

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 (%) | |
|-----------------------------------|-----------------------------|---------|-----------------------------|---------|
| | | rounded | | rounded |
| Number (%) of patients with AE(s) | 543 (52.1) | | 251 (49.5) | |
| 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)

| Laboratory test (unit) | Criterion | Terbinafine N=1042 | | | Griseofulvin N=507 | | |
|--|-----------|-----------------------|-----|--------|-----------------------|----|--------|
| | | 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 $\leq 3000/\mu\text{l}$ vs. $< 3 \times 10^9/\text{L}$ and neutrophil count $\leq 1000/\mu\text{l}$ vs. $< 1 \times 10^9/\text{L}$). 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 $10^9/\text{L}$ | ABS NEU $10^9/\text{L}$ | 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 $2 \times 10^9/L$). See Table 52, following.

Table 52: Subjects Having Very High (above $2 \times 10^9/L$) 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 x10⁹/L, ABS LYM < .5x10⁹ 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 .5 10⁹/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 | | NEU | EOS | LYM | BAS | MON |
|---------------|--------|-----------|--------|------------|---------|-------|---------|-------|----------|
| | | | A:5-16 | B:4.5-13.5 | 45-75 % | 0-8 % | 16-46 % | 0-3 % | 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 (<1.5x10⁹/L) at points during the study. Of note, subject 5416 had a decline in neutrophils from 1.4x10⁹/L at baseline to .945x10⁹/L at the end of study visit. Another subject, 5425, had an isolated low neutrophil count .9x10⁹/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)

| Laboratory test (unit) | Criterion | Terbinafine N=1042 | | | Griseofulvin N=507 | | |
|-----------------------------------|-----------|-----------------------|-----|--------|-----------------------|----|--------|
| | | 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 | | Females | |
|-------------------|-------------|---------------|-------------|---------------|
| | Older range | Current range | 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 | | 32 | 37 | 19 | 3 | 44 | 4.6 | 17 | 245 | | |
| 0553-09 | | | | | | | | | | | |
| 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 | | |

Clinical Review
 Patricia C. Brown, MD
 NDA 22-071
 LAMISIL® (terbinafine hydrochloride) Oral Granules

| 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 | | 32 | 37 | 19 | 3 | | |
| 0553-09 | | | | | | | |
| 3) BRA | 5M | 21 | 100 | 155* | 3 | No | Yes |
| C2302 | | 43 | 69 | 145* | 3 | Abnormal lab value | |
| 0203-03 | | | | | | | |

* 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 $.83 \times 10^3/\mu\text{L}$ (baseline had been $1.37 \times 10^3/\mu\text{L}$ and lower limit of normal = $1.35 \times 10^3/\mu\text{L}$). Terbinafine was discontinued on day 41 and the neutropenia was resolving by day 45, visit 4, with a count of $1.30 \times 10^3/\mu\text{L}$. At visit 5 this value was $1.58 \times 10^3/\mu\text{L}$. 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 $\geq 7\%$ 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)

| Vital Signs (Unit) | Criterion | Terbinafine | | | Griseofulvin | | |
|--------------------|--|-------------|----|-------|--------------|----|-------|
| | | 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)

| Vital Signs (Unit) | Criterion | Terbinafine | | | Griseofulvin | | |
|--------------------|-------------------------|-------------|----|-------|--------------|----|-------|
| | | 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 \leq 55, DBP \leq 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 \leq 55, DBP \leq 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 | | |

Clinical Review
 Patricia C. Brown, MD
 NDA 22-071
 LAMISIL® (terbinafine hydrochloride) Oral Granules

| | | | | | | | |
|--------------|----|-----|------|------|-------|-------------------|-------------------|
| 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*† | | |
| Griseofulvin | | | | | | | |
| 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 $\geq 7\%$ 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, $\geq 10\%$ 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, $\geq 10\%$ 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 ($\geq 10\%$ 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 53 μ mol/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 dysgeusia 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, Cotrimoxazole 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 <i>Trichophyton</i> 42 days for patients with <i>Microsporum</i> | 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: <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 ██████████ (175mg ██████████) | 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 <i>Trichophyton</i> | 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 <i>Microsporum</i> | 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 Africa¹. 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) |

¹Overview 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 Tinea 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 dysgeusia 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 ($< 1 \times 10^9/L$) 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 $.5 \times 10^9/L$ 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 $\geq 3 \times$ 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 is sensitive to acids and acidic food with pH < 5 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 fluconazole, 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 C_{max} 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 (C_{max} 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 1966¹ 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.

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

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MEDICAL OFFICER

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

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nulldate
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Medical Officer's Consultative Review of ND 22-071
Ophthalmology Consult
Addendum to Ophthalmology Consult #1

Submission date: September 8, 2006

Review date: June 20, 2007

Sponsor: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

Drug: Lamisil (terbinafine hydrochloride)

Proposed Indication: Treatment of Tinea Capitis

Consult Request: Ophthalmology Review of Ophthalmic Findings

Reviewer's Comments: *This is an addendum to Ophthalmology Consult Review #1.*

Two clinical studies (2301 and 2302) have been reviewed. As described in the initial consult review, these two studies are flawed in the execution of the ophthalmic portion of the studies. The flaws are significant enough to cast doubt in the validity of any of the ophthalmic information found in these studies. The studies cannot be used to identify any areas of ophthalmic safety concern, nor can they be used to resolve any potential issues of safety concern. The studies are not sufficient to support any labeling statements related to ocular events.

A re-review of previously reported ophthalmic adverse events has also been completed. This reviewer is unable to identify any pattern of reported ophthalmic adverse events which would lead to a specific ophthalmic safety concern.

Unless new ocular events are reported with the use of terbinafine hydrochloride or unless the applicant requests labeling statements related to ocular safety or efficacy, there does not appear to be sufficient ophthalmic concern to request additional ophthalmic safety studies. If additional ocular events are reported, ophthalmic monitoring as described in the original consultation is recommended.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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Medical Officer's Consultative Review of ND 22-071
Ophthalmology Consult

Submission date: September 8, 2006

Review date: April 30, 2007

Sponsor: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

Drug: Lamisil (terbinafine hydrochloride)

Dosage Form: Oral Granules

Proposed Indication: Treatment of Tinea Capitis

Consult Request: Ophthalmology Review of Ophthalmic Findings

Reviewer's Comments: *Comments are limited to areas of ophthalmologic concern.*

Two clinical studies (2301 and 2302) have been reviewed.

Within the ophthalmology sections of the clinical study reports there are significant discrepancies, missing visits and clinical inconsistencies. These errors include, but are not limited to:

1. Visual acuity results not matching with the line for visual acuity.
2. Number of letters seen is often missing.
3. Approximately 8% of follow-up visits are blank.
4. Patient 1, Site 152, Study 2302 had an abnormal color vision on follow-up in each eye. The assessment is "Unchanged" for each eye. The patient evaluation was "Improved" and the final status for the eyes was "Normal."
5. Patient 18, Site 601, Study 2302 had an abnormal color vision in each eye and was listed as normal.
6. Patient 24, Site 601, Study 2302 had an abnormal color vision in one eye, abnormal dilated fundus, and abnormal visual field and was listed as normal.
7. Patient 3, Site 101, Study 2302 had an abnormal visual acuity in each eye and was listed as normal.
8. Patient 13, Site 133, Study 2302 had an abnormal color vision in each eye and was listed as normal.
9. Patient 1, Site 152, Study 2302 had an abnormal color vision in each eye and was listed as normal.
10. Visual acuity was supposed to be measured with HOTV or LEA symbols. From patient to patient, the number of letters seen on visual acuity chart varied, but the visual acuity

- score is the same. The score should have been based on the number of letters seen and would therefore be the same for the same number of letters seen.
11. In Study 2301, 18/747 (2.4%) of patients have visual acuity recorded as "Not Done" and an additional 63 have nothing recorded for their follow-up visit.
 12. In Study 2302, 12/802 (1.5%) of the patients have visual acuity recorded as "Not Done" and an additional 67 have nothing recorded for their follow-up visit.
 13. The type of color vision test is not recorded on the case report tabulations. Since the test used could have varied, this should have been reported.
 14. In Study 2301, 45/747 (6%) have color vision recorded as "Not Done" and an additional 63 have nothing recorded for their follow-up visit.
 15. In Study 2302, 41/802 (5.1%) have color vision recorded as "Not Done" and an additional 67 have nothing recorded for their follow-up visit.
 16. Visual field testing was supposed to have been conducted in all patients 11 years of age and older and should have been conducted with an automated, threshold perimeter. The type of visual field testing should have been reported for each examination. The type of visual field testing performed was recorded for 50 examinations. Sixteen exams used a perimeter which is not automated and do not measure a threshold vision at each point. Two additional listings list test methods for a type of examination which does not measure visual field. The rest of the listings do not include the method used.
 17. In Study 2301, 11/61 (18%) have a visual field recorded as "Not Done."
 18. In Study 2302, 11/58 (19%) have a visual field recorded as "Not Done."
 19. Dilated funduscopy (or color fundus photography) to evaluate the potential for refractile irregularities in the retina was supposed to have been conducted in all patients.
 20. In Study 2301, 19/747 (2.5%) of patients have a dilated funduscopy listed as "Not Done" and an additional 63 have nothing recorded for their follow-up visit.
 21. In Study 2302, 16/802 (2%) of patients have a dilated funduscopy listed as "Not Done" and an additional 67 have nothing recorded for their follow-up visit.
 22. The number of symbols listed as "correct" and "total shown" should have been blank if the method used was Roth 28 or "not done." The Roth-28 test was to be evaluated utilizing the instructions developed by the manufacturer. The test was interpreted by assessing the diagram of the sequence of discs. Since symbols are not used, it should not have been possible to record the number of symbols correct. The following patients for example are all eleven and twelve year olds who should have had a Roth 28 or 40 test, yet there are Letters shown/seen recorded for them:

CSFO327C2302_0351_00005
 CSFO327C2301_0513_00004
 CSFO327C2301_0556_00009
 CSFO327C2302_0113_00005
 CSFO327C2302_0157_00004
 CSFO327C2301_0302_00011
 CSFO327C2301_0404_00005
 CSFO327C2301_0402_00017
 CSFO327C2301_0402_00019
 CSFO327C2301_0405_00002
 CSFO327C2301_0517_00019

CSFO327C2301_0310_00006
CSFO327C2302_0106_00006
CSFO327C2302_0131_00003
CSFO327C2302_0131_00013
CSFO327C2301_0401_00001
CSFO327C2302_0355_00001
CSFO327C2301_0506_00003
CSFO327C2301_0513_00002
CSFO327C2301_0513_00010
CSFO327C2301_0525_00006
CSFO327C2302_0103_00010
CSFO327C2302_0253_00005
CSFO327C2301_0702_00014
CSFO327C2302_0503_00012
CSFO327C2301_0302_00005
CSFO327C2301_0302_00007
CSFO327C2301_0303_00001
CSFO327C2301_0403_00006
CSFO327C2301_0517_00012
CSFO327C2302_0401_00002
CSFO327C2302_0401_00029
CSFO327C2302_0401_00036
CSFO327C2302_0601_00007
CSFO327C2301_0301_00011
CSFO327C2301_0303_00010
CSFO327C2301_0402_00022
CSFO327C2301_0405_00017
CSFO327C2301_0405_00025
CSFO327C2301_0511_00003
CSFO327C2301_0551_00005
CSFO327C2301_0803_00019
CSFO327C2302_0355_00026
CSFO327C2302_0355_00028
CSFO327C2302_0502_00032
CSFO327C2302_0123_00016
CSFO327C2302_0310_00006

23. Roth 28 or 40 hue test results should include the area derived from the confused caps.
This should have been reported.

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The sponsor provided a response to a request for additional ophthalmological information. The response did not provide any significant new information. Comments on these responses are listed below:

Color Vision

The sponsor confirmed that the test used was the one listed in the line listings. This would therefore confirm that many of the tests conducted were not the correct color vision tests. It is relevant because tests such as Ishihara do not evaluate acquired defects.

The reason that many of the 11 and 12 year olds had a value for the number of symbols was that they had the wrong test performed.

The area derived from the confused caps was to be recorded on the scoring sheet, but that information was not listed and therefore not collected in the database. The sponsor reports that it is therefore not available.

Visual Acuity

The sponsor did not have an explanation for why the number of symbols was not constant for all patients with the same test. I do not have an explanation for what the investigators did.

Visual fields

The sponsor repeated back that there were patients without visual fields. Some were because treatment was stopped early. There is no explanation for the others.

Neither the Threshold or the Mean Deviation was routinely recorded on the case report form. Threshold is the actual value from the visual field; mean deviation is the difference between the threshold and the expected normal value. The sponsor collected Mean Deviation for a few patients (7 terbinafine patients had Visit 2 and 4 mean deviations reported, and 6 of the Griseofulvin patients has Visit 2 and 4 mean deviations reported). This is out of the 119 patients that were supposed to have threshold visual fields.

Labeling decisions cannot be reliably made with this data. Some are normal, some are abnormal. In addition, the sponsor has listed the test used when listed as "other." As previously noted, some of these tests such as Goldmann and Confrontation are not threshold tests.

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Summary and Conclusions:

Studies 2301 and 2302 are flawed in execution. Studies 2301 and 2302 cannot be used to support labeling statements with respect to any ophthalmic findings.

To the extent that there are reported ophthalmic adverse events that need to be investigated in a well controlled study, it is recommended that the following ophthalmic monitoring be included with each eye being tested separately:

1. Best correct distance visual acuity with reporting of the test performed and the results,
2. Automated threshold visual fields of the central 24 degrees with reporting of the test performed and the actual recorded threshold visual field information.
3. Color vision using a Farnsworth Munsell 28, 40 or 100 hue test and a reporting of the test performed, the ordering of the caps and the cumulative area error score derived from the misordering.
4. Color fundus photography of the central 45 degrees of the retina with reporting of the photograph.

The number of patients to be studied should depend on the incidence rate to be ruled out using the rule of 3's.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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