

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**22-071**

**STATISTICAL REVIEW(S)**



US Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION  
NEW DRUG APPLICATION  
ADDENDUM TO STATISTICAL REVIEW

**NDA/Serial Number:** 22-071/SN000  
**Drug Name:** Lamisil (terbinafine) Oral Granules  
**Indication(s):** Tinea Capitis  
**Applicant:** Novartis

**Dates:** Submitted: 09/08/2006  
PDUFA: 07/08/2007

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics III  
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**Keywords:** active-control, superiority

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## 1 INTRODUCTION

The statistical review was completed and signed into DFS on May 15, 2007. On August 14, 2007 the clinical review team requested statistical input for the assessment of the ophthalmology data. This addendum to the original review contains summary results of the ophthalmology data.

The data set used for the analysis of ophthalmology assessment is located at `//Cdsesub1/n22071/N_000/2006-09-08/crt/datasets/`. Specifically, the `a_oph.XPT` data set for Studies 2301 and 2302 is analyzed.

## 2 OPHTHALMOLOGY SAFETY ASSESSMENT

In discussions with the clinical review team, three specific areas of ophthalmologic assessment were identified which are listed below.

1. Visual Acuity
2. Dilated fundoscopy
3. Color vision

In the review, each of the above areas of ophthalmology is assessed individually for each study.

### 2.1 Visual Acuity

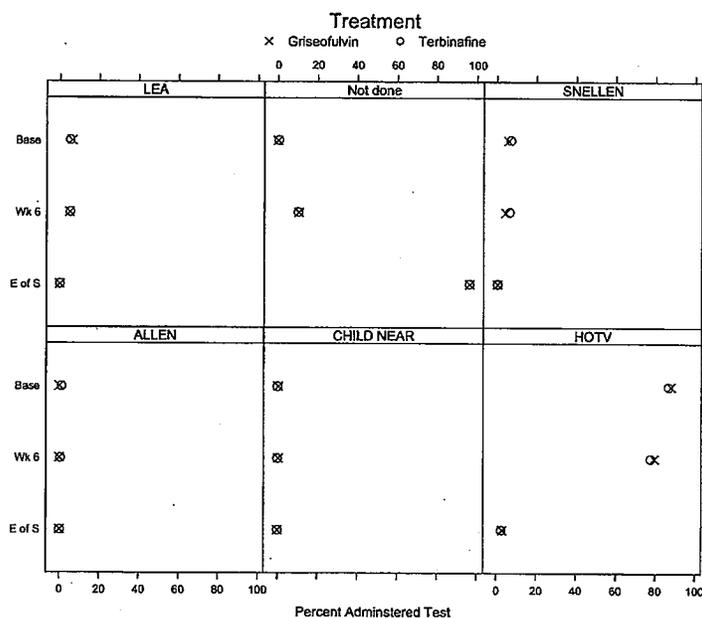
The visual acuity was measured using one of nine methods: ALLEN, CHILD NEAR, ECHART, HOTV, LEA, ORLOVA, PICTURES, SIVCEN-SIV, or SNELLEN in Studies 2301 and 2302. Of interest, as based on discussions with the clinical review team, are the methods ALLEN, HOTV, and LEA. The following sections contain summaries of the percentage of subjects who were issued an exam by visit as well as tabulating the number of subjects with post-baseline logMAR changes  $\geq 0.3$  and changes  $\leq -0.3$ .

The assessment of visual acuity required the creation of a data subset from the original file (`a_oph.XPT`) such that there was only one measurement per subject per visit. The Appendix Section A.1 contains the R code used to create the data set used in the analysis. Variables used to derive analysis results are: `V.METHOD`, `VIS1N`, `TRT1S`, `LCG_LOGM`, and `RCG_LOGM`.

#### 2.1.1 Visual Acuity in Study 2301

Figure 1 depicts the percentage of subjects who were administered an ophthalmology exam to assess visual acuity. This figure shows that almost all subjects were given an exam at baseline and nearly all subjects were not given an exam at the end of study which was a 4 week post-treatment follow-up visit. The most prevalent test administered was the HOTV which was administered to nearly 80% of subjects at the end of week 6, the end of treatment visit.

Figure 1: Percent Administered Exam over Time in Study 2301



To assess the change in visual acuity, the change in logMAR from baseline was measured. A clinically meaningful change suggesting a reduction in visual acuity is a logMAR change of at least 0.3. In addition to examining the negative case of a reduction in visual acuity, a positive increase in visual acuity is also summarized by tabulating subjects with a change in logMAR  $\leq -0.3$ . Table 1 depicts the number of subjects with logMAR change  $\geq 0.3$  and  $\leq -0.3$  for Study 2301.

Table 1: Change<sup>†</sup> in logMAR Study 2301\*

	Left Eye		Right Eye	
	terbinafine	griseofulvin	terbinafine	griseofulvin
$\Delta$ in logMAR $\geq 0.3$	3/416 (0.7%)	3/206 (1.5%)	6/417 (1.4%)	3/206 (1.5%)
$\Delta$ in logMAR $\leq -0.3$	2/416 (0.5%)	4/206 (1.9%)	2/417 (0.5%)	3/206 (1.5%)

<sup>†</sup> Change is from baseline to Week 6 (end of treatment).

\* Results are presented only for subjects who were assessed using ALLEN, HOTV, or LEA methods.

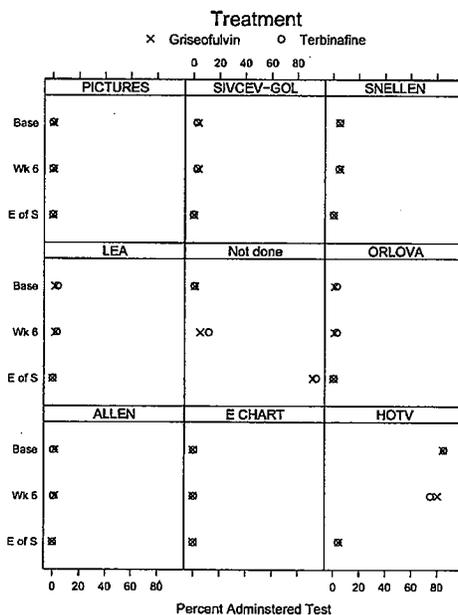
Of the nine cases with logMAR changes  $\geq 0.3$  in subjects treated with terbinafine, this corresponded to six subjects (i.e. three subjects had changes  $\geq 0.3$  in both eyes). A total of

three subjects treated with griseofulvin had logMAR changes  $\geq 0.3$ .

### 2.1.2 Visual Acuity in Study 2302

Figure 2 depicts the percentage of subjects who were administered an ophthalmology exam to assess visual acuity in Study 2302. This figure shows that almost all subjects were given an exam at baseline and nearly all subjects were not given an exam at the end of study which was a 4 week post-treatment follow-up visit. The most prevalent test administered was the HOTV which was given to more than 75% of subjects at week 6.

Figure 2: Percent Administered Exam over Time in Study 2302



As with Study 2301, logMAR changes from baseline to week 6 of  $\geq 0.3$  and  $\leq -0.3$  are used to assess visual acuity. Table 2 depicts the number of subjects with logMAR change  $\geq 0.3$  and  $\leq -0.3$  for Study 2302.

Of the seven cases with logMAR changes  $\geq 0.3$  in subjects treated with terbinafine, this corresponded to five subjects (i.e. two subjects had changes  $\geq 0.3$  in both eyes). A total of four subjects treated with griseofulvin had logMAR changes  $\geq 0.3$ .

Table 2: Change<sup>†</sup> in logMAR Study 2302\*

	Left Eye		Right Eye	
	terbinafine	griseofulvin	terbinafine	griseofulvin
$\Delta$ in logMAR $\geq$ 0.3	5/419 (1.2%)	4/219 (1.8%)	2/420 (0.5%)	1/219 (0.5%)
$\Delta$ in logMAR $\leq$ -0.3	8/419 (1.9%)	5/219 (2.3%)	11/420 (2.6%)	5/219 (2.3%)

<sup>†</sup> Change is from baseline to Week 6 (end of treatment).

\* Results are presented only for subjects who were assessed using ALLEN, HOTV, or LEA methods.

## 2.2 Dilated Fundoscopy

The same derived data set used for assessing visual acuity as described in the Appendix is used to assess dilated fundoscopy. The variables of interest for this analysis were: VIS1N, TRT1S, RFRPRT1C, FDSLFT1A, and FDSRGT1A. To assess if fundoscopy was assessed at a visit, the a\_oph.XPT data set was subsetted on OPHTYP1C == 16 and tabulated based on the variables OPHLFT2C and OPHRGT2C.

### 2.2.1 Dilated Fundoscopy in Study 2301

The number (percentage) of subjects who did not receive a dilated fundoscopy exam at baseline and week 6 is provided in Table 3. Note that the week 6 results uses the denominator which excludes subjects with missing data.

Table 3: Percent of Subjects with no Dilated Fundoscopy Exam (Study 2301)

	Baseline		Week 6	
	terbinafine	griseofulvin	terbinafine	griseofulvin
<b>Left Eye</b>				
Not Done	4/503 (0.8%)	0/244 (0%)	11/460 (2.4%)	5/223 (2.2%)
<b>Right Eye</b>				
Not Done	3/503 (0.6%)	0/244 (0%)	10/460 (2.2%)	5/223 (2.2%)

In addition to the above dilated fundoscopy exams, subjects were examined for refractile bodies. At no time point during Study 2301 were any refractile bodies present for either terbinafine or griseofulvin. However, several subjects had abnormalities reported. The subjects are listed in Table 4 along with the abnormalities as provided in the electronic data sets. Note that only abnormalities that occurred after receiving treatment are presented. Table 7 in Appendix Section A.2 contains a table of all baseline abnormalities.

Table 4: Listing of Subjects with Eye Abnormalities (Study 2301)

Subject ID	Treatment	Visit	Abnormality Description
<b>Left Eye</b>			
303-3†	terbinafine	Wk 6	DARKNESS CAPSULAR POSTERIOR MILD AND EXCAVATION POSTERIOR 20%
505-5	terbinafine	Wk 6	Large optic nerve cups, likely physiologic
701-8	terbinafine	Wk 6	Generalized retinal pigmentation
701-9	terbinafine	Wk 6	Glaucoma suspect
701-24	griseofulvin	Wk 6	Glaucoma suspect
<b>Right Eye</b>			
303-3†	terbinafine	Wk 6	DARKNESS CAPSULAR POSTERIOR MILD AND EXCAVATION POSTERIOR 20%
505-5	terbinafine	Wk 6	Large optic nerve cups, likely physiologic
530-6	terbinafine	Wk 6	2- small choroid nevus
701-8†	terbinafine	Wk 6	Generalized retinal pigmentation
701-9†	terbinafine	Wk 6	Glaucoma suspect
701-16†	terbinafine	Wk 6	Glaucoma suspect
701-24†	griseofulvin	Wk 6	Glaucoma suspect

† Depicts subjects with the abnormality also present at the baseline visit.

## 2.2.2 Dilated Fundoscopy in Study 2302

The number (percentage) of subjects who did not receive a dilated fundoscopy exam at baseline and week 6 is provided in Table 6. Note that the week 6 results uses the denominator which excludes subjects with missing data.

Table 5: Percent of Subjects with no Dilated Fundoscopy Exam (Study 2302)

	Baseline		Week 6	
	terbinafine	griseofulvin	terbinafine	griseofulvin
<b>Left Eye</b>				
Not Done	3/537 (0.6%)	3/265 (1.1%)	7/480 (2.3%)	3/253 (1.2%)
<b>Right Eye</b>				
Not Done	3/537 (0.6%)	3/265 (1.1%)	8/480 (2.1%)	3/253 (1.2%)

In addition to the above dilated fundoscopy exams, subjects were examined for refractile bodies. At no time point during Study 2302 were any refractile bodies present for either terbinafine or griseofulvin. However, several subjects had abnormalities reported. The subjects are listed in Table 6 along with the abnormalities as provided in the electronic data set. Note that only abnormalities that occurred after receiving treatment are presented. Table 8 in Appendix Section A.2 contains a table of all baseline abnormalities.

Table 6: Listing of Subjects with Eye Abnormalities (Study 2302)

Subject ID	Treatment	Visit	Abnormality Description
<b>Left Eye</b>			
119-5	griseofulvin	Wk 6	peripheral retinal scarring consistent with retinopathy of prematurity
121-2 <sup>†</sup>	griseofulvin	Wk 6	optic neuropathy
253-6 <sup>†</sup>	terbinafine	Wk 6	myopic fundus
351-6	griseofulvin	Wk 6	CUP:DISC RATIO IS 0.4-CLINICALLY INSIGNIFICANT ABNORMALITY
401-5 <sup>†</sup>	griseofulvin	Wk 6	A pigment are around the disc of nervus opticus and venous hyperemia
401-42 <sup>†</sup>	griseofulvin	Wk 6	Lights venous hyperemia blood vessels of retina
601-24	terbinafine	Wk 6	patient has a significant cataract
<b>Right Eye</b>			
119-5	griseofulvin	Wk 6	peripheral retinal scarring consistent with retinopathy of prematurity
121-2 <sup>†</sup>	griseofulvin	Wk 6	optic neuropathy
253-6 <sup>†</sup>	terbinafine	Wk 6	myopic fundus
351-6	griseofulvin	Wk 6	CUP:DISC RATIO IS 0.4-CLINICALLY INSIGNIFICANT ABNORMALITY
401-5 <sup>†</sup>	griseofulvin	Wk 6	A pigment are around the disc of nervus opticus and venous hyperemia
401-42 <sup>†</sup>	griseofulvin	Wk 6	Lights venous hyperemia blood vessels of retina
601-18	griseofulvin	E of S	Small dot like lens opacity in superior nasal quad of lens.

<sup>†</sup> Depicts subjects with the abnormality also present at the baseline visit.

## 2.3 Color Vision

The data set which required some data preparation from the original a\_oph.XPT data set used in the evaluation of vision acuity is also used for the assessment of color vision. In addition, the data is subset to only include subjects who had a color blindness assessed using the SPP2 method per request from the clinical review team. The following variables are used in the summary of color blindness: C\_METHOD, TRT1S, VIS1N, LBS\_CET, LBS\_COR, CETLFT1N, TSTLFT1N, RBS\_CET, RBS\_COR, CETRGT1N, and TSTRGT1N.

To assess change from baseline the following calculation will take place for both eyes for each subject with non-missing week 6 data.

$$\Delta = (N_c^b/N_s^b) - (N_c^6/N_s^6), \text{ where}$$

$N_c$  and  $N_s$  correspond to the number correct and number shown, respectively. In addition the superscripts correspond to baseline ( $b$ ) and week 6 ( $6$ ). Thus, a negative difference implies improvement from baseline in the percent of symbols correctly identified.

2.3.1 Color Vision in Study 2301

When a subset data set was created to only include subjects who were administered the SPP2 exam, an examination of the number of symbols shown varied; ranging from 2 to 26 with the most frequent number of symbols shown to be 12 ( $N = 178$  at baseline) and 20 ( $N = 250$  at baseline). As it is unclear how the number of symbols may affect the differences in proportions, results are summarized taking into account the baseline number of symbols shown.

Figure 3 depicts the number of subjects (seen as the characters on the plotting surface) according to the baseline number of symbols shown and the difference in proportions from baseline to week 6 for the left eye. Note that rounding to the first decimal place of the difference in percents was done to add clarity to the graph. Also the x-axis of the graph is truncated to include only subjects with baseline symbols shown between 10 and 25. Roughly, within each treatment arm, there is a balance between those with improvement in the color blindness assessment and those who showed a decrease. There also appears to be two subjects treated with terbinafine who are outliers with rather marked increases in the color blind tests. The subject ID's for these two outliers are: 520-4 and 601-2.

Figure 3: Difference in Number of Symbols Correctly Counted (Base - Week 16) Study 2301

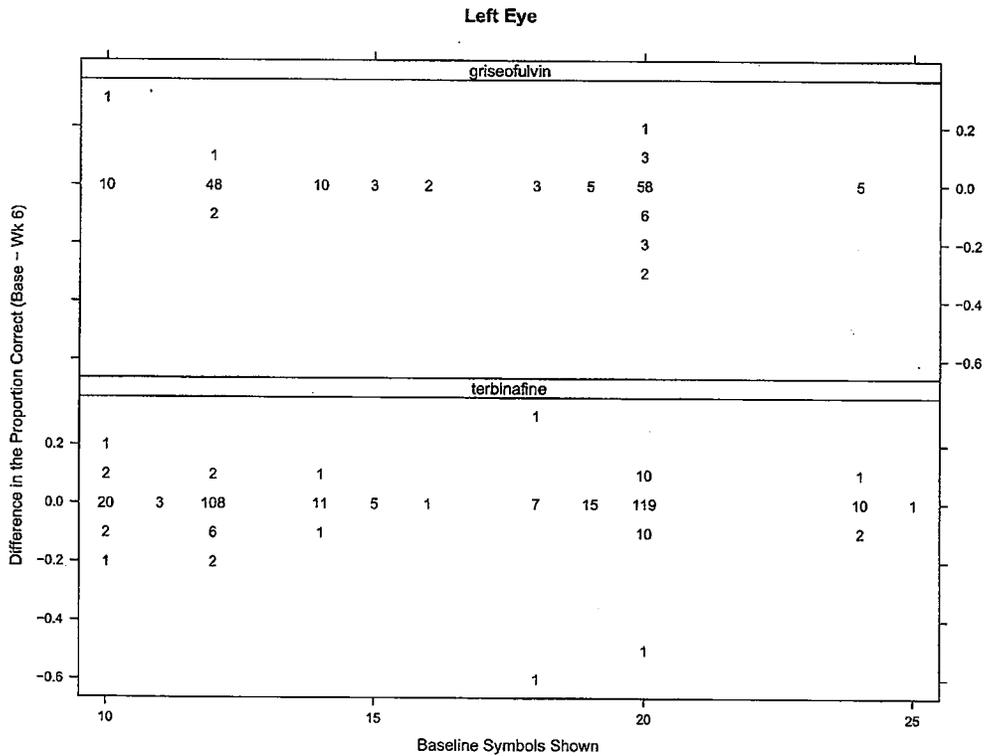
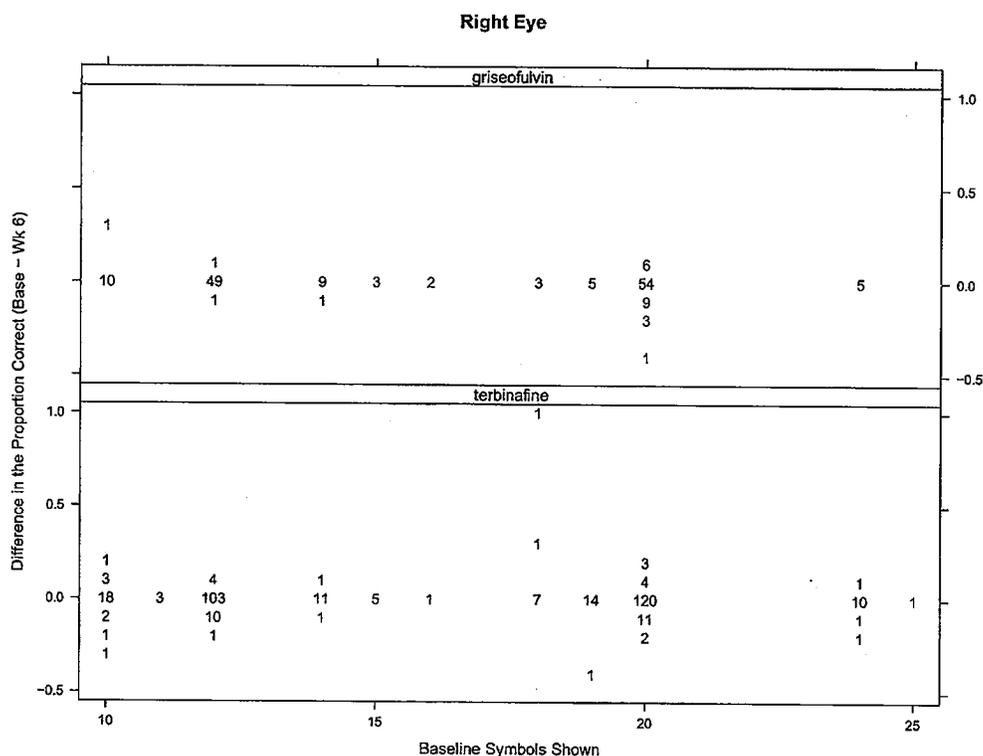


Figure 4 contains color blind results for the right eye in study 2301. Note that plotting features are the same as those discussed in the depiction of the left eye. Overall, the majority of subjects tended to have no change from baseline to week 6. The outlier on the plot corresponds to subject 601-18 who correctly identified 18 out of 18 symbols correctly at baseline but misidentified all 6 symbols shown at week 6.

Figure 4: Difference in Number of Symbols Correctly Counted (Base - Week 16) Study 2301



### 2.3.2 Color Vision in Study 2302

When a subset data set was created to only include subjects who were administered the SPP2 exam, an examination of the number of symbols shown varied; ranging from 3 to 50 with the most frequent number of symbols shown to be 12 ( $N = 95$  at baseline) and 20 ( $N = 225$  at baseline). As with Study 2301, results for study 2302 are summarized taking into account the baseline number of symbols shown.

Figure 5 depicts the number of subjects (seen as the characters on the plotting surface) according to the baseline number of symbols shown and the difference in proportions from baseline to week 6 for the left eye. Note that the features of the graph are similar to those previously

described. In general neither treatment arm suggests an unbalance towards a reduction in the proportion of symbols correctly identified at week 6.

Figure 5: Difference in Number of Symbols Correctly Counted (Base - Week 16) Study 2302

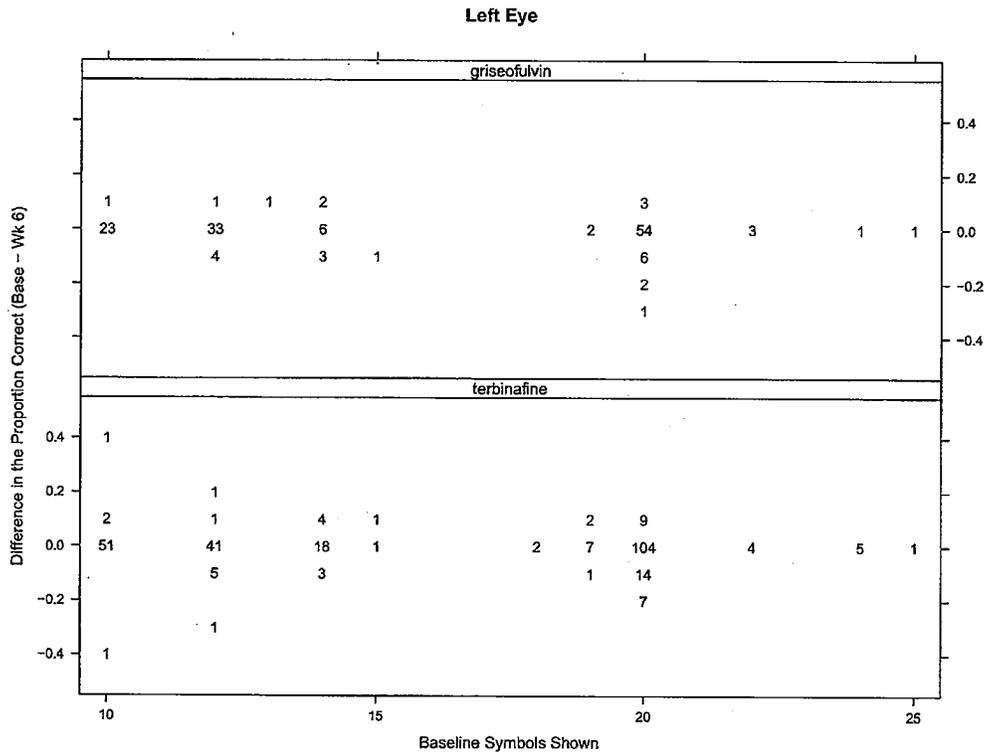
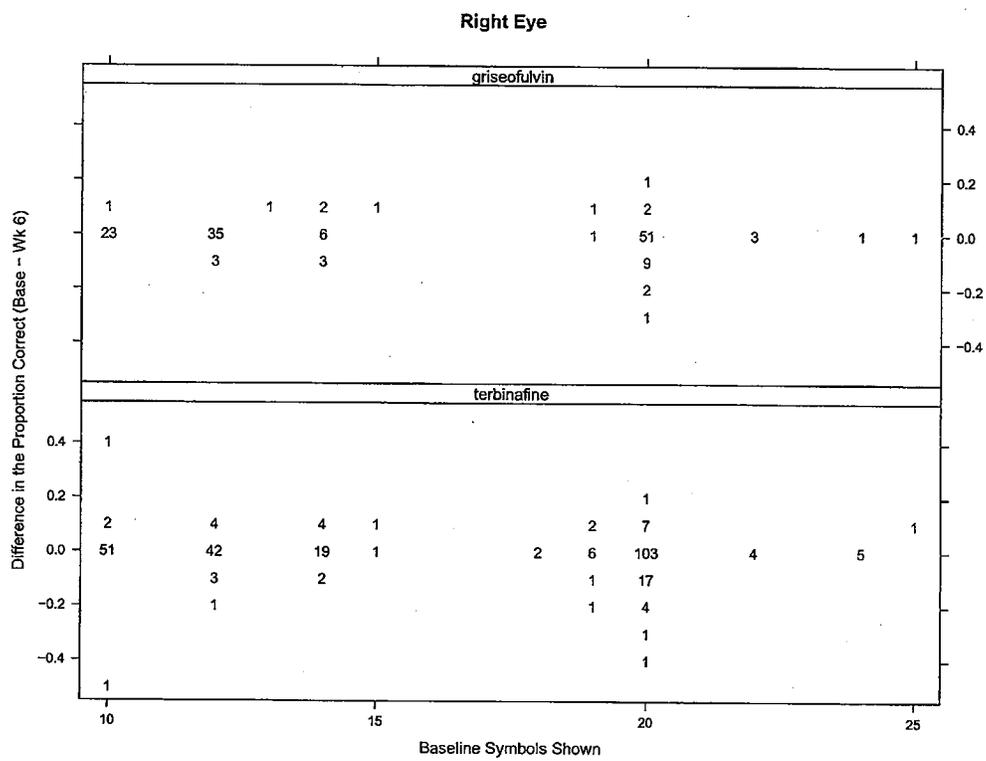


Figure 6 contains color blind results for the right eye for Study 2302. Overall, the majority of subjects tended to have no change from baseline to week 6 and no apparent trend is seen showing a reduction in the proportion of symbols correctly classified at week 6 from baseline.

### 3 CONCLUSION

The intent of the following assessment was not meant to form any statistical conclusions. Rather, the objective was to present the ophthalmology data for the clinical review team to use in making clinical decisions about the safety of terbinafine.

Figure 6: Difference in Number of Symbols Correctly Counted (Base - Week 16) Study 2302



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## APPENDIX

### A.1 R Code: Data Creation Visual Acuity Assessment

```
# Code is shown for Study 2301 only; Study 2302 is similar
oph1 <-
read.xport("//Cdsesub1/nonectd/n22071/N_000/2006-09-08/crt/datasets/2301/derived/a_oph.xpt")
names(oph1) <- tolower(names(oph1))

# Reduce this to one measurement per subject per visit
uid <- unique(oph1$stysid1a)
visits <- c(2,4,777)
rrows <- NULL
for(i in 1:length(uid)){
  sdat <- subset(oph1, stysid1a%in%uid[i])
  rid <- NULL
  for(j in 1:3){
    sdat2 <- subset(sdat, vis1n%in%visits[j])
    rid[j] <- list(sdat2[1,])
  }
  rrows[i] <- list(do.call('rbind', rid))
}

rdat <- do.call("rbind", rrows)
```

### A.2 Baseline Abnormalities

The following are summaries of the baseline abnormalities from Studies 2301 and 2302.

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Table 7: Listing of Subjects with Eye Abnormalities (Study 2301)

Subject ID	Treatment	Visit	Abnormality Description
<b>Left Eye</b>			
303-3	terbinafine	Base	DARKNESS CAPSULAR POSTERIOR MILD AND EXCAVATION PAPILAR 10%
303-4	terbinafine	Base	DARKNESS CAPSULAR POSTERIOR MILD
510-2	terbinafine	Base	Increased cup to disc ratio OD <sub>i</sub> OS
530-6	terbinafine	Base	1-normal
551-1	terbinafine	Base	Peripheral congenital pigmentation nasally
551-9	terbinafine	Base	cup/disc asymmetry
701-12	terbinafine	Base	Deep Glaucomatous cupping
<b>Right Eye</b>			
303-3	terbinafine	Base	DARKNESS CAPSULAR POSTERIOR MILD AND EXCAVATION PAPILAR 10%
303-4	terbinafine	Base	DARKNESS CAPSULAR POSTERIOR MILD
510-2	terbinafine	Base	Increased cup to disc ratio OD <sub>i</sub> OS
530-6	terbinafine	Base	2-abnormal, small choroidal nevus right fundus
701-8	terbinafine	Base	Generalized retinal pigment disturbances
701-9	terbinafine	Base	Glaucoma suspect
701-12	terbinafine	Base	Deep Glaucomatous cupping
701-16	terbinafine	Base	Glaucoma suspect
701-18	terbinafine	Base	Glaucomatous discs
701-20	terbinafine	Base	Retinal pigmentary changes
701-24	griseofulvin	Base	Glaucomatous discs
701-26	terbinafine	Base	Glaucomatous discs

Table 8: Listing of Subjects with Eye Abnormalities (Study 2302)

Subject ID	Treatment	Visit	Abnormality Description
<b>Left Eye</b>			
112-4	terbinafine	Base	slightly increased cup disk
121-2	griseofulvin	Base	optic neuropathy
253-6	terbinafine	Base	myopic fundus
355-11	terbinafine	Base	hypopigmented patch near macula-not clinically significant
401-5	griseofulvin	Base	A pigment are around the disc of nervus opticus and venous hyperemia
401-42	griseofulvin	Base	Lights venous hyperemia blood vessels of retina
<b>Right Eye</b>			
121-2	griseofulvin	Base	optic neuropathy
152-1	griseofulvin	Base	OD has c/d of 0.65 (05=0.5)
253-6	terbinafine	Base	myopic fundus
401-5	griseofulvin	Base	A pigment are around the disc of nervus opticus and venous hyperemia
401-42	griseofulvin	Base	Lights venous hyperemia blood vessels of retina

## SIGNATURES/DISTRIBUTION LIST

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STATISTICAL REVIEW AND EVALUATION  
NEW DRUG APPLICATION  
CLINICAL STUDIES

**NDA/Serial Number:** 22-071/SN000  
**Drug Name:** Lamisil (terbinafine) Oral Granules  
**Indication(s):** Tinea Capitis  
**Applicant:** Novartis

**Dates:** Submitted: 09/08/2006  
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**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics III  
**Statistics Reviewer:** Mat Soukup, Ph.D.  
**Concurring Reviewer:** Mohamed Alosh, Ph.D.

**Medical Division:** Division of Dermatology and Dental Products  
**Clinical Team:** Reviewer: Trish Brown, M.D. (DDDP)  
Lead: Jill Lindstrom, M.D. (DDDP)

**Project Manager:** Kalyani Bhatt, (DDDP)

**Keywords:** active-control, superiority

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# 1 EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

Tinea capitis, which occurs primarily in children, is caused by a dermatophyte infection of the scalp hair follicles. In the U.S. the most prevalent dermatophyte species is *T. tonsurans* which is estimated to be around 95% [4, 3, 5]. The only current FDA approved drug product for the treatment of tinea capitis is griseofulvin which was approved in the early 1960's. Since the approval of griseofulvin, it has continually been prescribed at higher doses or longer treatment durations due to the lack of efficacy of the labeled dose [1].

Discussion of the development of terbinafine in the treatment of tinea capitis was initially performed under IND 57,093. The sponsor met with the Agency on 11/13/2000 for an End of Phase 2 Meeting. At this time the Division recommended that the sponsor choose one of the following comparisons for addressing the efficacy of terbinafine.

- Superiority of terbinafine to griseofulvin when griseofulvin is used at the labeled dose.
- Non-inferiority of terbinafine to griseofulvin when griseofulvin is used at a dose of 20 mg/kg.

The Biostatistics comments from this meeting state, "...the lack of a control group makes it difficult to make a casual interpretation of any observed treatment effect. Even a small control group might be helpful."

On 12/19/2000 the sponsor submitted a proposed pediatric study request (PPSR) to assess the safety and efficacy of terbinafine in the treatment of tinea capitis. On 12/28/2001 a pediatric written request (PWR) was issued to the sponsor in response to the PPSR which requested an active comparator-controlled trial to assess the safety and efficacy of terbinafine. Further, the PWR stated that the comparator, griseofulvin, should be used at the maximum labeled dose.

On 07/02/2002 the sponsor met with the Agency to discuss the PWR issued on 12/28/2001. At this time the sponsor proposed to first test that terbinafine is non-inferior to griseofulvin, and if this test reached statistical significance they would test if terbinafine is superior to griseofulvin. In response the Division stated the following.

"Because of the reported low efficacy rates of the labeled dose of griseofulvin, the agency does not believe that it is in the best interest of the Public Health to evaluate another drug based on non-inferiority especially given the potential for serious adverse events. The studies in the [P]WR will remain superiority studies."

On 07/14/2003 the Agency issued a revised PWR which now included a clause that, "The superiority hypothesis tests may be nested." However, with the request for superiority of terbinafine to griseofulvin, no placebo arm was incorporated into the PWR. The primary efficacy

assessment was based upon the proportion of subjects with complete clearance: clinical cure (signs and symptoms score of 0) and mycological cure (negative culture and microscopy).

Per the PWR, the sponsor conducted two identically designed safety and efficacy Phase 3 trials, Studies 2301 and 2320. Study 2301 initiated enrollment on 06/23/2004 and completed on 03/15/2006. Study 2302 initiated enrollment on 07/18/2004 and completed on 03/14/2006.

In Study 2301, it was demonstrated that terbinafine is superior to griseofulvin ( $p = 0.0013$ ). However in Study 2302, the point estimates of the proportion with complete clearance were nearly identical for terbinafine and griseofulvin which did not reach statistical significance ( $p = 0.9539$ ). It should be noted however that although none of the studies were powered for subgroup analysis, for the most prevalent dermatophyte species in the U.S., *T. tonsurans*, both studies showed treatment effects favoring terbinafine,  $\delta = 21.7$  (11.0, 32.4)<sup>1</sup> and  $\delta = 11.2$  (0.1, 22.3)<sup>1</sup> for Studies 2301 and 2302, respectively. In the remaining dermatophyte species studied, there is not a clear increase in the efficacy of terbinafine over griseofulvin and in some instances, the response rates of griseofulvin are greater than terbinafine. The evaluation of safety did not show any notable asymmetry suggesting similar safety profiles of terbinafine and griseofulvin.

## 1.2 Brief Overview of Clinical Studies

Studies 2301 and 2302 were of identical design: randomized, investigator-blind, active-controlled, parallel group studies to compare the safety and efficacy of terbinafine to griseofulvin with the efficacy objective of establishing the superiority of terbinafine over griseofulvin. Enrolled subjects were treated with drug once daily for 6 weeks with the primary efficacy time point assessed at week 10. Study 2301 was conducted in 74 centers from Canada (7), Columbia (9), Egypt (3), Peru (5), South Africa (2), U.S. (44), and Venezuela (4) enrolling a total of 747 subjects of which 608 were included in the primary analysis population, mITT. Study 2302 was conducted in 72 centers from Brazil (2), Ecuador (3), Egypt (4), France (4), Guatemala (2), India (5), Russia (3), South Africa (1), and the U.S. (48) enrolling a total of 802 subjects of which 678 were included in the mITT analysis population. The primary efficacy endpoint was the proportion of subjects with complete clearance: clinical cure (signs and symptoms score of 0) and mycological cure (negative culture and microscopy).

## 1.3 Statistical Issues and Findings

The statistical analysis methods issued in the pediatric written request were followed by the sponsor and the primary analysis for the percent of subjects with complete clearance was based on the mITT population, defined as all subjects randomized to treatment with positive microscopy and culture, based on CMH stratified by pooled center. Protocol defined method of

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<sup>1</sup>95% confidence interval with Yates continuity correction for  $\delta$ =terbinafine - griseofulvin.

data imputation is LOCF.

Based upon the protocol defined primary analysis, Study 2301 established the superiority of terbinafine to griseofulvin while Study 2302 failed to establish the superiority of terbinafine to griseofulvin (results shown in Table 1). In Study 2302 the response rate for terbinafine is similar to that observed in Study 2301, but the response rate for griseofulvin in Study 2302 is approximately 10% greater than in Study 2301.

Table 1: Complete Cure Results (mITT-LOCF)

	Study 2301		Study 2302	
	Terbinafine (N = 411)	Griseofulvin (N = 197)	Terbinafine (N = 441)	Griseofulvin (N = 237)
Success (%)	190 (46.2)	67 (34.0)	194 (44.0)	103 (43.5)
p-value <sup>†</sup>	-	0.0013	-	0.9539

Source: Table 11-4 in each study report; results reproduced by reviewer.

<sup>†</sup> CMH stratified by pooled center.

Note that in the PWR issued on 07/14/2003, the analysis stated the superiority hypotheses may be nested as the effectiveness of the drug product may be dependent upon the dermatophyte species. The protocol did not pre-specify a nested hypothesis testing approach and rather just listed the analysis by dermatophyte species as a subgroup analysis. In the U.S. it is estimated that the prevalence of the dermatophyte species *T. tonsurans* is approximately 95% [4, 3, 5]. Table 2 depicts efficacy results by *T. tonsurans* and all other species combined (Not *T. tonsurans*). In the subgroup of *T. tonsurans* infested subjects, the treatment effects in both studies favor terbinafine over griseofulvin in Study 2301 and Study 2302, respectively. However, treatment effects in non-*T. tonsurans* species favor griseofulvin over terbinafine.

Safety assessment by the proportion and relative risks of adverse events according MedDRA dictionary defined preferred terms did not reveal any notable differences between terbinafine and griseofulvin. A secondary safety objective of assessing the change in appetite revealed slightly higher percentages of subjects with a change in appetite in subjects randomized to griseofulvin than terbinafine.

## 2 INTRODUCTION

Tinea capitis is a dermatophyte infection of the scalp hair follicles that occurs primarily in children. The infection is caused by a relatively small group of dermatophytes in the genera *Trichophyton* and *Microsporum* with dispersion of organisms varying by geographic regions. The treatment of Tinea capitis has two important goals: to remove the organism from the hair

Table 2: Complete Clearance Results by Dermatophyte Species (mITT)

	Study 2301		Study 2302	
	Terbinafine	Griseofulvine	Terbinafine	Griseofulvin
<i>T. Tonsurans</i>	<i>N</i> = 264	<i>N</i> = 131	<i>N</i> = 243	<i>N</i> = 126
Success (%)	148 (56.1)	45 (34.4)	116 (47.7)	46 (36.5)
C.I. for $\delta^\dagger$	-	(11.0, 32.4)	-	(0.1, 22.3)
Not <i>T. Tonsurans</i>	<i>N</i> = 147	<i>N</i> = 66	<i>N</i> = 198	<i>N</i> = 111
Success (%)	42 (28.6)	22(33.3)	78 (39.4)	57(51.4)
C.I. for $\delta^\dagger$	-	(-19.4, 9.9)	-	(-24.2, 0.3)

<sup>†</sup> 95% C.I. with Yates continuity correction for  $\delta$ =terbinafine - griseofulvin.

Source: Reviewer's Analysis.

follicle to cure the symptoms of the subject, and to eradicate the organism from the hair shaft to prevent relapse or epidemic spread of the infection. The current standard of care for *Tinea capitis* infection is oral griseofulvin[Source: Sponsor's study report].

To assess the treatment of tinea capitis with terbinafine the original pediatric written request (PWR) was issued to Novartis on 12/28/2001. The PWR contained three studies: one PK study to assess the systemic exposure of terbinafine and two safety and efficacy clinical Phase 3 studies with the objective of demonstrating terbinafine is superior to griseofulvin in the treatment of tinea capitis in pediatric patients due to specific organisms. As the studies were conducted according to the PWR, the Pediatric Exclusivity Board granted pediatric exclusivity.

## 2.1 Overview

Lamisil Granules (terbinafine) is a new pediatric formulation for oral intake once daily in the treatment of tinea capitis. The current standard of care for tinea capitis is oral griseofulvin once daily. For filing the NDA, the sponsor has submitted two pivotal Phase 3 clinical studies, Study 2301 and Study 2302. Both studies are of identical design with approximately 50% of enrolled subjects in US sites and 50% from non-US sites. A list of the clinical trials used in the development of terbinafine for the treatment of tinea capitis is provided in Table 3. The efficacy and safety review covers the two pivotal trials with oral dosing of terbinafine once daily for six weeks.

## 2.2 Data Sources

The submission contains both derived and raw data sets with definition files for both the raw and derived data sets. The derived data sets used for the assessment of safety and efficacy are

Table 3: Phase 3 Clinical Trial Summaries

Study	Objective	Drug Products	N <sup>†</sup>	Dates <sup>‡</sup>
Study 2301	Superiority of terbinafine	terbinafine	503	06/23/2004 to
		griseofulvin	244	03/15/2006
Study 2302	Superiority of terbinafine	terbinafine	537	07/18/2004 to
		griseofulvin	265	03/14/2006

<sup>†</sup> N corresponds to the number of subjects enrolled.

<sup>‡</sup> Dates correspond to the start and completion of the study.

Source: Reviewer's Analysis.

located in //Cdsesub1/n22071/N\_000/2006-09-08/crt/datasets.

### 3 STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1 Study Design

The two studies are identical in design. The design is a randomized, investigator blinded, active-controlled, parallel-group study to compare the efficacy and safety of 6-week treatment terbinafine new pediatric formulation versus 6 week treatment griseofulvin pediatric suspension in children with tinea capitis with the efficacy objective of establishing superiority of terbinafine over griseofulvin. The study consists of three periods: screening period (3 - 7 days), treatment period 6 weeks (Day 1 – Day 42), and a follow-up period 4 weeks (Day 43 – Day 70). Note that visits should take place within  $\pm 3$  days from the visit date calculated according to the protocol.

After enrollment into the study, eligibility of the subjects will be verified and confirmed based on laboratory test results during the screening period. Eligible subjects with a positive culture and microscopy will then be randomized in a 2:1 ratio to receive terbinafine new pediatric formulation or griseofulvin given once a day. Doses of both terbinafine and griseofulvin will be based on weight as shown below.

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

- griseofulvin
  - < 14 kg: 125 mg/day
  - 14 to 23 kg: 250 mg/day
  - > 23 kg: 500 mg/day

After the last dose, patients will be followed up for 4 additional weeks where the primary time point for efficacy evaluation will occur at week 10.

Note that the initial draft of the protocol defined dosing for griseofulvin to be < 15, 15 – 25, and > 25 which is lower than the labeled dose of griseofulvin. On July 30, 2004 the sponsor was sent comment that dosing for griseofulvin should correspond to the maximum labeled dosage. However, subject enrollment had already begun in both studies and it wasn't until protocol amendment 2 did the protocols change the dosing for the griseofulvin treatment arm. Impacts on efficacy are explored as a sensitivity analysis in Section 3.1.8.2.

### 3.1.2 Endpoints

In the definitions of the primary and secondary endpoints the following definitions are used.

**Mycological Cure** Negative dermatophyte culture and negative KOH microscopy.

**Clinical Cure** Complete Clearance of baseline Total Signs and Symptoms (TSSS= 0).

**Complete Cure** Both mycological and clinical cure.

The protocol-defined primary endpoint is the proportion of subjects with complete clearance 10 weeks from taking the drug (4 weeks after last dose).

Three secondary endpoints are proposed in the protocol and are defined as follows.

**Effective Treatment** Yes if the following conditions are met; assessed on week 10.

- Mycological cure
- TSSS  $\leq$  2 with no individual item > 1.

**Clinical Cure** Assessed at week 10.

**Mycological Cure** Assessed at week 10.

Note that the protocol did not specify the time point for the evaluation of the secondary endpoints. However, the time point used in the study reports is consistent with the time point used for the primary endpoint (i.e. 10 weeks). Lastly, the study reports nor the labeling report results for the secondary endpoint effective treatment which are also not reported in this review.

### 3.1.3 Patient Disposition and Baseline Characteristics

**3.1.3.1 Patient Disposition** Analysis populations for efficacy assessment are provided in Table 4. The following are protocol definitions of the analysis populations.

- The **ITT** population is defined as all subjects randomized and received at least one dose of treatment.
- The **mITT** population is defined as all subjects in the ITT population who also had a positive culture at baseline.
- The **PP** population consists of a subset of the ITT population which excludes subjects with major protocol violations.

The protocol-defined primary efficacy analysis population is the mITT population with the PP considered to provide supportive evidence.

Table 4: Analysis Populations<sup>†</sup>

	Study 2301		Study 2302	
	Griseofulvin	Terbinafine	Griseofulvin	Terbinafine
ITT	244(100%)	503 (100%)	265 (100%)	537 (100%)
mITT	197 (81%)	411 (82%)	237 (89%)	441 (82%)
PP	136 (56%)	335 (67%)	173 (65%)	348 (65%)

<sup>†</sup> Numbers in parentheses correspond to the percent randomized.

Source: Table 11-1 of the Study Reports; results verified by reviewer.

Table 5 depicts the number of subjects included in the mITT population and the reason for drop out for subjects that did not complete the week 10 visit. In both studies the percent of drop outs is slightly higher in the terbinafine arm than in the griseofulvin arm, but the rate of drop out was not high for the mITT population.

**3.1.3.2 Baseline Characteristics** The following examines baseline distributions of demographic factors as well as prognostic factors which might have an impact on efficacy.

**3.1.3.2.1 Demographics** Results of the baseline comparisons for age, gender, race, and country are provided in Tables 20 and 21 in Appendix Section A.1 on page 33. Note that baseline comparisons are provided only for subjects included in the mITT population. In Study 2301 a higher percentage of females in the mITT population were randomized to griseofulvin than terbinafine, 43% and 33%, respectively. Also in Study 2301 the age of subjects in the mITT population is younger for subjects randomized to terbinafine than griseofulvin. No large baseline differences were found in Study 2302.

Table 5: Subject Disposition (mITT)

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

Values in the table correspond to counts with percentages in parentheses.

Source: Reviewer's Analysis.

**3.1.3.2.2 Prognostic Factors** The following set of prognostic factors were examined for baseline distribution by treatment.

- Total Signs and Symptoms Score (TSSS)
- Area of involvement (localized or diffuse)
- Dermatophyte species
- Duration of the current infection (in days)

Note that the prevalence of dermatophyte species in the US population is estimated to be 95% *T. tonsurans* and 5% *M. canis*[4, 3, 5].

Based upon Wilcoxon tests for continuous factors and Pearson tests for categorical factors, no differences were found between treatment arms in either study for any of the prognostic factors listed above. Results are presented in the Appendix Section A.2 on page 33 for the mITT population (results were also not significant for the ITT population, results not provided). Thus, due to the balance in the baseline distributions it is not expected that one treatment will be favored over another treatment arm for efficacy.

### 3.1.4 Statistical Methodology

The following section consists of the protocol-defined statistical methods throughout unless otherwise stated. The following hypothesis will be tested using Cochran-Mantel-Haenszel (CMH) test controlling for center at the one-sided 2.5% significant level in the mITT population.

$$H_0 : P_t \leq P_g \text{ vs. } H_a : P_t > P_g,$$

where  $P_g$  is the proportion of patients achieved complete cure at week 10 in the griseofulvin group and  $P_t$  is the proportion of patients achieved complete cure at week 10 in the terbinafine group. Homogeneity of odds ratios across centers will be assessed using Breslow-Day statistics. Note that since enrollment was small in many centers the small centers were pooled for the primary analysis.

In the primary analysis missing values will be imputed using last observation carried forward (LOCF) approach regardless of reason for missing. As a sensitivity analysis, the analysis of the primary endpoint will be repeated using the following two additional imputation approaches when the primary endpoint is missing (i.e., no measurement at week 10 visit).

1. No imputation for missing value: only patients with available data will be included in the analysis at this time point.
2. Patients without the assessments at week 10 were considered as failures or non-responders at week 10.

To support the primary analysis, the primary efficacy variable will be analyzed using the CMH test controlling for pooled center in ITT population. It will also be repeated for the PP population if needed. As a supportive analysis, the protocols specifies that the primary endpoint will also be compared for subgroups defined by baseline dermatophyte species and area of involvement (diffused vs. localized) at baseline.

### 3.1.5 Primary Endpoint Results (mITT)

The protocol-defined primary endpoint is the proportion of subjects with complete clearance 10 weeks from taking the drug (4 weeks after last dose). Missing data at week 10 is imputed using LOCF. As pre-specified in the protocol, Breslow-Day tests are used to test for the homogeneity of the odds ratios across pooled sites. The tests resulted in p-values of 0.0846 and 0.0968 for Study 2301 and Study 2302, respectively. Each of these tests did reach statistical significance at the  $\alpha = 0.10$  level (Division's typical level of significance threshold), however the analysis by dermatophyte species (see Section 4.2.3) showed that efficacy varied by dermatophyte species. As the prevalence of dermatophyte species varies by region/country it is plausible to see center/countries with treatment effects in opposite directions and hence resulting in a significant treatment by center interaction effect.

Results for Studies 2301 and 2302 are displayed in Table 6. In Study 2301 terbinafine is statistically superior to griseofulvin, yet in Study 2302 the percent achieving complete clearance is nearly identical resulting in no statistical significance. The discrepancy in the two studies is due to the fact that the percent of subjects achieving complete clearance in griseofulvin is higher in Study 2302 than in Study 2301 while the percent of subjects achieving complete clearance for terbinafine is similar in Studies 2301 and 2302.

Table 6: Complete Cure Results (mITT-LOCF)

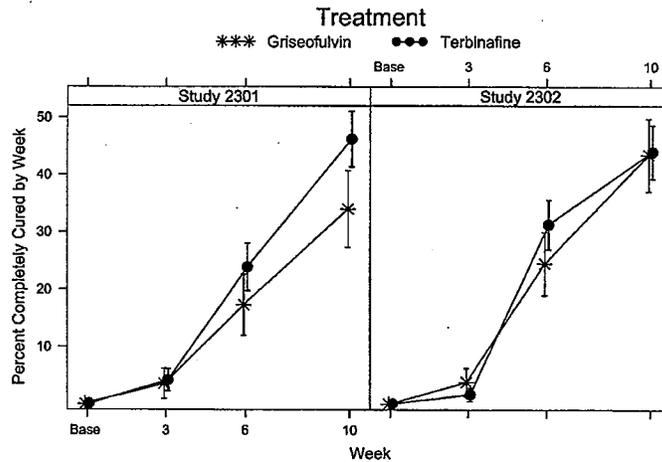
	Study 2301		Study 2302	
	Terbinafine (N = 411)	Griseofulvin (N = 197)	Terbinafine (N = 441)	Griseofulvin (N = 237)
Success (%)	190 (46.2)	67 (34.0)	194 (44.0)	103 (43.5)
p-value	-	0.0013	-	0.9539

Source: Table 11-4 in each study report; results reproduced by reviewer.

3.1.6 Primary Endpoint Across Study Visits

Figure 1 depicts the percent of subjects that are complete cures at each of the study visits along with unadjusted 95% confidence bands. In Study 2301 the treatment effect continued to get larger in favor of terbinafine over time. In Study 2302 the treatment effect was in favor of terbinafine at week 6, and this week 6 treatment effect was similar to the week 6 treatment effect of study 2301. However, at week 10 the response rate of terbinafine did not increase at the same rate as griseofulvin resulting in near identical response rates at week 10 (i.e. treatment effect of near zero). One possible influence on the near zero treatment effect for Study 2302 is the method of imputation of week 10 data which is covered in Section 3.1.8.

Figure 1: Complete Cure at Each Visit (mITT)



3.1.7 Primary Endpoint Results (ITT)

As a supportive analysis to the primary analysis, all subjects randomized to treatment are analyzed. Missing data at week 10 is imputed using LOCF. Results are provided in Table 7,

and efficacy conclusions are consistent with those for the mITT population.

Table 7: Complete Cure Results (ITT-LOCF)

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

Source: Table 11-5 in each study report; results reproduced by reviewer.

In addition to the supportive analysis on the ITT population, the analysis on the PP population yielded consistent results. Efficacy results for the PP population are shown in the Appendix Section A.3 on page 35.

### 3.1.8 Sensitivity Analysis of the Primary Endpoint

**3.1.8.1 Sensitivity to Method of Data Imputation** Table 8 depicts the amount of missing data for the primary endpoint evaluated at week 10 and the subject's success status at week 6 (last day of treatment) which would be the value used for the mITT-LOCF evaluation. In Study 2301 a higher proportion of missing are treated as success for terbinafine than griseofulvin which implies the LOCF imputation strategy may inflate the treatment effect if missing is truly at random (i.e. near equal missing percentages for each treatment arm). In Study 2302 the opposite occurs in that a higher percentage of week 10 missing are treated as successes for griseofulvin than terbinafine. This in turn implies that if dropout is truly at random then the treatment effect may be underestimated when imputing missing data using LOCF.

Table 8: Missing Data Summary

	Study 2301		Study 2302	
	Griseofulvin (N = 197)	Terbinafine (N = 411)	Griseofulvin (N = 237)	Terbinafine (N = 441)
Week 10 NA <sup>†</sup> (%)	32 (16.2)	62 (15.1)	29 (12.2)	64 (14.5)
No. Week 6 Successes	2	9	8	12
% NA at week 10 LOCF success	6.3%	14.5%	27.6%	18.8%

<sup>†</sup> Number missing followed by percent missing in parentheses.

Source: Reviewer's Analysis.

In the following sensitivity analysis to data imputation, all missing data are imputed using

various proportions of successes for the week 10 missing data. This can vary from the extremes, all missing data for the control arm are imputed as successes and all missing data from the active arm are imputed as failures to the case where all missing controls are failures and all missing active are success. Everything in between the extremes is covered in this analysis. Once imputed these data are combined with the complete data and a Chi-square test is performed. The Chi-square test is performed for every possible proportion of imputed successes and the response surface of the Chi-Square statistic is plotted in a perspective plot.

Figure 2 is a perspective plot depicting the response surface of all possible ways to impute success in Study 2301 for the mITT population. The white line dissecting the surface in half corresponds to the cases where the response rate being imputed for the active and control arms is equal. To reach statistical significance at the  $\alpha = 0.05$  level (i.e. assuming no multiplicity adjustment), the value of the Chi-square statistic should be 3.84 or greater. This value is represented between blue ( $\chi^2 = 3$ ) and cyan or light blue ( $\chi^2 = 4$ ) in the perspective plot. Thus, for points falling in the cyan range, this area would correspond to statistical significance. Therefore any range above this would also correspond to statistical significance. Note that values with no coloring in the upper-right hand quadrant of the figure are extreme  $\chi^2$  values.

Considering the cases when both arms are imputed with the same response rate (i.e. missing is random), this analysis shows that terbinafine is always statistically superior to griseofulvin in study 2301. Even when all the missing values for griseofulvin are imputed as success and all missing for terbinafine are imputed as failures, the  $\chi^2$  value is 1.45 which demonstrates griseofulvin is not statistically superior to terbinafine even in such a favorable condition for griseofulvin. Thus, for Study 2301 the efficacy conclusion is quite robust to the method of data imputation.

Figure 3 is the same sensitivity analysis for the mITT population in Study 2302. When response rates are imputed using the same response rate for both treatment arms (i.e. missing at random),  $\chi^2 \not\geq 1$  implying a failure to demonstrate that terbinafine is statistically superior to griseofulvin. In order for terbinafine to show statistical superiority to griseofulvin, the imputed response rate of terbinafine needs to be approximately 45% higher than the imputed response rate of griseofulvin. Overall, when response rates are imputed with similar response rates, Study 2302 *fails* to demonstrate that terbinafine is statistically superior to griseofulvin.

In addition to the above sensitivity analysis of the primary endpoint, the protocol also pre-specified a sensitivity analysis for the mITT population including only subjects that have a visit at week 10. Conclusions are consistent with the previous analyses and results are shown in the the Appendix Section A.4 on page 35.

Figure 2: Sensitivity Analysis Study 2301 (mITT)

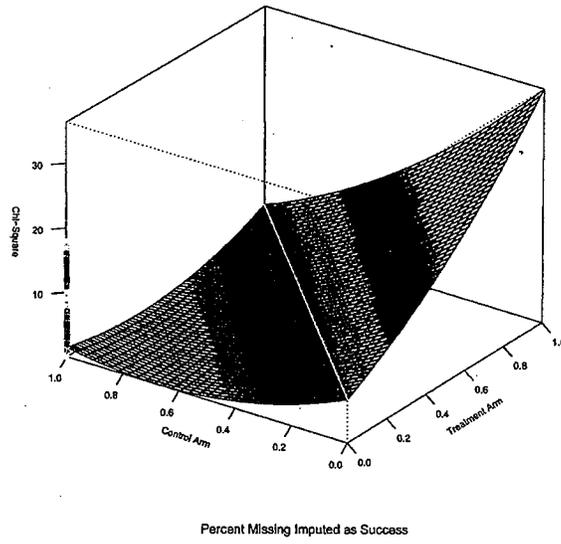
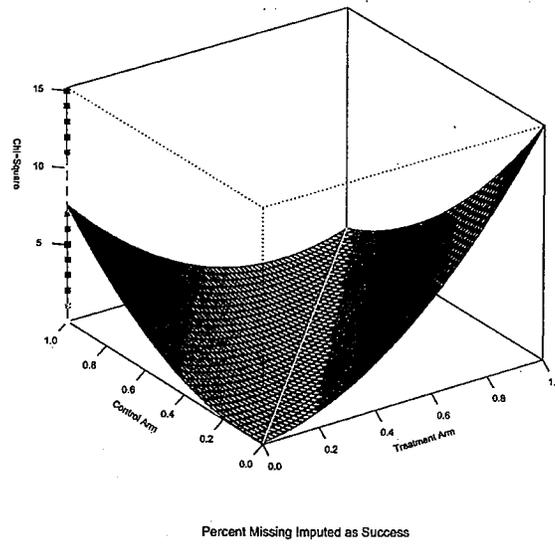
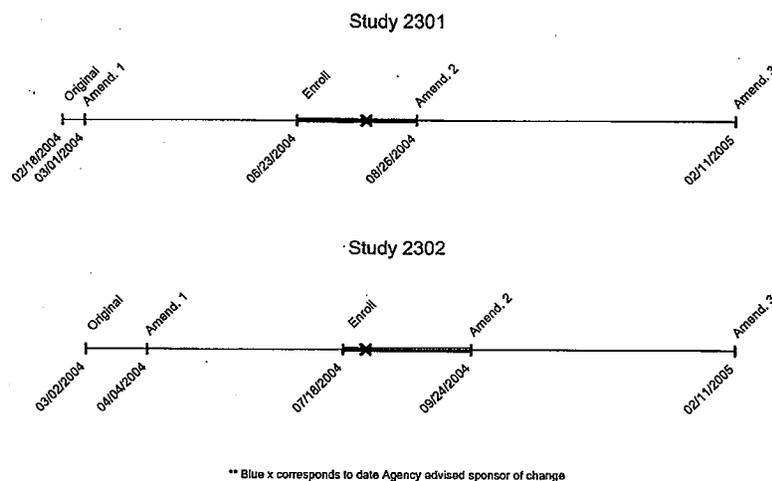


Figure 3: Sensitivity Analysis Study 2301 (mITT)



**3.1.8.2 Sensitivity Analysis of Change in Griseofulvin Dosage** Recall from Section 3.1.1 that on July 30, 2004 the sponsor was faxed comment that the dosing for subjects randomized to griseofulvin should pertain to the maximum labeled dose. Such a change was made to the protocol in amendment 2 and the dates for these changes are shown in Figure 4. The shaded regions along the time axis indicates the period in which subjects were enrolled and the time in which subjects randomized to griseofulvin received lower than the maximum labeled doses. In both studies, the time from first subject being enrolled until the time of the second protocol amendment which contained the dosing for griseofulvin was about 2 months.

Figure 4: Important Dates for Studies 2301 and 2302



In Study 2301 a total of 19 subjects included in the mITT population were enrolled during this period of time with 6 subjects randomized to griseofulvin. In Study 2302 a total of 75 subjects included in the mITT population were enrolled during this period of time with 28 subjects randomized to griseofulvin. Table 9 depicts the efficacy results for subjects according to whether they were enrolled prior to amendment 2 or not. Curiously, subjects exposed to the lower dose griseofulvin (i.e. enrolled prior to amendment 2) in Study 2302 had a higher response than subjects randomized after amendment 2 though the total sample size was small ( $n = 28$ ). Note that this might be a result of a higher percentage of subjects being enrolled from non-US sites at this point on the study (refer to Section 4.2 for further discussion about efficacy by country).

Overall, results from this sensitivity analysis do not alter the efficacy findings from the proto-

Table 9: Efficacy Results Before and After Amendment 2

	Study 2301		Study 2302	
	Terbinafine	Griseofulvin	Terbinafine	Griseofulvin
Before Amend. 2	$\frac{6}{13}$ (46.2)	$\frac{1}{6}$ (16.7)	$\frac{18}{47}$ (38.3)	$\frac{15}{28}$ (53.6)
After Amend. 2	$\frac{184}{398}$ (46.2)	$\frac{66}{191}$ (34.6)	$\frac{176}{394}$ (44.7)	$\frac{88}{209}$ (42.1)

Source: Reviewer's analysis using the mITT-LOCF analysis population.

col specified primary analysis on the mITT population which is that Study 2301 provides robust findings of superiority of terbinafine to griseofulvin, whereas Study 2302 fails to demonstrate terbinafine is superior to griseofulvin.

### 3.1.9 Secondary Endpoint Results

The two secondary endpoints reported in the study reports are mycological and clinical cure at week 10.

**3.1.9.1 Mycological Cure** Mycological cure is defined as a negative culture and negative microscopy at week 10. Table 10 depicts the efficacy results at week 10 for the mITT population with missing week 10 imputed using LOCF. Based on CMH stratified by pooled site, Study 2301 demonstrated terbinafine was statistically superior to griseofulvin in mycological cure, and Study 2302 failed to demonstrate terbinafine was statistically superior to griseofulvin in mycological cure.

Table 10: Mycological Cure Results (mITT-LOCF)

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

Source: Table 11-6 in each study reports; results reproduced by reviewer.

**3.1.9.2 Clinical Cure** A clinical cure is defined as complete clearance of baseline total signs and symptoms (i.e. TSSS = 0). Table 11 depicts the efficacy results at week 10 for the mITT population with missing week 10 data imputed using LOCF. Based on CMH stratified by pooled site, neither Study 2301 or Study 2302 demonstrated terbinafine was statistically superior to griseofulvin in clinical cure at the  $\alpha = 0.05$  level.

Table 11: Clinical Cure Results (mITT-LOCF)

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

Source: Table 11-7 of each study report; results reproduced by reviewer.

## 3.2 Evaluation of Safety

The evaluation of safety is based upon the safety population which is defined as all subject that receive at least one dose of drug product and have at least one post-baseline safety assessment. The protocol also lists several safety endpoints which include assessment of adverse events, changes in vision, and changes in taste. This review assesses AE's and change in appetite; review of the change in vision is covered by the medical officer in the Division of Anti-Infective and Ophthalmology Products.

### 3.2.1 Adverse Events

In the adverse event section, AE rates are calculated as the percentage of subjects that experience the AE and not the number of times the AE occurred (i.e. if one subject experience erythema at two visits, erythema is counted only once in the tables that follow). Also note that safety results are displayed according to the actual treatment received which accounts for the two subjects randomized to griseofulvin but received terbinafine. The two Phase 3 trials are combined for the AE reporting.

Table 12 provides the rates of AE's according to the MedDRA system organ class (SOC) and preferred terms (PT) when the combined AE rate for any PT for both treatment groups occurred in at least 1.5% of all subjects. Overall, AE incidence according to PT and SOC are quite similar between terbinafine and griseofulvin.

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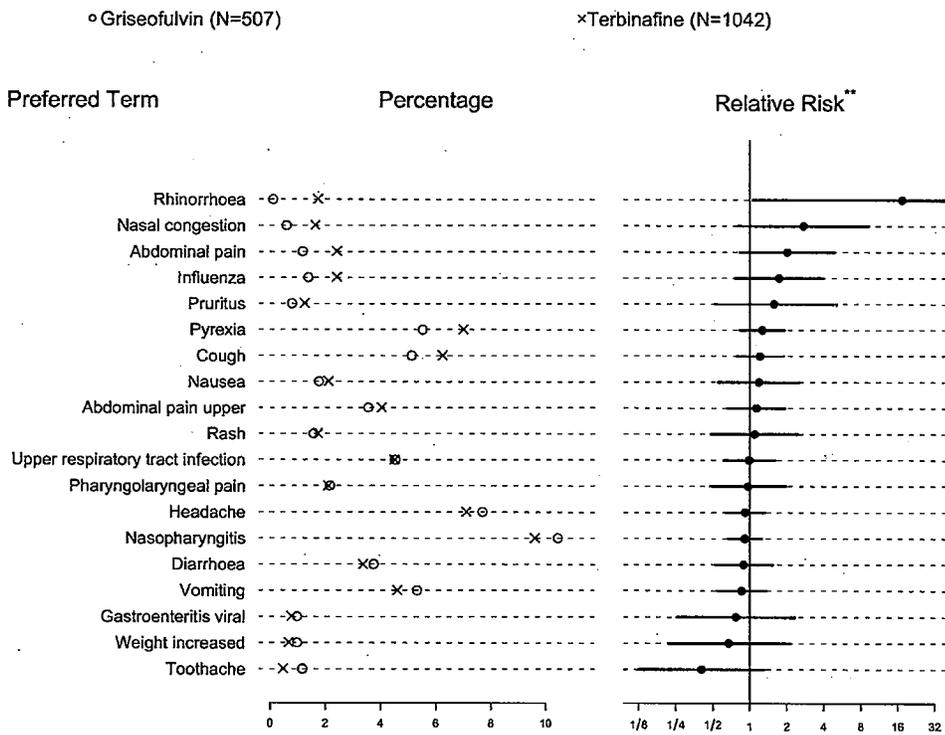
Table 12: Adverse Events by System Organ Class and Preferred Term

	Terbinafine (N = 1042)	Griseofulvin (N = 507)
<b>Gastrointestinal disorders</b>		
Vomiting	48 ( 4.6 )	27 ( 5.3 )
Abdominal pain upper	42 ( 4.0 )	18 ( 3.6 )
Diarrhoea	35 ( 3.4 )	19 ( 3.7 )
Abdominal pain	25 ( 2.4 )	6 ( 1.2 )
Nausea	22 ( 2.1 )	9 ( 1.8 )
Toothache	5 ( 0.5 )	6 ( 1.2 )
<b>General disorders and administration site conditions</b>		
Pyrexia	73 ( 7.0 )	28 ( 5.5 )
<b>Infections and infestations</b>		
Nasopharyngitis	100 ( 9.6 )	53 ( 10.5 )
Upper respiratory tract infection	47 ( 4.5 )	23 ( 4.5 )
Influenza	25 ( 2.4 )	7 ( 1.4 )
Gastroenteritis viral	8 ( 0.8 )	5 ( 1.0 )
<b>Investigations</b>		
Weight increased	7 ( 0.7 )	5 ( 1.0 )
<b>Nervous system disorders</b>		
Headache	74 ( 7.1 )	39 ( 7.7 )
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	65 ( 6.2 )	26 ( 5.1 )
Pharyngolaryngeal pain	22 ( 2.1 )	11 ( 2.2 )
Rhinorrhoea	18 ( 1.7 )	0 ( 0.0 )
Nasal congestion	17 ( 1.6 )	3 ( 0.6 )
<b>Skin and subcutaneous tissue disorders</b>		
Rash	18 ( 1.7 )	8 ( 1.6 )
Pruritus	13 ( 1.2 )	4 ( 0.8 )

Source: Reviewer's analysis using data sets a\_aev.xpt from each study.

Figure 5 graphically depicts the AE's according to the PT's which appear in Table 12. In the figure, the PT are sorted according to the value of the relative risk. In addition, a 95% confidence interval for the relative risk is displayed for each PT. Note that the only CI which does not intersect the threshold of 1, is rhinorrhea. This confidence interval is very wide, and the result appears to be due to the notion that no cases of rhinorrhea are observed in subjects who took griseofulvin and 1.7% of subjects who took terbinafine. Note that to mitigate the troubles of logging a zero value in the confidence interval calculation, the zero is replaced by a value of 0.5 in the calculation. Overall, this method of summarizing the data shows similar safety profiles for terbinafine and griseofulvin.

Figure 5: Adverse Events sorted by Relative Risk



3.2.2 Serious Adverse events

All recorded serious AE's are presented in Table 13 on page 22. Of the ten reported serious AE's in the two Phase 3 trials, nine of the subjects received terbinafine. The relationship to study drug was also recorded by the investigator and only one serious AE was suspected as

being related to study drug, terbinafine, in Subject 0601-00024 who developed a cataract.

Table 13: All Serious AEs listed by MedDRA Preferred Term

Subject ID	Treatment	Preferred Term	Severity	Relation to Drug
0403-00017	Terbinafine	Hepatitis viral	Moderate	Not Suspected
0404-00028	Terbinafine	Head injury	Moderate	Not Suspected
0511-00022	Terbinafine	Nausea	Severe	Not Suspected
0511-00022	Terbinafine	Pyrexia	Severe	Not Suspected
0511-00022	Terbinafine	Pruritus	Severe	Not Suspected
0511-00022	Terbinafine	Pain of skin	Severe	Not Suspected
0601-00015	Terbinafin	Pneumonia	Moderate	Not Suspected
0601-00024	Terbinafine	Cataract	Moderate	Suspected
0601-00024	Terbinafine	Glaucoma	Severe	Not Suspected
0601-00052	Griseofulvin	Arthritis bacterial	Severe	Not Suspected

Source: Reviewer's Analysis.

### 3.2.3 Change in Appetite

The change in appetite is listed as one of the secondary safety objectives of the trial. For the two Phase 3 trials combined, Table 14 on page 22 depicts the percent of subjects that had a change in appetite according to the interview with the care giver. During the trial both terbinafine and griseofulvin had similar rates of change in appetite with a slightly higher percentage being reported by subjects treated with griseofulvin. At study completion, 4 weeks from last dosing, the rate is lower than during days while on treatment.

Table 14: Change in Appetite

	Terbinafine	Griseofulvin
Day 22	129/968 (13.3)	72/489 (14.7)
Day 42	93/989 (9.4)	56/493 (11.4)
Study Completion	43/921 (4.7)	25/456 (5.5)

Source: Reviewer's Analysis

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

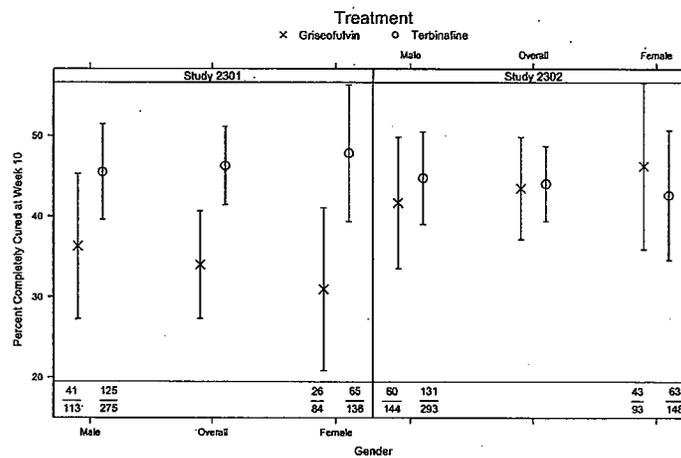
Section 4.1 provides a graphical assessment of efficacy by subgroup, for full tabled results refer to Appendix Section A.5; note that the number of successes and samples sizes for a given level

of the subgroup are provided in each plot. Section 4.2 examines efficacy of subgroups which might be impacted by one of the levels of the subgroup. All results are reported using the primary efficacy population and imputation strategy, mITT-LOCF. Note that the protocol did not pre-specify any subgroup analysis which controlled the overall Type I error rate.

### 4.1 Gender, Race, and Age

Figure 6 depicts efficacy results according to gender along with unadjusted 95% confidence intervals. In Study 2301, efficacy is consistent with the overall study as in each gender, terbinafine has a higher response rate than griseofulvin. However, in Study 2302, the response rate in females is lower for terbinafine than in griseofulvin.

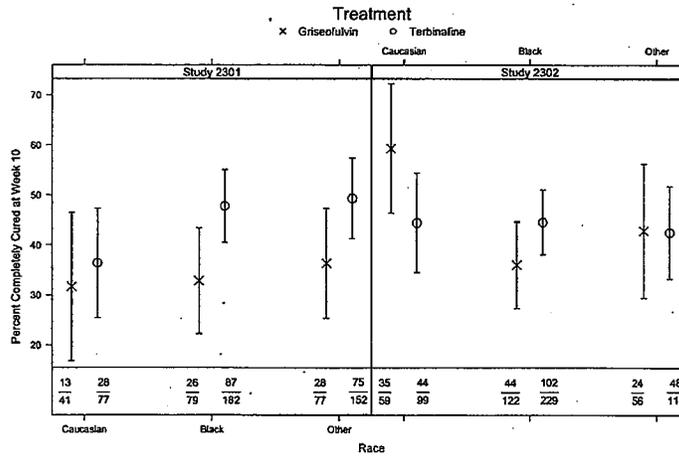
Figure 6: Efficacy by Gender (mITT)



Race was broken into three categories: Caucasian, Black, and Other. Baseline distributions are provided in the tabled information of Figure 7. In Study 2301, the treatment effect is smallest in Caucasians. In Study 2302 the efficacy in Caucasians is higher in griseofulvin than terbinafine. Overall, there are not large differences in conclusions reached from the whole population.

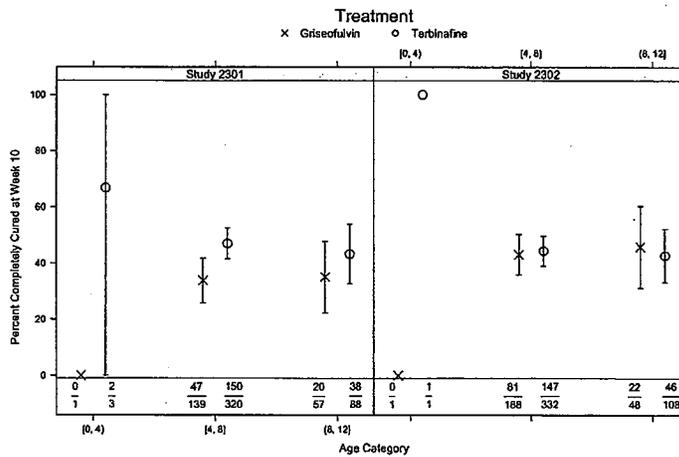
The subject's baseline age was broken into three categories: less than 4 years old, between 4 and 8 years old, and between 9 and 12 years old. Baseline distributions are provided in the tabled information of Figure 8. With sparse data for subjects less than 4 years old it is difficult to draw conclusions about efficacy in this subgroup. For subjects in the two oldest cohorts, response rates were higher in terbinafine than in griseofulvin in Study 2301, however, as seen with the

Figure 7: Efficacy by Race (mITT)



study population as a whole, response rates are similar for terbinafine and griseofulvin in these two cohorts.

Figure 8: Efficacy by Age Category (mITT)



## 4.2 Other Special/Subgroup Populations

### 4.2.1 Primary Efficacy Results by Country

Approximately 50% of subjects enrolled were from outside the United States. The impact this may have is that the prevalence of dermatophyte species may vary between countries and the effectiveness of the drug product across dermatophyte species may vary which is explored in the next section. Figure 9 depicts the response rates for each country along with the sample sizes enrolled at each country. From these figures it can be seen that in some countries the response rates of terbinafine is lower than griseofulvin. In the United States, response rates are higher for terbinafine than griseofulvin for both studies, while the treatment effect is larger in study 2301.

Figure 9: Efficacy by Country (mITT)

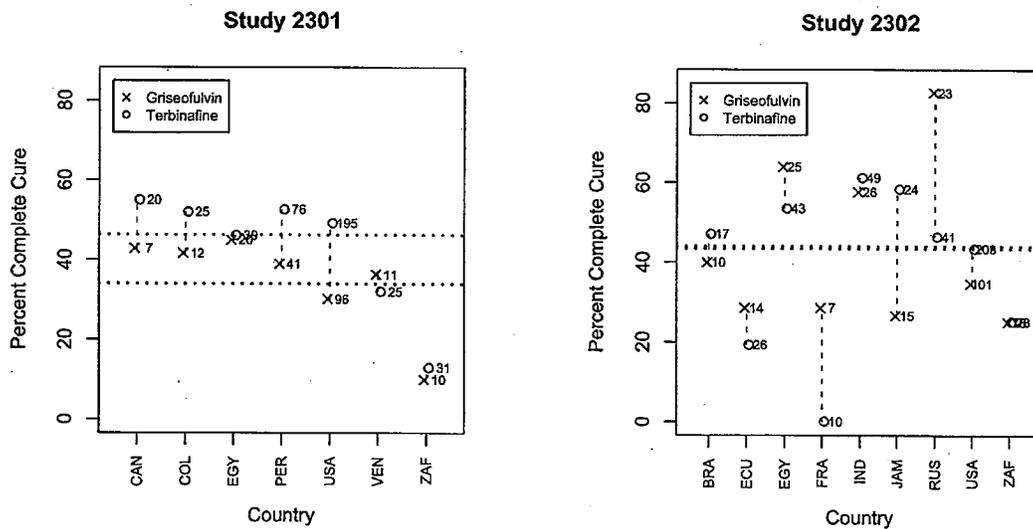


Table 15 depicts the primary efficacy results for U.S. and non-U.S. subjects from each Phase 3 trial. As with the efficacy conclusion for Study 2301 as a whole, terbinafine shows higher efficacy than griseofulvin in the U.S. However, Study 2301 does not show a clear efficacy signal in non-U.S. countries, though the treatment effect shows a trend in favor of terbinafine. Consistent with the efficacy conclusion for the overall population of no statistical superiority of terbinafine over griseofulvin in Study 2302, efficacy results do not demonstrate superiority of terbinafine to griseofulvin in either the U.S. or non-US populations. In the U.S., the treatment effect shows a trend in favor of terbinafine,  $\delta = 8.6$ , whereas the treatment effect in non-U.S. sites depicts a negative treatment effect favoring griseofulvin,  $\delta = -5.5$ .

Table 15: Complete Cure Results by Country (mITT)

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

$^\dagger$  95% C.I. with Yates continuity correction for  $\delta$ =terbinafine - griseofulvin.

Source: Reviewer's analysis.

#### 4.2.2 Primary Efficacy Results by Dermatophyte Genus

The following subgroup analysis examines efficacy by the two genera, *Trichophyton* and *Microsporum* (note that the very small number of species originally classified as "Other", 6 in Study 2301 and 4 in Study 2302, are excluded from this analysis). Results are displayed in Table 16 with 95% confidence intervals for the difference between terbinafine and griseofulvin.

This analysis shows that terbinafine is superior to griseofulvin for the genus *Trichophyton* in Study 2301, but fails to show superiority in Study 2302. However, treatment effects in Study 2302 for the genus *Trichophyton* is in favor of terbinafine. For the genus *Microsporum*, both studies showed a treatment effect in favor of griseofulvin.

Table 16: Complete Clearance Results by Dermatophyte Genus (mITT)

	Study 2301		Study 2302	
	Terbinafine	Griseofulvin	Terbinafine	Griseofulvin
<i>Trichophyton</i>	( <i>N</i> =321)	( <i>N</i> =158)	( <i>N</i> =348)	( <i>N</i> =185)
Success (%)	164 (51.1)	54 (34.2)	166 (47.7)	75 (40.5)
C.I. for $\delta^\dagger$	-	(7.2, 26.6)	-	(-2.1, 16.4)
<i>Microsporum</i>	( <i>N</i> =85)	( <i>N</i> =38)	( <i>N</i> =91)	( <i>N</i> =50)
Success (%)	21 (24.7)	13 (34.2)	27 (29.7)	26 (52.0)
C.I. for $\delta^\dagger$	-	(-29.1, 10.1)	-	(-40.6, 52.0)

$^\dagger$  95% C.I. with Yates continuity correction for  $\delta$ =terbinafine - griseofulvin.

Source: Reviewer's Analysis

### 4.2.3 Primary Efficacy Results by Dermatophyte Species

Rather than look at the whole genus, Table 17 depicts results for the percentage of subjects that achieved complete clearance at week 10 according to the baseline dermatophyte species. Note that the group defined as "Other" in the table consisted of the following dermatophyte species, but were small in number for any statistical comparison: *T. mentagrophytes*, *T. rubrum*, *M. gypseum*, and *M. vanbreuseghemii*.

For the most prevalent dermatophyte species in the U.S., *T. tonsurans*, both studies showed terbinafine to be superior to griseofulvin with the treatment effect in Study 2301 more than double the treatment effect in Study 2302. Note, however that for the second most prevalent U.S. dermatophyte species, *M. canis*, both studies showed a higher percent with a complete cure in the griseofulvin treatment arm than the terbinafine treatment arm. Such a trend is also seen for *T. violaceum*.

Table 17: Complete Cure by Dermatophyte Species (mITT)

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

$\dagger$  95% C.I. with Yates continuity correction for  $\delta$ =terbinafine - griseofulvin.

Source: Reviewer's analysis.

#### 4.2.4 Primary Efficacy Results by Country and Dermatophyte Species

In this section, the relation of complete cure and treatment conditional on country and dermatophyte species is explored. For this summary, the following variable choices are used.

- Country is categorized as U.S. or Non-U.S.
- Dermatophyte species is represented by *T. tonsurans*, *T. violaceum*, and *M. Canis*. All other species are dropped as they account for only 1% of the species in Study 2301 and 4% of the species in Study 2302.

The method used to visualize the data is a mosaic display which has been suggested in the statistical literature by Hartigan and Kleiner[2]. The mosaic display shows the frequencies in an  $n$ -way contingency table by nested rectangular regions whose area is proportional to the frequency in a cell.

Figures 10 and 11 are mosaic displays for Studies 2301 and 2302, respectively. In these mosaic displays the regions are shaded according to response (i.e. clinical cure). Also, treatment labels are denoted as 'T' and 'G' corresponding to terbinafine and griseofulvin, respectively. As the randomization was 2:1 to terbinafine and griseofulvin, the *height* of the region for terbinafine will be about double the *height* of the region for griseofulvin within a given organism. For a visualization of the treatment effect for a given dermatophyte species within country, the *length* of the darkly shaded region for terbinafine can be compared to the *length* of the darkly shaded region for griseofulvin.

Figures 10 and 11 show that in Study 2302 fewer Non-U.S. subjects were enrolled who were infested by *T. tonsurans*. Study 2302 included more subjects infested with *T. violaceum*. For a given species and country, the treatment effect is quite similar for both studies. For example, the treatment effect in Non-U.S. subjects infested with *T. violaceum* enrolled in Study 2301 is quite similar to that in Study 2302.

Overall, there appears to be two factors which have the potential to decrease treatment effects in Study 2302.

1. Non-U.S. sites enrolled fewer subjects infested with *T. tonsurans*.
2. The treatment effect in U.S. subjects infested with *T. tonsurans* is smaller in 2302 than in Study 2301 due to an increased response rate in subjects treated with griseofulvin.

Potentially these factors played a role in in Study 2302 where it was observed that terbinafine is not superior to griseofulvin.

Figure 10: Efficacy by Country and Dermatophyte Species (mITT)

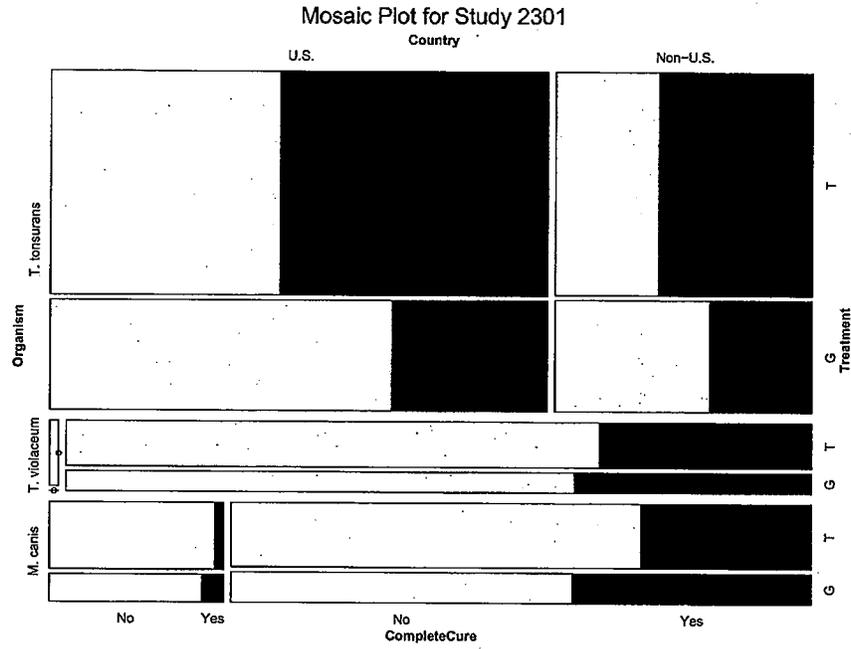
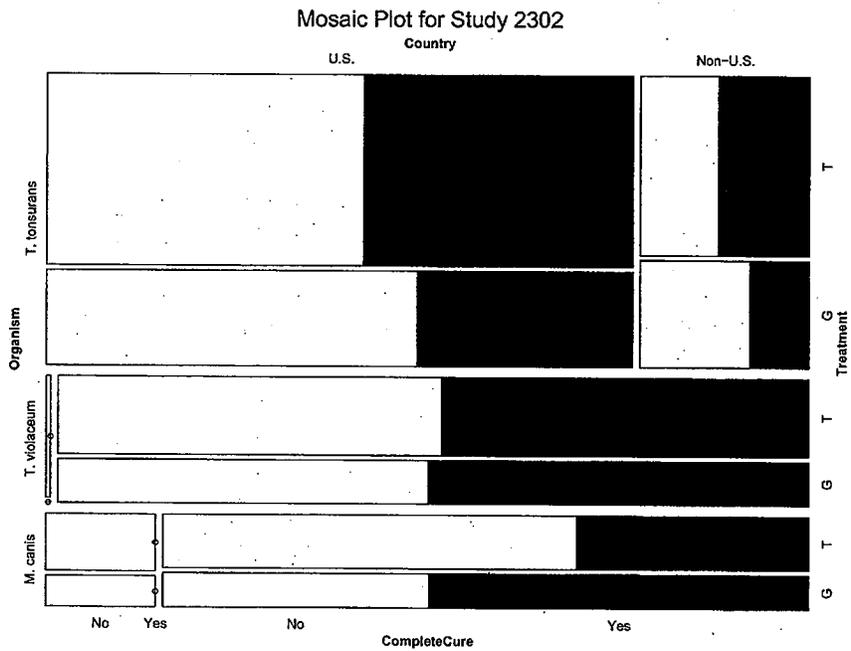


Figure 11: Efficacy by Country and Dermatophyte Species (mITT)



## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The statistical analysis methods issued in the pediatric written request were followed by the sponsor and the primary analysis for the percent of subjects with complete clearance was based on the mITT population, defined as all subjects randomized to treatment with positive microscopy and culture, based on CMH stratified by pooled center. Protocol defined method of data imputation is LOCF.

Based upon the protocol defined primary analysis, Study 2301 established the superiority of terbinafine to griseofulvin, while Study 2302 failed to establish the superiority of terbinafine to griseofulvin (results shown in Table 18). In Study 2302 the response rate for terbinafine is similar to that observed in Study 2301, but the response rate for griseofulvin in Study 2302 is approximately 10% greater than that in Study 2301.

Table 18: Complete Cure Results (mITT-LOCF)

	Study 2301		Study 2302	
	Terbinafine (N = 411)	Griseofulvin (N = 197)	Terbinafine (N = 441)	Griseofulvin (N = 237)
Success (%)	190 (46.2)	67 (34.0)	194 (44.0)	103 (43.5)
p-value <sup>†</sup>	-	0.0013	-	0.9539

Source: Table 11-4 in each study report; results reproduced by reviewer.

<sup>†</sup> CMH stratified by pooled center.

In the PWR issued on 07/14/2003, the analysis stated the superiority hypotheses may be nested as the effectiveness of the drug product may be dependent upon the dermatophyte species. The protocol did not pre-specify a nested hypothesis testing approach and rather just listed the analysis by dermatophyte species as a subgroup analysis. In the U.S. it is estimated that the prevalence of the dermatophyte species *T. tonsurans* is approximately 95%[4, 3, 5]. Table 19 depicts efficacy results by *T. tonsurans* and all other species combined (Not *T. tonsurans*). In the subgroup of *T. tonsurans* infested subjects, the treatment effects in both studies favor terbinafine over griseofulvin in Study 2301 and Study 2302, respectively. However, treatment effects in non-*T. tonsurans* species favor griseofulvin over terbinafine.

Safety assessment by the proportion and relative risks of adverse events according MedDRA dictionary defined preferred terms did not reveal any notable differences between terbinafine and griseofulvin. A secondary safety objective of assessing the change in appetite revealed slightly higher percentages of subjects with a change in appetite in subjects randomized to griseofulvin than terbinafine.

Table 19: Complete Clearance Results by Dermatophyte Species (mITT)

	Study 2301		Study 2302	
	Terbinafine	Griseofulvine	Terbinafine	Griseofulvin
<i>T. Tonsurans</i>	<i>N</i> = 264	<i>N</i> = 131	<i>N</i> = 243	<i>N</i> = 126
Success (%)	148 (56.1)	45 (34.4)	116 (47.7)	46 (36.5)
C.I. for $\delta^\dagger$	-	(11.0, 32.4)	-	(0.1, 22.3)
Not <i>T. Tonsurans</i>	<i>N</i> = 147	<i>N</i> = 66	<i>N</i> = 198	<i>N</i> = 111
Success (%)	42 (28.6)	22(33.3)	78 (39.4)	57(51.4)
C.I. for $\delta^\dagger$	-	(-19.4, 9.9)	-	(-24.2, 0.3)

<sup>†</sup> 95% C.I. with Yates continuity correction for  $\delta$ =terbinafine - griseofulvin.

Source: Reviewer's Analysis.

## 5.2 Conclusions and Recommendations

Efficacy results from Study 2301 were quite robust in establishing the superiority of terbinafine to griseofulvin for the percent of subjects achieving complete clearance at week 10. Study 2302 failed to establish the superiority of terbinafine to griseofulvin with observed response rates of complete clearance nearly equal for the two treatment arms. It should be noted however that although none of the studies were powered for subgroup analysis, for the most prevalent dermatophyte species in the U.S., *T. tonsurans*, both studies showed treatment effects favoring terbinafine,  $\delta = 21.7$  (11.0, 32.4)<sup>2</sup> and  $\delta = 11.2$  (0.1, 22.3)<sup>2</sup> for Studies 2301 and 2302, respectively. In the remaining dermatophyte species studied, there is not a clear increase in the efficacy of terbinafine over griseofulvin and in some instances, the response rates of griseofulvin are greater than terbinafine. Safety assessment by the proportion and relative risks of adverse events according MedDRA dictionary defined preferred terms did not reveal any notable differences between terbinafine and griseofulvin.

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<sup>2</sup>95% confidence interval with Yates continuity correction for  $\delta$ =terbinafine - griseofulvin.

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## APPENDIX

## A.1 Baseline Demographic Tables

The following tables for baseline demographics are for the mITT population only.

Table 20: Baseline Factors by Treatment (Study 2301)

	Griseofulvin ( <i>N</i> = 197)	Terbinafine ( <i>N</i> = 411)	Test Statistic
Age in years	5 7 9	5 6 8	$F_{1,606} = 4.95, P = 0.0264^1$
Gender : Female	43% ( 84)	33% (136)	$\chi_1^2 = 5.26, P = 0.0218^2$
Race : Caucasian	21% ( 41)	19% ( 77)	$\chi_2^2 = 0.99, P = 0.608^2$
Black	40% ( 79)	44% (182)	
Other	39% ( 77)	37% (152)	
Country : non-US	51% (101)	53% (216)	$\chi_1^2 = 0.09, P = 0.766^2$

*a b c* represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies. Tests used: <sup>1</sup>Wilcoxon test; <sup>2</sup>Pearson test. Source: Reviewer's Analysis.

Table 21: Baseline Factors by Treatment (Study 2302)

	Griseofulvin ( <i>N</i> = 237)	Terbinafine ( <i>N</i> = 441)	Test Statistic
Age in years	5 6 8	5 6 8	$F_{1,676} = 2.5, P = 0.114^1$
Gender : Female	39% ( 93)	34% (148)	$\chi_1^2 = 2.17, P = 0.141^2$
Race : Caucasian	25% ( 59)	22% ( 99)	$\chi_2^2 = 0.65, P = 0.723^2$
Black	51% (122)	52% (229)	
Other	24% ( 56)	26% (113)	
Country : non-US	57% (136)	54% (238)	$\chi_1^2 = 0.73, P = 0.394^2$

*a b c* represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies. Tests used: <sup>1</sup>Wilcoxon test; <sup>2</sup>Pearson test. Source: Reviewers Analysis.

## A.2 Baseline Prognostic Factors (mITT)

Tables 22 and 23 depict baseline summaries of each prognostic factor for subjects included in the mITT population. Both the mITT and ITT populations (not shown) are similar for each of the studies. Also, within a study, the baseline prognostic factors are balanced implying no likely initial baseline differences exists which would favor of one treatment group over another.

Table 22: Prognostic Factors by Treatment (Study 2301)

	Griseofulvin (N = 197)	Terbinafine (N = 411)	Test Statistic
Total Signs and Symptoms Score	2 2 3	2 2 4	$F_{1,606} = 1.49, P = 0.223^1$
Area of Involvement : Localized	46% (91)	51% (208)	$\chi_1^2 = 1.04, P = 0.308^2$
Organism : <i>T. tonsurans</i>	66% (131)	64% (264)	$\chi_4^2 = 1.79, P = 0.774^2$
<i>T. violaceum</i>	13% (25)	14% (57)	
<i>M. canis</i>	19% (37)	19% (80)	
<i>M. audouinii</i>	0% (0)	1% (3)	
Other	2% (4)	2% (7)	
Duration of Infection (days)	30 90 180	30 84 180	$F_{1,606} = 1.97, P = 0.161^1$

*a b c* represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies. Tests used: <sup>1</sup>Wilcoxon test; <sup>2</sup>Pearson test.

Source: Reviewer's Analysis.

Table 23: Prognostic Factors by Treatment (Study 2302)

	Griseofulvin (N = 237)	Terbinafine (N = 441)	Test Statistic
Total Signs and Symptoms Score	2 3 4	2 3 4	$F_{1,676} = 0, P = 0.985^1$
Area of Involvement : Localized	53% (126)	50% (222)	$\chi_1^2 = 0.49, P = 0.483^2$
Organism : <i>T. tonsurans</i>	53% (126)	55% (243)	$\chi_4^2 = 3.64, P = 0.457^2$
<i>T. violaceum</i>	24% (57)	23% (103)	
<i>M. canis</i>	19% (45)	16% (72)	
<i>M. audouinii</i>	2% (4)	4% (17)	
Other	2% (5)	1% (6)	
Duration of Infection (days)	21 42 90	21 56 90	$F_{1,675} = 1.09, P = 0.297^1$

*a b c* represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies. Tests used: <sup>1</sup>Wilcoxon test; <sup>2</sup>Pearson test.

Source: Reviewer's Analysis.

### A.3 Primary Endpoint Results (PP)

As a supportive analysis to the primary analysis, a subset of the mITT population who had no major protocol violations were included in the PP population. A list of major protocol violations was provided prior to database lock according to the statistical analysis plan. Major protocol violators were patients with the following criteria.

- KOH result at week 10 visit was missing.
- Culture result at week 10 visit was missing.
- Patient was randomized but did not take  $\geq 80\%$  of study drug as prescribed, either in term of number of days dosed or amount of the dose taken.
- Wrong study treatment was dispensed during the whole study
- Wrong dose of study drug was dispensed during the whole study
- Study drug was switched to a different arm for more than 50% during the trial

Efficacy results on the PP population are provided in Table 24. Consistent with efficacy conclusions for the mITT and ITT population, terbinafine is statistically superior to griseofulvin in Study 2301, but fails to show statistical superiority in Study 2302.

Table 24: Complete Cure Results (PP)

	Study 2301		Study 2302	
	Terbinafine ( <i>N</i> = 335)	Griseofulvin ( <i>N</i> = 136)	Terbinafine ( <i>N</i> = 348)	Griseofulvin ( <i>N</i> = 173)
Success (%)	176 (52.5)	57 (41.9)	169 (48.6)	85 (49.1)
p-value	-	0.0200	-	0.9163

Source: Table 14.2-1.3 in each study report; results reproduced by reviewer.

### A.4 Primary Endpoint Results (mITT Completers Only)

The protocol also specifies that as a sensitivity analysis it would only analyze subjects that complete the trial and have a week 10 visit - completers only analysis population. The percent of subjects with complete cures at week 10 are presented in Table 25.

Table 25: Complete Cure Results (mITT-Completers)

	Study 2301		Study 2302	
	Terbinafine (N = 349)	Griseofulvin (N = 165)	Terbinafine (N = 377)	Griseofulvin (N = 208)
Success (%)	181 (51.9)	65 (39.4)	182 (48.3)	95 (45.7)
p-value	-	0.0021	-	0.6498

Source: Table 14.2-1.4 in each study report; results verified by reviewer.

## A.5 Efficacy by Subgroup Tables

Tables 26 - 28 all depict efficacy results corresponding to the percent who were classified as complete cure at week 10 for the mITT analysis population with missing data imputed using LOCF. The tables are meant to compliment Figures 6 - 8 in Section 4.1.

Table 26: Efficacy Results by Gender (mITT-LOCF)<sup>†</sup>

	Study 2301		Study 2302	
	Griseofulvin	Terbinafine	Griseofulvin	Terbinafine
Male	36.3% $\frac{41}{113}$	45.5% $\frac{125}{275}$	41.7% $\frac{60}{144}$	44.7% $\frac{131}{293}$
Female	31.0% $\frac{26}{84}$	47.8% $\frac{65}{136}$	46.2% $\frac{43}{93}$	42.6% $\frac{63}{148}$

Source: Table 14.2-1.6 in each study report; results reproduced by reviewer.

<sup>†</sup> Percentages correspond to the percent complete cure at week 10.

Table 27: Efficacy Results by Race (mITT-LOCF)<sup>†</sup>

	Study 2301		Study 2302	
	Griseofulvin	Terbinafine	Griseofulvin	Terbinafine
Caucasian	31.7% $\frac{13}{41}$	36.4% $\frac{28}{77}$	59.3% $\frac{35}{59}$	44.4% $\frac{44}{99}$
Black	32.9% $\frac{26}{79}$	47.8% $\frac{87}{182}$	36.1% $\frac{44}{122}$	44.5% $\frac{102}{229}$
Other	36.4% $\frac{28}{77}$	49.3% $\frac{75}{152}$	42.9% $\frac{24}{56}$	42.5% $\frac{48}{113}$

Source: Table 14.2-1.6 in each study report; results reproduced by reviewer.

<sup>†</sup> Percentages correspond to the percent complete cure at week 10.

Table 28: Efficacy Results by Age Category (mITT-LOCF)<sup>†</sup>

	Study 2301		Study 2302	
	Griseofulvin	Terbinafine	Griseofulvin	Terbinafine
[0, 4)	0.0% $\frac{0}{1}$	66.7% $\frac{2}{3}$	0.0% $\frac{0}{1}$	100.0% $\frac{1}{1}$
[4, 8]	33.8% $\frac{47}{139}$	46.9% $\frac{150}{320}$	43.1% $\frac{81}{188}$	44.3% $\frac{147}{332}$
(8, 12]	35.1% $\frac{20}{57}$	43.2% $\frac{38}{88}$	45.8% $\frac{22}{48}$	42.6% $\frac{46}{108}$

Source: Table 14.2-1.6 in each study report; results reproduced by reviewer.

<sup>†</sup> Percentages correspond to the percent complete cure at week 10.

## A.6 Comparison of Griseofulvin Across Studies

While the overall response rates for terbinafine in the two studies were similar, it was the increased response rate of griseofulvin in Study 2302 which resulted in Study 2302 failing to establish terbinafine was superior to griseofulvin. Table 29 compares griseofulvin across each study for differences in baseline characteristics.

Table 29: Griseofulvin Baseline Factors Comparison by Study

	Study 2301	Study 2302	Test Statistic
	<i>N</i> = 197	<i>N</i> = 237	
Age in years	5 7 9	5 6 8	$F_{1,432} = 5.19, P = 0.0232^1$
Gender : Female	43% ( 84)	39% ( 93)	$\chi_1^2 = 0.51, P = 0.473^2$
Race : Caucasian	21% ( 41)	25% ( 59)	$\chi_2^2 = 12.17, P = 0.00228^2$
Black	40% ( 79)	51% (122)	
Other	39% ( 77)	24% ( 56)	
Country : non-US	51% (101)	57% (136)	$\chi_1^2 = 1.62, P = 0.203^2$
Total Signs and Symptoms Score	2 2 3	2 3 4	$F_{1,432} = 2.32, P = 0.129^1$
Area of Involvement : Localized	46% ( 91)	53% (126)	$\chi_1^2 = 2.09, P = 0.148^2$
Organism : <i>T. tonsurans</i>	66% (131)	53% (126)	$\chi_4^2 = 13.91, P = 0.0076^2$
<i>T. violaceum</i>	13% ( 25)	24% ( 57)	
Other	2% ( 4)	2% ( 5)	
<i>M. canis</i>	19% ( 37)	19% ( 45)	
<i>M. audouinii</i>	0% ( 0)	2% ( 4)	
Duration of Infection (days)	30 90 180	21 42 90	$F_{1,432} = 29.82, P < 0.001^1$

*a b c* represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies. Tests used: <sup>1</sup>Wilcoxon test; <sup>2</sup>Pearson test. Source: Reviewer's analysis.

Several differences exist from this table, the most important, likely being the difference in the distribution of the dermatophyte species. In Section 4.2.3 the response rate for griseofulvin for

the *T. tonsurans* species was consistent across studies and this was the lowest response rate among the dermatophyte species. In Table 29 it can be seen that the percent of subjects enrolled in Study 2302 and randomized to griseofulvin with *T. tonsurans* was lower than the percent enrolled in Study 2301. Thus, this may be a contributing factor to the overall failure of Study 2302 to establish the superiority of terbinafine to griseofulvin as the most treatment effect is seen in the *T. tonsurans* species.

## SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Mat Soukup, Ph.D.

Date: May 9, 2007

Statistical Team Leader: Mohamed Alesh, Ph.D.

cc:

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# STATISTICAL REVIEW AND EVALUATION

## FILEABILITY REVIEW

**NDA/Serial Number:** 22-071/SN000  
**Drug Name:** Lamisil Mini-tablets(Terbinafin)  
**Indication(s):** Tinea Capitis  
**Applicant:** Novartis

**Dates:** Submitted: 09/08/2006  
PDUFA: 07/08/2007

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics III  
**Statistics Reviewer:** Mat Soukup, Ph.D.  
**Concurring Reviewer:** Mohamed Alish, Ph.D.

**Medical Division:** Division of Dermatology and Dental Products  
**Clinical Team:** Trish Brown, M.D. (DDDP)  
**Project Manager:** Kalyani Bhatt (DDDP)

### 1 Submission Information

**Submission Type:** The submission was sent in an eNDA/CTD hybrid format, utilizing the CTD folder structure while still retaining the eNDA folder navigation (i.e. a PDF table of contents as opposed to the CTD XML backbone).

**Data Comments:** The submission contains electronic data in SAS transport files located at \\Cdsesub1\n22071\N\_000\2006-09-08\crt\datasets. For the two pivotal Phase 3 studies the sponsor has submitted both raw data sets and derived data sets with thorough documentation on the derived data sets. In addition to the electronic data sets an annotated electronic CRF is submitted to define variable and data set location. At this time the data sets appear to be sufficient to assess the AE rates and efficacy of Lamisil Mini-tablets.

**Study Reports:** The two study reports for each Phase 3 trial were assessed. The statistical results section of the protocol appear to follow protocol defined statistical analysis procedures. Further, results provided in the study reports appear to match those of the reviewer analysis utilizing the derived data sets. Thus, the study reports appear to be adequate to assess the

safety and efficacy of Lamisil Mini-Tablets.

## 2 Result Summary

### 2.1 Study Design Details

- The two Phase 3 trials, Studies 2301 and 2302, were international studies with approximately 50% of enrollment occurring in the US.
- Efficacy objective is to demonstrate Lamisil Mini-tablets are superior to Griseofulvin.
- Dosing of pediatric subjects (3 - 12 years of age) is based upon subjects baseline weight.

### 2.2 Primary Endpoint Results

The protocol-defined primary endpoint is the proportion of subjects with complete clearance 10 weeks from taking the drug (4 weeks after last dose).

Complete Cure = Total Signs and Symptoms Score = 0 (Clinical cure) and mycological cure.

Table 1: Complete Cure Results (mITT-LOCF)

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

Source: Table 11-4 in each study report; results reproduced by reviewer.

As supportive and as pre-specified in the protocol efficacy results are also carried out on the PP and ITT populations which have consistent results with that of the primary analysis population reported above.

## 2.3 Primary Efficacy by Dermatophyte Species

Table 2: Complete Cure by Dermatophyte Species (mITT)

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

<sup>†</sup> Fisher's Exact Test.

Source: Reviewer's analysis.

## 3 Fileability Conclusions

From a statistical perspective this submission, or indications therein, is reviewable with no further input from the sponsor at this time.

## 4 74 Day Letter Comments

At this time the statistical review team does not have any request for further information from the sponsor.

Primary Statistical Reviewer: Mat Soukup, Ph.D.

Date: October 26, 2006

Statistical Team Leader: Mohamed Alesh, Ph.D.

cc:

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