# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**76005**

# STATISTICAL REVIEW(S)

**Statistical Report: Taro Pharmaceuticals, Inc., Econazole Nitrate Cream, 1%; Office of Generic Drugs; ANDA 76-005**

**OGD reviewer: Mary M. Fanning, MD, Ph.D.**

This was a double-blind, randomized, three treatment, parallel-group, vehicle-controlled study in 453 subjects with signs and symptoms of tinea pedis but otherwise reasonably healthy. The purpose of the study was to show the therapeutic equivalence between the test product, Taro Pharmaceuticals, Inc., Econazole Nitrate cream, 1%, and the reference products, Ortho-McNeil Pharmaceuticals, Spectazole® creams, 1%, and show effectiveness between the active treatments and placebo, cream vehicle.

## Study Design

This was a 3 arm parallel double-blind study in subjects with signs and symptoms of tinea pedis. The three creams were the test product, Taro Pharmaceuticals, Inc., Econazole Nitrate cream, 1%, the reference products, Ortho-McNeil Pharmaceuticals, Spectazole ® cream, 1%, and the placebo, a cream vehicle.

A total of 453 subjects were enrolled and randomly assigned to three treatment groups in the study. At the enrollment visit, the subjects with clinical signs and symptoms of tinea pedis had a skin scraping taken from an area of active lesions for 10% KOH wet mount and fungal culture. The signs and symptoms, erythema, scaling, fissuring, bullae, itching, and burning, were measured by using a score (0-4, none to severe). The eligible subjects, who had a positive fungal culture and met the eligibility criteria, were instructed to apply the cream to the clean, dry study foot twice a day for four weeks. The mycological evaluation (both KOH and culture test) and clinical evaluation (signs and symptoms) were performed at visit 2 (4 weeks on treatment) and visit 3 (week 6, 2 weeks after the end of treatment).

## Outcome Variables

According the FDA medical officer's review, the **primary variable** used to assess efficacy and equivalence was the rate of therapeutic cure, defined as both a mycological cure and a clinical cure at visit 3 (week 6, 2 weeks after end of treatment). The secondary variables were the rates of the mycological cure and clinical cure at visit 3 (week 6), and the rates of the mycological cure, clinical cure, and therapeutic cure at visit 2 (week 4).

The mycological cure was both KOH and culture negative at the visit. The clinical cure was defined in this way: the subject had a total score 2 or less and a severity score of no more than 1 for any of the 6 signs and symptoms at the visit.

## Statistical Analysis Methods

*Efficacy Analysis*

Tests of comparisons for therapeutic cure rate, mycological cure rate, and clinical cure rate were made between treatment arms at the (two-sided) 5% level significance. The efficacy analysis for each active treatment was tested separately by comparing it with the placebo. All treatment arms should be similar for sign/symptom scores at the enrollment visit. The active treatments should be more distinguishable from placebo as the study progressed.

The efficacy analyses for all cure rates were carried out by using Fisher's exact test for each active treatment versus placebo.

*Equivalence Analysis*

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in proportions between test and reference treatment should be contained within -.20 to .20 in order to establish equivalence.

The compound hypothesis to be tested is:

$H_0$: $p_T - p_R \leq -.20$

or $p_T - p_R \geq .20$

versus

$H_A$: $-.20 < p_T - p_R < .20$

where $p_T$ = cure rate of test treatment $p_R$ = cure rate of reference treatment

Let $n_T$ = sample size of test treatment

$n_R$ = sample size of reference treatment

$Z_{.05}$ = .95 percentile of the normal distribution

and $se = (\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{1/2}$

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - Z_{.05}\, se - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + Z_{.05}\, se + (1/n_T + 1/n_R)/2.$$

The null hypothesis is rejected if L > -.20 and U < .20. Rejection of the null hypothesis $H_0$ supports the conclusion of equivalence of the two products.

We analyzed the data for efficacy and equivalence for mycological cure rate, clinical cure rate, and therapeutic cure rate at the week 4 and 6 visits. The analysis was performed for the modified intent-to-treat (MITT) and modified evaluable (MEP) populations.

**Statistical Analysis Results**

Of the total 453 subjects enrolled, 199 had a negative fungal culture, 2 withdrew before the first dosing, and 3 did not return after visit 1. Therefore, 249 males and females with ages ranging from 19 to 83 were eligible for inclusion in the study (MITT).[1] Of these 249 eligible subjects, 2 subjects did not return after visit 2 and 7 were outside of visit 3 window (≥46 days). Thus, the modified evaluable population (MEP) was reduced to 240 subjects.

The following table shows the populations and exclusions per treatment arm.

| | Ortho | Taro | Vehicle | Total |
|---|---|---|---|---|
| Enrollment | 152 | 151 | 150 | 453 |
| Baseline culture negative | 67 | 69 | 63 | 199 |
| Withdrew before first dosing | 1 | 1 | | 2 |
| Did not return after visit 1 | 1 | | 2 | 3 |
| Modified Intent-to-treat population (MITT) | 83 | 81 | 85 | 249 |
| Did not return after visit 2 | 2 | | | 2 |
| Outside the visit 3 window | 2 | | 5 | 7 |
| Modified Evaluable population (MEP) | 79 | 81 | 80 | 240 |

*Baseline check*

A summary of the frequencies and chi-square tests for the negative KOH measurements for the MITT and MEP populations at the enrollment visit is given as below.

| Population | Ortho | Taro | Vehicle | Chi-square test P-value |
|---|---|---|---|---|
| MITT | 47 (56.6%) | 36 (44.4%) | 41 (48.2%) | 0.278 |
| MEP | 43 (54.4%) | 36 (44.2%) | 38 (47.5%) | 0.434 |

Although there were no significant differences between treatment arms at the enrollment visit, More than 10% of the subjects in the Ortho group had negative KOH compared to the Taro group.

[1] In the MITT population, there were 124 subjects who had negative KOH and 17 subjects who had lower scaling score (score=1) at baseline visit. However, the FDA medical reviewer pointed out: 1) The subject who had tinea pedis could obtain negative KOH at baseline. Therefore, the subject who had positive culture, but negative KOH at baseline should be eligible for the study. 2) The subjects had lower scaling score, but had high scores for other signs and symptoms at baseline. These subjects could be included in the analysis.

A summary of the frequencies and chi-square tests for homogeneity of sign/symptom scores for the MITT and MEP populations at the enrollment visit is given in Table 1. There were no significant differences between treatment arms for all the signs/symptoms at the enrollment visit.

*Efficacy Analysis*

A summary of the efficacy analysis results for mycological cure rate, clinical cure rate, and therapeutic cure rate for the MITT and MEP populations at the week 4 and 6 visits is given in Table 2.

**Primary variable:** The active treatments were significantly better than placebo for both populations ($P \leq 0.001$).

**Secondary variables:** The test and reference treatments were significantly better than placebo for all variables for both populations at the week 4 and 6 visits with three exceptions. The clinical cure rates were not significantly better (at the 0.05 level) than placebo for Taro for both populations at the week 4 visit and for Ortho for MITT population at the week 4 visit.

*Equivalence Analysis*

The results of the equivalence analyses are summarized in Table 2 for the MITT and MEP populations. Both populations had similar results.

**Primary variable:** The equivalence test failed for Taro versus Ortho for both populations since the Taro product was more effective than the Ortho product.

**Secondary variables:** The therapeutic cure passed the equivalence test for both populations at the week 4 visit. The clinical cure passed the equivalence test for both populations at both visits.

The mycological cure failed the equivalence test for both populations at both visits due to the fact that the Taro product was less effective at the week 4 visit and more effective at the week 6 visit compared to the Ortho product. The mycological cure rates may be influenced by the imbalance in the rates of negative KOH at baseline between two treatment groups.

Figure 1 shows the mycological, clinical, and therapeutic cure rates at the week 4 and 6 visits for both MITT and MEP populations.

**Safety**

No adverse events were reported during this study.

## Comments on the Sponsor's Equivalence Analyses

The sponsor performed equivalence analyses for the evaluable population (247 subjects).[2] The mycological cure was defined as both culture and KOH negative at the week 4 and 6 visits.[3] The clinical cure was defined as a total score of 2 or less and a severity score of no more than 1 for any of the 6 clinical parameters at the week 6 visit. The therapeutic cure was defined as both mycological cure and clinical cure. The therapeutic cure rates at week 6 were 46.9% Ortho, 53.1% Taro, and 20.0% placebo. The Blackwelder 90% confidence limits for the therapeutic cure rates was (-0.191, 0.067) for Ortho versus Taro. The sponsor concluded that test drug, Taro cream, passed the equivalence test since the 90% confidence was within ±20%.

We recalculated the 90% confidence intervals using the therapeutic cure rates and evaluable population defined by the sponsor. The confidence interval was (-0.203, 0.080) with Yates continuity correction and (-0.191, 0.067) without Yates correction for Ortho versus Taro.

## Conclusion

**Efficacy:** Our analysis showed that the test and reference products were both significantly better than placebo for therapeutic cure, mycological cure, and clinical cure for both populations at both visits with three exceptions. The clinical cure rates were not significantly better than placebo for Taro for both populations at the week 4 visit and for Ortho for MITT population at the week 4 visit

**Equivalence:** The **primary variable**, therapeutic cure at the week 6 visit, failed the equivalence test for both populations. The therapeutic cure passed the equivalence test for both populations at the week 4 visit. The mycological cure failed the equivalence test for both populations at both visits. The clinical cure passed the equivalence test for both populations at both visits. The Taro product was more effective than the Ortho product at week 6.

/S/ 12/10/01

Huaixiang Li, Ph.D.
Mathematical Statistician, OB/QMRS

/S/ 12/10/01

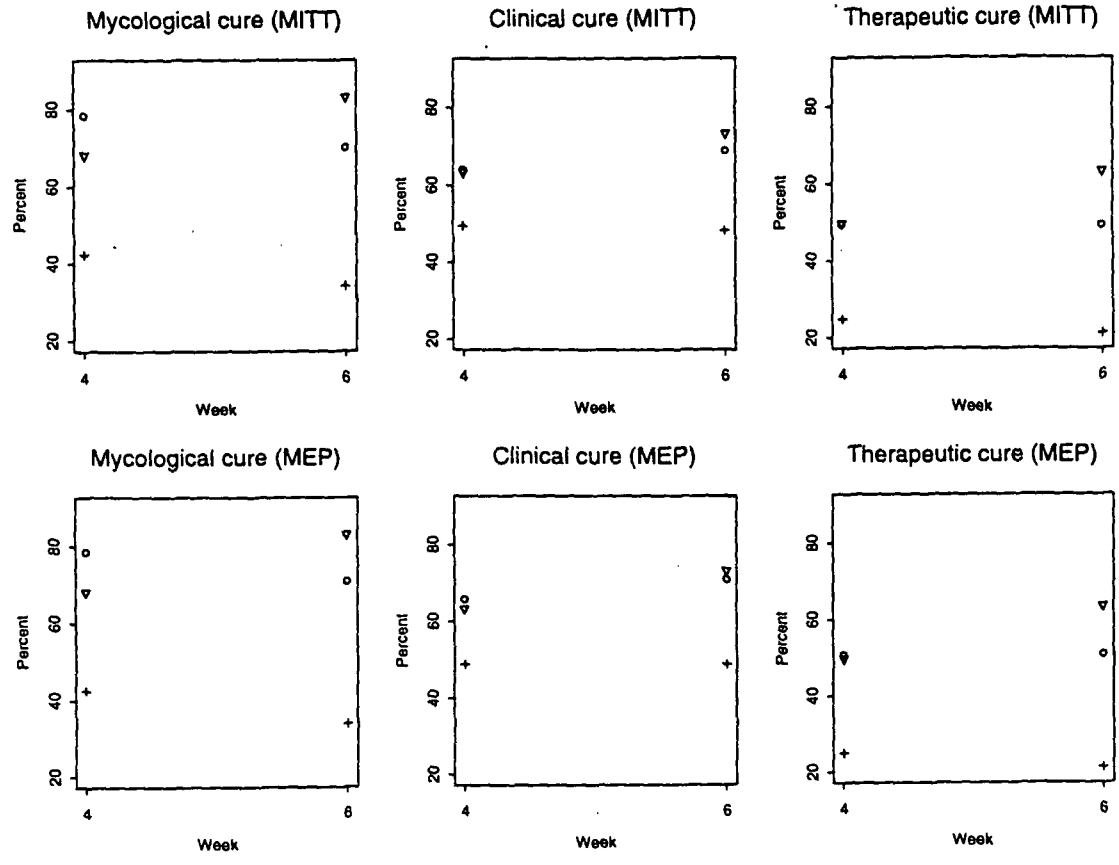
Concur: Stella G. Machado, Ph.D.
Director, OB/QMRS

[2] Our modified evaluable population (MEP) included 240 subjects. The sponsor did not exclude the 7 subjects who were outside of visit 3 window (≥46 days). Consequently, the sponsor's evaluable population had 247 subjects.

[3] The FDA medical reviewer pointed out: The mycological cure should be defined as culture and KOH negative at either week 4 or week 6, not at week 4 and 6. The different definitions for the mycological cure caused lower therapeutic cure rates in the sponsor's analysis than ours.

cc:
HFD-615 Harvey Greenberg
HFD-655 Mary Fanning
HFD-705 Stella Machado
HFD-705 Huaixiang Li
HFD-705 QMR Chron

**Figure 1: Mycological, clinical, and therapeutic cure rates for modified intent-to-treat (MITT) and modified evaluable (MEP) populations**




∇∇∇ Taro ○○○ Ortho +++ Vehicle.

**Table 1: Baseline signs and symptoms**

| | | Score (%) | | | | | Chi-square test for homogeneity of groups |
|---|---|---|---|---|---|---|---|
| | N | 0 | 1 | 2 | 3 | 4 | P-value |
| Modified intent-to-treat population (MITT) | | | | | | | |
| Scaling | | | | | | | |
| Ortho | 83 | | 3( 4) | 36( 43) | 34( 41) | 10( 12) | 0.637 |
| Taro | 81 | | 7( 9) | 27( 33) | 39( 48) | 8( 10) | |
| Vehicle | 85 | | 7( 8) | 31( 36) | 35( 41) | 12( 14) | |
| Erythema | | | | | | | |
| Ortho | 83 | | 5( 6) | 64( 77) | 14( 17) | | 0.312 |
| Taro | 81 | | 5( 6) | 56( 69) | 18( 22) | 2( 2) | |
| Vehicle | 85 | | 11( 13) | 54( 64) | 19( 22) | 1( 1) | |
| Fissuring | | | | | | | |
| Ortho | 83 | | 52( 63) | 27( 33) | 4( 5) | | 0.651 |
| Taro | 81 | | 45( 56) | 27( 33) | 7( 9) | 2( 2) | |
| Vehicle | 85 | | 45( 53) | 32( 38) | 7( 8) | 1( 1) | |
| Itching | | | | | | | |
| Ortho | 83 | | 7( 8) | 30( 36) | 18( 22) | 28( 34) | 0.916 |
| Taro | 81 | | 3( 4) | 29( 36) | 20( 25) | 29( 36) | |
| Vehicle | 85 | | 7( 8) | 30( 35) | 18( 21) | 30( 35) | |
| Bullae | | | | | | | |
| Ortho | 83 | 79( 95) | 4( 5) | | | | 0.736 |
| Taro | 81 | 75( 93) | 5( 6) | 1( 1) | | | |
| Vehicle | 85 | 80( 94) | 3( 4) | 1( 1) | 1( 1) | | |
| Burning | | | | | | | |
| Ortho | 83 | 2( 2) | 3( 4) | 32( 39) | 17( 20) | 29( 35) | 0.984 |
| Taro | 81 | 4( 5) | 4( 5) | 29( 36) | 16( 20) | 28( 35) | |
| Vehicle | 85 | 5( 6) | 5( 6) | 30( 35) | 17( 20) | 28( 33) | |
| Modified evaluable population (MEP) | | | | | | | |
| Scaling | | | | | | | |
| Ortho | 79 | | 3( 4) | 34( 43) | 33( 42) | 9( 11) | 0.669 |
| Taro | 81 | | 7( 9) | 27( 33) | 39( 48) | 8( 10) | |
| Vehicle | 80 | | 6( 8) | 28( 35) | 34( 43) | 12( 15) | |
| Erythema | | | | | | | |
| Ortho | 79 | | 4( 5) | 63( 80) | 12( 15) | | 0.235 |
| Taro | 81 | | 5( 6) | 56( 69) | 18( 22) | 2( 2) | |
| Vehicle | 80 | | 10( 13) | 51( 64) | 18( 23) | 1( 1) | |
| Fissuring | | | | | | | |
| Ortho | 79 | | 50( 63) | 25( 32) | 4( 5) | | 0.650 |
| Taro | 81 | | 45( 56) | 27( 33) | 7( 9) | 2( 2) | |
| Vehicle | 80 | | 42( 53) | 31( 39) | 6( 8) | 1( 1) | |
| Itching | | | | | | | |
| Ortho | 79 | | 7( 9) | 28( 35) | 18( 23) | 26( 33) | 0.891 |
| Taro | 81 | | 3( 4) | 29( 36) | 20( 25) | 29( 36) | |
| Vehicle | 80 | | 7( 9) | 28( 35) | 17( 21) | 28( 35) | |
| Bullae | | | | | | | |
| Ortho | 79 | 75( 95) | 4( 5) | | | | 0.642 |
| Taro | 81 | 75( 93) | 5( 6) | 1( 1) | | | |
| Vehicle | 80 | 76( 95) | 2( 3) | 1( 1) | 1( 1) | | |
| Burning | | | | | | | |
| Ortho | 79 | 2( 3) | 3( 4) | 30( 38) | 17( 22) | 27( 34) | 0.978 |
| Taro | 81 | 4( 5) | 4( 5) | 29( 36) | 16( 20) | 28( 35) | |
| Vehicle | 80 | 5( 6) | 5( 6) | 30( 38) | 15( 19) | 25( 31) | |

**Table 2: Efficacy and equivalence analysis***

| | Cure rate % (Cure/Total) | | | Efficacy analysis | | Equivalence analysis Taro vs. Ortho | |
|---|---|---|---|---|---|---|---|
| Group | Taro | Ortho | Vehicle | P-value Ortho vs. Vehicle | P-value Taro vs. vehicle | 90% confidence interval | Pass /Fail |
| Modified Intent-to-treat Population (MITT) | | | | | | | |
| Week 4 | | | | | | | |
| Mycological cure | 67.9 ( 55/ 81) | 78.3 ( 65/ 83) | 42.4 ( 36/ 85) | <.001 | 0.001 | (-0.23, 0.02) | F |
| Clinical cure | 63.0 ( 51/ 81) | 63.9 ( 53/ 83) | 49.4 ( 42/ 85) | 0.064 | 0.087 | (-0.14, 0.13) | P |
| Therapeutic cure | 49.4 ( 40/ 81) | 49.4 ( 41/ 83) | 24.7 ( 21/ 85) | 0.001 | 0.001 | (-0.14, 0.14) | P |
| Week 6 | | | | | | | |
| Mycological cure | 82.7 ( 67/ 81) | 69.9 ( 58/ 83) | 34.1 ( 29/ 85) | <.001 | <.001 | (0.01, 0.25) | F |
| Clinical cure | 72.8 ( 59/ 81) | 68.7 ( 57/ 83) | 48.2 ( 41/ 85) | 0.008 | 0.001 | (-0.09, 0.17) | P |
| **Therapeutic cure** | **63.0 ( 51/ 81)** | **49.4 ( 41/ 83)** | **21.2 ( 18/ 85)** | **<.001** | **<.001** | **(0.00, 0.27)** | **F** |
| Modified Evaluable Population (MEP) | | | | | | | |
| Week 4 | | | | | | | |
| Mycological cure | 67.9 ( 55/ 81) | 78.5 ( 62/ 79) | 42.5 ( 34/ 80) | <.001 | 0.002 | (-0.23, 0.02) | F |
| Clinical cure | 63.0 ( 51/ 81) | 65.8 ( 52/ 79) | 48.8 ( 39/ 80) | 0.037 | 0.082 | (-0.17, 0.11) | P |
| Therapeutic cure | 49.4 ( 40/ 81) | 50.6 ( 40/ 79) | 25.0 ( 20/ 80) | 0.001 | 0.002 | (-0.16, 0.13) | P |
| Week 6 | | | | | | | |
| Mycological cure | 82.7 ( 67/ 81) | 70.9 ( 56/ 79) | 33.8 ( 27/ 80) | <.001 | <.001 | (0.00, 0.24) | F |
| Clinical cure | 72.8 ( 59/ 81) | 70.9 ( 56/ 79) | 48.8 ( 39/ 80) | 0.006 | 0.002 | (-0.11, 0.15) | P |
| **Therapeutic cure** | **63.0 ( 51/ 81)** | **50.6 ( 40/ 79)** | **21.3 ( 17/ 80)** | **<.001** | **<.001** | **(-0.02, 0.26)** | **F** |

*: The cure rate equals the number of cured divided by the total number, then multiplied by 100.
The P-value was from the paired Fisher's exact test.

# Addendum to Statistical Report

**ANDA 76-005**
**Drug Product: Econazole Nitrate Cream, 1%**
**Sponsor: Taro Pharmaceuticals, Inc.**
**Reference Listed Drug (RLD): Spectazole® creams, 1%,**
**Ortho-McNeil Pharmaceuticals**
**Submission Date: October 10, 2000**

**Reviewer: Huaixiang Li, Ph.D., QMRS/OB/CDER**
**Requestors: Lawrence Yu, Ph.D., OGD/CDER, 7/1/02**
**Dena Hixon, MD, OGD/CDER, 9/5/02**
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**Remark**: Two data sets (elig and inelig) used in the statistical analyses were supplied by the firm on one diskette and received on October 2, 2001 by OGD.

## Background

This was a double-blind, randomized, three treatment, parallel-group, vehicle-controlled study in 453 subjects with signs and symptoms of tinea pedis but otherwise reasonably healthy. The purpose of the study was to show the therapeutic equivalence between the test product, Taro Pharmaceuticals, Inc., Econazole Nitrate cream, 1%, and the reference products, Ortho-McNeil Pharmaceuticals, Spectazole® creams, 1%, and show effectiveness between the active treatments and placebo, cream vehicle.

The original statistical report was finished on December 10, 2001. The analysis was performed for the modified intent-to-treat (MITT) and modified evaluable (MEP) populations. The MITT population included 249 subjects who were eligible for inclusion in the study. Of these 249 subjects, the MEP population was reduced to 240 subjects due to no return after the week 4 visit (2 subjects) and falling outside the visit window at the week 6 visit (7 subjects).

According to the FDA medical officer's review, the **primary endpoint** used to assess efficacy and equivalence was the rate of therapeutic cure, defined as both a mycological cure and a clinical cure at visit 3 (week 6, 2 weeks after end of treatment). The secondary endpoints were the rates of ~~the~~ mycological cure and clinical cure at visit 3 (week 6), and the rates of the mycological cure, clinical cure, and therapeutic cure at visit 2 (week 4).

Mycological cure was both KOH and culture negative at the visit. Clinical cure was defined in this way: the subject had a total score of 2 or less and a severity score of no more than 1 for any of the 6 signs and symptoms at the visit.

The analysis in the original statistical report reached the following conclusions:
**Efficacy:** Our analysis showed that the test and reference products were both significantly better than placebo for therapeutic cure, mycological cure, and clinical cure

for both populations at both visits with three exceptions: the clinical cure rates were not significantly better than placebo for Taro for both populations at the week 4 visit and for Ortho for the MITT population at the week 4 visit

**Equivalence:** The **primary endpoint,** therapeutic cure at the week 6 visit, failed the equivalence test for both populations. Therapeutic cure passed the equivalence test for both populations at the week 4 visit. Mycological cure failed the equivalence test for both populations at both visits. Clinical cure passed the equivalence test for both populations at both visits.

**Additional Analysis**

This additional analysis was performed for the modified intent-to-treat (MITT) and modified evaluable (MEP) populations. The populations and the statistical analysis methods were the same as described in the original report. However, the definitions of mycological cure, clinical cure, and therapeutic cure were revised to be mycological cure, clinical cure, and therapeutic cure, respectively, at *both* the week 4 (end of treatment) visit *and* week 6 (2 weeks after end of treatment) visit.

Summary of the efficacy and equivalence analysis for the MITT and MEP populations
Cure rates incorporated the results at the week 4 and 6 visits
Test: Taro, Reference: Ortho

| Population | Test* % of cure (No. of cure) | Reference* % of cure (No. of cure) | Placebo* % of cure (No. cure) | P-value# for Test vs. placebo | P-value# for Reference vs. placebo | 90% Confidence interval for Test vs. ref. (%) | 90% CI is within (-20%, 20%) |
|---|---|---|---|---|---|---|---|
| MITT$ | 81 | 83 | 85 | | | | |
| Mycological cure | 66.7 ( 54 ) | 65.1 ( 54 ) | 25.9 ( 22 ) | <0.001 | <0.001 | ( -11.8, 15.0) | Yes |
| Clinical cure | 60.5 ( 49 ) | 59.0 ( 49 ) | 37.7 ( 32 ) | 0.005 | 0.009 | ( -12.4, 15.3) | Yes |
| Therapeutic cure | 45.7 ( 37 ) | 39.8 ( 33 ) | 16.5 ( 14 ) | <0.001 | 0.001 | ( -8.0, 19.8) | Yes |
| MEP$ | 81 | 79 | 80 | | | | |
| Mycological cure | 66.7 ( 54 ) | 67.1 ( 53 ) | 26.3 ( 21 ) | <0.001 | <0.001 | ( -13.9, 13.1) | Yes |
| Clinical cure | 60.5 ( 49 ) | 62.0 ( 49 ) | 38.8 ( 31) | 0.007 | 0.004 | ( -15.5, 12.4) | Yes |
| Therapeutic cure | 45.7 ( 37 ) | 41.8 ( 33 ) | 16.3 ( 13 ) | <0.001 | <0.001 | ( -10.2, 18.0) | Yes |

*: %of cure equals the number ~~of~~ cured divided by the total number, then multiplied by 100.
#: The P-values were from the Fisher's exact test (2-sided).
$: The total number of subjects in each treatment group.

**Efficacy**: The additional analysis showed that the test and reference products were both significantly better than placebo for therapeutic cure, mycological cure, and clinical cure for both populations.

**Equivalence**: The equivalence test for the Taro product versus the Ortho product was passed for therapeutic cure, mycological cure, and clinical cure for both populations.

/S/ 9/30/02
**Huaixiang Li, Ph.D.**
Mathematical Statistician, QMR

/S/ 9/30/02
**Donald J. Schuirmann**
Expert Mathematical Statistician, QMR

/S/ 9/30/02
**Stella G. Machado, Ph.D.**
Director, QMR

cc:
HFD-655 Lawrence Yu, Dena Hixon
HFD-650 Dale Conner, Lizzie Sanchez, Krista Scardina, Carol Kim
HFD-705 Stella G. Machado, Donald J. Schuirmann, Huaixiang Li
HFD-705 QMR Chron