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STATISTICAL REVIEW AND EVALUATION
NEW DRUG APPLICATION
CLINICAL STUDIES

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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 ~~_____~~. 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)¹ and $\delta = 11.2$ (0.1, 22.3)¹ 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

¹95% confidence interval with Yates continuity correction for δ =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 [†]	-	0.0013	-	0.9539

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

[†] 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