SYNOPSIS

Issue Date: 15 September 2010

Name of Sponsor/Company	Janssen Pharmaceutica NV
Name of Finished Product	To be determined
Name of Active Ingredient(s)	Ketoconazole 2% Cream (F126)

Protocol No.: KETFUN3001

Title of Study: A double-blind, randomized, parallel group comparison of Nizoral® cream (F012), ketoconazole 2% cream (F126) and placebo (F000) in the treatment of interdigital Tinea pedis.

EudraCT Number: 2006-006513-33

Coordinating Investigator: Alan G. Wade, CPS Research, [redacted] United Kingdom

Publication (Reference): none

Study Period: 02 July 2007 to 31 March 2009

Phase of Development: 3b

Objectives:

Primary: To determine whether ketoconazole 2% cream (F126) is non-inferior to Nizoral cream (F012) in effecting a mycological cure (MC) following 4 weeks of treatment, following determination of superiority of both active treatment arms to placebo, in the treatment of symptomatic uncomplicated interdigital *Tinea pedis*. MC (defined as negative potassium hydroxide [KOH] microscopy and fungal culture) was assessed at Week 6.

Secondary: To compare the overall cure (OC) of ketoconazole 2% cream (F126) and Nizoral cream (F012), versus placebo (F000), at 6 weeks following a 4-week treatment regimen in the treatment of symptomatic uncomplicated interdigital *Tinea pedis*. OC was defined as MC in addition to a global clinical evaluation of either "Completely cleared" or "Marked Improvement" (assessed at Week 6).

Safety: To study the safety and tolerability of ketoconazole 2% cream (F126) in this subject population.

Pharmacokinetics (PK): To determine systemic exposure to ketoconazole following topical application of ketoconazole 2% cream (F126) and Nizoral cream (F012) in a subset of subjects.

Methods:

This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter Phase 3b non-inferiority study.

Subjects eligible for the study were assigned by randomized schedule in a 2:2:1 ratio to receive either Nizoral cream (F012), ketoconazole 2% cream (F126), or placebo cream (F000). The study consisted of 4 visits: a baseline visit (Visit 1), follow-up treatment visits after 2 and 4 weeks (Visit 2 and Visit 3), followed by a final off-treatment follow-up visit at Week 6 (Visit 4).

The study was terminated prematurely by the sponsor because of a lower than expected overall MC rate and significant discrepancies between KOH and fungal culture results.

Number of Subjects (planned and analyzed):

It was planned that between 900 and 1,050 subjects would be randomly assigned to study medication and treated (approximately 1,300 screened) to provide 418 subjects eligible for efficacy analysis. Plasma samples were to be obtained from a subset of 80 subjects.

A total of 776 subjects were screened and 583 subjects were randomized and treated before early termination of the study (234 subjects received ketoconazole, 230 subjects received Nizoral, and 119 subjects received placebo).

Diagnosis and Main Criteria for Inclusion:

Inclusion: Male or female, aged 18 years or more with symptomatic uncomplicated interdigital *Tinea pedis* confirmed by positive KOH microscopy examination were randomized. Subjects with negative baseline fungal cultures reported after randomization were considered not evaluable for the primary analysis but were not withdrawn from the study.

Exclusion: Subjects with confluent, diffuse moccasin type *Tinea pedis* of the entire plantar surface, onychomycosis; other dermatomycosis requiring active treatment; sensitivity to imidazole antifungal agents or other ingredients; prior oral antifungals < 6 weeks; prior topical antifungals < 2 weeks; oral antibiotics, corticosteroids or topical antibiotics and corticosteroids applied to the feet < 2 weeks; pregnancy or breast feeding were not included in the study.

Test Product, Dose and Mode of Administration, Batch No.:

Test product: Ketoconazole 2% cream (F126).

Dose and mode of administration: Subjects were provided with two 15 g tubes of cream (one given at the first visit and the subsequent tube dispensed at Visit 2 if required). Subjects were instructed to apply the study medication once daily (at night or in the evening) to affected areas of the feet.

Batch no.: 6LB3X00 and 8IB5R00

Reference Therapy, Dose and Mode of Administration, Batch No.:

Reference therapies: Nizoral cream (F012) and placebo cream (F000)

Dose and mode of administration: as for test product

Batch no.: 6LB4400 and 8IB1600 (F012), 7CB4E00 and 8IB6500 (F000)

Duration of Treatment:

The median duration of active or placebo treatment was 28 days (range 1 to 90 days) and the median duration of subject participation in the study including follow-up was 43 days (range 1 to 104 days).

Criteria for Evaluation

The efficacy evaluation was based on

- mycology data obtained from KOH microscopy (positive or negative) and fungal culture (positive, plus named pathogen or negative) at Visit 1 (baseline) and Visit 4 (Week 6),
- clinical signs and symptoms (absent, mild, moderate, severe) measured at all visits and
- a global clinical evaluation (*Tinea pedis* completely cleared, marked improvement, mild-moderate improvement, unchanged, worse) performed at Visit 3 (Week 4) and Visit 4 (Week 6).

The primary efficacy endpoint was MC (% of subjects) at Week 6. The secondary endpoint was OC (% of subjects) at Week 6.

The safety evaluation was based on the analysis of adverse events (AEs).

Plasma samples were obtained from a subset of subjects at Visit 1 (baseline), Visit 2 (Week 2) and Visit 3 (Week 4) to investigate systemic exposure during treatment.

Statistical Methods:

The study was designed to establish whether ketoconazole 2% cream (F126) is non-inferior to Nizoral cream (F012) in the therapy of *Tinea Pedis*.

Inferiority of F126 to F012 was to be rejected if the lower bound of the 95% two-sided confidence interval of the estimated difference (ie, F126 MC% – F012 MC%) was greater than -15%. This test was performed on subjects in the positive baseline culture set (PBCS), which was defined as subjects with a positive fungal culture at baseline. Prior to performing the test above, both active treatment arms were compared with and had to be superior to placebo with respect to the primary endpoint in subjects with a positive mycological assessment at baseline.

Inferiority of F126 to F012 in the secondary efficacy endpoint (OC) was to be rejected if the lower bound of the 95% two-sided confidence interval of the estimated difference (ie, F126 OC% – F012 OC%) in the PBCS was greater than -20%.

The analysis of safety data (eg, AEs) was based on subjects in the safety set (SS), ie, all randomized subjects who received at least one dose of study treatment.

The PK results were not statistically analyzed due to insufficient quantifiable data.

Results:

Of the 583 subjects who were randomized and treated, 519 subjects completed the study and 64 subjects (11%) discontinued during the study period. The main reason for discontinuation was lost to follow-up (5.8%). Withdrawals did not vary notably between treatment groups.

The overall mean age in the full analysis set (FAS) was 45.4 years (SD 14.5). The majority of subjects were male (71.7%) and White (93.6%). Demographic characteristics were comparable between treatment groups and analysis sets.

<u>EFFICACY RESULTS:</u>

The primary efficacy endpoint was the proportion of subjects in the PBCS with MC at Week 6. MC was achieved by 64 subjects (56.1%) in the ketoconazole (F126) treatment group, 64 subjects (57.7%) in the Nizoral (F012) treatment group and 11 subjects (19.6%) in the placebo group. As differences between the active treatment groups and placebo were statistically significant (both $p<0.001$) and the lower limit of the 95% confidence interval (CI; -0.146, 0.116) was greater than the pre-defined threshold for non-inferiority (-15.0%), .there was evidence to support non-inferiority of ketoconazole to Nizoral based on MC.

The secondary efficacy endpoint was the proportion of subjects in the PBCS with OC at Week 6. OC was achieved by 50 subjects (43.9%) in the ketoconazole treatment group, 55 subjects (49.5%) in the Nizoral treatment group and 5 subjects (8.9%) in the placebo group. As differences between the active treatment groups and placebo were statistically significant (both $p<0.001$) and the lower limit of the 95% CI was -18.8% and thus greater than the pre-defined threshold for non-inferiority (-20.0%), there was also supportive evidence of non-inferiority of ketoconazole to Nizoral based on OC.

Supportive analyses of MC and OC based on the full analysis set (FAS) confirmed these results.

SAFETY RESULTS: During the 4-week treatment period and the 2-week follow-up period, the frequency of subjects experiencing treatment emergent AEs (TEAEs) was comparable between treatment groups.

	Ketoconazole (F126) N = 234 n (%)	Nizoral (F012) N = 230 n (%)	Placebo (F000) N = 119 n (%)
Subjects with ≥1 TEAEs	57 (24.4)	54 (23.5)	30 (25.2)
Subjects with ≥1 mild TEAEs [a]	36 (15.4)	33 (14.3)	17 (14.3)
Subjects with ≥1 moderate TEAEs [a]	19 (8.1)	16 (7.0)	11 (9.2)
Subjects with ≥1 severe TEAEs [a]	2 (0.9)	5 (2.2)	2 (1.7)
Subjects with ≥1 treatment-related TEAEs [b]	4 (1.7)	12 (5.2)	3 (2.5)
Subjects who withdrew from study due to TEAEs [c]	4 (1.7)	5 (2.2)	2 (1.7)
Subjects who had study medication suspended due to TEAEs	2 (0.9)	2 (0.9)	0
Subjects with ≥1 serious TEAEs	2 (0.9)	5 (2.2)	2 (1.7)
Subjects with ≥1 TEAE of specific interest [d]	15 (6.4)	20 (8.7)	10 (8.4)

[a] Subjects are counted only once in the category for their most severe event.
[b] Investigator assessments of "probable", "possible", or "unknown" relationship.
[c] Subjects [redacted] (ketoconazole), [redacted] (Nizoral), [redacted] (placebo) and [redacted] (placebo) are included above as subjects who withdrew from the study due to a TEAE however their primary reason for withdrawal in was a lack of efficacy and not non-serious or serious adverse event
[d] Symptoms of "irritation", "burning" and "dermatitis" were defined as TEAEs of specific interest.

N = number of randomized subjects in analysis set and treatment group; n = number of subjects with observation; TEAE = treatment-emergent adverse event; % = percentage based on N.

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The overall frequency of subjects with TEAEs on the system organ class (SOC) and preferred term level and the frequency of subjects with TEAEs of specific interest were similar in the 3 treatment groups except for gastrointestinal disorders and skin and subcutaneous tissue disorders:

Gastrointestinal disorders were reported more frequently for subjects in the ketoconazole (F126) treatment group (10 subjects, 4.3%), than in the Nizoral (F012) and placebo groups (4 subjects, 1.7%, and 3 subjects, 2.5%, respectively). Gastrointestinal disorders that occurred in more than 1 subject were diarrhoea (3 subjects, 1.3%), abdominal pain upper, and vomiting (2 subjects each, 0.9%) in the ketoconazole treatment group and dyspepsia (2 subjects, 0.9%) in the Nizoral group.

Skin and subcutaneous tissue disorders (all defined as TEAEs of specific interest), were reported more frequently in the active treatment groups (ketoconazole: 10 subjects, 4.3%; Nizoral: 11 subjects 4.8%), than in the placebo group (2 subjects 1.7%). The following skin and subcutaneous tissue disorders were reported for more than 1 subject: pruritus (5 subjects) and rash (2 subjects) in the ketoconazole treatment group; and erythema, pruritus (3 subjects each), blister, dermatitis, and rash (2 subjects each) in the Nizoral treatment group.

In each of the 3 treatment groups the frequency of subjects with severe TEAEs or TEAEs that were assessed as treatment related by the investigator was low.

Eleven severe TEAEs were reported for 9 subjects; 2 subjects (0.9%) treated with ketoconazole, 5 (2.2%) treated with Nizoral, and 2 (1.7%) in the placebo group. Four severe TEAEs were of specific interest.

Twenty-seven TEAEs assessed as treatment-related by the investigator were reported for 19 subjects. The frequency was higher in the Nizoral treatment group (12 subjects, 5.2%) than in the ketoconazole treatment group (4 subjects, 1.7%) or in the placebo group (3 subjects, 2.5%). Twenty-four treatment-related TEAEs were of specific interest, the majority (15 events) in the Nizoral treatment group: pruritus (3 subjects), dermatitis, erythema, rash (2 subjects each), application site pruritus, application site reaction, tinea pedis [ie, worsening of *Tinea pedis*], blister, rash pruritic, and skin irritation (1 subject each). In the ketoconazole treatment group, 6 events of specific interest related to study medication were reported (application site reaction, oedema peripheral, dermatitis contact, pruritus, skin discolouration, and skin irritation). In the

placebo group 3 events of specific interest were assessed as related to study treatment by the investigator (application site erythema, tinea pedis [ie, worsening of *Tinea pedis*], and pruritus).

Nine serious TEAEs were reported in 9 subjects. No subject died. There was no TEAE of specific interest among the serious TEAEs. The majority of subjects with serious TEAEs had been treated with Nizoral (5 subjects, 2.2%). Two subjects had been treated with ketoconazole (0.9%) and 2 had received placebo (1.7%). Eight of the 9 serious TEAEs were assessed by the investigator as not related to treatment. In one case the relationship was unknown.

Sixteen TEAEs leading to withdrawal were reported for 11 subjects. Seven events in 4 subjects (1.7% of subjects) occurred in the ketoconazole treatment group. Another 7 events were reported for 5 subjects (2.2%) in the Nizoral treatment group; 2 events were reported for 2 subjects (1.7%) in the placebo group. Thirteen TEAEs leading to withdrawal were of specific interest with no relevant differences between the 3 treatment groups.

Eleven TEAEs leading to suspension of the study treatment were reported for 4 subjects. In the ketoconazole treatment group 5 events were reported for 2 subjects (0.9% of subjects); in the Nizoral treatment group 6 events were reported for 2 subjects (0.9%). TEAEs leading to suspension of the study treatment did not occur in the placebo group. Six TEAEs leading to suspension of the study treatment were of specific interest with no relevant differences between the 2 active treatment groups.

STUDY LIMITATIONS: The study was terminated prematurely by the sponsor because of a lower than expected overall MC rate and significant discrepancies between KOH and fungal culture results.

CONCLUSION: Study KETFUN3001 was designed to demonstrate non-inferiority of the new ketoconazole 2% cream (F126) formulation to the currently marketed Nizoral cream (F012) formulation in the treatment of symptomatic uncomplicated interdigital *Tinea pedis*.

The study provides evidence of non-inferiority of ketoconazole 2% (F126) to Nizoral (F012) cream with regard to efficacy although the study was prematurely terminated with fewer subjects included than originally planned.

The safety results imply a similar tolerability of the new formulation F126 compared to the current formulation F012.

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