0.004
Griseofulvin (N=197)	67	34.01			
Study C2302					
Terbinafine (N=441)	194	43.99	0.53 (-7.30, 8.36)	0.954	0.894
Griseofulvin (N=237)	103	43.46			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-16, Page 33, Source: [Study C2301, PT-Table 14.2-1.1] and [Study C2302, PT-Table 14.2-1.1]

Complete Cure is defined as negative culture and microscopy and TSSS = 0.

Table 19* **Complete Cure Rates at EOS in the Pivotal Studies (ITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Study C2301					
Terbinafine (N=503)	224	44.53	8.05 (0.62, 15.50)	0.022	0.036
Griseofulvin (N=244)	89	36.48			
Study C2302					
Terbinafine (N=537)	223	41.53	0.40 (-6.85, 7.64)	0.940	0.915
Griseofulvin (N=265)	109	41.13			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-17, Page 33, Source: [Study C2301, PT-Table 14.2-1.2] and [Study C2302, PT-Table 14.2-1.2]

Complete Cure is defined as negative culture and microscopy and TSSS = 0

Note: Additional analyses of Complete Cure rates in [Study C2301] and [Study C2302] (per-protocol population, sensitivity analyses, subgroups and by study center) are found in [Study C2301, PT-Tables 14.2-1.3 to 14.2-1.7] and [Study C2302, PT-Tables 14.2-1.3 to 14.2-1.7].

Clinical Microbiology Comments:
In the aforementioned **Table 18** and **Table 19**, the Clinical Cure Rates at EOS in Study C2301, for both the mITT and ITT populations; terbinafine [46.23% (190/411) & 44.53% (224/503)] are higher and close than griseofulvin [34.01% (67/197) & 36.48% (43.46% (103/237)] which are lower and close.

In the aforementioned **Table 18** and **Table 19**, the Clinical Cure Rates at EOS in Study C2302, for both the mITT and ITT populations; terbinafine [43.99% (194/441) & 41.53% (223/537)] and griseofulvin [43.46% (103/237) & 41.13% (109/265)] are similar.

Secondary Efficacy Results
The secondary efficacy variables are **Mycological Cure** and **Clinical Cure**. Mycological cure and Clinical Cure rates at EOS for the mITT populations are shown in the following **Table 20** and **Table 21**, respectively.

Table 20* **Mycological Cure Rates at EOS in the Pivotal Studies (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Study C2301					
Terbinafine (N=411)	256	62.29	12.04 (3.62, 20.44)	0.003	0.005
Griseofulvin (N=197)	99	50.25			
Study C2302					
Terbinafine (N=441)	268	60.77	0.85 (-6.87, 8.58)	0.892	0.828
Griseofulvin (N=237)	142	59.92			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-18, Page 34, Source: [Study C2301, PT-Table 14.2-2.1] and [Study C2302, PT-Table 14.2-2.1].

Mycological cure is defined as negative culture and microscopy.
Clinical Microbiology Comments:

In the aforementioned **Table 20** the Mycological Cure Rates in Study C2301 and Study C2302 for the pooled mITT population data, terbinafine [62.29% (256/411) & 60.77% (268/441)] are similar and higher than griseofulvin [50.25% (99/197) & 59.92% (142/237)].

Table 21* **Clinical Cure Rates at EOS in the Pivotal Studies (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Study C2301					
Terbinafine (N=411)	258	62.77	6.42 (-1.93, 14.78)	0.059	0.129
Griseofulvin (N=197)	111	56.35			
Study C2302					
Terbinafine (N=441)	279	63.27	2.51 (-5.17, 10.18)	0.585	0.521
Griseofulvin (N=237)	144	60.76			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-19, Page 34, Source: [Study C2301, PT-Table 14.2-2.1] and [Study C2302, PT-Table 14.2-2.1].

Mycological cure is defined as negative culture and microscopy

Clinical Microbiology Comment:
In the aforementioned **Table 21**, the Clinical Cure Rates for Study C2301 and Study C2302 in the mITT population, terbinafine [62.77% (258/411) & 63.27% (279/441)] are similar and higher than griseofulvin [56.35% (111/197) & 60.76% (144/237)].

Combined Efficacy Data

A combined data analysis for efficacy is planned prospectively and is performed using the 2 pivotal studies. The analysis is performed essentially according to the same plan as that used for the individual studies.

Table 22 presents the results of the analysis of **Complete Cure** at EOS, end-of-study, in the pooled mITT population, the primary efficacy criterion in the individual studies.

Table 22* **Complete Cure Rates at EOS in the Pooled Data (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Terbinafine (N=852)	384	45.07	5.90 (0.22, 11.58)	0.024	0.043
Griseofulvin (N=434)	170	39.17			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-20, Page 35, Source: [PT-Table 2.7.3.6-3.1].

Complete Cure is defined as negative culture and microscopy and TSSS = 0

Clinical Microbiology Comment:
In the aforementioned **Table 22**, the Clinical Cure Rate at EOS for the pooled mITT population data, terbinafine [45.07% (384/852)] is higher than griseofulvin [39.17% (170/434)].

Table 23 presents the results of the analysis of Mycological Cure at EOS in the pooled mITT

population.

Table 23* **Mycological Cure Rates at EOS in the Pooled Data (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Terbinafine (N=852)	524	61.50	5.97 (0.27, 11.68)	0.029	0.039
Griseofulvin (N=434)	241	55.53			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-21, Page 36, Source: [PT-Table 2.7.3.6-4.1].

Complete Cure is defined as negative culture and microscopy and TSSS = 0

Clinical Microbiology Comments:
In the aforementioned **Table 23**, the Mycological Cure Rate at EOS for the pooled mITT population data, terbinafine [61.50% (524/852)] is much higher than griseofulvin [55.53% (241/434).

Table 24 presents the results of the analysis of Clinical Cure at EOS in the pooled mITT population.

Table 24* **Clinical Cure Rates at EOS in the Pooled Data (mITT Population)**

Treatment	n	Proportion (%)	Difference (95% CI) [1]	p-value [2]	p-value [3]
Terbinafine (N=852)	537	63.03	4.27 (-1.38, 9.93)	0.091	0.136
Griseofulvin (N=434)	255	58.76			

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C, Tinea capitis, CTD 2.7.3, Table 3-22, Page 36, Source: [PT-Table 2.7.3.6-5.1].

Complete Cure is defined as negative culture and microscopy and TSSS = 0

Clinical Microbiology Comments:
In the aforementioned **Table 24**, the Clinical Cure Rate at EOS for the pooled mITT population data, terbinafine [63.03% (537/852)] is higher than griseofulvin [58.76% (434/434).

Comparison of Efficacy Results in Specific Subgroups

- Demographic factors

The demographic subgroups evaluated are race (Caucasian, Black, Oriental, Other), sex and age group (< 4 years, 4 to 8 years, 9 to 12 years). Country (US or non-US) subsets are also evaluated.

- Disease Factors

The pooled data and the data in the individual studies are evaluated for the dermatophyte species subgroups.

- Overall, about 50% of the 1,549 (actually 1,548) patients randomized into the 2 key studies are infected with *Trichophyton tonsurans.*
- Patients with *Trichophyton violaceum* and *Microsporum canis* infections each comprised about 15% of the population.
- Approximately 17% of patients had a negative culture at baseline.
- The remaining patients (~3%) are infected with *Microsporum audouinni,*

Microsporum vanbreuseghemii, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, and *Microsporum gypseum*.
- 10 patients have other infections.

- The aforementioned proportions remain similar within the terbinafine and griseofulvin treatment group
- Because the causative dermatophyte species in the US is predominantly *Trichophyton tonsurans*, the data for the US and non-US populations are discussed here along with the data for *Trichophyton*.

Table 25* shows the comparisons between terbinafine and griseofulvin in the mITT population for the *Trichophyton tonsurans* and US subsets of the population studied, by study and for the pool.

Table 25* Statistically Superior Results for Terbinafine in the mITT Population for the *Trichophyton tonsurans* and USA Subgroups

	Complete Cure			Mycological Cure			Clinical Cure		
Study:	**C2301**	**C2302**	**Pooled**	**C2301**	**C2302**	**Pooled**	**C2301**	**C2302**	**Pooled**
T. tonsurans	X	X	X	X	X	X	X	Num**	X
USA	X	Num**	X	X	Num**	X	Num**	Num**	Num**

* Adapted from eNDA 22-071, Letter Date: 09/260/07, Protocol No: SFO327C 2301, CTD 2.7.3, Table 3-22, Page 37.

X = terbinafine statistically superior to griseofulvin
** **Num** = terbinafine numerically but not statistically superior to griseofulvin

In the aforementioned **Table 25**, the numerically greater/higher Results for terbinafine in the mITT population for the *Trichophyton tonsurans* and US subsets of the population studied, by study and for the pool, give the following general results:
- Terbinafine is numerically greater / higher in 8 of 9 comparisons for *Trichophyton tonsurans*.
- Comparisons for the US subsets of the population yielded numerically greater/higher results for terbinafine in 4 of 9 comparisons.

Table 26* shows the Primary Efficacy by Dermatophyte Species (mITT Population).

2.3 Primary Efficacy by Dermatophyte Species

Table 2: Complete Cure by Dermatophyte Species (mITT)

	Study 2301		Study 2302	
	Terbanafin	Griseofulvin	Terbanafin	Griseofulvin
T. Tonsurans	($N = 264$)	($N = 131$)	($N = 243$)	($N = 126$)
Success (%)	148 (56.1)	45 (34.4)	116 (47.7)	46 (36.5)
p-value†	-	< 0.0001	-	0.0464
T. violaceum	($N = 57$)	($N = 25$)	($N = 103$)	($N = 57$)
Success (%)	16 (28.1)	8(32.0)	50 (48.5)	29(50.9)
p-value†	-	0.7941	-	0.8691
Other	($N = 7$)	($N = 4$)	($N = 6$)	($N = 5$)
Success (%)	7 (100.0)	1 (25.0)	2 (33.3)	3 (60.0)
p-value†	-	0.0242	-	0.5671
M. canis	($N = 80$)	($N = 37$)	($N = 72$)	($N = 45$)
Success (%)	19 (23.8)	13(35.1)	22 (30.6)	23(51.1)
p-value†	-	0.2646	-	0.0324
T. audouini	($N = 3$)	($N = 0$)	($N = 17$)	($N = 4$)
Success (%)	0 (0.0)	0 (0.0)	4 (23.5)	2 (50.0)
p-value†	-	NA	-	0.5439

† Fisher's Exact Test.

Source: Reviewer's analysis.

* Mat Soukup, FDA/Biometrics, Subsection 2.3, Review Analysis Table 2, Date: May 2007.
Complete Cure = negative mycology and "TSSS" = 0
Mycological Cure = negative culture and microscopy.
TSSS = "total signs and symptoms score".

Clinical Microbiology Comments:
In the aforementioned FDA analysis **Table 26,** the primary efficacy ("complete cure") success results for Study 2301 and Study 2302 in the mITT population are as follows:

- For *Trichophyton tonsurans*: terbinafine [56.1% (148/264) & 47.7% (116/243) are higher than griseofulvin [34.4% (45/131) & 36.5% (46/126)]. The griseofulvin success results (34.4% & 36.5%) are very close to each other.
- For *Microsporum canis*: terbinafine [23.8% (19/80) & 30.6% (22/72) are lower than griseofulvin (35.1% (13/37) & 51.1% (23/45)].
- For *Trichophyton violaceum*: terbinafine [28.1% (16/57) & 48.5% (50/103)] are lower than griseofulvin [32.0% (8/25) & 50.9% (29/57)]. The *Trichophyton violaceum* success results for Study 2301 are low as compared to the results observed in Study 2302.

Overall Clinical Microbiology Summarization of Efficacy Results

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NDA 22-071 / SN-000 **DATE REVIEW COMPLETED: 05/20/07**

The Clinical and Microbiology (mycology) data (Study 2301 and Study 2302) demonstrates that terbinafine is efficacious in the clinical and mycological treatment of tinea capitis in children infected with *Trichophyton tonsurans*, the most prevalent causative organism in the USA.

MIC Expert Report

(SFO327C)

Susceptibility of Dermatophyte Isolates Obtained from a Large Worldwide Terbinafine Tinea Capitis Clinical Trial

Author(s)

b(5)

- **Document Type:** Expert Report / **Document Status:** Final **Release Date:** 08/04/06

Introduction

Tinea capitis is a common fungal infection of the scalp occurring mainly in prepubertal children [8]. The disease is been recognized as an important public health problem in the U.S. with 13% of school children, especially those of African-American descent, testing positive for dermatophytes (carrier state) [9]. Fungal species causing these infections belong to the 2 dermatophytic genera *Trichophyton* (anthropophilic, human reservoir) and *Microsporum* (zoophilic, animal reservoir). Understanding the epidemiology and antifungal susceptibility of the organisms is critical, because management of infections caused by different genera may differ [10], and cures for different dermatophytes species vary, with *Microsporum* often involved in recalcitrant infections [11].

Recent reports shows *Trichophyton tonsurans* to be the main causative organism infecting children with tinea capitis in the United States, achieving near exclusionary proportions [12] and confirming data from a two-decade survey (1961 to 1980) conducted in Chicago [13]. Further, a recent study conducted by in the Center for Medical Mycology in Cleveland showed that, of 123 isolates obtained from local children attending schools, 122 are *Trichophyton tonsurans* and only one is *Microsporum canis* [9]. Similarly, *Trichophyton tonsurans* is the dominant dermatophyte infecting the hair and scalp of children in Canada, replacing *Trichophyton verrucosum*, *Microsporum canis,* and *Microsporum audouinii* [14]. Conversely, *Microsporum canis* is more common in Europe [15,16,17,18,19,20], though the largest increase in recent years is *Trichophyton tonsurans* [10]. *Trichophyton tonsurans* and *Microsporum canis* are both commonly found in Puerto Rico and South America [21,22,23,24,25]. Interestingly, in the Middle East, the predominant organisms are *Microsporum canis*, *Trichophyton tonsurans*, and *Trichophyton violaceum* [26,27,28,], while *Trichophyton violaceum* is reported from >90% of tinea capitis cases across Africa [29,30,31,32]. Similarly, the main infecting agent in children with tinea capitis in India [33,34,35] is also *Trichophyton violaceum.*

To date, the susceptibility patterns of dermatophytes and possible differences in these patterns among isolates taken from different geographic regions of the world is lacking, possibly due to the fact that a reference method to determine the antifungal susceptibility of dermatophytes has not been established. Under the auspices of the Clinical and Laboratory Standards Institute (CLSI) [formerly the National Committee for Clinical Laboratory Standards (NCCLS)] a collaboration of 8

laboratories recently developed a method to determine the susceptibility of dermatophytes to various antifungals [**36,37**], and shows that the method has good inter- and intra- laboratory agreement [**38**].
In the study, the antifungal susceptibility profile of a **representative** sample of (**n = 302**) baseline isolates, collected from subjects enrolled in 2 large, multinational tinea capitis clinical trials ([**CSFO327C 2301**] and [**CSFO327C 2302**]), is determined according to the modification of the CLSI M38 method developed at the ——————————Patients enrolled in the trials come from different geographical regions of the world, including **U.S.** and **non-U.S.** sites. b(4)
Countries involved include **Canada, Puerto Rico, Jamaica, Colombia, Ecuador, Venezuela, Peru, Egypt, South Africa, France, Russia, and India.** As expected, *Trichophyton tonsurans* is the predominant dermatophyte isolated from patients came from the U.S. sites, while isolates form non-U.S. sites were evenly divided between *Trichophyton tonsurans*, *Microsporum canis*, and *Trichophyton violaceum*.

Clinical Microbiology Comments:

- **Represented Study Centers ("collected baseline isolates"):**

  Protocol No. CSFO327C 2301 [Study Center(s): Total = 74 center]:
  United States (44), Canada (7), Colombia (9), Egypt (3), Peru (5), Venezuela (4), and South Africa (2).

  Protocol No. CSFO327C 2302 [Study center(s): 72 Centers]:
  United States (48), Ecuador (3), Egypt (4), France (4), South Africa (1), India (5), Russia (3), Brazil (2), and Guatemala (2).

  MIC Expert Report (SFO327C):
  United States, Canada, Colombia, Ecuador, Egypt, Peru, France, South Africa, Venezuela, and India, Russia, Puerto Rico, and Jamaica.

- **Clinical Microbiology Comments:**
  - Puerto Rico and Jamaica clinical isolates are not represented in either Study 2301 or Study 2302.
  - Brazil and Guatemala clinical isolates are represented in Study 2303, but **not** here.
  - United States, Canada, Colombia, Ecuador, Egypt, Peru, France, South Africa, Venezuela, India, and Russia clinical isolates are represented here.

  - Some of the Clinical Microbiology MIC conclusions may be problematic. The **INDICATIONS AND USAGE** Package Insert label may be "approved" ——————————— b(4)
    ————————, actually not specifying genus and species. There, the problematic differences may not be so significant.

Dermatophytes Tested Include
- *Trichophyton tonsurans*, *Trichophyton violaceum*, *Microsporum canis*, and *Microsporum audouinii*.

Materials And Methods

Isolates
A **representative** 302 baseline isolates are chosen for testing their susceptibility to terbinafine. Samples are selected as following: all samples are used if a total number of samples for a given

isolate is less than 50. The remaining of 300 samples are evenly divided among those isolates with large samples and randomly selected.

All isolates are identified to genus and species level by colonial and microscopic characteristics, as well as standard biochemical tests. Isolates are frozen at -80°C and batched for susceptibility testing.

Table 27 shows the distribution of isolates tested.

Table 27[x] **Dermatophyte Strains from US and non-US sites**

Isolate	US	Non-US
T. tonsurans	63	62
M. canis	32	62
M. audouinii	ND*	19
T. violaceum	2	62

[x] Adapted from eNDA 22-071, Letter Date: 09/260/07, Expert Report, TD 2.7.3, SFO327C/ Lamisil® mini-tablets Table 1, Page 5.

* There are **no** *Microsporum audouinii* isolates obtained from patients enrolled in the clinical trial at US sites.

Antifungal Agent
Terbinafine powder (Lot # 3008844, Batch7A8F1) is provided by Novartis Pharma AG, Basel, Switzerland.

Dermatophyte Antifungal Susceptibility Method
The minimum inhibitory concentration (MIC) of terbinafine against each isolate is determined according to the modification of the CLSI M38A method for susceptibility testing of dermatophytes developed at the [redacted] [38].

b(4)

Isolates are subcultured onto potato dextrose agar [redacted] and incubated at 30°C until good condition is achieved, usually within 7 days. *Trichophyton violaceum* isolates characteristically form compact colonies with numerous chlamydospores and no conidia. In order to obtain conidia for susceptibility testing, the method of Ogasawara et al. [39] are followed, incubating the *Trichophyton violaceum* colonies for 6 weeks or longer until conidia-bearing white fluffy colonies appears on the surface of the original growth. [redacted]

b(4)

Terbinafine powder is reconstituted in DMSO [redacted] and dilutions in the range of 0.5 to 0.001 µg/mL are prepared in accordance with CLSI M38A [40]. [redacted]

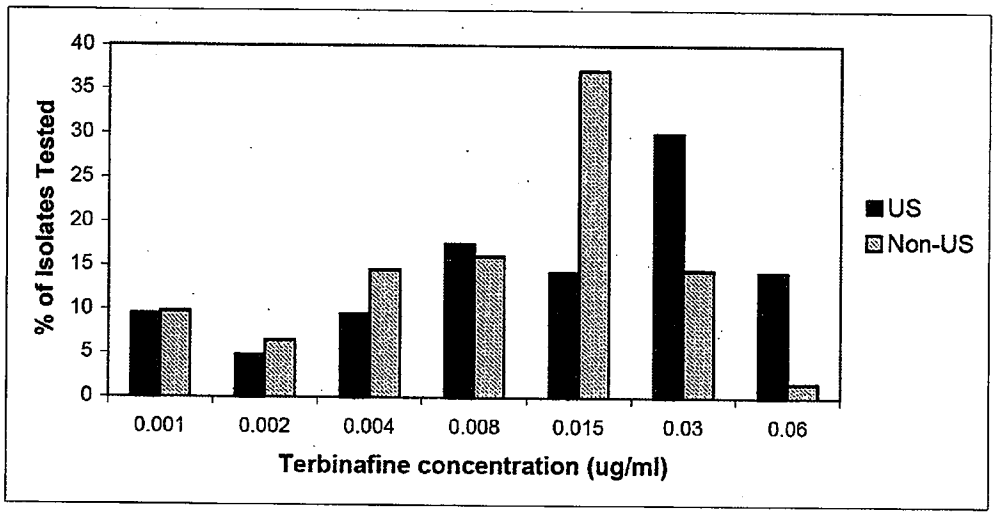
b(4)

[redacted] The MIC endpoint is defined as the lowest concentration that inhibited **80%** of fungal growth as compared to the growth control.

Results

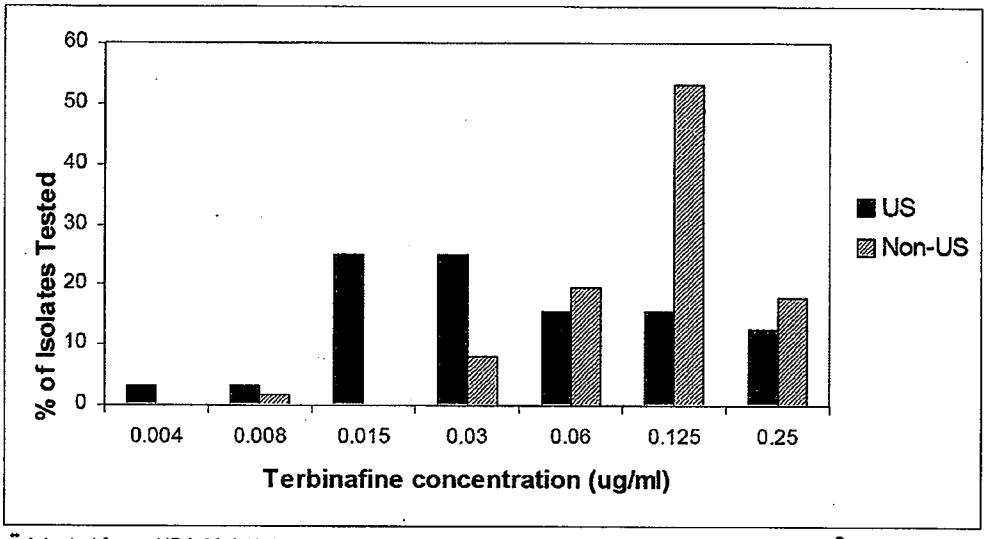
Terbinafine is effective against all dermatophyte isolates obtained in this study, with an MIC range of 0.001 to 0.125 µg/mL (**Figure 9 and Figure 10**).

Figure 9[*] **Comparison of the MICs of *Trichophyton tonsurans* isolated from US and non-US sites**



[*] Adapted from eNDA 22-071, Letter Date: 09/260/07, Expert Report, TD 2.7.3, SFO327C/ Lamisil® mini-tablets Section 3, Figure 1, Page 6.

Figure 10[*] **Comparison of the MICs of *Microsporum canis* isolated from US and non-US sites**



** Adapted from eNDA 22-071, Letter Date: 09/260/07, Expert report, TD 2.7.3, SFO327C/ Lamisil® mini-tablets Section 3, Figure 2, Page 6.

In order to determine whether there is a difference in susceptibility among isolates obtained from US and non-US sites, the MIC_{50} and **MIC_{90}** (defined as the minimum concentration that inhibits 50% and **90%** of isolates, respectively) for each group of isolates are compared, as summarized below in **Table 28**. An inherent 1-dilution **variation** exists in MIC microdilution testing, and a 2-dilution difference meets the generally accepted criteria for agreement **[41]**.

Table 28** **MIC Range, MIC_{50} and MIC_{90} data (in µg/mL) for all Dermatophyte Isolates**

Isolate Group	Range	MIC_{50}	MIC_{90}
T. tonsurans US n=63	0.001-0.06	0.015	0.06
T. tonsurans non-US n=62	0.001-0.06	0.015	0.03
M. canis US n=32	0.004-0.25	0.03	0.25
M. canis non-US n=62	0.008-0.25	0.125	0.25
T. violaceum US n=2	0.002-0.015	0.002	N/A*
T. violaceum non-US n=62	0.001-0.125	0.002	0.03
M. audouinii non-US n=19	0.002-0.125	0.06	0.125

** Adapted from eNDA 22-071, Letter Date: 09/260/07, Expert report, TD 2.7.3, SFO327C/ Lamisil® mini-tablets Section 3, Table 2, Page 7.

* N/A = too few isolates to calculate MIC_{90}

The terbinafine MIC range for all isolates tested is 0.001 to 0.25 µg/mL. The MIC_{90} for

Microsporum canis is identical for both US and non-US sites, while the MIC_{90} for *Trichophyton tonsurans* is within 1 dilution for US and non-US sites.

Clinical Microbiology Comments:
- To determine a valid MIC_{90}, 100 isolates are required.
- "Generally, the acceptable reproducibility of the test is within one twofold dilution of the actual end point. To avoid greater variability, the dilution test must be standardized and carefully controlled....[**42**]."

The MIC_{90} values of the *Trichophyton tonsurans* US and non-US isolates are very close (MIC_{90}s = 0.06 and 0.03 µg/mL). The MIC_{90} values of the *Microsporum canis* US and non-US isolates and *Microsporum audouinii* non-US isolates are identical (MIC_{90}s = 0.25 µg/mL). There appears very little variation in MIC values within the 2 clinical study dermatophyte species themselves. There are very small elevated terbinafine MICs among the 2 clinical study isolates tested from US and non US sources indicating that *Trichophyton tonsurans* and *Microsporum canis* susceptibility results from non-US sites can be compared to results from US sites.

The **MIC Expert Report (SFO327C)**, "Susceptibility of Dermatophyte Isolates Obtained from a Large Worldwide Terbinafine" along with the aforementioned **Table 28** discusses and shows the MIC Range, MIC_{50} and MIC_{90} data (in µg/mL) for the 2-pivotal clinical study dermatophyte isolates tested.

The PK data from the aforementioned PK Study [full study in **Appendix A**] and **Figure 2** and the PK data from the aforementioned, **Pharmacokinetic (PK) Study CSFO327C2101**, **Table 2**, indicates the concentration of terbinafine (base) achieved at the site of infection using the dosing regimen proposed by the Applicant is higher then the MIC_{90} values in the aforementioned **Table 28 – "MIC Range, MIC_{50} and MIC_{90} Data (in µg/mL) for all Dermatophyte Isolates.**

The following **Clinical Microbiology Package Insert Labeling** (revised) is as follows:

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

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CONCLUSIONS

The Clinical Microbiology Conclusions can be found on pages 21 & 22, Package Insert Label (Clinical Microbiology - revised) on pages 23 & 24, and Package Insert Label (Clinical Microbiology - clean) on pages 25, respectively.

Harold V. Silver
Clinical Microbiology Reviewer
DAIOP/HFD-520

cc: NDA 22-071
DAIOP/Division File
DAIOP/Micro/H. V. Silver

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