EudraCT Synopsis
DE0109

Title of Trial:

Randomized, parallel-group study of efficacy and tolerability of the association of Amycor Onychoset® with Amycor® cream and terbinafine versus terbinafine administration in adults suffering from toenail onychomycosis with matrix involvement.

Investigational Products:

Amycor Onychoset® / Amycor® cream

Trial No.:

DE0109

2009-012208-18

Study Centers:

A total of 15 active centers participated in the study in France.

Trial Initiation Date:

26 October 2009

Trial Completion Date:

10 May 2012

Development Phase:

Phase 4

Publication (reference):

None

Study Objectives:

Primary Objective:

- To compare the overall treatment response (failure, improvement, success) at 12 months on the target nail, 9 months after treatment cessation between two groups of patients with toenail onychomycosis with matrix involvement, and treated with either an association of terbinafine for 3 months concomitantly with Amycor Onychoset® for 1-3 weeks (until the fall of the target nail) followed by Amycor® cream for 8 weeks, or 3 months of terbinafine alone.

Secondary Objectives:

- To compare the overall treatment response (failure, improvement, success) at 6 months on the target nail, 3 months after treatment cessation between the two groups of patients defined above.
- To compare the treatment clinical response (failure, improvement, success) at 6 and 12 months on the target nail between the two patient groups defined above.

- To evaluate and compare the success time on the target nail between the two patient groups defined above.
- To evaluate and compare time to relapse on the target nail between the two patient groups defined above.
- To evaluate and compare the relapse rate at 12 and 18 months on the target nail between the two patient groups defined above.
- To evaluate and compare the clinical response (failure, improvement, success) on the other nails injured than the target nail at 6 and 12 months between the two groups of patients defined above.

Methodology:

National, multicenter, randomized, open, parallel-group, controlled compared to the reference drug (terbinafine).

Number of Subjects (Planned and Analyzed):

The planned number of patients was 130, i.e. 65 per treatment group.

In total, 90 patients were selected. Among these 90 patients, 42 patients were randomized in the study (21 in the Group A = Amycor Onychoset® / Amycor® + terbinafine and 21 in the Group B = terbinafine alone).

Diagnosis and Main Criteria for Inclusion/Exclusion:

- Men and women aged 18 to 75 years,
- Experiencing onychomycosis of 1 or more toenails with matrix involvement of target nail,
- Having a positive culture of dermatophyte species at 4 weeks,
- Having interrupted any systemic antifungal therapy at least 6 months prior to enrollment and any local antifungal therapy at least 3 months before inclusion,
- Having been informed of the study objectives and having given their written informed consent to participate,
- Affiliate(s) to social security system or beneficiaries of such a plan.

Study Treatment:

Test Product: Amycor Onychoset® ointment (bifonazole 1%, urea 40%), 1 application per day for 1-3 weeks until the fall of the target nail and treated nails, followed by a daily application of Amycor® 1% cream (bifonazole 150 mg) on the nail bed for 8 weeks.

Reference Product: Terbinafine Almus® 250 mg (terbinafine), scored tablet, one tablet per day administered once daily for 3 months.

Treatment Duration: 9-11 weeks of topical treatment in association with 12 weeks of oral treatment (group A) or 12 weeks of oral therapy alone (group B). The maximum duration of treatment was 3 months in each of the treatment groups.

Criteria for Evaluation:

Efficacy:

Primary:

- Percentage of responders to patients at 12 months of the nail target (between V1 and V5 visits).

A responder was defined as scoring success on a scale of three levels (failure / improvement / success).

Secondary:

- Evaluation of the overall response at 6 months between V1 and V4 on the target nail
- Evaluation of clinical response at 6 months (between V1 and V4) and 12 months (V1 and V5) on the target nail
- Evaluation of the overall success time on the target nail
- Evaluation of relapse rates at 12 months and 18 months (V5 and V6) on the target nail
- Evaluation of time to relapse on the target nail
- Evaluation of the clinical response of other nails than the target nail at 6 months and 12 months (between V1 and V4 and V1 and V5).

Safety Evaluations:

- Evaluation of local and systemic tolerance of the 3 products associated or not in the two treatment groups (recording and monitoring all local or systemic AE and serious AE [SAE])
- Systematic laboratory tests at patient selection (V0), one month after treatment (V2) and at the end of the treatment period of 3 months.

Statistical Methods:

Descriptive and exploratory statistical analyses were conducted on intent-to-treat (ITT), full analysis set (FAS) and per -protocol (PP) populations.

Quantitative variables were described by the number of available values, number of missing data, mean, standard deviation (SD), the 1st and 3rd quartiles, median, minimum (min) and maximum (max.). Regarding the qualitative variables, these have been described by the number of available values, number of missing values, the frequency and percentage per modality.

Results

Efficacy results

Primary Endpoint

The primary endpoint was the responder rate at 12 months on the target nail (overall response).

In the FAS population, the responder rate (success) by Last Observation Carried Forward analysis (LOCF) method was higher in the group of patients treated with t Amycor® + terbinafine (66.7%, 95% CI of [41.0, 86.7]) compared to those receiving terbinafine alone (52.9%, 95% CI of [27.8, 77.0]), but no statistically significant differences could be found between the 2 treatment groups ($p = 0.50$).

Secondary Endpoints

Similarly, the proportion of responders at 6 months (V4) 3 months after treatment cessation, according to the LOCF method, was comparable in the two treatment groups: 61.1% in the group combining Amycor® vs. 47.1 % in the terbinafine alone group without statistically significant difference between the 2 groups ($p = 0.73$).

A similar trend was observed for the clinical response defined as disappearance of all lesions on the target nail or residual total area < 10 % compared to baseline just as well at 6 months (61.1% in the group combining Amycor® vs. 52.9% in the alone terbinafine group, $p = 0.69$) as at 12 months (respectively, 66.7% vs. 52.9 %, $p = 0.51$).

Regarding the median global and clinical success time, they were identical and amounted to 24.0 days in each of the 2 treatment groups.

Finally, the relapse rate was low in each of the 2 groups without statistically significant difference at 12 months (11.8% in Amycor® + terbinafine vs. 0 % with terbinafine alone, $p = 0.50$) and at 18 months (respectively 0% vs. 10.0%, $p = 0.43$).

In addition, the clinical course of patients in the study showed an improvement in symptoms at the end of the study (M18) from baseline with a disappearance of the tablet thickening, the distoproximales rockets, of onycholysis in the majority of patients, a lack of melanonychia and a decrease in injured surface of the target nail and other nails by onychomycosis, and a good clinical response with a quasi-disappearance of all lesions on the target nail in the majority of cases. With a few exceptions, the results were generally comparable between the 2 treatment groups.

A trend in favor of Amycor® + terbinafine was observed concerning the reduction of the injured target nail mean area since inclusion that seemed greater in this group compared with terbinafine alone group at each visit (from W4 to M18), however, this difference was not sufficient to demonstrate a statistically significant difference ($p \geq 0.14$).

Finally, the majority of patients who had more than three injured nails by onychomycosis at inclusion had only 1-2 affected by the disease at the end of study, this finding was observed faster in the terbinafine alone group after 1 month of treatment (W4) than in the Amycor® + terbinafine group after 3 months of treatment (W12).

Safety Results

The safety profile was generally similar between the two treatment groups. The overall incidence of AEs was comparable between the two groups: 66.7% in the Amycor® + terbinafine group vs. 61.9% in the alone terbinafine group (p = 1). The most frequently reported AE was fatigue (9.5%) in the Amycor® + terbinafine group while arthralgia (9.5%) was the most frequently reported AE in the terbinafine alone group. All other AEs occasionally occurred with an incidence equal to 4.8%.

The majority of AEs reported during the study were mild to moderate (56 AEs/58 AEs). A total of 2 AEs were considered severe: traumatic brain injury reported by a patient (4.8 %) in the Amycor® + terbinafine group and arthralgia reported by a patient (4.8 %) receiving terbinafine alone.

During the study, no deaths occurred, and 4 SAEs were reported: severe head injury in patients with Amycor® + terbinafine, arthralgia of severe intensity, moderate inguinal hernia and moderate pulmonary superinfection in the terbinafine group. Only the causality assessment of "arthralgia" as SAE was considered possibly related to treatment.

The proportion of patients with at least one AE considered related to treatment (23.8% in the Amycor® + terbinafine group vs. 9.5% in the terbinafine alone group, p = 0.41) or having resulted in a final treatment discontinuation (19.0 % vs 4.8 %, p = 0.34) were statistically comparable between treatments.

Few AEs led to premature withdrawal from the study occurring in 9.5 % of patients with Amycor ® + terbinafine vs. 4.8 % of patients in the terbinafine alone group).

No significant difference could be demonstrated on the results of the general clinical examination and renal function tests.

Conclusion(s):

The efficacy of the terbinafine association for 3 months concomitantly with Amycor Onychoset® for 1-3 weeks (until the fall of the target nail) followed by Amycor® cream for 8 weeks in patients suffering from toenails onychomycosis with matrix involvement was comparable to that of patients treated with 3 months of terbinafine.

The overall treatment response (failure, improvement, success) at 12 months on the nail target, 9 months after treatment discontinuation, was higher in the group treated with Amycor® + terbinafine group (66.7%) compared with terbinafine alone (52.9%), but no statistically significant difference could be demonstrated (p = 0.50) due to low numbers.

The safety profile was comparable in each of the two treatment groups.