Clinical Study Synopsis for Public Disclosure

The clinical study synopsis

- is supplied for information purpose only
- was authored with best practice and applicable legal and regulatory requirements at the time of study completion
- may include non-approved uses or formulations. Please note that the results from a single trial does not provide the overall risks and benefits of all data currently available for a product.

Synopsis

Name of company: Moberg Derma AB	Individual study table Referring to part of the dossier	*(For National Authority Use Only)*
Name of finished product: n.a.	Volume:	
Name of active ingredient: Lactic acid (5 %), Propylene glycol (20 %), Urea (5 %)	Page:	

Title of study: Assessment of the effects on barrier impairment, clinical features and bacterial colonization of topical formulations in patients with atopic eczema; a phase IIa, single-center, randomized, observer-blind study
Investigator(s):
Study center(s): Germany
Publication (reference): Not applicable to this study

Studied period (years): 2009	Phase of development: IIa

Objectives: The purpose of this study was the assessment of the barrier impairment (TEWL measurements), clinical skin condition (corneometric measurements and clinical assessments) and bacterial colonization of Staphylococcus aureus status in patients with atopic eczema following topical treatment with K201 cream and the comparator Jellin® Basis Creme over a 4-week treatment period.
Methodology: Topical application of approximately 2 – 5 mg/cm² of the study preparation and the comparator per treatment area (20 - 50 cm²). Treatments were performed twice daily (morning and evening) over a 4-week treatment period. Assessments and measurements were performed on study days 1, 8, 15, 22 and 29 (TEWL, corneometry and clinical assessment). Bacteria samples for the determination of bacterial counts of Staphylococcus aureus were collected on study days 1 and 29.
Number of patients (planned and analyzed): Thirty male or female patients were planned and included in the study. Data from all 30 patients were valid for ITT and safety analyses. Data from 29 patients were valid for PP analyses. There was one dropout due to a major protocol violation.
Diagnosis and main criteria for inclusion: Thirty male or female patients, aged 18 years or older with manifest atopic eczema meeting Hanifin and Rajka's criteria; at least two comparable lesional areas; TEWL in the lesional areas at least 12 g/m²h
Test product(s), dose and mode of administration, batch number: K201 cream [Lactic acid (5 %), Propylene glycol (20 %), Urea (5 %)], batch no.: M8033A Topical application of approximately 2 – 5 mg/cm² of the study preparation per treatment area (20 - 50 cm²).
Duration of treatment: Twice daily (morning and evening) over a 4-week treatment period
Reference therapy or controls, dose and mode of administration, batch number: Jellin® Basis Creme [Propylene glycol (15 %)], batch no.: 224M01 Topical application of approximately 2 – 5 mg/cm² of the comparator per treatment area (20 - 50 cm²).
Duration of treatment: Twice daily (morning and evening) over a 4-week treatment period

Synopsis (continued)

Name of company: Moberg Derma AB	Individual study table Referring to part of the dossier	*(For National Authority Use Only)*
Name of finished product: n.a.	Volume: Page:	
Name of active ingredient: Lactic acid (5 %), Propylene glycol (20 %), Urea (5 %)		

Criteria for evaluation:

Efficacy:

- TEWL values measured on study days 1, 8, 15, 22, and 29
- corneometric values measured on study days 1, 8, 15, 22, and 29
- clinical assessment of erythema, edema/papulation, oozing/crusts, excoriations and lichenification (SCORAD intensity scale) on study days 1, 8, 15, 22, and 29
- bacterial counts of Staphylococcus aureus on study days 1 and 29

Safety: Screening and final clinical examinations, recording of adverse events.

Statistical methods:

Analysis populations

Efficacy populations

An intent-to-treat (ITT) analysis was conducted based on the Full Analysis Set (FAS). The Full Analysis Set included all randomized patients who received at least one dose of study medication, and had at least one post-baseline assessment. The Last Observation Carried Forward (LOCF) method was applied for missing efficacy measurements and assessments.

A per-protocol (PP) analysis was conducted based on the Valid-Cases-Set. The Valid-Cases-Set included all patients

- without any major protocol violation including violation of inclusion criteria;
- who applied at least 80 % of the trial medication dosages;
- who completed the study day 29 visit and missed no more than one visit.

Safety population

The Safety Set included all patients who received any trial medication at least once; all safety analyses were based on the Safety Set.

Statistical methods

Efficacy analyses

Hypotheses

No formal hypotheses were generated in this exploratory study.

Statistical analyses

The evaluation of epidermal barrier impairment by measurement of transepidermal water loss (TEWL) was based on the analysis of the intraindividual and intratreatment change to baseline in TEWL for each post baseline study visit separately.

Summaries are presented for the absolute outcomes and for their changes from baseline by treatment and study visit giving descriptive statistics (number of patients, mean, standard deviation, median, inter-quartile range, 95 % confidence interval of mean).

Synopsis (continued)

Name of company: Moberg Derma AB	Individual study table Referring to part of the dossier	*(For National Authority Use Only)*
Name of finished product: n.a.	Volume: Page:	
Name of active ingredient: Lactic acid (5 %), Propylene glycol (20 %), Urea (5 %)		

Statistical methods (continued)

Differences in treatment effects were evaluated by two-sided confidence intervals with coverage probability of 95 % of the mean difference in changes from baseline. In case the confidence interval did not cover the treatment effect of 0 this was equivalent to a significant treatment effect assessed by the comparison of the mean changes from baseline applying the paired t-test at a significance level of $\alpha = 0.05$ comparing the hypothesis of equal means vs. the two-sided alternative of difference in means. No adjustment for multiplicity was applied.

The analysis of skin moisture (corneometry) was performed along the lines of the analysis of TEWL outcomes.

The clinical assessments of erythema, edema/papulation, oozing/crusts, excoriations and lichenification are presented by frequency tables and descriptive statistics by treatment and visit. The total clinical assessment score was determined as the sum of the individual clinical assessments of erythema, edema/papulation, oozing/crusts, excoriations and lichenification for each patient, treatment and visit and was analyzed along the lines of the analysis of TEWL outcomes.

The analysis of the bacterial count of Staphylococcus aureus was restricted to the subpopulation of patients with a bacterial count of > 0 for both treatment areas on study day 1.

The **number of bacteria per skin surface [count/cm²]** was determined as:

Number of colonies / dilution step / 3.8,

where dilution step was one of the applied dilution steps 10^{-1} to 10^{-10} or 1 in case of no dilution. The normalization factor 3.8 was the skin surface in cm^2 affected by bacterial sampling.

Since bacteria numbers are considered to have a logarithmic normal distribution, the bacteria numbers were expressed as logarithm to the base 10, i.e. as **log number of bacteria per skin surface [log count/cm²]** determined as:

$$Y = \log_{10} (\text{number of bacteria per skin surface} + 1)$$

For each patient and test area the **reduction in log number of bacteria per skin surface [log count/cm²]** was then calculated as:

$$Z = \log_{10} (\text{number of bacteria per skin surface on study day 1} + 1) - \log_{10} (\text{number of bacteria per skin surface on study day 29} + 1)$$

Summary statistics (number of patients, mean, standard deviation, median, inter-quartile range and range, 95 % confidence interval of mean) were provided for the log number of bacteria per skin surface [log count/cm²] and reduction in log number of bacteria per skin surface [log count/cm²].

Differences in treatment effects were evaluated by two-sided confidence intervals with coverage probability of 95 % of the reduction in log number of bacteria per skin surface [log count/cm²].

Synopsis (continued)

Name of company: Moberg Derma AB	Individual study table Referring to part of the dossier	*(For National Authority Use Only)*
Name of finished product: n.a.	Volume: Page:	
Name of active ingredient: Lactic acid (5 %), Propylene glycol (20 %), Urea (5 %)		

Safety analyses

Extent of exposure to study drug

The total amount of study drug (g) applied, amount of study drug per application (mg) and amount of study drug per application and treatment area (mg/cm^2) were determined from the weighing log of distributed and returned containers and are presented by descriptive statistics including number of patients, mean, standard deviation, median, minimum and maximum.

Adverse events

Adverse events were summarized descriptively with differentiation whether the adverse event occurred within or outside the treatment area.

Efficacy results:

Twice daily application of K201 cream over a 4-week treatment period showed a decrease in TEWL values, an increase in skin hydration and improvement in the clinical assessment, which were statistically significant. The bacterial counts of Staphylococcus aureus indicated a decrease after treatment with K201 cream, although this difference from baseline was not statistically significant. The clinical assessment showed an improvement for the comparator Jellin® Basis Creme. However, no changes in TEWL, corneometric values, nor in the bacterial counts were observed for Jellin® Basis Creme.

The TEWL measurements showed that treatment with K201 cream led to a decrease in the mean TEWL values over the 4-week treatment period (mean change to baseline: -5.1 g/m²h). The change from baseline was statistically significant for K201 cream at the end of study ($p = 0.0230$). No relevant change from baseline in mean TEWL (0.7 g/m²h) was noted in the test fields treated with Jellin® Basis Creme and no statistically significant difference was found.

The statistical comparisons between the K201 cream and the comparator demonstrated that the mean changes from baseline in TEWL were statistically significant at all test points (day 8: $p = 0.0012$, day 15: $p = 0.0148$, day 22: $p = 0.0005$ and day 29: $p < 0.0001$).

The corneometric measurements showed that treatment with K201 cream led to an increase in skin hydration over the 4-week treatment period (mean change to baseline: 4.3 a.u.). The change from baseline was statistically significant for K201 cream at the end of study ($p = 0.0258$). Largely constant mean corneometric values were noted for the comparator Jellin® Basis Creme over the study period. A mean change to baseline of -0.5 a.u. was noted at the end of the study, which was not statistically significant. The comparisons between the K201 cream and the comparator demonstrated that the mean change to baseline in skin hydration was statistically significant at all test points (day 8: $p = 0.0001$, day 15: $p = 0.0026$, day 22: $p = 0.0016$ and day 29: $p = 0.0004$).

A decrease in the mean and median total clinical assessment score was noted for the K201 cream (baseline: mean = 3.9, median = 4, day 29: mean = 2.2, median = 2) as well as for the Jellin® Basis Creme (baseline: mean = 4.1, median = 4, day 29: mean = 2.6, median = 3). The change from baseline to day 29 in total clinical assessment score was statistically significant for K201 cream and the comparator ($p < 0.0001$ and $p = 0.0001$, respectively). The comparisons between K201 cream and Jellin® Basis Creme showed no statistically significant differences in change from baseline in the total clinical assessment score. In the individual parameters an improvement was mainly seen for erythema, edema/papulation and excoriations.

Synopsis (continued)

Name of company: Moberg Derma AB	Individual study table Referring to part of the dossier	*(For National Authority Use Only)*
Name of finished product: n.a.	Volume: Page:	
Name of active ingredient: Lactic acid (5 %), Propylene glycol (20 %), Urea (5 %)		

Summary, conclusions:

Efficacy results (continued):

The mean log number of bacteria per skin surface was comparable in the test fields to be treated with K201 cream or the comparator Jellin® Basis Creme at baseline (3.04 and 2.79 log count/cm²). At the end of the study a mean reduction in bacteria number of 1.05 log count/cm² was noted following 4-week treatment with K201 cream. However, this change from baseline was not statistically significant. No relevant change was noted for the mean log number of bacteria per skin surface after four weeks of treatment with the comparator (mean reduction: 0.27 log count/cm²). The comparison between K201 cream and comparator in change from baseline to study day 29 in mean log number of bacteria per skin surface was not statistically significant.

Safety results:

Altogether four nonserious AEs were reported in four patients in this study. All four AEs were considered to be unlikely related to study medication. The four patients suffered from cold. This AE was classified as mild in three patients and as moderate in one patient.

Conclusion:

Overall, under the conditions of this study a positive effect on barrier impairment, skin hydration and clinical features was observed during four weeks of twice daily treatment with K201 cream. This was confirmed by a decrease in TEWL, an increase in skin hydration and an improvement of the clinical assessment scores, which were statistically significant. In contrast, a positive effect following treatment with the comparator was only seen in the clinical assessment.

Although a reduction of one magnitude in mean log number of Staphylococcus aureus was observed following treatment with K201 cream, this difference was not statistically significant. In addition, the sample size is small making the implications of this particular finding uncertain.

In summary, the results of this study show that K201 cream has beneficial effects in patients with mild-moderate atopic eczema and is well tolerated.

Date of the report: September 07, 2009