# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75-581**

## STATISTICAL REVIEW(S)

**Statistical Report: Teva Pharmaceuticals, Ketoconazole, 2% Cream ; Office of Generic Drugs; ANDA 75-581**
**OGD reviewer: Mary M. Fanning, MD, Ph.D.**

## Introduction

The objective of the study was to compare the safety profile and show the therapeutic equivalence between TEVA Pharmaceuticals USA ketoconazole 2% cream (test product) and Janssen Pharmaceutica Nizoral 2% cream (reference product), and show efficacy of the active treatments compared to placebo, Vehicle cream, manufactured by TEVA Pharmaceuticals USA, in the treatment of patients with tinea pedis.

## Study Design

This was a double-blind, multicenter, randomized, parallel-group, vehicle-controlled comparative study with three study arms. It followed 606 subjects (males and females, age 18 to 80) with interdigital tinea pedis (positive KOH preps) but otherwise reasonably healthy. All treatments were applied once daily for 42 days with a two-week untreated follow-up period. The subjects were examined at visit 1 (Day 0, baseline), visit 2 (Day 22+/-5, Week 3), visit 3 (Day 43+/-5, Week 6, end of treatment), visit 4 (Day 57+/-5, Week 8, follow-up). Mycological evaluation (both KOH and culture test) was performed at each visit. A positive culture at baseline for one of T. rubrum, T. metagrophytes or E. floccosum was necessary for the patient to be included in the Intent-to-Treat (ITT) group.

The ITT cohort included all eligible culture positive individuals who applied at least one dose of study medication. The Per-Protocol (PP) cohort included those subjects in the ITT population who completed all visits and procedures required by the study protocol. The Safety-Intent-to-Treat (SITT) cohort included all 606 enrolled patients who received study medications. The subjects were randomized to one of the three treatment groups.

Table 1

| | Ketoconazole | Nizoral | Placebo | None (failed screening) | Total |
|---|---|---|---|---|---|
| Screened | 201 | 199 | 206 | 122 | 728 |
| SITT | 201 | 199 | 206 | N/A | 606 |
| ITT | 124 | 121 | 127 | N/A | 372 |
| PP | 80 | 92 | 98 | N/A | 270 |

## Endpoints

The primary endpoint was the rate of overall cure, defined as both a clinical cure (physician's global assessment of complete/100% improvement) and a mycological cure (both KOH and culture negative) at the Week 8 visit. The overall cure rate, calculated for the Week 6 data, was a secondary endpoint.

The sponsor used the ITT cohort for assessing both efficacy and equivalence and the SITT cohort (606 subjects), for assessing safety. At the recommendation of the medical reviewer the PP cohort was used in this report for assessing equivalence. This is supported by the fact that the data did not show a difference between treatments in dropout rates or adverse effects. However, for the entire analysis, the results are similar to the sponsor's.

The last observation was carried forward for missing values of the clinical and mycological evaluations in the ITT population.

## Statistical Analysis Methods and Results

*Efficacy Analysis*

Tests of comparisons for overall cure rate, mycological cure rate, and clinical cure rate were made between treatment arms at the (two-sided) 5% level significance (Fisher's exact test). The efficacy analysis for each active treatment was tested separately by comparing it with the placebo. The primary time point for comparison was the Week 8 visit. The primary efficacy analysis was done in the intent to treat population for rate of overall success.

Table 2: ITT efficacy analysis (Week 8 visit)

| Treatment | % success (p-value*) | Endpoint |
|---|---|---|
| Ketoconazole | 55/124=44.4% (<0.0001) | Overall success |
| Nizoral | 49/121=40.5% (<0.0001) | Overall success |
| Placebo | 13/127=10.2% | Overall success |
| Ketoconazole | 83/124=66.9% (<0.0001) | Mycological success |
| Nizoral | 74/121=61.2 %(<0.0001) | Mycological success |
| Placebo | 26/127=20.5% | Mycological success |
| Ketoconazole | 60/124=48.4% (<0.0001) | Clinical success |
| Nizoral | 59/121=48.8% (<0.0001) | Clinical success |
| Placebo | 20/127=15.8% | Clinical success |

* Fisher's exact test, compares compound to placebo.

Table 3: PP efficacy analysis (Week 8 visit)

| Treatment | % success (p-value*) | Endpoint |
|---|---|---|
| Ketoconazole | 40/80=50% (<0.0001) | Overall success |
| Nizoral | 44/92=48% (<0.0001) | Overall success |
| Placebo | 13/98=13% | Overall success |
| Ketoconazole | 58/80=72.5% (<0.0001) | Mycological success |
| Nizoral | 62/92=67.3% (<0.0001) | Mycological success |
| Placebo | 22/98=22.5% | Mycological success |
| Ketoconazole | 43/80=53.7% (<0.0001) | Clinical success |
| Nizoral | 50/92=54.4% (<0.0001) | Clinical success |
| Placebo | 19/98=19.4% | Clinical success |

* Fisher's exact test, compares compound to placebo.

The Week 6 data show similar trends:

Table 4: ITT efficacy analysis (Week 6 visit)

| Treatment | % success (p-value*) | Endpoint |
|---|---|---|
| Ketoconazole | 31/124=25% (<0.0001) | Overall success |
| Nizoral | 24/121=20% (0.0009) | Overall success |
| Placebo | 7/127=6% | Overall success |
| Ketoconazole | 75/124=60% (<0.0001) | Mycological success |
| Nizoral | 71/121=59%(<0.0001) | Mycological success |
| Placebo | 18/127=14% | Mycological success |
| Ketoconazole | 33/124=27% (0.0005) | Clinical success |
| Nizoral | 33/121=27% (0.0003) | Clinical success |
| Placebo | 12/127=9% | Clinical success |

* Fisher's exact test, compares compound to placebo.

Table 5: PP efficacy analysis (Week 6 visit)

| Treatment | % success (p-value*) | Endpoint |
|---|---|---|
| Ketoconazole | 20/80=25% (0.0013) | Overall success |
| Nizoral | 24/92=26% (0.0006) | Overall success |
| Placebo | 7/98=7% | Overall success |
| Ketoconazole | 51/80=63% (<0.0001) | Mycological success |
| Nizoral | 61/92=66% (<0.0001) | Mycological success |
| Placebo | 15/98=15% | Mycological success |
| Ketoconazole | 20/80=25% (0.0072) | Clinical success |
| Nizoral | 27/92=29% (0.004) | Clinical success |
| Placebo | 9/98=9% | Clinical success |

* Fisher's exact test, compares compound to placebo.

*Equivalence Analysis*

Based on the usual method used in OGD for binary outcomes, the protocol asks for the 90% confidence interval for the difference in proportions between test and reference treatment to 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

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

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

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)$$

and we reject $H_0$ if L > -.20 and U < .20.

Rejection of the null hypothesis $H_0$ supports the conclusion of equivalence of the two products.

The sponsor did not use Yates' correction, but the results are similar.

We analyzed the data for efficacy and equivalence for overall cure rate, mycological cure rate, and clinical cure rate in the per protocol population at the Week 8 visit. The sponsor performed the same analysis in the intent to treat population.

Table 6: 90% Confidence interval for difference of proportions of success ($P_{Ketoconazole} - P_{Nizoral}$), per protocol population, Week 8 visit.

| **Endpoint** | **90% Confidence Interval for $P_{Ketoconazole} - P_{Nizoral}$** |
|---|---|
| Overall success | (-12, .16) |
| Mycological success | ( -.08, .18) |
| Clinical success | (-.14, .13) |

The confidence intervals are included in the interval (-.20, .20), so equivalence of the two products is supported. From Table 3, note that the success rates of both active treatments are much more than .20 above the success rate of the placebo arm, suggesting that the treatment arms are not equivalent (in the sense defined above) to placebo.

The demographics of the per protocol population appear similar to those of the intent to treat population.

Table 7: The racial, gender and age distributions, Intent To Treat Population:

| Treatment | Gender male/female | Race Asian/Black/Caucasian/Hispanic/Other | Age Mean (Standard Deviation) |
|---|---|---|---|
| Ketoconazole | 79/45 | 3/27/80/12/2 | 46.6 (13.4) |
| Nizoral | 89/32 | 2/21/86/12/0 | 40.2 (13.6) |
| Placebo | 95/32 | 2/23/93/8/1 | 39.0 (13.4) |

Table 8: The racial, gender and age distributions, Per Protocol Population:

| Treatment | Gender male/female | Race Asian/Black/Caucasian/Hispanic/Other | Age Mean (Standard Deviation) |
|---|---|---|---|
| Ketoconazole | 56/24 | 3/16/50/10/1 | 41.4 (13.6) |
| Nizoral | 64/28 | 0/14/69/9/0 | 40.6 (14.1) |
| Placebo | 75/23 | 2/18/73/5/0 | 39.4 (13.4) |

As we can see from the following tables, the distribution of infection type of tinea pedis (interdigital or moccasin) among the different treatment arms and populations appear similar, too. In addition, cure rates between different types of tynea pedis appear similar for each (active) treatment arm and population.

Table 9: Distribution of interdigital vs. moccasin-type infection, Intent To Treat Population:

| Type of Tinea pedis | Ketoconazole | | Nizoral | | Placebo | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Total | Success | Total | Success | Total | Success | Total | Success |
| Interdigital | 61 | 30 (49%) | 58 | 24 (41%) | 68 | 8 (12%) | 187 | 62 (33%) |
| Moccasin-type | 63 | 25 (40%) | 63 | 25 (40%) | 59 | 5 (8%) | 185 | 55 (29%) |

Table 10: Distribution of interdigital vs. moccasin-type infection, Per Protocol Population:

| Type of Tinea pedis | Ketoconazole | | Nizoral | | Placebo | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Total | Success | Total | Success | Total | Success | Total | Success |
| Interdigital | 42 | 23 (54%) | 43 | 21 (48%) | 54 | 8 (15%) | 139 | 52 (37%) |
| Moccasin-type | 38 | 17 (44%) | 49 | 23 (46%) | 44 | 5 (11%) | 131 | 45 (34%) |

Also, the distribution of types of fungal infection among the different treatment arms and populations appear similar. In addition, cure rates between different types of fungal infection appear similar for each (active) treatment arm and population.

Table 11: Distribution of fungal infection, Intent To Treat Population:

| Type of infection | Ketoconazole | | Nizoral | | Placebo | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Total | Success | Total | Success | Total | Success | Total | Success |
| T. rubrum | 109 | 50 (46%) | 102 | 37 (36%) | 113 | 11 (10%) | 324 | 98 (30%) |
| T. metagrophites | 10 | 4 (40%) | 10 | 6 (60%) | 10 | 2 (20%) | 30 | 12 (40%) |
| E. floccosum | 5 | 1 (20%) | 11 | 7 (64%) | 7 | 0 | 23 | 8 (35%) |

Table 12: Distribution of fungal infection, Per Protocol Population:

| Type of infection | Ketoconazole | | Nizoral | | Placebo | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Total | Success | Total | Success | Total | Success | Total | Success |
| T. rubrum | 73 | 37 (50%) | 75 | 33 (44%) | 87 | 11 (13%) | 235 | 81 (34%) |
| T. metagrophites | 5 | 3 (60%) | 8 | 5 (62%) | 8 | 2 (25%) | 21 | 10 (48%) |
| E. floccosum | 2 | 0 | 10 | 7 (70%) | 5 | 0 | 17 | 7 (41%) |

*Safety Analysis*

Treatment duration was similar among the three treatment groups: 39.7+/-7.1 days, Ketoconazole: 40.3+/-5.9 days Nizoral, 40.3+/-5.3 days, Placebo. There were few adverse events and these were evenly distributed across the treatment groups.

Table 13: Adverse events occurring in 10 subjects or more

| | Ketoconazole | Nizoral | Placebo | Total |
|---|---|---|---|---|
| Headache | 19 (9.5%) | 17 (8.5%) | 16 (7.8%) | 52 |
| Infection | 8 (4%) | 7 (3.5%) | 12 (5.8%) | 27 |
| Lab test abnormality | 6 (3%) | 5 (2.5%) | 10 (4.9%) | 21 |
| Pain | 9 (4.5%) | 9 (4.5%) | 8 (3.9%) | 26 |
| Pharyngitis | 3 (1.5%) | 4 (2%) | 6 (2.9%) | 13 |
| Rhinitis | 7 (3.5%) | 7 (3.5%) | 8 (3.9%) | 22 |
| Sinusitis | 3 (1.5%) | 2 (1%) | 5 (2.4%) | 10 |
| Pruritus | 4 (2%) | 12 (6%) | 8 (3.9%) | 24 |
| Rash | 5 (2.5%) | 10 (5%) | 11 (5.3%) | 26 |
| Dysmenorrhea | 5 (2.5%) | 3 (1.5%) | 4 (1.9%) | 12 |

*Dropout rates*

The dropout pattern between the two types of tynea pedis seems to be similar across the treatments.

Table 14: Dropout rates PP/ITT by treatment and type of tynea pedis

| Type of Tinea pedis | Ketoconazole* | Nizoral* | Placebo* | Total* |
|---|---|---|---|---|

*Dropout rates*

The dropout pattern between the two types of tynea pedis seems to be similar across the treatments.

Table 14: Dropout rates PP/ITT by treatment and type of tynea pedis

| Type of Tinea pedis | Ketoconazole* | | Nizoral* | | Placebo* | | Total* | |
|---|---|---|---|---|---|---|---|---|
| | Total | Success | Total | Success | Total | Success | Total | Success |
| Interdigital | 42/61 (31%) | 23/30 (23%) | 43/58 (26%) | 21/ 24 (12%) | 54/68 (21%) | 8 /8 (0%) | 139/187 (26%) | 52/62 (16%) |
| Moccasin-type | 38/63 (40%) | 17/25 (32% ) | 49/63 (22%) | 23/25 (8%) | 44/59 (25%) | 5/ 5 (0%) | 131/185 (29%) | 45/55 (18%) |

*) Stay-in rate (dropout percentage)

Given the small number of E. floccosum infected patients and the imbalanced way they were randomized to treatment, (5-11-7), it is hard to claim that a significant difference in dropout rates and efficacy was observed.

Table 15: Dropout rates PP/ITT by treatment and type of mycological infection

| Type of infection | Ketoconazole* | | Nizoral* | | Placebo* | | Total* | |
|---|---|---|---|---|---|---|---|---|
| | Total | Success | Total | Success | Total | Success | Total | Success |
| T. rubrum | 73/109 33% | 37/ 50 26% | 75/102 26% | 33/37 11% | 87/113 23% | 11/11 0% | 235/324 27% | 81/98 17% |
| T. metagrophites | 5/10 50% | 3/4 25% | 8/10 20% | 5/6 17% | 8/10 20% | 2/2 0% | 21/30 30% | 10/12 17% |
| E. floccosum | 2/5 60% | 0/1 0% | 10/11 9% | 7/7 0% | 5/7 27% | 0/0 | 17/23 26% | 7/8 12% |

*) Stay-in rate (dropout percentage)

**Statistical Analysis Conclusions**

Both active treatment arms appear to be effective when compared to the placebo arm. The submitted data support the claim that TEVA's Ketoconazole and the reference drug, Nizoral, are equivalent. The analyses of the secondary endpoints confirm the findings for the primary endpoints. At the request of the medical reviewer, we checked and confirm that the statistical plan and the protocol, including the changes, are appropriate. The plan to include the moccasin-type tinea pedis infected patients in the trial is appropriate. The demographics, type of tinea pedis and type of infection did not differ among treatment groups, for either the ITT or PP population. The adverse events table summary reported by the sponsor is in concordance with the electronically submitted data. It shows that the adverse events were few and evenly distributed across the treatment groups.

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