2 Synopsis

Sponsor:	Dermapharm AG, Grünwald	
Study title:	Double-blind, randomised clinical study comparing efficacy and safety of diclofenac 3% gel vs. Solaraze® 3% gel vs. vehicle in patients with actinic keratosis	
Study phase:	Phase III	
Investigators / study centres:	12 investigators in 12 study centres; a list of investigators and study centres is attached in appendix 16.1.4	
Publication:	No	
Study period:	First patient first visit December 08, 2011	Last patient last visit March 22, 2013
Number of patients:	Planned: 330 (randomised)	Analysed: 338 (safety data set)
Objectives:	Assessment of efficacy and safety of a new diclofenac 3% gel versus the approved diclofenac preparation Solaraze® 3% gel versus the underlying vehicle in patients with actinic keratosis. The study aims to show therapeutic equivalence (two-sided) of the test preparation as compared to Solaraze® and superiority of both active medications over the vehicle.	
Study indication:	Actinic keratosis (AK)	
Test drug:	Diclofenac 3% gel	
Active ingredients:	Diclofenac sodium 30 mg/g	
Comparators:	Solaraze® 3% gel (diclofenac sodium 30 mg/g) Vehicle	
Daily dose:	2x ca. 0.5 g gel/ 25 cm^2 area	
Mode of administration:	To be rubbed in slightly on the affected skin areas twice daily (in the morning, in the evening)	
Batch no:	110901 for patients 001 to 114, 120301 for patients 115 to 339	
Duration of treatment:	13 weeks (91 days)	

Main criteria for inclusion:

- Immunocompetent women and men ≥ 18 years of age
- Diagnosis of “actinic keratosis” according to generally accepted criteria
- Presence of an area of 5 x 5 cm^2 on the face or on a hairless part of the scalp which requires medical treatment
- Identification of 5 to 10 delimitable lesions in the treatment area which have the following properties: diameter ≥ 4 mm, not hyperkeratotic, not hypertrophic

Methodology:

- Randomised, double-blind, multi-centre study with three parallel treatment groups
- Evaluation of the number of actinic lesions in the test area at Visit 1 (*Target Lesion Number Score*, TLNS) and all follow-up visits (*Cumulative Lesion Number Score*, CLNS)
- Evaluation of therapeutic success by the investigator (*Investigator's Global Improvement Index,* IGII) and by the patient (*Patient's Global Improvement Index*, PGII) by means of a 7-point rating scale
- Documentation of adverse events
- Evaluation of tolerability by the investigator and by the patient by means of a 4-point rating scale

Criteria for evaluation:

Efficacy

Primary efficacy variable:

Proportion of patients with 100% clearance of all AK lesions in the test area (i.e. CLNS = 0) at the main visit (Visit 5, Day 119), i.e. 30 days after end of study treatment

Secondary efficacy variables:

- Proportion of patients with a decrease in the number of AK lesions in the test area from baseline of at least 75% at Visit 5
- Proportion of patients with 100% clearance of all AK lesions in the test area (i.e. CLNS = 0) at the end of the treatment phase (Visit 4, Day 91)
- Value of CLNS at Visit 1, Visit 2, Visit 3, Visit 4 and Visit 5, respectively
- Proportion of patients with IGII = 4 (="cured") at Visit 5
- Proportion of patients with PGII = 4 (="cured") at Visit 5

Safety

- Number and classification of adverse events
- Clinical relevance of laboratory parameters at Visit 1 and Visit 4
- Evaluation of tolerability by the investigator at Visit 2, Visit 3 and Visit 4
- Evaluation of tolerability by the patient at Visit 2, Visit 3 and Visit 4
- Proportion of patients with premature study termination due to an AE with "possible" causal relationship to study medication

Statistical methods:

Three testing problems based on pairwise comparison of the primary efficacy variable between treatments. Confirmatory tests with experiment-wise significance level α = 5% (simultaneous testing):

Test 1: Diclofenac 3% gel vs. Solaraze® 3% gel (testing for equivalence)

Test 2: Diclofenac 3% gel vs. Vehicle (testing for superiority)

Test 3: Solaraze® 3% gel vs. Vehicle (testing for superiority)

All other statistical tests were exploratory.

Summary of results:

Efficacy results:

With respect to the intention-to-treat (ITT) data set, the percentage of patients with 100% clearance at Visit 5 (primary efficacy variable) was 18.0% for Diclofenac 3% gel (DicloGel), 15.6% for Solaraze® 3% gel (Solaraze) and 10.5% for the underlying vehicle. The corresponding results for the per-protocol (PP) data set were 19.0%, 15.2% and 10.9%, respectively.

Equivalence between DicloGel and Solaraze could be statistically proven for both the PP-(primary) and the ITT data set. Testing for superiority of the two active treatments over the vehicle failed to reach statistical significance for both the ITT (primary) and the PP data set. Therefore the primary objective of this study could not be fully achieved.

However, superiority of DicloGel over the vehicle was shown for all secondary efficacy variables, whereas superiority of Solaraze over the vehicle could be shown at least for two of them. The following p-values resulted for testing DicloGel vs. the vehicle and Solaraze vs. the vehicle:

I. Decrease in the number of lesions of at least 75% between Visit 1 and Visit 5:
DicloGel: p = 0.0021, Solaraze: p = 0.0213

II. 100% clearance of all AK lesions Visit 4:
DicloGel: p = 0.0120, Solaraze: p = 0.0723

III. Number of AK lesions at Visit 5:
DicloGel: p = 0.0079, Solaraze: p = 0.0524

IV. Proportion of patients with Investigator's Global Improvement Index = 4 (= *cured*) at Visit 5: DicloGel: p = 0.0333, Solaraze: p = 0.1056

V. Proportion of patients with Patient's Global Improvement Index = 4 (= *cured*) at Visit 5:
DicloGel: p = 0.0217, Solaraze: p = 0.0323

With respect to the secondary efficacy variables there were no statistically significant differences between DicloGel and Solaraze.

Safety results:

One patient in the DicloGel group and 4 patients under the vehicle group had serious adverse events (SAEs). No SAE was causally related with the study medication.

There were 38 patients (DicloGel: 15, Solaraze: 18, Vehicle: 5) who had at least one adverse drug reaction (ADR), i.e. an AE with *possible* or *not assessable* causal relationship to the study medication. For the two active treatments, mostly skin disorders and administration site reactions were reported.

At the end of the treatment phase 8 patients (DicloGel: 3, Solaraze: 2, Vehicle: 3) had clinically relevant laboratory parameters that were documented as an AE. None of these AEs was considered as causally related to the study medication.

The investigators rated tolerability as *very good* or *good* at each study visit for 72.1% of DicloGel patients, 72.3% of Solaraze patients and 86.8% of patients under the vehicle. The corresponding proportions for the ratings by the patients were 64.9%, 65.2% and 76.3%, respectively.

Conclusion:

Efficacy conclusions:

- The main study objective was partially met, i.e. showing equivalence between DicloGel and Solaraze.
- Superiority of both active treatments over the underlying vehicle could not be demonstrated for the primary efficacy variable.
- Superiority of DicloGel over the vehicle could be shown for all secondary variables, and of Solaraze for two variables.

Safety conclusions:

- The application of all three preparations was well tolerated and safe, despite a relatively high number of local adverse events in the active treatment arms.
- There were no critical or new findings regarding safety for any of the tested preparations.

Overall conclusions:

- Equivalence of DicloGel versus Solaraze could be shown for both data sets.
- Statistical superiority of the two active treatments over vehicle could not be shown for the primary efficacy variable in either of the two data sets.
- However, the overall results can be regarded as supporting the study hypothesis.
- The application of all three preparations was safe, and tolerability was rated good or very good in the majority of patients.

Date of report:	July 30, 2013 (version 1.0)
Earlier reports:	July 25, 2013 (version 0.3) July 17, 2013 (version 0.2) June 28, 2013 (version 0.1)