2 SYNOPSIS

Name of sponsor: Almirall S.A., Rda. General Mitre. 151, 08022 Barcelona, Spain represented by: Almirall Hermal GmbH, Scholtzstraße 3, 21465 Reinbek, Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of finished product: Not applicable yet	Volume:	
Name of active ingredient: 50 mg/g diclofenac sodium (5% diclofenac gel), topical application of 1.0 mg diclofenac sodium/cm², twice daily for 90 days	Page:	
Reference to the corresponding CSR: LAS 41007-III CSR Final Version 1.0 dated 19 Nov 2012		Date of synopsis: 19 Nov 2012

Title of study:

Double-blind, randomized, vehicle- and comparator-controlled, multi-center trial to evaluate the efficacy and safety of LAS41007 in the treatment of actinic keratosis

Study number H 569 000 - 1004 EudraCT number 2010-022244-20

Investigators:

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Overall 54 study sites of a total of 61 initiated study sites participated actively in this study – a list of all principal investigators and study sites is given in appendix 16.1.4 of the CSR.

Study sites:

40 study sites in Germany, 5 study sites in the United Kingdom and 9 study sites in Poland

Publication (reference): Not applicable to this study

Studied period:	Date of first patient first visit: 11 Nov 2010 Date of last patient completed: 12 Jul 2012 (last patient last visit in the non-interventional part prior to premature discontinuation of study)	**Clinical study phase:** Phase III

Methodology (design of study):

This study was performed as a randomized, comparator- and vehicle-controlled, double-blind, three-armed, parallel-group, multi-center phase III study, comprising an interventional phase that was planned to be followed by a non-interventional phase in which all patients were to be followed up for 12 months after the end of treatment (EoT).

Interventional phase:

During the interventional phase eligible patients were treated with a twice daily topical application of LAS41007, or Solaraze® 3% gel or the vehicle of LAS41007 for a period of 90 days. Patients were observed during study treatment and up to the final post-treatment visit. Regular visits during this phase were to be performed after 21, 56 and 90 days of treatment (= end of treatment (EoT)) and at 60 days post-treatment (PT-visit, day 150) and the treatment efficacy was evaluated by means of histological clearance of one AK target lesion, selected at screening and biopsied at 60 days PT.

Non-interventional phase:

The non-interventional phase was planned to comprise two follow-up (FU) visits, scheduled at 6 months (FU M6) and 12 months (FU M12) after the EoT, to assess the long term treatment effect.

Based on the efficacy results obtained for the interventional phase of the trial which failed to show superiority of LAS41007 compared to Solaraze® 3% gel, Almirall Hermal GmbH, as a representative of Almirall S.A., in agreement with the Coordinating Investigator, decided to prematurely discontinue the non-interventional phase of the study. Due to the disparate nature of data, collected up to the date of premature discontinuation of the study, it was decided that no useful information would be provided by undertaking any formal analysis.

Objectives:

The aim of the interventional part of the study was to determine the efficacy, safety and tolerability of twice daily topical application of LAS41007 (5% diclofenac gel) compared to a twice daily application of Solaraze® 3% gel (3% diclofenac gel) as comparator and compared to a twice daily application of vehicle in the treatment of mild (grade I) to moderate (grade II) AK.

Primary objective:

The primary objectives were to show:

- superiority of LAS41007 compared to vehicle
- superiority of LAS41007 compared to Solaraze® 3% gel

in the treatment of clinically diagnosed AK with grade I and/or grade II according to Olsen scale (Olsen et al., 1991, modified) and histological confirmed AK according to Röwert-Huber classification (Röwert-Huber et al., 2007), each assessed by histology to evaluate the histological clearance of one pre-selected AK target lesion at 60 days post-treatment (PT, V6).

Secondary objectives:

The secondary objectives were to show:

- superiority of LAS41007 compared to vehicle
- improved clinical efficacy of LAS41007 compared to Solaraze® 3% gel

in the treatment of clinically diagnosed AK with grade I and/or grade II with respect to clinical efficacy.

Other objectives were to assess the safety and tolerability of twice daily topical application of LAS41007 compared to a twice daily application of Solaraze® 3% gel as comparator and compared to a twice daily application of vehicle. Patient's compliance was also assessed.

The aim of the non-interventional phase was to assess the long term treatment effect with respect to the maintenance of complete clinical clearance or, alternatively, recurrence, and incidence of invasive squamous cell carcinoma (SCC).

Number of patients planned:

The sample size estimation for the test on superiority of the test product (LAS41007) to vehicle (placebo) was based on the following assumptions:

- The percentage of patients with histological clearance of the target lesion was estimated to be:
  - 43% at a maximum for treatment with placebo (vehicle of the test product);
  - approximately 65% for treatment with test product.
- the significance level was set to α = 0.025 for a 1-sided test and
- the power had to be at least 80%;

Under these assumptions the sample size available for analysis was calculated to be N=80 in each treatment group.

The sample size estimation for the superiority hypothesis of the test product (LAS41007) to the comparator (Solaraze® 3% gel) was based on the following assumptions:

- The percentage of patients with histological clearance of the target lesion was estimated to be:
  - approximately 54% for treatment with comparator;
  - approximately 65% for treatment with test product.
- the significance level is set to α = 0.025 for a 1-sided test and
- the power had to be at least 80%;

Under these assumptions the sample size available for analysis was calculated to be N=315 in each treatment group.

The calculated minimum sample size for each of the treatment groups was to be rounded off, taking into account that treatments were applied with a ratio of 3:3:1 for test product, comparator and vehicle (placebo), resulting in a total number of 318:318:106 patients = 742 patients to be randomized.

Allowing for an expected drop-out rate of around 10%, gave a total sample size of N=824 patients to be randomized.

Regarding the non-interventional phase of the study all patients who completed the interventional part of the trial as regular study course completers (including patients who had an early therapeutic success) and patients who prematurely discontinued the treatment during the interventional phase of the study, but for whom data of V5 (EoT visit) and / or V6 (60 days PT visit) were available, were regarded as eligible to enter the non-interventional phase of the study. Assuming these patients were not withdrawn from the trial they were scheduled to perform the study visits FU M6 (V7) and FU M12 (V8) of the non-interventional phase.

Number of patients treated:

- LAS41007 gel twice daily: 381
- Solaraze® 3% gel twice daily: 381
- Vehicle to LAS41007 twice daily: 127

Further information on the patients' validity for the analysis sets and their eligibility to enter the non-interventional phase of the study is given below.

Diagnosis and main criteria for inclusion:

The study included Caucasian male or female patients of at least 18 years of age who were required to have at least 6 but not more than 16 clinically dignosed mild to moderate AK target lesions (i.e. classified as grade I to II according to Olsen et al., 1991, modified) and additionally one representative AK lesion for histological confirmation of the AK diagnosis (according to Röwert-Huber et al., 2007).

The AK target lesions had to be located on the face including the forehead (excluding eyelids, lips and mucosa) and/or the bald scalp. The total treatment area (TTA), containing the AK lesions comprised up to 3 individual treatment areas (ITAs) with a maximum size of 25 cm^2 per TA. For inclusion, the AK target lesions had to be discrete and quantifiable; the distance from one lesion to its neighbor lesion had to be greater than 1.0 cm and the diameter of each AK target lesion had to be between 0.5 cm and 1.5 cm.

Test product:	LAS41007 gel (diclofenac 5% gel)
Dose:	0.5 - 1.5g gel per application, application twice daily, resulting dose of active ingredient: 50 - 150mg diclofenac sodium per day
Route of administration:	topical
Batch number:	032KK01
Duration of treatment:	90 days, or until lesions have completely cleared or ulceration within the treatment area occurs or if other medical reasons apply (e.g. adverse event)
Reference therapy (Comparator):	Solaraze® 3% gel
Dose:	0.5 - 1.5g gel per application, application twice daily resulting in 30 - 90mg diclofenac sodium per day
Route of administration:	topical application
Batch number:	032KK01
Duration of treatment:	90 days, or until lesions have completely cleared or ulceration within the treatment area occurs or if other medical reasons apply (e.g. adverse event)
Vehicle to LAS41007 (Placebo):	Vehicle to LAS41007 (containing no active ingredients)
Dose:	0.5 - 1.5g gel per application, application twice daily
Route of administration:	topical
Batch number:	032KK01
Duration of treatment:	90 days, or until lesions have completely cleared or ulceration within the treatment area occurs or if other medical reasons apply (e.g. adverse event)

Interventional phase:

Criteria for efficacy evaluation:

Primary efficacy variable:

- Percentage of patients with histological clearance of one pre-selected AK target lesion at 60 days PT (V6) (i.e. the histological status of the PT biopsy served as primary efficacy variable to determine the percentage of patients showing histological clearance of AK)

Secondary efficacy variables:

- Percentage of patients with target lesion number score (TLNS) = 0 at 60 days PT (V6) assessed by AK lesion count.
- Percentage of patients with target lesion number score (TLNS) = 0 at each visit during the treatment (V3-V5) following baseline (V2), assessed by AK target lesion count.
- Percentage of patients with cumulative lesion number score (CLNS, defined as the sum of the TLNS, the number of non-target treatment area lesions, plus the number of new treatment area lesions) = 0 at each visit following baseline (V2) until 60 days PT (V3-V6), assessed by target plus non-target plus new AK lesion count.
- Percentage change of TLNS from baseline (V2) to 60 days PT (V3-V6), assessed by the target AK lesion count.
- Percentage change of CLNS from baseline (V2) to 60 days PT (V3-V6), assessed by the target plus non-target plus new AK lesion count.
- Reduction of total AK target lesion area per patient (assessed by comparing the total AK target lesion area at baseline (V2) with the total AK target lesion area at each visit (V3-V6) following

baseline (V2)).

- Improvement of target lesions (individual and overall target lesion response, assessed by rating the individual and overall target lesion area reduction at each visit (V3-V6) compared to baseline (V2)).
- Change in AK severity scoring (assessed according to Olsen et al., 1991, modified) at EoT (V5) and 60 days PT (V6) compared to baseline (V2).
- Investigator's Global Improvement Index (IGII) at each visit (V3-V6) following baseline (V2).
- Patient's Global Improvement Index (PGII) at EoT (V5) and 60 days PT (V6).
- Change in Dermatology Life Quality Index (DLQI) at 60 days PT (V6) compared to baseline (V2).

Criteria for safety and tolerability evaluation:

- Investigator's Global Tolerability Assessment (IGTA) at each visit (V3-V6) following baseline (V2).
- Patient's Global Tolerability Assessment (PGTA) at EoT (V5) and 60 days PT (V6).
- Change in dermatological assessment of the TAs (severity of cutaneous side-effects) from baseline (V2) until 60 days PT (V6).
- Change in physical examination at EoT (V5) and 60 days PT (V6) compared to screening (V1).
- Change in vital signs at baseline (V2), EoT (V5) and 60 days PT (V6) compared to screening (V1).
- Urine pregnancy test at baseline (V2) and EoT (V5)
- Change in clinical laboratory variables at EoT (V5) and at 60 days PT (V6) compared to screening (V1) (performed in 6 pre-selected study sites in Germany, for ~120 patients only).
- Bioanalytics for systemic diclofenac exposure at screening (V1), baseline (V2), EoT (V5) and at 60 days PT (V6) (performed in 6 pre-selected study sites in Germany, for ~120 patients only).
- Occurence of AEs/SAEs from signing the informed consent until 60 days PT (V6)

Additional variables:

- Demographics / habits at screening (V1).
- Skin type according to Fitzpatrick's (1988) at screening (V1).
- Relevant medical and surgical history including AK history at screening (V1).
- Prior and concomitant treatment during the entire interventional phase of the study (V1-V6).
- Patient's compliance during the treatment phase (V2-V5).

Non-interventional phase:

Criteria for long term treatment efficacy evaluation:

- Maintainance of AK lesion clearance / AK recurrence / occurrence of invasive SCC since EoT (V5) assessed by visual assessment of TAs at FU M6 (V7) and FU M12 (V8)
- AK severity scoring (assessed according to Olsen et al., 1991, modified) for AK lesions present at FU M6 and FU M12 compared to EoT (V5)
- AK lesion count (TLNS and CLNS) for AK lesions present at FU M6 and FU M12 compared to EoT (V5)
- AK lesion area assessment for AK lesions present at FU M6 and FU M12 compared to EoT (V5)
- AK therapies in the target area since EoT (V5)
- Use of skin care products (including sunscreens and make-up) in the target area since EoT (V5)

Statistical methods:

The primary study objectives, to show superiority of LAS41007 (5% diclofenac gel) compared to vehicle (placebo) and compared to active comparator (Solaraze® 3% gel) by means of histological clearance, were formalized in the following hierarchical hypotheses:

$H_{0,1}$: The percentage of patients with histological clearance under treatment with 5% diclofenac gel is stochastically smaller than or equal to the percentage of patients with histological clearance under treatment with placebo (vehicle of the test product).

$H_{1,1}$: The percentage of patients with histological clearance under treatment with 5% diclofenac gel is stochastically larger than the percentage of patients with histological clearance under treatment with placebo (vehicle of the test product).

and

$H_{0,2}$: The percentage of patients with histological clearance under treatment with 5% diclofenac gel is stochastically smaller than or equal to the percentage of patients with histological clearance under treatment with Solaraze® 3% gel.

$H_{1,2}$: The percentage of patients with histological clearance under treatment with 5% diclofenac gel is stochastically larger than the percentage of patients with histological clearance under treatment with Solaraze® 3% gel.

Statistical evaluation of the primary efficacy variable was performed as confirmatory analysis on the Full Analysis Set (FAS), which included all patients for whom the study diagnosis was histologically confirmed and for whom data on efficacy variables after use of IMP were available, regardless of any protocol deviations. For patients with a second punch biopsy from an AK target lesion different from the AK lesion pre-selected at screening, the histological outcome from the second punch biopsy was taken as reported and no data imputation was performed. For patients with a missing second punch biopsy the histological outcome was imputed by taking into account the outcome of selected clinical parameters at 60 days PT as follows:

- For patients who attended Visit 6 but who did not have a biopsy performed, missing histological results were imputed as:
  - 'histological clearance' if the lesion that should have been the second punch biopsy lesion was clinically 'cleared' at visit 6 - that is the measurable dimensions of the particular lesion were 0.0 cm x 0.0 cm - and if, in addition, the patients showed one of the following clinical results:
    - TLNS ≤2 and IGII 3 (='significantly improved') or 4 (='completely improved') at Visit 6,

    or
    - TLNS ≤1 and IGII 1 (='slightly improved') or 2 ('moderately improved') or 3 or 4 at Visit 6.
  - 'no histological clearance' if clinical results did not match the definitions given above.
- For all patients who dropped out from the study and did not attend Visit 6 at 60 days PT, the missing histological results were imputed as 'no histological clearance'.

The one-sided hypotheses regarding the study objectives were tested using the Wald test with continuity correction with an error probability of α=0.025 for a one-sided test, and estimates for the difference between treatment groups were calculated using the two-sided test-based 95% confidence interval (CI). The study hypotheses were tested in an *a priori* ordered sequence. The secondary hypothesis was to be tested only if the first null-hypothesis was rejected.

According to the *a priori* order of testing the error probability for these procedures had not to be adjusted for multiple testing.

Given that p_0 and p_1 were the percentages of patients with histological clearance in the treatment groups to be compared, and given that n_0 and n_1 were the corresponding sample sizes, the Wald test statistic w= (d)/ SE(d) was derived as follows:

$d = (p_0 – p_1) - cc$ (if $p_0-p_1 > 0$) or $d = (p_0 – p_1) + cc$ (if $p_0-p_1 < 0$),

with continuity correction $cc = (1/n_0 + 1/n_1)/2$

$SE(d) = \sqrt{(p_0(1-p_0)/n_0 + p_1(1-p_1)/n_1)}$

One-sided p-values were computed using the SAS procedure FREQ (with Method= Wald). Two-sided confidence intervals were constructed taking into account the continuity correction $cc = (1/n_0 + 1/n_1)/2$.

Regarding the Per Protocol Set (PPS), including all patients, who adhered reasonably well to this study protocol without relevant protocol deviations, statistical evaluation of the primary efficacy variable was performed as sensitivity analysis using one-sided tests. The study hypotheses were tested according to

the *a priori* ordered sequence.

In addition, a sensitivity analysis was performed on the FAS considering all patients with a missing second punch biopsy as treatment failures. Another sensitivity analysis was performed on the FAS, reducing the FAS by excluding all patients with a missing second punch biopsy from analysis (rFAS). The study hypotheses were tested according to the *a priori* ordered sequence using one sided tests.

A third sensitivity analysis was performed as a post-hoc analysis, excluding those patients from the PPS population, who had elevated diclofenac serum levels (i.e. higher than the lower limit of quantification: 2 ng/mL) at screening/baseline and for whom a pre-existing systemic diclofenac exposure could not be excluded (rPPS). For this purpose the statistical evaluation of the primary efficacy variable was performed using a one-sided test and the study hypotheses were again tested according to the *a priori* ordered sequence. The secondary efficacy variables (percentage of patients with an improved target lesion count resulting in either TLNS=0 or CLNS=0 at 60 days PT) were compared exploratively between treatment groups using Chi-Square tests.

Secondary efficacy variables were compared exploratively between treatment groups at V6 (60 days PT) on the FAS using Chi-Square tests for frequencies of patients (percentage of patients with an improvement of target lesions to either TLNS=0, or CLNS=0 at 60 days PT) and the Wilcoxon-Mann-Whitney test (percentage change of TLNS and CLNS from baseline, percentage change of total AK target lesion area, overall target lesion response, IGII and PGII, change in DLQI).

Descriptive analyses including the calculation of 95% confidence intervals for the treatment differences are provided for all secondary efficacy variables at each visit. This was performed for the FAS and the PPS.

Safety variables were compared exploratively between treatment groups at V6 (60 days PT) using the Wilcoxon-Mann-Whitney test (change in dermatological assessment of the treatment area, IGTA and PGTA).

Summary and Conclusions:

Study population:

A total number of 1013 patients was enrolled and screened for the interventional part of the study in 54 study sites in Germany, Poland and UK. 124 (12.2%) of the screened patients were screening failures and not included in the treatment phase. In total 889 patients (87.8% of all screened patients) entered the treatment phase of the study and received study medication.

The 889 patients were randomly assigned under double-blind conditions to the 3 different treatment groups with a ratio of 3:3:1: diclofenac 5% gel twice daily ('LAS41007'), diclofenac 3% gel twice daily ('Solaraze® 3% gel'), and vehicle of LAS41007 twice daily.

The mean age of the safety population was 72.7 years (ranging from 39 to 94 years). Most of the patients were males (89%). Relevant differences in demographic and baseline data were not detected between treatment groups in any of the analysis sets, except that elevated diclofenac serum levels (≥2 ng/ml) were detected at time of screening/baseline in 17 of 140 analysed patients (LAS41007=8/60, Solaraze® 3% gel=4/63 and vehicle=5/17) from whom blood had been taken to check for systemic diclofenac exposure, indicating that those patients had been exposed to systemic diclofenac at time of screening/baseline.

The compliance rate was calculated for each patient relating the actual number of applications (as reported in the diaries) to the expected number of applications (usually 2 applications per treatment day). In the vehicle group (96.4%) the compliance rate was slightly higher than in both of the other treatment groups (LAS41007=88.3%, Solaraze® 3%=89.8%).

837 patients (94.2% of all treated patients: LAS41007=353/381, Solaraze® 3% gel=365/381 and vehicle=119/127) completed the study. 16 of these patients (1.8% of all treated patients: LAS41007=6/381, Solaraze® 3% gel=8/381 and vehicle=2/127) were assessed as an early therapeutic success and completed the study with a shortened study course.

52 patients (5.8% of all treated patients: LAS41007=28/381, Solaraze® 3% gel=16/381 and vehicle=8/127) discontinued the study prematurely. In addition to those patients who prematurely discontinued the study, there were 29 patients (3.3% of all patients treated: LAS41007=13/381, Solaraze® 3% gel=13/381 and vehicle=3/127) who completed the study with the 60 days PT-visit, but without having

the second punch biopsy taken.

The most frequent reasons for a premature discontinuation of study were the occurrence of an AE/SAE including cutaneous side effects (44.2%), withdrawal of consent (36.5%) or lost to follow-up (11.5%). All other reasons for premature discontinuation occurred in at most only 2 patients per reason.

According to the definitions for the different analysis sets (see section 'Statistical methods' before), patients were valid for the different analysis sets, as follows:

Number of patients valid for:	LAS41007	Solaraze® 3% gel	Vehicle	Total
Safety set	381	381	127	889
Full analysis set	376	380	127	883
Reduced full analysis set (i.e. excluding all patients with a missing second punch biopsy)	340	352	116	808
Per protocol set	287	294	105	686
Reduced per protocol set (i.e. excluding all patients with diclofenac serum levels ≥ 2ng/ml at screening/baseline)	279	290	100	669

883 patients (99.3% of all randomized patients) were valid for the FAS analysis. A total of 6 randomized patients (LAS41007 group: 5/381 patients; Solaraze® 3% gel group: 1/381 patients) were excluded from the FAS, because the patients dropped out early and no post-baseline efficacy data were available. Further 75 patients (LAS41007 group: 36/381 patients; Solaraze® 3% gel group: 28/381 patients and vehicle group: 11/127 patients) were excluded from the FAS, as having no second punch biopsy performed. Therefore 808 patients (90.9% of all randomized patients) were valid for the analysis on the rFAS ('complete case analysis'). A total of 208 patients (23.4%: LAS41007 group: 94/381 patients; Solaraze® 3% gel group: 87/381 patients and vehicle group: 22/127 patients) were judged to have had at least one major protocol deviation, which finally resulted in the exclusion of 203 patients (22.8%) from the PPS. According to a decision on the BDRM, some major protocol deviations in a total of 5 patients, which were regarded as having no influence on the primary outcome, did not lead to an exclusion of a patient from the analyses on the PPS in general, but to the exclusion of selected clinical data only. Consequently the PPS was comprised of 686 patients (77.2%). The lack of compliance with the study protocol for the 17 patients (LAS41007=8/60, Solaraze® 3% gel=4/63 and vehicle=5/17) with elevated diclofenac serum levels at time of screening/baseline, at EoT (V5) and at 60 days PT (V6) raised the possibility of this also happening throughout the study. Consequently those 17 patients (12.1% of 140 patients analysed for systemic diclofenac exposure) were excluded from the PPS, resulting in the creation of a rPPS comprising 669 patients (75.3% of all randomized patients).

Out of the 889 patients randomized in total, 861 patients (96.9%: LAS41007 group: 362/381 patients; Solaraze® 3% gel group: 376/381 patients and vehicle group: 123/127 patients) were valid to enter the non-interventional phase of the study. Until the date of premature discontinuation of the trial, 723 out of 861 patients (83.9%: LAS41007 group: 305/362 patients; Solaraze® 3% gel group: 313/376 patients and vehicle group: 105/123 patients) entered the non-interventional phase of the study.

Regarding the patients in the LAS41007 group, 122 patients (40.0%) completed the non-interventional study phase with the 12 months follow-up (V8). 294 out of 305 patients (96.4%) performed at least the 6 months follow-up visit (V7) and 5 of these patients (1.6%) prematurely discontinued the trial after performing V7. For another 10 patients (3.3%) who entered the non-interventional phase, only their premature discontinuation from trial was documented in the eCRF without performance of V7 or V8.

In the Solaraze® 3% gel group a total of 296 patients (94.5%) performed V7 and 118 patients (37.7%) performed both follow-up visits (V7 and V8). 16 patients (5.1%) prematurely discontinued the interventional phase of the study without having a follow-up visit. In addition, 4 patients (1.3%) terminated the study prematurely after performing the 6 months follow-up visit.

Regarding the vehicle group, 105 (85.4%) out of 123 eligible patients entered the long term follow-up. Of these, 102 patients (97.1%) performed at least V7 and 39 patients (37.1%) completed the study with the 12 months follow-up visit. Three patients (2.9%) prematurely discontinued the trial without performing V7 or V8, and one further patient (1.0%) discontinued the trial prematurely after performing V7.

Premature discontinuation of those patients who entered the non-interventional part of the study was documented for 39 out of 723 patients (5.4%). This rate was lowest in the vehicle group (4 patients, 3.8% of all patients in this group) and highest in the Solaraze® 3% gel group (20 patients, 6.4% of all patients in this group). The most frequent reasons for a premature discontinuation of the non-interventional part of the study were withdrawal of consent (in 20 of 39 patients, 51.3%) and lost to follow-up (in 11 of 39 patients, 28.2%). The occurrence of an AE/SAE as reason for premature discontinuation was documented for a total of 7 patients (17.9%). For another 2 patients (5.1%) the reason for premature discontinuation was not further specified.

Summary of Efficacy:

1. Primary efficacy variable:

The primary study objective was to show superiority of 5% diclofenac gel twice daily (LAS41007) compared to both placebo (vehicle of the test product) and the active comparator (Solaraze® 3% gel) by means of the primary efficacy variable, the percentage of patients with histological clearance of one pre-selected AK target lesion at 60 days post-treatment (V6). The primary study objective was analyzed based on the Full Analysis Set (FAS).

Histological clearance was confirmed for 170 out of 340 patients from the LAS41007 group, for 173 out of 352 patients from the Solaraze® 3% gel group, and for 42 out of 116 patients from the vehicle group (rFAS). Imputation of missing data was performed for the 29 patients belonging to the FAS without a second punch biopsy. For the 29 patients who attended V6 but did not have the punch biopsy performed at V6, histological clearance could be imputed for 9 of 13 patients treated with LAS41007, for 8 of 13 patients treated with Solaraze® 3% gel, and for 1 of 3 patients from the vehicle group, on the basis of the clinical data as described previously. 'No histological clearance' was assumed for the remaining 11 patients who did not attend V6. For 6 patients in the FAS (LAS41007=2; Solaraze® 3% gel=3 and vehicle=1) who had a second punch biopsy taken from an AK lesion other than the pre-selected one, histological clearance was confirmed for only one patient of the LAS41007 group, whereas no histological clearance was seen for the remaining 5 patients. Therefore 179 out of 376 patients from the LAS41007 group, 181 out of 380 patients from the Solaraze® 3% gel group, and 43 out of 127 patients from the vehicle group included in the FAS, were considered 'histologically cleared'.

The percentage of patients with histological clearance at 60 days post-treatment was more pronounced for the LAS41007 group than for the vehicle group (47.6%; 179/376 patients versus 33.9%; 43/127 patients) with a 95% confidence interval (CI) for the treatment difference ranging from 3.6% to 23.9%. This difference in favor of the LAS41007 group was statistically significant (p=0.0036, Wald test, 1-sided).

The percentage of patients with histological clearance at 60 days PT was identical for both treatment groups (47.6%; 179/376 patients in the LAS41007 group and 181/380 patients in the Solaraze® 3% gel group). The 95% CI for the treatment difference ranged from -7.4% to 7.4%. Therefore a statistically significant difference between the LAS41007 and Solaraze® 3% gel treatment groups could not be confirmed (p=0.4737, Wald test, 1-sided).

Sensitivity analyses performed on the FAS considering all patients with a missing second punch biopsy as treatment failures, on the rFAS, on the Per Protocol Set (PPS) and on the rPPS confirmed the results obtained for the FAS. The difference between the LAS41007 group and the vehicle group was statistically significant for all analyses performed while a statistically significant difference between the treatment groups LAS41007 and Solaraze® 3% gel could not be demonstrated.

2. Secondary efficacy variables:

All secondary efficacy variables were analyzed for the FAS. With regard to the PPS, only descriptive analyses were performed, which were in line with the results detailed for the FAS.

Percentage of patients showing complete clinical clearance (TLNS=0; CLNS=0) at 60 days PT (V6):

At 60 days PT (V6), numerically more patients treated with LAS41007 showed a complete clinical clearance of all target lesions (TLNS=0) than patients treated with Solaraze® 3% gel (27.1%; 102/376 patients and 23.4%; 89/380 patients, respectively) The treatment difference between the two groups was 3.7% with 95% CI ranging from -2.7% to 10.2%. The difference was however not statistically significant (p=0.2409, Chi-Square test).

Regarding the vehicle group, TLNS=0 was observed for 12.6% (16/127 patients) of the patients. The treatment difference between the LAS41007 group and the vehicle group was 14.5% with 95% CI ranging from 6.7% to 22.4%, which was statistically significant (p=0.0008, Chi-Square test).

60 days after the end of treatment the percentage of patients with complete clinical clearance regarding CLNS (CLNS=0) was higher in the LAS41007 group than for patients treated with Solaraze® 3% gel (23.9%; 90/376 patients and 20.0%; 76/380 patients, respectively).The treatment difference between the two groups was 3.9% with 95% CI ranging from -2.2% to10.1%.

Regarding the vehicle group, CLNS=0 was observed for 10.2% (13/127 patients) of the patients. The treatment difference between the LAS41007 group and the vehicle group was 13.7% with 95% CI ranging from 6.4% to 21.0%.

In line with the findings for TLNS, the treatment difference between LAS41007 and the active comparator Solaraze® 3% gel was not statistically significant (p=0.1911, Chi-Square test), while a statistically significant difference was observed comparing the LAS41007 group to the vehicle group (p=0.0009).

Percentage of patients showing complete clinical clearance (TLNS=0; CLNS=0) at each visit during the treatment phase (V3-V5):

14 days after start of treatment (V3) one patient each in the LAS41007 group (0.3%; 1/376 patients) and in the Solaraze® 3% gel group (0.3%; 1/380 patients) showed a complete clinical clearance of all target lesions (TLNS=0), while at V4 (Day 56) TLNS=0 was observed for 6 patients (1.6%; 6/376 patients) treated with LAS41007, for 5 patients (1.3%; 5/380 patients) treated with Solaraze® 3% gel and for 2 patients (1.6%; 2/127 patients) from the vehicle group.

At the end of the treatment phase (V5), the percentage of patients with a complete clinical clearance of all target lesions was nearly identical for the LAS41007 group and the Solaraze® 3% gel group (17.6% compared to 17.4%) - 66 patients in each group - and for both treatment groups higher than in the vehicle group, where 17 patients showed complete clinical clearance of all target lesions (13.4%; 17/127 patients).

Correspondingly, the percentage of patients with a complete clinical clearance regarding CLNS (CLNS=0) at V5 was nearly identical for the treatment groups LAS41007 and Solaraze® 3% (15.2%; 57/376 patients compared to 15.3%; 58/380 patients), while this percentage was lower in the vehicle group (12.6%; 16/127 patients).

Percentage change of TLNS and CLNS from baseline (V2) to 60 days PT (V3-V6):

Within all three treatment groups the TLNS decreased continuously during the course of the study: the median TLNS decreased from 7.0 at baseline to 5.0 at V5 (end of treatment) and to 3.0 at V6 in the LAS41007 group, from 8.0 to 5.0 at V5 and to 3.0 at V6 in the Solaraze® 3% group, and from 7.0 to 5.0 at V5, and to 4.0 at V6 in the vehicle group.

Correspondingly the median percentage change of TLNS from baseline to end of treatment (V5) was identical for the patients treated with LAS41007 (-33.33%) and the patients treated with the vehicle (-33.33%) and only slightly higher for the patients treated with Solaraze® 3% gel (-37.50%).

At 60 days after end of treatment (V6) the median percentage change from baseline was again comparable between the LAS41007 group and the active comparator group, -63.39% against -63.07% (p=0.9842; Wilcoxon-Mann-Whitney test, 2-sided), but more pronounced in the LAS41007 group than in the vehicle group, -63.39% against -44.44% (p=0.0023).

Similar results were observed for the change of CLNS from baseline to V6. Median CLNS changed from 9.0 at baseline to 3.0 at V6 (LAS41007), from 9.0 to 4.0 (Solaraze® 3% gel), and from 9.0 to 6.0 (vehicle group).

The median percentage change of CLNS from baseline to end of treatment (V5) was lowest in the LAS41007 group (-39.35%) and comparable in both of the other treatment groups (Solaraze® 3% gel: -44.4%; vehicle: -43.75%).

The median percentage change of CLNS from baseline to 60 days PT (V6) was comparable for the LAS41007 group and the Solaraze® 3% gel group (-64.17% versus -62.50%) and more pronounced than in the vehicle group (-45.45%). The difference between the LAS41007 group and the vehicle group was statistically significant (p=0.0049, Wilcoxon-Mann-Whitney test, 2-sided), while no statistically significant difference was seen between the LAS41007 group and the active comparator group (p=0.9039).

Reduction of total AK target lesion area per patient from baseline (V2) to 60 days PT (V3-V6):

The area of each target lesion was approximated by multiplying the two reported perpendicular diameters, which when summed together allowed an arithmetical approximation of the total AK area being treated.

With regard to the total AK target lesion area per patient, the median values changed from 4.39 cm² at baseline to 1.00 cm² at V5 (EoT) (LAS41007 group), from 4.66 cm² to 0.94 cm² (Solaraze® 3% gel group), and from 4.52 cm² to 1.11 cm² (vehicle group). Further reduction of total AK target lesion area was seen until 60 days PT, which was more pronounced in the LAS41007 group (median value: 0.50°cm²) and the active comparator group (median value: 0.51°cm², and less pronounced in the vehicle group (median value: 1.00 cm²).

The median percentage change of the total AK target lesion area at the end of treatment (V5) compared to baseline was -75.92% in the LAS41007 group and -78.67% in the Solaraze® 3% gel group. At V6 (60 days PT) the median percentage change was comparable between the treatment groups LAS41007 and Solaraze® 3% gel (-87.80% versus -88.67%) and more pronounced than in the vehicle group (-77.36%).

No statistically significant difference was detected at V6 (60 days PT) between the treatment groups LAS41007 and Solaraze® 3% gel (p=0.6075, Wilcoxon-Mann-Whitney test, 2-sided), while the difference between the LAS41007 group and the vehicle group was statistically significant (p=0.0003).

Improvement of target lesions (overall target lesion response) at each visit (V3-V6) compared to baseline (V2):

Regarding the improvement score at end of treatment (V5), 17.6% (66/376 patients) of the LAS41007 patients, 17.4% (66/380 patients) of the Solaraze® 3% gel patients, and 13.4% of the patients (17/127 patients) from the vehicle group showed a complete response. 60 days after the end of treatment (V6) a complete response was seen for 27.1% (102/376 patients) of the LAS41007 group, for 23.4% (89/380 patients) of the Solaraze® 3% gel group, and for 12.6% (16/127 patients) of the vehicle group.

No statistically significant difference was seen between the LAS41007 group and the Solaraze® 3% gel group (p=0.3789, Wilcoxon-Mann-Whitney test, 2-sided) at 60 days PT, while the difference between the LAS41007 group and the vehicle group was statistically significant (p=0.0012).

Change in overall AK severity score (Olsen et al, 1991 modified) at EoT (V5) and 60 days PT (V6) compared to baseline (V2):

As more than one treatment area per patient could be rated by the investigator, the average AK severity score was derived per patient for each visit.

The median change of the average AK severity score from baseline (V2) to the end of treatment (V5) was highest in the Solaraze® 3% gel group (median reduction: 1.00) and less pronounced in both of the other treatment groups (median reduction of 0.67). At V6 (60 days PT) the median reduction in the average severity score was comparable between LAS41007 and the active comparator, resulting in a median reduction of 1.00 in both treatment groups, whereas the median reduction in the vehicle group declined from 0.67 at the end of treatment to 0.5 at 60 days PT.

Investigator's Global Improvement Index (IGII) and Patient's Global Improvement Index (PGII) up until 60 days PT (V3-V6):

The overall change in AK lesion status was compared to baseline by the physician and by the patient using a 7-point score ranging from -2 (significantly worse) to 4 (completely improved).

Concerning the Investigator's Global Improvement Index (IGII), the overall change in AK lesion status 60

days PT (V6) received comparable physician ratings for both treatment groups, LAS41007 and Solaraze® 3% gel (median IGII=3.0, i.e. significant improvement for both treatment groups). Regarding the Patient's Global Improvement Index (PGII) at V6, the median PGII was higher for the LAS41007 treatment group (3.0, indicating a significant improvement of AK) than for the Solaraze® 3% gel group (2.0, indicating a moderate improvement of AK). Nonetheless no statistically significant differences were seen between the treatment groups LAS41007 and Solaraze® 3% gel (IGII: p=0.7536 and PGII: p=0.3118, Wilcoxon-Mann-Whitney test, 2 sided).

Regarding the vehicle group at 60 days PT, physicians and patients rating of improvement resulted in a median value of 2.0. Differences between the vehicle group and the LAS41007 group were statistically significant (IGII: p=0.0040 and PGII: p=0.0004, Wilcoxon-Mann-Whitney test, 2-sided).

Change in Dermatology Life Quality Index (DLQI) at 60 days PT (V6):

The Dermatology Life Quality Index (DLQI) is a 10-question patient's questionnaire aimed to assess how much the quality of life is affected by the underlying skin disease. The sum of the 10 scores ranged between 0 and 30 with categories for the sum ranging from 0-1 (no effect at all on patient's life) to 21-30 (extremely large effect on patient's life).

60 days after end of treatment (V6) the DLQI score had changed on average from 2.0 at baseline to 1.0 under LAS41007 treatment; from 1.9 to 1.0 under Solaraze® 3% gel treatment, and from 1.6 to 1.1 in the vehicle group. A DLQI score of 0-1 was observed for 79.6% of patients treated with LAS41007, for 80.3% of patients treated with Solaraze® 3% and for 81.5% in the vehicle group.

Comparison of the DLQI score change from baseline revealed no statistically significant differences between the treatment groups.

Summary of Safety:

1. Adverse events:

Overview of adverse events:

During the trial, a total of 2960 treatment emergent adverse events (TEAEs), including cutaneous side effects (CSEs) considered as pre-defined AEs related to IMP, occurred in 782 of 889 patients, constituting 88.0% of the Safety Set (SS) population. TEAEs were reported for a similar proportion of patients for the three treatment groups - for 87.1% (332/381 patients) of the LAS41007 group; 87.4% (333/381 patients) of the Solaraze® 3% gel group and 92.1% (117/127 patients) of the vehicle group. The average number of TEAEs per patient was slightly higher for the LAS41007 group and the Solaraze® 3% gel group (3.46 TEAEs/patient and 3.31 TEAEs/patient, respectively) as compared to the vehicle group (3.00 TEAEs/patient).

Of 2960 TEAEs, 2554 events (86.3% of all TEAES) in 751/889 patients (84.5%) were assessed as being at least possibly treatment related. The proportion of patients with TEAEs at least possibly related to IMP was 83.2 % (317/381 patients) in the LAS41007 group, 83.7% (319/381 patients) in the Solaraze® 3% gel group and 90.6% (115/127 patients) in the vehicle group. The highest number of at least possibly IMP related TEAEs per patient was seen in the LAS41007 group (TEAEs/patient: 3.07), followed by the Solaraze® 3% gel group with a mean number of 2.82 TEAEs/patient and the vehicle group (TEAEs/patient: 2.44).

The proportion of patients that were withdrawn due to TEAEs was 2.6 % (23/889 patients) of the total SS population, with 11/381 patients (2.9%) of the LAS41007 group, 8/381 patients (2.1%) of the Solaraze® 3% gel group and 5/127 patients (3.9%) of the vehicle group.

Cutaneous side effects (CSEs), defined as each worsening of the signs, erythema, edema, pruritus (= itching), rash, and skin exfoliation (= scaling), as rated in the dermatological assessment, were considered a pre-defined AE, as these adverse drug reactions are already well known for the comparator, Solaraze® 3% gel. Therefore a similar occurrence of comparable side effects was expected in this trial.

As expected CSEs, with a total number of 2447 pre-defined AEs represent the majority (82.7%) of all TEAEs in the trial. CSEs occurred in 747 patients (84.0%) of the SS population. The proportion of patients with at least one CSE was similar in the LAS41007 group (82.4%; 314/381 patients with a mean

number of 2.92 CSEs/patient) and the Solaraze® 3% gel group (83.5%; 318/381 patients with a mean number of 2.70 CSEs/patient) and slightly higher in the vehicle group (90.6%; 115/127 patients with a mean number of 2.41 CSEs/patient). CSEs leading to premature discontinuation of treatment with IMP were more frequent in patients treated with LAS41007 (13.6 %; 52/381 patients) and Solaraze® 3% gel (12.3 %; 47/381 patients) compared to the vehicle group (2.4 %; 3/127 patients). Most of those CSEs leading to premature discontinuation of treatment with IMP were of moderate intensity. In 3.4% (13/381 patients) of the patients in the LAS41007 group CSEs were of severe intensity, as compared to 2.4% (9/381 patients) in the Solaraze® 3% gel group and 0.8 % (1/127 patients) in the vehicle group.

Excluding the pre-defined AEs, 513 TEAEs (17.3% of all TEAEs) occurred in 318/889 patients of the SS population (35.8%) of which 107 events in 72 (8.1%) of patients were assessed as being at least possibly treatment related. The mean number of TEAEs (excluding the CSEs) was similar for all treatment groups. A mean number of 0.54 TEAEs/patient in 33.3% (127/381 patients) of the patients was reported for the LAS41007 group, a mean number of 0.61 TEAEs/patient in 36.5% (139/381 patients) of patients for the Solaraze® 3% gel group and a mean number of 0.59 TEAEs/patient in 40.9% (52/127 patients) of patients for the vehicle group.

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

Most TEAEs classified as at least possibly related to IMP were dermatological adverse events and affect the SOC ‘Skin and subcutaneous disorders’ in 82.7 % of patients (315/381 patients) in the LAS41007 group (TEAEs/patient: 2.94), 83.5% (318/381 patients) of patients in the Solaraze® 3% gel group (TEAEs/patient: 2.71) and 90.6% (115/127 patients) in the vehicle group (TEAEs/patient: 2.42). Skin exfoliation, erythema and pruritus were reported in 50-70% of patients with no major treatment group related differences. Rash and skin edema was more frequent in the LAS41007 (36.2%; 138/381 patients and 19.9%; 76/381 patients, respectively) and Solaraze® 3% gel groups (31.0%; 118/381 patients and 14.4%; 55/381 patients, respectively) compared to the vehicle group (18.9%; 24/127 patients and 9.4%; 12/127 patients), respectively). The second most TEAEs related to IMP affected the SOC ‘General disorders and administration site conditions’, affecting 5.0% (15/381) of patients in the LAS41007 group (TEAEs/patient: 0.08), 6.8% (26/381) of patients in the Solaraze® 3% gel group (TEAEs/patient: 0.08) and 0.8% (1/127) of patients in the vehicle group (TEAEs/patient: 0.01). The only other SOC of particular interest in respect of the number of treatment related TEAEs is ‘eye disorders’ (eyelid edema, conjunctivitis, eye irritation) reported in 9/381 patients in the LAS41007 group (2.4%; TEAEs/patient: 0.03), 4/381 patients in the Solaraze® 3% gel group (1.0%; TEAEs/patient: 0.01), and 1/127 patients in the vehicle group (0.8%; TEAEs/patient: 0.01).

Serious adverse events / Significant adverse events:

17 serious TEAEs were observed in 13/381 patients (3.4%) after LAS41007 administration, 23 serious TEAEs in 16/381 patients (4.2%) following Solaraze® 3% gel administration and 9 TEAEs in 8/127 patients (6.3%) following vehicle administration. None of the serious TEAEs were assessed as at least possibly related to IMP.

Serious TEAEs most frequently affected the SOC ‘Cardiac disorders’ (12 events in 8/889 patients in the SS population) and the SOC ‘Neoplasms benign, malignant and unspecified (including cysts and polyps)’ (11 events in 9/889 patients in the SS population), with a mean number of 0.02 TEAEs/patient at most in each of the treatment groups.

For the SOC ‘Cardiac disorders’ more serious TEAEs were reported for the Solaraze® 3% gel group (8 events in 7 patients) and the vehicle group (3 events in 2 patients) compared to the LAS41007 group (1 event in 1 patient).

A larger number of neoplasms were observed in the LAS41007 group (7 events in 5 patients) and the vehicle group (3 events in 3 patients) compared to the Solaraze® 3% group (1 event in 1 patient). One case of SCC each was classified as a serious event in the vehicle and LAS41007 group. Considering all TEAEs, basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) were reported in a larger proportion of the vehicle group (BCC: 3.9%; 5/127 patients; SCC: 1.6%; 2/127 patients) as compared to the LAS41007 group (BCC: 1.3%; 5/381 patients; SCC: 0.3%; 1/381 patients) and the Solaraze® 3% gel group (BCC: 1.0%; 4/381 patients; SCC: 0.3%; 1/381 patients).

Two cases of death (related to 3 SAEs in total) occurred during the course of the study; one in the

LAS41007 group (acute myeloid leukemia) and one in the vehicle group (atrial fibrillation, cardiac failure). The events were classified as unlikely to be related to IMP application.

2. Tolerability and dermatological assessment of treatment areas:

LAS41007 was statistically significantly inferior to the vehicle (p=0.0001) but was not different from Solaraze® 3% with respect to Investigator's Global Tolerability Assessment during the treatment period. Differences disappeared during the post-treatment period of 60 days.

In line with the investigator assessment, patient assessment of global tolerability was inferior for LAS41007 as compared to the vehicle, but not different from Solaraze® 3% gel during the treatment period. This worse tolerability applies to all individual aspects rated (inflammation: p <0.0001; itching: p=0.0068; burning: p=0.0038; pain: p=0.0418). The patient assessed tolerability issues tended to improve, although still present, within the 60 days post-treatment period, in particular inflammation (p<0.0001), but also burning (p=0.0138) and pain (p=0.0277).

The dermatological assessment of the treatment areas indicated induction of inflammatory changes during treatment with LAS41007 comparable to Solaraze® 3% gel. This was more evident for erythema, pruritus, and skin exfoliation (mean change of 0.4 ± 1.0 on a 4-point scale for all three) and rash (0.3 ± 0.8), than for edema (0.1 ± 0.6). The treatment induced inflammatory changes improved in the post-treatment period, and in some instances the post-treatment dermatological condition after exposure to LAS41007 was even better than that in the group exposed to the vehicle only.

3. Other Safety Parameters:

Among the 140 subjects in the subgroup investigated by laboratory testing, there were no notable changes in the mean or median values of any of the parameters after dosing compared to the values before dosing.

Individual laboratory findings were classified as clinically relevant in only 4 cases:

For hematology, 1/17 patients (5.9%) in the vehicle group presented anemia with low hemoglobin levels, and low hematocrit and erythrocyte numbers at screening. The anemia worsened during treatment and deteriorated further in the PT period.

One patient of 63 (1.6%) in the Solaraze® 3% gel group presented a clinically relevant increase in liver enzymes at the PT visit. Gamma GT was already elevated at screening.

For the LAS41007 group, 2/60 patients (3.3%) presented elevated creatinine levels at each visit (screening, EoT and PT), assessed as being clinically relevant.

No relevant changes in vital signs were reported for any treatment group.

For the analysis of systemic diclofenac exposure after topical application of diclofenac 49/59 patients (83.5%) in the LAS41007 group, 46/62 patients (74.2%) in the Solaraze® 3% gel group (and 1/17 patients (5.9%) in the vehicle group presented elevated diclofenac serum levels higher than the lower limit of quantification (≥ 2 ng/mL). The median diclofenac serum concentrations at the end of treatment was 9.9 ng/mL in the LAS41007 group, 7.4 ng/mL in the Solaraze® 3% gel group, and 3.2 ng/ml in the vehicle group. These values gave no evidence of substantial accumulation of diclofenac serum levels during exposure with LAS41007 or Solaraze® 3% gel.

Overall conclusions:

Analyses of the primary efficacy variable, the percentage of patients with histological clearance of one pre-selected AK target lesion at 60 days PT in subjects of the FAS, gave clear evidence for superiority of treatment with LAS41007 compared to treatment with the vehicle of the test product (p=0.0036). The primary analysis failed to support the hypothesis for superiority of treatment with LAS41007 compared to treatment with Solaraze® 3% gel (p=0.4737). This result was confirmed by various sensitivity analyses of the primary efficacy variable.

The percentage of patients with histological clearance was identical under treatment with LAS41007 and the active comparator Solaraze® 3% gel (47.6% each, corresponding to 179/376 patients in the LAS41007 group and to 181/380 patients in the Solaraze® 3% gel group). Both diclofenac formulations were more effective than the vehicle group in terms the percentage of patients achieving histological

clearance (33.9%, corresponding to 43/127 patients).

The results of the primary efficacy analysis are also supported by the analyses of the secondary efficacy variables, which in general failed to show any difference between the LAS41007 treatment and Solaraze® 3% gel. Numerically the percentage of patients showing complete clinical clearance at 60 days PT (TLNS=0: 102/376, 27.1% patients and CLNS=0: 90/376, 23.9% patients in the LAS41007 group versus TLNS=0: 89/380, 23.4% patients and CLNS=0: 76/380, 20.0% in the Solaraze® 3% gel group) was slightly higher in the LAS41007 group, but the differences were not statistically significant (p=0.2409 for TLNS=0 at 60 days PT, p=0.1911 for CLNS=0 at 60 days PT). The percentage of patients showing complete clinical clearance by the end of treatment (V5), the percentage change of TLNS and CLNS from baseline until 60 days PT, the reduction of total AK target lesion area per patient, the improvement of target lesions (overall target lesion response) at each visit, the assessment of global improvement by both the investigator (IGII) and patient (PGII) and the change in overall AK severity score were comparable for the two diclofenac-containing products.

Comparison of the secondary efficacy variables between LAS41007 and the vehicle group consistently confirmed superiority of LAS41007, with the exception of the DLQI, where the scores were already very low at baseline and so did not provide much scope for detecting a change on treatment.

Analyses of the efficacy outcome variables at different time points (end of treatment, 60 days PT) and various post-hoc analyses supported the robust results of the primary and secondary efficacy analyses.

Analyses of the safety parameters showed only modest differences between the three treatment groups. Slightly higher numbers of IMP related TEAEs per patient were reported for the LAS41007 and the Solaraze® 3% gel group compared to the vehicle group. The majority of TEAEs affected the SOC 'Skin and subcutaneous disorders' in 82.7 % of patients (315/381) in the LAS41007 group (TEAEs/patient: 2.94), 83.5% (318/381) of patients in the Solaraze® 3% gel group (TEAEs/patient: 2.71) and 90.6% (115/127) in the vehicle group (TEAEs/patient: 2.42). Almost all these AEs presented a worsening of the most prominent dermatological signs - erythema, edema, pruritus (= itching), rash, and skin exfoliation (= scaling) - already known as adverse drug reactions of Solaraze® 3%. Most of the remaining TEAEs related to IMP were other application site reactions, classified in the SOC 'General disorders and administration site conditions' (LAS41007: 15/381 patients (5.0%), TEAEs/patient: 0.08; Solaraze® 3% gel: 26/381 patients (6.8%), TEAEs/patient: 0.08; vehicle: 1/127 patients (0.8%), TEAEs/patient: 0.01) and 'eye disorders', such as eye irritation, conjunctivitis or eyelid edema (LAS41007: 9/381 patients (2.4%), TEAEs/patient: 0.03; Solaraze® 3% gel: 4/381 patients (1.0%), TEAEs/patient: 0.01; vehicle: 1/127 patients (0.8%), TEAEs/patient: 0.01). Both, most of the application site reactions as well as the AEs reported in the SOC 'eye disorders' were previously known and are listed in the current SPC of Solaraze® 3% gel.

Serious TEAEs most frequently affected the SOC 'Cardiac disorders' (12 events in 8/889 patients in the SS population) and the SOC 'Neoplasms benign, malignant and unspecified (including cysts and polyps)' (11 events in 9/889 patients in the SS population), but with a total number of not more than 0.02 TEAEs/patient in one of the treatment groups, no particular high level of serious adverse events was seen for any preferred term in any MedDRA-SOC. None of the serious TEAEs were assessed as at least possibly related to IMP.

The results of the AE profile were supported by the patient's and investigator's tolerability assessments of the treatment area showing comparable tolerability of LAS41007 and Solaraze® 3% gel, but better tolerability for the vehicle.

There were no notable changes in the mean or median values of any of the laboratory parameters after dosing compared to the values before dosing and no relevant changes in vital signs were reported for any treatment group.

In summary patients treated with LAS41007 showed a comparable safety and tolerability profile to patients treated with Solaraze® 3% gel which was in line with current knowledge of the product. Almost without exception there were only local site reactions, with no evidence for systemic side effects or substantial accumulation of diclofenac in serum.

No new safety concerns were detected for Solaraze® 3% gel or for the new 5% diclofenac formulation of the LAS41007 test product.