CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-385

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Medical Division: **Division of Dermatologic & Dental Drug Products (DDDDP)**
HFD-540
Biometrics Division: **Division of Biometrics III**
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Table of Contents

1 Executive Summary of Statistical Findings

1.1 Conclusions and Recommendations

The sponsor has conducted two phase 3 trials to demonstrate the efficacy and safety of sertaconazole nitrate cream 2% in the treatment of interdigital tinea pedis. In tinea pedis trials, the efficacy endpoint preferred by the Division is complete cure (negative KOH, negative culture, and all signs and symptoms of tinea pedis have completely resolved). The complete cure rate for sertaconazole was 13.1% in the first study and 27.2% in the second study. The corresponding vehicle complete cure rates were 3.3% and 4.9%. The treatment effect for sertaconazole for complete cure is statistically significant in each of the two pivotal studies with p-values ≤ 0.01 for the MITT population. Statistical significance was also demonstrated for effective treatment ($p \leq 0.001$) and mycological cure ($p < 0.0001$) for the MITT population in each study.

1.2 Overview of Clinical Program and Studies Reviewed

The efficacy and safety of sertaconazole nitrate cream 2% in the twice daily for 4 weeks treatment of interdigital tinea pedis were assessed in two phase 3 trials (SER-960602 and SER-960603). Study 602 enrolled 299 patients (151 sertaconazole/148 vehicle) including 191 MITT patients with positive baseline cultures (99 sertaconazole/92 vehicle). Study 603 enrolled 289 patients (146 sertaconazole/143 vehicle) including 206 MITT patients (103 sertaconazole/103 vehicle). All of the investigative centers for these studies were located in the United States.

1.3 Principal Findings

The statistically significant effect of sertaconazole was demonstrated in both the sponsor's and the reviewer's analyses. The primary statistical issues discussed in this review include:

- Handling of patient dropout
- Handling of subjects with inclusion criteria violations
- Handling of subjects with missing or unknown KOH
- Handling discrepancies between the physician's global evaluation and signs and symptoms scores

Analyses conducted by the sponsor and reviewer with various methods of handling the above issues consistently demonstrated a statistically significant effect for sertaconazole in terms of complete cure, effective treatment, and mycological cure. All sensitivity analyses were significant, except one extreme analysis that used the most conservative method for handling missing data and defining clinical cure that had a p-value of 0.059 for complete cure in Study 602. Thus, since complete cure rates were low (< 5%) on the vehicle arms of the two studies, sertaconazole was shown to be statistically superior to its vehicle with complete cure rates of 13% and 27% in two studies.

The majority of subjects (approximately 80%) were infected with *T. rubrum*, and the efficacy of sertaconazole for this pathogen is statistically supported. Because so few subjects presented with infections due to *T. mentagrophytes* and *E. floccosum*, and the studies were not powered to detect treatment differences among subgroups, it is difficult to determine the efficacy of sertaconazole in the latter two pathogens. However, the trend favored sertaconazole in both of these latter pathogens, and the observed success rates were similar to those observed in subjects with *T. rubrum*. In subgroups based on age, gender and race, the trend favored sertaconazole in nearly all cases, except for a few subgroups with very small sample sizes.

Adverse event rates for the two studies were similar for the sertaconazole and vehicle arms, with 17% of vehicle and 20% of sertaconazole patients experiencing adverse events. Eight treatment related adverse events were reported during the two double-blind studies. Of these 8 events, 4 were on the sertaconazole arm and 4 were on the vehicle arm. Most of the treatment related adverse events were related to the skin.

Thus, the sponsor has statistically demonstrated the efficacy of sertaconazole nitrate cream 2% applied twice daily for four weeks with regards to complete cure, effective treatment, and mycological cure in the treatment of interdigital tinea pedis.

2 Statistical Review and Evaluation of Evidence

2.1 Introduction and Background

The sponsor has submitted an application for sertaconazole nitrate cream 2% for the treatment of interdigital tinea pedis. Sertaconazole nitrate is a new molecular entity in the United States, although it has been previously marketed in Spain and several other countries. The clinical program for sertaconazole consisted of two phase 3 studies, SER-960602 and SER-960603 (referred to in this review as Studies 602 and 603). The sponsor also conducted a small phase 2 study (CL-3) in Spain with sertaconazole cream 1% and 2% in patients with dermatophytosis, including some patients with dermatophytosis of the foot. In addition, the sponsor conducted two European phase 3 trials of sertaconazole cream 2% versus miconazole (CL-4) or clotrimazole (CL-6), which enrolled patients with general dermatomycoses, including some patients with tinea pedis or dermatomycoses of the foot. These foreign studies will not be discussed further in this review, as the sponsor does not rely on these studies for any demonstration of efficacy. This review will focus on the two U. S. pivotal studies, which enrolled 299 and 289 subjects respectively, that support the efficacy and safety of sertaconazole in the treatment of interdigital tinea pedis.

2.2 Data Analyzed and Sources

The studies included in the sponsor's clinical program for interdigital tinea pedis are presented in Table 1. The European studies enrolled subjects with general dermato-mycoses, not just interdigital tinea pedis. Study CL-3 enrolled 20 patients, including 8 patients with dermatophytosis of the foot (Table 3, Vol. 42, pg. 8-17-57). Study CL-4 enrolled 692 patients, including 166 patients with tinea pedis (Table 1, Vol. 44, pg. 8-19-70). Study CL-6 enrolled 266 patients, including 136 with mycosis of the foot (Vol. 45, pg. 8-20-374). Only the two phase 3, vehicle controlled studies conducted in the U. S. are considered in this review, as the European studies are not used by the sponsor to establish efficacy.

Table 1 – Clinical Program for Sertaconazole Cream 2% (Interdigital Tinea Pedis)

Study	*Type of Study (Indication)*	*Number of Subjects*	*Location*	*Level of Review*
602	Phase 3 Efficacy & Safety (Interdigital Tinea Pedis)	Serta. 2% (151/99[a]) Vehicle (148/92[a])	U.S.	Full
603	Phase 3 Efficacy & Safety (Interdigital Tinea Pedis)	Serta. 2% (146/103[a]) Vehicle (143/103[a])	U.S.	Full
CL-3	Phase 2 (Dermatophytosis)	Serta. 2% (10) Serta. 1% (10)	Europe	None
CL-4	Phase 3 (Cutaneous Mycosis)	Serta. 2% (358) Miconazole (334)	Europe	None
CL-6	Phase 3 (Dermatomycoses)	Serta. 2% (133) Clotrimazole (134)	Europe	None

[a] (# Enrolled / # in MITT) (MITT = subjects with positive baseline cultures)

The sponsor submitted electronic data sets for the phase 3 efficacy and safety studies. Table 2 lists the data sets used in this review. In the initial submission of the NDA, the sponsor submitted the efficacy results for KOH (SX03.XPT), culture (CULTURE.XPT), physician's global evaluation (MDEVAL.XPT), and signs and symptoms scores (SX02.XPT) in separate data sets. These efficacy results are used to define the primary and secondary endpoints of complete cure, effective treatment, and mycological cure. However, no overall classification of subjects as complete cure, effectively treated, or mycological cure was provided in the submitted data sets. After the Agency requested a data set containing the overall classifications on November 19, 2001, the sponsor submitted an additional file including these classifications (MITT.XPT) on January 4, 2002.

Table 2 – SAS Transport Data Sets used in the Review

Data Set	*Contents*
DEMO1.XPT	Demographic variables
SX02.XPT	Signs & Symptoms Severity
SX03.XPT	KOH Results
CULTURE.XPT	Culture Results
MDEVAL.XPT	Physician's Global Results
MITT.XPT	Complete Cure & Effective Treatment Results

The data file MITT contains results from both Studies 602 and 603. For the other data sets, the sponsor provided one file for each study. The files DEMO1, SX02, SX03, CULTURE, and MDEVAL are archived in the Electronic Document Room at \\CDSESUB1\N21385\N_000\2001-09-28\sert02 and \sert03 for the respective studies. The file MITT is located in \\CDSESUB1\N21385\N_000\2002-01-04. Descriptions of the variables are provided in the files 'datadescription.pdf' in folders '2001-09-28' and '2002-01-04'.

2.3 Statistical Evaluation of Evidence on Efficacy and Safety

2.3.1 Study Design

Studies 602 and 603 are phase 3, randomized, multi-center, double-blind, parallel group, vehicle controlled efficacy and safety studies in subjects with interdigital tinea pedis. Both studies involved twice daily application of sertaconazole cream or vehicle cream for 4 weeks. The primary efficacy timepoint is Week 6, two weeks after the end of treatment. Eligible subjects were aged 12 and over, with clinical signs and symptoms of tinea pedis (including at least moderate erythema, moderate scaling, and mild pruritus) and positive KOH. Baseline cultures were evaluated at Day 14, and subjects with negative baseline cultures were withdrawn from the study and excluded from the efficacy population. Subjects were evaluated at baseline, Week 1, Week 2, Week 4, and Week 6.

Efficacy assessments included KOH and culture evaluations, signs and symptoms evaluations, and the Physician's Global Evaluation. Erythema, scaling, and pruritus were

evaluated at each visit on the scale 0 = absent (normal appearing skin), 1 = mild (barely abnormal), 2 = moderate (distinctly present abnormality), and 3 = marked (intense involvement or marked abnormality). The Physician's Global Evaluation consisted of the following categories:

> 1 = Clinical Cure (normal appearance of skin in all interdigital web spaces, signs and symptoms associated with interdigital tinea pedis have completely resolved)
> 2 = Effective Clinical Treatment (marked improvement over baseline in the signs and symptoms of interdigital tinea pedis, at most mild residual erythema and/or scaling in all treated interdigital web spaces remain without other signs of interdigital tinea pedis)
> 3 = Moderate Clinical Improvement (most baseline signs and symptoms of interdigital tinea pedis have shown a definite decrease)
> 4 = Mild Clinical Improvement or No Change (some baseline signs and symptoms of interdigital tinea pedis have decreased, significant evidence of disease remains)
> 5 = Worsening of Clinical Status (some baseline signs and symptoms of interdigital tinea pedis are more severe and/or new signs and symptoms are present)

The following nested efficacy categories were defined:

- Complete Cure – negative KOH, negative culture, and Physician's Global = 1
- Effective Treatment – negative KOH, negative culture, and Physician's Global = 1 or 2*
- Mycological Cure – negative KOH and negative culture

In the sponsor's protocol, the proportion of subjects achieving 'Effective Treatment' (referred to as Successful Treatment Outcomes in the protocol) at Week 6 is specified as the primary efficacy endpoint. The secondary efficacy endpoints were
(a) time to successful clinical and mycological treatment outcomes
(b) the percent of patients who demonstrate marked improvement in the signs and symptoms of tinea pedis with at most mild residual erythema and/or scaling in the most affected area of the involved foot (Effective Clinical Treatment)
(c) the percent of patients who demonstrate negative KOH preparations and fungal cultures (Mycological Cure)

At the End of Phase 2 Meeting held with the sponsor on June 23, 1997, the Agency recommended that the primary efficacy endpoint be defined as complete cure with effective treatment and mycological cure defined as secondary endpoints. As complete cure is the primary endpoint preferred by the Division, complete cure will be considered the primary endpoint in this review with effective treatment and mycological cure as secondary endpoints.

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* The sponsor's protocol defines 'Successful Treatment Outcome' as negative KOH, negative culture, and Physician's Global = 1 or 2 and 'Effective Treatment' as negative KOH, negative culture, and Physician's Global = 2.

2.3.2 Statistical Methods

In the protocol, the sponsor defined the primary analysis population (MITT) as all subjects randomized and dispensed treatment who return for at least one post-baseline treatment, have positive baseline culture, and have no major protocol violations. Last observation carried forward was planned for missing data. At the End of Phase 2 meeting held with the sponsor on June 23, 1997, the sponsor was advised that a "Modified Intent-to-Treat analysis, where only those patients with a positive baseline culture are included in the MITT population, should be performed on the data. The MITT includes all such patients dispensed study treatment" (pg. 4, End of Phase 2 Meeting Minutes). The sponsor was again advised of this definition of the MITT at the Pre-NDA meeting held on October 18, 2000. Subsequent to this meeting, the sponsor re-analyzed the data defining the MITT population as all subjects randomized and dispensed treatment who qualified for the study. 'Qualified' subjects were subjects who had positive baseline cultures and met certain inclusion criteria. Five subjects in Studies 602 and 603 were randomized into the study even though they did not meet all inclusion criteria, and these subjects are excluded from the sponsor's MITT population. These 5 subjects will be discussed further in Section 2.3.5.

The sponsor's per protocol population was the same as the protocol-defined MITT (randomized, dispensed treatment, returned for a post-baseline evaluation, and had no major protocol violations) except that it only included subject visits falling within a ± 3 day window. Various methods to impute missing data were used in the per protocol analyses, including last observation carried forward (LOCF), missing values treated as failures, and observed cases only.

For the analysis of success rates, the sponsor proposed either chi-square tests or Fisher's exact test in the protocol. This proposal was updated in the Statistical Analysis Plan (dated February 3, 1998, finalized while the studies were ongoing) to specify that the Cochran-Mantel-Haenszel (CMH) test stratified by investigator would be used. Centers with fewer than 7 enrolled patients would be pooled for the analysis. The CMH analysis proposal from the Statistical Analysis Plan was followed in the study report.

One additional difference observed between the study protocol and the study reports was the block size used in randomization. The protocol stated that blocks of size 4 would be used, while the study report states that blocks of size 6 were used. It is unclear why this change was made, but the fact that the block size used differed from the proposed block size does not appear to be a cause for concern, as the randomization was carried out prior to the study.

2.3.3 Patient Disposition and Demographics

Study 602 enrolled 299 subjects, 148 on vehicle and 151 on sertaconazole at 20 centers. Of the enrolled subjects, 56 vehicle (38%) and 52 sertaconazole patients (34%) had negative baseline cultures and were discontinued from the study, although some patients with negative baseline cultures withdrew for other reasons before learning their culture status. Of the remaining 92 vehicle and 99 sertaconazole patients, 79 vehicle (86%) and 86 sertaconazole (87%) patients completed the study. Table 17 in the appendix lists the disposition of enrolled subjects. No subjects in Study 602 discontinued because of an adverse event. The most common reasons for discontinuation were lost to follow up and voluntary withdrawal.

Study 603 enrolled 289 subjects, 143 on vehicle and 146 on sertaconazole at 15 centers. Of the enrolled subjects, 40 vehicle (28%) and 43 sertaconazole patients (29%) had negative baseline cultures and were discontinued from the study, although some patients with negative baseline cultures withdrew for other reasons before learning their culture status. Of the remaining 103 vehicle and 103 sertaconazole patients, 94 vehicle (91%) and 90 sertaconazole patients (87%) completed the study. Table 17 in the appendix lists the disposition of enrolled subjects. One subject (vehicle) withdrew because of an adverse event before being discontinued due to a negative baseline culture. The most common reasons for discontinuation were protocol violations and lost to follow up.

Table 18 and Table 19 in the appendix present the subjects' baseline and demographic data for the two studies. Approximately three-fourths of the subjects were male, over 60% were Caucasian, 16 - 24% were black, and 9 – 20% were Hispanic. There are no obvious or statistically significant demographic imbalances between the treatment arms. The demographics for the MITT population are similar to the demographics for all randomized subjects, and there does not appear to be any tendencies for subjects with negative baseline cultures to come from any particular demographic subgroups.

2.3.4 Sponsor's Primary Efficacy Results

The sponsor provided two sets of efficacy results: results based on the protocol and corresponding statistical analysis plan, and the re-analysis conducted by the sponsor following discussion at the pre-NDA meeting of October 18, 2000.

Sponsor's Protocol Results

The sponsor's protocol-defined primary efficacy endpoint was Effective Treatment (referred to in the sponsor's submission as Successful Treatment Outcome) defined as mycological cure plus either effective clinical treatment or clinical cure. The MITT population was defined as all subjects randomized, dispensed treatment with at least one post-baseline assessment, and no major protocol violations. The major protocol violations that were used to exclude subjects from the analysis were no post-baseline assessments (Subjects 06.101, 09.162, 12.253, 12.259, and 12.262 in 602, Subjects 34.228, 34.229, 34.230, and 37.301 in 603), and insufficient baseline signs/symptoms (Subjects 09.163 and 11.033 in 602, Subjects 35.045, 35.046, and 35.047 in 603). LOCF was used for missing data imputation. Table 3 displays the results of this analysis.

Table 3 – Sponsor's Protocol Efficacy Results (Protocol MITT[a], LOCF)

	Study 602			Study 603		
	Vehicle	Serta.	p-value[b]	Vehicle	Serta.	p-value[b]
Effective Treatment	12/88 (13.6%)	35/96 (36.5%)	0.0006	16/100 (16.0%)	56/99 (56.6%)	<0.0001

[a] Randomized, dispensed treatment, positive baseline culture, post-baseline assessment, and no major protocol violations.
[b] p-values based on the CMH test stratified on center.
Source: Sponsor's Table EFF.1.2, Vol. 27, pg. 8-2-317, and Vol. 34, pg. 8-9-302.

In Study 602, 37% of sertaconazole and 14% of vehicle patients achieved effective treatment. In Study 603, 57% of sertaconazole and 16% of vehicle patients achieved effective treatment. Statistical significance was attained for this endpoint in each of the two studies ($p \leq 0.0006$).

According to the Statistical Analysis Plan, centers which enrolled fewer than 7 subjects were pooled for the CMH analysis. The Breslow-Day test was used to test for treatment by center interaction, and interactions were tested at $\alpha = 0.10$. The p-values for the Breslow-Day test were $p = 0.3190$ in Study 602, and $p=0.2718$ in Study 603, indicating that significant treatment by center interactions were not detected in these studies. Pooling of centers is discussed further in the reviewer's analysis in Section 2.3.12

Sponsor's Post-Hoc Results

Several recommendations regarding protocol design were made by the Agency at the End of Phase 2 meeting, and were re-iterated to the sponsor at the pre-NDA meeting. These comments included (1) complete cure should be considered the primary endpoint, with effective treatment and mycological cure secondary, (2) missing values should be treated as failures, and (3) all subjects randomized and dispensed medication with positive baseline cultures should be included in the MITT population. Following the pre-NDA meeting, the sponsor re-analyzed the data to comply with the above recommendations. The sponsor redefined the MITT population as all subjects randomized and dispensed medication with positive baseline cultures who qualified for the study. Subjects who had been excluded in the sponsor's original analysis due to no post-baseline assessments were now included in the MITT. Subjects who were randomized even though they had insufficient baseline symptoms and were later discontinued, however, are not included in the sponsor's MITT population. Table 4 lists the efficacy results from the sponsor's re-analysis. In Study 602, 13% of sertaconazole and 3% of vehicle patients achieved complete cure. In Study 603, 28% of sertaconazole and 5% of vehicle patients achieved complete cure. Statistical significance was attained for complete cure, effective treatment, and mycological cure in each of the two studies ($p \leq 0.0096$).

Table 4– Sponsor's Post-Hoc Efficacy Results (Post-Hoc MITT[a], MVTF[b])

	Study 602			Study 603		
	Vehicle	Serta.	p-value[c]	Vehicle	Serta.	p-value[c]
Complete Cure	3/92 (3.3%)	13/97 (13.4%)	0.0096	5/102 (4.9%)	28/101 (27.7%)	<0.0001
Effective Treatment	12/92 (13.0%)	34/97 (35.1%)	0.0007	16/102 (15.7%)	54/101 (53.5%)	<0.0001
Mycological Cure	18/92 (19.6%)	48/97 (49.5%)	<0.0001	20/102 (19.6%)	71/101 (70.3%)	<0.0001

[a] Randomized, dispensed treatment, positive baseline culture, and qualified for the study.
[b] Missing Values Treated as Failures
[c] p-values based on the CMH test stratified on center.
Source: Sponsor's Table 2, Vol. 50, pg. 8-25-22.

2.3.5 MITT Population

When the sponsor redefined the MITT population following the pre-NDA meeting, the sponsor re-entered 5 subjects in Study 602 and 4 subjects in Study 603 who had not returned for any follow-up visits. These subjects were all classified as failures, as they had no follow-up data. There were, however, some patients who had failed to meet all inclusion/exclusion criteria but were still randomized into the study and dispensed treatment. These subjects were not included in the sponsor's MITT population. The excluded patients (2 from Study 602 and 3 from Study 603) and their reason for exclusion are listed in Table 5.

Table 5 – Randomized Subjects Excluded from Sponsor's MITT

Subject	*Study*	*Treatment*	*Number of Visits*	*Reason for Exclusion*
11.033	602	Serta.	6	Mild Erythema at Baseline
09.163	602	Serta.	1	Delayed Laboratory Exclusion
35.045	603	Vehicle	1	Mild Erythema at Baseline
35.046	603	Serta.	1	Mild Erythema at Baseline
35.047	603	Serta.	1	Mild Erythema at Baseline

Source: Sponsor's submission, Vol.27, pg. 8-2-152 and Vol. 34, pg. 8-9-147.

Four of the five subjects were found to have had mild erythema at baseline. For three of these subjects, the protocol violation was discovered before their second visit, and these subjects were discontinued from the study. The protocol violation for the other mild erythema subject was only discovered at the conclusion of the study after this subject had completed all visits. Subject 11.033 was classified as 'Effective Treatment' at the conclusion of the study (negative KOH, negative culture, at most mild residual erythema and/or scaling).

Subject 09.163 had elevated liver function tests at baseline. Four other subjects in Study 602, and four subjects in Study 603 also had positive baseline cultures and elevated baseline liver function tests but were, however, included in the MITT population. Since other subjects were included in the MITT population, even though they had elevated liver

function tests, it is unclear why the sponsor excluded 09.163 from the MITT. Other subjects with inclusion criteria violations, such as applying topical anti-fungal therapy to feet within 30 days of study entry, were included in the sponsor's MITT population. The sponsor did not state in the protocol which protocol violations would be used to exclude subjects from MITT population. Since the Agency stated at the End of Phase 2 meeting that the MITT population should be defined as all subjects randomized and dispensed study medication with a positive baseline culture, and the sponsor did not specify in the protocol what major protocol violations could exclude a subject from the MITT, this reviewer feels that these 5 subjects should be included in the MITT population, and these subjects are included in the reviewer's MITT analyses.

2.3.6 Subjects with Missing Week 6 KOH

In Study 602, 9 subjects had 'unknown' KOH evaluations at Week 6, even though the Week 6 culture and physician's global results were recorded. The definition of effective treatment is negative KOH, negative culture, and physician's global ≤ 2 (where 1 = clinical cure and 2 = effective clinical treatment). To be classified as a complete cure, a subject must have negative KOH and culture and physician's global = 1. Of the 9 subjects with unknown Week 6 KOH results, 5 subjects (06.104, 06.106, 11.332, 13.245, and 16.223) could be classified as failures based on the culture or global results, with either missing or positive Week 6 cultures, or a physician's global results of 4 = 'mild clinical improvement or no change'. The remaining 4 subjects in Study 602 with 'unknown' Week 6 KOH results were classified by the sponsor as 'effectively treated' and are listed in Table 6. None of these subjects were classified by the sponsor as complete cures, however. According to the study report (Vol. 27, pg. 8-2-154), the sponsor claims that Subject 01.203 was classified as a 'failure' in the physician's global analysis, due to a global score of 3, but was classified as a success in the signs and symptoms analysis (based on erythema and scaling scores). However, in the data set provided by the sponsor (MITT.XPT), which was based on the physician's global score, Subject 01.203 is actually classified as 'effectively treated' in the physician's global analysis, contrary to the text of the study report.

Table 6– Subjects Classified as 'Effective Treatment' with Missing or 'Unknown' Week 6 KOH.

Subject	*Study*	*Trt.*	*KOH*	*Culture*	*Phys. Global*[a]
01.203	602	Vehicle	Unknown	Neg.	3
11.331	602	Serta.	Unknown	Neg.	1
13.020	602	Serta.	Unknown	Neg.	2
17.279	602	Serta.	Unknown	Neg.	2
34.174	603	Serta.	Missing	Neg.	1
36.146	603	Serta.	Unknown	Neg.	1

[a] 1 = 'Clinical Cure', 2 = 'Effective Clinical Treatment', 3 = 'Moderate Clinical Improvement'
Source: Data files CULTURE.XPT, SXO3.XPT, MDEVAL.XPT, and MITT.XPT

In Study 603, 3 subjects had 'unknown' or missing KOH evaluations at Week 6 with available culture or global evaluation results. Of these 3 subjects, one subject (25.242)

was classified as 3 = 'moderate clinical improvement' at Week 6 and was considered a failure. The remaining 2 subjects had physician's global scores of 1 and were classified by the sponsor as 'Effective Treatment'. Table 6 lists the Week 6 efficacy results for the 2 patients who were classified as 'Effective Treatment' while having unknown or missing Week 6 KOH.

As the sponsor noted in the study report text (which contradicts the data set used in their analysis), Subject 01.203 should be considered a failure due to a physician's global score of 3. For the remaining subjects with unknown KOH, the sponsor apparently did not distinguish between subjects with physician's global scores of 1 and 2, as all were classified as effectively treated, rather than classifying some as effectively treated and some as completely cured. This may be due to the fact that complete cure was not analyzed as a separate efficacy endpoint in the sponsor's original analysis. The fact that some subjects were classified as effectively treated, even though the Week 6 KOH was 'unknown' was mentioned in the study report for Study 602 (but not for Study 603). However the sponsor provides no rationale for assuming a favorable KOH result for these subjects.

The protocol specified that a negative KOH at Week 6 was a requirement for success, and the sponsor has not provided a compelling reason to ignore this requirement for the above subjects. There were many other subjects with complete data whose only reason for not being classified as effectively treated was because of positive KOH (18 subjects [15 sertaconazole/3 vehicle] in Study 602 and 19 subjects [10 sertaconazole/9 vehicle] in Study 603 had positive KOH, negative cultures, and physician's global scores ≤ 2). Therefore it does not seem reasonable to assume that the 5 subjects with 'unknown' KOH, negative cultures, and physician's global ≤ 2 should all be classified as effective treatment, because there were many other subjects who were failures only because of their KOH. As all of the disputed subjects who met the culture and physician's global requirements for success were on the sertaconazole arm, treating them as failures would be the most conservative approach. Thus, subjects with 'unknown' KOH were all treated as failures in the reviewer analyses.

2.3.7 Reviewer MITT Analysis

In the analysis set used by this reviewer, the MITT population is defined as all subjects randomized and dispensed study medication with positive baseline cultures. This definition includes subjects enrolled with mild erythema at baseline and subjects with elevated liver function tests. This reviewer feels that this definition is most consistent with the advice provided to the sponsor at the End of Phase 2 meeting. All but one of the subjects who had mild erythema at baseline were discontinued from the study, and thus are counted as failures. However, subject 11.033 completed the study and was classified as 'Effective Treatment'. This subject is included in the MITT analysis as a success for 'Effective Treatment' and 'Mycological Cure' in the reviewer's analyses. In addition, this reviewer feels that the sponsor has not provided sufficient rationale for classifying certain subjects with missing or 'unknown' KOH results at Week 6 as 'effectively treated', and therefore has classified these subjects as failures in the reviewer analyses.

Table 7 displays the results for complete cure, effective treatment, and mycological cure using the reviewer's MITT data set. The results are similar to the results from the sponsor's MITT data set with comparable levels of significance. The treatment effect for sertaconazole is statistically significant for complete cure, effective treatment, and mycological cure in each study ($p \leq 0.0101$).

Table 7 – Efficacy Results (Reviewer MITT[a], MVTF[b])

	Study 602			Study 603		
	Vehicle	Serta.	p-value[c]	Vehicle	Serta.	p-value[c]
Complete Cure	3/92 (3.3%)	13/99 (13.1%)	0.0101	5/103 (4.9%)	28/103 (27.2%)	<0.0001
Effective Treatment	11/92 (12.0%)	32/99 (32.3%)	0.0010	16/103 (15.5%)	52/103 (50.5%)	<0.0001
Mycological Cure	18/92 (19.6%)	49/99 (49.5%)	<0.0001	20/103 (19.4%)	71/103 (68.9%)	<0.0001

[a] Randomized, dispensed treatment, and positive baseline culture.
[b] Missing Values Treated as Failures
[c] p-values based on the CMH test stratified on center.
Source: Reviewer Analysis.

2.3.8 Per Protocol Analyses

The sponsor's definition of the per protocol population is very similar to their original definition of the MITT population (randomized, dispensed medication, positive baseline culture, at least one post-baseline assessment, and no major protocol violations), except that it also required subject visits to fall within ± 3 days of the scheduled date. The sponsor included all of the subjects with unknown or missing Week 6 KOH in the per protocol population, classified as they were in the MITT population. (See Section 2.3.6 for a discussion of these subjects.) In the reviewer's per protocol analysis results, subjects with unknown or missing Week 6 KOH were excluded from the per protocol population for not having complete data. Thus the reviewer's per protocol population has 9 fewer subjects in Study 602 and 3 fewer subjects in Study 603 than the sponsor's analysis did. Otherwise the results of the sponsor's and reviewer's analyses are similar. The results of the reviewer's per protocol analysis are presented in Table 8. The per protocol analysis supports the MITT analysis in demonstrating the statistical superiority of sertaconazole for complete cure, effective treatment, and mycological cure.

Table 8 – Per Protocol Efficacy Results (Reviewer PP[a], Observed Cases)

	Study 602			Study 603		
	Vehicle	Serta.	p-value[b]	Vehicle	Serta.	p-value[b]
Complete Cure	2/67 (3.0%)	12/72 (16.7%)	0.0062	5/88 (5.7%)	27/92 (29.4%)	<0.0001
Effective Treatment	10/67 (14.9%)	27/72 (37.5%)	0.0057	16/88 (18.2%)	51/92 (55.4%)	<0.0001
Mycological Cure	15/67 (22.4%)	42/72 (58.3%)	<0.0001	19/88 (21.6%)	70/92 (76.1%)	<0.0001

[a] Randomized, dispensed treatment, positive baseline culture, Week 6 assessment with known KOH result, no major protocol violations, and visit within ± 3 days.
[b] p-values based on the CMH test stratified on center.
Source: Reviewer Analysis.

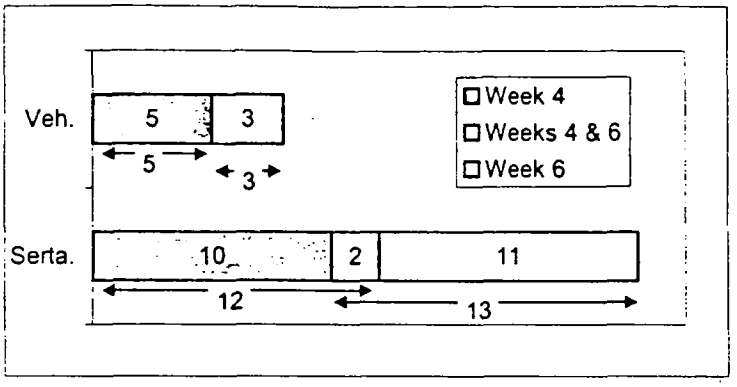
2.3.9 Handling of Patient Dropout

Since the Agency's recommendation at the End of Phase 2 meeting was to treat subjects with missing values as failures (MVTF), rather than with LOCF, MVTF is the method used in reviewer analyses. However, since the sponsor's protocol specified LOCF as the primary method for imputation, it is important to explore the effect of each method of handling missing data. The number of subjects affected by the method of imputation is small, as only 3 subjects across both studies are classified as effectively treated or completely cured under LOCF, but not MVTF. All 3 subjects were sertaconazole patients (1 from study 602 and 2 from Study 603). The subject from Study 602 was classified as a complete cure at Week 3 and did not return for the final two visits. Of the two subjects from Study 603, one was classified as effectively treated at Week 4 and the other was classified as completely cured at Week 4, but neither subject returned for the Week 6 visit. Since all of the affected subjects were on the sertaconazole arm, the MVTF analysis is slightly more conservative than the LOCF analysis. The p-value for complete cure in Study 602 using LOCF is $p = 0.0061$ (compared to $p = 0.0101$ for MVTF). In Study 603 the p-values for complete cure using LOCF and MVTF are both < 0.0001. The conclusions remain unchanged under each method of imputation, as all p-values are significant for the 3 levels of success in both studies for LOCF and MVTF.

Another reason for considering MVTF rather than LOCF, is that a noticeable proportion of subjects are classified as successes at Week 4, but failures at Week 6. Figure 1 and Figure 2 display the number of subjects classified as complete cures at Weeks 4 and 6. In Study 602, 10 sertaconazole patients were classified as complete cures at Week 4, but not at Week 6. Only 2 sertaconazole subjects were classified as complete cures at both Week 4 and Week 6. Similarly, in Study 603, 7 sertaconazole patients were classified as complete cures at Week 4, but not at Week 6, while 13 sertaconazole subjects were classified as complete cures at both Week 4 and Week 6. Thus, in Study 602 only 2 out of 12 (17%) sertaconazole patients maintained complete cure status from Week 4 to Week 6, although the rate was higher in Study 603 with 13 out of 20 (65%) sertaconazole patients maintaining complete cure status from Week 4 to Week 6. With a substantial number of relapses such as this, it could be misleading to use LOCF and carry forward a

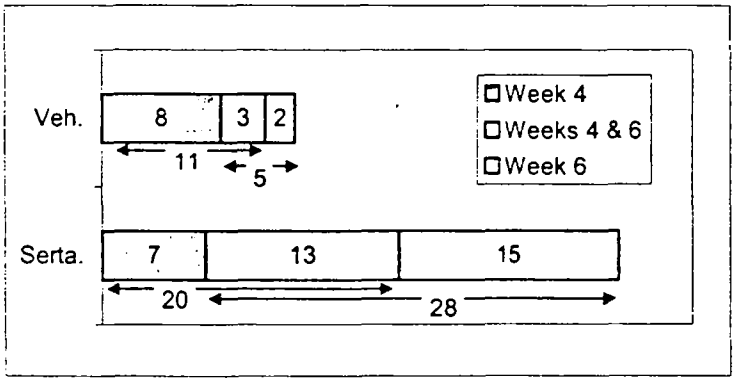
Week 4 (or earlier) result to Week 6. The two subjects (one from each study) who were classified as complete cures at earlier visits and did not return for the Week 6 visit and were classified as successes under LOCF but not MVTF were both on the sertaconazole arm. Thus, using MVTF would be more conservative than LOCF.

Figure 1 – Number of Subjects with Complete Cure at Weeks 4 and 6 (Study 602)



Reviewer Graphic.

Figure 2 – Number of Subjects with Complete Cure at Weeks 4 and 6 (Study 603)

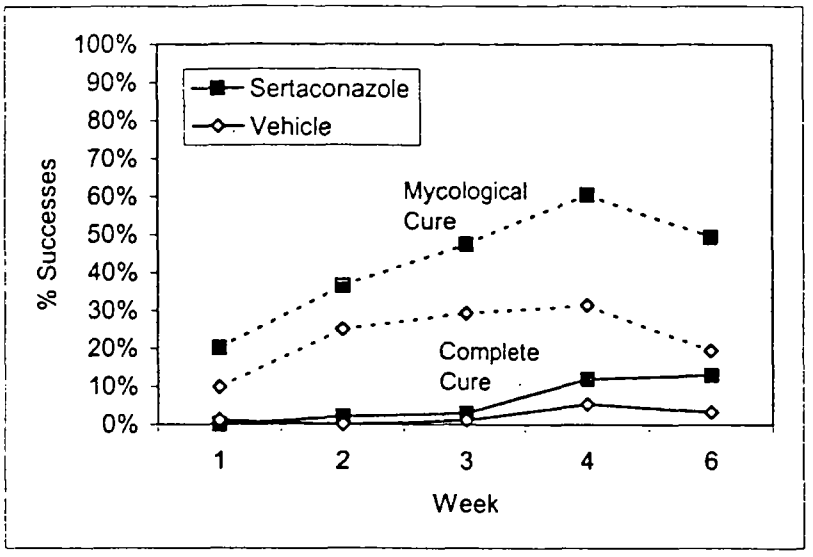


Reviewer Graphic.

2.3.10 Efficacy Results By Week

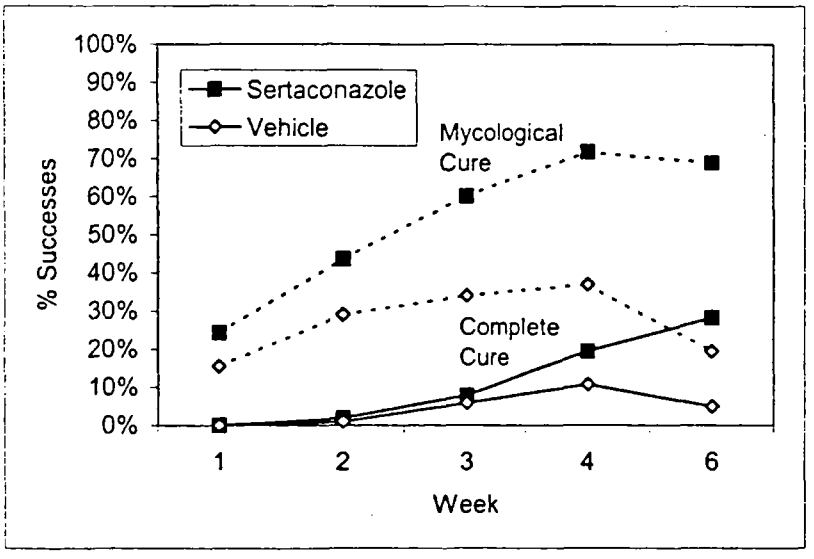
Efficacy results for complete cure and mycological cure by week are presented in Figure 3 and Figure 4. Mycological cure rates were higher at Week 4 than Week 6 for both sertaconazole and vehicle in both studies. Complete cure rates on the sertaconazole arm reached their highest points at Week 6 in each study. The treatment difference between sertaconazole and vehicle was largest for both endpoints at the primary time point, Week 6.

Figure 3– Complete Cure and Mycological Cure Rates by Week in Study 602



Reviewer Graphic.

Figure 4- Complete Cure and Mycological Cure Rates by Week in Study 603



Reviewer Graphic.

2.3.11 Physician's Global versus Signs and Symptoms Scores

In the protocol, Effective Clinical Treatment and Clinical Cure were defined using the Physician's Global Evaluation. Effective Clinical Treatment was defined as 'at most mild residual erythema and/or scaling ... without other signs of interdigital tinea pedis'. Clinical cure was defined as 'signs and symptoms of interdigital tinea pedis have completely resolved'. During the clinical evaluations, erythema, scaling, and pruritus were also specifically evaluated on a scale of 0 = none, 1 = mild, 2 = moderate, and 3 =

severe. Effective clinical treatment with regards to signs and symptoms corresponds to pruritus = 0, and erythema and scaling ≤ 1. In the sponsor's original report, they used two methods for defining effective treatment based on signs and symptoms: one where pruritus had to equal 0, and one where the pruritus score was ignored (and thus could equal any value). In either case, erythema and scaling had to be ≤ 1. Only the case where pruritus = 0 and erythema and scaling are ≤ 1 is considered here. For a clinical cure based on signs and symptoms, the sponsor considered the subjects for whom all 3 signs and symptoms equaled 0. It is expected that the physician's global score should correspond to the signs and symptoms scores, though some discrepancies may be present.

The number of subjects classified as a success by the physician's global and signs and symptom scores are compared in Table 9. Slightly more subjects were classified as successes using the physician's global assessment than using the signs and symptoms scores. Across both studies, 4 subjects (3 sertaconazole and 1 vehicle) were classified as complete cure using the physician's global, but not the individual signs and symptoms, while 1 subject (sertaconazole) was classified as a complete cure using the signs and symptoms, but not the physician's global. Similarly, 15 subjects (9 sertaconazole and 6 vehicle) were classified as effective treatment using the physician's global, but not the individual signs and symptoms, while 10 subjects (8 sertaconazole and 2 vehicle) were classified as effectively treated using the signs and symptoms, but not the physician's global.

Table 9 – Number of Subjects Classified as Success by either Physician's Global (PG) or Signs and Symptoms (SS) Scores (Reviewer MITT, MVTF)

		Vehicle			*Sertaconazole*		
	Study	PG only	PG & SS	SS only	PG only	PG & SS	SS only
Complete Cure	602	0	3	0	3	10	1
	603	1	4	0	0	28	0
Effective Treatment	602	3	8	0	4	28	6
	603	3	13	2	5	47	2

PG only – # of subjects classified as a success on physician's global, and failure on signs and symptoms
PG & SS – # of subjects classified as success on both methods
SS only – # of subjects classified as a success on signs and symptoms, and failure on physician's global
Total number of successes on physician's global is ('PG only' + 'PG & SS')
Total number of successes on signs and symptoms is ('SS only' + 'PG & SS')
Source: Reviewer analysis.

Complete cure and effective treatment still demonstrate statistical significance when success is defined using the signs and symptoms scores, rather than the physician's global. Complete cure has a p-value of 0.0378 in Study 602 and a p-value <0.0001 in Study 603. Effective treatment has p-values < 0.0001 in both studies. An even more extreme criteria would be to require both the physician's global and signs and symptoms scores to agree before classifying a subject as a success. In this situation, complete cure has a p-value of 0.0591 in Study 602 and a p-value < 0.0001 in Study 603. For the case where both methods must agree, effective treatment has a p-value of 0.0005 in Study 602 and a p-value < 0.0001 in Study 603. (Source: Reviewer analysis, Reviewer MITT,

MVTF, CMH test). By using the most stringent definition of success, which has 1 less complete cure on the sertaconazole arm than the signs and symptoms analysis in Study 602, the p-value for complete cure in Study 602 does cross the 0.05 significance threshold. Thus, the analysis which uses the most conservative method of data imputation (MVTF), and the most stringent criteria for concluding clinical cure (physician's global and signs and symptoms must agree) does not quite meet the threshold for statistical significance in one of studies, although all other less extreme analyses do demonstrate statistical significance for complete cure in both studies. Since the protocol specified the physician's global assessment as the primary method of assessing clinical effectiveness, that method is considered primary in this review.

2.3.12 Efficacy Results by Center

The statistical analysis plan stated that centers that enrolled 7 or fewer patients would be pooled for analyses. This decision rule was based on the number of enrolled subjects, not the number of subjects with positive baseline cultures (MITT population). Since approximately 36% of enrolled subjects in Study 602 and 29% of enrolled subjects in Study 603 were excluded due to negative baseline cultures, some centers which enrolled more than 7 patients ended up with only a small number of patients in the MITT population, and a few centers had no MITT patients at all. Table 20 and Table 21 in the appendix display the enrollment numbers by center. In Study 602, 6 sites with a total of 10 MITT subjects were pooled. In Study 603, 6 sites with a total of 14 MITT subjects were pooled. Many of the centers in Study 603 that were not included in the pooling process were sufficiently large, and only 1 center had fewer than 12 MITT subjects after the pooling algorithm was applied (Center 35 with 5 subjects). However, in Study 602, many small centers still remained after pooling, as 7 centers still had fewer than 12 MITT subjects.

To see if the pooling algorithm had any effect on the conclusions, a sensitivity analysis was conducted. For the sensitivity analysis, the sponsor's pooling algorithm was applied to the number of MITT subjects, rather than the number of enrolled subjects. That is, centers with no more than 7 MITT subjects were pooled. The results of this analysis are nearly identical to the original results. For complete cure, the p-value was 0.0133 (vs. 0.0101 in the original analysis) in Study 602, and the p-values were <0.0001 for both the original and sensitivity analyses in Study 603. The results for effective treatment are similar. Therefore, the fact that pooling was based on enrolled subjects rather than MITT subjects appears to have no effect on the results or conclusions.

Complete cure rates by center are presented in Table 10. The Breslow-Day test for treatment by center interaction was not significant at $\alpha = 0.10$ in either study under the sponsor's pooling algorithm. Since one of the assumptions of the Breslow-Day test is that there are a 'large' number of subjects in each stratum and many of the centers are still quite small even after applying the sponsor's pooling algorithm, the test was also conducted under the algorithm based on number of MITT patients rather than enrolled patients. The p-values under both pooling algorithms are also presented in Table 10. The results under both pooling algorithms are quite similar, with Breslow-Day p-values of

about 0.4 in Study 602 and 0.2 in Study 603 under either algorithm. The results for effective treatment and mycological cure are similar. Thus the pooling algorithm has little effect on the results of the test for treatment by center interaction.

Although the Breslow-Day tests indicate that significant treatment by center interactions have not been detected, visual inspection of the data shows that many of the complete cures in Study 602 came from one center. Center 03 was responsible for 5 of the 13 successes on the sertaconazole arm. These 5 successes represent 38% of the complete cures observed on that arm, while the 14 sertaconazole patients at that site represent only 14% of sertaconazole subjects in that study.

Table 10 – Complete Cure Rates by Center (MVTF, Reviewer MITT)

Study 602					Study 603				
Site	*Vehicle*		*Serta.*		*Site*	*Vehicle*		*Serta.*	
01	0/6		0/8		25	0/6		2/6	
03	0/12		5/14		27	0/9		2/10	
05	0/1		1/3		29	0/19		7/17	
06	0/6		1/5		32	0/8		3/8	
09	0/8		0/9		34	2/13		3/13	
11	1/14		1/17		35	0/3		0/2	
12	0/5		1/3		36	1/10		4/13	
13	1/8		1/7		37	0/19		2/19	
14	0/10		0/9		38	2/8		3/9	
15	0/1		0/3		26*	0/1		0/0	
16	0/7		0/7		28*	0/2		1/2	
17	0/2		0/4		30*	0/0	0/8	0/0	3/6
18	0/4		1/2		31*	0/2		0/1	
21	0/4		1/2		33*	0/2		2/3	
04*	1/2		0/2		39*	0/1		0/0	
07*	0/0		0/0						
10*	0/2	1/4	0/3	1/6					
08*	0/0		0/0						
19*	0/0		0/0						
20*	0/0		1/1						
Total	3/92		13/99		Total	5/103		28/103	
Breslow-Day p-value: 0.4061 (original pooling[a])					Breslow-Day p-value: 0.2073 (original pooling[a])				
Breslow-Day p-value: 0.4402 (sensitivity pooling[a])					Breslow-Day p-value: 0.2153 (sensitivity pooling[a])				

* Pooled centers per statistical analysis plan.
Complete Cure Rate = # of Complete Cures/# in MITT
[a] original pooling = ≤ 7 enrolled subjects, sensitivity pooling = ≤ 7 MITT subjects
Source: Reviewer Analysis

To see to what extent the significant overall results for Study 602 are dependent on the results from Center 03, two sensitivity analyses were conducted. In the first analysis,

Center 03 was deleted. The p-value in this analysis for complete cure is p=0.1092. This result is not significant, although by deleting the center, the overall sample size has been decreased, thus reducing power. In the second sensitivity analysis, the overall sample size of the study is maintained and the number of complete cures at Center 03 on the sertaconazole arm is modified to be proportional to the rate observed at the other centers. The complete cure rate on the sertaconazole arm for all centers except Center 03 is 9.4%. For the 14 sertaconazole subjects at Center 03, this rate would correspond to 1.3 complete cures. Thus we will consider the case where Center 03 is assumed to have either 1 or 2 complete cures on the sertaconazole arm. If 1 complete cure is imputed for Center 03, the p-value would be p=0.0708. If 2 complete cures are imputed for Center 03, the p-value would be p=0.0451. Thus, in this sensitivity analysis, significance depends on whether the average from the other centers is rounded up or down. With success rates in the range of 3% – 15% and the sample sizes considered here, significance can be affected by the classification of only 1 or 2 subjects. The overall conclusions of Study 602 regarding complete cure depend on least some contribution to efficacy from Center 03. At least 2 of the 5 observed complete cures on sertaconazole at this center are needed to maintain the overall significance for the study.

Although the complete cure analysis depends on the results from Center 03, effective treatment maintains a high level of significance in all sensitivity analyses regarding Center 03, and does not depend on the specific results obtained at that center. It should also be noted that the results from Center 03, which stand out in Study 602, however, are not that unusual when compared to centers of comparable size in Study 603. Although it is unclear why one site in Study 602 demonstrated a higher degree of efficacy than the others in that study, the fact that many of the other centers in Study 602 were small and thus more highly variable may have played a role.

2.3.13 Analysis by Baseline Pathogen

Four dermatophytes were isolated in the baseline cultures: *T. rubrum, T. mentagrophytes, E. floccosum*, and *T. kanei*[†]. *T. rubrum* was the most common baseline pathogen, isolated in 81% of baseline cultures in Study 602 and 78% of baseline cultures in Study 603. *T. mentagrophytes* was the next most common pathogen with 9% of subjects in Study 602 and 18% of subjects in Study 603. *E. floccosum* was identified in 9% of subjects in Study 602 and 4% of subjects in Study 603. One subject in Study 602 was identified as having *T. kanei*. Table 11 and Table 12 present the success rates for complete cure, effective treatment, and mycological cure broken down by baseline pathogen. The sponsor included analyses by baseline pathogen in their subgroup analysis section, along with other subgroup analyses by age, race, and gender. The study was not designed to detect statistical significance within subgroups. However, the sponsor has proposed to list the three pathogens in the label, so the subgroup analysis results are discussed here.

[†] Subject 09.236 was identified as "*Trichophyton* sp., other" at baseline, and *T. kanei* at Weeks 2 and 4. (Source: data file sert02\CULTURE.XPT)

Table 11 – Efficacy Results by Baseline Pathogen in Study 602 (MITT, MVTF)

	Vehicle	Sertaconazole	p-value[a]
T. rubrum			
Complete Cure	3/77 (3.9%)	10/78 (12.8%)	0.0788
Effective Trt.	9/77 (11.7%)	24/78 (30.81%)	0.0055
Mycol. Cure	15/77 (19.5%)	38/78 (48.7%)	0.0002
T. mentag.			
Complete Cure	0/7 (0.0%)	2/10 (20.0%)	0.4853
Effective Trt.	1/7 (14.3%)	5/10 (50.0%)	0.3043
Mycol. Cure	2/7 (28.6%)	5/10 (50.0%)	0.6221
E. floccosum			
Complete Cure	0/8 (0.0%)	1/10 (10.0%)	>0.999
Effective Trt.	1/8 (12.5%)	3/10 (30.0%)	0.5882
Mycol. Cure	1/8 (12.5%)	6/10 (60.0%)	0.0656

[a] p-values based on Fisher's Exact test
Source: Reviewer Analysis

Table 12 – Efficacy Results by Baseline Pathogen in Study 603 (MITT, MVTF)

	Vehicle	Sertaconazole	p-value[a]
T. rubrum			
Complete Cure	2/78 (2.6%)	22/82 (26.8%)	<0.0001
Effective Trt.	13/78 (16.7%)	43/82 (52.4%)	<0.0001
Mycol. Cure	15/78 (19.2%)	60/82 (73.2%)	<0.0001
T. mentag.			
Complete Cure	3/20 (15.0%)	5/18 (27.8%)	0.4381
Effective Trt.	3/20 (15.0%)	8/18 (44.4%)	0.0741
Mycol. Cure	5/20 (25.0%)	10/18 (55.6%)	0.0960
E. floccosum			
Complete Cure	0/5 (0.0%)	1/3 (33.3%)	0.3750
Effective Trt.	0/5 (0.0%)	1/3 (33.3%)	0.3750
Mycol. Cure	0/5 (0.0%)	1/3 (33.3%)	0.3750

[a] p-values based on Fisher's Exact test
Source: Reviewer Analysis

Since most of the subjects were in the *T. rubrum* group, efficacy for this pathogen appears to be established. However, because a relatively small number of patients were enrolled with either *T. mentagrophytes* or *E. floccosum*, the studies are not as conclusive for these two pathogens. The studies were powered to detect an overall treatment difference, and not to detect differences within the individual pathogens, so it is not surprising that significant results were not attained.

To see if additional insight can be gained into the pathogens with smaller sample sizes, results from the two studies were pooled. The pooled results are presented in Table 13. The pooled sample sizes for *E. floccosum*, with only 13 subjects per arm, are still insufficient to demonstrate an effect for complete cure or effective treatment. For

T. mentagrophytes, the p-value for complete cure is non-significant (p = 0.2955) in the pooled sample, although the p-value for effective treatment is significant (p = 0.0186).

Table 13 – Efficacy Results by Baseline Pathogen, Pooled Studies (MITT, MVTF)

	Vehicle	Sertaconazole	p-value[a]
T. rubrum			
Complete Cure	5/155 (3.2%)	32/160 (20.0%)	<0.0001
Effective Trt.	22/155 (14.2%)	67/160 (41.9%)	<0.0001
Mycol. Cure	30/155 (19.4%)	98/160 (61.3%)	<0.0001
T. mentag.			
Complete Cure	3/27 (11.1%)	7/28 (25.0%)	0.2955
Effective Trt.	4/27 (14.8%)	13/28 (46.4%)	0.0186
Mycol. Cure	7/27 (25.9%)	15/28 (53.6%)	0.0543
E. floccosum			
Complete Cure	0/13 (0.0%)	2/13 (15.4%)	0.4800
Effective Trt.	1/13 (7.7%)	4/13 (30.8%)	0.3217
Mycol. Cure	1/13 (7.7%)	7/13 (53.9%)	0.0302

[a] p-values based on Fisher's Exact test
Source: Reviewer Analysis

2.3.14 Subgroup Analyses

Subgroup analyses were conducted for gender, race, and age. For the analysis by age, the sponsor used the age groups '≤ median' and '> median'. The median age was 35 in Study 602 and 33 in Study 603. To better examine the effects in pediatric and geriatric patients, this reviewer selected the following age groups in consultation with the clinical reviewer: ≤ 17, 18 – 35, 36 – 64, and ≥ 65. Table 22 through Table 25 in the appendix present the results for complete cure and effective treatment by age, gender, and race subgroups. Two small subgroups had numerically higher success rates on vehicle than sertaconazole in Study 602, Hispanics (complete cure) and subjects 65 and over (effective treatment). Due to the small sample sizes in some subgroups, this type of reversal in some small subgroups is not unexpected. All other subgroups had numerically higher (or equal) success rates on sertaconazole than vehicle. Since many of the subgroups are small, p-values should be viewed as indications of the magnitude of the effect relative to the sample size, and not as formal tests of hypotheses.

In the age subgroups, there is some observed evidence of a trend, with a larger treatment effect observed among younger subjects than older subjects. This trend is observed to some extent in both studies for complete cure and effective treatment. However, in an exploratory post-hoc logistic regression model of clinical cure, the age covariate was not significant (p ≥ 0.2250). For effective treatment, the age covariate was significant for Study 603 (p = 0.0136), but not 602 (p = 0.3022). Thus any effect of age is not sufficient to generate a statistically significant result for complete cure.

2.3.15 Safety Assessment

The minimum exposure to treatment in Studies 602 and 603 was 1 day, and the maximum exposure was 35 days. The average exposure to sertaconazole in all treated patients was 21.1 days in Study 602 and 22.1 days in Study 603. The average exposure to vehicle was 19.8 days in Study 602 and 23.0 days in Study 603. For the two studies combined, 64% of sertaconazole and 62% of vehicle patients were exposed for at least 22 days.

For the two studies combined, 58 sertaconazole patients (19.5%) experienced adverse events, compared with 50 vehicle patients (17.2%). Four sertaconazole patients (1.3%) experienced adverse events considered by the investigator to be 'possibly' or 'probably' related to treatment. Four vehicle patients (1.4%) also experienced adverse events considered by the investigator to be 'possibly' or 'probably' related to treatment. All but one of the treatment related adverse events (cholesterol blood increase) involved the skin. Table 14 presents the treatment related adverse events.

Table 14 – Treatment Related Adverse Events (All Randomized Subjects)

	Study 602		Study 603	
	Vehicle N=148	Serta. N=151	Vehicle N=143	Serta. N=146
All Adverse Events	23 (15.5%)	25 (16.6%)	27 (18.9%)	33 (22.6%)
Treatment Related	1 (0.7%)	3 (2.0%)	3 (2.1%)	1 (0.7%)
Burning Skin	1	0	0	0
Cholesterol Blood Incr.	0	1	0	0
Odor Body	0	1	0	0
Dermatitis Contact	0	1	1	0
Tenderness	0	0	1	0
Reaction, Applic. Site	0	0	1	0
Skin Dry	0	0	0	1

Source: Sponsor's Vol. 27, Table 23, pg. 8-2-189, and Table 24, pg. 8-2-191; Vol.34, Table 22, pg. 8-9-184, and Table 23, pg. 8-9-186.

The rates of adverse events on the two arms are similar. The most common adverse events were common cold, headache, and upper respiratory infection. Table 15 presents the adverse events reported by >1% of subjects on either treatment arm in either study. One serious adverse event was reported during the study period. A vehicle subject in Study 603 suffered a moderate pneumothorax and fractured clavicle after falling from scaffolding. The subject was subsequently discontinued due to negative baseline culture.

Table 15 – Adverse Events Reported by > 1% of Patients in Either Treatment Arm (All Randomized Subjects)

	Study 602		Study 603	
	Vehicle N=148	Serta. N=151	Vehicle N=143	Serta. N=146
All Adverse Events	23 (15.5%)	25 (16.6%)	27 (18.9%)	33 (22.6%)
Common Cold	4	5	6	2
Headache	5	2	3	9
Coughing	2	0	0	1
Upper Resp. Infection	2	2	7	5
Urinary Tract Infection	2	0	0	1
Hangover	0	0	2	1
Head Fullness	0	0	0	2
Uric Acid Blood Incr.	0	0	0	2

Source: Sponsor's Table 23, Vol. 27, pg. 8-2-189, and Table 22, Vol. 34, pg. 8-9-184.

2.4 Statistical Evaluation of Collective Evidence

The sponsor has demonstrated a statistically significant effect of sertaconazole in the treatment of interdigital tinea pedis (twice daily application for 28 days). Complete cure, effective treatment, and mycological cure are all statistically significant in each study. Efficacy results for complete cure, effective treatment, and mycological cure are summarized in Table 16 for the two phase 3 studies.

Table 16 – Efficacy Results (Reviewer MITT[a], MVTF[b])

	Study 602			Study 603		
	Vehicle	Serta.	p-value[c]	Vehicle	Serta.	p-value[c]
Complete Cure	3/92 (3.3%)	13/99 (13.1%)	0.0101	5/103 (4.9%)	28/103 (27.2%)	<0.0001
Effective Treatment	11/92 (12.0%)	32/99 (32.3%)	0.0010	16/103 (15.5%)	52/103 (50.5%)	<0.0001
Mycological Cure	18/92 (19.6%)	49/99 (49.5%)	<0.0001	20/103 (19.4%)	71/103 (68.9%)	<0.0001

[a] Randomized, dispensed treatment, and positive baseline culture.
[b] Missing Values Treated as Failures
[c] p-values based on the CMH test stratified on center.
Source: Reviewer Analysis.

The MITT analysis population defined in the protocol was more like a per protocol population in that it excluded subjects with protocol violations. Even after the sponsor revised the definition of the MITT population after the study to include subjects without post-baseline assessments, the sponsor and the reviewer still had differing opinions about whether subjects who were enrolled despite not meeting all entrance criteria should be included in the MITT. The sponsor and reviewer also disagreed on how to classify subjects whose Week 6 KOH was 'unknown', as there was no provision in the protocol for dealing with this situation. The sponsor classified the subjects with 'unknown' KOH,

negative culture and physician's global ≤ 2 as effective treatment. All of these disputed subjects were on the sertaconazole arm. This disagreement only involved subjects whose highest efficacy classification was effective treatment, as the sponsor did not classify any of these subjects as complete cures. Since the Week 6 KOH was not confirmed negative, which was a requirement for determining a "success", this reviewer elected to classify the subjects as failures. However, the method used to define the MITT population or handle unknown KOH values does not affect the conclusions of the study, as analyses with both the sponsor's and reviewer's population demonstrate statistical significance.

Sensitivity analyses were conducted comparing LOCF vs. MVTF (missing values treated as failures), and defining complete cure using the physician's global, signs and symptoms, or both. In Study 603, all analyses demonstrate statistical significance for complete cure, effective treatment, and mycological cure. In Study 602, all analyses demonstrate statistical significance for effective treatment and mycological cure. The most conservative analysis for complete cure (MVTF, physician's global and signs and symptoms must agree), just misses statistical significance with p=0.0591. However, all other analyses using either LOCF or only one of the methods for determining clinical cure demonstrated statistical significance for complete cure in Study 602 at $\alpha = 0.05$. In the analysis proposed by the sponsor for the label, the p-values for complete cure were 0.0096 (Study 602) and < 0.0001 (Study 603), while the p-values for the reviewer's preferred analysis were 0.0101 (Study 602) and < 0.0001 (Study 603). Thus, the method used to handle missing data or define efficacy does not substantially affect the conclusions of the study. The sponsor has demonstrated a statistically significant treatment effect for sertaconazole in the treatment of interdigital tinea pedis with regards to complete cure, effective treatment, and mycological cure in two studies.

2.5 Conclusions and Recommendations

The sponsor has conducted two phase 3 trials to demonstrate the efficacy and safety of sertaconazole in the treatment of interdigital tinea pedis. For the efficacy endpoint preferred by the Division, complete cure, the success rate for sertaconazole was 13.1% in Study 602 and 27.2% in Study 603. The corresponding vehicle complete cure rates were 3.3% in Study 602 and 4.9% in Study 603. These success rates are statistically significant for complete cure in each of the two pivotal studies with p-values ≤ 0.01 for the MITT population. Statistical significance was also attained for effective treatment ($p \leq 0.001$) and mycological cure ($p < 0.0001$) in the MITT population in each study.

Adverse event rates for the two studies were similar for the sertaconazole and vehicle arms, with 17% of vehicle and 20% of sertaconazole patients experiencing adverse events. Eight treatment related adverse events were reported in the two double-blind studies. Of these 8 events, 4 were on the sertaconazole and 4 were on the vehicle arm. Most of the treatment related adverse events were related to the skin.

2.6 Appendix of Additional Tables

Table 17 – Patient Disposition in Studies 602 and 603

	Study 602		Study 603	
	Vehicle	Serta.	Vehicle	Serta.
Enrolled	148	151	143	146
Negative Baseline Culture	56[a] (38%)	52[b] (34%)	40[c] (28%)	43[d] (29%)
Positive Baseline Culture	92 (62%)	99 (66%)	103 (72%)	103 (71%)
Completed	79 (86%)	86 (87%)	94 (91%)	90 (87%)
Discontinued	13 (14%)	13 (13%)	9 (9%)	13 (13%)
Lost to Follow-up	7	4	2	5
Withdrew Voluntarily	2	4	1	0
Administrative/Other	2	1	2	1
Treatment Failure	1	1	2	0
Non-Compliance	1	0	0	0
Protocol Violations	0	3	2	7

[a] Includes 4 subjects with negative baseline cultures but withdrawn for other reasons: withdrew voluntarily (2), lost to follow-up (1), and administrative/other (1).
[b] Includes 8 subjects with negative baseline cultures but withdrawn for other reasons: withdrew voluntarily (2), lost to follow-up (3), administrative/other (1), protocol violation (1), and non-compliance (1).
[c] Includes 7 subjects with negative baseline cultures but withdrawn for other reasons: protocol violations (4), adverse event (1), administrative/other (2).
[d] Includes 3 subjects with negative baseline cultures but withdrawn for other reasons: lost to follow-up (1), protocol violation (2).
Source: Sponsor's Vol. 27, pg. 8-2-148 and Vol. 34, pg. 8-9-143

Table 18– Baseline Demographic Data (Study 602)

	All Randomized Subjects		MITT		
	Vehicle N=148	Serta. N=151	Vehicle N=92	Serta. N=99	p-value[a]
Age					
Mean	36	37	34	36	0.4187
Range	(12 – 86)	(12 – 71)	(13 – 86)	(12 – 71)	
Sex					
Male	107 (72%)	113 (75%)	67 (73%)	75 (76%)	0.6430
Female	41 (28%)	38 (25%)	25 (27%)	24 (24%)	
Race					
Caucasian	99 (67%)	97 (64%)	62 (67%)	71 (71%)	0.4283
Black	36 (24%)	36 (24%)	21 (23%)	18 (18%)	
Hispanic	13 (9%)	13 (9%)	9 (10%)	7 (7%)	
Asian	0 (0%)	4 (3%)	0 (0%)	2 (2%)	
Other	0 (0%)	1 (1%)	0 (0%)	1 (1%)	

[a] p-values from ANOVA (Age), and chi-square test (Sex, Race)
Source: Sponsor's Table 11, Vol. 27, pg. 8-2-159, and Reviewer Analysis

Table 19– Baseline Demographic Data (Study 603)

	All Randomized Subjects		MITT		
	Vehicle N=148	Serta. N=151	Vehicle N=92	Serta. N=99	p-value[a]
Age					
Mean	34	35	34	36	0.3146
Range	(11 – 76)	(13 – 74)	(12 – 76)	(13 – 74)	
Sex					
Male	112 (78%)	104 (71%)	78 (76%)	71 (69%)	0.2756
Female	31 (22%)	42 (29%)	25 (24%)	32 (31%)	
Race					
Caucasian	88 (62%)	88 (60%)	60 (58%)	61 (59%)	0.5432
Black	21 (15%)	24 (16%)	15 (15%)	12 (12%)	
Hispanic	32 (22%)	27 (19%)	26 (25%)	24 (23%)	
Asian	1 (1%)	6 (4%)	1 (1%)	5 (5%)	
Other	1 (1%)	1 (1%)	1 (1%)	1 (1%)	

[a] p-values from ANOVA (Age), and chi-square test (Sex, Race)
Source: Sponsor's Table 10, Vol. 34, pg. 8-9-154, and Reviewer Analysis.

Table 20– Number of Enrolled and MITT Subjects by Center (Study 602)

Site	# Enrolled	# in MITT	Site	# Enrolled	# in MITT
01	24	14	12	16	8
03	42	26	13	17	17
04*	5	4	14	21	19
05	13	4	15	10	4
06	17	11	16	21	14
07*	7	0	17	10	6
08*	2	0	18	9	6
09	29	17	19*	2	0
10*	6	5	20*	1	1
11	39	31	21	8	6

* Pooled centers per statistical analysis plan.

Table 21 - Number of Enrolled and MITT Subjects by Center (Study 603)

Site	# Enrolled	# in MITT	Site	# Enrolled	# in MITT
25	18	12	33*	6	5
26*	6	1	34	38	26
27	29	19	35	12	5
28*	7	4	36	36	23
29	42	36	37	42	38
30*	2	0	38	21	17
31*	7	3	39*	3	1
32	20	16			

* Pooled centers per statistical analysis plan.

Table 22 – Complete Cure Subgroup Analyses for Study 602 (MITT, MVTF)

Complete Cure	Vehicle	Sertaconazole	p-value[a]
Age ≤ 17	0/6 (0.0%)	3/8 (37.5%)	0.2088
Age 18 – 35	2/45 (4.4%)	5/45 (11.1%)	0.4340
Age 36 – 64	1/39 (2.6%)	5/42 (11.9%)	0.2030
Age ≥ 65	0/2 (0.0%)	0/4 (0.0%)	NA
Male	2/67 (3.0%)	8/75 (10.7%)	0.1025
Female	1/25 (4.0%)	5/24 (20.8%)	0.0983
Caucasian	1/62 (1.6%)	11/71 (15.5%)	0.0055
Black	1/21 (4.8%)	1/18 (5.6%)	>0.999
Asian	0/0	0/2 (0.0%)	NA
Hispanic	1/9 (11.1%)	0/7 (0.0%)	>0.999
Other	0/0	1/1 (100%)	NA

[a] p-values based on Fisher's Exact test. *Source*: Reviewer Analysis

Table 23 – Effective Treatment Subgroup Analyses for Study 602 (MITT, MVTF)

Effective Trt	Vehicle	Sertaconazole	p-value[a]
Age ≤ 17	0/6 (0.0%)	5/8 (62.5%)	0.0310
Age 18 – 35	5/45 (11.1%)	17/45 (37.8%)	0.0062
Age 36 – 64	5/39 (12.8%)	9/42 (21.4%)	0.3842
Age ≥ 65	1/2 (50.0%)	1/4 (25.0%)	0.9333
Male	8/67 (11.9%)	25/75 (33.3%)	0.0028
Female	3/25 (12.0%)	7/24 (29.2%)	0.1706
Caucasian	8/62 (12.9%)	25/71 (35.2%)	0.0044
Black	1/21 (4.8%)	3/18 (16.7%)	0.3183
Asian	0/0	0/2 (0.0%)	NA
Hispanic	2/9 (22.2%)	3/7 (42.8%)	0.5962
Other	0/0	1/1 (100%)	NA

[a] p-values based on Fisher's Exact test. *Source*: Reviewer Analysis

Table 24 – Complete Cure Subgroup Analyses for Study 603 (MITT, MVTF)

Complete Cure	Vehicle	Sertaconazole	p-value[a]
Age ≤ 17	0/6 (0.0%)	3/7 (42.9%)	0.1923
Age 18 – 35	3/54 (5.6%)	14/43 (32.6%)	0.0008
Age 36 – 64	2/40 (5.0%)	10/49 (20.4%)	0.0582
Age ≥ 65	0/3 (0.0%)	1/4 (25.0%)	>0.999
Male	1/78 (1.3%)	22/71 (31.0%)	<0.0001
Female	4/25 (16.0%)	6/32 (18.8%)	>0.999
Caucasian	5/60 (8.3%)	23/61 (37.7%)	0.0002
Black	0/15 (0.0%)	0/12 (0.0%)	NA
Asian	0/1 (0.0%)	1/5 (20.0%)	>0.999
Hispanic	0/26 (0.0%)	3/24 (12.5%)	0.1033
Other	0/1 (0.0%)	1/1 (100%)	>0.999

[a] p-values based on Fisher's Exact test. *Source*: Reviewer Analysis

Table 25 - Effective Treatment Subgroup Analyses for Study 603 (MITT, MVTF)

Effective Trt	Vehicle	Sertaconazole	p-value[a]
Age ≤ 17	1/6 (16.7%)	6/7 (85.7%)	0.0291
Age 18 – 35	10/54 (18.5%)	26/43 (60.5%)	<0.0001
Age 36 – 64	5/40 (12.5%)	19/49 (38.8%)	0.0077
Age ≥ 65	0/3 (0.0%)	1/4 (25.0%)	>0.999
Male	10/78 (12.8%)	38/71 (53.5%)	<0.0001
Female	6/25 (24.0%)	14/32 (43.8%)	0.1649
Caucasian	15/60 (25.0%)	36/61 (59.0%)	0.0002
Black	1/15 (6.7%)	3/12 (25.0%)	0.2940
Asian	0/1 (0.0%)	3/5 (60.0%)	>0.999
Hispanic	0/26 (0.0%)	9/24 (37.5%)	0.0005
Other	0/1 (0.0%)	1/1 (100%)	>0.999

[a] p-values based on Fisher's Exact test. *Source*: Reviewer Analysis

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