SYNOPSIS

Study No.: **X-03016-3271**

EudraCT No.: **2007-004884-24**

Title of the study:

Long-term effects of Aldara® 5% cream and Solaraze® 3% gel in the treatment of actinic keratoses on the face or scalp (LEIDA)

Sponsor:

MEDA Pharma GmbH & Co. KG, Benzstraße 1, D- 61352 Bad Homburg, Germany

Coordinating investigator:

Magdeburg, Germany

Study centres:

26 centres in Germany, Austria, and France.

Publication (reference):

None at time of this report.

First visit of first patient: 06 Nov 2008 **Clinical phase:** IV

Last visit of last patient: 20 Nov 2012 **Type of study:** Therapeutic

End of study: 20 Nov 2012 (*i.e.* end of the study as defined in the protocol)

Premature discontinuation or interruption: Not applicable

Substantial amendments:

No.	Date issued	In force	Modifications
1	1 Sep 2008	Upon approval by Competent Authority (CA) / Ethics Committee (EC) First patients enrolled based on this version.	Protocol amendment version 03: Taking up further recommendations of the European Medicines Agency (EMA).
2	15 May 2012	Upon approval by EC / CA	Protocol amendment version 5.1: Summary of Product Characteristics (SPC) of Solaraze® had been modified by the comparator's Marketing Authorisation Holder and this had to be announced to investigators and patients (Solaraze patients who had not yet had their visit Month 36 received new "supplementary Solaraze consent form"). Additional non-substantial modifications.

Duration of treatment for each patient:

Depending on the treatment success, patients underwent 1 to maximum 6 treatment cycles; each treatment cycle lasted 20 weeks.

For patients randomised to Aldara® 5% cream (imiquimod 5% cream):
1 or 2 course(s) of treatment (COTs) lasting 4 weeks each and separated by a 4 weeks treatment pause were possible. If the study treatment area (STA) was cleared 4 weeks after end of the first COT of a cycle, the patient received no further treatment for the next 12 weeks. If not cleared 4 weeks after end of the first COT of a cycle, the patient received a second COT lasting for 4 weeks.
For patients randomised to Solaraze® 3% gel (diclofenac 3% gel):
1 course lasted 12 weeks of treatment.

Objectives:
The **primary objective** of the study was to compare the long-term outcome of treatment with Aldara® 5% cream (IMIQ) and Solaraze® 3% gel (DIC) regarding recurrence rates.
Secondary objectives included the time to recurrence, long-term outcome with respect to development of squamous cell carcinoma (SCC, *in situ* and/or invasive), need of rescue treatment, haematological changes, and cosmetic outcome.

Methodology:
Randomised, active controlled, open-label, multicentre, multinational study with 2 parallel groups with follow-up over 3 years after randomisation. To reduce allocation bias to the extent possible, a central randomisation procedure was used.
Efficacy was assessed:
- Clinically, by inspection of the study treatment area by a blinded investigator (until recurrence) not involved in other operational aspects with this study (during screening prior to biopsy and at regular follow-up visits)
- Incidence of SCC (determined by blinded central histological examination of biopsy specimen).
- Cosmetically, by the blinded investigator and the patient.

Dermatological exams for efficacy checks were scheduled after 20 weeks and then half-yearly (starting at Month 6) to decide on further treatment.
The study treatment area (STA) of up to 50 cm^2 and the most suspicious lesion and there from the most pathological area to be biopsied was defined by the operating and blinded investigator together during screening. At selected sites the STA was documented using digital photography (using ring flash or indirect light and a resolution of at least 5 megapixel).

Number of patients planned and analysed:
It was planned to randomise 240 patients using 1:1 allocation.

Diagnosis and main selection criteria:
Immunocompetent patients with 5 to 10 typical visible actinic keratoses (AKs) in 1 contiguous area of up to 50 cm^2 on the face or scalp (to be defined as STA, excluding eyelids, the inside of the nostrils or ears, or the lip area inside the vermilion border were enrolled. A positive histological finding for AK grade I or II (determined from the most suspicious lesion in the STA and there from the most pathological area biopsied during screening visit) was required for inclusion.
Most relevant exclusion criteria comprised: presence of AK lesions in the STA with clinically marked hyperkeratosis or hypertrophy as seen in cutaneous horns; any topical or systemic AK treatment at the STA within the last 2 months prior to randomisation; persisting AK lesion at screening visit following topical treatment with imiquimod or diclofenac in the STA; topical treatment with imiquimod or diclofenac anywhere else on the body within the last 2 months prior to randomisation; presence of any histologically confirmed skin tumour in the STA: *in situ* SCC including Bowen's disease, invasive SCC, basal cell carcinoma, or other malignant tumours; any dermatological disease or condition that may exacerbate by treatment with imiquimod or diclofenac (*e.g.* rosacea, psoriasis,

atopic dermatitis); any dermatological disease or condition in the STA that causes difficulty with examination (*e.g.* eczema); systemic immunomodulatory treatment such as interferon, azathioprine, cyclosporine, retinoids, any oral or injectable corticosteroids, or inhaled or nasal corticosteroids with dosages of >1200 µg/day beclomethasone or equivalent within 4 weeks before start of study treatment; various other criteria intended to ensure enrolment of patients with rather low overall risks.

Study medication, dose and mode of administration, batch number(s):
Original trade ware was used throughout the trial. Each box carried an additional unique identifier.

Group	Trade name	Mode of administration
Imiquimod (IMIQ) 5%, cream	Aldara® Batches used: GJL022A, GJL064B, GJL067A, GKJ073B, GLA054B, GLB012C, GLF045C, GLF078A, GMD073C, GJB059A, GJA087B, GIJ060C	One COT consisting of an overnight application of IMIQ (1 sachet for up to 50 cm^2), applied 3 nights per week (*e.g.* Monday, Wednesday, Friday) for 4 weeks followed by a 4 weeks treatment pause. If necessary, this could be followed by a second COT.
Diclofenac (DIC) 3%, gel	Solaraze® Batches used: 809243, 848421, 851461, 951772, 951782, 030163, 746212, 918511, 809242, 735171	Solaraze® was applied locally to the skin 2 times daily and smoothed in to the skin gently. The amount needed depends on the size of the lesion. Normally 0.5 grams (the size of a pea) of the gel is used on a 25 cm² lesion site. The duration of therapy was 12 weeks.

Concerning treatment cycles see above (duration of treatment per patient).
An interruption of a COT (*i.e.* IMIQ treatment) was to be considered if intense local inflammatory reactions occurred or if super-infection was observed at the treatment site. In this latter case, appropriate other measures were to be taken. A COT was not to be extended to more than 4 weeks due to missed doses; the treatment pause after the first COT had always to be 4 weeks. Altogether, the second COT in a treatment cycle was to end 12 weeks after start of a treatment cycle.
For the time being, there was no recommendation concerning interruptions of DIC dosing. If the investigator considered an interruption of treatment with DIC as medically necessary, treatment should not be extended beyond Week 12 due to missed doses after start of treatment.
Any concurrent AK lesions outside STA were to be treated with cryotherapy.
Rescue:
If 1 or more AK lesions remained in the STA after a complete treatment cycle (*i.e.* at Week 20 of a given treatment cycle), the most suspicious lesion had to be biopsied and histologically characterised. Similarly, any lesion suspicious for **invasive SCC** had to be biopsied and histologically characterised **at any time** during the course of the study. Any invasive SCC that was identified after randomisation had to be excised surgically as soon as possible. In case of an invasive SCC in the STA, patients had to be withdrawn from study treatment (last endpoint reached). Further treatment of the STA was at the discretion of the investigator. However, all patients randomised, even those withdrawn from study treatment, were to be followed-up until Month 36.

Criteria for evaluation:
a) Primary Endpoint: Recurrence with respect to the study treatment area. A patient was classified as recurrent when cleared at Visit Week 20 and having later on at least 1 clinically diagnosed AK lesion in the study treatment area.

b) Histological classification.
c) Incidence of histological progression to *in situ* SCC and/or invasive SCC in the STA during the course of the trial.
d) Incidence of histological progression to invasive SCC in the STA during the course of the trial.
e) Incidence of withdrawal from study treatment due to lack of efficacy.
f) Percent clinical clearance (complete = 100%, partial = 75%, and individual clearance) of baseline AK lesions in the study treatment area 8 weeks after end of treatment and at Week 20.
g) Lesion clearance 8 weeks after end of treatment and at Week 20.
h) Number of treatment cycles per patient in the STA during the study.
i) Number of patients with cryotherapy in the STA during the study.
j) Number of cryotherapies in the STA by patient.
k) Total number of lesions treated with cryotherapy in the STA during the study.
l) Cosmetic outcome (investigator and patient) at Week 20 and then at Month 12, 18, 24, 30 and 36.
m) Local skin reactions (LSRs).
n) Haematological test results (including differential blood count).
o) Adverse events of special interest (AESIs): Haematological adverse events including (immune) thrombocytopenia, stimulation or exacerbation of (auto) immune conditions, alopecia, adverse events in study treatment area.
p) Other adverse events.

Statistical methods:

Adequate descriptive statistics were provided for each variable.

a) The primary endpoint was the recurrence rate until Month 12. For this analysis, withdrawals from treatment and patients not cleared at Week 20 had to be classified as recurrent.
To maintain the global one-sided type I error level $\alpha = 2.5\%$ a 2-step approach was applied to the primary endpoint. Here the second step was only to be considered for the confirmatory analysis if the first was passed successfully.
1.) Non-inferiority test on risk differences (according to protocol [ATP]): The non-inferiority margin δ was chosen as 6%.
2.) Superiority (intention-to treat [ITT]): Cochran-Mantel-Haenszel-test (CMH-test) with adjustment for centre effects (2-sided type I error level $\alpha = 5\%$).
Exploratory CMH-tests for recurrence rates until any other time point were conducted.
Time to recurrence was time of visit of occurrence minus time of visit Week 20, and was described by Kaplan-Meier-curves, the life-table method and tested using the log-rank test.
These analyses were to be repeated excluding those patients not achieving initial clearance at Week 20 (recurrence in strict sense).
b) Incidences and occurrences.
c)-d) Kaplan-Meier curves, χ^2-tests and Fisher's exact tests as applicable.
e) χ^2-tests and Fisher's exact tests as applicable.
f) χ^2-tests and Fisher's exact tests as applicable, centre adjusted rank test for individual percent clearance.
g)-k) Descriptive statistics only.
l) Centre adjusted rank test (non-parametric analysis of variance [ANOVA]).
m) Centre adjusted rank test on maximum intensity per symptom until Week 20, all other time points descriptively (non-parametric ANOVA).

n) Baseline adjusted analysis of covariance (ANCOVA) with factors treatment and centre on changes from baseline. Incidences for decreases from normal to abnormal were analysed by χ^2-tests and Fisher's exact tests as applicable.

o),p) Incidences, χ^2-tests and Fisher's exact tests as applicable.

Results - background:

Overall, 343 patients were screened; 261 patients were randomised, and of these thereof 260 were exposed to at least 1 dose of study medication and therefore included in the safety and full analysis sets. One patient in the DIC group did not use the study medication. Major protocol violations were recorded for 29 patients. The ATP set thus consisted of 232 patients. Overall, 93 patients (35.8%) discontinued from the study treatment. Withdrawals from study treatment occurred more frequently in the DIC group than in the IMIQ group (IMIQ: 29.3%, DIC: 42.5%). Withdrawals during follow-up were reported in both groups at similar frequencies.

The majority of patients in the full analysis set (FAS) were male (227 of 260, 87.3%). All patients were Caucasians. The mean age was 70.88 ± 7.597 years (median 70 years). 61.9% of patients had Fitzpatrick Skin Type II (tans minimally; always burns easily), 26.9% had Skin Type III (tans gradually; burns moderately) and the remaining patients had Skin Types I, IV, or V. 44.2 % of the STAs were located on the scalp and 38.1% on the forehead. At screening, the patients had a median of 7.0 lesions in the STA. 73.1% of patients of patients had AK grade II and 26.9% had AK grade I.

Results - efficacy:

Primary endpoint

A 2-step approach was performed for the confirmatory analysis of the primary efficacy endpoint, **recurrence rate until Month 12**. For this analysis, patients withdrawn from study treatment before Week 20 and patients not cleared at Week 20 were classified as recurrent. In the non-inferiority-test based on the ATP set, the recurrence rate until Month 12 was lower in the IMIQ group (65.8%) than in the DIC group (78.6%). The upper bound of the 2-sided 95% CI for the difference between recurrence rates was -1.3% (Farrington-Manning test). This value was below the pre-defined non-inferiority margin (≤6%), and consequently, IMIQ was shown to be non-inferior to DIC. Since this step was successful, superiority was tested using the FAS. Based on the FAS, the recurrence rates until Month 12 were 68.4% in the IMIQ group and 80.3% in the DIC group (2-sided p-value from CMH test ≤0.05 [p = 0.0315]); thus superiority of IMIQ relative to DIC was demonstrated. Consequently, both confirmatory hypotheses for this study were met.

Results for all sensitivity analyses (*e.g.* using the FAS for the non-inferiority test and the ATP set for the superiority test, various methods for imputation of missing values) supported the confirmatory analysis.

Secondary endpoints

In on the FAS, **initial clearance at Week 20** was achieved by more patients in the IMIQ group than in the DIC group (IMIQ: 42.9%, DIC: 33.9%). The difference between treatment groups was not statistically significant (p = 0.1199).

The **recurrence rates** increased over time up to the Month 36 visit, from 68.4% at Month 12 to 83.5% at Month 36 in the IMIQ group and from 80.3% to 90.6% in the DIC group. The percentage of recurrent patients was numerically higher in the DIC group than in the IMIQ group at all visits.

Time to recurrence was of borderline significance in favour of IMIQ (p = 0.0524; log-rank test).

In the **subgroup analysis** of patients initially cleared recurrence rates until Month 12 were 26.3% with IMIQ and 41.9% with DIC (in the FAS, p = 0.6327). The recurrence rates in patients with initial clearance at Week 20 increased over time up to the Month 36 visit from 26.3% to 61.4% in the IMIQ group and from 41.9% to 72.1% in the DIC group. The p-value based on the log-rank test to assess differences in time to recurrence between the IMIQ group and the DIC group was not statistically significant (p = 0.2090) due to relatively small sample sizes in this subgroup analysis.

Based on the **histological classification** during the treatment period more patients in the IMIQ group had no AK/SCC or no biopsy necessary compared to patients in the DIC group (IMIQ: 41.4%, DIC: 26.8%). More patients in the DIC group had the biopsy finding of AK grade II (IMIQ: 21.8%, DIC: 38.6%). The same pattern was observed until last follow-up (no AK or no biopsy necessary - IMIQ: 50.4%, DIC: 31.5%; AK grade II – IMIQ 21.8%, DIC 41.7%). AK grade I was reported as the worst finding overall at similar frequencies in both treatment groups (during study treatment period - IMIQ: 13.5%, DIC: 10.2%; until last follow-up – IMIQ: 13.5%, DIC: 11.8%).

Histological progression to *in situ* SCC or invasive SCC was observed in 14 patients during the study treatment period (IMIQ: 6 patients, DIC: 8 patients) and in 23 patients during follow-up (IMIQ: 10, DIC: 13). The majority of patients were diagnosed by Month 12 (patients in the study treatment period – IMIQ: 6, 4.5% of the FAS; DIC: 7, 5.5%; patients during follow-up - IMIQ: 9, 6.8%; DIC: 10, 7.9%). The differences between treatments were not statistically significant.

Progression to invasive SCC was observed in 4 patients treated with IMIQ and 5 patients treated with DIC. The majority of patients were diagnosed by Month 12 (IMIQ: 3 patients, 2.3% of the FAS; DIC: 4 patients, 3.1%). The differences between treatments were not statistically significant.

Withdrawals from study treatment due to lack of efficacy occurred more frequently in the DIC group than in the IMIQ group (IMIQ: 7 patients, 5.3%, DIC: 19 patients, 15.0%). The difference between treatments was statistically significant (p = 0.0092; χ^2-test).

Percentage clinical clearance at Week 20 of the initial treatment cycle was statistically significantly higher in the IMIQ than in the DIC group (mean IMIQ: 77.45%, mean DIC: 66.69%; p = 0.0003, non-parametric ANOVA).

Complete clearance rate at Week 20 (*i.e.* the proportion of patients achieving 100% clearance) was statistically significantly higher in the IMIQ group (51.1%) than in the DIC group (37.0%) (p = 0.0219, χ^2-test).

Partial clearance rate at Week 20 (*i.e.* the proportion of patients achieving ≥75% clearance) was significantly higher with IMIQ treatment compared to DIC treatment (66.9% *vs.* 48.0%, p = 0.0021; χ^2-test).

The **lesion clearance rate** at Week 20 of the initial treatment cycle was higher in the IMIQ than in the DIC group (IMIQ: 80.1%, DIC: 67.3%). Whilst the number of lesions at baseline was similar in both treatment groups (IMIQ: 911 lesions, DIC: 857 lesions), at

Week 20 patients in the IMIQ group had fewer AK lesions in the STA than patients in the DIC group (181 *vs.* 280 lesions).

Similar results for percentage clinical clearance, complete clearance, partial clearance and lesion clearance were observed 8 weeks after the end of treatment.

The mean **number of treatment cycles** per patient was comparable between the treatment groups (IMIQ: 2.3, DIC: 2.8). More patients in the IMIQ group than in the DIC group received only 1 treatment cycle (IMIQ: 37.6%, DIC 24.4%).

About twice as many patients in the DIC group received **cryotherapy** in the STA compared with patients in the IMIQ group (IMIQ: 16.5%, DIC: 31.5%) and about twice as many lesions were treated by cryotherapy in the DIC group (median - IMIQ: 2.0, DIC: 4.0). The mean number of cryotherapies per STA was higher in the DIC group than in the IMIQ group (IMIQ: 1.4, DIC: 1.8).

Cosmetic outcomes were rated as being statistically significantly higher by patients and investigators in the IMIQ group compared with those in the DIC group at all time points from as early as Week 20 of the initial cycle up to Month 18 ($p<0.05$, non-parametric ANOVA). The majority of patients and investigators rated the cosmetic outcomes associated with both study medications as “excellent” or “good” at all visits. In the DIC group “excellent” ratings were provided less frequently than in the IMIQ group throughout the entire duration of the study.

Results - safety:

All of the patients in the safety set 89.5% of patients (119 of 133) in the IMIQ group and 85.0% (108 of 127) in the DIC group experienced at least 1 treatment emergent adverse event (TEAE). Treatment-related TEAEs (causality of likely or not assessable) were reported slightly more frequently in the IMIQ group (27.8% of patients) than in the DIC group (21.3%). Serious TEAEs (SAEs) occurred less frequently in the IMIQ group (17.3% of patients) than in the DIC group (32.3%). Overall, 7 patients (5 in the IMIQ group and 2 in the DIC group) had serious TEAEs leading to death. None of the SAEs (including deaths) were treatment related. The majority of TEAEs were mild or moderate in intensity. Severe TEAEs were reported for fewer patients in the IMIQ group (18.0%) than in the DIC group (27.6%). TEAEs leading to study discontinuation (including deaths) were reported for 10.5% of patients in the IMIQ group and 13.4% of patients in the DIC group. No suspected unexpected serious adverse reactions (SUSARs) were observed in this study.

Due to the flexibility of the study design and the different treatment regimens for IMIQ and DIC, the most reliable data for comparison of safety between the 2 treatment groups are those obtained between Day 1 and Week 20 of the first treatment cycle. During this period, similar numbers of TEAEs were reported for both treatment groups. 201 TEAEs (98 mild, 90 moderate, 13 severe) occurred in 73 patients in the IMIQ group and 185 TEAEs (102 mild, 59 moderate, 24 severe) occurred in 73 patients in the DIC group.

The most common TEAEs by preferred term (PT) in both treatment groups between Day 1 and Week 20 of the first treatment cycle were nasopharyngitis, application site pruritus, headache, back pain, basal cell carcinoma (BCC), and application site irritation, which occurred in more than 3% of patients in the overall safety set. Of these, application site pruritus and application site irritation were defined as AESIs. The majority of cases of application site pruritus, headache and application site irritation were assessed as related

to treatment (application site pruritus - IMIQ: 7.5% of patients, *i.e.* all patients with event, DIC: 9.4%, headache - IMIQ: 3.8%, DIC 1.6%, application site irritation - IMIQ: 3.0%, DIC: 3.1%). None of the differences between treatment groups in the most common groups during the initial treatment cycle were statistically significant.

Slightly more AESI in the STA were reported for patients in the DIC group than for those in the IMIQ group prior to study treatment withdrawal and during the entire duration of the study: 9 AESIs occurred in 6 patients after IMIQ and 17 AESIs occurred in 10 patients after DIC prior to study treatment withdrawal; 34 AESIs occurred in 24 patients in the IMIQ group and 48 AESIs occurred in 30 patients in the DIC group during the entire duration of the study. Application site pruritus was the most frequent AESI in both treatment groups. This event was reported prior to study treatment withdrawal for 2.3% of patients in the IMIQ group and for 3.1% of patients in the DIC group and during the entire duration of the study for 7.5% of patients in the IMIQ group and 10.2% of patients in the DIC group. None of the other AESIs occurred in more than 3.1% of patients in the safety set. None of the differences between treatment groups in AESI were statistically significant.

The most severe LSRs on a scale of none = 0 to severe = 3 during the initial treatment cycle were erythema (IMIQ: mean: 2.0 points, median 2.0 points; DIC: mean: 1.3, median: 1.0), scabbing/crusting (IMIQ: mean 1.7, median 2.0; DIC: mean 0.9, median 1.0), and flaking/scaling dryness (IMIQ: mean 1.3, median: 1.0; DIC: mean 1.4, median: 1.0). The differences between the groups in all types of LSRs investigated were statistically significant (*i.e.* higher severity in the IMIQ group for erythema, oedema, weeping/exudates, vesicles, erosion/ulceration, and scabbing/crusting; and indicating higher severity in the DIC group for: flaking/scaling/dryness; $p<0.05$, non-parametric ANOVA). Similar descriptive results were obtained for the evaluation of LSRs through Month 36 and prior to withdrawal of study treatment.

Assessments of laboratory variables (haematology and differential blood count) were restricted to the first treatment cycle. Although statistically significant changes were found for some of the laboratory values these were not considered to be clinically relevant.

Conclusions:

Aldara® 5% cream (IMIQ) was superior to Solaraze® 3% gel (DIC) in terms of AK recurrence on the face or scalp until Month 12. The probability of not experiencing recurrence was higher in the IMIQ group than in the DIC group for the entire duration of the study (36 months). Histological progression to in situ SCC and/or invasive SCC was observed in slightly more patients in the DIC group than in the IMIQ group. Percentage clinical clearance, complete clearance, and partial clearance were statistically significantly higher in the IMIQ than in the DIC group at Week 20 of the initial treatment cycle. Significantly fewer patients treated with IMIQ compared to DIC withdrew throughout the study due to lack of efficacy. At all time points from Week 20 of the initial cycle up to Month 36, both patients and investigators provided higher ratings for cosmetic outcomes in the IMIQ group than in the DIC group.

IMIQ was safe and well-tolerated in patients with AK on the face or scalp. The overall rate of treatment emergent and related adverse events was 27.8% for IMIQ and 21.3% for DIC. No serious treatment emergent and treatment related AEs or treatment related AEs leading to death were reported for either group. TEAEs leading to study discontinuation were seen in 10.5% of patients in the IMIQ group compared to 13.4% of patients in the DIC group.

The frequencies of TEAEs in general, SAEs, AEs related to study treatment, AEs leading to study discontinuation, and AESI were comparable between the 2 treatment groups and did not indicate a particular safety problem, nor were there any unexpected adverse reactions. No SUSARs were observed. No clinically relevant haematological changes were detected. The AE profile documented for both treatments did not result in any change of their known risk-benefit profile.