CLINICAL REVIEW

Application Type	NDA 505(b)(1)
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Letter Date	September 8, 2006
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Reviewer Name	Patricia Brown, MD
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Established Name	Terbinafine hydrochloride
Trade Name	LAMISIL®
Therapeutic Class	Antifungal product
Applicant	Novartis Pharmaceuticals Corp.
Priority Designation	S
Formulation	Oral Granules
Dosing Regimen	Once daily for 6 weeks
Indication	Tinea capitis due to a dermatophyte
Intended Population	Children

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Lamisil® (terbinafine hydrochloride) Oral Granules be approved for oral administration for the treatment of tinea capitis in subjects 4 years and older.

1.2 Recommendation on Post-Marketing Actions

1.2.1 Risk Management Activity

The standard risk management measures of prescription status, professional labeling, and spontaneous adverse event reporting are adequate risk management activities for this drug at this time.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are necessary at this time.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests are necessary.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Lamisil® Oral Granules are intended to be taken by mouth once a day for 6 weeks for the treatment of tinea capitis. Dosing is based on weight and is as follows:

<25 kg 125 mg/day
25-35 kg 187.5 mg/day
>35 kg 250 mg/day

The sponsor has submitted a 505(b)(1) application.

To support the indication, the sponsor has performed two pivotal, multi-center (US and foreign), Phase 3 trials to evaluate safety and efficacy. These trials, SFO327C 2301 and SFO327C 2302, hereinafter referred to as C2301 and C2302 had two arms, Lamisil® oral granules and an active comparator, griseofulvin. A total of 1549 subjects were randomized in these studies, 1040 to the

terbinafine oral granules and 509 to griseofulvin. Since two subjects were randomized to griseofulvin but received terbinafine in error, those subjects receiving terbinafine were 1042 and those receiving griseofulvin were 507. The Phase 2 program included 5 dose-finding trials only one of which, C2101 enrolling 16 subjects, was conducted with the final-to-be-marketed formulation. The remaining four trials, W352, L2306, T201, and T202 enrolled a total of 388 subjects. The safety database includes a total of 1058 subjects exposed to Lamisil oral granules in the two pivotal Phase 3 trials and the Phase 2 study CSFO327C 2101, hereinafter referred to as C2101. Other studies in the clinical development program include two single dose bioavailability studies, L2104 and C2303, and four drug interaction studies; SF W152, SF W153, SF W154, and SF W156.

1.3.2 Efficacy

The applicant has submitted data from two (Study 2301 and Study 2302) randomized, well controlled clinical trials to demonstrate the efficacy and safety of Lamisil® Oral Granules taken once daily for six weeks for the treatment of tinea capitis due to dermatophyte infection in subjects ages 4 to 12. Dosing was based on body weight to achieve 5-8mg/kg . Griseofulvin at the maximum labeled strength (10-20 mg/kg) was used as a comparator.

A total of 1042 subjects were exposed to the terbinafine oral granules and 507 to griseofulvin. The studies were multicenter, US and international, with 768 (49.6%) subjects in the pooled ITT population (all subjects randomized and receiving at least one dose of treatment) being from the US and 781 (50.4%) subjects from non-US sites. In the mITT (all ITT subjects who also had a positive culture at baseline) population 48% of the subjects in study C2301 were from the US and in study C2302 45% of subjects were from the US.

The duration of each of these trials was 10 weeks, with treatment occurring for 6 weeks. The primary efficacy endpoint was complete cure defined as negative KOH, negative culture, and no signs of disease at week 10.

In reference to primary endpoint results, for study C2301, terbinafine achieved superiority over griseofulvin (46.2% versus 34% with a p value of .0013) in the mITT population. In study C2302, superiority was not achieved and treatment effects were nearly the same (44% versus 43.5% with a p value of .9539). Results in the ITT population were consistent with those for the mITT population.

Employing stratification (for primary endpoint) by genus and species of fungal organism, for *T. tonsurans*, terbinafine showed a superior treatment effect as compared with griseofulvin in both studies 2301 and 2302, $\delta = 21.7$ and 11.2 for the two studies respectively. In study 2301 the treatment effect is almost twice that seen in study 2302. For *M. canis*, however, both studies 2301 and 2302 showed negative treatment effects favoring griseofulvin, $\delta = -11.3$ and -20.5, respectively. These findings are of significance in view of the fact that in the U.S., *T. tonsurans*

is the predominant cause of tinea capitis, incidence estimated to be 90-95%.[1,2] *M. canis* is the second most prevalent cause of tinea capitis, incidence estimated to be 1-5%.[1,2]

1.3.3 Safety

To evaluate safety, the sponsor conducted two pivotal Phase 3 trials, C2301 and C2301 and one Phase 1 pharmacokinetic study, C2101. These three studies were conducted with the final-to-be marketed formulation. These three studies also were similar in population and indication studied. Design was also generally similar except that C2101 employed no control while the Phase 3 trials employed an active control, griseofulvin. Information from other trials, W352, L2306, T201 and T202 is considered supportive for safety, as these did not use the oral granule formulation, and generally studied different populations with different dosing regimens.
The three principal safety studies enrolled a total of 1058 subjects who were exposed to the terbinafine oral granule formulation, 1042 in the pivotal studies and 16 in the Phase 1 study. For the pivotal studies, median duration of exposure was 42 days. For the Phase 1 study, all 16 patients finished the study, duration of treatment was 42 days and no instances of study drug discontinuation were reported. The 4 month safety update report was reviewed and did not contain new safety information.

No deaths were reported in the pivotal trials or in the dose finding trials. A total of ten serious adverse events involving 6 subjects occurred in the two pivotal trials. In the terbinafine groups, these included events of viral hepatitis, pneumonia, traumatic head injury, fever, nausea, scalp itching, scalp pain, traumatic cataract and traumatic glaucoma. In the griseofulvin group an episode of bacterial arthritis was noted. For 8 of 10 of these events in the terbinafine group a relationship to study drug appears unlikely. For two of them, scalp itching and scalp pain, a relationship to study drug in the terbinafine group is equivocal.

In the pooled pivotal trials, 17/1042 (1.6%) subjects in the terbinafine group and 6/507 (1.2%) subjects in the griseofulvin group experienced discontinuations of study drug for adverse events. In the terbinafine group more subjects experienced study drug discontinuations due to gastrointestinal disorders .6%, infections and infestations .3%, and skin and subcutaneous disorders .6% than in the griseofulvin group; .2%, 0%, and .2% respectively. In the griseofulvin group more subjects experienced study drug discontinuations due to investigations (abnormal) .6% than in the terbinafine group .1%. Subjects having adverse events leading to dose adjustment/temporary interruptions of study drug were 30/1042 (2.9%) in the terbinafine group and 15/507 (3%) in the griseofulvin group.

Overall, roughly the same percentage of subjects 52% (541/1042 exposed to terbinafine as those exposed to griseofulvin 49% (249/507) experienced adverse events. Adverse event rates

[1] Foster KW, Ghannon MA. Epidemiologic surveillance of cutaneous fungal infection in the United States from 1999 to 2002. J. American Academy of Dermatology 2004;50:748-752.
[2] Kenna ME, Elewski BE. A U.S. epidemiologic survey of superficial fungal diseases. J. American Academy of Dermatology 1996;539-542.

between the two study drugs were very similar, differing by less than three percent, across system organ class and preferred term. The most common adverse event across treatment groups was nasopharyngitis occurring in 9.6% of subjects (100/1042) exposed to terbinafine and 10.5% of subjects (53/507) of those exposed to griseofulvin. The second most common adverse event was headache occurring in 7.1% of subjects (74/1042) exposed to terbinafine and 7.7% (39/507) of those exposed to griseofulvin. The third most common adverse event was pyrexia occurring in 7.0% (73/1042) of those exposed to terbinafine and in 7.7% (30/507) of those exposed to griseofulvin.

Of subjects exposed to terbinafine 9.2% (96/1042) were assessed as having treatment related adverse events. Of subjects exposed to griseofulvin 8.3% (42/507) were assessed as having treatment related adverse events. Vomiting occurred in 1.6% (17/1042) of subjects on terbinafine as compared with 1.6% (8/507) of those on griseofulvin. Upper abdominal pain occurred in 1.2% (13/1042) of subjects on terbinafine as compared with 1.0% (5/507) of those on griseofulvin. Diarrhea occurred in 1.1% (11/1042) of subjects on terbinafine as compared with 1.0% (5/507) of those on griseofulvin. Headache occurred in 1.0% (10/1042) of subjects on terbinafine as compared with 1.4% (7/507) of those on griseofulvin. Nausea occurred in 1.0% (10/1042) of subjects on terbinafine as compared with 1.2% (6/507) of those on griseofulvin. Abdominal pain occurred in 1.0% (10/1042) of subjects on terbinafine as compared with .2% (1/507) of those on griseofulvin.

The most common adverse events suspected to be related to study drug and not in current Lamisil labeling include; increased weight, decreased weight, increased appetite, dizziness, hypoesthesia, somnolence, and insomnia. These were not included in the label since the evidence that the drug caused the effect was not strong. An additional three subjects having sore scalp may have been experiencing the effects of terbinafine on fungal organisms. Other adverse events reported in the safety population included neutropenia and elevated transaminases.

1.3.4 Dosing Regimen and Administration

The dosing regimen for Lamisil® Oral Granules is once a day for six weeks based on body weight as follows:

<25 kg	125 mg/day
25-35 kg	187.5 mg/day
>35 kg	250 mg/day

This is the dose that was studied in one Phase 2 trial, C2101, and in the pivotal Phase 3 trials, C2301 and C2302. In study C2101 the parent/guardian was instructed to put the terbinafine study medication into 1 teaspoon of pudding, administer to subject, and then follow with water. Subjects were instructed not to chew the medication but to swallow it whole. For trials C2301 and C2302, because the active comparator griseofulvin needed to be taken with food, all subjects

were instructed to take study medication with a meal. Instructions were to empty bottles containing terbinafine oral granules on to a tablespoon of pudding and the entire tablespoon was to be swallowed. The instructions specified that acidic foods (e.g. orange juice and grapefruit juice) must be avoided when taking study medication. This latter advice was necessary because the terbinafine [redacted] is sensitive to acids and acidic food with pH [redacted] such as orange juice or other fruit juices.

1.3.5 Drug-Drug Interactions

Studies for drug-drug interactions were not performed with the oral granule formulation.

Four randomized, open-label, single-dose studies were performed to assess the interaction of the already approved product, Lamisil® tablets , with fluconazole (SF W152), Cotrimoxazole DS (SF W153), zidovudine (SF W154) and theophylline (SF W156).

The proposed labeling for Lamisil® Oral Granules will follow that for the already approved product Lamisil® Tablets with the addition of the following statements:

The influence of terbinafine on the pharmacokinetics of flucanazole, trimethoprim, sulfamethoxazole, zidovudine or theophylline was not considered to be clinically significant.

Co-administration of a single dose of fluconazole (100mg) with a single dose of terbinafine resulted in a 52% and 69% increase in terbinafine Cmax and AUC, respectively. Fluconazole is an inhibitor of CYP 2C9 and CYP 3A enzymes. Based on these findings, it is likely that other CYP 2C9 inhibitors (e.g. amiodarone) and CYP 3A inhibitors (e.g. ketoconazole) may also lead to a substantial increase in the systemic exposure (Cmax and AUC) of terbinafine.

1.3.6 Special Populations

Pediatrics:
The indication for Lamisil® Oral Granules is tinea capitis which affects children primarily between ages 3 and 7.[1] Lamisil® Oral Granules is a new dosage form; therefore a pediatric assessment is required by the Pediatric Research Equity Act (PREA). In accord with the Best Pharmaceuticals for Children Act, the FDA issued a Pediatric Written Request (PWR) for terbinafine on December 28, 2001. This was amended July 14, 2003, October 17, 2003, March 16, 2006, and May 15, 2006.

Lamisil® Oral Granules were studied in two Phase 3 trials enrolling 1042 subjects, ages 4 to 12, having tinea capitis, and who were treated with Lamisil® oral granules (1021 at a known dose). Subjects received oral granules at the labeled dose for 6 weeks (mean exposure was 39.8 days, median was 42 days). The most common adverse reactions were nasopharyngitis, headache,

[1] Elewski BE. Tinea capitis: A current perspective. Continuing Medical Education. Journal Of American Academy of Dermatology 2000;42:1-20.

pyrexia, vomiting, upper respiratory tract infection, abdominal pain (including upper), and diarrhea.

Lamisil® Oral Granules were tested for safety and efficacy within the pediatric population across subgroups including age, race, and gender. Notable differences within and between these subgroups were not seen for efficacy or safety.

Pregnancy:
For the pivotal studies, females of childbearing potential (all post-menarche females) must have had a negative serum pregnancy test at entry and were required to use a medically acceptable contraception method during the study and for one month after termination of treatment. This is appropriate since there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because treatment of tinea capitis can be postponed until after pregnancy is completed, it is recommended that LAMISIL® (terbinafine hydrochloride) Oral Granules not be initiated during pregnancy. The pregnancy category assigned is B.

Nursing Mothers:
Recommended labeling generally follows that for the already approved product, Lamisil® Tablets and is as follows: After oral administration, terbinafine is present in breast milk of nursing mothers. The ratio of terbinafine in milk to plasma is 7:1. Treatment with LAMISIL® Oral Granules is not recommended in nursing mothers.

Geriatric Use:
Recommended labeling generally follows that for the already approved product, Lamisil® Tablets and is as follows: LAMISIL® (terbinafine hydrochloride) Oral Granules has not been studied in geriatric patients.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor, Novartis, has submitted a 505(b)(1) application for Lamisil® (terbinafine hydrochloride) Oral Granules. The oral granules are immediate release, film-coated oral granules packaged in a laminated aluminum packet. Each packet contains approximately either 30 or 45 off-white to yellowish, round, biconvex, film-coated tablets, corresponding to single total doses of 125 mg or 187.5 mg (terbinafine base equivalent) per packet. Each granule contains 4.6875 mg of terbinafine hydrochloride, corresponding to 4.167 mg of terbinafine base. The active ingredient, terbinafine hydrochloride, is a synthetic allylamine derivative that exerts a fungicidal effect by specific inhibition of fungal squalene epoxidase with resultant deficiency of ergosterol (an essential component of fungal cell membranes), over-accumulation of sqaulene, and resultant fungal cell death. Inactive Ingredients include the following: basic butylated methacrylate copolymer, colloidal silicon dioxide NF, dibutyl sebacate nf, hypromellose USP, magnesium stearate NF, microcrystalline cellulose NF, nitrogen NF (filling gas), polyethylene glycol NF, sodium lauryl sulfate NF, and sodium starch glycolate NF. See product review by Yichun Sun, PhD.

2.2 Currently Available Treatment for Indications

The only FDA approved drug for the indication of tinea capitis is griseofulvin, which has been available for approximately 50 years. The recommended has been 10-15 mg/kg/day of the microsize form; however, an increasing number of treatment failures has been seen with this dose. The adverse effects are generally minor, with headache and gastrointestinal upset being the most common. Serious side effects are rare and no laboratory monitoring is required.[1]

Another product is itraconazole, approved for the treatment of onychomycosis. There are generally few controlled studies of this drug in tinea capitis; however this drug has been approved for use in infants age 6 and older for treatment of oral thrush. Recommended doses include 5mg/kg/day for a month or pulse therapy 5mg/kg/day for 1 week per month for 1 to 3 pulses. Reported adverse effects include nausea, vomiting, and liver function abnormalities (approximately 1 %).[2]

A third product is fluconazole, approved for prophylaxis against fungal infections. There are few studies involving this drug, and standard dosing has not been established according to Pomeranz and Sabnis.[3] Sobera and Elewski[4] list a suggested regimen for fluconazole as 6mg/kg/day for 3

[1] Pomeranz AJ and Sabnis SS. Tinea Capitis: Epidemiology, Diagnosis and Management Strategies. Pediatric Drugs 2002;4:12:779-783.
[2] *Ibid, p. 781.*
[3] *Ibid, pp. 781-782.*
[4] Sobera JO and Elewski BE. Chapter 77 Fungal Diseases, p.18 in Dermatology Online: Bologna JL, Jorizzo JL, and Rapini RP, Elsevier © 2007.

to 6 weeks. The most common adverse events are nausea, vomiting, and liver enzyme elevations.[1]

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient, terbinafine hydrochloride, is available in the United States in the form of Lamisil® tablets approved in 1996 for the treatment of onychomycosis (NDA 20-539). The active ingredient is also available as a cream (NDA 20-980) and a solution (NDA 20-749).

2.4 Important Issues with Pharmacologically Related Products

Terbinafine has been associated with hepatic injury (including failure), leucopenia, and neutropenia.

Prior reviewers have expressed concerns relating to changes in the ocular lens and retina. There have been reports of loss of visual fields as well as changes in color vision that were associated with the use of terbinafine.

Some patients experience loss of taste that resulted in significant weight loss in the adult population.

2.5 Pre-submission Regulatory Activity

On January 21, 1998 a meeting was held with the sponsor Novartis with respect to [redacted]

On November 13, 2000 an End-of-Phase 2 meeting was held to provide regulatory guidance on the sponsor's proposed Phase 3 development plan in support of a marketing application for terbinafine [redacted] for the treatment of tinea capitis in children.

Among the discussion items at this meeting were the following:
- The Agency stated that the relevance of using patients exposed to European variants of *T. tonsurans* and *M. canis* may be questionable and requested separate analysis of the U.S. sites.
- The Agency requested that during follow-up, subjects be asked specific questions regarding change in vision, including color vision, change in taste, in addition to constitutional questions.
- If an active control arm is used, the Agency stated that superiority should be demonstrated against griseofulvin micronized suspension used as labeled, or non-inferiority against griseofulvin at the 20mg/kg dose level "(clinical standard)".

[1] Pomeranz AJ and Sabnis SS. Tinea Capitis: Epidemiology, Diagnosis and Management Strategies. Pediatric Drugs;4:12:779-783.

• However in an additional Agency comment it is noted that the lack of a control group makes it difficult to make a causal interpretation of any observed treatment effect and that even a small control group might be helpful.
• The proposed primary end-point for both trials is to be complete cure at end of study, defined as negative microscopy and culture and a total signs and symptoms score equal to 0.
• For fungal infections, the definition of ITT has been modified to allow those subjects with no confirmed fungal infection to be excluded from the efficacy analysis; such an allocation is called a Modified Intent-to-Treat (MITT) population.

On April 18, 2001 the sponsor submitted a [redacted] After discussion with the Agency the sponsor withdrew the protocol from the IND and planned to address safety concerns with additional information.

On December 19, 2000 the sponsor had submitted a Proposed Pediatric Study Request for [redacted] The Division determined that a larger public health benefit would result from study of the oral formulation for the treatment of tinea capitis. A Pediatric Written Request (PWR) was therefore issued on December 28, 2001 and specified Study 1 as a systemic study utilizing an appropriate (new) formulation and the oral tablet to establish relative bioavailability. Studies 2 and 3 were to be performed to evaluate safety and efficacy in tinea capitis.
Key elements of the December 28, 2001 PWR include the following:
• Dosage form is to be appropriate for pediatric population (i.e [redacted]
• Studies 2 and 3 should include patients ages 6-12 years. The sponsor may propose methods to study the adverse events associated with terbinafine in order to conduct this study in the youngest population that is feasible.
• Entry criteria specify patients with a clinical diagnosis of tinea capitis and that the patients enrolled in these studies should be representative of the patients who will be treated in the U.S. All patients should have potassium hydroxide (KOH) wet mount and culture. Baseline CBC and differential should be examined for clinically significant abnormalities.
• The endpoint for studies 2 and 3 is specified as complete cure (mycological and clinical) in the mITT population (those patients who are randomized and dispensed medication and had a positive culture at baseline). A subgroup analysis for each of the dermatophyte species determined by fungal culture is needed.
• Study evaluation is to include LFTs and CBC. Assessments should also be made for changes in vision (visual field loss, color vision) as well as food diaries and weight monitoring in order to assess taste disturbances.

• Drug specific safety concerns include hepatic injury (including failure), leucopenia, neutropenia, changes in ocular lens and retina, loss of visual fields as well as color changes, and loss of taste that has resulted in significant weight loss in the adult population.

On July 2, 2002 a meeting was held with to discuss major changes proposed by the sponsor to the Pediatric Written Request. Key elements of discussion included the following:
• It was agreed that the sponsor would initiate a new PK study designed to evaluate the pharmacokinetics of higher doses of terbinafine in children, these doses being required as it appears that children have decreased systemic levels compared with adults following scaled doses. The sponsor was also encouraged to develop a true pediatric dosage form as this is one of the goals of the Pediatric Rule.
• The comparator griseofulvin should be used at the maximum dose labeled.
• An Independent Data Safety Monitoring Committee should be used to establish and monitor stopping rules.
• Because of reported low efficacy rates of the labeled dose of griseofulvin, the Agency did not believe that it was in the best interest of the Public Health to evaluate another drug based on non-inferiority – especially given the potential for serious adverse events. The studies in the WR were to remain superiority studies.

On July 14, 2003 the Agency amended the Written Request based on proposed changes submitted by the sponsor dated February 19, 2003. Key elements of this written request are as follows:
• The pharmacokinetic study (Study 1) should be a multiple dose study of at least six weeks duration in pediatric patients with tinea capitis, and should include a minimum of 15 evaluable subjects.
• Regarding Studies 2 and 3, each of these studies should be powered with a probability of 95% to detect events from terbinafine that occur at 1%. Also the studies should be powered to show superiority to the active comparator with a test of hypothesis using an alpha of 0.05 (which may require more than 300 patients).
• Age groups to be studied should include patients ages 4-8 years for Study 1 and patients aged 4-12 years for Studies 2 and 3.
• Study evaluations for Study 1 are to include PK assessment at Baseline, Week 3 and Week 6. For Studies 2 and 3 evaluations are to occur at Baseline, Week 3, Week 6 (end-of-treatment evaluation) as well as at Week 10 to assess efficacy. LFTs and CBC should be performed at Baseline, Week 3, and Week 6.
• Studies to assess potential changes in vision (visual field loss, color vision) at baseline and at week 6 would include:
1. Visual acuity being measured with HOTV or LEA symbols as long as the same method is used for both baseline and final acuity, and visual acuity is best corrected.
2. Acceptable to use SPP2 to test color vision in patients less than 11 years of age, patients 11 years of age and older should be tested with a Roth 28-hue or 40-hue.
3. Patients 11 years of age and older should have visual field testing performed with an automated threshold perimeter.

4. Dilated fundoscopy (or color fundus photography) in all patients to evaluate the potential for refractile irregularities in the retina.
- Studies should also include food diaries, weight monitoring and subject and caregiver interviews to assess for taste disturbances at all visits.
- For Clinical Studies 2 and 3, the superiority hypothesis tests may be nested and the primary efficacy variable (complete cure) will be analyzed using Cochran Mantel Haenszel (CMH) test, stratified by center. All efficacy analysis will be presented for the ITT and mITT populations.

On September 11, 2003 a meeting was held to discuss the revised Pediatric Written Request (July 14, 2003). The discussion centered on bioavailabity and PK studies, with the Agency stating that the sponsor should perform two trials. One of these should be a single dose two-way crossover relative bioavailability study in adults comparing the currently marketed 250 mg tablet to the proposed pediatric mini-tabs. The second study should be a single arm six week PK study in children between the ages of 4-8 with tinea capitis. It was noted that because of current policy only study 2 will be directly described in the revised PWR.

On October 17, 2003 the Agency amended the Written Request based on changes proposed by the sponsor and discussed at the meeting of September 11, 2003. Key revised elements of this written request are as follows:
- Study 1 is to be a systemic exposure study in affected patients at steady state utilizing an appropriate pediatric formulation which has had relative bioavailability established versus the currently marketed 250 mg tablet as established in adults. This study is to be performed prior to conducting Studies 2 and 3 in order to assess the appropriate dose.
- A Data Safety Monitoring Committee with pertinent expertise should be used to provide ongoing oversight of trial data regarding the continuing safety of subjects as well as the continuing validity and scientific merit of the trials. The charter of the Committee should include guidelines for monitoring as well as stopping rules.

On March 22, 2004 a meeting was held with the sponsor to discuss the Pediatric Written Request. Key elements of discussion at this meeting included the following:
- The Agency requested that the sponsor revise the category descriptors for the Total Signs and Symptoms Score (TSSS) such that they are clear, static, and specific for the sign or symptom described. The Agency and the sponsor reached agreement on revised category descriptors.
- The Agency made a number of comments regarding the charter of the Data Safety Monitoring Board as provided by the sponsor in the February 27, 2004 Briefing Package. These included the statement by the Agency that only the terbinafine arm needs to be monitored by the DSMB as well as a request by the Agency that the unblinded Novartis statistician be removed from involvement with the data to be provided to the DSMB.

On June 8, 2004 the sponsor requested that the Pediatric Written Request dated October 17, 2003 be amended. The sponsor reported that they received feedback from approximately 10% of its U.S. based investigators stating that they were unable to perform the Roth 28-hue and 40-hue exams. They stated that these exams were rarely used, too long for children to adequately perform and problematic in interpretation of results. The sponsor proposed to amend the WR as

follows: "Acceptable to use SPP2 to test color vision in patients less than 11 years of age, patients 11 years of age and older should be tested with SPP2 or Roth 28-hue or 40-hue." The ophthalmology consultant disagreed, stating that there are significant differences between SPP2 test and Farnsworth-Munshell (FM-100) derived tests such as Roth 28-hue or 40-hue. The consultant recommended that no changes to the Pediatric Written Request be made at this time.

On June 3, 2004 the sponsor submitted protocols for the pivotal Phase 3 studies. These were reviewed and comments sent to the sponsor on July 30, 2004. Key elements of the comments included the following:

- Subjects in the comparator arm should receive griseofulvin at the maximum dose labeled which for Grifulvin V is as follows:

Weight (lbs)	Weight (kg)	Griseofulvin dose
<30	<14	125 mg/day
30-50	14-23	250 mg/day
>50	>23	>500mg/day

- The PWR specifies that ALT, AST, GGT, alkaline phosphatase, and bilirubin should be measured at baseline, week 3, and week 6. The Agency requested that GGT and alkaline phosphatase be added to the serum chemistries planned at these time-points.
- The Agency requested that (as specified in the PWR) a complete blood count with differential be performed at baseline, week 3, and week 6.

On September 16, 2004 a teleconference with the sponsor was held to discuss the Agency's decision to deny the sponsor's request of June 8, 2004 to amend the Pediatric Written Request. The sponsor reiterated its disagreement with using the Roth 28 or Roth 40 test for color vision assessment of pediatric patients ages 11 and 12 enrolled in the pediatric studies being conducted per the Written Request. The Agency reiterated the wide use of the Roth 28 and Roth 40 tests for color vision testing in pediatric patients ages 11 and 12 years old. The Applicant agreed to submit its plans to the Agency for employing the Roth 28 and Roth 40 tests for assessment of color vision testing in pediatric patients ages 11 and 12.

On October 24, 2005 the Pre-NDA meeting was held with the sponsor. Key elements of discussion include the following:

- The Agency stated that the proposal to have the examining ophthalmologist decide whether a visual field defect or a missed plate is clinically significant is not acceptable. Any visual field defect that did not exist at baseline should be considered clinically significant. Any missed number on any plate in the SPP2 test should be considered significant. It is not recommended that the sponsor deviate from the PWR.
- The Agency stated that the primary efficacy population should be the MITT with LOCF. The primary efficacy variable should be complete cure and the efficacy results should be reported for each study.

On December 21, 2005 the sponsor submitted a request that the PWR be amended in reference to ophthalmology testing. The request was reviewed by the ophthalmology consultant and key conclusions from that review follow:

• A recommendation is made that the PWR be amended to include the following tests; SPP3 test for color vision testing in patients less than 11 years of age, Roth 28-hue test for color vision testing in patients less than 11 years of age, and Allen test for visual acuity only foe children who cannot read.
• The Orlova visual acuity test is not acceptable. The Sivtsev-Golovin visual acuity test might be acceptable, but insufficient information is provided.

On March 16, 2006 the Agency amended the Written Request based on proposed changes submitted by the sponsor dated December 21, 2005. Key elements of revision include the following:
• Studies to assess potential changes in vision (visual field loss, color vision) at baseline and at week 6 would include:
1. Best corrected distance visual acuity must be measured on a standardized chart of Arabic numerals or Latin letters in patients who can read. Best corrected distance visual acuity must be measured with HOTV or LEA symbols, as long as the same method is used for both baseline and final acuity, in patients who cannot read.
2. Color vision must be measured in patients less than 11 years of age using a SPP2, SPP3, Roth 40-hue or Roth 28-hue vision test at the end of the study. Color vision must be measured in patients 11 years or older using a Roth 28-hue or 40-hue color vision test at the end of the study.
3. Patients 11 years of age and older must have visual field testing performed at baseline and end of study with an automated threshold perimeter.
4. All patients must have dilated fundoscopy or color fundus photography at the end of study to evaluate the potential for refractile irregularities in the retina.

On April 5, 2006 the sponsor requested clarification regarding the timing requirements for ophthalmology examinations. The sponsor noted that the study protocol is following the requirements of the Pediatric Written Request dated October 17, 2003 with ophthalmology examinations performed at baseline and at week 6 (end of treatment). Only patients with new abnormalities noted at week 6 would have the examination repeated at week 10 (end of study). The amended Written Request dated March 16, 2006 includes statements that color vision testing, visual field testing, and dilated fundoscopy or color fundus photography be performed at end of study. Also on April 5, 2006 the sponsor provided additional information regarding the Sivtsev-Golovin visual acuity test. The sponsor's submission was evaluated by the ophthalmology consultant on May 8, 2006. Key elements of the consultant's response include:
• The consultant stated that ophthalmology was not concerned whether the ophthalmology exams were performed at baseline and week 6 or baseline and week 10. The concern was that study subjects have the second ophthalmic examination even if they discontinue the trial early. To accommodate these comments it was recommended that the Written Request be amended for clarity.
• The Sivtsev-Golovin visual acuity test is not acceptable.

On May 15, 2006 the Agency amended the Written Request based on proposed changes submitted by the sponsor dated December 21, 2005 and April 5, 2006. Key elements of revision include the following:

• Studies to assess potential changes in vision (visual field loss, color vision) at baseline and at week 6 would include:
1. Visual acuity testing unchanged from March 16, 2006 amendment
2. Color vision must be measured in patients less than 11 years of age using a SPP2, SPP3, Roth 40-hue or Roth 28-hue vision test at baseline and at least six weeks after initiation of treatment. Color vision must be measured in patients 11 years or older using a Roth 28-hue or 40-hue color vision test at baseline and at least six weeks after initiation of treatment.
3. Patients 11 years of age and older must have visual field testing performed with an automated threshold perimeter at baseline and at least six weeks after initiation of treatment.
4. All patients must have dilated fundoscopy or color fundus photography at the end of study to evaluate the potential for refractile irregularities in the retina at least six weeks after initiation of treatment.
• Also changed was wording under the regimen section regarding, among related issues, the use of an age-appropriate formulation in the studies described in the Written Request and the fact that development of a commercially marketable formulation is preferable.

2.6 Other Relevant Background Information

This is a new formulation (oral granules) of terbinafine HCl and therefore there is no additional foreign regulatory information available at this time.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please see Chemistry Review by Yichun Sun, PhD. For details regarding the drug substance, reference is made to NDA 20-539, for Lamisil® tablets, approved May 10, 1996.

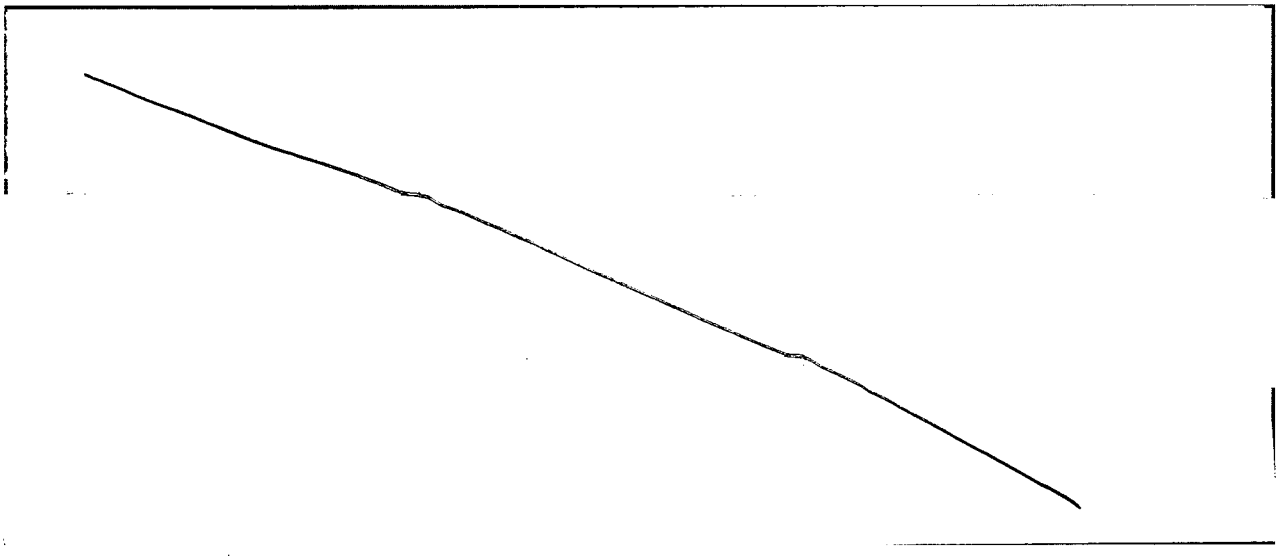
This application is recommended for approval from the Chemistry, Manufacturing, and Controls perspective.

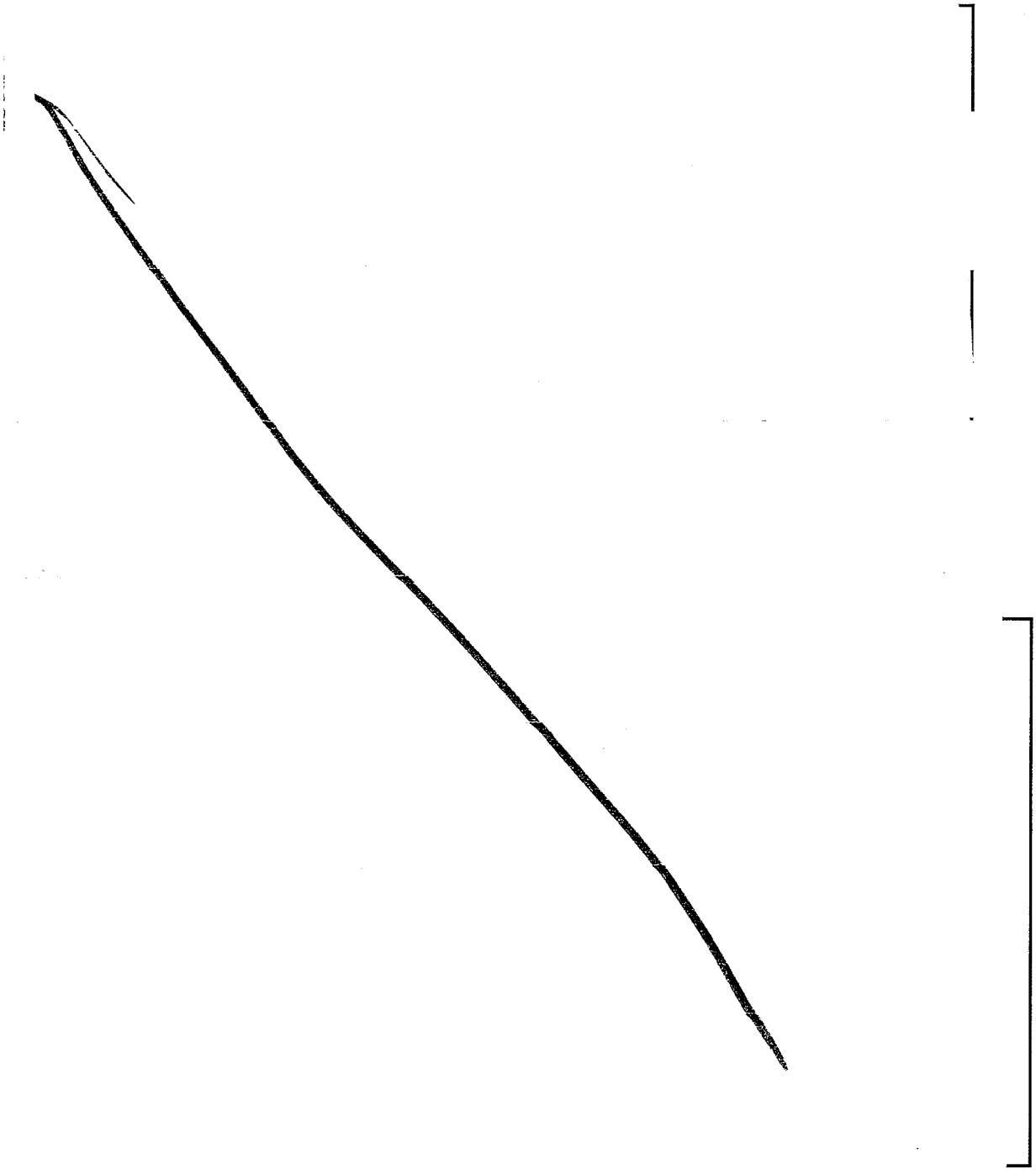
The decision for approval is based on the following from the review by Yichun Sun, PhD:
• The drug substance, terbinafine hydrochloride, is the same compound used in the following marketed products: Lamisil® Tablets (NDA 20-539), Cream (NDA 20-980), and Solution (NDA 20-749).

• The sponsor provided adequate information for composition of the drug products. The drug substance and excipients are controlled to ensure the quality and performance of the drug product.
• The sponsor provided adequate information for the manufacturing process of the drug products.
• The sponsor provided adequate in-process controls to ensure quality of the drug products.
• The test methods used for identification and quantitation of the drug product and its impurities were validated.
• The proposed specifications provided by the sponsor are adequate for ensuring quality of the drug products.
• The packaging materials chosen are safe and are adequate to hold and protect the products.
• A 24 months expiration period for film coated oral granules in packets was proposed by the sponsor based on the results of 12 month stability studies conducted.
• The manufacturing sites have been found acceptable with the Office of Compliance. The EER has an acceptable overall recommendation (16-Nov-2006).

3.2 Animal Pharmacology/Toxicology

Please see animal pharmacology/toxicology review by Dr. Barbara Hill. Based on the nonclinical data available for terbinafine HCl, Dr. Hill found that NDA 22-071 for Lamisil Oral granules is approvable from a pharmacology/toxicology perspective provided that recommended changes are made in the label. The nonclinical portions of the Lamisil tablets/Oral granules label are provided below with recommended insertions indicated by <u>underlining</u> and recommended deletions indicated by ~~strikeout~~.





4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data used in the review of the Lamisil® oral granules drug product came entirely from the sponsor's NDA submission. This also includes the 120 day safety update received on January 8, 2007.

4.2 Tables of Clinical Studies

Table 1: Biopharmaceutic Studies (Bioavailability and Bioequivalence)

Study No.	Study objective, population	subjects	Treatment duration	Dosage	Type of control
C2303	Randomized, open-label, single dose, three period crossover in healthy adult subjects	24 enrolled, 24 completed	3 days	terbinafine tablets or oral granules, single dose 1) group 1- 1 250 mg tab 2) group 2- 2 125 mg tabs 3) group 3- 60 mini-tabs	crossover study
L2104	Randomized, open-label, three period crossover in healthy adults	24 enrolled 23 completed	3 treatment periods over 8 days	3 periods 1) 250 mg tablet fasted 2) 350 mg [redacted] fasted 3) 350 mg [redacted] fed [redacted]	crossover study
L2306	Randomized, open-label, multiple-dose, two-period, crossover food effect on PK, healthy adults	24 enrolled 23 completed	30 days (15+15)	terbinafine [redacted] (175mg [redacted]	crossover study

Source: Sponsor's NDA submission, adapted from CTD Tabular listing of clinical studies, pp. 4-7.

Table 2: Pharmacokinetic Studies in Healthy Volunteers

Study No.	Study objective, population	subjects	Treatment duration	Dosage	Type of control
SF W152	Randomized, open-label, single dose, 3 period Latin square crossover to assess the PK interaction of Lamisil with fluconazole	18 subjects	6 treatment sequences each with 3 treatment periods	Lamisil 250 mg tabs Triflucan 250 mg caps	crossover study
SF W153	Randomized, open-label, single dose, 3 period, 3 treatment study conducted as two 3x3 Latin squares to assess the PK interaction of Lamisil with Cotrimoxazole DS	18 subjects	6 treatment sequences each with 3 treatment periods	Lamisil 250 mg tabs Bactrim Forte tablets (160mg trimethoprim + 800 mg sulfamethoxazole)	crossover study
SF W154	Randomized, open-label, single dose, 3 period Latin square crossover to assess the PK interaction of Lamisil with zidovudine	18 enrolled 17 completed	6 treatment sequences each with 3 treatment periods	Lamisil 250 mg tabs Retrovir 100 mg capsules	crossover study
SF W156	Randomized, open-label, single dose, 3 period Latin square crossover to assess the PK interaction of Lamisil with zidovudine	18 subjects	6 treatment sequences each with 3 treatment periods	Lamisil 250 mg tabs Theolair 125 mg tabs	crossover study

Source: Sponsor's NDA submission, adapted from CTD Tabular listing of clinical studies, pp. 10-14.

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Table 3: Phase 2 Dose-Finding Trials

Study No.	Study objective, population	Planned patients	Treatment duration	Dosage	Type of control
W352	Open-label, multiple-dose PK in children 4–8 years with Tinea capitis	16 (22 enrolled)	28 days for patients with *Trichophyton* 42 days for patients with *Microsporum*	terbinafine tablets, by body weight: <25 kg - 125 mg/day, 25-35 kg - 187.5 mg/day, >35 kg - 250 mg/day	none
C2101	Open-label, multiple-dose PK in children 4–8 years with Tinea capitis	16 (16 enrolled)	42 days	terbinafine oral granules by body weight: 15-<25kg = 125 mg/day 25-35 kg = 187.5 mg/day >35 kg = 250 mg/day	none
T201	Randomized, double-blind, parallel-group study to identify a safe and appropriate treatment duration in patients (>4 yrs) with Tinea capitis caused by *Trichophyton*	150 (177 enrolled)	1, 2, or 4 weeks	terbinafine tablets <20 kg = 62.5 mg/day 20-40 kg = 125 mg/day >40 kg = 250 mg/day	none
T202	Randomized, double-blind, parallel-group study to identify a safe and appropriate treatment duration in patients (>4 yrs) with Tinea capitis caused by *Microsporum*	150 (165 enrolled)	6, 8. 10 or 12 weeks	terbinafine tablets <20 kg = 62.5 mg/day 20-40 kg = 125 mg/day >40 kg = 250 mg/day	active (griseofulvin)

Source: Sponsor's NDA submission, adapted from Summary of Clinical Safety, p. 9.

Table 4: Phase 3 Controlled Efficacy Trials

Study No.	Study objective, population	Planned patients	Treatment duration	Dosage	Type of control
C2301	Randomized, investigator-blinded, parallel-group safety and efficacy study in patients 4 – 12 years of age with Tinea capitis.	720 (748 enrolled)	42 days	Terbinafine oral granules 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 oral granules by body weight: <25 kg - 125 mg/day, 25-35 kg - 187.5 mg/day, >35 kg - 250 mg/day	active (griseofulvin)

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 9.

4.3 Review Strategy

The pivotal Phase 3 trials, C2301 and C2302, were reviewed in detail with regard to safety and efficacy. The Phase 2 study C2101, employing the granule formulation with the same dosing by weight and age groups but no comparator, is reviewed for safety. This study is considered part of the safety database.

The Phase 2 trials; W352, L2306, T201, and T202 are reviewed for safety.

4.4 Data Quality and Integrity

A review of pivotal trial data by the biostatistician and this reviewer did not reveal significant anomalous findings or sites. Therefore the Division of Scientific Integrity (DSI) was not consulted to audit the applicant's data or study sites.

4.5 Compliance with Good Clinical Practices

The sponsor states that all studies were conducted in full compliance with Good Clinical Practice.

4.6 Financial Disclosures

The sponsor states that no clinical investigators are full or part-time employees of Novartis Pharmaceuticals Corporation.

The sponsor has provided FDA Form 3454 with responses from 157 out of 191 principal investigators involved with trials; C2301, C2302, C2101, L2306, T201, T202, C2303. Financial disclosures were not collected for study CSFO327 W352, an open label PK study involving 22 children ages 4 to 8.

The sponsor has also provided FDA Form 3455 with disclosable financial arrangements and interests, which were as follows:

Table 5: Disclosable Financial Arrangements

Investigator	Study No.	Center No.	Subjects enrolled	Amount Disclosed	Category of Disclosure
[redacted]			1.9%	$45,000	Institutional Grant
			1.1%		Stock in the company
			11%	> $25,000	Honoraria for lectures
			14%		Spouse has a grant with Ciba Vision and is PI on a Novartis study

Source: Sponsor's NDA submission, adapted from Financial Disclosure, p. 3.

Study T201 involved 14 principal investigators and was double blind. Study C2301 involved 73 principal investigators and was investigator-blinded. It would appear that potential bias that could result from these financial arrangements is mitigated by the blinding of the trials and the fact that multiple investigators were involved in these trials.

5 CLINICAL PHARMACOLOGY

Please see Office of Clinical Pharmacology Review by Abimbola Adebowale, Ph.D.

5.1 Pharmacokinetics

Single and multiple dose pharmacokinetics of terbinafine oral granules were examined in study C2101 in children ages 4-8 years of age with tinea capitis. In study W352 multiple dose pharmacokinetics were also studied in children 4 to 8 years old, however; the 125 mg tablet (not marketed in the US) was used.

Comparing the results of studies C2101 and W352, conducted in children, with two reference studies in adults revealed that the systemic exposure (AUC and Cmax) of terbinafine in children given 187.5 mg terbinafine oral granules was similar to that obtained in adults given 250 mg terbinafine tablets. However, the systemic exposure in children given 125 mg terbinafine oral granules was lower (median AUC_{0-24} was 30 to 50% lower and median Cmax was 31 to 40% lower) than that obtained in adults given 250 mg terbinafine tablets. These results were supported by a population PK analysis that showed clearance of terbinafine was dependent on body weight in a nonlinear manner.

The lower exposure observed with the 125 mg dose did not result in a lower efficacy in clinical trials.

Table 6: Efficacy versus Weight/Dose

	Study 2301		Study 2302	
	N	% Responder	N	% Responder
<25 kg: 125 mg/day	245	46.1	254	42.9
25 to 35 kg: 187.5 mg/day	124	46.0	143	44.1
> 35 kg: 250 mg/day	42	47.6	44	50.0

Source: Mat Soukup PhD., FDA Biostatistician

The data provided adequately support the efficacy of this product in all dose groups. Therefore, the lower exposure (compared to adult exposure) observed in the lower pediatric dose group (125mg/day) in the PK studies did not result in a difference in efficacy in this dose group compared to the higher pediatric dose groups that had a comparable exposure to the adult population.

Drug Interactions:
Four drug interaction studies (SFOW152, 153, 154, and 156) were performed. These studies demonstrated the influence of terbinafine on the pharmacokinetics of trimethoprim, sulfamethoxazole, zidovudine or theophylline was not clinically significant.

Co-administration of a single dose of fluconazole (100 mg) with a single dose of terbinafine resulted in a 52% and a 69 % increase in terbinafine Cmax and AUC, respectively. Fluconazole is an inhibitor of CYP 2C9 and CYP 3A enzymes. Based on these findings, it is likely that other CYP 2C9 inhibitors (e.g. amiodarone) and CYP 3A inhibitors (e.g. ketoconazole) may also lead to a substantial increase in the systemic exposure (Cmax and AUC) of terbinafine.

Bioavailability:
The relative bioavailability of the oral granule formulation compared to the marketed tablets was examined in study C2303. This study showed that 250 mg of terbinafine administered to healthy adult subjects as 60 oral granules was bioequivalent to one 250 mg or to two 125 mg marketed tablets.

Food Effect:
The effect of food upon oral granule bioavailability was examined in study L2104 and study L2306, performed in healthy adult subjects and using the [redacted]
The Clinical Pharmacology reviewer states that dissolution data provided by the sponsor indicates that the dissolution profiles of the Lamisil® min-tablets were not similar to that of the [redacted] Also the formulations used were not the same strength as the to-be-marketed formulation. The Clinical Pharmacology reviewer therefore did not consider the sponsor's extrapolation of the food effect data from the [redacted] formulation to the oral granule formulation to be useful for labeling purposes..

5.2 Pharmacodynamics

Please see Clinical Microbiology Review by Harold V. Silver.

- The terbinafine MIC ranges for all dermatophyte species isolated in these trials is .001 to .125µg/mL. The MIC_{90} values of *Trichophyton tonsurans* US and non-US isolates are very close (MIC90s = 0.06 and 0.03 µg/mL). The MIC90 values of the *Microsporum canis* US and non-US isolates are identical (MIC90s = 0.25 µg/mL). *Trichophyton tonsurans* and *Microsporum canis* susceptibility results from non-US sites can be compared to results from US sites.
- 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. Data submitted indicate that concentrations in sebum and hair samples were several-fold higher than simultaneous concentrations in plasma samples.
- Data submitted indicate that the concentration of terbinafine (base) achieved at the site of infection using the dosing regimen proposed by the Applicant is higher than the MIC_{90} values for all dermatophyte species isolated in these trials.

5.3 Exposure-Response Relationships

Data from two Phase 2 trials, study T210 and study T202, was used to choose doses to be used in the pivotal Phase 3 trials. According to the applicant, studies T210 and T202 demonstrated that subjects who received >4.5mg/kg/day terbinafine had a statistically better response on all efficacy parameters. A population PK evaluation that had been done to support dose selection for the PK studies, C2101 and W352, had shown that Clearance (CL/F) was influenced by body weight.

The information above was synthesized to derive the dosing for children on a body weight basis; <25 kg to receive 125 mg qd, 25-35 kg to receive 187.5 mg qd and > 35 kg to receive 250 mg qd.

Two pharmacokinetic studies, C2101 and W352, in children aged 4-8 years old, were performed to assess the dosing regimen. Please also see section 5.1 above. This dosing regimen was then used in the two Phase 3 pivotal trials.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for Lamisil (terbinafine hydrochloride) Oral Granules is for the treatment of tinea capitis.

6.1.1 Methods

The efficacy evaluation is based on the detailed review of two pivotal trials, SFO327C2301 and SFO327C2302 hereinafter referred to respectively as C2301 and C2302.

6.1.2 General Discussion of Endpoints

For both pivotal studies, C2301 and C2302, the primary efficacy endpoint was defined as the proportion of subjects having complete clearance 10 weeks (dichotomized to success/failure) from beginning study drug and 4 weeks after last dose. The following definitions are used:
A) Mycological cure - negative microscopy, and negative culture for dermatophyte
B) Clinical cure - Complete clearance of baseline total signs and symptoms (TSSS=0)
C) Complete cure - negative microscopy, negative culture for dermatophyte, and TSSS = 0

The Total Signs and Symptoms Score consisted of the sums of scores for erythema, desquamation/scaling and papules/pustules. This endpoint is static and has a specific point of cure. Agreement was reached upon this endpoint was obtained at the End-of-Phase 2 meeting of

November 13, 2000. At that same meeting it was stated that for fungal infections, the definition of ITT has been modified to allow those subjects with no confirmed fungal infection to be excluded from the efficacy analysis and that such an allocation is called a Modified Intent-to-Treat (mITT) population.

6.1.3 Study Design

The Phase 3 pivotal trials performed as part of the clinical development program were of identical design. The protocol review that follows will apply to both studies unless otherwise noted.

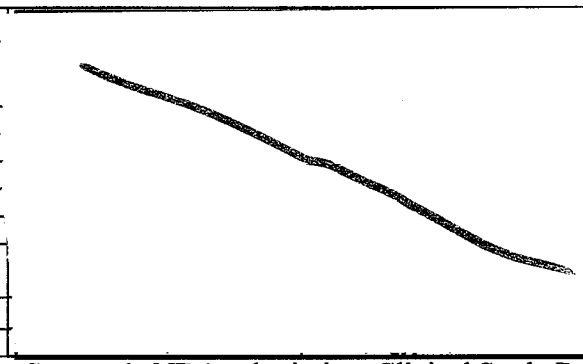
Pivotal Phase 3 Studies: Protocol Number: SFO327C 2301
Protocol Number: SFO327C 2302

Title: "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"

Table 7: Investigators Study C2301

Center No.	Investigator and other important participants	Facility	Number of patients recruited
202			1
203			3
204			2
205			2
207			20
208			3
210			1
301			14
302			11
303			12
304			5
305			1
306			7
307			1
309			1
310			8
401			27
402			20
403			32
404			32
405			20
504			9

505	[redacted]	14
506		3
507		3
509		9
510		12
511		14
513		14
514		4
515		7
516		6
517		14
518		10
519		14
520		12
521		20
522		7
523		1
525		6
526		4
527		10
529		9
530		12
531		8
532		7
534		6
536		5
537		9
538		10
539		5
541		6
544		8
546		7
547		7
551		8
553		9
556		23
557		3
558		5
559		12
560		2

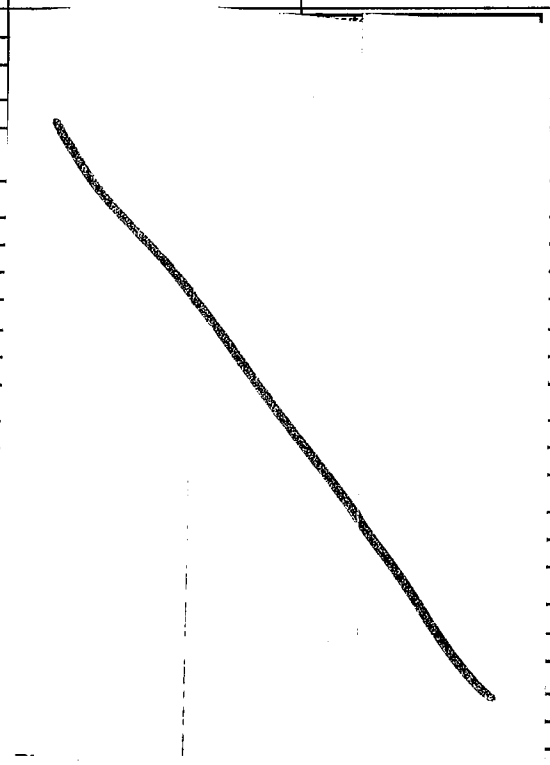
562		5
565		9
601		14
602		1
603		13
604		10
701		24
702		26
801		22
802		21
803		22

Source: Sponsor's NDA submission, Clinical Study Report, Study 2301, Section 16.1.4, pp. 852-857

Study 2301 had 74 Centers: Canada 7, Columbia 9, Egypt 3, Peru 5, S. Africa 2, U.S. 44, and Venezuela 4.

For study 2301, the first subject enrolled June 23, 2004 and the last subject completed March 15, 2006.

Table 8: Investigators Study C2302

Center No.	Investigator and other important participants	Facility	Number of patients recruited
101			4
103			7
105			2
106			42
110			4
111			12
112			5
113			9
116			4
117			3
118			8
119			6
120			9
121			6
122			6
123			17
124			4
126			12
127			2
128			8
129			1
130			17
131			6
132			7

133		12
134		9
138		5
139		1
141		7
142		17
143		11
144		3
145		7
146		3
147		1
148		3
149		6
150		5
151		6
152		9
153		13
154		25
156		19
157		10
158		2
159		4
161		9
162		2
166		1
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252		19
253		19
254		19
301		2
303		3
307		7
310		8
351		8
352		5
353		11
354		31
355		27
401		43
402		20
403		2
461		9
462		15
463		17
502		28
503		15
601		50

Source: Sponsor's NDA submission, Clinical Study Report, Study 2302, Section 16.1.4, pp. 887-893

Study 2302 had 72 Centers: Brazil 2, Ecuador 3, Egypt 4, France 4, Guatemala 2, India 5, Russia 3, South Africa 1, and U.S. 48.

For study 2302, the first subject enrolled July 18, 2004 and the last subject completed March 14, 2006.

Objectives Studies 2301 and 2302:
The primary objective of these studies was to demonstrate that the efficacy of six weeks of treatment with approximately 5-8 mg/kg terbinafine in the new formulation is superior to the efficacy of six weeks treatment with the maximum labeled dose of griseofulvin in the treatment of Tinea capitis in children. Success in assessed by complete cure rates at Visit 5 (week 10).

Secondary objectives included the following:
1) Using the secondary outcome measures, clinical and mycological cure rates at the end of study, to assess the efficacy of 6 weeks treatment with approximately 5-8 mg/kg terbinafine pediatric formulation as compared to 6 weeks maximum labeled dose of griseofulvin.
2) Demonstration that the safety of 6 weeks treatment with approximately 5-8 mg/kg terbinafine pediatric formulation is similar to the safety of 6 weeks treatment with the maximum labeled dose of griseofulvin for Tinea capitis in children.

Overall Study Design:
Studies 2301 and 2302 were conducted as multicenter, randomized, investigator blind, active-controlled, parallel-group trials involving subjects ages 4 to 12 having Tinea capitis. Eligible subjects were randomized 2:1 to the terbinafine or griseofulvin treatment groups, respectively. Subjects in the terbinafine and griseofulvin arms received treatment at doses determined by body weight. Study treatment visits occurred at weeks 3 and 6 and a follow-up visit at week 10.

Protocol:
The protocol for study 2301 was amended three times. Subjects were enrolled under Amendment 1 (April 1, 2004), Amendment 2 (August 26, 2004), and Amendment 3 (February 11, 2005).

The protocol for study 2302 was amended three times. Subjects were enrolled under Amendment 1 (April 1, 2004), Amendment 2 (September 24, 2004), and Amendment 3 (February 11, 2005).

The three major amendments for the studies 2301 and 2302 were essentially the same. Study 2302 included a local amendment for Egypt that excluded children with a creatinine clearance $\leq$ 50 ml/min. Study 2302 also included a local amendment for Russia incorporating the decision that Sivtsev-Golovin or Orlova tables, based on Cyrillic not Latin alphabet, will be used in Russia instead of HOTV and LEA tests for Visual Acuity. In addition, the local Rabkin test, common for color vision examination in Russia, were to be used until SPP2 and Roth 28- or 40-hue tests became available in Russia and approved officially for local trial sites.

Important aspects of Amendment 2 included compliance with FDA requests as follows:
• revised weight groups in griseofulvin treatment arm,

This might have had an impact on the response rates to griseofulvin, since the body weight categories for a given dose of griseofulvin were shifted downward mildly under this amendment. Please also see study procedures, Table 9. Consultation with the FDA statistician resulted in the performance of a sensitivity analysis that addressed this issue and showed no effects on the efficacy findings from the primary analysis specified by the protocol.

• added measurement of gamma GT, alkaline phosphatase, hemoglobin, hematocrit and red blood cells to laboratory tests
• removed Physician Global Assessment from efficacy endpoints
• added a requirement to perform liver function tests for all patients who discontinued treatment due to weight loss ≥ 7 %,
• revised the definition of the safety population to include all patients who received at least one dose of study medication without any other restriction (and drop the requirement for having at least one post baseline safety assessment.)

Amendment 2 also provided for revision of study procedures as follows:
• information to be collected on screening failures: only demography,
• mycology sampling: samples were permitted to be taken from different lesions during the course of the study, instead of a specified target lesion,
• **Appendix 2: changed the word 'notable' to 'significant' in the title, clarified the definition of** clinically significant values and added new tests to the table
• Appendix 7: replaced information on visual examinations with a detailed manual for performing the ophthalmology examinations.

Amendment 3 addressed the following:
FDA requests were included in the Ophthalmology testing manual:
• deleted the time limit for performing the Roth 28 or 40-hue test
• removed the option for bilateral testing of the Roth 28-hue in the source document by replacing the page with a protocol specific source document

Clarified refractile bodies in the study (as recommended by the DSMB):
• added an exclusion criterion for patients with confirmed refractile bodies present at baseline
• added a description for differentiating true refractile bodies from other observations to the ophthalmology manual, and added instructions on how to handle and communicate such an event

Inclusion Criteria

1) Male or female patients 4 to 12 years old with a clinical diagnosis of Tinea capitis, confirmed by positive KOH microscopy, as determined by the central laboratory
2) Females of childbearing potential (all post-menarche females) must have had a negative serum pregnancy test at entry and were required to use a medically acceptable contraception method during the study and for one month after termination of treatment
3) Written Informed Consent must have been obtained prior to performing any study related procedure, according to local regulations.
4) Patients who would be available for the entire study duration

Exclusion Criteria

1) Pregnancy or breast feeding
2) Kerions requiring immediate treatment or treatment with systemic corticosteroids and/or systemic antibiotics
3) Skin disease on the scalp, or any other condition or prior/present treatment which in the opinion of the investigator would interfere **with evaluation of the drug's effect**
4) History of liver disease or current/active liver disease or with elevation of liver enzymes (ALT, AST, GGT, bilirubin) outside of the normal range corresponding to their age, as defined by the central laboratory
5) Clinically significant biochemistry and hematological abnormalities
6) Non-acidic gastroduodenitis, malabsorption syndrome, chronic diarrhea, or any other serious GI disease
7) Systemic antifungal treatment within 2 months prior to the screening visit
8) Use of antifungal agents, corticosteroid preparations, zinc pyrithione or selenium sulfide or tar containing topical treatments for their scalp within 1 week prior to the baseline visit
9) Immunosuppressant therapy, cytostatic therapy or radiation therapy within one month prior to the screening visit
10) Treatment with any investigational drug or biologic within 8 weeks prior to the screening visit or who intend to use other investigational drugs or biologics during the study
11) Hypersensitivity to terbinafine, griseofulvin or any of the inactive ingredients including aspartame
12) Uncooperative, known to miss appointments **(according to the subject's records) or unlikely** to follow medical instructions or were not willing to attend regular visits
13) History of systemic lupus erythematosus (SLE) (added by Amendment 1 as an overall exclusion criterion instead of listed as an exclusion criterion solely for patients taking griseofulvin) or a confirmed diagnosis of refractile bodies (confirmed by a second ophthalmologist) present at baseline (added by Amendment 3).

The following exclusion criteria were necessitated by labeling for griseofulvin microsize suspension:
14) Males who were planning to father children during the treatment period or in the 6 months after the end of treatment - Sexually active males were required to use a barrier method of contraception.
15) Subjects taking substances known to interact with griseofulvin
16) Porphyria or a history of photosensitivity

17) Subjects with penicillin sensitivity were enrolled into the study at the discretion of the investigator because of the possibility of griseofulvin cross-sensitivity with penicillin.

Concomitant Therapy
A number of drugs were excluded from use prior to and during the study. Appendix 4 of the study protocols contains the complete list which was not modified in subsequent protocol amendments. In general, the drugs involved included the following groups:
• medicated topical treatments for the scalp (e.g. corticosteroids, zinc pyrithione, or products containing tar or selenium sulfide)
• systemic antifungal therapies, and topical antifungal therapies used on the scalp
• drugs known to induce an immunocompromised state such as cyclosporine, or tacrolimus
• drugs known to significantly decrease the potency of griseofulvin, e.g. barbiturates and Rifampicin (rifampin)

Subjects taking concomitant medications metabolized by the cytochrome P450 2D6 pathway could be enrolled, but were to be monitored closely for adverse events.

Subjects were instructed to avoid sharing any hair product (shampoo, hair gel, pomades) used by other family members. Subjects were also instructed to avoid thermal/chemical cosmetic hair treatments (e.g. colorants, permanents, medicated conditioners etc.).

Withdrawal Criteria
1) Pregnancy
2) Any of the following changes noted and confirmed by immediate repeat measurements:
   - AST and/or ALT $\geq$ 3 X ULN
   - bilirubin $\geq$ 1.5 X ULN
   - WBC $\leq$ 3000/µl
   - neutrophil count $\leq$ 1000/µl
   - weight loss of $\geq$ 7%

Blinding
Studies 2301 and 2302 were designed as randomized, active controlled trials which were investigator blind. The investigator, assessors, Novartis personnel, and all data analysts were blinded to treatment identity from randomization to database lock. Study drugs were dispensed by a pharmacist or other site personnel who were not involved in study conduct. Subjects were instructed not to reveal the form of medication (minitablets or syrup) they were taking to any site personnel performing assessments or recording data.

Study Procedures:
Subjects in both treatment arms were to take the assigned medication once daily for six weeks. Medication dose depended on body weight.

Table 9: 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

* The griseofulvin weight groups were originally <15 kg, 15-25 kg, >25 kg. They were revised in Amendment 2, per FDA's request.

Source: Sponsor's NDA submission, Clinical Study report, Study 2301, p. 29.

This regimen was designed to provide approximately 5-8.3 mg/kg/day of terbinafine and 10-20 mg/kg/day griseofulvin (maximum labeled dose).

The investigational products were supplied by the sponsor. Terbinafine was provided in bottles containing 62.5 mg/bottle of terbinafine oral granules (15 oral granules per bottle). Ortho Pharmaceutical Corporation, USA, manufactured the Grifulvin V® microsize suspension used in the study. This suspension consisted of griseofulvin oral suspension, 125 mg/5 ml, 120 ml per bottle and was supplied with a spoon.

Subjects took the first dose on Visit 2, Day 1, the day of randomization. If the subject's weight changed categories during the treatment period, the dose did not change. Study medications could be taken in the morning or evening, however, the choice of time of day of administration was to be made at the start of treatment and was to remain constant throughout treatment. Since best absorption of griseofulvin occurs with food, subjects were instructed to take study medication with meals. The spoon provided was to be used to measure the griseofulvin suspension. Since the terbinafine [redacted] is sensitive to acids, acidic food with pH < [redacted] such as orange juice or other fruit juices was to be avoided. According to the protocol, the terbinafine bottles may be emptied onto a tablespoon of pudding and the entire spoonful swallowed.

The study consisted of six weeks of treatment. Visits occurred at Screening (Visit 1), Day 1 or Baseline (Visit 2), Day 22 (Visit 3), Day 42 (Visit 4), and Day 70 (Visit 5).
Efficacy assessments: mycology, clinical signs and symptoms, and a global physician assessment.

Table 10: Assessment Schedule

Procedure	Category*	Pre-treatment Screening	Baseline	Treatment		Post-treatment Follow-up
		Visit 1 Day –7 to –3	Visit 2 Day 1	Visit 3 Day 22	Visit 4 Day 42	Visit 5 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	X
Physical examination	D					
Ophthalmologic evaluations[1]	D	X				
- visual acuity			X		X	X[2]
- visual field testing			X		X	X[2]
- funduscopy			X		X	X[2]
Physician's global assessment	D					X
Mycology	D					
-microscopy		X[3]		X	X	X
-culture (central laboratory)		X		X	X	X
Laboratory evaluations:						
- chemistry, hematology	D	X		X	X	X[2]
- pregnancy test [4]		X		X	X	X[2]
Taste disturbance						
- weight monitoring	D		X	X	X	X
- caregiver interview	D			X	X	X
- food diary	S		X	X	X	X
Randomization			X			
Dispense drug			X	X		
Dosing	D	←----------				
Adverse events recording	D	←----------		As necessary ----------		→
Serious adverse events recording	D	←----------		As necessary ----------		→

*indicates which data are entered into the database (D) and which remain in source documents only (S)
**Total signs and symptoms score
1 baseline must be done before the first dose
2 if abnormality is detected at wk 6
3 performed by the central mycology laboratory
4 serum pregnancy test at Screening visit only, all others are urine pregnancy tests

Source: Sponsor's NDA Submission, Clinical Study Report Study No. SFO327C 2301 and Study No. SFO327C, p. 33.

Efficacy was assessed through mycology results (microscopy and culture), observation of clinical signs and symptoms, and performance of a global physician assessment. Several composite efficacy variables, including the complete cure, clinical cure, and effective treatment rates, were calculated using the Total Signs and Symptoms Score (TSSS). The TSSS consisted of the sum of the scores for erythema, desquamation/scaling and papules/pustules.

Table 11: Signs and Symptoms

Signs & symptom	**0 - absent**	**1 - mild**	**2 - moderate**	**3 - severe**
erythema	None	Pinkness	Redness	Bright redness
desquamation/ scaling	None	Scattered, fine scaling	Diffuse, fine scaling or plaque type scales	Diffuse, adherent plaque type scales
papules/pustules	None	Few, scattered lesion	Numerous scattered lesions	Generalized, almost confluent or confluent lesions

Source: Sponsor's NDA submission, Protocol Amendment No. 1 (Study 2301 and Study 2302), p. 7.

Samples for KOH microscopy and fungal culture were obtained: screening, Visit 3 (week 3), Visit 4 (week 6) and at the end of study Visit 5 (week 10), or at early discontinuation.
Signs and symptoms were evaluated by the investigator on all areas involved at baseline at Visit 1, Visit 3 (week 3), Visit 4 (week 6), and at the end of study (Visit 5, week10). The signs and symptoms evaluated were: erythema, desquamation/scaling, and papules/pustules. Hair loss/breakage, pruritus (evaluated by parent or guardian for patients <10 years of age), lymphadenopathy and scalp dryness were recorded as present or absent. The physician performed an overall assessment of clinical improvement at the end of study as compared to baseline

Safety:
Safety was assessed by monitoring the frequency and severity of adverse events (including clinically significant laboratory abnormalities), changes in vision and changes in vital signs.

Identified in the study protocol were:
The **Primary Safety Endpoint**, consisting of the frequency and severity of the AEs including clinically significant laboratory abnormality changes.
The **Secondary Safety Endpoint**, consisting of the frequency of clinically significant changes in vision and taste.

Safety assessments consisted of physical examinations, monitoring of vital signs and taste disturbances, ophthalmologic evaluation, adverse events, serious adverse events, and laboratory evaluations.
Taste disturbances were to be monitored by weight monitoring, caregiver interview, and patient/food diary.

Patients were to be weighed at Screening, Baseline, Week 3, Week 6, and at end of study (Week 10) or at early discontinuation. A 7% decrease in weight compared to baseline was designated as a clinically significant weight loss, reportable as an adverse event (AE).

The caregiver was to be interviewed at Week 3, Week 6, and at end of study (Week 10) or at early discontinuation regarding whether there had been any significant change in the subject's eating habits since the last visit. Results were to be recorded in the eCRF.

Each subject was given a diary card to be completed daily by the subject's parent/guardian, indicating whether the study drug was taken and if there was a change in appetite or eating habits. The diary was to be returned on the following visit to be reviewed by the study coordinator to aid in determination whether there had been any significant change in the patient's eating habits.

Analysis Populations:
Randomized – all patients who received a randomization number.

Intent-to-treat population (ITT) - all patients who were randomized and dispensed study drug
They were analyzed according to the treatment group assigned at randomization.

Modified ITT (mITT) - all ITT patients who had a positive culture at baseline
These patients were analyzed according to the treatment group assigned. This was the primary analysis population for efficacy.

Per-protocol population –all mITT patients who had no major protocol violations
The per-protocol population was used to provide confirmation of efficacy findings from the modified ITT population.

Safety Population - All patients that received at least one dose of study drug.
Patients were analyzed according to the treatment they received.

Efficacy Endpoints:

Efficacy variables
A) Complete cure - negative microscopy, negative culture for dermatophyte, and TSSS = 0
B) Mycological cure - negative microscopy, and negative culture for dermatophyte
C) Clinical cure - TSSS=0

Primary Efficacy Analysis:
The primary efficacy variable was defined as the complete cure rate at the end of the study (4 weeks after the last dose of study drug) in the mITT population.

The primary efficacy variable was tested under the null hypothesis that there is no difference between terbinafine and griseofulvin (H_0: $P_{terbinafine} = P_{griseofulvin}$) against alternative hypothesis that there is a difference (Ha: $P_{terbinafine} \neq P_{griseofulvin}$), where $P_{terbinafine}$ is the proportion of patients in the terbinafine group who achieved complete cure at the end of the study and $P_{griseofulvin}$ is the proportion of patients in the griseofulvin group who achieved complete cure at the end of the study.

If CMH test was significant in favor of terbinafine, then superiority of terbinafine over griseofulvin was concluded.

For subgroup analyses, the primary endpoint was compared (using chi-square or Fisher's exact test where appropriate) across race, gender, baseline dermatophyte species determined by fungal culture (including patients with negative culture), area of involvement (diffuse vs. localized) at baseline, and hair care habits.

Secondary Efficacy Analysis:
Secondary efficacy variables included mycological cure rate and clinical cure rate. Superiority of terbinafine over griseofulvin was for the variable if the CMH test favored terbinafine significantly.

Descriptive statistics were presented for the TSSS.

Sample Size Determination:
The Pediatric Written Request stated that each of the individual studies "...should be powered with a probability of 95% to detect events from terbinafine that occur at 1%. Therefore, each study should have at least 300 patients who completed the course of terbinafine at the to-be-marketed dose or higher per treatment arm. In addition, the study should be powered to show superiority to the active comparator with a test of hypothesis using and alpha of 0.05 (which may require more than 300 patients)." Assuming that the complete cure rate for griseofulvin is 60% and expected complete cure rate from terbinafine is 75%, the sponsor calculated that the minimum number of patients required would be 321 patients treated with Lamisil and 161 patients treated with griseofulvin in the modified ITT population. The sponsor planned to randomize a total of 720 patients at a ratio of 2:1 terbinafine to griseofulvin because of uncertainty regarding the rate of negative culture at baseline. With the assumption of a 50% screening failure rate, the sponsor expected to screen approximately 1440 patients in order to obtain the 720 to be randomized.

6.1.4 Efficacy Findings

Efficacy Findings:
Study SFO327C 2301 was conducted at 74 investigational sites, 30 of these were foreign and 44 were in the United States. The first subject was recruited June 24, 2004 and the last subject completed March 15, 2006. In total, 747 subjects were randomly assigned to one of two drug treatments: 503 to Terbinafine and 244 to Griseofulvin. Enrollment and disposition of subjects are summarized by treatment group for the randomized patients in Table 12. Study design allowed subjects to do the following: discontinue both the treatment and the study, discontinue treatment and remain in the study, or complete treatment but later discontinue from the study. Approximately 90% of subjects completed treatment.

Similar percentages of subjects discontinued the study in both treatment arms, 10.9% Terbinafine and 11.9% Griseofulvin. Similar percentages of subjects also discontinued from treatment in both treatment arms, 9.1% Terbinafine and 7.4% Griseofulvin. The most common reason for discontinuation whether from treatment or study was loss to follow-up. The second most common reason was subject withdrawal of consent.

Table 12: Subject Disposition Study 2301

	Terbinafine	**Griseofulvin**	**Total**
Number of patients	**n (%)**	**n (%)**	**n (%)**
Randomized	**503**	**244**	**747**
Treated	503 (100.0)	244 (100.0)	747 (100.0)
Completed treatment	457 (90.9)	226 (92.6)	683 (91.4)
Completed study	448 (89.1)	215 (88.1)	663 (88.8)
Discontinued from treatment	**46 (9.1)**	**18 (7.4)**	**64 (8.6)**
Lost to follow-up	17 (3.4)	10 (4.1)	27 (3.6)
Subject withdrew consent	14 (2.8)	2 (0.8)	16 (2.1)
Adverse Event(s)	9 (1.8)	1 (0.4)	10 (1.3)
Protocol violation	5 (1.0)	1 (0.4)	6 (0.8)
Unsatisfactory therapeutic effect	1 (0.2)	2 (0.8)	3 (0.4)
Abnormal laboratory value(s)	0 (0.0)	2 (0.8)	2 (0.3)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued from study	**55 (10.9)**	**29 (11.9)**	**84 (11.2)**
Lost to follow-up	27 (5.4)	19 (7.8)	46 (6.2)
Subject withdrew consent	17 (3.4)	5 (2.0)	22 (2.9)
Adverse Event(s)	6 (1.2)	0 (0.0)	6 (0.8)
Protocol violation	3 (0.6)	2 (0.8)	5 (0.7)
Unsatisfactory therapeutic effect	1 (0.2)	3 (1.2)	4 (0.5)
Administrative problems	1 (0.2)	0 (0.0)	1 (0.1)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)

Source: Sponsor's NDA, Clinical Study Report SFO327C 2301, p. 43.

Study SFO327C 2302 was conducted at 72 investigational sites, 24 of these were foreign and 48 were in the United States. The first subject was recruited July 18, 2004 and the last subject completed March 14, 2006. In total, 802 subjects were randomly assigned to one of two drug treatments: 539 to Terbinafine and 263 to Griseofulvin. Enrollment and disposition of subjects are summarized by treatment group for the randomized patients in Table XX. Study design allowed subjects to do the following: discontinue both the treatment and the study, discontinue treatment and remain in the study, or complete treatment but later discontinue from the study. Approximately 90% of subjects completed treatment.

Patients who discontinued from treatment were 10.1% in the Terbinafine arm and 5.3% in the Griseofulvin arm. More similar percentages of subjects discontinued from the study in both treatment arms, 9.1% Terbinafine and 7.4% Griseofulvin. The most common reason for discontinuation whether from treatment or study was loss to follow-up. The second most common reason was subject withdrawal of consent.

Table 13: Subject Disposition Study 2302

Number of patients	Terbinafine n (%)	Griseofulvin n (%)	Total n (%)
Randomized	**537**	**265**	**802**
Treated	537 (100.0)	265 (100.0)	802 (100.0)
Completed treatment	483 (89.9)	251 (94.7)	734 (91.5)
Completed study	468 (87.2)	241 (90.9)	709 (88.4)
Discontinued from treatment	54 (10.1)	14 (5.3)	68 (8.5)
Lost to follow-up	23 (4.3)	6 (2.3)	29 (3.6)
Subject withdrew consent	11 (2.0)	2 (0.8)	13 (1.6)
Protocol violation	8 (1.5)	1 (0.4)	9 (1.1)
Adverse Event(s)	6 (1.1)	3 (1.1)	9 (1.1)
Administrative problems	2 (0.4)	2 (0.8)	4 (0.5)
Abnormal laboratory value(s)	2 (0.4)	0 (0.0)	2 (0.2)
Unsatisfactory therapeutic effect	2 (0.4)	0 (0.0)	2 (0.2)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued from study	69 (12.8)	24 (9.1)	93 (11.6)
Lost to follow-up	38 (7.1)	18 (6.8)	56 (7.0)
Subject withdrew consent	15 (2.8)	2 (0.8)	17 (2.1)
Protocol violation	6 (1.1)	0 (0.0)	6 (0.7)
Adverse Event(s)	5 (0.9)	2 (0.8)	7 (0.9)
Unsatisfactory therapeutic effect	3 (0.6)	1 (0.4)	4 (0.5)
Administrative problems	2 (0.4)	1 (0.4)	3 (0.4)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)

Source: Sponsor's NDA, Clinical Study Report SFO327C 2302, p. 43.

The following table indicates the number of subjects in the mITT population for both studies and the reason for drop out for subjects who did not complete the week 10 visit.

Table 14: Subject Disposition (mITT)

	Study 2301		Study 2302	
	Griseofulvin (N = 197)	Terbinafine (N = 411)	Griseofulvin (N = 237)	Terbinafine (N = 441)
Adverse Event(s)	1 (1)	8 (2)	3 (1)	5 (1)
Abnormal laboratory value(s)	2 (1)	0 (0)	0 (0)	2 (0)
Unsatisfactory therapeutic effect	0 (0)	1 (0)	0 (0)	1 (0)
Protocol violation	1 (1)	2 (0)	1 (0)	7 (2)
Withdrew consent	2 (1)	8 (2)	2 (1)	9 (2)
Lost to follow-up	7 (4)	14 (3)	5 (2)	21 (5)
Administrative problems	0 (0)	0 (0)	2 (1)	2 (0)
Total	13 (7)	33 (8)	13 (5)	47 (11)

Values in the table correspond to counts with percentages in parentheses.
Source: Statistical Review and Evaluation NDA 22-071, Mat Soukup, Ph.D., Table 5, p. 11.

For Study 2301 subjects screened but not randomized numbered 235.
For Study 2302 subjects screened but not randomized numbered 317.

Table 15: Disposition of Screening Failures (Non-Randomized Patients) Study 2301 and 2302

Disposition Reason	Total (Study 2301) N=235 N (%)	Total (Study 2302) N=317 N (%)
Primary reason(s) for not continuing [1]	235 (100.0)	317 (100.0)
Unacceptable past medical history/concomitant diagnosis	8 (3.4)	7 (2.2)
Intercurrent medical event	1 (0.4)	2 (0.6)
Unacceptable laboratory value(s)	46 (19.6)	86 (27.1)
Unacceptable test procedure result(s)	34 (14.5)	47 (14.8)
Did not meet diagnosis/severity criteria	64 (27.2)	80 (25.2)
Unacceptable use of excluded medications/therapies	3 (1.3)	2 (0.6)
Subject withdrew consent	48 (20.4)	60 (18.9)
Unknown	1 (0.4)	0
Other	50 (21.3)	67 (21.1)

1] Patient could have more than one reason for not continuing.
Source: Sponsor's NDA Submission, Clinical Study Report SFO327C 3201, p. 66.

Protocol Deviations:
As defined by the sponsor, major protocol deviations included; having a missing KOH and/or culture result at week 10, having taken less than 80% of the total dose, or the use of prohibited concomitant medication. Table XX summarizes major protocol violations.

Table 16: Major Protocol Violations (ITT Population) Study 2301

	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)

Source: Sponsor's NDA Submission, Clinical Study Report SFO327C 2301, p. 44.

Table 17: Major Protocol Violations (ITT Population) Study 2302

	Terbinafine N=537 n (%)	**Griseofulvin N=265 n (%)**	**Total N=802 n (%)**
Number of patients with major protocol violations	116 (21.6)	67 (25.3)	183 (22.8)
Number of patients excluded from per-protocol population	189 (35.2)	92 (34.7)	281 (35.0)
Major protocol violations:			
KOH and/or culture result missing week 10	80 (14.9)	30 (11.3)	110 (13.7)
Less than 80% of total dose taken	77 (14.3)	48 (18.1)	125 (15.6)
Used prohibited medication	3 (0.6)	0 (0.0)	3 (0.4)

Source: Sponsor's NDA Submission, Clinical Study Report SFO327C 2302, p. 44

In study 2301 a higher percentage of patients (44.3%) was excluded from the griseofulvin arm as compared with the terbinafine arm (33.4%).

It appears that a number of patients had more than one major protocol violation.

Minor protocol deviations as defined by the sponsor included items such as; enrollment of a few patients less than 4 years old, performance of ophthalmology tests sometimes outside the specified time window due to accessibility of the ophthalmologist, and evaluation of some patients with ophthalmology tests not permitted in the protocol due to, according to the sponsor, misunderstanding or lack of availability of the test. Revisions in the Pediatric Written Request later allowed some of these tests; however, amendments were not made to the protocol.

Analysis Populations:

Table 18: Analysis Populations by Treatment Study 2301

	Terbinafine	Griseofulvin	Total
Analysis Populations:	**n (%)**	**n (%)**	**n (%)**
Randomized	503	244	747
ITT	503 (100.0)	244 (100.0)	747 (100.0)
mITT	411 (81.7)	197 (80.7)	608 (81.4)
Per-protocol	335 (66.6)	136 (55.7)	471 (63.1)
Safety	503 (100.0)	244 (100.0)	747(100.0)

Denominator used in the percentage calculations is all randomized patients.
Source: Sponsor's NDA, Clinical Study Report SFO327C 2301, p. 68 (also Table 11-1 p.44).

Table 19: Analysis Populations by Treatment Study 2302

	Terbinafine	Griseofulvin	Total
Analysis populations:	**n (%)**	**n (%)**	**n (%)**
Randomized	537	265	802
ITT	537 (100.0)	265 (100.0)	802 (100.0)
mITT	441 (82.1)	237 (89.4)	678 (84.5)
Per-protocol	348 (64.8)	173 (65.3)	521 (65.0)
Safety	539 (100.4)*	263 (99.2)	802 (100.0)

*2 patients randomized to griseofulvin were given terbinafine in error and are analyzed for safety in the terbinafine group.
Source: Sponsor's NDA, Clinical Study Report SFO327C 2302, p. 44.

In study 2301 a lower percentage of subjects in the griseofulvin arm (55.7%) was included in the per-protocol population than in the terbinafine arm (66.6%).

Protocol Changes during the Study:
Important protocol changes during the course of the study included the following:
Amendment 2:
• revised weight groups in griseofulvin treatment arm:
This might have had an impact on the response rates to griseofulvin, since the body weight categories for a given dose of griseofulvin were shifted downward mildly under this amendment. Please also see study procedures, Table 9. Consultation with the FDA statistician resulted in the performance of a sensitivity analysis that addressed this issue and showed no effects on the efficacy findings from the primary analysis specified by the protocol.

• mycology sampling: Samples were permitted to be taken from different lesions during the course of the study, instead of a specified target lesion
• Appendix 7: Replaced information on visual examinations with a detailed manual for performing the ophthalmology examinations.

Amendment 3:
FDA requests were included in the Ophthalmology testing manual:

• deleted the time limit for performing the Roth 28 or 40-hue test
• removed the option for bilateral testing of the Roth 28-hue in the source document by replacing the page with a protocol specific source document

Demographic and Baseline Characteristics:

Table 20: Demographic Summary (mITT Population) Study 2301

	Terbinafine N=411	Griseofulvin N=197	Total N=608
Sex - n (%)			
Male	275 (66.9)	113 (57.4)	388 (63.8)
Female	136 (33.1)	84 (42.6)	220 (36.2)
Race - n (%)			
Caucasian	77 (18.7)	41 (20.8)	118 (19.4)
Black	182 (44.3)	79 (40.1)	261 (42.9)
Oriental	0 (0.0)	0 (0.0)	0 (0.0)
Other	152 (37.0)	77 (39.1)	229 (37.7)
Age (years)			
Mean	6.6	7.0	6.7
SD	2.19	2.31	2.24
Median	6.0	7.0	6.0
Min - Max	3-12	3-12	3-12
Age groups - n (%)			
<4 years	3 (0.7)	1 (0.5)	4 (0.7)
4 - 8 years	320 (77.9)	139 (70.6)	459 (75.5)
9 - 12 years	88 (21.4)	57 (28.9)	145 (23.8)
Weight (kg)			
Mean (SD)	25.1 (8.55)	25.6 (7.92)	25.2 (8.35)
Median	23.0	24.5	23.5
Min - Max	13-70	12-65	12-70
Country - n (%)			
USA	195 (47.4)	96 (48.7)	291 (47.9)
Non-USA	216 (52.6)	101 (51.3)	317 (52.1)

Source: Sponsor's NDA, Clinical Study Report SFO327C 2301, pp. 71-72.

In study 2301 (mITT population) a higher percentage (66.9%) of subjects randomized to the terbinafine arm were male than in the griseofulvin arm (57.4%). Conversely, more subjects randomized to the griseofulvin arm (42.6%) were female than in the terbinafine arm (33.1%). With respect to age, a higher proportion of subjects randomized to the terbinafine arm were in the 4 – 8 year old age group (77.9%) as compared with the griseofulvin arm (70.6%).

Table 21: Demographic Summary (mITT Population) Study 2302

	Terbinafine N=441	Griseofulvin N=237	Total N=678
Sex - n (%)			
Male	293 (66.4)	144 (60.8)	437 (64.5)
Female	148 (33.6)	93 (39.2)	241 (35.5)
Race - n (%)			
Caucasian	99 (22.4)	59 (24.9)	158 (23.3)
Black	229 (51.9)	122 (51.5)	351 (51.8)
Oriental	1 (0.2)	0 (0.0)	1 (0.1)
Other	112 (25.4)	56 (23.6)	168 (24.8)
Age (years)			
Mean (SD)	6.8 (2.23)	6.5(2.14)	6.7 (2.20)
Median	6.0	6.0	6.0
Min – Max	3 - 12	3 - 12	3 - 12
Age groups - n (%)			
<4 years	1 (0.2)	1 (0.4)	2 (0.3)
4 - 8 years	332 (75.3)	188 (79.3)	520 (76.7)
9 - 12 years	108 (24.5)	48 (20.3)	156 (23.0)
Weight (kg)			
Mean (SD)	25.0 (8.31)	23.6 (7.63)	24.5 (8.10)
Median	23.0	22.0	23.0
Min – Max	11 - 125	13 - 106	11 - 125
Country - n (%)			
USA	203 (46.0)	101(42.6)	304 (44.8)
Non-USA	238 (54.0)	136 (57.4)	374 (55.2)

Source: Sponsor's NDA, Clinical Study Report SFO327C 2302, pp. 71-72.

In study 2302 (mITT population) significant baseline demographic differences between treatment arms were not seen.

Table 22: Baseline Disease Characteristics by Treatment (mITT Population) Study 2301

	Terbinafine N=411	**Griseofulvin N=197**	**Total N=608**
Dermatophyte species - n (%)			
T. tonsurans	264 (64.2)	131 (66.5)	395 (65.0)
T. violaceum	57 (13.9)	25 (12.7)	82 (13.5)
T. mentagrophytes	0 (0.0)	1 (0.5)	1 (0.2)
T. rubrum	0 (0.0)	1 (0.5)	1 (0.2)
M. canis	80 (19.5)	37 (18.8)	117 (19.2)
M. gypseum	1 (0.2)	1 (0.5)	2 (0.3)
M. audouinni	3 (0.7)	0 (0.0)	3 (0.5)
M. vanbreuseghemii	1 (0.2)	0 (0.0)	1 (0.2)
Other	5 (1.2)	1 (0.5)	6 (1.0)
Total sign and symptom score (TSSS)			
Mean (SD)	2.7 (1.43)	2.6 (1.35)	2.7 (1.41)
Median	2.0	2.0	2.0
Min - Max	0 - 9	1 - 9	0 - 9
Duration of present Tinea capitis infection (days)			
Mean (SD)	210.9 (393.91)	212.2 (328.55)	211.3 (373.72)
Median	84.0	90.0	90.0
Min - Max	2 - 2880	2 - 1800	2 - 2880
Area of involvement - n (%)			
Diffuse	203 (49.4)	106 (53.8)	309 (50.8)
Localized	208 (50.6)	91 (46.2)	299 (49.2)

Source: Sponsor's NDA, Clinical Study Report SFO327C 2301, pp. 81-82.

Table 23: Baseline Disease Characteristics by Treatment (mITT Population) Study 2302

	Terbinafine N=441	**Griseofulvin N=237**	**Total N=678**
Dermatophyte species - n (%)			
T. tonsurans	243 (55.1)	126 (53.2)	369 (54.4)
T. violaceum	103 (23.4)	57 (24.1)	160 (23.6)
T. mentagrophytes	1 (0.2)	1 (0.4)	2 (0.3)
T. rubrum	1 (0.2)	1 (0.4)	2 (0.3)
M. canis	72 (16.3)	45 (19.0)	117 (17.3)
M. audouinni	17 (3.9)	4 (1.7)	21 (3.1)
M. vanbreuseghemii	2 (0.5)	1 (0.4)	3 (0.4)
Other	2 (0.5)	2 (0.8)	4 (0.6)
Total sign and symptom score (TSSS)			
Mean (SD)	2.9 (1.57)	2.9 (1.69)	2.9 (1.61)
Median	3.0	3.0	3.0
Min - Max	0 - 9	0 - 9	0 - 9
Duration of present Tinea capitis infection (days)	440	237	677
Mean (SD)	122.9 (242.16)	104.4 (225.99)	116.4 (236.62)
Median	56.0	42.0	56.0
Min - Max	2 - 2520	1 - 2160	1 - 2520
Area of Involvement - n (%)			
Diffuse	219 (49.7)	111(46.8)	330 (48.7)
Localized	222 (50.3)	126(53.2)	348 (51.9)

Source: Sponsor's NDA, Clinical Study Report SFO327C 2302, pp. 81-82

Within each of the two studies, 2301 and 2302, baseline disease characteristics (or prognostic factors) are generally balanced between treatment arms for the mITT population. In addition, comparing the two studies to each other for, for the two treatment arms, baseline disease factors are also generally balanced.

Table 24: Baseline Disease Characteristics by Treatment, USA Population (mITT Population) Study 2301

	Terbinafine N=195	**Griseofulvin N=96**	**Total N=291**
Dermatophyte species - n (%)			
T. tonsurans	174 (89.2)	86 (89.6)	260 (89.3)
T. violaceum	1 (0.5)	0 (0.0)	1 (0.3)
T. mentagrophytes	0 (0.0)	1 (1.0)	1 (0.3)
M. canis	19 (9.7)	8 (8.3)	27 (9.3)
M. gypseum	1 (0.5)	1 (1.0)	2 (0.7)
Total sign and symptom score (TSSS)			
Mean (SD)	2.9 (1.50)	2.8 (1.43)	2.8 (1.48)
Median	3.0	2.5	3.0
Min - Max	0 - 9	1 - 9	0 - 9
Duration of present Tinea capitis infection (days)	195	96	291
Mean (SD)	149.3 (321.66)	145.2 (257.45)	147.9 (301.55)
Median	60.0	60.0	60.0
Min - Max	2 - 2160	5 - 1800	2 - 2160
Area of involvement - n (%)			
Diffuse	106 (54.4)	49 (51.0)	155 (53.3)
Localized	89 (45.6)	47(49.0)	136 (46.7)

Source: Sponsor's NDA, Clinical Study Report SFO327C 2301, pp. 83-84.

Comparing the baseline disease characteristics for the US and non-US population (table following) within study 2301, the treatment arms are generally balanced within these two population groups. It should be noted that the US population has a much higher percentage of subjects (89.3%) having *T. tonsurans* than the non-US population (42.6%).

Table 25: Baseline Disease Characteristics by Treatment, Non-USA Population (mITT Population) Study 2301

	Terbinafine N=216	**Griseofulvin N=101**	**Total N=317**
Dermatophyte species - n (%)			
T. tonsurans	90 (41.7)	45 (44.6)	135 (42.6)
T. violaceum	56 (25.9)	25 (24.8)	81 (25.6)
T. rubrum	0 (0.0)	1 (1.0)	1 (0.3)
M. canis	61 (28.2)	29 (28.7)	90 (28.4)
M. audouinni	3 (1.4)	0 (0.0)	3 (0.9)
M. vanbreuseghemii	1 (0.5)	0 (0.0)	1 (0.3)
Other	5 (2.3)	1 (1.0)	6 (1.9)
Total sign and symptom score (TSSS)			
Mean (SD)	2.6 (1.35)	2.4 (1.27)	2.5 (1.32)
Median	2.0	2.0	2.0
Min - Max	0 - 8	1 - 7	0 - 8
Duration of present Tinea capitis infection (days)			
Mean (SD)	266.5 (442.72)	276.0 (374.42)	269.5 (421.59)
Median	90.0	90.0	90.0
Min - Max	2 - 2880	2 - 1440	2 - 2880
Area of involvement – n (%)			
Diffuse	97 (44.9)	57 (56.4)	154 (48.6)
Localized	119 (55.1%)	44 (43.6)	163 (51.4)

Source: Sponsor's NDA, Clinical Study Report SFO327C 2301, pp. 85-86.

Table 26: Baseline Disease Characteristics by Treatment, USA Population (mITT Population) Study 2302

	Terbinafine N=203	**Griseofulvin N=101**	**Total N=304**
Dermatophyte species - n (%)			
T. tonsurans	191 (94.1)	95 (94.1)	286 (94.1)
T. violaceum	1 (0.5)	0 (0.0)	1 (0.3)
M. canis	11 (5.4)	6 (5.9)	17 (5.6)
Total sign and symptom score (TSSS)			
Mean (SD)	2.9 (1.39)	2.7 (1.55)	2.8 (1.45)
Median	3.0	2.0	3.0
Min - Max	0 - 7	0 - 8	0 - 8
Duration of present Tinea capitis infection (days)			
n	202	101	303
Mean (SD)	163.8 (304.96)	90.0 (164.81)	139.2 (268.53)
Median	60.0	60.0	60.0
Min - Max	2 - 2520	1 - 1440	1 - 2520
Area of involvement - n (%)			
Diffuse	117(57.6)	56 (55.4)	173 (56.9)
Localized	86 (42.4)	45 (44.6)	181 (43.1)

Source: Sponsor's NDA, Clinical Study Report SFO327C 2302, pp. 83-84.

Table 27: Baseline Disease Characteristics by Treatment, Non-USA Population (mITT Population) Study 2302

	Terbinafine N=238	**Griseofulvin N=136**	**Total N=374**
Dermatophyte species - n (%)			
T. tonsurans	52 (21.8)	31 (22.8)	83 (22.2)
T. violaceum	102 (42.9)	57 (41.9)	159 (42.5)
T. mentagrophytes	1 (0.4)	1 (0.7)	2 (0.5)
T. rubrum	1 (0.4)	1 (0.7)	2 (0.5)
M. canis	61 (25.6)	39 (28.7)	100 (26.7)
M. audouinni	17 (7.1)	4 (2.9)	21 (5.6)
M. vanbreuseghemii	2 (0.8)	1 (0.7)	3 (0.8)
Other	2 (0.8)	2 (1.5)	4 (1.1)
Total sign and symptom score (TSSS)			
Mean (SD)	2.8 (1.71)	3.1 (1.78)	2.9 (1.73)
Median	2.0	3.0	2.0
Min - Max	1 - 9	1 - 9	1 - 9
Duration of present Tinea capitis infection (days)			
Mean (SD)	88.2 (164.65)	115.2 (262.46)	98.0 (205.74)
Median	42.0	42.0	42.0
Min - Max	7 - 1440	5 - 2160	5 - 2160
Area of Involvement – n (%)			
Diffuse	102 (42.9)	55 (40.4)	157 (42.0)
Localized	136 (57.1)	81 (59.6)	217 (58.0)

Source: Sponsor's NDA, Clinical Study Report SFO327C 2302, pp. 85-86.

Comparing the baseline disease characteristics for the US and non-US population within study 2302, the treatment arms are generally balanced within these two population groups. A mild exception may be the duration of present Tinea capitis infection, however the standard deviation on the means is large and the differences between the means of the two treatment arms do not appear to be significant. It should again be noted that the US population has a much higher percentage of subjects (94.1%) having *T. tonsurans* than the non-US population (22.2%).

Primary Endpoint Result

Table 28: Complete Cure Results (mITT-LOCF)

	Study 2301		**Study 2302**	
Treatment	Terbinafine	Griseofulvin	Terbinafine	Griseofulvin
N	411	197	441	237
Success (%)	190 (46.2)	67 (34.0)	194 (44.0)	103 (43.5)
p-value	-	0.0013	-	0.9539

Source: Sponsor's NDA, Clinical Study Reports SFO327C 2301, p. 47 and SFO327C 2302, p. 47.

As can be seen, terbinafine achieved superiority over griseofulvin in study 2301 in the mITT population with a robust p value of 0.0013. In study 2302 superiority was not achieved; the treatment effects (those achieving complete cure) were nearly the same.

Table 29: Complete Cure Results (ITT-LOCF)

	Study 2301		**Study 2302**	
Treatment	Terbinafine	Griseofulvin	Terbinafine	Griseofulvin
N	503	244	537	265
Success (%)	224 (44.5)	89 (36.5)	223 (41.5)	109 (41.1)
p-value	-	0.0223	-	0.9397

Source: Sponsor's NDA, Clinical Study Reports SFO327C 2301, p. 47 and SFO327C 2302, p. 47.

The results in the ITT population were consistent with those for the mITT population.

Secondary Endpoint Results

Table 30: Mycological cure rates at the end of study (mITT population, LOCF)

	Study 2301		**Study 2302**	
Treatment	Terbinafine	Griseofulvin	Terbinafine	Griseofulvin
N	411	197	441	237
Success (%)	256 (62.3)	99 (50.3)	268 (60.8)	142 (59.9)
p-value	-	0.0027	-	0.8923

Source: Sponsor's NDA, Clinical Study Reports SFO327C 2301, p. 48 and SFO327C 2302, p. 48.

Mycological cure was defined as negative microscopy and negative culture at week 10. Terbinafine achieved superiority on this measure over griseofulvin in study 2301 again with a robust p value of 0.0027. The results for study 2302, however, showed near parity in mycological cure for the two treatment arms.

Table 31: Clinical cure rates at the end of study (mITT population, LOCF)

	Study 2301		**Study 2302**	
Treatment	Terbinafine	Griseofulvin	Terbinafine	Griseofulvin
N	411	197	441	237
Success (%)	258 (62.8)	111 (56.3)	279 (63.3)	144 (60.8)
p-value	-	0.0594	-	0.5854

Source: Sponsor's NDA, Clinical Study Reports SFO327C 2301, p. 48 and SFO327C 2302, p. 48.

Clinical cure was defined as TSSS = 0 (clearance of baseline total signs and symptoms) at week 10. In neither study 2301 or 3202 did terbinafine achieve superiority over griseofulvin.

Table 32: Subgroup Analysis Study 2301 - Complete Cure Rates at End of Study (mITT population, LOCF)

	Terbinafine	Griseofulvin	
Subgroup	n / m (%)	n / m (%)	Difference (95% CI) [1]
Race:			
Caucasian	28 / 77 (36.4)	13 / 41 (31.7)	4.65 (-13.19, 22.50)
Black	87 / 182 (47.8)	26 / 79 (32.9)	14.89 (2.24, 27.54)
Oriental	0 / 0	0 / 0	
Other	75 / 152 (49.3)	28 / 77 (36.4)	12.98 (-0.39, 26.34)
Sex:			
Male	125 / 275 (45.5)	41 / 113 (36.3)	9.17 (-1.47, 19.81)
Female	65 / 136 (47.8)	26 / 84 (31.0)	16.84 (3.87, 29.81)
Baseline dermatophyte species:	148 / 264 (56.1)	45 / 131 (34.4)	21.71 (11.61, 31.81)
T. tonsurans	16 / 57 (28.1)	8 / 25 (32.0)	-3.93 (-25.62, 17.76)
T. violaceum	0 / 0	1 / 1 (100.0)	
T. mentagrophytes	0 / 0	0 / 1 (0.0)	
T. rubrum	19 / 80 (23.8)	13 / 37 (35.1)	-11.39 (-29.37, 6.60)
M. canis	1 / 1 (100.0)	0 / 1 (0.0)	100.00
M. gypseum	0 / 3 (0.0)	0 / 0	
M. audouinni	1 / 1 (100.0)	0 / 0	
M. vanbreuseghemii	5 / 5 (100.0)	0 / 1 (0.0)	100.00
Other			
Age group:			
<4 years	2 / 3 (66.7)	0 / 1 (0.0)	66.67
4 - 8 years	150 / 320 (46.9)	47 / 139 (33.8)	13.07 (3.48, 22.64)
9 - 12 years	38 / 88 (43.2)	20 / 57 (35.1)	8.09 (-8.05, 24.24)

n = the number of subjects with complete cure; m = the number of subjects in each category
[1] Difference is Terbinafine minus Griseofulvin. 95% CI of difference is based on the normal approximation to the binomial.
Source: Sponsor's NDA, Clinical Study Report SFO327C 2301, pp. 124, 125.

In Study 2301 efficacy across gender is consistent with overall study results. On the basis of race large differences are not seen in efficacy. On the basis of age groups, in the two older age groups terbinafine shows higher efficacy than griseofulvin, mirroring overall study results. For the youngest age group, the numbers are too small to make a reliable conclusion.

In Study 2301, when stratified by genus and species, terbinafine was superior to griseofulvin in treatment effect for *T. tonsurans*. **The FDA analysis yielded results similar to the sponsor's** analysis, showing success for terbinafine as 56.1% and for griseofulvin as 34.4% and 95% confidence intervals for the difference ($\delta = 21.7$) being (11.1, 32.4)[1]. Please also see Table 36.

[1] Mat Soukup, Ph.D., FDA, Statistical review and Evaluation, NDA 22-071, Table 17, p. 27.

Table 33: Subgroup Analysis Study 2302 Complete Cure Rates at End of Study (mITT population, LOCF)

	Terbinafine	Griseofulvin	
Subgroup	n / m (%)	n / m (%)	Difference (95% CI)[1]
Race:			
Caucasian	44 / 99 (44.4)	35 / 59 (59.3)	-14.88 (-30.78, 1.03)
Black	102 / 229 (44.5)	44 / 122 (36.1)	8.47 (-2.20, 19.16)
Oriental	1 / 1 (100.0)	0 / 0	
Other	47 / 112 (42.0)	24 / 56 (42.9)	-0.90 (-16.75, 14.97)
Sex:			
Male	131 / 293 (44.7)	60 / 144 (41.7)	3.04 (-6.82, 12.90)
Female	63 / 148 (42.6)	43 / 93 (46.2)	-3.67 (-16.56, 9.22)
Baseline dermatophyte species:			
T. tonsurans	116 / 243 (47.7)	46 / 126 (36.5)	11.23 (0.74, 21.72)
T. violaceum	50 / 103 (48.5)	29 / 57 (50.9)	-2.34 (-18.51, 13.84)
T. mentagrophytes	0 / 1 (0.0)	0 / 1 (0.0)	0.00
T. rubrum	0 / 1 (0.0)	0 / 1 (0.0)	0.00
M. canis	22 / 72 (30.6)	23 / 45 (51.1)	-20.55 (-38.63, -2.49)
M. audouinni	4 / 17 (23.5)	2 / 4 (50.0)	-26.47
M. vanbreuseghemii	1 / 2 (50.0)	1 / 1 (100.0)	-50.00
Other	1 / 2 (50.0)	2 / 2 (100.0)	-50.00
Age group:			
<4 years	1 / 1 (100.0)	0 / 1 (0.0)	100.00
4 - 8 years	147 / 332 (44.3)	81 / 188 (43.1)	1.19 (-7.68, 10.06)
9 - 12 years	46 / 108 (42.6)	22 / 48 (45.8)	-3.24 (-20.14, 13.66)

n = the number of subjects with complete cure; m = the number of subjects in each category
[1] Difference is Terbinafine minus Griseofulvin. 95% CI of difference is based on the normal approximation to the binomial
Source: Sponsor's NDA, Clinical Study Report SFO327C 2302, pp. 124, 125.

In Study 2302 efficacy across gender does generally mirror overall study results with response rates to terbinafine and griseofulvin being very similar. On the basis of race, large differences are not seen in efficacy. On the basis of age groups, in the two older age groups terbinafine shows similar efficacy to griseofulvin, mirroring overall study results. For the youngest age group, the numbers are too small to make a reliable conclusion.

In Study 2302, when stratified by genus and species, terbinafine was superior to griseofulvin in treatment effect for *T. tonsurans*; however this was about half the treatment effects seen in Study 2301. The FDA analysis yielded results similar to the sponsor's analysis, showing success for terbinafine as 47.7% and for griseofulvin as 36.5% and 95% confidence intervals for the difference ($\delta = 11.2$) being (1.3, 22.3)[1]. Please also see Table 36.

[1] Mat Soukup, Ph.D., FDA, Statistical review and Evaluation, NDA 22-071, Table 17, p. 27.

Table 34: Complete Cure Results by Country (mITT)

	Study 2301		Study 2302	
Treatment	**Terbinafine**	**Griseofulvin**	**Terbinafine**	**Griseofulvin**
Non-U.S. (N)	216	101	238	136
Success (%)	94 (43.5)	38 (37.6)	106 (44.5)	68 (50.0)
C.I. for $\delta^{\dagger}$	-	(-6.4, 18.2)	-	(-16.6, 5.6)
U.S. (N)	195	96	203	101
Success (%)	96 (49.2)	29 (30.2)	88 (43.3)	35 (34.7)
C.I. for $\delta^{\dagger}$	-	(-6.6, 31.4)	-	(-3.6, 21.0)

†95% C.I. with Yates continuity correction for δ = terbinafine – griseofulvin.
Source: Analysis by Mat Soukup, Ph.D., FDA, Statistical Review and Evaluation, NDA 22-071, Table 15, p. 26.

When stratified by country, Study 2301, terbinafine shows higher efficacy than griseofulvin in the US population, $\delta = 19.0$, as compared with the non-U.S. population, $\delta = 5.9$. However in Study 2302, while a trend in favor of terbinafine was seen in the U.S. population, $\delta = 8.6$, in the non-U.S. population the treatment effect was negative and favored griseofulvin, $\delta = -5.5$.

Table 35: Complete Clearance Results by Dermatophyte Genus (mITT)

	Study 2301		Study 2302	
Treatment	**Terbinafine**	**Griseofulvin**	**Terbinafine**	**Griseofulvin**
Trichophyton (N)	321	158	348	185
Success (%)	164 (51.1)	54 (34.2)	166 (47.7)	75 (40.5)
C.I. for $\delta^{\dagger}$	-	(7.2, 26.60	-	(-2.1, 16.4)
Microsporum (N)	85	38	91	50
Success (%)	21 (24.7)	13 (34.2)	27 (29.7)	26 (52.0)
C.I. for $\delta^{\dagger}$	-	(-29.1, 10.1)	-	(-40.6, 52.0)

†95% C.I. with Yates continuity correction for δ = terbinafine – griseofulvin.
Source: Analysis by Mat Soukup, Ph.D., FDA, Statistical Review and Evaluation, NDA 22-071, Table 16, p. 26.

When a subgroup analysis was performed by dermatophyte genus, terbinafine showed superiority over griseofulvin in Study 2301 for treatment of Trichophyton, $\delta = 16.9$. In Study 2302, while terbinafine showed a greater treatment effect as compared with griseofulvin for treatment of Trichophyton, this effect ($\delta = 7.2$) is much less than that seen in Study 2301.

For the genus Microsporum, both studies 2301 and 2302 showed negative treatment effects favoring griseofulvin, $\delta = -9.5$, and -22.3 for the respective studies.

Table 36: Complete Cure by Dermatophyte Species

	Study 2301		Study 2302	
	Terbinafine	**Griseofulvin**	**Terbinafine**	**Griseofulvin**
T. tonsurans (N)	264	131	243	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	25	103	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	4	6	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	37	72	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. audouni (N)	3	0	17	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.
*Other: Too small individually for statistical comparison; T. mentagrophytes, T. rubrum, M. gypseum, and M. vanbreuseghemii
Source: Analysis by Mat Soukup, Ph.D., FDA, Statistical Review and Evaluation, NDA 22-071, Table 17, p. 27.

As shown in Table 36 for *T. tonsurans*, terbinafine showed a superior treatment effect as compared with griseofulvin in both studies 2301 and 2302, $\delta = 21.7$ and 11.2 for the two studies respectively. In study 2301 the treatment effect is almost twice that seen in study 2302. For *M. canis*, however, both studies 2301 and 2302 showed negative treatment effects favoring griseofulvin, $\delta = -11.3$ and -20.5, respectively.

6.1.5 Clinical Microbiology

Please see Clinical Microbiology Review by Harold V. Silver. Pertinent conclusions from this review include the following:

- The terbinafine MIC ranges for all dermatophyte species isolated in these trials is .001 to .125µg/mL. The MIC_{90} values of *Trichophyton tonsurans* US and non-US isolates are very close (MIC90s = 0.06 and 0.03 µg/mL). The MIC90 values of the *Microsporum canis* US and non-US isolates are identical (MIC90s = 0.25 µg/mL). *Trichophyton tonsurans* and *Microsporum canis* susceptibility results from non-US sites can be compared to results from US sites.
- 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. Data submitted indicate

that concentrations in sebum and hair samples were several-fold higher than simultaneous concentrations in plasma samples.

- Data submitted indicate that the concentration of terbinafine (base) achieved at the site of infection using the dosing regimen proposed by the Applicant is higher than the MIC_{90} values for all dermatophyte species isolated in these trials.

6.1.6 Efficacy Conclusions

Pivotal Phase 3 trials C 2301 and C2302 were multicenter, randomized, investigator blind, active-controlled, parallel-group trials. These trials were of adequate design and sufficiently powered to study the safety and efficacy of Lamisil Oral granules at a daily dose determined by weight (5-8 mg/kg) for six weeks in subjects ages 4 (a very few were age 3) to 12 having tinea capitis.

Baseline disease characteristics were notable for the presence of a much higher percentage of subjects in both pivotal studies (2301-89.3% and 2302-94.1%) having *T. tonsurans* in the US population as compared with the non-US population (Study 2301 - 42.6% and Study 2302 - 22.2%).

In reference to primary endpoint results, for study 2301, terbinafine achieved superiority over griseofulvin (46.2% versus 34% with a p value of .0013) in the mITT population. In study 2302, superiority was not achieved and treatment effects were nearly the same (44% versus 43.5% with a p value of .9539). Results in the ITT population were consistent with those for the mITT population.

In reference to secondary endpoint results, for study 2301 terbinafine achieved superiority over griseofulvin (62.3% to 50.3% p=.0027) in mycological cure (defined as negative microscopy and negative culture at week 10). The results for study 2302, however, showed near parity in mycological cure for the two treatment arms (60.8% versus 59.9%, p=.8923). For clinical cure, (defined as clearance of baseline total signs and symptoms at week 10), terbinafine did not achieve superiority in either study 2301 (62.8% vs. 56.3%, p=.0594) or study 2302 (63.3% vs. 60.8%, p=.5854).

In both studies 2301 and 2302, when results for the primary endpoint (complete cure mITT population) are stratified by gender, race, and age group notable differences within and between the groups are not seen.

Although the studies were not powered for subgroup analysis, potentially useful information regarding treatment effects is noted in examination of Studies 2301 and 2302.
When stratified by country for Study 2301, terbinafine showed higher efficacy in the U.S. population, $\delta = 19.0$, as compared with the non-U.S. population, $\delta = 5.9$. For Study 2302 while a trend in favor of terbinafine was seen in the U.S. population, $\delta = 8.6$, in the non-U.S. population the treatment effect was negative and favored griseofulvin, $\delta = -5.5$.

Employing stratification (for primary endpoint) by genus and species of fungal organism, for *T. tonsurans*, terbinafine showed a superior treatment effect as compared with griseofulvin in both studies 2301 and 2302, $\delta = 21.7$ and 11.2 for the two studies respectively. In study 2301 the treatment effect is almost twice that seen in study 2302. For *M. canis*, however, both studies 2301 and 2302 showed negative treatment effects favoring griseofulvin, $\delta = -11.3$ and -20.5, respectively.

When a subgroup analysis was performed by dermatophyte genus (primary endpoint), terbinafine showed superiority over griseofulvin in Study 2301 for treatment of Trichophyton, $\delta = 16.9$. In Study 2302, while terbinafine showed a greater treatment effect as compared with griseofulvin for treatment of Trichophyton, this effect ($\delta = 7.2$) is much less than that seen in Study 2301. For the genus Microsporum, both studies 2301 and 2302 showed negative treatment effects favoring griseofulvin, $\delta = -9.5$, and -22.3 for the respective studies.

The protocols for studies 2301 and 2302 were amended 3 times. Amendment 2 to the protocols included a mild revision downward of the body weight categories for a given dose of griseofulvin in order to better comply with the maximum dose labeled for the comparator, Grifulvin V. Since this might have had an impact on griseofulvin response rates, consultation with the FDA biostatistician resulted in the performance of a sensitivity analysis that addressed this issue. No effects were found on the efficacy findings from the protocol specified primary analysis.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety review of the sponsor's terbinafine product will focus on adverse events and systemic safety. The safety database consists first of all of the pooled data from the 2 pivotal studies, C2301 and C2302. This data is used for subgroup analysis. The safety data base also includes data from the Phase 1 study C 2101, since the population studied, the dosing by weight, and the formulation used were the same as the pivotal studies. Data from dose ranging trials is also reviewed for consistency and to add to the overall database where appropriate. However, in these trials the oral granule formulation was not used. These trials include W352, L2306, T201, and T202.

7.1.1 Deaths

No deaths occurred in the pivotal trials or in the dose ranging trials.

7.1.2 Other Serious Adverse Events

In study C2301 seven serious events involving four subjects and in study C2302 three serious adverse events involving two subjects were noted.

Table 37: Serious Adverse Events (Pivotal Studies)

	Terbinafine N=1042 n (%)	**Griseofulvin N=507 n (%)**
Number (%) of patients with SAE(s)	5 (0.5)	1 (0.2)
System organ class and event		
Eye disorders	**1 (0.1)**	**0 (0.0)**
Cataract	1 (0.1)	0 (0.0)
Glaucoma	1 (0.1)	0 (0.0)
Gastrointestinal disorders	**1 (0.1)**	**0 (0.0)**
Nausea	1 (0.1)	0 (0.0)
General disorders and administration site conditions	**1 (0.1)**	**0 (0.0)**
Pyrexia	1 (0.1)	0 (0.0)
Infections and infestations	**2 (0.2)**	**1 (0.2)**
Hepatitis viral	1 (0.1)	0 (0.0)
Pneumonia	1 (0.1)	0 (0.0)
Arthritis bacterial	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications	**1 (0.1)**	**0 (0.0)**
Head injury	1 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders	**1 (0.1)**	**0 (0.0)**
Pain of skin	1 (0.1)	0 (0.0)
Pruritus	1 (0.1)	0 (0.0)

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 27.

In study C2301 seven serious adverse events occurred involving four subjects.
1) A 4 year old male (Subject 0403-17) experienced fever, malaise, and loss of appetite on day 23. Terbinafine was discontinued and the subject was hospitalized. On day 30 a diagnosis of viral hepatitis was confirmed by laboratory tests. On day 70 laboratory tests were normal. No relationship to study drug was suspected by the investigator.
2) An 8 year old female (Subject 0404-28) in the terbinafine group fell from her bed and hit her head on day 2. The subject had headache and was hospitalized for observation. No relationship to study drug was suspected by the investigator.
3) A 10 year old male (Subject 0511-22) in the terbinafine group was hospitalized from day 15 to day 17 for fever, nausea, and scalp itching and scalp pain. Study drug was interrupted from day 13 to day 19. At day 24 the subject's condition was improving. The investigator did not suspect a relationship to study drug.

4) A 4 year old female (Subject 0601-15) in the terbinafine group presented on Day 7 with a high fever, cough, and appetite loss. On day 22 a chest x-ray revealed pneumonia in the right lung and the patient was hospitalized.

The sponsor also notes an SAE, reported as an SAE "in error".
A 9 year old male (Subject 0601-11) in the terbinafine treatment group had an ophthalmology report indicating changes in color vision (subject missed 6 of 18 symbols on the color plates that were not missed at baseline) on Day 44, visit 4. Terbinafine was discontinued.
Although this was considered to be a clinically significant, the investigator reportedly clarified that, according to the protocol, the event was not considered to be an SAE. On day 70 an ophthalmology test was performed and was normal. At the sponsor's request, the subject was referred to a retinal specialist who found the retina to be completely normal on two exams. The retinal specialist performed color vision testing on two occasions; on October 23, 2005 with subject missing symbols on 4 plates (out of 10) in the right eye and 2 plates in the left eye, and on March 24, 2006 with the subject missing symbols on 2 plates in the right eye and 3 plates in the left eye. After the first visit the retinal specialist assessed "probable acquired dyschromatosis, on research" and "doubt in reliability". The investigator assessed the visual disturbance as mild in severity and suspected a relationship between this event and the study drug.

In study C2302, three serious adverse events occurred, involving two subjects.
1) A 12 year old male (Subject 0601-24) in the terbinafine group had a cataract and glaucoma of traumatic origin (previous injury-hit in the eye with a ball). Although the investigator could not exclude a causal role for the study drug for the cataract, the event was compatible with a traumatic cause. The subject was evaluated by an ophthalmologist who found that the cataract was most likely due to the accident and not the study drug. The glaucoma was not suspected to be related to study drug.

2) A 6 year old male (Subject (0601-52) in the griseofulvin group had bacterial arthritis diagnosed on day 17. The subject was hospitalized. The investigator did not suspect a relationship to the study drug.

Other studies
No SAE's occurred in the dose-ranging studies W352, C2101, or L2306. One SAE occurred in each study, T201 and T202.
1) In study T201, an 8 year old black female (Patient 511-0016) in the 1 week Lamisil treatment group had a history of sickle cell disease and a spleenectomy. The subject experienced a sickle cell crisis and was hospitalized at study week 10. The subject improved and completed the study. The investigator did not suspect a relationship between study medication and this event.

2) In study T202, a 6 year old male (Patient 052-0017) in the Lamisil 10 week treatment group had no relevant medical history reported upon study entry. At week 6 laboratory results showed a low neutrophil count (680/mm^3). The investigator did not feel this was clinically relevant since it arrived at the central laboratory 4 days after being obtained. Study drug was continued. At the week 8 and week 10 visits neutrophil counts remained low (1380/mm^3 and 880/mm^3,

respectively). Study drug was discontinued and one week later the neutrophil count increased to 4132/mm^3. The event was evaluated as being related to study medication. Neutropenia is listed in the precautions section of the current Lamisil® label.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 38: **Participation and withdrawals (pivotal studies, pooled randomized population)**

	Terbinafine	**Griseofulvin**
Number of patients	**n (%)**	**n (%)**
Randomized	(1040*) 1042	(509*) 507
Treated	1040 (100.0)	509 (100.0)
Completed treatment	940 (90.4)	477 (93.7)
Completed study	916 (88.1)	456 (89.6)
Discontinued from treatment	**100 (9.6)**	**32 (6.3)**
Lost to follow-up	40 (3.8)	16 (3.1)
Subject withdrew consent	25 (2.4)	4 (0.8)
Adverse Event(s)	15 (1.4)	4 (0.8)
Protocol violation	13 (1.3)	2 (0.4)
Unsatisfactory therapeutic effect	3 (0.3)	2 (0.4)
Abnormal laboratory value(s)	2 (0.2)	2 (0.4)
Administrative problems	2 (0.2)	2 (0.4)
Abnormal test procedure result(s)	0	0
Death	0	0
Discontinued from study	**124 (11.9)**	**53 (10.4)**
Lost to follow-up	65 (6.3)	37 (7.3)
Subject withdrew consent	32 (3.1)	7 (1.4)
Adverse Event(s)	11 (1.1)	2 (0.4)
Protocol violation	9 (0.9)	2 (0.4)
Unsatisfactory therapeutic effect	4 (0.4)	4 (0.8)
Administrative problems	3 (0.3)	1 (0.2)
Abnormal laboratory value(s)	0	0
Abnormal test procedure result(s)	0	0
Death	0	0

*two patients were randomized to griseofulvin but received terbinafine in error. The 2 patients are analyzed for safety with the terbinafine group (other tables reflect 1042 patients in the terbinafine group and 507 in the griseofulvin group).

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 15.

Study design allowed subjects to do the following: discontinue both the treatment and the study, discontinue treatment and remain in the study, or complete treatment but later discontinue from the study.

Of the randomized subjects a total of 9.6% (100/1042) in the terbinafine group and 6.3% (32/507) in the griseofulvin group discontinued from treatment. The major reasons were lost to follow-up and subject withdrew consent. The number of subjects withdrawing consent was somewhat higher in the terbinafine group 2.4% (25/1042) than in the griseofulvin group .8% (4/507). Also slightly higher in the terbinafine group was the number of subjects withdrawing due to an adverse event, 1.4% (15/1042) vs. .8% (4/507). Withdrawal due to abnormal laboratory values included .2% (2/1042) in the terbinafine group versus .4% (2/507) in the griseofulvin group.

Of the randomized subjects a total of 11.9% (124/1042) in the terbinafine group and 10.4% (53/507) in the griseofulvin group discontinued from the study. The major reasons were; lost to follow-up, subject withdrew consent, and adverse events. Somewhat higher numbers of subjects withdrew consent 3.1% (32/1042) or discontinued due to an adverse event 1.1% (11/1042) in the terbinafine group than in the griseofulvin group, 1.4% (7/507) and .4% (2/507) respectively.

7.1.3.2 Adverse events associated with dropouts

All of the subjects who were discontinued from the study due to adverse events also were withdrawn from treatment due to adverse events (11/1042 terbinafine and 2/507 griseofulvin).

Please see Table 39, next page.

Table 39: **Discontinuations of Study Drug for Adverse Events (Pivotal Studies, Pooled Safety Population)**

	Terbinafine N=1042 n (%)	Griseofulvin N=507 n (%)
Number (%) of patients with AE related discontinuations	17 (1.6)	6 (1.2)
System organ class and event		
Blood and lymphatic system disorders	**1 (0.1)**	**0 (0.0)**
Neutropenia	1 (0.1)	0 (0.0)
Gastrointestinal disorders	**6 (0.6)**	**1 (0.2)**
Vomiting	4 (0.4)	0 (0.0)
Abdominal pain upper	2 (0.2)	1 (0.2)
Diarrhea	1 (0.1)	0 (0.0)
Nausea	1 (0.1)	0 (0.0)
General disorders and administration site conditions	**1 (0.1)**	**0 (0.0)**
Pyrexia	1 (0.1)	0 (0.0)
Infections and infestations	**3 (0.3)**	**0 (0.0)**
Hepatitis viral	1 (0.1)	0 (0.0)
Kerion	1 (0.1)	0 (0.0)
Lice infestation	1 (0.1)	0 (0.0)
Investigations	**1 (0.1)**	**3 (0.6)**
Hepatic enzyme abnormal	1 (0.1)	0 (0.0)
Neutrophil count decreased	0 (0.0)	1 (0.2)
Transaminases increased	0 (0.0)	1 (0.2)
White blood cell count decreased	0 (0.0)	1 (0.2)
Metabolism and nutrition disorders	**1 (0.1)**	**0 (0.0)**
Anorexia	1 (0.1)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**1 (0.2)**
Dysgeusia	0 (0.0)	1 (0.2)
Skin and subcutaneous tissue disorders	**6 (0.6)**	**1 (0.2)**
Urticaria	1 (0.1)	1 (0.2)
Dermatitis	1 (0.1)	0 (0.0)
Pain of skin	1 (0.1)	0 (0.0)
Rash	1 (0.1)	0 (0.0)
Rash maculopapular	1 (0.1)	0 (0.0)
Urticaria localized	1 (0.1)	0 (0.0)

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 30.

In the terbinafine group, 1.6% (17/1042) of subjects, and in the griseofulvin group, 1.2% (6/507) of subjects, experienced study drug discontinuation due to an adverse event. In the terbinafine group vs. griseofulvin group more subjects were discontinued from study drug due to gastrointestinal disorders .6% (6/1042) vs. .2% (1/507), infections and infestations .3% (3/1042)

vs. 0% and skin and subcutaneous disorders .6% (6/1042) vs. .2% (1/507). In the griseofulvin group more subjects were discontinued from study drug due to investigations (abnormal) .6% (3/507) than in the terbinafine group .1% (1/1042).

The narratives of the subjects who were discontinued due to adverse events were reviewed, and a summary of pertinent information follows in table 40. In general, this reviewer agrees with the investigator assessments as listed indicating relationship to study medication. However, review of provided narrative and laboratory data may indicate an association in the case of the 6 year old F subject (COL C2301 0303/00013) having elevated transaminases that decreased after griseofulvin withdrawal. Also in the case of the 7 year old F subject (PER C2301 0403/00034) review of the narrative also suggests the possibility that griseofulvin was associated with the reported episode of urticaria. The urticaria started two days after beginning griseofulvin and ended two days after ending griseofulvin.

Table 40: Adverse Events Leading to Study Drug Discontinuation (Safety Population)

Country TX	Age/ Sex/ Study	Subject ID	SAE	A.E.	Start-Study Day	End-Study Day	Dura-tion (days)	Rel. to study med
Terbin-afine								
1) PER	4M/C2301	0403/00017	Yes	Hepatitis viral	23	70	48	Not susp.
2) PER	4F/C2301	0403/00036	No	Nausea Vomiting	1 1	11 11	11 11	Suspected Suspected
3) USA	5M/C2301	0506/00002	No	Abd. pain upper Dermatitis	2 20	28 28	27 9	Suspected Not susp.
4) USA	4M/C2301	0519/00006	No	Lice infestation	2	Continuing	>20	Not susp.
5) USA	4M/C2301	0520/00002	No	Pain of skin	4	5	2	Not susp.
6) USA	10F/C2301	0547/00003	No	Urticaria localized	22	25	4	Suspected
7) USA	4M/C2301	0562/00001	No	Diarrhoea Pyrexia	4 4	Continuing Data issue	>4 >4	Suspected Not susp.
8) VEN	7M/C2301	0601/00010	No	Kerion	31	Continuing	>1	Not susp.
9) VEN	4F/C2301	0601/00015	No Yes	Vomiting Pneumonia*	30 22	34 27	5 6	Suspected Not susp.
10)BRA	5M/C2302	0203/00003	No	Hepatic enzyme abnormal	37	Continuing	>35	Suspected
11)EGY	10M/C2302	0254/00025	No	Neutropenia	21	45	25	Suspected
12)JAM	7M/C2302	0503/00011	No	Urticaria	31	42	12	Suspected
13)USA	5M/C2302	0111/00001	No	Anorexia	4	5	2	Suspected
14)USA	10M/C2302	0112/00004	No	Rash maculo-papular	3	Continuing	>32	Suspected
15)USA	4F/C2302	0126/00002	No No	Vomiting Abdominal pain upper	2 4	21 Continuing	20 >26	Suspected Suspected
16)USA	8M/C2302	0132/00009	No	Rash	2	Continuing	>1	Suspected
17)USA	5M/C2302	0149/00006	No	Vomiting	12	16	5	Suspected

Griseo-fulvin								
1)COL	6F/C2301	0303/00013	No	Transaminases increased	27	50	24	Not susp.
2)PER	7F/C2301	0403/00034	No	Urticaria	30	33	4	Not susp.
3)USA	5F/C2301	0565/00003	No	Neutrophil count decreased	22	45	24	Suspected
4) USA	5M/C2302	0113/00008	No	Dysgeusia	1	7	7	Suspected
5)USA	6M/C2302	0128/00005	No	White blood cell count decreased	23	Continuing	>15	Suspected
6)USA	5M/C2302	0138/00002	No	Abdominal pain upper	7	9	3	Suspected

* This subject experienced a temporary study drug discontinuation due to the pneumonia, see also table 41 subject #10 terbinafine treatment group.
Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-1.3, Summary of Clinical Safety PTF, PTT, PTL, pp. 367-374.

Of note, six subjects taking terbinafine were withdrawn from study drug treatment due to adverse events in the system organ class of skin and subcutaneous disorders. One of these, subject 0506-02 study C2301, experienced dermatitis that was assessed as mild and not related to study drug. This patient also had stomach ache that was assessed as moderate in severity and as related to study drug. The study medicine, terbinafine, in this patient was discontinued due the stomach ache. The subject having pain of skin, subject 0520-02 study 2301, had a sore scalp assessed as moderate severity and was not suspected by the investigator as having a relationship to study medication. This subject is discussed further below. The remaining four subjects having skin related adverse events had either urticaria or rashes, these events are included in the current oral terbinafine label.

Subject 0520-02 study 2301 (USA) is 4 year old male who experienced sore scalp 4 days after beginning terbinafine. The terbinafine was discontinued on study day 4. In the adverse event listing it is stated that the adverse event ended on study day 5. This subject was diagnosed as having *T. tonsurans* by culture. Another subject reported to have scalp pain was a 10 year old male (subject 0511-22 study C2301 USA) who experienced fever, nausea, scalp itching/pain from study day 15 to day 17. The patient was hospitalized and terbinafine interrupted from day 13 to day 19. **By day 24 when this was reported as an SAE, the subject's condition was** improving. This subject was diagnosed as having *T. tonsurans* by culture and microscopic exam. By the end of the study this subject showed negative culture and negative microscopy. An additional subject, a 4 year old male (USA study 2301 0514-06) experienced a burning sensation **on the scalp starting on study day 1, treated with children's Motrin, and resolving the same day.** This subject was diagnosed with *T. tonsurans* by microscopy and culture at the beginning of the study, and both became negative at study completion. For these three subjects it is possible that the pain/burning sensation of the scalp could be an effect of the terbinafine killing the fungus.

Other studies:
Discontinuations from study or from study medication due to adverse events did not occur in studies C2101 (only other study to employ to-be-marketed formulation), W352, or L2306. One discontinuation due to an adverse event occurred in each study, T201 and T202.
1) In study T201, a four year old Caucasian male (Subject 508-0003) in the 1 week Lamisil treatment group discontinued from study drug and from the study at the completion of the 4 week treatment period because of tinea corporis located on the right eyebrow and arm. The investigator assessed this event as being mild in severity and not suspected to be related to study medication.
2) In study T 202, a five year old Caucasian male (subject 032-0001) in the 6 week Lamisil treatment group experienced urticaria of moderate severity after taking 125 mg Lamisil tablets for two weeks. Study drug was permanently discontinued. The investigator suspected a relationship between this event and use of study drug.

Urticaria is listed as an adverse event in the current label for Lamisil® tablets.

7.1.3.3 Other significant adverse events

Table 41: Adverse Events by Preferred Term Leading to Dose Adjustment/Temporary Interruption (Studies C2301 and C2302 Safety Population; Treatment = Terbinafine)

Country	Age/ Sex	SAE	A.E.	Start - Study day	End - Study Day	Duration (days)	Rel. to study medication	Severity
1) COL	10 F	No	Naosopharyngitis	19	20	2	Not susp	Mild
2) PER	11 F	No	Gingivitis	6	20	15	Not.susp.	Moderate
3) PER	5 F	No	Abd. pain	30	30	1	Not susp	Mild
4) PER	8 F	Yes	Head Injury	2	7	6	Not susp	Mod
5) PER	8 M	No	Contusion	20	23	4	Not susp	Moderate
6) US	10 M	Yes	Fever	15	24	10	Not susp	Severe
		Yes	Pruritus (of Scalp)	15	24	10	Not susp	Severe
		Yes	Pain of skin (scalp)	15	24	10	Not susp	Severe
		Yes	Nausea	15	24	10	Not susp	Severe
7) US	5 F	No	Abd. Pain upper	38	39	2	Not susp	Mild
8) US	5 M	No	Viral infection	14	14	1	Not susp	Moderate
9) US	4 M	No	Gastoenteritis viral	16	16	1	Not susp	Moderate
10) VEN	4 F	Yes	Pneumonia	22	27	6	Not susp	Moderate
11) VEN	4 M	No	Pyrexia	15	18	4	Not susp	Mild
12) VEN	4 F	No	Dengue fever	10	20	11	Not susp	Mild
13) ZAF	7 M	No	Circumcision	1	1	1	Not susp	Moderate
14) ZAF	4 M	No	Pyrexia	3	11	9	Not susp	Moderate
15) ECU	10 F	No	Headache	8	18	11	Suspected	Moderate
16) EGY	6 F	No	Bronchitis acute	13	19	7	Not susp	Mild
17) EGY	4 F	No	Bronchitis acute	2	9	8	Not susp	Moderate
18) IND	7 M	No	Abd. pain	18	19	2	Suspected	Moderate
19) IND	9 M	No	Abd. pain	18	19	2	Suspected	Moderate
20) JAM	7 M	No	Urticaria	23	24	2	Suspected	Mild
		No	Urticaria (Worsening)	25	29	5	Suspected	Moderate

21) US	4 M	No	Vomiting	6	7	2	Not susp	Mild
22) US	6 M	No	Influenza like illness	15	18	4	Not susp	Moderate
23) US	4 F	No	Gastroenteritis viral	2	4	3	Not susp	Mild
		No	Ear pain	7	8	2	Not susp	Mild
24) US	8 M	No	Urticaria	26	27	2	Suspected	Mild
25) US	5 M	No	Gastroenteritis viral	2	3	2	Not susp	Mild
26) US	7 F	No	Stomach discomfort	17	17	1	Not susp	Mild
		No	Pyrexia	39	39	1	Not susp	Mild
		No	Rhinitis	39	39	1	Not susp	Mild
27) US	11 M	No	Influenza	8	15	8	Not susp	Mild
28) US	4 M	No	Dermatitis contact	12	17	6	Not susp	Mild
29) US	7 M	No	Upper resp. tract infection	40	51	12	Not susp	Mild
30) US	6 F	No	Pharyngolaryngeal pain	4	18	15	Not susp	Mild

Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-1.4, Summary of Clinical Safety PTE, PTT, PTL, pp. 375-384.

Table 42: Adverse Events by Preferred Term Leading to Dose Adjustment/Temporary Interruption (Studies C2301 and C2302 Safety Population; Treatment = Griseofulvin)

Country	**Age/ Sex**	**SAE**	**A.E.**	**Start - Study day**	**End - Study Day**	**Duration (days)**	**Rel. to study med**	**Severity**
1) CAN	4 F	No	Neutrophil count decreased	26	33	8	Not susp	Moderate
2) COL	10 M	No	Vomiting	4	Continuing	>64	Suspected	Mild
3) EGY	5 M	No	Impetigo	6	Continuing	>65	Not susp	Mild
4) PER	9 M	No	Nasopharyngitis	17	19	3	Not susp	Moderate
5) PER	5 F	No	Vomiting	29	29	1	Suspected	Moderate
6) US	4 M	No	Dermatitis contact	6	26	21	Not susp	Moderate
7) US	4 F	No	Vomiting	20	20	1	Not susp	Mild
8) US	4 M	No	Scarlet fever	27	33	3	Not susp	Moderate
9) US	4 M	No	Headache	1	12	2	Not susp	Mild
10) VEN	4 F	No	Dermatitis	37	38	2	Not susp	Mild
11) VEN	4 M	No	Pyrexia	16	18	3	Not susp	Mild
12) ZAF	6 M	No	Upper resp. tract infection	24	30	7	Not susp	Moderate
13) BRA	5 M	No	Varicella	5	16	12	Not susp	Mild
14) US	5 F	No	Vomiting	8	19	12	Not susp	Mild
			Diarrhoea	8	22	15	Not susp	Mild
15) US	8 M	No	Ocular hyperaemia	31	31	1	Not susp	Mild
			Lacrimation increased	32	35	4	Not susp	Mild

Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-1.4, Summary of Clinical Safety PTE, PTT, PTL, pp. 385-389.

Examination of listings for adverse events leading to temporary dose adjustment/temporary interruption reveals involvement of 2.8% (30/1042) of subjects exposed to terbinafine and of 3%

(15/507) of subjects exposed to griseofulvin. In the terbinafine group, those adverse events suspected to be related to study drug included urticaria (3 cases), abdominal pain (2 cases), and headache (1 case). These adverse events of urticaria and abdominal pain are presently included in the Lamisil® tablet label.

Other studies:
Dose adjustments or temporary interruptions of study medication due to adverse events did not occur in studies W352, C2101, or L2306.

Study T201:
A 6 year old female (Subject 501 0011) in the Lamisil 1 week group experienced gastroenteritis (viral) that led temporary interruption of study medication. This event was assessed as mild and was not suspected to be related to study medication.

Other adverse events of note in study T01 included:
1) A 9 year old male (Subject 503 0034) in the Lamisil 4 week group experienced an event of transient leukocytopenia noted at the week 2 visit. By week 4 while still on study drug the leukocyte count had begun to rise and returned to normal by week 12 (8 weeks after treatment). This event was assessed as moderate and was suspected to be related to study medication.
2) A 7 year old female (Subject 503 0016) in the Lamisil 4 week group experienced scalp discomfort, coded as hyperesthesia, beginning at the 6 week visit and ending by week 7. This was assessed as moderate and suspected to be related to study medication.

Study T202:

Table 43: Subjects Having Dose Adjustments or Interruptions of Study Medicine due to Adverse Events – Study T202

Lamisil Treatment group	Age/ Sex	SAE	A.E.	Start - Study day	End – Study Day	Duration (days)	Relation to study med	Severity
1) 6 week	4 F	No	Diarrhoea Vomiting	56 56	59 56	4 1	Not susp Not susp	Mild Mild
2) 6 week	7 F	No	Rash (local skin rash)	24	26	3	Not susp	Mild
3) 8 week	9 M	No	Influenza-like symptoms	70	80	11	Not susp	Moderate
4) 10 week	5 M	No	Coughing Fever	53 53	55 55	3 3	Not susp Not susp	Mild Mild
5) 10 week	11 M	No	Influenza-like symptoms	7	11	5	Not susp	Moderate

Source: Sponsor's NDA submission, Adapted from listing 10.1-3, Clinical Study Report Study CSFO327 T202, pp. 492-494.

The number of subjects having dose adjustments or interruptions of study medication due to adverse events did not vary by length of terbinafine treatment in study T202.

7.1.4 Other Search Strategies

Table 44, following, describes severe adverse events in the safety population. Those events where there was a suspected relationship to study drug included an episode of diarrhea in a subject treated with terbinafine and episodes of upper abdominal pain and constipation in a subject treated with griseofulvin.

Table 44: Severe Adverse Events by Preferred Term

Country	Age/ Sex	SAE	A.E.	Start-Study day	End-Study day	Dura-tion (days)	Rel. to study med	Action taken	Treatment
Study 2301									
1) CAN	9 M	No	Abd. Pain	4	6	3	Not.susp.	None	Terbinafine
2) CAN	6 M	No	Abd. pain	17	17	1	Not susp	Con. Med taken	Terbinafine
3) US	10 M	Yes	Pyrexia	15	24	10	Not susp	Study drug dose adj.	Terbinafine
		Yes	Nausea	15	24	10	Not susp	Study drug dose adj.	
		Yes	Pruritus	15	24	10	Not susp	Study drug dose adj.	
		Yes	Pain of skin(scalp)	15	24	10	Not susp	Study drug dose adj.	
4) US	4 M	No	Diarrhea	4	Contin-uing	>4	Suspected	Study drug D/C	Terbinafine
5) VEN	7 M	No	Kerion	31	Contin-uing	>1	Not susp	Study drug D/C	Terbinafine
6) US	4 F	No	Tonsilitis	26	36	11	Not susp	Con. Med taken	Griseofulvin
Study 2302									
7) ZAF	12 M	Yes	Glaucoma	43	Contin-uing	>28	Not susp	Con Med. taken	Terbinafine
8) US	5 M	No	Abd. Pain upper	7	9	3	Suspected	Study drug D/C	Griseofulvin
		No	Constipat-ion	8	9	2	Suspected	None	
11)ZAF	6 M	Yes	Arthritis bacterial	17	Contin-uing	>54	Not susp	Con. Med taken	Griseofulvin

Source: Sponsor's NDA submission, compiled by reviewer from listing 16.2.7-1.1 Clinical Study Report 2301 and listing 16.2.7-1.1 Clinical Study Report 2302.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the two pivotal studies, C 2301 and C 2302, adverse events were detected by use of non-directive questioning of the subject at each visit during the study. Adverse events were also noted when they were volunteered by the subject during or between study visits. Adverse events also included clinically significant laboratory abnormalities, changes in vision and vital signs. Taste disturbances were to be monitored by weight monitoring, caregiver interview, and patient/food diary.

For studies C2101, CW352, L2306 adverse events were recorded whether reported spontaneously or elicited by questioning the subject. An adverse event was defined as any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event was not considered to be treatment related. Subjects/caretakers were supplied with diary cards to record any adverse events during the outpatient portion of the study. Abnormal laboratory values or test results constituted adverse events only if they induced clinical signs or symptoms or required therapy.

For studies T201 and T202 adverse events were recorded whether reported spontaneously or elicited by questioning the subject. An adverse event was defined as any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event was not considered to be treatment related. Abnormal laboratory values or test results constituted adverse events only if they induced clinical signs or symptoms, required therapy, or were part of a larger diagnosis.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor classified adverse events by MedDRA System Organ Class (SOC) and Preferred term. The sponsor's categorization of adverse events and use of preferred terms appears reasonable.

7.1.5.3 Incidence of common adverse events

Table 45, following, provides the sponsor's analysis by system organ class.

Table 45: Adverse Event Incidence Overall and by System Organ Class
(Pivotal Studies, Pooled Safety Population, Incidence >1%)

	Terbinafine N=1042 n (%)	**Griseofulvin N=507 n (%)**
Number (%) of patients with AE(s)	541 (51.9)	249 (49.1)
Infections and infestations	259 (24.9)	129 (25.4)
Gastrointestinal disorders	161 (15.5)	72 (14.2)
Respiratory, thoracic and mediastinal disorders	122 (11.7)	40 (7.9)
Nervous system disorders	87 (8.3)	45 (8.9)
General disorders and administration site conditions	86 (8.3)	35 (6.9)
Skin and subcutaneous tissue disorders	75 (7.2)	26 (5.1)
Investigations	26 (2.5)	26 (5.1)
Injury, poisoning and procedural complications	26 (2.5)	11 (2.2)
Eye disorders	24 (2.3)	10 (2.0)
Musculoskeletal and connective tissue disorders	15 (1.4)	7 (1.4)
Metabolism and nutrition disorders	13 (1.2)	5 (1.0)

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 20.

7.1.5.4 Common adverse event tables

Table 46: Adverse Events by Preferred Term
(Pivotal Studies, Pooled Safety Population, Incidence >1% in Either Group)

	Terbinafine N=1042 n (%)		**Griseofulvin N=507 n (%)**	
Number (%) of patients with AE(s)	543 (52.1)	rounded	251 (49.5)	rounded
Nasopharyngitis	100 (9.6)	10	53 (10.5)	11
Headache	74 (7.1)	7	39 (7.7)	8
Pyrexia	73 (7.0)	7	28 (5.5)	6
Cough	65 (6.2)	6	26 (5.1)	5
Vomiting	48 (4.6)	5	27 (5.3)	5
Upper respiratory tract infection	47 (4.5)	5	23 (4.5)	5
Abdominal pain upper	42 (4.0)	4	18 (3.6)	4
Diarrhea	35 (3.4)	3	19 (3.7)	4
Influenza	25 (2.4)	2	7 (1.4)	1
Abdominal pain	25 (2.4)	2	6 (1.2)	1
Pharyngolaryngeal pain	22 (2.1)	2	11 (2.2)	2
Nausea	22 (2.1)	2	9 (1.8)	2
Rash	18 (1.7)	2	8 (1.6)	2
Rhinorrhea	18 (1.7)	2	0 (0.0)	0
Nasal congestion	17 (1.6)	2	3 (0.6)	1
Pruritus	13 (1.2)	1	4 (0.8)	1
Toothache	5 (0.5)	1	6 (1.2)	1

Source: Analysis by FDA Biostatistician, Mat Soukup, Ph.D., using data sets a_aev.xpt from each study.

Table 46 provides the FDA analysis. This differs, in a minor fashion, from the sponsor's analysis by one subject in three preferred terms; nasopharyngitis (terbinafine FDA 100 vs. sponsor 99), cough (griseofulvin FDA 26 vs. sponsor 25), and vomiting (terbinafine FDA 48 vs. sponsor 47). The FDA statistician has performed an analysis sorting adverse events by relative risk. Subjects taking terbinafine were at an elevated risk, as compared with those taking griseofulvin, of having the following adverse events; rhinorrhea, nasal congestion, abdominal pain, influenza, pruritus, pyrexia, cough, nausea, abdominal pain upper, and rash. Overall this method of summarizing the data shows similar safety profiles for terbinafine and griseofulvin. Please see Statistical Review and Evaluation, NDA 22-087, Figure 5, p. 21.

The most common adverse event across treatment groups was nasopharyngitis occurring in 9.6% of subjects (100/1042) exposed to terbinafine and 10.5% of subjects (53/507) of those exposed to griseofulvin. The second most common adverse event was headache occurring in 7.1% of subjects (74/1042) exposed to terbinafine and 7.7% (39/507) of those exposed to griseofulvin. The third most common adverse event was pyrexia occurring in 7.0% (73/1042) of those exposed to terbinafine and in 7.7% (30/507) of those exposed to griseofulvin.

7.1.5.5 Identifying common and drug-related adverse events

Table 47: Most Frequent Adverse Events with Investigator Attribution to Study Drug (Pivotal Studies, Pooled Safety Population, Incidence at Least 0.5% in Either Group)

	Terbinafine N=1042 n (%)	**Griseofulvin N=507 n (%)**
Number (%) of patients with AE(s) judged related to study drug (Preferred Term)	96 (9.2)	42 (8.3)
Vomiting	17 (1.6)	8 (1.6)
Abdominal pain upper	13 (1.2)	5 (1.0)
Diarrhea	11 (1.1)	5 (1.0)
Headache	10 (1.0)	7 (1.4)
Nausea	10 (1.0)	6 (1.2)
Abdominal pain	10 (1.0)	1 (0.2)
Weight increased	4 (0.4)	3 (0.6)

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 22.

By the sponsor's analysis, of subjects exposed to terbinafine 9.2% (96/1042) were assessed as having treatment related adverse events. Of subjects exposed to griseofulvin 8.3% (42/507) were assessed as having treatment adverse events. The rate of treatment related adverse events across both treatment groups, in total and by the five most common preferred terms, is generally similar.

Table 48: Most Frequent AEs that were Suspected to be Related to Study Drug, and Not in Current Labeling for Lamisil Tablets (>1 Patient in Either Treatment Group, Pivotal Studies, Pooled Safety Population)

	Terbinafine N=1042 n (%)	**Griseofulvin N=507 n (%)**
Overall number (%) of patients with non-labeled AE(s) judged related to study drug by the investigator	32 (3.1)	13 (2.6)
Preferred term		
Weight increased	4 (0.4)	3 (0.6)
Increased appetite	3 (0.3)	2 (0.4)
Dizziness	3 (0.3)	0 (0.0)
Visual acuity reduced*	3 (0.3)	0 (0.0)
Somnolence	2 (0.2)	1 (0.2)
Hypoesthesia	2 (0.2)	0 (0.0)
Insomnia	2 (0.2)	0 (0.0)

*The ophthalmology manual that was part of the protocol for studies C2301 and C2302 specified that only acuity changes of 3 or more lines were to be recorded as adverse events.

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 22.

The narratives and, where appropriate, the case report forms for the unlabeled events for subjects exposed to terbinafine and for subjects exposed to griseofulvin have been reviewed. Adverse events of interest include dizziness, reduced visual acuity, hypoesthesia (and paresthesia), burning sensation, and insomnia (and somnolence).

With respect to dizziness according to the sponsor's information, three subjects in the terbinafine and no subjects in the griseofulvin group experienced this adverse event. Narratives are available for two subjects in the terbinafine group; a 7 year old male (USA study C2302 0138/00011) and an 8 year old female (USA study C2301 0556/00021) who also experienced abdominal pain. The 7 year old male experienced dizziness in association with headache. The episode started study day 16 and ended study day 17, with the investigator suspecting these events to be related to study medication. The 8 year old female experienced dizziness in association with headache on study day 23. The investigator suspected a relationship between study drug and dizziness. A narrative is present for a 10 year old subject (ECU study C2302 0463/00005) who was randomized to griseofulvin, but received terbinafine instead. This subject experienced dizziness that lasted for 40 days. This was suspected by the investigator to be related to study drug (as noted on CRF).

For a discussion of subjects having reduced visual acuity please see section 7.1.6.

Subjects experiencing hypoesthesia included two in the terbinafine group and none in the griseofulvin group. A 7 year old male (USA study 2302 0106/00021) experienced right arm numbness for one day (study day 5) and bilateral arm numbness for one day (study day 18). A 4 year old female subject (USA study 2302 0112/00001) experienced tongue numbness (study day 1 to study day 9). A third subject, 7 year old male, exposed to terbinafine (USA study 2302

0156/00014) reported (paraesthesia) tingling, numbness and cramping in the legs, feet and left arm starting on study day 2 and resolving on study day 3. This third subject is also indicated in the adverse events listing (16.2.7-1.1 study C2302) to have had hypoesthesia consisting of numbness of the legs, feet, and left arm starting on study day 2 and resolving on study day 3. No subjects exposed to griseofulvin experienced paraesthesia.

Two subjects exposed to terbinafine (and none exposed to griseofulvin) experienced burning sensation. A 10 year old female (USA study 2302 0156/00004) experienced burning and itching of the lower lip starting on study day 1 and ending on study day 4. The second subject, a 4 year old male (USA study 2301 0514/00006) experienced a burning sensation on the scalp starting on study day 1, treated with children's Motrin, and resolving the same day. (This subject was diagnosed with *T. tonsurans* by microscopy and culture at the beginning of the study, and both became negative at study completion.)

Subjects experiencing insomnia included two in the terbinafine group and none in the griseofulvin group. A 5 year old male (USA study 2302 0105/00002) experienced insomnia and psychomotor hyperactivity starting on study day 2 and continuing at least 5 days. Because the subject's baseline safety labs had not been completed due to a storm, the sponsor requested that the subject be discontinued from the study (termination due to administrative problems). An 8 year old male (ZAF study 2302 0601/00030) was reported to be not sleeping starting on study day 7 and lasting for 26 days.

Subjects experiencing somnolence included two in the terbinafine group and one in the griseofulvin group. A 5 year old male (USA study 2302 0154/00015) experienced episodes of sleepiness or excess sleeping on days 6, 22, 29, 35, and 38 with durations of 1 to 6 days. This same subject also experienced episodes of tiredness on days 23, 28, 32, and 36 with durations of 1 to 4 days. The second subject in the terbinafine group was a 4 year old male (BRA study 2302 0203/00002) who experienced somnolence on study day 36 (the last dose of terbinafine was day 42) and ongoing at the final examination (36 days later). A subject exposed to griseofulvin (USA study 2302 0154/00028) experienced somnolence on study day 37, with the event resolving the same day.

7.1.5.6 Additional analyses and explorations

Explorations for drug demographic interactions were performed for adverse events. Please see section 7.4.2.3.

7.1.6 Less Common Adverse Events

Three subjects in the terbinafine treatment group in study C 2301 experienced worsening visual acuity. This adverse event was not reported in the griseofulvin treatment group. The changes in visual acuity were reported as being 2 lines. The sponsor notes that the ophthalmology manual that was part of the protocol for studies C2301 and C2302 specified that only acuity changes of 3 or more lines were to be recorded as adverse events.

1) An eight year old Caucasian female (subject 527-08) began terbinafine on March 2, 2005, with baseline visual acuity in the right eye of LogMar=0.0. The subject was diagnosed with worsening visual acuity in the right eye (LogMar= 0.2) on Day 43. The last dose of study medicine was on Day 43. The investigator suspected a relationship between this event and study drug. The worsening of visual acuity was continuing at the final examination.
2) An eight year old male of ethnicity listed as Other (subject 601-06) began terbinafine on June 22, 2005 with baseline visual acuity in the right eye of LogMar = -0.1. Changes in visual acuity were noted in the right eye on Day 38 (LogMar = 0.1) and these changes resolved by the final visit on Day 70. The last dose of study medicine was on Day 42. The investigator suspected a relationship between this event and study drug.
3) A five year old Caucasian male (subject 802-01) began terbinafine on May 29, 2005 with baseline visual acuity in the left eye of LogMar = 0.0. On Day 12, the subject reported vomiting that resolved the same day. The last dose of terbinafine was taken on Day 42. On Day 43, the visual acuity in the left eye was reported as LogMar = 0.1. This change in visual acuity was still present at the final exam on Day 64. This event was considered by the ophthalmologist to be an insignificant abnormality. The investigator suspected that the two events of vomiting and worsening of visual acuity were related to study drug.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing performed in study C2101 (oral granule formulation studied) included:
1) Hematology; hemoglobin, RBC, hematocrit, WBC and differential, and platelet count.
2) Clinical 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.
3) 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.

Laboratory tests performed in the pivotal trials (C2301 and C2302) included:
1) Hematology; hemoglobin, RBC, hematocrit, WBC and differential, and platelet count.
2) Clinical chemistry; AST/SGPT, ALT/SGOT, GGT, alkaline phosphatase, total bilirubin, creatinine, and urea (BUN).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

No placebo controlled studies were performed in trials involving the safety population. Three studies were performed employing the oral granule formulation. The first of these is C2101, which was an open label Phase 2 PK study with no control. The second two were the two Phase

3 pivotal trials, C2301 and C2302. The control employed for these was an active one, griseofulvin.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on outliers or shifts from normal to abnormal

In the original protocols for the pivotal studies, Clinically Notable values were defined as grade 3 or 4 laboratory values using the NCI Common Toxicity Criteria Toxicity scale Version 2.0. This was amended in protocol Amendment 2 (Aug. 26, 2004 for Study C 2301, and Sept. 24, 2004 for Study C 2302) to state that; "The identification of notable values will be based on the lab values pre-defined in the analysis plan." The clinically notable laboratory values in the amended protocol appear to include age adjustments for the hematology and biochemistry values.

Examination of the statistical analysis plan for studies C 2301 and C 2302 reveals criteria for identifying clinically notable hematology as reflected in the tables 49, 52, and 53 in following sections.

Examination of shift tables for hematology values does not reveal substantial differences between the terbinafine and griseofulvin treatment groups in the pooled pivotal studies (safety population).

Table 49: Clinically Notable Hematology Values (Pivotal Studies, Pooled Safety Population)

		Terbinafine N=1042			Griseofulvin N=507		
Laboratory test (unit)	**Criterion**	**Total**	**n**	**(%)**	**Total**	**n**	**(%)**
Hematocrit (L/L)	<0.28	928	1	(0.1)	464	1	(0.2)
Hemoglobin (g/L)	<100	949	3	(0.3)	473	2	(0.4)
RBC (10^{12}/L)	<3.0	949	0	(0.0)	473	0	(0.0)
Absolute Neutrophils (Seg. + Bands) (10^9/L)	<1	958	12	(1.3)	482	13	(2.7)
Absolute Lymphocytes (10^9/L)	<1	958	5	(0.5)	482	3	(0.6)
Absolute Eosinophils (10^9/L)	>0.6	958	111	(11.6)	482	57	(11.8)
Platelet count (direct) (10^9/L)	<100	945	1	(0.1)	471	1	(0.2)
WBC (total) (10^9/L)	<3	958	9	(0.9)	483	5	(1.0)

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 35.

Clinically notable changes in hematology values were not common. Subjects exposed to griseofulvin had twice the rate (2.7%) of notable decreases in neutrophils as did those exposed to terbinafine (1.3%). It is possible that the high number of clinically notable values for eosinophils could reflect a criterion set somewhat too low. **Current Diagnosis & Treatment in Pediatrics** – 18th Ed. (2007) for 2 to 10 year old children lists a criterion for normal as <0.7 for boys (which overlaps the criterion set above) and for girls <0.3.

Subjects having outlier values for WBC (total) and ABS neutrophil count are captured by examining the listings for subjects with hematology laboratory values meeting criteria for discontinuation. The numerical criteria in this case are similar those for notable hematology values (WBC $\leq$ 3000/µl vs. < 3 10^9/L and neutrophil count $\leq$ 1000/µl vs. < 1x10^9/L). Examination of these listings for subjects exposed to terbinafine versus griseofulvin reveals that the magnitude of the outliers is generally similar between the two treatment groups. See following tables 50 and 51. Isolated cases of severe neutropenia are listed in the Precautions section of the current label for Lamisil® tablets.

Table 50: Subjects (Safety Population) with Hematology Laboratory Values Meeting the Criteria for Discontinuation of Study Drug; Treatment = Terbinafine

Country	**Age/ Sex**	**Study Day**	**WBC 10^9/L**	**ABS NEU 10^9/L**	**Completed Treatment**	**Completed Study**
1) CAN	6 M	20	5.81	1.00*	Yes	Yes
2) USA	4 M	22	4.32	.95*	Yes	Yes
3) USA	4M	43	2.89*	1.27	Yes	Yes
4) USA	7F	29	4.83	.97*	Yes	Yes
5) EGY	10M	21	3.66	.83*	No	Yes
C2302 0254-25					Abnormal lab value	Narrative in section 7.1.7.3.3, p. 87
6) JAM	11M	69	4.24	.84*	Yes	Yes
7) USA	5F	47	4.13	.87*	Yes	Yes
8) USA	4F	22	2.84*	.93*	Yes	Yes
9) USA	11F	44	2.74*	1.04	Yes	Yes
10) USA	9F	26	2.71*	1.17	No	No
					Subject withdrew consent	Subject withdrew consent
11) USA	6M	77	4.01	.98*	Yes	No
						Subject withdrew consent
12) USA	4M	23	4.58	.82*	Yes	No
						Lost to follow-up
13) USA	6M	46	2.81*	1.14	Yes	Yes
14) USA	8F	20	2.96*	1.45	Yes	Yes
15) USA	4M	24	4.05	.89*	No	No
					Protocol violation	Protocol violation
16) USA	7F	42	2.44*	.46*	Yes	Yes
		(47)	(4.41)	(1.74)		
17) USA	8M	23	2.63*	.87*	Yes	Yes
		(26)	(4.72)	(2.29)		
18) USA	6M	27	4.59	.89*	Yes	Yes
19) USA	8F	43	2.56*	1.12	Yes	No
						Subject withdrew consent

* Laboratory test meets criteria for discontinuing the study drug.
( ) Subsequent lab test
Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-2.1, Summary of Clinical Safety PTE, PTT, PTL, pp. 390-395.

Table 51: Subjects (Safety Population) with Hematology Laboratory Values Meeting the Criteria for Discontinuation of Study Drug; Treatment = Griseofulvin

Country	Age/ Sex	Study Day	WBC 10^9/L	ABS NEU 10^9/L	Completed Treatment	Completed Study
1) CAN	4F	26	3.59	.97*	Yes	Yes
2) USA	5F	22	4.40	.93*	Yes	Yes
3) USA	7M	22	1.97*	.74*	Yes	Yes
		(29)	(3.66)	(1.44)		
4) USA	6F	44	2.48*	.82*	Yes	Yes
		(72)	(4.86)	(2.22)		
5) USA	5F	22	4.68	.98*	No	Yes
		(31)	(3.86)	(.86*)	Abnormal lab value	
6) BRA	6M	24	3.74	.82*	Yes	Yes
7) BRA	4M	43	8.17	.98*	Yes	Yes
8) EGY	4F	45	5.01	.75*	Yes	Yes
9) JAM	10F	22	2.90*	.61*	Yes	Yes
		(36)	(2.76*)	(1.17)		
		(43)	(4.44)	(2.28)		
10) RUS	6M	23	3.48	.81*	Yes	Yes
11) RUS	6F	43	2.93*	.88*	Yes	Yes
		(70)	(4.93)	(2.03)		
12) USA	4M	42	4.53	.64*	Yes	Yes
13) USA	6M	23	2.87*	1.74	No	No
		(26)	3.34	.97*	Adverse event	Lost to follow-up
14) USA	4M	22	4.17	.88*	Yes	Yes

* Laboratory test meets criteria for discontinuing the study drug.
( ) Subsequent lab test
Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-2.1, Summary of Clinical Safety PTE, PTT, PTL, pp. 396-400.

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Examining the listing of subjects with notably abnormal hematology values reveals several subjects with fairly high values for eosinophils (above $2x10^9$/L). See Table 52, following.

Table 52: Subjects Having Very High (above $2x\ 10^9$/L) Eosinophil Counts (Safety Population)

Country	Age/ Sex	Study Day	ABS EOS 10^9/L		Completed Treatment	Completed Study	Treatment
1) BRA	4M	43	2.25*		Yes	Yes	Terbinafine
2) IND	9F	(-7)	(3.70)		Yes	Yes	Terbinafine
		22	2.70*				
		41	2.38*				
3) IND	7M	(-6)	(3.50)		Yes	Yes	Terbinafine
		24	3.60*				
		47	3.95*				
4) IND	9M	(-6)	(2.70)				Terbinafine
		24	2.80*		Yes	Yes	Terbinafine
5) IND	9F	(-5)	(3.30)		Yes	Yes	Terbinafine
		24	2.43*				
		43	2.32*				
6) IND	12M	(-3)	(1.50)		No	No	Terbinafine
		22	3.16*		Subject withdrew consent	Subject withdrew consent	
7) VEN	6F	(-18)	(2.62)		Yes	Yes	Griseofulvin
		91	2.03*				
8) IND	8M	(-6)	(3.13)		Yes	No	Griseofulvin
		22	2.73*			Lost to follow-up	
9) IND	8M	(-4)	(8.16)		Yes	Yes	Griseofulvin
		25	5.28*				
		43	5.27*				
10) USA	7M	(-7)	(2.09)		Yes	No	Griseofulvin
		29	.65*			Lost to follow-up	
		43	4.07*				

( ) Screening value
* Meet the notable abnormal laboratory criteria.
Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-2.3, CTD 5.3.5.3 SMAO Safety, pp.4-70; listing 16.2.1-1.1 Section 16.2 Study No# SFO327C 2301, pp. 2225-2293; and listing 16.2.1-1.1 Section 16.2 Study No# SFO327C 2302, pp. 2288-2361.

In all except one instance (number 1 in table 52), all of the subjects having very high eosinophil counts entered the studies having high eosinophil counts. This may be reflective of the presence of endemic parasites.

Table 53: Subjects with Hematology Outliers (Safety Population Pooled Studies)
Platelets < 100 x10^9L, ABS LYM < .5x10^9 below listed normal range for lab, Hgb < .4 g/L below listed normal range for lab, Hct < .2 L/L below listed normal range for lab

Country	Age/ Sex	Study Day	WBC 10^9/L	Platelets 10^9/L	ABS LYM 10^9/L	Hgb g/L	Hct L/L	Completed Treatment	Completed Study
Terbinafine									
1) PER	5M	43	6.86	401	.94*†	120	.40	Yes	Yes
2) ZAF	4M	45	4.79	272	.90*†	121	-	Yes	Yes
3) USA	8F	-3	3.39	304	1.44			Yes	Yes
		20	2.96*	25*	1.17	135	.41		
		43	4.70	347	1.66	125	.36		
4) USA	10M	-6	7.06	360	1.79	133	.41	Yes	Yes
		20	7.60	260	.51*†	126	.40		
		44	4.32	313	1.60	129	.40		
Griseofulvin									
1) EGY	9F	-7	7.88	235	3.88	141	.44	Yes	Yes
		22	6.63	273	3.30	135	.42		
		44	6.52	94*	2.77	134	.43		
2) USA	10M	-3	3.34	194	1.58	130	.37	Yes	Yes
		21	3.83	187	1.47	122	.38		
		42	3.69	181	.57*†	128	.37		
		70	3.05	172	1.48	126	.39		
3) EGY	5F	46	13.18	663	5.80	77*†	-	Yes	Yes
4) IND	5M	-15	14.40	767	5.80	105	.35	Yes	Yes
		30	8.20	596	2.70	53*†	.19*†		
		44	10.20	477	4.50	96*	.32		

* Meet the notable abnormal laboratory criteria.
† Meets criteria for outlier (exceeds notable laboratory criteria-see below).
Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-2.3, CTD 5.3.5.3 SMAO Safety, pp.4-70; listing 16.2.1-1.1 Section 16.2 Study No# SFO327C 2301, pp. 2225-2293; and listing 16.2.1-1.1 Section 16.2 Study No# SFO327C 2302, pp. 2288-2361.

Examination of listing 2.7.4.7-2.3 reveals only two subjects with notably low levels of platelets, one in each treatment arm. Information provided indicates that the subject in the terbinafine arm, 1) above, showed normal platelet numbers on repeat test. Examination of listing 2.7.4.7-2.3 reveals 4 subjects with very low lymphocyte counts (†more than .5 10^9/L below the normal range). Three of these were in the terbinafine group and one in the griseofulvin group. Examination of listing 2.7.4.7-2.3 reveals only two subjects with very low hemoglobin values (†more than .4 g/L below normal range). Both were in the griseofulvin group. Also examination of the same listing reveals only one subject, treated with griseofulvin, with a very low hematocrit (†more than .2 L/L below normal range).

In study C2101, neutrophil values were reported as % of WBC. Two patients in the 187.5 mg terbinafine (5108 and 5144) dose group had neutrophil counts that, when converted, were below

1500 cells/μl but above 1000 cells/μl. The following table (54) summarizes the differential cell counts for these two patients.

Table 54: Summary of Differential Cell Counts for Subjects 5108 and 5114, Study C2101

Subject (age)	Visit	Study Day	WBC A:5-16 B:4.5-13.5 10^6/L (?10^9/L)	NEU 45-75 %	EOS 0-8 %	LYM 16-46 %	BAS 0-3 %	MON 4-11 %
5108 (8yr)	**SCR**	**-6**	6.2 9.8	52.4	2.9	35.6	0.9 H	8.2 10.2
	BAS	**-1**		60.1	1.2	27.9	59	
	DAY21	**27**	4.2 L	56.3	2	29.5	0.3	11.9
	DAY27*	**27**	4.2 L	56.3	0.3	29.5	0.3	11.9
	DAY42	**42**	4.3 L	27.4 L	3	59.1 H	0.5	10
	EOS	**43**	3.7 L	29.7 L	3.6	57 H	0.5	9.2
5114 (5yr)	**SCR**	**-5**	7.2 5.5	44.1 L	1.7 H	44.1	0.5	9.6
	BAS	**-1**		54.7	8.6	30.9	0.4	5.4
	DAY21	**21**	3.6 L	32.8 L	7	52.7 H	0.2	7.3
	DAY42	**42**	4.3 L	38.8 L	4.5	47.2 H	0.7	8.8
	EOS	**43**	4.6	42.1 L	5.3	45.3	0.6	6.7

A: normal range for ages 4-6 yr
B: normal range for ages 7-8 yr
L: below LLN
H: above ULN
* repeat evaluation
Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 37.

As shown in table 54, the two subjects exposed to 187.5 mg terbinafine exhibited low, but not extremely so, neutrophil counts. These appeared associated with low WBC counts. In both subjects these values appeared to be improving at the end of study visit.

For Study W352, most hematology abnormalities were isolated. However, five subjects receiving 125 mg of terbinafine daily (<25 kg weight group) did experience low neutrophil counts (<1.5x10^9/L) at points during the study. Of note, subject 5416 had a decline in neutrophils from 1.4x10^9/L at baseline to .945x10^9/L at the end of study visit. Another subject, 5425, had an isolated low neutrophil count .9x10^9/L on Day 21 that returned to within normal limits by the end of study visit.

For Study L2306, out-of-range hematology test results were isolated and the Investigator did not consider these to be clinically significant.

In Study T201 subjects were treated with terbinafine for either 1, 2, or 4 weeks. Clinically meaningful differences in notable values between these treatment groups were not seen. Two subjects in the Lamisil 1-week group had newly occurring or worsening notable eosinophil values. These two subjects did not have other abnormal hematology parameters and did not experience AEs during the study. One of these subjects also suffered from asthma and eczema. Subjects with newly occurring or worsening notable hematocrit values included two with AEs of anemia (508 0012 and 512 0027) and one (501 0011) with an AE of gastroenteritis which led to

study medication interruption. Three subjects had newly occurring or worsening notable hemoglobin values (low); included in this group was a subject having sickle-cell disease. Five subjects were reported to have newly occurring or worsening notable neutrophil values (low). One of these subjects was reported to have the AE of leucopenia (503 0034).

In Study T202 subjects were treated with terbinafine for 6, 8, 10, or 12 weeks or were on griseofulvin. Clinically meaningful differences in notable values between these treatment groups were not seen. Nine newly occurring/worsening notable hematology values were noted in 7 subjects. For 6 of these subjects the notable hematology abnormalities were not considered to be clinically significant. The remaining subject (052 0017), in the Lamisil 10 week treatment group, experienced a SAE (neutropenia) that was suspected to be related to the study medication and was discontinued from the study.

Examination of shift tables for biochemistry values does not reveal substantial differences between the terbinafine and griseofulvin treatment groups for the pooled pivotal studies (safety population).

Table 55: Clinically Notable Biochemistry Values (Pivotal Studies, Pooled Safety Population)

		Terbinafine N=1042			**Griseofulvin N=507**		
Laboratory test (unit)	**Criterion**	**Total**	**n**	**(%)**	**Total**	**n**	**(%)**
Alkaline phosphatase, serum (U/L)	>2 ULN	951	2	(0.2)	476	0	(0.0)
Blood Urea Nitrogen (BUN)(mmol/L)	>1 ULN	984	7	(0.7)	495	0	(0.0)
Creatinine (umol/L)	>1 ULN	984	110	(11.2)	495	55	(11.1)
corrected creatinine*		984	4	(0.4)	495	3	(0.6)
SGOT (AST) (U/L)	>2 ULN	958	2	(0.2)	483	0	(0.0)
SGPT (ALT) (U/L)	>2 ULN	978	2	(0.2)	491	2	(0.4)
Bilirubin (total) (umol/L)	>1 ULN	981	4	(0.4)	493	1	(0.2)
Gamma Glutamyltransferase (U/L)	>2 ULN	951	1	(0.1)	475	3	(0.6)

Patients with missing baseline values were excluded.
* corrected creatinine does not appear in the source table.
Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 40.

Clinically notable changes in clinical chemistry values were not common. Marked differences in rates between the terbinafine and griseofulvin groups are not seen. Table 55 shows a number of abnormalities of creatinine. During the study the central lab revised the creatinine ranges; comparison with an older range yielded higher numbers of subjects flagged as having clinically notable creatinine values (See table 56 below). According to the sponsor, time restraints

prevented changes to the database. Use of the current ranges yields only 7 patients having abnormal creatinine values during the study.

Table 56: Corrected Creatinine Ranges

Age range (years)	**Males** Older range	Current range	**Females** Older range	Current range
4-6	14-48	44-71	14-48	44-71
7-9	23-57	53-80	14-57	44-80
10-12	23-66	53-88	23-66	53-88

Source: Sponsor's NDA submission, Clinical Study Reports, Study SFO327C 2301 p. 56, and Study SFO327C 2302 p. 56.

Table 57: Subjects Having Outlier Biochemistry Values (Safety Population Pooled Studies)
AST > 3xULN, ALT > 2.5xULN, Tot bili ≥ 5µmol/L above normal range, Creat > 25 µmol/L above normal range, BUN > 2.5 mmol/L above normal range,
GGT > 2xULN, Alk. Phos > 2xULN

Country TX	**Age/ Sex**	**Study Day**	**AST/ SGOT U/L**	**ALT/ SGPT U/L**	**Tot. bili. µmol/L**	**Creat µmol/ L**	**BUN mmol/L**	**GGT U/L**	**Alk. Phos U/L**	**Finish Treat.**	**Finish Study**
Terbin-afine											
1) PER‡	4M	22	215*†	195*†	<3	35	4.6	73*†	249	No	Yes
C2301		29	1531*†	1945*†	43*†	35	3.6	478*†	834*†	SAE-see	
0403-17		70	28	16	3	35	3.2	16	225	narrative	
2) USA	5M	20	33	15	5	53*	11.1*†	15	271	Yes	Yes
		42	32	19	5	44	8.6	12	214		
3) USA‡	7F	29	137*†	34	<3	44	6.1	17	244	Yes	Yes
C2301 0553-09		32	37	19	3	44	4.6	17	245		
4) USA	9M	46	32	22	<3	88*†	6.1	17	362	Yes	Yes
5) USA	12M	21	19	15	26*†	71*	5.0	13	237	Yes	Yes
		46	21	16	22*	44	3.6	15	290		
6) BRA‡	5M	21	100	155*†	3	44	5.0	31	345	No	Yes
C2302		43	69	145*†	3	44	5.0	40	351	Abnormal	
0203-03		71		16	<3	44	4.3	25	277	Lab value	
7) EGY	4F	48				74*†	8.7*	15	304	Yes	Yes
8) IND	11F	46	35	20	10	52	2.6	14	604*†	Yes	Yes
9) RUS	9M	67	16	11	5	83*†	3.3	11	102	Yes	Yes
10) RUS	5F	28	29	31	4	74*†	3.4	9	58	Yes	Yes
		48	34	20	<3	35	4.2	11	226		
		71	27	38	5	53*	4.4	25	56		

Griseo-fulvin											
1) COL‡	6F	27	56	101*†	5	35	2.9	51*†	187	No	Yes
C2301		34	36	47	5	35	2.5	33	162	Abnormal	see
0303-13										Lab value	narrative
2) JAM	7M	44	42	27	9	88*†	4.3	12	271	Yes	Yes
		72	-	-	-	53	4.6	12	299		
3) RUS	9M	21	28	17	4	39	3.5	12	150	Yes	Yes
		42	37	96*†	11	109*†	4.8	124*	80		
		48	27	68	10	102*†	5.4	97*†	79		
		62	28	59	5	96*†	4.8	85*†	93		
		70	25	17	11	87*†	4.0	11	78		
4) RUS	6M	23	22	22	10	86*†	4.9	21	47	Yes	Yes
		43	27	13	13	42	4.7	9	221	Also had	Lo neut #
5) ZAF	6F	43	39	49	7	42	4.2	67*†	329	Yes	Yes
		50	33	25	5	39	4.1	45	307		

* Meet the notable abnormal laboratory criteria.
† Meets criteria for outlier (exceeds notable laboratory criteria-see below).
‡ Additional comments in text.
Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-2.4, CTD 5.3.5.3 SMAO Safety, pp.71-122; listing 16.2.1-1.1 Section 16.2 Study No# SFO327C 2301, pp. 2225-2293; and listing 16.2.1-1.1 Section 16.2 Study No# SFO327C 2302, pp. 2288-2361.

In order to examine outliers for biochemistry values criteria were set (AST > 3xULN, ALT > 2.5xULN, Tot bili ≥ 5μmol/L above normal range, Creat > 25 μmol/L above normal range, BUN > 2.5 mmol/L above normal range, GGT > 2xULN, Alk. Phos > 2xULN) and used to generate table 57 above. In most cases (except for GGT and Alk Phos where they were the same) these criteria were more extreme than those used for the clinically notable biochemistry values in table 55. Marked outliers were generally isolated and generally showed return to normal ranges on repeat testing.

Marked outliers in the terbinafine group included a 4 year old subject (PER study C2301 0403/-17) who experienced a SAE of viral hepatitis and marked elevations of AST, ALT, Tot. bili, GGT, and Alk Phos. A 5 year old subject (BRA study 2302 0203-03, see also narrative, section 7.1.7.3.3, p. 87) discontinued treatment due to abnormal ALT values. An additional subject (USA C2301 0553-09) met criteria (AST ≥ 3 x ULN) for discontinuation of study drug. This subject was not withdrawn from treatment probably because repeat testing of AST showed return to normal range. Marked outliers in the griseofulvin group included a 6 year old female (COL study C2301 0303-13) who was discontinued from treatment due to high ALT values. Liver test abnormalities are listed in the adverse reaction section of the current Lamisil® tablet label.

Subjects having biochemistry lab value outliers are also captured through listing those subjects having biochemistry laboratory values meeting the criteria for discontinuation of study drug. The criteria as defined in the protocol are AST and/or ALT ≥ 3 x ULN and bilirubin ≥ 1.5 x ULN. The subjects meeting these criteria are listed in Table 58. Each of these three subjects has been discussed above in relation to Table 57.

Table 58: Subjects (Safety Population) with Biochemistry Laboratory Values Meeting the Criteria for Discontinuation of Study Drug; Treatment = Terbinafine

Country	Age/ Sex	Study Day	AST/SGOT U/L	ALT/SGPT U/L	Total bilirubin µmol/L	Completed Treatment	Completed Study
1) PER	4M	22	215*	195*	<3	No	Yes
C2301		29	1531*	1945*	43*	Serious adverse event	
0403-17		70	28	16	3		
2) USA	7F	29	137*	34	<3	Yes	Yes
C2301 0553-09		32	37	19	3		
3) BRA	5M	21	100	155*	3	No	Yes
C2302 0203-03		43	69	145*	3	Abnormal lab value	

* Laboratory test meets criteria for discontinuing the study drug.
Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-2.2, Summary of Clinical Safety PTE, PTT, PTL, p. 401.

In Study C2101 (oral granule formulation), one female subject (5101 in 125 mg terbinafine group) had mildly elevated AST values throughout the study; the value at screening was 51 U/L and at end-of study visit had a value of 58 U/L (female ULN upper limit of normal = 35 U/L). Another female subject (5116 also in the 125 mg terbinafine group) had a value of 45 U/L for AST at the end-of-study visit. Clinical chemistry results were otherwise unremarkable.

For Study W352, most abnormalities of clinical chemistry were isolated. Subject 5301 (187.5 mg terbinafine dose group) experienced mildly elevated AST (ULN: 40 U/L) levels including 45 at screening and 54 at end-of-study and at a repeat evaluation 2 weeks later. Subjects 5423 (125 mg dose group) and 5425 (125 mg dose group) had elevated CK (458 and 440 U/L; ULN 165 U/L) at screening which declined during the study. Two other subjects (5302, -125 mg dose group, and 5301 – 187.5 mg dose group) had mildly elevated CK which was found to be 100% MM throughout the study. Subject 5303 (125 mg dose group) had a moderately elevated CK that remained so throughout the study.

For study L2306, out of range clinical chemistry test results were isolated and the Investigator did not consider these to be clinically significant.

For Study T201, out of range clinical chemistry test results were isolated. In this study subjects were treated with terbinafine for 1, 2, or 4 weeks. Clinically meaningful differences between these groups in the incidence of notable biochemistry results were not apparent.

In Study T202 subjects were treated with terbinafine for 6, 8, 10, or 12 weeks or were treated with griseofulvin. Seven subjects showed an elevation of liver enzyme tests above the reference range. Three of these were in the Lamisil 6 week group (n = 35) one was in the Lamisil 8 week group (n =33), one was in the Lamisil 10 week group (n = 33) and two were in the griseofulvin group (n = 30). Differences among the treatment groups do not appear evident. One subject in

the griseofulvin group experienced clinically significant high total cholesterol, and was referred to a specialist. Apart from the preceding, clinically meaningful differences between treatment groups in the incidence of notable biochemistry results were not seen.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

In Study C2301, two subjects discontinued due to abnormal laboratory findings, both were in the griseofulvin treatment group.

1) Subject 0303-13; 6 years old; **female; ethnicity – other. On day 27, visit 3, testing revealed** high alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Griseofulvin was discontinued and a retest showed normal ALT and AST. This event was assessed by the investigator as being of mild severity and not related to study drug.

2) Subject 0565-03; 5 years old; **female; ethnicity – Black. On day 22, visit 3; testing revealed a** low neutrophil count. Griseofulvin was discontinued and the duration of the low neutrophil count was 24 days. This event was assessed by the investigator as being of mild severity and a relationship to study drug was suspected.

In Study C2302, three subjects discontinued due to abnormal laboratory findings, one in the griseofulvin a group and two in the terbinafine group.

Griseofulvin treatment group
1) Subject 0128-05; 6 years old; **male, ethnicity – Caucasian. On Day 17 the subject developed** a cold. On Day 23, visit 4; testing showed a low WBC count and griseofulvin was discontinued. This event was assessed by the investigator as being of mild severity and a relationship to study drug was suspected.

Terbinafine treatment group
2) Subject 0203-03; 5 years old, male, ethnicity – **Black. (See also discussion page 85.) On day** 37 testing revealed elevated alanine aminotransferase (ALT) 155 U/L, aspartate aminotransferase (AST) 100 U/L, alkaline phosphatase 345 U/L, and gamma-glutamyl transferase (GGT) 31 U/L. Study drug was discontinued and the subject discontinued the study. By the final visit, 4, these abnormalities had not resolved. This event was assessed by the investigator as being of moderate severity and a relationship to study drug was suspected.

3) **Subject 0254-25; 10 years old, male, ethnicity** – Caucasian. (See also Table 50, p. 78, subject 5 EGY C2302.) On day 21, visit 3, testing revealed a neutrophil count of .83 x $10^3/\mu L$ (baseline had been 1.37 x $10^3/\mu L$ and lower limit of normal = 1.35 x $10^3/\mu L$). Terbinafine was discontinued on day 41 and the neutropenia was resolving by day 45, visit 4, with a count of 1.30 x $10^3/\mu L$. At visit 5 this value was 1.58 x $10^3/\mu L$. This event was assessed as being of mild severity and a relationship to study drug was suspected.

7.1.7.4 Additional analyses and explorations

Subgroup analyses by race, age group, and sex were performed for clinically notable laboratory abnormalities. Significant differences within subgroups (Caucasian vs. Black vs. Other, 4-8 year old vs. 9-12 year old, Male vs. Female) are not seen. Of note, in both treatment groups, there is a variation by race in the number of subjects that have elevated eosinophil counts. In both treatment groups subjects of ethnicity **"other" had the highest number** 20 to 21% with elevated eosinophil counts. Those of ethnicity **"Caucasian" had 9 to 11 %** with elevated counts and those **of ethnicity "Black" had the lowest, 6 to 7%.**

7.1.7.5 Special assessments

No special assessments were performed

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were monitored in all of the clinical studies and included; pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP) and weight.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

No placebo controlled studies were performed in trials involving the safety population. Three studies were performed employing the oral granule formulation. The first of these is C2101, which was an open label Phase 2 PK study with no control. The second two were the two Phase 3 pivotal trials, C2301 and C2302. The control employed for these was an active one, griseofulvin.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The pivotal studies employed the following definitions for notable abnormalities of vital signs:

Pulse (b/m) either ≥120 + increase ≥25, or > 130 either ≤ 50 + decrease ≥ 30, or < 40

Systolic BP (mmHg) either ≥180 + increase ≥30, or > 200 either ≤90 + decrease ≥30, or < 75

Diastolic BP (mmHg) either ≥105 + increase ≥20, or > 115 either ≤50 + decrease ≥20, or < 40

A weight loss of ≥ 7% noted and confirmed by immediate repeat measurements required discontinuation of the patient from the pivotal studies.

The sponsor's analysis using criteria described above for pulse, systolic BP, and diastolic BP follows in Table 59.

Table 59: Vital Signs Meeting Notably Abnormal Criteria by Sign and Treatment (Safety Population)

		Terbinafine			Griseofulvin		
Vital Signs (Unit)	Criterion	N=1042			N=507		
		Total	n	(%)	Total	n	(%)
Pulse (b/m)	either (>= 120 + increase >= 25) or > 130 either (<= 50 + decrease >= 30) or < 40	1004	5	(0.5)	496	2	(0.4)
SBP (mmHg)	either (>= 180 + increase >= 30) or > 200 either (<= 90 + decrease >= 30) or < 75	1005	34	(3.4)	497	23	(4.6)
DBP (mmHg)	either (>= 105 + increase >= 20) or > 115 either (<= 50 + decrease >= 20) or < 40	1005	18	(1.8)	497	12	(2.4)

Source: Sponsor's NDA submission, SCS-PTF, PTT, PTL, p. 321.

Examination of the subjects meeting criteria for notably abnormal vital signs reveals generally similar rates across treatment groups for the three different measurements, pulse, SBP (systolic blood pressure) , and DBP (diastolic blood pressure).

Because there was concern that the criteria for vital signs used in Table 59 were not normalized for age, an information request to the sponsor was made. The sponsor provided a response, stating that the clinically notable ranges used above ..."seem to be wide."

Therefore, Novartis provided in their response, the information on vital signs meeting the following age corrected criteria for the definitions of notable vital sign abnormalities:

Systolic BP (Hgmm): <=70 or >=135 mmHg
Diastolic BP (Hgmm): <=40 or >=85
Pulse (b/m): <=45

Table 60: Vital Signs (post randomization) Meeting Notably Abnormal Criteria, Revised By Sign and Treatment (Safety Population)

		Terbinafine			Griseofulvin		
Vital Signs (Unit)	Criterion	N=1042			N=507		
		Total	n	(%)	Total	n	(%)
Pulse (b/m)	< = 45	1004	0	-	496	0	-
SBP (mmHg)	<=70 or >=135	1005	30	(3.0)	497	17	(3.4)
DBP (mmHg)	<=40 or >=85	1005	30	(3.0)	497	20	(5.6)

Source: Sponsor's NDA, Response to FDA request for information, dated May 18, 2007, Table 2.7.4.7-6.1.

Note that while the new criteria are narrower in some aspects, for pulse no upper limit is given and for both systolic and diastolic blood pressure no limits are placed on increase or decrease.

Examination of the subjects meeting the revised criteria for notably abnormal vital signs reveals generally similar rates across treatment groups for the three different measurements, pulse, SBP (systolic blood pressure) , and DBP (diastolic blood pressure).

To examine outliers, criteria were set (SBP≤55, DBP≤35, and Pulse>130). Those subjects meeting the outlier criteria are listed in Table 61. Examination of this table reveals that vital sign outliers appear generally isolated and tend to return to normal ranges upon repeat testing. Of note are the fairly large numbers of subjects in both treatment groups who are from Jamaica and show very low sitting systolic and diastolic blood pressures. Perhaps there is something unique to this population group that results in these low values.

Table 61: Vital Signs Outliers: SBP≤55, DBP≤35, and Pulse>130 (Safety Population)

Country TX	Age/ Sex	Study Day	Sitting SBP	Sitting DBP	Sitting Pulse	Completed Treatment	Completed Study
Terbin-afine							
1) CAN	5F	21	111	63	135*†	Yes	Yes
		43	108	66	112		
2) COL	4F	19	110	70	160*†	Yes	No
		1	90	70	130		Administrative problems
3) USA	7M	18	117	62	142*†	Yes	Yes
		43	115	68	117		
4) JAM	7M	-1	60*	40	96	Yes	Yes
		21	55*†	45	100		
		42	50*†	40	88		
		71	55*†	45	100		
5) JAM	8F	-6	60*	50	90	Yes	Yes
		17	55*†	40	96		
		44	55*†	40	96		
		72	50*†	40	90		
6) JAM	4M	-1	60*	30*†	100	Yes	Yes
		21	55*†	40	88		
		42	55*†	40	88		
		72	50*	40	96		
7) JAM	5F	-1	60*	35*†	100	Yes	Yes
		21	60*	35*†	100		
		42	50*†	40	92		
		70	55*†	40	96		
8) JAM	6M	1	60*	40	88	Yes	Yes
		22	60*	35*†	100		
		42	80	52	92		
9) JAM	8M	-1	75	50	90	Yes	Yes
		21	60*	50	88		
		42	60*	55	90		
		77	55*†	40	88		
10)JAM	6F	-8	50*†	40	90	Yes	No
		-1	60*	45	80		Lost to follow-up
		20	60*	50	84		
		42	65*	50	75		

11) USA	5F	-5	78	35*†	88	Yes	Yes
		1	80	50	84		
12) USA	4F	-8	109	66	112	Yes	Yes
		1	118	74	133*†		
		22	123	64	115		
13) USA	4M	-5	105	50	136*†	Yes	Yes
		1	90	60	100		
14) ZAF	4F	-6	110	63	122	Yes	No
		23	97	60	131*†		Lost to follow-up
		61	97	66	147*†		
Griseo-fulvin							
1) JAM	6F	-13	55*†	40	100	Yes	Yes
		-6	60*	40	92		
		17	60*	40	90		
		44	60*	40	90		
		72	55*	35*†	88		
2) JAM	4M	-8	55*†	40	88	No	No
		-2	55*†	45	90	Lost to follow-up	Lost to follow-up
		20	55*†	40	92		
3) JAM	8M	-1	60*	40	100	Yes	Yes
		21	60*	40	100		
		42	55*†	35*†	96		
		70	60*	40	94		
4) JAM	7M	-7	65*	30*†	92	Yes	Yes
		1	60*	30*†	100		
		22	70*	40	88		
		43	75	50	92		
5) JAM	5M	-8	50*†	25*†	98	Yes	Yes
		1	60*	40	90		
		21	50*†	25*†	98		
		42	60*	40	92		
6) USA	5F	1	128	71	133*†	Yes	Yes
		23	120	67	126		
		44	112	63	108		
		70	100	60	135*†		

* Meets criteria for notably abnormal vital sign.
† Meets criteria for vital sign outlier.
Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-3.1, CTD 5.3.5.3 SMAO Safety, pp.123-172; listing 16.2.1-1.1 Section 16.2 Study No. SFO327C 2301, pp. 2225-2293; and listing 16.2.1-1.1 Section 16.2 Study No. SFO327C 2302, pp. 2288-2361.

Taste disturbances were evaluated by weight monitoring, caregiver interview, and patient/food diary. Differences between the two treatment arms with respect to changes in eating habits and clinically significant weight loss were not notable, according to the sponsor's analysis. Please see table 62. Increased appetite was more common than decreased appetite.

One subject in the terbinafine arm (Study 2301) had both clinically significant weight loss and decreased appetite at Visit 3 (day 22). This is identified as a 4 year old female (VEN study 2301

0601-15) who presented on day 7 with a high fever, cough, and appetite loss. On day 22 a chest x-ray revealed pneumonia in the right lung and the subject was hospitalized. The subject was discharged from the hospital on day 24 and was reported to make a complete recovery by day 27. Then beginning on day 30 through day 34 the subject reported vomiting after taking terbinafine. The last dose of terbinafine was on day 34. The subject was discontinued due to AEs on day 37. Decreased appetite was reported at study visits 3 and 4 (Days 22 and 42).

One subject, a 5 year old male (USA study C2302 0111-01) experienced loss of appetite on study day 4 and lasting for two days. Terbinafine was discontinued permanently on day 4 and no loss of weight was noted. Other reported adverse events for this subject were runny nose on study day 1 and lasting 1 day and headache on study day 2 and lasting for 1 day.

Table 62: Significant Weight Loss and Change in Eating Habits
(Pivotal Studies, Pooled Safety Population)

	Terbinafine N=1042	**Griseofulvin N=507**
Visit	**n/m* (%)**	**n/m (%)**
Visit 3 (Day 22)		
Clinically significant weight loss [1]	3/966 (0.3)	7/486 (1.4)
Significant change in eating habits	129/971 (13.3)	72/487 (14.8)
Decreased appetite [2]	50/971 (5.1)	27/487 (5.5)
Increased appetite	75/971 (7.7)	42/487 (8.6)
Other	4/971 (0.4)	3/487 (0.6)
Having both [1] and [2]	1/965 (0.1)	0/486 (0.0)
Visit 4 (Day 42)		
Clinically significant weight loss [1]	7/986 (0.7)	3/486 (0.6)
Significant change in eating habits	93/993 (9.4)	56/491 (11.4)
Decreased appetite [2]	31/993 (3.1)	18/491 (3.7)
Increased appetite	59/993 (5.9)	33/491 (6.7)
Other	3/993 (0.3)	5/491 (1.0)
Having both [1] and [2]	0/984 (0.0)	0/486 (0.0)
Visit 5 (Day 70)		
Clinically significant weight loss [1]	5/916 (0.5)	2/453 (0.4)
Significant change in eating habits	43/924 (4.7)	25/454 (5.5)
Decreased appetite [2]	9/924 (1.0)	4/454 (0.9)
Increased appetite	32/924 (3.5)	18/454 (4.0)
Other	2/924 (0.2)	3/454 (0.7)
Having both [1] and [2]	0/915 (0.0)	0/453 (0.0)

[1] Clinically significant weight loss defined as >=7% decrease in weight as compared to the baseline value.
[2] Any significant decreased appetite in the subject's eating habits since the last visit noticed by caregiver.
*n/m = number with finding/number measured

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 44.

Weight loss outliers were examined by setting a criterion, ≥ 10% weight loss from baseline. Subjects meeting this criterion are shown in table 62, following. Subjects exposed to terbinafine

demonstrated weight loss outliers at a higher rate .07% (7/1042) than those exposed to griseofulvin .02% (1/507). However, 5 of the 7 subjects exposed to terbinafine, and showing weight loss outliers, had weight measurements that improved on subsequent measurement.

Table 63: Weight Loss Outliers, ≥ 10% Weight Loss from Baseline (Safety Population)

Country TX	Age/ Sex	Study Day	Weight (kg)	Change from baseline (kg)	% Change From baseline (kg)	Completed Treatment	Completed Study
Terbin-afine							
1) USA	6M	1	29.5			Yes	Yes
		25	28.2	-1.3	-4.41		
		55	26.8	-2.7	-9.15*		
		71	25.0	-4.5	-15.25*†		
2) USA	7M	-1	25.0			Yes	Yes
		23	25.0	-.5	-1.96		
		42	22.0	-3.5	-13.73*†		
		69	26.0	.5	1.96		
3) USA	8F	1	27.3			Yes	Yes
		21	26.8	-.5	-1.83		
		44	24.5	-2.8	-10.26*†		
		77	23.7	-3.6	-13.19*†		
4) USA‡	5M	1	19.2			Yes	Yes
C2301		20	19.4	.2	1.04	(also had abnormal	
0534-08		42	17.0	-2.2	-11.46*†	chemistry values)	
		69	19.6	.4	2.08		
5) USA‡	6F	1	17.5			No	Yes
C2301		23	15.6	-1.9	-10.86*†	Protocol	
0538-02		42	16.3	-1.2	-6.86	violation	
		71	16.5	-1.0	-5.71		
6) VEN‡	4F	1	17.8			No	Yes
C2301		23	10.9	-6.9	-38.76*†	(SAE)	
0601-15		37	17.7	-0.1	-.56	D/C due to AE	
7) USA	6M	-1	25.9				
		19	24.5	-1.4	-5.41	Yes	Yes
		41	23.0	-2.9	-11.20*†		
		69	25.0	-.9	-3.47		
Griseo-fulvin							
1) EGY	4M	-5	17.0	2		Yes	Yes
		22	15.0	-2.0	-11.76*†		
		44	16.0	-1.0	-5.88		
		73	16.0	-1.0	-5.88		

* Meets criteria for notable weight loss (> 7% from baseline).
† Meets criteria for weight loss outlier (≥10% from baseline).
‡ Additional comments in text.
Source: Sponsor's NDA submission, Adapted from listing 2.7.4.7-4.1, CTD 5.3.5.3 SMAO Safety, pp.173-179; listing 16.2.1-1.1 Section 16.2 Study No# SFO327C 2301, pp. 2225-2293; and listing 16.2.1-1.1 Section 16.2 Study No# SFO327C 2302, pp. 2288-2361.

Of note are three subjects listed in table 63 above. The first of these is a 5 year old male (USA study 2301 0534-08, see 4 in table above) who had a weight loss of 11.46% from baseline which improved markedly on repeat measurement. On study day 20 this subject was noted to have creatinine of 53μmol/L (NL 14-48) and a BUN of 11.1mmol/L (NL 1.4-8.6). This may suggest that a process other than change in taste was responsible for the weight loss. The second subject is a 6 year old female (USA study C2301 0538/00002) who had a weight loss of 10.86% from baseline on study day 23. By study day 42 this loss had improved to -6.86% from baseline and no longer notable. This was coded as an adverse event and not suspected to be related to study drug. This subject did not complete the study treatment due to protocol violation, which on examination of the case report form may have been related to missing several doses of medication between Visits 3 and 4. It is also noted that this subject had a negative initial culture result. The third subject is a 4 year old female (VEN study C2301 0601/00015) who had a weight loss of 38.76% from baseline on study day 23. The subject was diagnosed and hospitalized with pneumonia on study day 22, an SAE. The subject recovered by study day 27. Starting on study day 30 through 34 the subject began to vomit after taking terbinafine. On day 37 the subject was discontinued from treatment due to the adverse event of vomiting. Also on study day 37 the subject's weight loss had improved to a loss of only .56% from baseline.

To further examine the adverse event of weight loss, case report forms and narratives of all subjects with weight loss $\geq$ 7% from baseline were examined. Data relating to % weight change from baseline, adverse events, change in eating habits, and whether the subject had completed treatment were examined for the 21 subjects who met the weight loss criterion. Twelve subjects were identified in the terbinafine group from the safety population of the pooled pivotal studies. Of these twelve, two subjects had weight loss that did not appear to show connection to study drug use, one showed weight loss after finishing study drug the other was hospitalized for pneumonia at the time of greatest weight loss. For the 10 remaining subjects peak weight loss was -8%, -15%, -14%, -9%, -13%, -11%, -11%, -9%, -11%, and -8%. Of these remaining 10 subjects, 5 showed weight loss of -5% or greater from baseline at the end of study visit, generally around day 70, 4 weeks after finishing study drug. One of these 5 also was reported to have decreased appetite, which could reflect taste disturbance. The other 4 might be suspected to have possible taste disturbance as reflected in weight loss.

In the griseofulvin group, 9 subjects were identified having weight loss $\geq$ 7% in the pooled safety population of the 2 pivotal trials. Of these 9, 4 showed subsequent weight gain while on griseofulvin. One subject from India was reported to be fasting during the month of Ramadan. For the 4 remaining subjects, peak weight loss was -7%, -9%, -12%, and -8%. Of these remaining 4 subjects, three had a weight loss of 5% or greater at the end of study visit (around day 70). These three might be suspected to have a taste disturbance, reflected in weight loss. Please also note that the griseofulvin group is half the size of the terbinafine group.

Using the two groups of subjects with peak weight losses noted above, a Wilcoxin Rank Test was performed.
Terbinafine tt (8,15,14,9,13,11,11,9,11,8)
Griseofulvin gg (7,9,12,8)
p-value = 0.2408

This value indicates that there is likely that the difference between the two groups is produced by chance.

The side effect of dysguesia was reported in a total of four subjects, two in the terbinafine group and two in the griseofulvin group all in Study C2302.
Terbinafine treatment group
1) Subject 112-06; 9 years old, female, ethnicity – Caucasian. On the first day of taking study medication the subject reported a bad taste in the mouth which resolved and was not reported on subsequent days. The subject completed the study with no changes reported in eating habits or of weight. This event was assessed by the investigator as being of mild severity and a relationship to study drug was suspected.

2) Subject 149-01; 7 years old, male, ethnicity – Caucasian. On study day 8 the subject reported aftertaste that ended the same day. The investigator assessed this event as mild and did not suspect a relationship to study drug. On days 9 to 13 clear nasal drainage was reported, on days 10 to 13 cough was reported, and on day 14 decreased appetite was reported that ended the same day. Diarrhea that ended the same day was reported on days 1 and 15. These events were assessed as mild by the investigator and a relationship to study drug was not suspected. The subject completed the study and his weight was stable. He was also reported to be non-compliant with medication, not taking at least 80% of the study medication as prescribed.

Griseofulvin treatment arm
3) Subject 0113-08; 5 years old, male, ethnicity – Caucasian. On study day 1, the subject reported a bad, metallic, taste that resolved on day 7. On day 7 the griseofulvin was discontinued. The event was ongoing at the final examination. This event was assessed by the investigator as being of mild severity and a relationship to study drug was suspected. No weight loss was seen.

4) Subject 0141-03; 7 years old, male, ethnicity – Black. On study day 3 the subject reported an unappealing taste that resolved the same day. The last dose of griseofulvin was on day 42. The subjects also reported a number of episodes of increased thirst, and one episode each of headache and stomach cramps, both resolving the same day. The events of unappealing taste, and stomach cramps were assessed by the investigator as being of mild severity and a relationship to study drug was suspected. The episodes of increased thirst were assessed as moderate severity and suspected to be related to study drug. The episode of headache was assessed as mild severity and no relationship to study drug was suspected. Weight loss was not seen.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Pleas see previous Tables 59, 60, 61 and 63.

7.1.8.4 Additional analyses and explorations

Additional analyses and explorations were not performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were not performed in the pivotal studies nor in four of the five other studies. ECGs were performed in study L2306.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

In study L2306 twelve subjects had clinically insignificant ECG abnormalities at screening or at baseline. At study end all of the ECGs were normal. This study was a randomized open-label, multiple dose, two-period, crossover examination of food effect on PK in healthy adults.

7.1.9.4 Additional analyses and explorations

Additional analyses and explorations were not performed.

7.1.10 Immunogenicity

This is not applicable since the drug is not a therapeutic protein.

7.1.11 Human Carcinogenicity

No tumors were reported in any of the clinical studies. However the studies performed were short, consisting of only six weeks of treatment followed by a final visit at week 10.

7.1.12 Special Safety Studies

Drug-drug interaction studies with the already marketed formulation, Lamisil, were conducted in healthy subjects to assess pharmacokinetic interactions with fluconazole, Cotrimaoxazole DS, zidovudine, and theophylline. Please see section 7.4.2.5.

Ophthalmologic exams were performed requested by FDA Pediatric Written Request as part of the pivotal studies. The ophthalmology reviewer has also completed a re-review of previously reported ophthalmic adverse events. The reviewer is unable to identify any pattern of reported ophthalmic adverse events which would lead to a specific ophthalmic safety concern. The

ophthalmology reviewer states that there does not appear to be sufficient ophthalmic concern to request additional ophthalmic safety studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No instances of abuse have been reported in any of the studies in the clinical development program. Terbinafine is not known to possess the potential for abuse.

Withdrawal and rebound effects are not known to exist for terbinafine.

7.1.14 Human Reproduction and Pregnancy Data

No new information has been developed in the course of the current clinical development program. The current Lamisil® label includes the following statements:

Pregnancy
Pregnancy Category B: Oral reproduction studies have been performed in rabbits and rats at doses up to 300 mg/kg/day (12 × to 23 × the MRHD, in rabbits and rats, respectively, based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to terbinafine. There are, however, no adequate and well-controlled studies in pregnant women.
Because animal reproduction studies are not always predictive of human response, and because treatment of onychomycosis can be postponed until after pregnancy is completed, it is recommended that LAMISIL® not be initiated during pregnancy.

Nursing mothers
After oral administration, terbinafine is present in breast milk of nursing mothers. The ratio of terbinafine in milk to plasma is 7:1. Treatment with LAMISIL® Oral Granules is not recommended in nursing mothers.

7.1.15 Assessment of Effect on Growth

This is not applicable because the studies were of short duration.

7.1.16 Overdose Experience

No new information has been developed in the course of the current clinical development program. The current Lamisil® label includes the following statements:

Clinical experience regarding overdose with oral terbinafine is limited. Doses up to 5 grams (20 times the therapeutic daily dose) have been reported without inducing serious adverse reactions. The symptoms of overdose included nausea, vomiting, abdominal pain, dizziness, rash, frequent urination, and headache.

7.1.17 Post-marketing Experience

The drug product, terbinafine oral granules, has not been marketed in any country at the time of writing this review.

The chemical moiety, terbinafine hydrochloride, has been marketed as Lamisil® Tablets. An OSE consult has been obtained and has proposed adding pancytopenia, rhabdomyolysis, and acute pancreatitis to the Postmarketing Experience section of the Lamisil® Oral Granules label.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The clinical development program consisted of seven studies intended to demonstrate efficacy and contributing to safety. Of the five Phase 2 trials only one, C2101, was conducted with the to-be-marketed formulation. Please see Table 64, following.

Table 64: Phase 2 Dose-Finding Trials

Study No.	Study objective, population	Planned patients	Treatment duration	Dosage	Type of control
W352	Open-label, multiple-dose PK in children 4–8 years with Tinea capitis	16 (22 enrolled)	28 days for patients with *Trichophyton* 42 days for patients with *Microsporum*	terbinafine tablets, by body weight: <25 kg - 125 mg/day, 25-35 kg - 187.5 mg/day, >35 kg - 250 mg/day	none
C2101	Open-label, multiple-dose PK in children 4–8years with Tinea capitis	16 (16 enrolled)	42 days	terbinafine oral granules by body weight: <25kg = 125 mg/day 25-35 kg = 187.5 mg/day >35 kg = 250 mg/day	none
L2306	Randomized, open-label, multiple-dose, two-period, crossover food effect on PK, healthy adults	24 (24 enrolled)	30 days (15+15)	terbinafine [redacted] (175mg [redacted]	none
T201	Randomized, double-blind, parallel-group study to identify a safe and appropriate treatment duration in patients (>4 yrs) with Tinea capitis caused by *Trichophyton*	150 (177 enrolled)	1, 2, or 4 weeks	terbinafine tablets <20 kg = 62.5 mg/day 20-40 kg = 125 mg/day >40 kg = 250 mg/day	none
T202	Randomized, double-blind, parallel-group study to identify a safe and appropriate treatment duration in patients (>4 yrs) with Tinea capitis caused by *Microsporum*	150 (165 enrolled)	6, 8. 10 or 12 weeks	terbinafine tablets <20 kg = 62.5 mg/day 20-40 kg = 125 mg/day >40 kg = 250 mg/day	active (griseofulvin)

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 9.

Table 65: Phase 3 Controlled Efficacy Trials

Study No.	Study objective, population	Planned patients	Treatment duration	Dosage	Type of control
C2301	Randomized, investigator-blinded, parallel-group safety and efficacy study in patients 4 – 12 years of age with Tinea capitis.	720 (748 enrolled)	42 days	Terbinafine oral granules 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 oral granules by body weight: <25 kg - 125 mg/day, 25-35 kg - 187.5 mg/day, >35 kg - 250 mg/day	active (griseofulvin)

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 9.

The safety database as designated by the sponsor does not include two single dose bioavailability studies, L2104 and C2303, and four drug interaction studies; SF W152, SF W153, SF W154, and SF W156. Although important, these studies did not contribute significantly to total drug exposure since they were of short duration and performed in healthy subjects.

7.2.1.2 Demographics

In the pooled safety population from the Phase 3 clinical trials the two treatment arms were generally similar at baseline. Of note there was slight predominance of male subjects on terbinafine (63.9% vs. 36.1%) as compared with griseofulvin (58.6% vs. 41.1%).

In general, the predominant groups at risk for having tinea capitis are African-American, Afro-Caribbean, and black children in Africa[1]. In the two Phase 3 trials, racial groups involved were approximately 21% Caucasian, 48% Black, .1% Oriental, and 32% other. Please see Table 66, following.

[1] B E Elewski, Tinea capitis: A current perspective. J. Am. Acad. Dermatol. 2000 Jan;42(1 Pt 1):p. 9.

Table 66: Baseline Demographics (Pivotal Studies, Pooled Safety Population = Those Receiving at least one Dose)

		Terbinafine N=1042	**Griseofulvin N=507**
Sex - n (%)			
Male		666 (63.9)	297 (58.6)
Female		376 (36.1)	210 (41.4)
Race - n (%)	US Population[1]		
Caucasian	75.1%	215 (20.6)	115 (22.7)
Black	12.3%	495 (47.5)	234 (46.2)
Oriental		1 (0.1)	1 (0.2)
Other	(Hispanic 12.5%[†])	331 (31.8)	157 (31.0)
Age (years)			
Mean (SD)		6.9 (2.29)	6.8 (2.25)
Median		6.0	7.0
Min - Max		3-12	3-12
Age groups - n (%)			
<4 years		4 (0.4)	2 (0.4)
4 - 8 years		764 (73.3)	374 (73.8)
9 - 12 years		274 (26.3)	131 (25.8)
Weight (kg)			
Mean (SD)		26.2 (10.46)	25.5 (9.80)
Median		23.6	23.6
Min - Max		11-125	12-106
Country - n (%)			
USA		520 (49.9)	248 (48.9)
Non-USA		522 (50.1)	259 (51.1)

[1]Overview of Race and Hispanic Origin, U.S. census Bureau, Census 2000 Brief, March 2001, p. 3.
[†]In the Census 2000, "Hispanic or Latino" was employed as a category for ethnicity.
Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 16.

The baseline demographics in the pivotal trials differed from those of the dose-finding studies. Two studies, W352 and C2101, enrolled subjects 4 to 8 years of age and having Tinea capitis. Two studies, T201 and T202, enrolled subjects ≥ 4 years of age and having Tines capitis. Study L2306 enrolled healthy adult volunteers.

7.2.1.3 Extent of exposure (dose/duration)

Table 67: Exposure (pivotal studies, pooled safety population)

	Terbinafine N=1042	Griseofulvin N=507
Number of days taking study drug		
n	1021	500
Mean (SD)	39.8 (8.38)	40.2 (7.04)
Median	42.0	42.0
Min – Max	1-108	1-65
Total days dosed as % of expected - n (%)		
< 80%	94 (9.0)	54 (10.7)
80 -120%	909 (87.2)	436 (86.0)
> 120%	18 (1.7)	10 (2.0)
Total days dosed - n (%)		
Unknown	21 (2.0)	7 (1.4)
1 – 7	23 (2.2)	4 (0.8)
8 – 14	5 (0.5)	3 (0.6)
15 – 21	20 (1.9)	9 (1.8)
22 – 28	27 (2.6)	12 (2.4)
29 – 35	50 (4.8)	40 (7.9)
36 – 42	586 (56.2)	267 (52.7)
> 42	310 (29.8)	165 (32.5)

Source: Sponsor's NDA submission, Summary of Clinical Safety, p. 14.

In the pivotal trials a total of 1021 subjects received at least one dose of the terbinafine oral granule formulation.

Only one of the dose finding trials, C2101, involved exposure to the oral granule formulation. The design involved 16 patients treated with the oral granule formulation and dosed by body weight for 42 days. All 16 patients enrolled received at least one dose of the study medicine.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There were no secondary clinical data sources used to evaluate safety. All safety evaluations came from the clinical trials submitted to support approval of the NDA since the oral granule formulation of terbinafine has only been used in these studies.

7.2.2.2 Post-marketing experience

The oral granule formulation of terbinafine has not been approved in any other jurisdiction.

7.2.2.3 Literature

The sponsor has provided literature references pertaining to drug-drug interactions, drug metabolism, and antifungal susceptibility testing.

7.2.3 Adequacy of Overall Clinical Experience

In the pivotal trials 1042 subjects were exposed to the terbinafine oral granule formulation for a mean of 39.8 days. Of these, 21 had an unknown dose, according to the sponsor's Table 2-1, p. 14, CTD 2.7.4 Summary of Clinical Safety. The mean age was 6.9 years.

The racial composition, while differing from that of the US population, does provide a representation of racial groups that are at risk for tinea capitis (Caucasian 21%, Black 48%, other 32%).

The dosing by body weight, once daily for six weeks was based on data from trials T201 and T202. Supportive data for the doses chosen was provided by studies W352, C2101, and L2306.

The design of the clinical trials with terbinafine oral granule formulation compared with griseofulvin as active control is acceptable to assess safety and efficacy.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This appears adequate. Please see pharmacology/toxicology review.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing performed was adequate to assess the safety and efficacy of use for six weeks.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This appears adequate. Please see Biopharmaceutics review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Terbinafine has been associated with hepatic injury, leucopenia, and neutropenia. The sponsor performed laboratory testing that appears adequate to monitor for these events.

Some adult patients exposed to terbinafine have experienced loss of taste that resulted in significant weight loss. The sponsor monitored for taste disturbance by weight monitoring, caregiver interviews, and patient/food diary. These appear adequate to monitor for taste disturbance.

Associated with the use of terbinafine have been reports of loss of visual fields as well as color change as well as concerns of changes in the ocular lens and retina. Ophthalmologic testing was performed to evaluate for changes in the retina, refractile irregularities of the retina, changes in color vision, and changes in visual fields. Testing appears adequate to evaluate for the presence or absence of a safety signal.

7.2.8 Assessment of Quality and Completeness of Data

The data provided for the safety review was complete and of adequate quality.

7.2.9 Additional Submissions, Including Safety Update

The 120 day safety update was submitted on January 8, 2007. No new clinical information was reported.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Adverse events for the terbinafine oral granule formulation were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Those adverse events (incidence at least 1% in terbinafine group) considered to be drug related (terbinafine) in the pooled safety population (pivotal studies) follow in decreasing order of frequency:
1) Vomiting occurred in 1.6% (17/1042) of subjects on terbinafine as compared with 1.6% (8/507) of those on griseofulvin.
2) Abdominal pain, upper occurred in 1.2% (13/1042) of subjects on terbinafine as compared with 1.0% (5/507) of those on griseofulvin.
3) Diarrhea occurred in 1.1% (11/1042) of subjects on terbinafine as compared with 1.0% (5/507) of those on griseofulvin.
4) Headache occurred in 1.0% (10/1042) of subjects on terbinafine as compared with 1.4% (7/507) of those on griseofulvin.

5) Nausea occurred in 1.0% (10/1042) of subjects on terbinafine as compared with 1.2% (6/507) of those on griseofulvin.
6) Abdominal pain occurred in 1.0% (10/1042) of subjects on terbinafine as compared with .2% (1/507) of those on griseofulvin.

The significance of the adverse events listed above is somewhat difficult to determine since the control is active, griseofulvin, and not placebo.

Adverse events suspected by this reviewer to be related to study drug but not in current labeling for Lamisil tablets include increased weight, decreased weight, increased appetite, dizziness, somnolence, hypoesthesia, and insomnia.

Increased weight was experienced by .4% (4/1042) of those subjects on terbinafine as compared with .6% (3/507) of those on griseofulvin. A possibly related adverse event is increased appetite experienced by .3% (3/1042) of those subjects on terbinafine as compared with .4% (2/507) of those on griseofulvin. Both of these adverse events appear at fairly similar rates in both treatment groups.

Regarding decreased weight, subjects exposed to terbinafine demonstrated weight loss outliers (criterion $\geq$ 10% weight loss from baseline) at a higher rate .7% (7/1042) than those exposed to griseofulvin .2% (1/507). Although 5 of the 7 subjects exposed to terbinafine and showing weight loss outliers had weight measurements that improved on re-measurement, these five may have shown improvement due to being off of terbinafine. However, when the criterion for weight loss outlier was set at $\geq$ 7% weight loss from baseline, subjects exposed to terbinafine experienced outliers at a lower rate of 1.2% (12/1042) as compared with those exposed to griseofulvin, 1.8 % (9/507). The side effect of dysguesia was reported in a total of 4 subjects, two exposed to terbinafine and two exposed to griseofulvin. Weight loss was not seen for any of these subjects.

With respect to dizziness, .3% (3/1042) of subjects in the terbinafine group and no subjects in the griseofulvin group experienced this adverse event. In two subjects headache was experienced as well as dizziness.

With respect to reduced visual acuity, .3% (3/1042) of subjects in the terbinafine group and no subjects in the griseofulvin group experienced this event. The events in the three subjects that are discussed as adverse events involved changes of visual acuity of 2 lines. The sponsor notes that the ophthalmology manual that was part of the protocol for studies C2301 and C2302 specified that only acuity changes of 3 or more lines were to be recorded as adverse events. Changes of 2 lines can be considered within visit to visit variability.

With respect to hypoesthesia, .2% (2/1042) of subjects in the terbinafine group and no subjects in the griseofulvin group experienced this adverse event. This reviewer has grouped with these two subjects a third, also exposed to terbinafine, who experienced paresthesia and hypoesthesia. No subjects exposed to griseofulvin experienced paresthesia.

With respect to insomnia, .2% (2/1042) of subjects exposed to terbinafine and no subjects exposed to griseofulvin developed this adverse event. Somnolence may be a potentially related adverse event. A total of .2% (2/1042) of those in the terbinafine group and .2% (1/507) in the griseofulvin group experienced this adverse event.

In the pooled pivotal trials, in the terbinafine group, 1.6% (17/1042) of subjects, and in the griseofulvin group, 1.2% (6/507) of subjects, experienced study drug discontinuation due to an adverse event. In the terbinafine group vs. griseofulvin group more subjects were discontinued from study drug due to gastrointestinal disorders .6% (6/1042) vs. .2% (1/507), infections and infestations .3% (3/1042) vs. 0% and skin and subcutaneous disorders .6% (6/1042) vs. .2% (1/507). In the griseofulvin group more subjects were discontinued from study drug due to investigations (abnormal) .6% (3/507) than in the terbinafine group .1% (1/1042).

In the pooled pivotal trials, in subjects exposed to terbinafine, adverse events leading to study drug discontinuation included; events of vomiting (plus nausea in one subject) in four separate subjects, events of urticaria in two subjects (one of these localized urticaria), events of abdominal pain upper in two subjects, one event of dermatitis, pain of skin, rash, rash maculo-papular in each of 4 subjects, and events of anorexia in one subject, neutropenia in one subject, hepatic enzyme abnormal in one subject, diarrhea (and pyrexia) in one subject, and kerion in one subject. Other events leading to study drug discontinuation among those exposed to terbinafine included viral hepatitis in one subject, lice infestation in one subject, and pneumonia in one subject. These latter events do not appear related to study drug.

In the pooled pivotal studies, adverse events leading to temporary dose adjustment/temporary interruption involved of 2.8% (30/1042) of subjects exposed to terbinafine and of 3% (15/507) of subjects exposed to griseofulvin. In the terbinafine group, those adverse events suspected to be related to study drug included urticaria (3 cases), abdominal pain (2 cases), and headache (1 case).

In the pooled pivotal trials neutropenia ($< 1x10^9/L$) seen in the combined pivotal trials at a rate of 1.3% (12/1042) of those exposed to terbinafine as compared with 2.7% (13/507) of those exposed to griseofulvin. Additional examination of hematology outliers reveals 4 subjects with very low lymphocyte counts, more than .5 $10^9/L$ below the normal range. Three of these were in the terbinafine group and one in the griseofulvin group. In study C2101, employing the oral granule formulation, two subjects experienced neutrophil counts that were below 1500 cells/μl but above 1000 cell/μl. These low neutrophil counts were seen in association with WBC counts that were below normal range. One subject exposed to terbinafine was discontinued from study drug due to neutropenia.

In the pooled pivotal trials subjects exposed to terbinafine experienced elevations in transaminases (alk phos >2 ULN, AST > 2 ULN, ALT >2 ULN, and GGT>2 ULN) at a lesser rate, .7% (7/1042), versus those exposed to griseofulvin, rate of 1% (5/507).
In the pooled pivotal trials, examination of biochemistry value outliers reveals two subjects with elevated transaminases. A 5 year old subject discontinued treatment due to abnormal ALT values. An additional 7 year old subject met criteria (AST $\geq$ 3 x ULN) for discontinuation of

study drug. This subject was not withdrawn from treatment probably because repeat testing of AST showed return to normal range.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Adverse event data from the pivotal Phase 3 studies (C2301 and C2302) were pooled together. Test product, dose, mode of administration, and duration of treatment were the same for both studies. Also included in the safety database is data from one Phase 1 PK trial (C2101) in children 4 to 8 years old with Tinea capitis. Test product, dose, mode of administration, and duration of treatment were also the same.

7.4.1.2 Combining data

The data from the two Phase 3 studies were pooled together without weighting.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

This is not applicable since for the trials in the safety database, including the pivotal Phase 3 trials, only one dose by weight was studied.

7.4.2.2 Explorations for time dependency for adverse findings

Analyses for time dependency of adverse events were not performed. Both pivotal studies were of short duration, 6 weeks of dosing and a follow-up visit 4 weeks after end of dosing.

In the pivotal studies, 17 subjects exposed to terbinafine were withdrawn from study drug due to adverse events. Thirteen of these subjects had adverse events judged by the investigator to be related to the study drug, terbinafine. For nine of these subjects the adverse events was recorded as ceasing within 0 to 7 days of discontinuance of terbinafine. The subjects involved included one with nausea and vomiting (interval 1 day), one with upper abdominal pain (interval 7 days),

one with urticaria (interval 1 day), one with localized urticaria-face (interval 4 days), three with vomiting (interval 0 days for each), one with neutropenia (interval 4 days), and one with anorexia (interval 1 day).

7.4.2.3 Explorations for drug-demographic interactions

The sponsor performed sub-group analyses by race, age group, and sex. Marked differences between subgroups are not seen in these data.

Table 68: Subgroup Analysis

Race: Caucasian	Terbinafine N=215	Griseofulvin N=115
Preferred term	N (%)	N (%)
Total: Any adverse event	18 (8.4)	12 (10.4)
Vomiting	6 (2.8)	1 (0.9)
Nausea	3 (1.4)	1 (0.9)
Diarrhoea	2 (0.9)	2 (1.7)
Visual acuity reduced	2 (0.9)	0

Race: Black	Terbinafine N=495	Griseofulvin N=234
Preferred term	N (%)	N (%)
Total: Any adverse event	43 (8.7)	22 (9.4)
Abdominal pain upper	7 (1.4)	4 (1.7)
Vomiting	6 (1.2)	3 (1.3)
Diarrhoea	5 (1.0)	2 (0.9)

Race: Other	Terbinafine N=331	Griseofulvin N=157
Preferred term	N (%)	N (%)
Total: Any adverse event	35 (10.6)	8 (5.1)
Abdominal pain	7 (2.1)	0 (0.0)
Headache	6 (1.8)	2 (1.3)
Nausea	6 (1.8)	2 (1.3)
Vomiting	5 (1.5)	4 (2.5)
Abdominal pain upper	5 (1.5)	1 (0.6)
Diarrhoea	4 (1.2)	1 (0.6)

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Source: Sponsor's NDA submission, Summary of Clinical Safety, adapted from table 2.7.4.7-4.7 pp. 250-254.

Vomiting was more common among Caucasians in comparison with subjects of black or other race.

Table 69: Subgroup Analysis

Age Group: 4 – 8 years	Terbinafine N=764	Griseofulvin N=374
Preferred term	N (%)	N (%)
Total: Any adverse event	69 (9.0)	27 (7.2)
Vomiting	12 (1.6)	6 (1.6)
Abdominal pain upper	11 (1.4)	4 (1.1)
Nausea	9 (1.2)	3 (0.8)
Headache	8 (1.0)	2 (0.5)
Abdominal pain	8 (1.0)	1 (0.3)

Age Group: 9 – 12 years	Terbinafine N=274	Griseofulvin N=131
Preferred term	N (%)	N (%)
Total: Any adverse event	27 (9.9)	15 (11.5)
Vomiting	5 (1.8)	2 (1.5)
Diarrhoea	5 (1.8)	1 (0.8)

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Source: Sponsor's NDA submission, Summary of Clinical Safety, adapted from table 2.7.4.7-4.8 pp. 255-259.

Diarrhea was more common in the 9 to 12 year old age group as compared with the 4 to 8 year old age group.

Table 70: Subgroup Analysis

Gender: Male	Terbinafine N=666	Griseofulvin N=297
Preferred term	N (%)	N (%)
Total: Any adverse event	57 (8.6)	26 (8.8)
Vomiting	9 (1.4)	4 (1.3)
Abdominal pain upper	7 (1.1)	4 (1.3)

Gender: Female	Terbinafine N=376	Griseofulvin N=210
Preferred term	N (%)	N (%)
Total: Any adverse event	39 (10.4)	16 (7.6)
Vomiting	8 (2.1)	4 (1.9)
Diarrhoea	6 (1.6)	3 (1.4)
Nausea	6 (1.6)	2 (1.0)
Abdominal pain upper	6 (1.6)	1 (0.5)
Headache	5 (1.3)	1 (0.5)
Abdominal pain	4 (1.1)	0

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Source: Sponsor's NDA submission, Summary of Clinical Safety, adapted from table 2.7.4.7-4.9 pp. 260-263.

Diarrhea was more common in subjects of female gender than in those of male gender.

7.4.2.4 Explorations for drug-disease interactions

No formal analyses were performed for drug-disease interactions. The terbinafine oral granule formulation was studied only in subjects having tinea capitis.

7.4.2.5 Explorations for drug-drug interactions

Studies for drug-drug interactions were not performed with the oral granule formulation.

Four randomized, open-label, single-dose studies were performed to assess the interaction of the already approved product, Lamisil®, with fluconazole (SF W152), Cotrimoxazole DS (SF W153), zidovudine (SF W154) and theophylline (SF W156).

1) Study SFOW152 reached the following conclusions:
   a) Single 750 mg doses of Lamisil administered either alone or in combination with 100mg fluconazole were safe and well tolerated in 18 healthy subjects.
   b) A concurrent dose of fluconazole with Lamisil may require dosage adjustment.
   c) A concurrent single dose of Lamisil with fluconazole does not alter fluconazole pharmacokinetics.

2) Study SFOW153 reached the following conclusions:
   a) Single 750 mg doses of Lamisil administered alone or in combination with Cotrimoxazole DS (160 mg trimethoprim and 800 mg of sulfa methoxazole) were safe and well tolerated in 17 healthy subjects.
   b) A concurrent dose of Cotrimoxazole DS with Lamisil does not alter the kinetics of terbinafine (Lamisil) or its metabolite desmethylterbinafine.
   c) A concurrent dose of Lamisil with Cotrimoxazole DS does not alter the pharmacokinetics of trimethoprim or sulfamethoxazole.

3) Study SFOW154 reached the following conclusions:
   a) Single 750 mg doses of Lamisil administered either alone or in combination with 200mg of zidovudine were safe and well tolerated in 17 healthy subjects.
   b) A concurrent dose of zidovudine with Lamisil does not alter the kinetics of terbinafine (Lamisil) or its metabolite desmethylterbinafine.
   c) A concurrent single dose of Lamisil with zidovudine produced statistically significant changes in zidovudine pharmacokinetic parameters without substantially increasing drug exposure.

4) Study SFOW156 reached the following conclusions:
   a) Single 250 mg doses of Lamisil administered either alone or in combination with 375 mg of theophylline was safe and well tolerated in 18 healthy subjects.
   b) A concurrent dose of theophylline with Lamisil reduced the clearance of terbinafine (Lamisil). The small resultant increase in $AUC_{0-\infty}$ and C_{max}, according to the sponsor, does not pose any safety concern. No dosage adjustment of Lamisil is required when

coadministered with theophylline.

c) A concurrent dose of Lamisil with theophylline does not alter the pharmacokinetics of theophylline.

7.4.3 Causality Determination

The most common adverse events considered to be related to terbinafine are vomiting, upper abdominal pain, diarrhea, headache, nausea, and abdominal pain. Except for abdominal pain these occurred at roughly equivalent rates in those exposed to griseofulvin. Because the control was active, determination of the placebo rate is not possible in these studies. However, with respects to vomiting, nausea, and upper abdominal pain information from study drug discontinuation is supportive of causality. Please see section 7.4.2.2. For these and other adverse effects the fact that the onset of the adverse effect was often temporally close to start of study drug is also supportive of causality. Please see Tables 40 (p. 65) and 44 (p. 70).

With respect to laboratory values, for neutropenia, the case of subject 0254-25 (EGY study C2302) supports causality. This subject had a low neutrophil count on day 21, terbinafine was discontinued on day 41 and the neutropenia was resolving by day 45. With respect to SGPT (ALT), subject 0203-03 (BRA study C2302) showed elevated ALT and AST on day 37. Terbinafine was discontinued the same day. By day 43 the ALT and AST values were improving and by day 106 both values had returned to normal range.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen for Lamisil® Oral Granules is once a day for six weeks based on body weight as follows:

<25 kg	125 mg/day
25-35 kg	187.5 mg/day
>35 kg	250 mg/day

This is the dose that was studied in one Phase 2 trial, C2101, and in the pivotal Phase 3 trials, C2301 and C2302. In study C2101 the parent/guardian was instructed to put the terbinafine study medication into 1 teaspoon of pudding, administer to subject, and then follow with water. Subjects were instructed not to chew the medication but to swallow it whole. For trials C2301 and C2302, because the active comparator griseofulvin needed to be taken with food, all subjects were instructed to take study medication with a meal. Instructions were to empty bottles containing terbinafine oral granules on to a tablespoon of pudding and the entire tablespoon was to be swallowed. The instructions specified that acidic foods (e.g. orange juice and grapefruit juice) must be avoided when taking study medication. This latter advice was necessary because

the terbinafine [redacted] is sensitive to acids and acidic food with pH < [redacted] such as orange juice or other fruit juices.

8.2 Drug-Drug Interactions

Studies for drug-drug interactions were not performed with the oral granule formulation.

Four randomized, open-label, single-dose studies were performed to assess the interaction of the already approved product, Lamisil® tablets , with fluconazole (SF W152), Cotrimoxazole DS (SF W153), zidovudine (SF W154) and theophylline (SF W156).

The proposed labeling for Lamisil® Oral Granules will follow that for the already approved product Lamisil® Tablets with the addition of the following statements:

The influence of terbinafine on the pharmacokinetics of flucanazole, trimethoprim, sulfamethoxazole, zidovudine or theophylline was not considered to be clinically significant.

Co-administration of a single dose of fluconazole (100 mg) with a single dose of terbinafine resulted in a 52% and a 69 % increase in terbinafine Cmax and AUC, respectively. Fluconazole is an inhibitor of CYP 2C9 and CYP 3A enzymes. Based on these findings, it is likely that other CYP 2C9 inhibitors (e.g. amiodarone) and CYP 3A inhibitors (e.g. ketoconazole) may also lead to a substantial increase in the systemic exposure (Cmax and AUC) of terbinafine.

8.3 Special Populations

Pregnancy:
For the pivotal studies, females of childbearing potential (all post-menarche females) must have had a negative serum pregnancy test at entry and were required to use a medically acceptable contraception method during the study and for one month after termination of treatment. This is appropriate since there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because treatment of tinea capitis can be postponed until after pregnancy is completed, it is recommended that LAMISIL® (terbinafine hydrochloride) Oral Granules not be initiated during pregnancy. The pregnancy category assigned is B.

Nursing Mothers:
Recommended labeling generally follows that for the already approved product, Lamisil® Tablets and is as follows: After oral administration, terbinafine is present in breast milk of nursing mothers. The ratio of terbinafine in milk to plasma is 7:1. Treatment with LAMISIL® Oral Granules is not recommended in nursing mothers.

Geriatric Use:
Recommended labeling generally follows that for the already approved product, Lamisil® Tablets and is as follows: LAMISIL® (terbinafine hydrochloride) Oral Granules has not been studied in geriatric patients.

8.4 Pediatrics

The indication for Lamisil® Oral Granules is tinea capitis, an infection that primarily affects children. Lamisil® Oral Granules is a new dosage form; therefore a pediatric assessment is required by the Pediatric Research Equity Act (PREA). In accord with the Best Pharmaceuticals for Children Act, the FDA issued a Pediatric Written Request (PWR) for terbinafine on December 28, 2001. This was amended July 14, 2003, October 17, 2003, March 16, 2006, and May 15, 2006.

Lamisil® Oral Granules were studied in two Phase 3 trials enrolling 1042 subjects ages 4 to 12, having tinea capitis, and who were treated with Lamisil® Oral Granules (1021 at a known dose). Subjects received oral granules at the labeled dose for 6 weeks (mean exposure was 39.8 days). The most common adverse events were nasopharyngitis, headache, pyrexia, cough, vomiting, upper respiratory tract infection, abdominal pain (including upper), and diarrhea.
Lamisil® Oral Granules were tested for safety and efficacy within the pediatric population across subgroups including age, race, and gender. Notable differences within and between these subgroups were not seen for efficacy or safety.

8.5 Advisory Committee Meeting

No Advisory Committee was convened in response to this application.

8.6 Literature Review

A vigorous literature search was performed to determine griseofulvin response against placebo as well as the natural history of untreated disease. This also included an extensive search of original NDA submissions for griseofulvin, looking for placebo controlled trials. The findings were sparse.

One paper dated 1966[1] reported on a study, not double-blinded, involving 324 children with scalp ringworm. Of the total, 113 children were diagnosed with *T. tonsurans* by microscopy or culture. The doses of microcrystalline griseofulvin were either 3 grams (single dose) or 1 gram for 4 weeks. Also used was benzoic and salicylic acid ointment. At 4 weeks, 53% (16) of the single dose subjects were cured, 48% (18) of the 1 gram x 4 weeks dose subjects were cured, and 33% (15) of those not receiving griseofulvin (various proprietary topical medications were

[1] Zaias N, Taplin DT, and Rebell MS. Evaluation of Microcrystalline Griseofulvin Therapy in Tinea Capitis. JAMA 1966;198:805-7.

allowed) were cured. Also studied were 121 children with *Microsporum* infections. The dose of griseofulvin used was either single dose 3 grams or 2 grams, treatment otherwise was the same as for the *T. tonsurans* group. At 4 weeks, 81% (25) of the 3 gram dose subjects were cured, 73% (22) of the 2 gram dose subjects were cured, and 29% (17) of those not receiving griseofulvin were cured. Although some information on the natural history is obtained, the dosing regimen is not comparable to that of the current NDA.

8.7 Post-Marketing Risk Management Plan

The standard risk management measures of prescription status, professional labeling and spontaneous adverse event reporting are sufficient risk management activities for this drug at this time.

8.8 Other Relevant Materials

The sponsor originally submitted the name Lamisil® (terbinafine hydrochloride) mini-tablets. This was not found to be acceptable by ONDQA (Office of New Drug Quality and Assurance) as this formulation, mini-tablets, is not recognized by the CDER Labeling and Nomenclature Committee. "Oral Granules" was recommended by the CDER Labeling and Nomenclature Committee as the dosage form nomenclature for the finished product. DMETS also did not recommend using the terminology '[redacted]', in reference to product packaging, as this is similar to that used for [redacted]. DMETS suggested the use of terminology such as "packets". Therefore, ONDQA and Clinical recommended the use of the term 'packet' instead of '[redacted]' when describing the immediate packaging of the granules.

The sponsor proposed the use of two modifier options, 'Lamisil [redacted]' and 'Lamisil [redacted]'. Upon consultation, DMETS (Division of Medication Errors and Technical Support), did not recommend the use of either modifier for the oral granules product. Among other objections, DMETS stated that these modifiers are ambiguous and do not clearly convey the product differences they are intended to communicate.

9 OVERALL ASSESSMENT

9.1 Conclusions

Lamisil® Oral granules are an oral product intended to be taken once a day for 6 weeks for the treatment of tinea capitis. Dosing is based on weight and is as follows:

<25 kg 125 mg/day
25-35 kg 187.5 mg/day
>35 kg 250 mg/day

To support the indication, the sponsor has performed two well controlled, multi-center (US and foreign), Phase 3 trials to evaluate safety and efficacy. In study 2301 terbinafine showed robust statistical superiority over griseofulvin for the percentage of subjects achieving complete clearance at 10 weeks for tinea capitis, the primary endpoint. In study 2302 superiority was not achieved and treatment effects were nearly the same. When dermatophyte species are stratified by genus and species (for the primary endpoint), then for both studies C2301 and C2302, terbinafine exhibits a superior treatment effect compared with griseofulvin in the treatment of *T. tonsurans.*

Although superiority was not achieved over griseofulvin in the treatment of tinea capitis for both pivotal studies, the weight of the data support the fact that terbinafine is at least equivalent to griseofulvin for the general category of tinea capitis, and is a more effective agent for the treatment of *T. tonsurans.* In the US, where this new formulation is to be marketed, *T. tonsurans* is the predominant cause of tinea capitis, incidence estimated to be 90-95%.[1,2]

No deaths occurred during the development program. In the pivotal trials of a total of 10 serious adverse events 8 do not appear to be attributed to study drug use. In the case of the remaining two, scalp itching and scalp pain, the role of study drug appears equivocal.

Overall, roughly the same percentage of subjects 52% (541/1042 exposed to terbinafine as those exposed to griseofulvin 49% (249/507) experienced adverse events. Adverse event rates between the two study drugs were similar across system organ class and preferred term.

In the pooled pivotal trials, 17/1042 (1.6%) subjects in the terbinafine group and 6/507 (1.2%) subjects in the griseofulvin group experienced discontinuations of study drug for adverse events. Subjects having adverse events leading to dose adjustment/temporary interruptions of study drug were 30/1042 (2.9%) in the terbinafine group and 15/507 (3%) in the griseofulvin group.

The most common adverse events suspected to be related to study drug and not in current Lamisil labeling include; increased weight, decreased weight, increased appetite, dizziness, hypoesthesia, somnolence, and insomnia. These were not included in the label since the evidence that the drug caused the effect was not strong. An additional three subjects having sore scalp may have been experiencing the effects of terbinafine on fungal organisms. Other adverse events reported in the safety population included neutropenia and elevated transaminases.

The sponsor has demonstrated the efficacy of Lamisil® Oral Granules in the treatment of tinea capitis in subjects 4 years and older. In consideration of expected marketing in the US, labeling should give information regarding efficacy for *T. tonsurans.*

[1] Foster KW, Ghannon MA. Epidemiologic surveillance of cutaneous fungal infection in the United States from 1999 to 2002. J. American Academy of Dermatology 2004;50:748-752.
[2] Kenna ME, Elewski BE. A U.S. epidemiologic survey of superficial fungal diseases. J. American Academy of Dermatology 1996;539-542.

9.2 Recommendation on Regulatory Action

This reviewer recommends that Lamisil® (terbinafine hydrochloride) Oral Granules be approved for oral administration for the treatment of tinea capitis in subjects 4 years and older.

9.3 Recommendation on Post-marketing Actions

9.3.1 Risk Management Activity

The standard risk management measures of prescription status, professional labeling, and spontaneous adverse event reporting are adequate risk management activities for this drug at this time.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are necessary at this time.

9.3.3 Other Phase 4 Requests

No other Phase 4 requests are necessary.

9.4 Labeling Review

Please see section 10.2.

9.5 Comments to Applicant

There are no additional comments to be conveyed to the sponsor.

10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable since the pivotal trials were reviewed in detail in section 6.

10.2 Label

The label will be entered separately into DFS.

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/s/

Patricia Brown
6/22/2007 06:08:21 PM
MEDICAL OFFICER

Revised Draft

Jill Lindstrom
6/27/2007 12:12:14 PM
MEDICAL OFFICER

Susan Walker
6/29/2007 02:27:56 PM
DIRECTOR

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/s/

Patricia Brown
6/22/2007 06:08:21 PM
MEDICAL OFFICER

Revised Draft

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6/29/2007 02:27:56 PM
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DIRECTOR