2 Synopsis

Sponsor:	Dermapharm AG, Grünwald	
Study title:	Double-blind, randomised clinical study comparing efficacy and safety of a nystatin (100000 I.E./g) and hydrocortisone acetate (5 mg/g) containing paste versus a nystatin (100000 I.E./g) paste without hydrocortisone acetate in patients with moderate to severe inflammatory Candida skin disease	
Study phase:	Phase III	
Investigators / study centres:	6 investigators in 6 study centres; a list of investigators and study centres is attached in appendix 16.1.4	
Publication:	No	
Study period:	First patient first visit April 08, 2008	Last patient last visit March 03, 2010
Number of patients:	Planned: 280	Analysed: 276
Objectives:	Assessment of efficacy and safety of a nystatin and hydrocortisone acetate containing paste versus a nystatin paste without hydrocortisone acetate in patients with moderate to severe inflammatory Candida skin disease. Main focus is on the investigation of the hydrocortisone component in the test drug.	
Study indication:	Moderate to severe inflammatory Candida skin disease	
Test drug:	Nystaderm comp. Paste	
Active ingredients:	Nystatin (100000 I.E./g) and hydrocortisone acetate (5 mg/g)	
Comparator:	Nystatin (100000 I.E./g) containing paste without hydrocortisone acetate	
Dose:	Dependent on affected skin area	
Mode of administration:	To be rubbed in slightly in the affected and surrounding skin areas twice daily (morning, evening)	
Batch no:	Batch no. 080101 until January 15, 2010, no. 091004 thereafter	
Duration of treatment:	Day 0 to Day 7: Double-blind treatment with study drug Day 7 to Day 14: Open treatment with comparator drug	

Main criteria for inclusion:

- Males and females in the age of ≥ 18 years
- Diagnosis of "Candida skin disease" mycologically proven by a positive result of a swab revealing at least a moderate number of fungi
- At least moderate severity of inflammation parameters redness and exsudation (score value ≥ 2)
- Sum score of clinical parameters dysesthesia / burning, redness, pustulae / vesiculae, exsudation, maceration and expansion must be ≥ 10

Methodology:

- Randomised, double-blind, multi-centre, parallel group study with active comparator
- Evaluation of the clinical symptoms dysesthesia / burning, redness, pustulae / vesiculae, exsudation, maceration and expansion 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:

Change in the sum score of clinical parameters dysesthesia / burning, redness, pustulae / vesiculae, exsudation, maceration and expansion between Day 0 and Day 3, calculated as value at Day 0 minus value at Day 3

Secondary efficacy variables:

- Change in the sum score of the 6 clinical parameters between Day 0 and Day 7, Day 14 and Day 21, respectively
- Course of the individual clinical parameters dysesthesia / burning, redness, pustulae / vesiculae, exsudation, maceration and expansion and for the sum score between Day 0 and Day 21
- Number (proportion) of patients mycologically cured at Day 7, Day 14 and Day 21, respectively
- Number (proportion) of patients clinically cured at Day 7, Day 14 and Day 21, respectively
- Number (proportion) of patients mycologically and clinically cured at Day 7, Day 14 and Day 21, respectively
- Evaluation of therapeutic success by the investigator at Day 3, Day 7 and Day 14
- Evaluation of therapeutic success by the patient at Day 3, Day 7 and Day 14
- Global evaluation of overall therapeutic success by the investigator at Day 21

Safety

- Number and classification of adverse events
- Evaluation of tolerability by the investigator at Day 3, Day 7, Day 14 and Day 21
- Evaluation of tolerability by the patient at Day 3, Day 7, Day 14 and Day 21

Statistical methods:

Testing for significance between treatment groups for the primary efficacy variable using the two-sided t-test with $\alpha = 0.05$.

All other statistical tests were exploratory.

Summary of results:

Efficacy results:
The mean change in the sum score between Day 0 and Day 3 was equal to 4.36 points in both treatment groups ($p = 0.9907$). This means that superiority of the test preparation over the reference preparation could not be proven.

In both treatment groups continuous improvement during the study was observed for all clinical parameters. The clinical cure rates were slightly higher under the test preparation, but there were no treatment differences with respect to mycological cure.

Safety results:
Adverse events were reported in 13 patients (NYS-HCA: 4, NYS: 9). There was one serious adverse event (*tympanoplasty*), which occurred in the NYS-HCA group (no causality with the study medication).

Three patients (all in the NYS group) had AEs with suspected causal relationship to the study medication. The associated preferred terms were *dermatitis contact* (in 2 patients) and *application site pain*.

Conclusion:

Efficacy conclusions: a continuous improvement of the skin symptoms was observed during the study for all clinical parameters in both treatment groups. Both preparations were effective in treating moderate to severe inflammatory Candida disease. However, the study objective to prove the superiority of NYS-HCA over NYS was missed.

Safety conclusions: no relevant or critical findings regarding safety of both preparations could be observed during the study course and the application of both preparations appears to be safe.

Overall conclusions:

- Both preparations, NYS-HCA and NYS were effective in treating moderate to severe inflammatory Candida skin disease,
- There were no statistically significant differences between the treatment groups for any of the efficacy parameters analysed,
- There were some indications that NYS-HCA might have favorable effects compared to NYS, however, the evidence of these effects is limited by the fact that these effects might also have occurred randomly,
- The application of both preparations was safe with a low incidence of causally related adverse events in the NYS group only,
- It is possible that the addition of HCA to nystatin may prevent some adverse drug reactions like contact dermatitis or inflammatory reactions in some patients due to its anti-inflammatory and immunosuppressive actions of HCA.

Date of report:	May 12, 2010 (version 1.0)
Earlier reports:	April 29, 2010 (version 0.1), May 10, 2010 (version 0.2)