SYNOPSIS

Title of trial: Multicentre, randomised, parallel, double-blind clinical trial to evaluate the efficacy and safety of eberconazole 1% solution compared to placebo in the treatment of dermatophytoses

Investigators and Centre(s): Multicentre study

Objectives:
Primary objective: Comparison of the efficacy of eberconazole 1% solution against placebo in the treatment of dermatophytosis patients by clinical and mycological evaluation after five weeks.
Secondary objectives:
- To compare the changes in signs/symptoms obtained after two weeks of treatment with eberconazole 1% solution against placebo.
- To compare the changes in signs/symptoms obtained after four and five weeks with eberconazole 1% solution against placebo.
- To compare the mycological study results obtained in the cultures after five weeks with eberconazole 1% solution against those obtained with placebo.
- To compare the tolerability and safety of the two treatments.
- To compare the number of patients with (clinical) cure or improvement in each of the two treatments, after four and five weeks.

Methodology:
Multicentre, randomised, parallel, double-blind, phase III clinical trial, on male and female patients aged 18 years or over with a clinical diagnosis of dermatophytosis (*Tinea corporis*, *Tinea pedis* and *Tinea cruris*) suitable for local treatment. The patients were randomly assigned to one of the two treatment groups: eberconazole 1% solution or placebo.

This study consisted of three periods: inclusion, treatment and test of cure. The total duration of treatment in each group was 4 weeks. The study was planned according to the following visits:

Period 1:
Screening visit (V0, day -7 to 0)
Demographic data, baseline data, choice of reference lesion, evaluation of signs and symptoms (erythema, desquamation and pruritus) and sample collection to perform direct microscopic examination and mycological culture to demonstrate the presence of dermatophytes.

Inclusion visit (V1, day 0)
Assignment of treatment. Those patients who had a positive result in the direct microscopic examination at V0, could have V0 and V1 on the same day.

Period 2:
Follow-up visit (V2, day 14±4)
Evaluation of signs and symptoms (erythema, desquamation and pruritus). Safety.

End of treatment visit (V3, day 28±4)
Evaluation of signs and symptoms (erythema, desquamation and pruritus), measurement of treatment compliance and safety.

Period 3:
Test of cure visit (V4, day 35±4)
Evaluation of signs and symptoms (erythema, desquamation and pruritus), performing of mycological culture (if possible to take a sample) and safety.

Diagnosis and main criteria for inclusion:
- Male and female patients aged 18 years or over.
- Clinical diagnosis of dermatophytosis (*Tinea corporis, pedis and cruris*) suitable for local treatment.
- That a sample could be obtained for culture.
- With presence of signs and symptoms in the reference lesion: erythema (minimum score of 1), desquamation (minimum score of 2) and pruritus (minimum score of 1).
- Positive direct microscopy considering the presence of fungal elements as positive.
- Patients capable of correctly following the study instructions.
- Patients who had given their written Informed Consent to participate in the study.

Investigational product, dose and mode of administration, batch number:
Eberconazole 1% cutaneous spray solution
Therapeutic group: D01AC
Route of administration: topical
Mode of administration: twice a day (every 12 hours) for 4 weeks
Batch number: **G148/178C**

Reference therapy, dose and mode of administration, batch number:
Placebo with characteristics identical to the investigational product as regards visible physical characteristics, administered twice a day (every 12h) for 4 weeks
Batch number: **G148/178C**

Duration of treatment:
The duration of treatment for each patient was 4 weeks.

Criteria for evaluation:
(1) Efficacy:
- Primary endpoint: The primary objective of the study was to evaluate the efficacy of Eberconazole 1% solution for the treatment of dermatophytosis. The efficacy was measured from the percentage of effective responses (clinical and mycological combined variable) one week after having completed treatment.
- Secondary endpoints:
  - Changes in signs/symptoms after two weeks of treatment (V2).
  - Changes in signs/symptoms after four (V3) and five weeks (V4).
  - Mycological study results obtained in the cultures after five weeks (V4).
  - Percentage of patients with clinical cure or improvement in each of the two treatments after four and five weeks.

(2) Safety: Monitoring and recording of AE and SAE. The adverse events were coded according to the World Health Organisation classification for adverse events (MedDRA, version 11), and were described by a synonym (Preferred Term) and the system/organ (SOC) affected, severity, seriousness and causality relationship with the study treatment.

Statistical methods:
- Primary efficacy analysis: the clinical signs and symptoms, clinical assessment and results of the mycological culture were described one week after the end of treatment. The primary hypothesis was assessed by comparing the proportion of patients who experienced effective responses (clinically and by culture) against those who experienced failure, using a Chi-square test.
- Secondary efficacy analysis: the clinical assessment based on the evaluation of the signs and symptoms 2, 4 and 5 weeks after beginning treatment and the mycological study results after 5 weeks were evaluated using the Mann Whitney U test. The number of patients with (clinical) cure or improvement in each of the two treatments, after 4 and 5 weeks, was compared using the Chi-square test.

Both the primary and secondary efficacy analyses were performed for the modified intention-to-treat population, the intention-to-treat population and the modified per protocol population.
- Safety analysis: The safety population, which included all patients who took at least one dose of the study medication, was used.
- Previous history and demographic characteristics: the baseline characteristics have been tabulated for all the randomised patients, for each treatment and for the total population. The number of valid cases, mean, standard deviation, median, 25th percentile, 75th percentile, maximum value, minimum value, 95% confidence interval for the mean and standard error are shown for the continuous variables.

SUMMARY OF RESULTS/CONCLUSIONS

Efficacy results:
The primary efficacy analysis did not demonstrate the superiority of eberconazole 1% solution compared to placebo in the treatment of dermatophytoses. However, the results of the secondary efficacy analysis did show the superiority of eberconazole 1% solution compared to placebo in the treatment of dermatophytosis.
The results of the assessment of the characteristic signs/symptoms of superficial dermatophytoses showed the effectiveness of eberconazole in the attenuation of erythema and pruritus; the absence of differences in the assessment of desquamation between the two treatment groups may be due to the alcohol content of the solutions applied, therefore, having no direct link with the dermatophytosis under study. This situation justified performing an additional efficacy analysis, in which patients with mild desquamation and negative culture were considered as an effective response. In this analysis, a higher

proportion of effective responses was observed in the patient group treated with eberconazole 1% solution compared with placebo.
Eberconazole 1% solution administered for 4 weeks constitutes an effective treatment against dermatophytosis.

Safety results:
Treatment of dermatophytosis with eberconazole 1% solution administered in one application every 12 hours for 4 weeks has a good safety and tolerability profile.
The incidence of related adverse events was 1.6% in the patient group treated with eberconazole solution. In the patients treated with eberconazole solution, there was only one severe related AE, a case of pruritus. No serious adverse events were reported during the study.

Final conclusion:
Eberconazole 1% cutaneous spray solution administered every 12 hours for 4 weeks is an effective treatment against dermatophytoses. The results of clinical assessment of the reference lesion and the mycological evaluation show the superiority of eberconazole 1% solution compared to placebo in the treatment of dermatophytosis. The safety profile of eberconazole 1% cutaneous spray solution is equivalent to that of placebo administered with the same posological regimen and for the same period of time.