Clinical Study Synopsis for Public Disclosure

The clinical study synopsis

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SYNOPSIS

Name of sponsor: Moberg Derma AB (publ) Gustavslundsvägen 42, 5 tr SE-167 51 Bromma, SWEDEN	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of finished product: Limtop	Volume:	
Name of active ingredient: Imiquimod	Page:	
Reference to the according CSR: Limtop-I-CSR Final Version 3.0 dated 24 Jun 2013		Date of synopsis: 24 Jun 2013

Title of study:

A double-blind, randomized, multi-centre, vehicle-controlled study of efficacy and safety of a new topical formulation with imiquimod (Limtop) applied 1,3 or 7 times weekly during 2 x 2 weeks treatment for actinic keratosis on the head

Study number: LIMTOP-I EudraCT number: 2011-004538-32

Study sites:

5 study sites in Germany

Publication (reference):

Not applicable

Studied period:	Date of first patient first visit:	04 June 2012	**Clinical study phase:**
	Date of last patient completed:	18 January 2013	Phase II

Study Objectives:

The objective of this study was to assess efficacy and safety of different dosing regimens (once, three or seven times weekly) of Limtop in adults with actinic keratosis (AK) on the head (balding scalp or face).

Methodology (design of study):

This proof of concept study was initiated with EudraCT No. 2011-004538-32. It was performed as a double-blind, randomized, multi-center, four-armed, vehicle-controlled study of efficacy and safety of a new topical formulation with imiquimod 0.09% (Limtop) applied 1, 3 or 7 times weekly during 2 x 2 weeks treatment for actinic keratosis on the head.

Male or female patients aged ≥ 18 with 5-20 clinically confirmed, palpable or visible (grade I or II according to modified Olsen score), non-hyperkeratotic, non-hypertrophic AK lesions located within a contiguous (25-100 cm^2)

area on the balding scalp or face were to be randomized to one of the 4 different treatments.

The study was conducted in two treatment courses of 14 days each with daily application of IMP in each treatment course and a rest period of 4 weeks between the treatment courses. The 4 weeks rest phase in between was chosen to enable the TLR receptor to recover from the hyporesponsive state. Hence at start of the second treatment course the original response could have been retrieved.

In total the study comprised of 8 study visits: During both of the treatment courses patients were weekly observed (Visit 2 and Visit 3; Visit 5 and Visist 6) after receiving the IMP at the first day of each treatment course (Visit 1 and Visit 4). A further assessment was performed following a rest period of 4 weeks (Visit 4 and Visit 7) and the final assessment was performed 12 weeks after the second treatment course (EoS visit, Visit 8) to evaluate the clinical efficacy.

Number of patients (planned):

The sample size calculation was based on the results published in Hanke et al., 2010.

Assuming a common standard deviation of 39%, using a two-sided t-test at 5% significance level, a sample size of 21 patients per group was calculated to detect a difference in mean change in AK lesions of 35% (25% reduction in the vehicle group and 60% in the active treatment group), in order to obtain a power of at least 80%.

Assuming a drop-out rate of 12%, approximately 96 patients were planned to be randomized in order to obtain a total number of 84 evaluable patients.

Number of patients (analyzed):

98 patients signed the informed consent form (ICF), 97 patients were randomized as follows:

Treatment group A (Limtop once a week):	25
Treatment group B (Limtop three times a week):	24 (22 who applied IMP at least once)
Treatment group C (Limtop seven times a week):	25
Treatment group D (vehicle):	23

Two patients that were randomized to treatment group B did not apply any IMP. Therefore 95 patients were valid for the safety analysis set. 93 patients (82 males, 11 females) were valid for the full analysis set (FAS) and 71 patients were valid for the per-protocol analysis set (PPAS).

Diagnosis and main criteria for inclusion:

Main inclusion criteria:

- Male and female patients aged 18 years or older
- Immunocompetent patients with 5-20 clinically confirmed, palpable or visible (grade I or II according to modified Olsen score), nonhyperkeratotic, nonhypertrophic AK lesions located within a contiguous 25 - 100 cm² area on the balding scalp or face
- Any skin type or race, providing the skin pigmentation will allow discernment of erythema

Main exclusion criteria:

- Evidence of clinically significant, unstable cardiovascular or immunosuppressive, hematologic, hepatic, neurologic, renal, endocrine, collagen-vascular, or gastrointestinal abnormalities or disease
- Diagnosed autoimmune diseases and anaemia
- Any dermatological disease and or condition in the treatment or surrounding area that might have exacerbated by treatment with imiquimod or cause difficulty with examination (e.g. rosacea, psoriasis, atopic dermatitis, eczema)
- Any significant findings (e.g. tattoos) in the potential application site area that might have impaired examination of treatment or surrounding area
- Confirmed squamous cell or basal cell carcinoma anywhere on the head in the past 3 months
- Patients who experienced an unsuccessful outcome from previous imiquimod therapy
- Known allergy or sensitivity to imiquimod or any of the excipients (butyl lactate, isopropyl myristate, propylene glycol, butylated hydroxy anisole) in the IMP
- Known infectious diseases (e.g. HIV, hepatitis)

Prohibited medication: - Topical retinol products, corticosteroids, curettage, cryosurgery, 5-fluorouracil preparations or other topical AK treatments in the treatment area 28 days prior to randomization and during the study - Treatment with COX-2 inhibitors 14 days prior to randomization and during the study - Treatment with imiquimod for AK in the predetermined treatment area within the past 3 months prior to randomization - Systemic steroids 2 months prior to randomization and during the study except inhalative corticosteroids (<1200 μg/day for beclomethasone, or <600 μg/day for fluticasone) - Systemic cancer chemotherapy, psoralen plus UVA therapy, UVB therapy, laser abrasion, dermabrasion, glycolic acids, or chemical peels 6 months prior to randomization and during the study	
Test products: Treatment group A, B and C differ in total amount imiquimod per week, only	Limtop solution for topical use with the active ingredient imiquimod in the concentration 0.09% (w/w)
Dosages, schedule and duration of treatment:	• **Treatment duration:** o 1st treatment course: 2 weeks with daily applications o 4 weeks rest period o 2nd treatment course: 2 weeks with daily applications • **Amount of IMP:** o per application a sufficient amount of IMP was to be applied to cover the complete treatment area (25 – 100 cm²) with a thin layer o per application at most 0.5 ml of test product solution was to be applied o at each test product application at most 0.43 mg imiquimod was to be applied on the 25 – 100 cm² treatment area • **Treatment groups:** Treatment group A: Limtop once a week • Application of Limtop on day 1 and day 8. The remaining days (day 2- 7 and day 9-14) vehicle solution was to be used for application Treatment group B: Limtop three times a week • Application of Limtop on day 1, 3, 5, 8, 10, and 12. The remaining days (day 2, 4, 6, 7, 9, 11, 13, and 14) vehicle solution was to be used Treatment group C: Limtop seven times a week • daily application of Limtop (on each day from day 1- 14)
Batch number:	K1014A (Limtop)/K1015A (vehicle)
Reference therapy:	Vehicle of test product Limtop; solution for topical use without the active ingredient imiquimod
Dosages, schedule and duration of treatment:	Treatment group D: Vehicle seven times a week; • **Treatment duration:** o 1st treatment course: 2 weeks with daily applications o 4 weeks rest period o 2nd treatment course: 2 weeks with daily applications • **Amount of IMP:** o per application a sufficient amount of IMP was to be applied to cover the complete treatment area (25 - 100 cm²) with a thin layer o per application at most 0.5 ml of vehicle solution was to be applied, i.e. 7 ml vehicle at most during each treatment course and 14 ml during the entire study
Batch number:	K1015A (vehicle)

Criteria for evaluation:

Efficacy variables

Primary efficacy variable

Percentage change in the number of target AK lesions at end of study, i.e., the percentage change from baseline to Visit 8.

Percentage change is defined as 100·x ('post-baseline value'–'baseline value')/'baseline value'.

Secondary efficacy variables:

- Percentage change in the number of target AK lesions during the study (from baseline to Visits 4 and 7).
- Percentage change in the overall AK lesion count (*i.e.*, target, non-target and new lesions) during the study (from baseline to Visits 4, 7, and 8).
- Percentage change in the number of non-target AK lesions during the study (from baseline to Visits 4, 7, and 8).
- Global severity score: AK severity scoring at baseline and Visits 4, 7, and 8.
- Existence or absence of nine defined criteria regarding two subclinical lesions within the treatment area, at Visits 4 and 8 as assessed by reflectance confocal microscopy in a subset of patients (patients at site of Prof. Stockfleth).

Safety variables

- Local skin reactions: the intensity of cutaneous symptoms in the treatment area at baseline and at each post-baseline visit as assessed by a 4-point score.
- Incidence of adverse events and serious adverse events during the entire study period.
- Physical examination including vital signs, at screening/baseline (Visit 1) and the end of study visit.
- Blood concentration of imiquimod after 2 weeks treatment (Visit 3), for a subset of about 24 patients from two predefined study sites.

Additional variables

- Urine pregnancy test at screening/baseline (Visit 1) and the end of study visit, for female patients of childbearing potential.
- Demographics (including sex and year of birth) at screening/baseline (Visit 1).
- Relevant medical history at screening/baseline (Visit 1).
- Prior and concomitant treatment at screening/baseline (Visit 1) and throughout the study.
- Clinical grading of individual AK lesions at baseline (Visit 1): AK severity scoring of each AK lesion located within the treatment area.
- Patients' compliance regarding IMP administration during the treatment phases

Statistical methods:

A more detailed elaboration of the statistical analysis is documented in a separate statistical analysis plan (see appendix 16.1.9).

All efficacy analyses were performed on both the FAS and the PPAS. The analyses performed on the FAS are considered as main. The safety analyses were performed on the safety analysis set.

Efficacy evaluation:

Each of the active treatment groups was compared to vehicle in a hierarchical structure of analysis with closed tests of hypotheses conducted in a predefined order, to protect the type I error.

Percentage change in AK lesion counts (including the primary efficacy variable) was analyzed using ANCOVA models adjusted for treatment group, baseline value and center.

The global severity score was analyzed using a mean score statistics test (Cochran–Mantel–Haenszel) adjusted for treatment group, baseline value and center.

Criteria assessed by reflectance confocal microscopy were presented descriptively only.

Last observation carried forward (LOCF) was used to impute missing values of efficacy variables. No imputations were done for the analyses on the PPAS.

Safety evaluation:

The intensity of local skin reactions was analyzed using a mean score statistics test adjusted for treatment group, baseline value and center. The hierarchical structure that was used for the efficacy analyses was not applied.

The incidence of adverse events and serious adverse events were presented as the number and percentage of subjects, and the number of mentions, for each observed SOC and PT. Adverse events were also presented by relationship to the IMP and by intensity. Dermatological adverse events within the treatment area, other dermatological adverse events, and systemic adverse events were presented separately.

Summary and Conclusions:

Summary of Efficacy:

For all treatment arms, the number of target AK lesions and the overall AK lesion count decreased over time, but there were no statistically significant differences between Limtop and vehicle.

The adjusted mean percentage change in the number of AK target lesions (and corresponding 95% confidence interval) was -40.12 (-52.02, -28.22) for treatment group A, -37.47 (-49.88, -25.07) for treatment group B, -44.20 (-56.34, -32.06) for treatment group C and -44.27 (-56.37, -32.17) for treatment group D. There was no statistically significant difference between treatment groups C (Limtop 7 times per week) and D (vehicle) in the percentage change from baseline to Visit 8 in the number of target AK lesions (p=0.9940).

The number of non-target AK lesions was small throughout the study, for all treatment arms, and no differences were observed.

The global severity score was similar across all treatment groups; except for treatment group A in which the proportion of subjects with higher severity scores seemed to be greater than for the other treatment groups at Visits 4 and 7.

The analysis of the reflectance confocal microscopy criteria revealed some differences between visits and between treatment groups, but there does not seem to be any association between treatment and existence/absence of a criterion.

Summary of Safety:

AEs were observed in 9 patients (40.9%, n=12 AEs) in treatment group B, 7 patients (28.0%) in both treatment group A (n=13 AEs) and C (n=16 AEs), and 8 patients (34.8 %, n=10 AEs) in treatment group D (vehicle group).

Both numbers of 'dermatological AEs in treatment area and other' (n=17 in 14 patients) as well as 'systemic AEs' (n=34 in 22 patients) were comparable between treatment groups. The occurrence of AEs (n=51 in 31 patients) revealed no tendencies regarding unexpected clustering in any SOC.

In total, only one systemic AE was considered related to the IMP (treatment group D).

Five SAEs accounting to a total of 6 preferred terms and related to a total of three cases were reported in three patients, one each in treatment groups A, B and C. None of the SAEs was considered as related to IMP administration.

One case of death (related to 2 SAEs splitted into 3 different preferred terms in total) occurred during the course of the study.

Other significant events include one case of severe erythema and local pain on treatment area and one case of irritation and pain of both eyes (in the vicinity to the treatment area located on the forehead right side) that led to discontinuation of study drug application. Both cases belong to treatment group D.

Local skin reactions were reported at a frequency between 63.6% for patients in treatment group A and 78.3% for patients within treatment group D. The most prominent symptoms were 'erythema', 'scabbing/crusting', 'burning' and 'itching'. The majority of those reactions were of mild intensity (77.2%) and only 2.7% of all events were regarded as severe. For none of the treatment groups A, B or C, an obvious increase of local skin reactions as compared to the vehicle (treatment group D) can be derived, except for 'erythema' in treatment group C at Visit 3.

Compared to screening/baseline, there were no clinically relevant changes of any vital signs parameters or findings of the physical examination at EoS for any of the treatment groups.

The imiquimod serum concentrations were below the lower limit of quantification.

Overall conclusions:

Analyses of the primary efficacy variable gave no evidence for statistically significant differences between Limtop and vehicle. Hence the primary analysis failed to support the hypothesis for superiority of treatment with Limtop even in the most frequent dosing regimen (Limtop applied 7 times a week) compared to treatment with vehicle. This result was confirmed by analyses of the secondary efficacy variables and the analyses on the PPAS.

The incidence of AEs and all details of the events (e.g. maximum intensity, outcome at end of study and action taken in IMP treatment) were in line with the expectations for the study population treated in this study and were not substantially different between treatment groups.

Also local skin reactions did not reveal any relevant differences between treatment groups which led to the conclusion that they are most likely caused by the ingredients of the vehicle formulation.

Overall there is no evidence for an inferior safety and tolerability profile of treatment groups A, B and C as compared to the vehicle (treatment group D).