2 Synopsis

Sponsor:	Dermapharm AG, Grünwald	
Study title:	Double-blind, randomised clinical study comparing efficacy and safety of terbinafine cream 1% vs. Lamisil® cream vs. vehicle in patients with tinea pedis	
Study phase:	Phase III	
Investigators / study centres:	5 investigators in 5 study centres; a list of investigators and study centres is attached in appendix 16.1.4	
Publication:	No	
Study period:	First patient first visit February 13, 2009	Last patient last visit April 16, 2010
Number of patients:	Planned: 325	Analysed: 323
Objectives:	Evaluation of efficacy and safety of a new preparation terbinafine cream 1% versus the approved preparation Lamisil® cream versus vehicle in patients with tinea pedis. The study aims to show therapeutic equivalence (non-inferiority) of the test preparation as compared to Lamisil® and superiority of both active medications over the vehicle.	
Study indication:	Tinea pedis	
Test drug:	Terbinafine cream 1%	
Active ingredient:	Terbinafine	
Comparators:	Lamisil® cream Underlying vehicle	
Dose:	Dependent on affected skin area	
Mode of administration:	To be rubbed in slightly in the affected and surrounding skin areas once daily	
Batch no:	080901	
Duration of treatment:	Day 0 to Day 7: Double-blind treatment with study drug	

Main criteria for inclusion:

- Males and females in the age of ≥ 18 years
- Diagnosis of “tinea pedis interdigitalis” proven by a positive microscopic native preparation in 30 % potash lye
- At least moderately severe clinical picture, i.e. the value of sum score of the clinical parameters pruritus, erythema, desquamation, exsudation, vesiculae and pustules is ≥ 4

Methodology:

- Randomised, double-blind, multi-centre study with three parallel treatment groups
- Evaluation of the clinical symptoms erythema, desquamation, pruritus, vesiculae, pustules and exsudation by means of a 4-category ranking scale
- Evaluation of mycological culture
- Evaluation of therapeutic success by the investigator and the patient by means of a 5-category ranking scale
- Global evaluation of overall therapeutic success by the investigator by means of a 4-category ranking scale

Criteria for evaluation:

Efficacy

Primary efficacy variable:

Proportion of patients (in %) with clinical and mycological therapeutic success at Day 21

Clinical success: Sum score of clinical parameters ≤ 2 and score values of all individual clinical parameters ≤ 1

Mycological success: Negative result of the laboratory mycological investigation

Secondary efficacy variables:

- Proportion of patients with clinical and mycological therapeutic success at Day 7
- Proportion of patients with clinical therapeutic success at Day 7 and at Day 21
- Proportion of patients with mycological success at Day 7 and at Day 21
- Changes in the sum score of the 6 clinical parameters between Day 0 and Day 7 and between Day 0 and Day 21
- Course of the individual clinical parameters between Day 0 and Day 7 and between Day 0 and Day 21
- Evaluation of therapeutic success by the investigator at Day 7
- Evaluation of therapeutic success by the patient at Day 7 and Day 21
- Global evaluation of overall therapeutic success by the investigator at Day 21
- Proportion of patients with “relapse” at Day 21

Safety

- Number and classification of adverse events
- Evaluation of tolerability by the investigator at Day 7
- Evaluation of tolerability by the patient at Day 7

Statistical methods:

Non-inferiority test for terbinafine cream as compared to Lamisil® cream with $\alpha = 0.025$

Significance test between terbinafine cream and the vehicle and between Lamisil® cream and the vehicle with $\alpha = 0.05$ for each test

All other statistical tests were exploratory.

Summary of results:

Efficacy results:

The proportion of patients with clinical **and** mycological cure at Day 21 was 64.3% (ITT data set) / 63.3% (PP data set) for Ter-C, 59.7% (ITT data set) / 59.1% (PP data set) for Lam-C and 47.6% (ITT data set) / 48.1% (PP data set) for the vehicle. Non-inferiority of Ter-C vs. Lam-C ($p = 0.0012$ for the PP data set) and superiority of Ter-C over the vehicle ($p = 0.0299$ for the ITT data set) could be statistically proven, but Lam-C failed to provide a statistically significant result when compared to the vehicle ($p = 0.1241$ for the ITT data set).

The clinical cure rates (irrespective of mycological success) at Day 21 were higher for Ter-C than for Lam-C (79.8% vs. 66.9%), for the mycological cure rates (irrespective of clinical success) it was the other way around (Ter-C: 80.6%, Lam-C: 89.1%). For the vehicle the percentages were smaller (64.1% and 66.7%, respectively).

One patient in each of the two active treatment groups and 3 patients under the vehicle had a relapse at the end of the study.

Safety results:

Adverse events were reported for 15 patients (Ter-C: 6, Lam-C: 6, Vehicle: 3).

There were three patients (Lam-C: 2, Vehicle: 1) with serious adverse events, but none of the events were causally related to the study medication. One patient in the Ter-C group had an AE with suspected causal relationship. The associated preferred term was *pruritus*, and the symptom was observed outside the test area. The intensity was *mild* and the patient recovered without sequelae.

Conclusion:

Efficacy conclusions:

In summary, the main study objective, i.e. to show the non-inferiority of the new terbinafine cream compared to the approved Lamisil® cream could be statistically proven. In addition, the superiority of the test drug over the underlying vehicle could be proven although the proof of superiority of the approved regimen Lam-C over the vehicle failed. This means that the statistical testing procedure for the composite testing problem was not successful, but only due to the failed proof of superiority of the approved regimen Lam-C over the underlying vehicle.

Safety conclusions:

In conclusion, the application of all three preparations was well tolerated and safe. There were no critical or new findings regarding safety for any of the tested preparations.

Overall conclusions:

- the non-inferiority of the new terbinafine cream as compared to Lamisil® cream could be statistically proven,
- the new terbinafine cream showed equal efficacy compared to the approved Lamisil® cream containing the same active ingredients,
- the superiority of the new terbinafine cream over the underlying vehicle could be proven,
- the statistical testing procedure for the composite testing problem was not successful, but only due to the failed proof of superiority of the approved regimen Lam-C over the underlying vehicle,
- the sum score and the individual symptoms improved steadily during the study in all treatment groups,
- the application of all three preparations was well tolerated and safe.

Date of report:	June 28, 2010 (version 1.0)
Earlier reports:	No