2 SYNOPSIS

Name of sponsor: Almirall Hermal GmbH, Scholtzstraße 3, 21465 Reinbek, Germany	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of finished product: Not applicable yet		
Name of active ingredient: 50 mg/g diclofenac sodium (5% diclofenac gel), topical application of 1.0 mg diclofenac sodium/cm² Tested in two different doses: - once daily for 90 days - twice daily for 90 days		
Reference to the according CSR: LAS 41007 CSR Final Version 2.0 dated 08 July 2011		Date of synopsis: 08 July 2011

Title of study:

Double-blind, randomized, multi-centre phase II study to evaluate the efficacy and safety of topically applied LAS41007 once daily and LAS41007 twice daily versus Solaraze® 3% gel twice daily in the treatment of actinic keratosis grade I to II

Study number H569 000 - 0908 EudraCT number 2009-012063-33

Investigators:

Coordinating investigator ("LKP"): [redacted] SCIderm GmbH [redacted] Hamburg, Germany

A total of 7 principal investigators participated in this study – a list of all principal investigators and study sites is given in Appendix 16.1.4.

Study sites:

7 study sites in Germany

Publication (reference):

Not applicable to this study

Studied period:	Date of first patient first visit: 12 Aug 2009 Date of last patient completed: 25 Jan 2010	**Clinical study phase:** Phase II

Objectives:

Aim of the study was to determine the efficacy, safety and tolerability of either a once or twice daily topical application of 5% diclofenac gel compared to a twice daily application of 3% Solaraze® gel in the treatment of actinic keratosis.

Primary objective:

The primary study objectives were to compare the efficacy of 5% diclofenac gel twice daily to Solaraze® 3% gel twice daily, assessed by histology (according to Röwert-Huber, 2007) to evaluate the clearance of one pre-selected target lesion at 30 days post-treatment (PT), and assessed by AK lesion count (using the target lesion number score (TLNS)) to evaluate the complete clinical clearance (indicated by TLNS = 0) of all target lesions in the treatment area at 30 days PT (V8).

Secondary objectives:

A secondary study objective was to compare the efficacy of 5% diclofenac gel once daily to Solaraze® 3% gel twice daily, measured by the same primary efficacy variables, as stated for the primary objectives.

A further secondary objective was to compare the efficacy of 5% diclofenac gel twice daily to Solaraze® 3% gel twice daily with regard to a decreased time to complete clinical clearance, assessed by AK lesion count (TLNS) to evaluate the complete clinical clearance (indicated by TLNS = 0) at each visit during the treatment (V3-V7) following Baseline (V2).

Further secondary objectives were to assess the safety and tolerability of 5% diclofenac gel, either applied once daily or twice daily compared to Solaraze® 3% applied twice daily. Patient's compliance was also controlled.

Methodology (design of study):

This study was performed as a randomized, comparator-controlled, double-blind, three-armed, parallel-group, multi-center phase II study. Treatment over 90 days with topical application of 5% diclofenac once daily, 5% diclofenac twice daily or of twice daily application of 3% Solaraze® gel.

Regular visits where to be performed after 14, 42, 56, 70 and 90 days of treatment and 30 days post treatment (Day 120).

Number of patients planned:

Approximately 100 (randomized), including a calculated drop out rate of 10%

Number of patients treated:

In total 107 patients were enrolled into the 3 treatment groups and analysed:

- Solaraze® 3% gel twice daily: 39 patients
- 5% diclofenac gel once daily: 35 patients
- 5% diclofenac gel twice daily: 33 patients

Further information on the patients´ validity for analysis sets is given below.

Diagnosis and main criteria for inclusion:

Clinically diagnosed actinic keratosis (AK) grade I to II and histological confirmed actinic keratosis in the face, scalp and/or forehead

Test product 1:	5% diclofenac gel, twice daily
Dose:	1.0g gel per application, twice applications daily, resulting dose of active ingredient:100mg diclofenac sodium per day
Route of administration:	topical application (gel)
Batch number:	931KK01
Duration of treatment:	90 days, or until lesions have completely cleared or ulceration within the treatment area occurs or if other medically reasons apply (e.g. AE)

Test product 2:	5% diclofenac gel, once daily
Dose:	1.0g gel per application, once daily, for second daily application placebo gel (vehicle without active ingredient) was used resulting dose of active ingredient: 50mg diclofenac sodium per day
Route of administration:	topical application (gel)
Batch number:	931KK01
Duration of treatment:	90 days, or until lesions have completely cleared or ulceration within the treatment area occurs or if other medically reasons apply (e.g. adverse event)
Reference therapy:	Solaraze® 3% gel
Dose:	1.0g gel per application, twice applications daily resulting in 60mg diclofenac sodium per day
Route of administration:	topical application (gel)
Batch number:	931KK01
Duration of treatment:	90 days, or until lesions have completely cleared or ulceration within the treatment area occurs or if other medically reasons apply (e.g. adverse event)

Criteria for efficacy evaluation:

Primary efficacy variables:

- Histological clearance of one pre-selected target lesion at 30 days PT, assessed by histology
- Complete clinical clearance of all target lesions in the treatment areas at 30 days PT, assessed by AK lesion count

Secondary variables:

- Rate of clinical clearance - assessed by AK lesion count at each visit, comparing the target lesion number score (TLNS) and the cumulative lesion number score (CLNS), respectively, at each visit during the treatment phase (V3-V7) with the TLNS baseline and CLNS baseline (V2), respectively. The final evaluation to determine the rate of clinical clearance will be performed at 30 days PT (V8).
- Rate of responders showing complete clinical clearance - measured by TLNS and CLNS giving the percentage of patients with total clinical clearance (TLNS = 0, respectively CLNS = 0) at each visit during the treatment (V3-V7) following Baseline (V2) and the number of patients with total clinical clearance of cumulative lesions (CLNS = 0) at 30 days PT (V8).
- Reduction of total AK target lesion area per patient - assessed by comparing the total target lesion area at Baseline (V2) with the total AK lesion target area at EoT (V7) and 30 days PT (V8).
- Improvement of target lesions - individual and overall target lesion response, assessed by rating the individual and overall target lesion area reduction at EoT (V7) and 30 days PT (V8) compared to Baseline (V2).
- AK severity scoring (assessed according to Olsen et al, 1991, modified) at Screening (V1), Baseline (V2), EoT (V7) and 30 days PT (V8).
- Investigator's Global Improvement Index (IGII) on study day 56 (V5), EoT (V7) and 30 days PT (V8).
- Patient's Global Improvement Index (PGII) on study day 56 (V5), EoT (V7) and 30 days PT (V8).
- Investigational laboratory to be performed in two pre-selected study sites only. A blood sample for laboratory assessment will be collected at Screening, EoT (V7) and 30 days PT (V8).

Criteria for safety evaluation:

- Physician's Global Tolerability Assessment (PGT) on study day 56 V5, EoT (V7) and 30 days PT (V8).

- Patient's Assessment on overall tolerability on study day 56 V5, EoT (V7) and 30 days PT (V8).
- Dermatological Assessment of the treatment areas (Severity of cutaneous side effects) from V2 – V8.
- Physical examination at Screening (V1), EoT(V7) and 30 days PT (V8), including vital signs
- Appearance of AEs/SAEs during the entire study

Statistical methods:

With regard to the primary study objective, the following hypotheses were tested for the primary target variables histological clearance of one pre-selected target lesion and the complete clinical clearance (indicated by TLNS = 0) at 30 days post treatment:

$H_{0,1}$: The clearance rate for patients under treatment with 5% diclofenac gel twice daily is stochastically smaller or equal than the rate under treatment with Solaraze® 3% gel twice daily.

$H_{1,1}$: The clearance rate for patients under treatment with 5% diclofenac gel twice daily is stochastically larger than the rate under treatment with Solaraze® 3% gel twice daily.

With regard to the secondary study objective, corresponding hypotheses were tested for the primary target variables:

$H_{0,2}$: The clearance rate for patients under treatment with 5% diclofenac gel once daily is stochastically smaller or equal than the rate under treatment with Solaraze® 3% gel twice daily.

$H_{1,2}$: The clearance rate for patients under 5% diclofenac gel once daily is stochastically larger than the rate under treatment with Solaraze® 3% gel twice daily.

Hypotheses were exploratively tested using a Chi-Square test with a one-sided significance level of p=0.025. The error probabilities for these procedures were not adjusted for multiple testing.

Estimates between treatment groups were calculated using the 95% confidence intervals.

Secondary efficacy variables were exploratively compared between treatment groups using Chi-Square tests for frequencies of patients (responder rates, improvement of target lesions) and the Wilcoxon-Mann-Whitney test (relative change of TLNS and CLNS, reduction of total AK target lesion area, investigator's as well as patient's global improvement index).

Study population:

A total number of 121 patients was enrolled and screened for the study in 7 study sites. 14 (11.6%) of the screended patients were screening failures not included in the treatment phase. In total 107 patients (88% of all screened patients) entered the treatment phase of the study and received study medication.

The 107 patients were assigned with a ratio of 1:1:1 into the 3 different treatment groups: 5% diclofenac gel once daily ('Diclo QD'), 5% diclofenac gel twice daily ('Diclo BID'), and Solaraze® 3% twice daily ('Sol').

Patients were valid for the different analysis sets as follows:

Number of patients valid for	Solaraze® 3% twice daily	5% diclofenac gel once daily	5% diclofenac gel twice daily	Total
Safety set	39	35	33	107
Full analysis set	39	33	33	105
Per protocol set	29	25	27	81

The compliance rate was comparable in all three treatment groups (Sol=93.8%, Diclo QD=94.2%, Diclo BID=94.6%).

Summary of Efficacy:

1. Primary efficacy variables:

Two primary efficacy variables were used: the histological clearance of one pre-selected target lesion assessed by histology and the complete clinical clearance defined as the disappearance of all target lesions (assessed by AK lesion count (TLNS=0)). Both primary efficacy variables were evaluated 30 days after end of treatment with IMP (V8).

The primary study objective was to compare the efficacy of 5% diclofenac gel twice daily (Diclo BID) to Solaraze® 3% gel twice daily (Sol) by means of both primary efficacy variables (histological clearance and complete clinical clearance). The primary study objective was analyzed for the Per Protocol Set (PPS). Histological clearance could be determinded for all patients with a valid punch biopsy of the pre-selected target lesion at V8 (Sol: N=28; Diclo BID: N=26) and the data for complete clinical clearance was available for all patients in the PPS (Sol: N=29; Diclo BID: N=27). As a consequence, for each treatment group less than the anticipated number of 30 patients per group were available regarding the primary efficacy variables.

Histological clearance at V8 (30 days PT) was more pronounced in the Diclo BID group than in the Sol group: 53.6% of patients treated with Sol and 65.4% of Diclo BID patients obtained histological clearance. The 95% confidence interval (CI) for the treatment difference was beween -14.4%, and 38.0% and the statistical test (Chi-Square test, 2-sided) does not reveal any significant differences (p=0.3774). The treatment difference between Diclo BID and Sol (11.8%) was only one-third of the treatment difference which should be detected with a power of >80% according to the sample size calculation.

The complete clinical clearance rates 30 days PT (V8) were nearly similar for both treatment groups, but slightly higher under Diclo BID: 37.9% of Sol patients and 40.7% of Diclo BID patients obtained a complete clinical clearance. The 95% CI for the treatment difference was beween -22.8% and 28.4% and the statistical test (Chi-Square test, 2-sided) does not reveal any significant differences (p=0.8297).

That implies that for both primary efficacy variables, the Chi-Square test does not support the hypothesis of superiority of Diclo BID.

The secondary study objective was to compare the efficacy of 5% diclofenac gel once daily (Diclo QD) to Solaraze® 3% gel twice daily (Sol), measured by means of both primary efficacy variables (histological clearance and complete clinical clearance). This objective was analyzed for the PPS: The histological clearance was analyzed für 28 patients (Sol) and 23 patients (Diclo QD), respectively, the complete clinical clearance was available for all patients in the PPS (Sol: N=29; Diclo QD: N=25).

The histological clearance rate was about 5.7% smaller (95% CI: (-33.3%, 21.8%)) in the Diclo QD group (47.8%) compared to the Sol group, but differences were not statistically significant (p=0.6830, Chi-Square test, 2-sided).

The complete clinical clearance rates 30 days PT were higher in the Sol treatment group (37.9%) than under Diclo QD treatment (24.0%). The 95% CI for the treatment difference was beween -38.8% and 10.9% and was statistically not significant (p=0.2717, Chi-Square test, 2-sided).

Both primary target variables were additionally analyzed for the Full Analysis Set (FAS: N=105). The histological clearance could be evaluated for 84 patients, while the complete clinical clearance was available for all 90 patients who attended V8/30 days PT (85.7%).

The histological clearance rates were nearly identical compared to the results obtained for the PPS with highest clearance rates in the DICLO BID group (Sol=53.1%; DICLO QD=46.2%; Diclo BID=65.4%).

Regarding complete clinical clearance of target lesions, the rate was slightly better for the treatment group Diclo BID (40.7%) compared to the Sol treatment (34.3%) (with 95% CI between -17.8% and 30.7%), while the rate was smallest for the Diclo QD group (21.4%).

As well as in the PPS, the Chi-Square test does not support the hypothesis of superiority of Diclo BID or Diclo QD against Sol.

2. Secondary efficacy variables:

All secondary efficacy variables were analyzed for the FAS only.

Rate of clinical clearance by means of target lesion number score (TLNS) and cumulative lesion number score (CLNS):

The median relative change of the TLNS from baseline to end of treatment (EoT/V7), was highest in the Sol treatment group and lowest in the Diclo QD group (Sol= -55.0%; Diclo QD = -20.0%; Diclo BID= -45.0%), but those differences were not statistically significant.

30 days after stop of treatment (V8) the median change from baseline was clearly more pronounced but similar in all treatment groups: -60.0% for Sol, -58.3% for Diclo QD, and -60.0% for Diclo BID. No statistically significant differences between treatment groups were detected.

The CLNS was defined as the sum of the TLNS, the number of non-target treatment area lesions and the number of new treatment area lesions.

At EoT/V7 the median relative changes of CLNS were between -55.8% (Diclo BID) and -63.1% (Sol) in all treatment groups. No statistical differences between treatments could be observed.

30 days after stop of treatment (V8) the CLNS had changed on average from 8.1 at baseline to 2.3 under Diclo BID, from 7.3 to 2.8 under Diclo QD and from 8.1 to 2.8 with Sol treatment. The median relative changes from baseline were -75.0% (Sol and Diclo BID), -65.2% (Diclo QD). Differences between treatments were statistically not significant.

Rate of responders with complete clinical clearance (TLNS and CLNS = 0):

One secondary objective was to compare the efficacy of Diclo BID to treatment with Sol with regard to a decreased time to complete clinical clearance (indicated by TLNS = 0) at each visit during the treatment (V3-V7) following Baseline (V2).

Overall, 4 of the 39 patients treated with Sol showed an early complete clinical clearance of all lesions and completed the treatment phase with a shortened study course. On the other side, only 1 of the 33 patients from the Diclo QD group and no patient from the Diclo BID group showed early therapeutic success.

At EoT/V7 the rate of responders with complete clinical clearance regarding TLNS or CLNS were more pronounced for Sol (31.6% and 26.3%) than for the Diclo treatment groups: Responder rates were 13.3% (TLNS and CLNS, each) for Diclo BID and 15.2% (TLNS and CLNS, each) for Diclo QD. No statistical differences between treatments could be observed.

In contrast, comparing Diclo BID with Sol 30 days after end of treatment (V8) the complete clinical clearance rates regarding CLNS were higher for Diclo BID (40.7% versus 31.4%). Comparing Diclo QD with Sol, complete clinical clearance rate was 10.0% less for the Diclo QD. Results regarding TLNS at V8 are already presented above (primary efficacy variables). The corresponding Chi-Square tests showed no significant differences.

Reduction of AK target lesion area:

The reduction in the average AK target lesion area per patient from baseline to V8 (30 days PT) was comparable between treatment groups: mean values changed from 68.5 mm^2 to 13.2 mm^2 (Diclo BID), from 64.8 mm^2 to 15.0 mm^2 (Diclo QD), and from 63.0 mm^2 to 16.8 mm^2 (Sol).

The relative change of the total AK target lesion area from baseline to V7 (EoT) was more pronounced for the treatment group Sol with -86.7% (Sol) compared to -65.2% for Diclo BID and compared to -73.2% for Diclo QD. 30 days after treatment stop (V8)the reduction of area was 84.2% (Sol), 82.6% (Diclo QD) and 90.5% (Diclo BID) with the strongest reduction in the Diclo BID treatment group. No statistically significant differences between treatment groups were detected.

Improvement of target lesions

Regarding the improvement score at EoT/V7 31.6% of the Sol patients, 15.6% of the Diclo QD patients, and 12.1% of Diclo BID patients showed a complete response. 30 days after the end of treatment (V8) a complete response was seen for 40.7% of the Diclo BID patients, for 21.4% of the Diclo QD patients and for 34.3% of the Sol patients. None of the differences between treatment groups were statistically significant.

Overall AK severity score

30 days after stop of treatment (V8), patients in the Diclo BID group were more often rated as 'Grade 0' (none) than patients treated with Sol: 51.9% and 48.1% (Diclo BID) versus 42.9% and 48.6% (Sol) for both treatment areas. Contrary, at EoT/V7 higher rates of patients with AK severity score 'Grade 0' could be observed for the treatment group Sol compared to Diclo BID.

Improvements were less pronounced for patients treated with Diclo QD: EoT(28.1% and 25.0%) and 30 days PT (39.3% and 25.0%).

However it must be considered that patients in the Diclo BID treatment group on average started with lower baseline values of the AK severity score than patients of the Sol treatment group as there were more grade I values at baseline in the Diclo BID (39.4%) than in Sol (29.5%), whereas Diclo QD had the lowest number of grade I values (24.2%).

Investigator's and Patient's Global Improvement Index

Concerning the Investigator's Global Improvement Index (IGII) and to the Patient's Global Improvement Index (PGII), no statistically significant differences were seen between the treatment groups at EoT/V7. 30 days PT (V8), the overall change in AK lesion status was assessed by patients more favourable for the treatment group Sol (mean PGII 2.9 on a scale ranging from -2 (significantly worse) to 4 (completely recovered)), while mean PGII was 2.5 for the treatment group Diclo QD (p=0.0449, Wilcoxon-Mann-Whitney test, 2-sided). No statistically significant differences were seen between Diclo BID (mean PGII was 2.6; p=0.3298, Wilcoxon-Mann-Whitney test, 2-sided) and Sol. Comparisons of the IGII revealed no differences between the treatment groups Diclo BID and Diclo QD versus Sol at 30 days PT (V8).

Summary of Safety:

1. Adverse events:

Incidence rates:

The total incidence rate of AEs (number of AEs per patient in treatment group) was higher in the Diclo QD group (80.0%) than in the Sol group (46.2%) and in the Diclo BID group (51.5%).

The incidence rate of 'IMP related' AEs (Sol = 23.1%, Diclo QD = 37.1%, and Diclo BID = 33.3%) as well as the number of patients with 'IMP related' AEs (Sol = 12.8%, Diclo QD = 17.1%, and Diclo BID = 15.2%) was highest under treatment with Diclo QD.

The number of patients that permanently stopped the application of IMP due to an AE was nearly identical between the groups (Sol = 12.8%, Diclo QD = 17.1%, Diclo BID = 15.2%). However, the incidence (AEs/patient) of AEs leading to stop of IMP application was highest in the Diclo BID group (Sol = 23.1%, Diclo QD = 28.6%, and Diclo BID = 36.4%).

Furthermore, slighty more patients suffered from 'severe' AEs in the Diclo BID group than in both other groups(Sol = 5.1%, Diclo QD = 11.4%, Diclo BID = 15.2%).

Diagnoses of adverse events and respective MedDRA-System Organ Class:

Most 'IMP related' AEs were classified as 'General Disorders and Administration Site Conditions' and 'Skin and Subcutaneous Tissue Disorders' with the highest incidence rate in the Diclo QD group and the lowest incidence rate in the Diclo BID group (Sol: 23.1%, Diclo QD: 28.6%, Diclo BID: 21.2%).

The most often documented AEs that were not considered to be 'IMP related' were classified as 'Blood and Lymphatic System Disorders' with the most prominent symptom 'Leukopenia' (six AEs in six patients).

Serious adverse events:

Seven SAEs were reported in four patients, of which none was judged as related to the IMP. One SAE led to a withdrawal from the study (cardial infarction). The other SAEs (mamma carcinoma, left breast, slipped disk, nausea, gastroenteritis, dehydration and auricule fibrillation (the last four occurred in only one single patient)) did not lead to a withdrawal from the study. No significant differences in incidence rates between the study groups were found.

2. Tolerability and dermatological assessment of treatment area:

The tolerability and the cutaneous side effects of the IMP were evaluated by means of the following assessments:

The Physician's Global Tolerability assessment (PGT) revealed a good tolerability of the IMP during the whole course of the study with no evident differences between the respective study groups.

The patients' assessment on overall tolerability revealed that inflammation and itching were more often reported than burning; and pain only occurred occasionally. Inflammation and itching was slightly stronger in the Diclo BID group, whereas burning and pain seemed to occur slightly more often in the Diclo QD group. Interestingly, symptoms (except pain) had not completely resolved by 30 days PT (V8) in all treatment groups. Nevertheless, the overall-tolerability as rated by the patients can be considered good.

In the dermatological assessment of the treatment area, 'erythema' was the most often reported symptom and occurred in more than three-quarters of the patients in each treatment group (Sol= 97.4%; Diclo QD= 77.1%, Diclo BID=100%). In the Diclo BID group, more patients suffered from at least moderate erythema (45.5%) than in the Diclo QD group (20%) and in the Sol group (25.6%).

Also 'skin exfoliation (scaling)' turned up in most of the patients (Sol= 89.7%; Diclo QD= 80.0%, Diclo BID= 93.9%). Patients treated with Diclo BID also suffered from stronger (at least moderate) 'scaling' than the patients in the other two groups (Sol = 30.8%, Diclo QD = 28.6%, Diclo BID = 42.4%). During the post treatment phase all symptoms decreased but, in particular, 'erythema' and 'scaling' did not resolve completely. Edema completely healed until 30 days PT (V8).

'Pruritus (itching)' occurred in more than half of the patients in each treatment group (Sol= 53.8%; Diclo QD= 51.4%, Diclo BID= 69.7%). 'Rash' only occurred in every fourth patient and was mostly of mild intensity. 'Edema' developed only in few patients and was of mild intensity.

In summary, 'erythema' and 'skin exfoliation' nearly always occurred when IMP was applied twice daily (Sol group and Diclo BID group) as compared to a once daily application (Diclo QD group). Also edema was more often perceived unter twice daily application. Pruritus and rash seemed to be more pronounced in the Diclo BID group.

Overall, even if the differences between groups were discrete, the most favorable cutaneous side-effect profile was documented for the Diclo QD group. Differences between the Sol and Diclo BID treatment are less pronounced, however, the symptoms tend to be of higher severity in the Diclo BID group.

Additionally, it should be considered that despite the mostly good tolerability, some patients (Sol = 5, Diclo QD = 6, Diclo BID = 5) suffered from more severe local symptoms like erythema, scaling, pain, inflammation or pruritus (AE reported term) that forced them to stop their IMP treatment.

3. Safety Laboratory Parameters

In this study blood samples for safety laboratory parameters were collected at Screening, V7 (EoT) and V8 (30 days PT) from a subset of patients who had been recruited in two pre-selected study centers. At Screening in total 32 patients were included.

Concerning the blood values of all safety laboratory parameters, no significant changes were detected in none of the treatment groups.

However, three patients showed increased count of leukocytes and ten patients had leukopenia during the course of the study. All of them were not considered related to the study drug and were probably caused by other underlying diseases or concomitant medications.

Overall conclusions:

Analyses of the primary efficacy variables do not clearly support the hypothesis favoring Diclo BID against Sol. The rates of histological clearance rates indicate a more beneficial effect of the Diclo BID treatment 30 days PT (V8).

Data for the treatment with Diclo QD do not support the hypothesis of a superiority of Diclo QD compared to the treatment with Sol.

The results for the secondary target variables do not reveal any evidence for superiority of the Diclo treatments versus Sol at the end of the treatment phase (V7). 30 days after end of treatment (V8) the results underline the findings obtained for the primary efficacy variables.

Comparing the occurrence of the safety parameters only discrete differences between the three treatment groups could be detected. Diclo QD caused the highest incidence rates of AEs and 'IMP related' AEs, whereas in the tolerability assessments, the most favourable symptom profile was documented for this group. Overall in the Diclo BID group more AEs occurred that led to a stop of IMP compared with the two other groups.

Most of related AEs that occurred in the three treatment groups were already known under the treatment with Solaraze® 3% gel. Only the AEs ‘dry mouth’, ‘increased intraocular pressure’ and ‘headache’ that occurred in one patient are not listed in the SmPC of Solaraze® 3%, but other ocular symptoms are already known (conjunctivitis, ocular pain, dry eye). A relation to the study medication therefore can not be excluded.
As expected, no IMP related laboratory findings were documented.
Overall, no new safety concerns could be detected for Solaraze® 3% or for the new 5% diclofenac formulations.