EXPLORATIVE, DOUBLE-BLIND, RANDOMIZED, CONTROLLED MULTI-CENTER PHASE II STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOPICALLY APPLIED COMBINATIONAL PRODUCT LAS41003 ONCE DAILY VERSUS CORRESPONDING MONO-PREPARATIONS IN THE TREATMENT OF SUPERFICIAL INFECTED ECZEMA

Short title: **LAS41003**

Date: 20 December 2012

Study number:	**H 552 000-0911**	**Name of the sponsor:**	**Almirall Hermal GmbH, Scholtzstraße 3, 21465 Reinbek, Germany**
Test product:	**0.25% octenidine / 0.25% prednicarbate cream (2.5 mg octenidine dihydro-chloride/g + 2.5 mg prednicarbate/g)**	**Clinical Study Phase:**	**Phase II**
		EUDRACT No:	**2009-011931-11**
Indication:	**Super-infected or impetiginized eczema**	**Early Termination:**	**Not applicable**
Study initiation date:	**06 November 2009**	**Study completion date:**	**18 June 2010**
Coordinating investigator ("LKP"):	[redacted] **Klinik für Dermatologie und Allergologie der Ruhr-Universität Bochum** [redacted]		
Responsible medical officer:	[redacted] **Almirall Hermal GmbH** **Scholtzstraße 3, 21465 Reinbek, Germany** [redacted]		
Person responsible for the study report at the sponsor:	[redacted] **Almirall Hermal GmbH** **Scholtzstraße 3, 21465 Reinbek, Germany** [redacted]		
Earlier reports from the same study:	**Not applicable**		
-continued-			

Study design:	**Explorative, double-blind, randomized, controlled, three-armed, parallel-grouped multi-center phase II study.** **During the study eligible patients were treated with a once daily topical application of the combinational cream LAS41003 (0.25% octenidine + 0.25% prednicarbate), or 0.25% octenidine cream mono-preparation, or 0.25% prednicarbate cream mono-preparation in the treatment of superficial infected eczema for a period of 14 days. Patients were observed during study treatment and up to the final follow up period visit. Regular visits during this phase were to be performed after 3, 7, 10 and 14 days of treatment (= end of treatment (EoT)) and at 14 days post-treatment (follow up period visit = end of study (EoS), day 28). The treatment efficacy was compared by means of therapeutic success (composite variable of microbial AND simultaneous clinical success) at EoT, regarding one target site of clinically diagnosed superficial infected eczema, selected at Screening / Baseline.**

This study was conducted in accordance with Good Clinical Practice (GCP), including the archiving of essential documents.

Final Version 3.0

2 SYNOPSIS

Name of sponsor: 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: 2.5 mg/g octenidine dihydrochloride + 2.5 mg/g prednicarbate	Page:	
Reference to the according CSR: LAS41003 CSR Final Version 3.0 dated 20 December 2012		Date of synopsis: 20 December 2012

Title of study:

Explorative, double-blind, randomized, controlled multi-center phase II study to evaluate the efficacy and safety of topically applied combinational product LAS41003 once daily versus corresponding mono-preparations in the treatment of superficial infected eczema

Study number H 552 000-0911 EudraCT number 2009-011931-11

Investigators:

Coordinating investigator ("LKP"): [redacted]
Klinik für Dermatologie und Allergologie der Ruhr-Universität Bochum
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Germany

A total of 16 principal investigators participated in this study – a list of all principal investigators and study sites is given in appendix 16.1.4.

Study sites:

16 study sites in Germany

Publication (reference):

Not applicable to this study

Studied period:	Date of first patient first visit: 06 Nov 2009 Date of last patient completed: 18 Jun 2010	**Clinical study phase:** Phase II

Objectives:

The objective of this phase II study was to assess the efficacy of a once daily topical application of the combinational cream LAS41003 (0.25% octenidine + 0.25% prednicarbate) compared to a once daily application of 0.25% octenidine, respectively to a once daily application of 0.25% prednicarbate cream mono-preparation in the treatment of superficial infected eczema.

Primary objective:

The primary study objective was to compare the efficacy between the three treatment groups, regarding the rate of therapeutic success, i.e. the proportion of patients with therapeutic success (defined as the combination of clinical AND microbial success) with respect to the target eczema at EoT (V5, day 14) as primary efficacy variable.

Secondary objectives:

One secondary study objective was to further compare the efficacy between the three treatment groups, regarding the following efficacy variables: the rate of bacteriological success, the rate of clinical success, the time to clinical success, the IESS at each visit and single signs incorporated in the IESS at each visit, the patient's assessment of itching and pain, the patient's global improvement index (PGII), the investigator's global improvement index ($IGII_{related\ to\ BASELINE}$ and $IGII_{related\ to\ EoT}$) and the investigator's assessment of overall efficacy.

Further secondary objectives were to assess the safety, regarding the occurrence of adverse events (AEs) during the entire study period and to evaluate the patient's compliance.

Methodology (design of study):

This study was performed as a prospective randomized, controlled, double-blind, three-armed, parallel-group, multi-center phase II study. Topical treatment over 14 days with the combinational cream LAS41003 (0.25% octenidine + 0.25% prednicarbate) once daily, with 0.25% octenidine cream once daily, or with 0.25% prednicarbate cream once daily.

Regular visits were to be performed at day 0, after 3, 7, 10 and 14 days of treatment and 14 days post treatment (day 28).

Number of patients planned:

Approximately 180 (randomized), including a calculated dropout rate of 20%

Number of patients treated:

In total 220 patients were enrolled into the 3 treatment groups, representing the safety set (SS):

- LAS41003 cream: 68 patients
- Octenidine cream: 75 patients
- Prednicarbate cream: 77 patients

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

Diagnosis and main criteria for inclusion:

Caucasian male or female patients aged ≥18 years with at least one site of clinically diagnosed superficial infected eczema

Test product:	LAS41003 (Combinational product): 0.25% Octenidine + 0.25% Prednicarbate
Dose:	maximum daily dose: 2.0 g cream, once daily, sufficient to treat an area of about 1200 cm^2 of affected skin maximum daily dose of active ingredients: 5 mg Octenidine + 5 mg Prednicarbate
Route of administration:	topical application
Batch number:	938KK02; 001KK03
Duration of treatment:	14 days in maximum

Reference therapy 1:	0.25% Octenidine cream
Dose:	maximum daily dose: 2.0 g cream, once daily, sufficient to treat an area of about 1200 cm^2 of affected skin maximum daily dose of active ingredients: 5 mg Octenidine
Route of administration:	topical application
Batch number:	938KK02; 001KK03
Duration of treatment:	14 days in maximum
Reference therapy 2:	0.25% Prednicarbate cream
Dose:	maximum daily dose: 2.0 g cream, once daily, sufficient to treat an area of about 1200 cm^2 of affected skin maximum daily dose of active ingredients: 5 mg Prednicarbate
Route of administration:	topical application
Batch number:	938KK02, 001KK03
Duration of treatment:	14 days in maximum

Criteria for efficacy evaluation:

During the study it became obvious that:

1: fungal infection was only of minor relevance with regard to superficial infected eczema.

2: bacteria with very different pathogenicities were detected in the microbial samples, which could not be processed equally with regard to their relevant microbial load.

Thus it was decided during the BDRM:

1: to grade the microorganisms according to their pathogenicity into different categories:

Category I: known pathogenic bacteria or fungi

Category II: facultative pathogenic bacteria or fungi

Category III: facultative pathogenic bacteria or fungi suspected to be of low pathogenic potential

2: to analyse different evaluation sets, considering both fungi and bacteria (Analysis set 1 as requested per protocol), respectively considering bacteria only, irrespective of their bacterial load and pathogenicity (Analysis set 2) and considering bacteria according to their clinical relevance with regard to bacterial load and pathogenicity (Analysis set 3).

In summary three different analysis sets were defined for efficacy analysis:

Analysis set 1 (FAS1/PPS1):

All patients for whom study diagnosis had been confirmed by any positive microbial finding (bacteria and/or fungi) at Screening / Baseline (V1).

Analysis set 2 (FAS2/PPS2):

All patients for whom study diagnosis had been confirmed by any positive bacteriological finding at Screening / Baseline (V1).

Analysis set 3 (FAS3/PPS3):

All patients for whom study diagnosis had been confirmed at Screening / Baseline (V1) by detection of bacteria regarded as relevant for skin infections, taking into account both the pathogenicity of detected bacteria as well as their clinically relevant load.

Primary efficacy variables:

As defined in the study protocol the following primary efficacy variable was analyzed:

- Rate of therapeutic success$_{\text{regarding pretreatment microorganisms}}$ of the target eczema at EoT Visit (V5, day 14).

  Therapeutic success$_{\text{regarding pretreatment microorganisms}}$ was defined as both microbial success$_{\text{regarding pretreatment microorganisms}}$ AND clinical success.

  The rate of therapeutic success$_{\text{regarding pretreatment microorganisms}}$ of the target eczema was given as the percentage of patients for whom at EoT Visit (V5, Day 14):

  1) **Microorganisms detected at Screening / Baseline (V1)** were at least almost cleared and without clinical relevance at EoT (V5)

  And

  2) The IESS was not greater than 5 and additionally none of the individual signs of the IESS was classified as greater than grade 1 (mild intensity) at EoT (V5).

In addition a further primary efficacy variable was defined, as it became obvious, that for microbial success also microorganisms, which first appeared during the treatment phase should be considered:

- Rate of therapeutic success$_{\text{regarding all microorganisms}}$ of the target eczema at EoT Visit (V5, day 14).
  Therapeutic success$_{\text{regarding all microorganisms}}$ was defined as both microbial success$_{\text{regarding all microorganisms}}$ AND clinical success.

  The rate of therapeutic success$_{\text{regarding all microorganisms}}$ of the target eczema was given as the percentage of patients for whom at EoT Visit (V5, Day 14):

  1) **All microorganisms** were at least almost cleared and without clinical relevance at EoT (V5)

  And

  2) The IESS was not greater than 5 and additionally none of the individual signs of the IESS was classified as greater than grade 1 (mild intensity) at EoT (V5).

Secondary variables:

The following secondary efficacy variables were analyzed:

- Rate of microbial success at EoT (V5):

  Rate of microbial success$_{\text{regarding pretreatment microorganisms}}$ at EoT (V5) = percentage of patients with microbial success$_{\text{regarding pretreatment microorganisms}}$ in the target eczema site at EoT (V5). Thereby microbial success$_{\text{regarding pretreatment microorganisms}}$ was achieved if those microorganisms (either bacteria or fungi), which had been detected at Screening / Baseline (V1) were

  - at least almost cleared and without clinical relevance (for analysis set 1 and 3)

  or

  - completely cleared (for analysis set 2)

  Rate of microbial success$_{\text{regarding all microorganisms}}$ at EoT (V5) = percentage of patients with microbial success$_{\text{regarding all microorganisms}}$ in the target eczema site at EoT (V5). Thereby microbial success$_{\text{regarding all microorganisms}}$ was achieved if all microorganisms (either bacteria or fungi) were

  - at least almost cleared and without clinical relevance (for analysis set 1 and 3)

  or

  - completely cleared (for analysis set 2)

- Rate of mycological success was specified according to the explanations above to:

  Rate of mycological success$_{\text{regarding pretreatment fungi}}$ at EoT (V5) = percentage of patients with mycological success$_{\text{regarding pretreatment fungi}}$ in the target eczema site at EoT (V5). Thereby mycological success$_{\text{regarding pretreatment fungi}}$ was achieved if those fungi, which had been detected at Screening / Baseline (V1) were at least almost cleared and without clinical relevance (analysis set 1)

Rate of mycological success$_{\text{regarding all fungi}}$ at EoT (V5) = percentage of patients with mycological success$_{\text{regarding all fungi}}$ in the target eczema site at EoT (V5). Thereby mycological success$_{\text{regarding all fungi}}$ was achieved if all fungi were at least almost cleared and without clinical relevance (analysis set 1)

- Rate of bacteriological success at EoT (V5):

  Rate of bacteriological success$_{\text{regarding pretreatment bacteria}}$ at EoT (V5) = percentage of patients with bacteriological success$_{\text{regarding pretreatment bacteria}}$ in the target eczema site at EoT (V5). Thereby bacteriological success$_{\text{regarding pretreatment bacteria}}$ was achieved if those bacteria, which had been detected at Screening / Baseline (V1) were

  - at least almost cleared and without clinical relevance (for analysis set 1 and 3)

  or

  - completely cleared (for analysis set 2)

  Rate of bacteriological success$_{\text{regarding all bacteria}}$ at EoT (V5) = percentage of patients with bacteriological success$_{\text{regarding all bacteria}}$ in the target eczema site at EoT (V5). Thereby bacteriological success$_{\text{regarding all bacteria}}$ was achieved if all bacteria were

  - at least almost cleared and without clinical relevance (for analysis set 1 and 3)

  or

  - completely cleared (for analysis set 2)

- Rate of clinical success of the target eczema at each visit following Screening / Baseline (V1) assessed by IESS, giving the percentage of patients at each visit with IESS not greater than 5 and with none of the signs exceeding grade 1
- Time to clinical success: The time to clinical success was calculated as the time period between start of treatment and clinical success for each patient
- Investigator's Global Improvement Index$_{\text{related to BASELINE}}$ (IGII$_{\text{related to BASELINE}}$) at V2 to V5, related to the IGII at Screening / Baseline (V1) according to a 5-point score (complete remission, significantly improved, improved, no change, worsen)
- Investigator's Global Improvement Index $_{\text{related to EoT}}$ (IGII$_{\text{related to EoT}}$) at time of Follow up Visit (V6), related to the IGII at EoT (V5) according to a 5-point score (complete remission, significantly improved, improved, no change, worsen)
- Investigator's assessment of overall efficacy at EoT (V5) and at time of Follow up Visit (V6)
- Patient's Global Improvement Index (PGII) at each visit after Screening / Baseline (V1) until the EoT (V2-V5) according to a 5-point score (excellent improvement, good improvement, moderate improvement, no changes, worsening)
- Patient's assessment of itching (according to a 4-point score, Intensities: None = 0, Mild = 1, Moderate = 2, Severe = 3) at each visit (V1-V6)
- Patient's assessment of pain (according to a 4-point score, Intensities: None = 0, Mild = 1, Moderate = 2, Severe = 3) at each visit (V1-V6)

Additionally, the following secondary efficacy variables were considered:

- Change in IESS until V6 (EoS), relative to the IESS at Screening / Baseline (V1). The IESS is calculated as the sum of the 4-point scales (ranging from 0 = none to 3 = severe) for the typical signs of superficial infected eczema (exudation / crusting, oozing, erythema, edema/ indurations, papulo-vesicles, pustules and scaling)
- Change in each of the individual signs of superficial infected eczema incorporated in the IESS (exudation / crusting, oozing, erythema, edema/ indurations, papulo-vesicles, pustules and scaling) until V6 (EoS), related to the corresponding 4-point scales (ranging from 0 = none to 3 = severe) at Screening / Baseline (V1)

Criteria for safety evaluation:

- Physical examination at Screening / Baseline (V1) and at EoT (V5), including vital signs.
- Incidence of AEs / SAEs during the entire study (V1-V6).

Other variables:

- Medical history, i.e. relevant medical and surgical history, including eczema and skin disease history at Screening / Baseline (V1).
- Prior and concomitant treatment / medication during the entire study (V1-V6).
- Urine pregnancy test at Screening / Baseline (V1) and EoT (V5).
- Patient's compliance (V2-V5)

Statistical methods:

The study objectives were exploratively tested using a 2-sided Chi-Square test (SAS procedure PROC FREQ) for each of the primary efficacy variables at EoT (V5):

- Rate of therapeutic success$_{\text{regarding pretreatment microorganisms}}$
- Rate of therapeutic success$_{\text{regarding all microorganisms}}$

The error probability was set to $\alpha = 0.05$ for a 2-sided test.

Due to the explorative character of the study no significance testing was performed for the primary efficacy variables – rate of therapeutic success –. The error probabilities (p-values) for the 2-sided Chi-Square tests were reported. The p-values were used to describe the differences between the treatment groups.

Estimates for the difference in the therapeutic success rates between the combination treatment and each of the mono-therapies were calculated using 100*(1- α) % = 95% confidence intervals.

Explorative analyses of the secondary efficacy variables were done using Chi-Square tests and the Wilcoxon-Mann-Whitney test. This was done for variables at the EoT Visit (V5) and at the Follow up Visit (V6). The time to clinical success was calculated by Kaplan-Meier estimates and compared by Log-rank test between treatment groups.

For calculation only valid values were used. Additionally, for variables at the EoT Visit (V5) calculation was performed using imputed data (LOCF-method).

Appropriate descriptive statistics were computed and displayed (by visit and other key variables if applicable) for both continuous and categorical variables. Statistics for continuous variables included: n (number of patients with non-missing values), mean, standard deviation (SD), as well as median, minimum, and maximum. Statistics for categorical variables consisted of listing out the possible categorical outcomes (or collections of categories) providing the total counts and percentages of patients falling within them.

In general, percentages were based on the total number of patients in the analysis set. For descriptive by-visit presentations the number of patients with non-missing values at the visit was used as denominator for derivation of percentages.

Study population:

A total number of 220 patients was enrolled and screened for the study in 16 study sites. All 220 patients were randomized and received at least one dose of study medication.

The patients were assigned with a ratio of 1:1:1 into the 3 different treatment groups: combinational product LAS41003 (0.25% octenidine / 0.25% prednicarbate), 0.25% octenidine mono-preparation (OCT), and 0.25% prednicarbate mono-preparation (PRED).

Patients were valid for the different analysis sets as follows:

Number of patients valid for:	LAS41003	OCT	PRED	Total
Safety set	68	75	77	220
Delayed exclusions	16	23	12	51
Analysis set 1 (taking into account bacterial and mycological samples)				
Valid for FAS1 Analysis	52	52	64	169
Valid for PPS1 Analysis	40	43	48	131
Analysis set 2 (taking into account bacterial samples only, irrespectively of the bacterial load)				
Valid for FAS2 Analysis	51	50	60	161
Valid for PPS2 Analysis	48	48	55	151
Analysis set 3 (taking into account bacterial samples with relevant bacterial load only)				
Valid for FAS3 Analysis	46	46	55	147
Valid for PPS3 Analysis	43	44	51	138

The compliance rate was comparable in all three treatment groups (LAS41003=96.2%, OCT=98.1%, PRED=96.9%).

The mean age of the FAS1 population was about 49 years (ranged from 18 to 87 years) and patients separated almost homogeneously into males and females. Relevant differences in demographic and baseline data had not been detected between treatment groups or different analysis sets.

Summary and Conclusions:

Summary of Efficacy Analyses:

The exploratory efficacy analysis was mainly performed on the FAS.

The infected eczema in the study was mainly caused by infections with bacteria. More than two third of the patients, i.e. 128 out of 169 patients (76.3%) had positive microbial samples at Screening / Baseline (V1) caused by bacteria only. In addition 32 out of 169 patients (18.9%) had both a positive microbial and a positive mycological sample. Only 8 patients out of 169 patients in the complete study had a positive sample caused by fungi alone. Thus infection with fungi made only a minor contribution to superficial infected eczema.

Moreover, only in 25% of the positive mycological samples, the mycological load was clinically relevant (5.9% of patients with a positive microbial sample), and in only 4 of the patients, who had a positive sample caused by fungi alone, the mycological samples had a relevant load.

Thus the efficacy analysis taking into account both bacteria and fungi (FAS1 with 169 patients comprising LAS41003: N=52; Oct: N=52 and PRED: N=64) was mainly restricted to the analysis of the primary efficacy variables (rate of therapeutic success$_{\text{regarding pretreatment microorganisms}}$ and rate of therapeutic success$_{\text{regarding all microorganisms}}$).

A complete efficacy analysis was concentrated on the infection with bacteria. Primary and secondary efficacy variables were analysed in the two sets FAS2 and FAS3, taking into account only the results from bacteriological sampling.

In FAS3 (with 147 patients comprising LAS41003: N=46; OCT: N=46 and PRED: N=55) those patients with bacteria, which are known to be relevant for skin infections and were present with a relevant bacterial load, were considered. The FAS3 was regarded as the most clinically relevant evaluation set.

The evaluation approach in FAS2 (with 161 patients comprising: LAS41003: N=51; OCT: N=50 and PRED: N=60) can be regarded as a sensitivity analysis, as it takes into consideration all bacteria detected, irrespective of their load – whether for inclusion or for evaluation of success. This might allow conclusions

on the impact of bacteria which were regarded as irrelevant for infection either due to their low pathogenic potential, or due to their low bacterial load.

1. Primary efficacy analyses:

The efficacy was compared by means of the primary efficacy variable 'rate of therapeutic success' which is a composite variable of 'microbial success' and simultaneous 'clinical success'.

As 'microbial success' was calculated on the basis of two reference points – 'regarding pretreatment microorganisms' (which means, that elimination rates were calculated for only those microorganisms, which were present before treatment) and 'regarding all microorganisms' (which means, that elmininations rates also considered those which have newly been appeared during the course of the treatment) – two primary efficacy variables resulted: the rate of therapeutic success$_{\text{related to pretreatment microorganisms}}$ and the rate of therapeutic success$_{\text{related to all microorganisms}}$ at the End of Treatment (EoT, V5).

The following table summarizes the values of the single variables as well as of the composite variable of the different analysis sets:

FAS 1: Patients with bacteria and / or fungi at Screening / Baseline (V1)								
Clinical Success			**Microbial Success** (defined as '**almost cleared and without clinical relevance**')			**Therapeutic Success**		
LAS41003	**OCT**	**PRED**	**LAS41003**	**OCT**	**PRED**	**LAS41003**	**OCT**	**PRED**
67.3%	53.8%	75.4%	regarding pretreatment microorganisms			regarding pretreatment microorganisms		
			71.2%	63.5%	40.0%	42.3%	38.5%	30.8%
			regarding all microorganisms			regarding all microorganisms		
			40.4%	48.1%	27.7%	25.0%	28.8%	24.6%

FAS 2: Patients with bacteria at Screening / Baseline (V1) irrespective of the load								
Clinical Success			**Bacteriological Success** (defined as '**completely cleared**)			**Therapeutic Success**		
LAS41003	**OCT**	**PRED**	**LAS41003**	**OCT**	**PRED**	**LAS41003**	**OCT**	**PRED**
66.7%	52.0%	78.3%	regarding pretreatment bacteria			regarding pretreatment bacteria		
			74.5%	66.0%	55.0%	47.1%	38.0%	41.7%
			regarding all bacteria			regarding all bacteria		
			45.1%	44.0%	23.3%	29.4%	26.0%	20.0%

FAS 3: Patients with bacteria with relevant load at Screening / Baseline (V1)								
Clinical Success			**Bacteriological Success** (defined as '**almost cleared and without clinical relevance**)			**Therapeutic Success**		
LAS41003	**OCT**	**PRED**	**LAS41003**	**OCT**	**PRED**	**LAS41003**	**OCT**	**PRED**
67.4%	52.2%	78.2%	regarding pretreatment bacteria			regarding pretreatment bacteria		
			80.4%	67.4%	52.7%	52.2%	39.1%	38.2%
			regarding all bacteria			regarding all bacteria		
			47.8%	50.0%	29.1%	34.8%	28.3%	25.5%

For the FAS1 the rates of therapeutic success$_{\text{regarding pretreatment microorganisms}}$ at EoT and the rates of therapeutic success$_{\text{regarding all microorganisms}}$ at EoT were higher in the LAS41003 group (ranging between 42.3% and 25.0%) than in the PRED group (ranging between 30.8% and 24.6%). The rates of therapeutic success$_{\text{regarding pretreatment microorganisms}}$ at EoT were also higher in the LAS41003 group (42.3%) when compared to the OCT group (38.5%), and only slightly lower (3.8%) with respect to all microorganisms (therapeutic success$_{\text{regarding all microorganisms}}$: LAS41003: 25.0% and OCT: 28.8%). Nonetheless all differences between treatment groups were not of statistical significance (Chi-Square test, 2-sided) and thus did not support evidence for superiority of LAS41003 treatment compared to PRED treatment or OCT treatment.

The rates of therapeutic success at EoT of FAS2 and FAS3 ranged from 29.4% (regarding all bacteria) to 52.2% (regarding pretreatment bacteria) for the LAS41003 group compared to a range of 26.0% to 39.1% in the OCT group and a range of 20.0% to 38.2% in the PRED group. This analysis overall indicates that LAS41003 treatment showed a trend to be more effective compared to the treatment with one of the mono components, even though the statistical analyses gave no clear evidence for superiority of LAS41003 in any case.

2. Secondary efficacy analyses:

Rate of bacteriological success at EoT (V5):

For FAS3 bacteriological success was achieved if bacteria were at least almost cleared and without clinical relevance. For FAS2 bacteriological success was achieved if bacteria were completely cleared.

The rate of bacteriological success$_{\text{regarding pretreatment bacteria}}$ at EoT for the LAS41003 group was 80.4% for FAS3 and 74.5% for FAS2.

Lower rates of bacteriological success$_{\text{regarding pretreatment bacteria}}$ at EoT was seen for OCT (67.4% for FAS3, 66.0% for FAS2) as well as for PRED (52.7% for FAS3, 55.0% for FAS2).

The rate of bacteriological success$_{\text{regarding all bacteria}}$ at EoT in the LAS41003 group was 47.8% for FAS3 and 45.1% for FAS2. Comparable rates of bacterial success$_{\text{regarding all bacteria}}$ were obtained under OCT treatment (50.0% for FAS3, 44.0% for FAS2) and a lower rate of bacterial success$_{\text{regarding all bacteria}}$ was obtained under PRED treatment (29.1% for FAS3, 23.3% for FAS2).

The bacteriological success at EoT under OCT treatment compared to LAS41003 treatment did not reveal statistically significant differences (Chi-Square test, 2-sided); although the higher rates of bacteriological success$_{\text{regarding pretreatment bacteria}}$ seen on LAS41003 treatment might suggest that LAS41003 to give a more favourable outcome compared to the treatment with OCT.

With the exception of the analysis of bacteriological success$_{\text{regarding all bacteria}}$ for FAS3, statistically significant lower rates of bacteriological success at EoT were obtained for the PRED treatment group compared to LAS41003 treatment, indicating superiority of LAS41003 regarding the elimination of bacteria.

Rate of clinical success at each visit and time to clinical success:

The rate of clinical success at EoT gives the percentage of patients at EoT, in which the Infected Eczema Severity Score (IESS) was not greater than 5 and none of the signs exceeded grade 1 (mild intensity). It was higher in the LAS41003 group (67.4% for FAS3, 66.7% for FAS2) compared to the OCT group (52.2% for FAS3, 52.0% for FAS2). Although the difference was about 15% higher in favor to the LAS41003 treatment, the Chi-Square test and the corresponding p-value did not support superiority of LAS41003 compared to OCT on clinical grounds.

For both analysis sets, the highest rates of clinical success at EoT were obtained for the PRED group (78.2% for FAS3, 78.3% for FAS2), but these differences were again not of statistical significance, and the corresponding p-values did not establish non-inferiority of LAS41003 compared to PRED.

Comparing the LAS41003 treatment group with the OCT treatment group, higher rates of clinical success were obtained for the LAS41003 treatment group not only at EoT, but also at each individual visit, suggesting the possibility that LAS41003 is more effective than OCT treatment by this criterion, and that there is a trend for clinical success to be reached faster under LAS41003 treatment than under OCT treatment. Analysing the time to success, using the Meier-Kaplan estimate, 50% of the patients were clinically cleared after 12 days of treatment in the LAS41003 treatment group, whereas 15 days of treatment were necessary to reach the same rate of clinical success in the OCT treatment group. However this numerical difference was not of statistical significance (Log-Rank test: p=0.2372 for FAS3,

p=0.18806 for FAS2) and therefore it was not possible to conclude superiority of LAS41003 compared to OCT.

A more pronounced effect was seen for the PRED group, as only 8 days of treatment were necessary to obtain 50% clinical success. However, again the data regarding a faster onset of action compared to the LAS41003 group was not of statistical significance (time to clinical success, tested by Log-Rank test: p=0.0505 for FAS3, p=0.0609 for FAS2).

At the end of the treatment a number of patients did not enter the follow up period due to persisting signs. In the course of the follow up period additionally a number of patients received – on the decision of the investigator – further medication, e.g. due to recurrent clinical signs or due to a worsening of infected eczema. All these patients were not considered in the assessment at EoS. Thus, the number of patients valid for analysis at EoS in the FAS3 was reduced by 5 patients in the LAS41003 group (10.9%), by 13 patients in the OCT group (28.3%) and by 11 patients (20.0%) in the PRED group (FAS2: -5 patients for LAS41003, - 16 patients for OCT, -14 patients for PRED).

The highest rate of clinical success at EoS was seen for the OCT group with 69.7 % for FAS3 (70.6% for FAS2), here reaching an even about 15% higher level than at EoT. The rate of clinical success in the two other groups decreased from EoT to EoS. The rate of clinical success at EoS in the LAS41003 treatment group was 61.0% for FAS3 (58.7 % for FAS2) and thus about 7% lower compared to EoT. In the PRED group the rate of clinical success at EoS for FAS3 was 56.8% (58.7% for FAS2) and here a decrease of about 20% in comparison to EoT became apparent.

Nonetheless corresponding tests on differences using a 2-sided Chi-Square test did not reveal any statistically significant differences between treatment groups.

Change in IESS from Baseline to EoS:

The IESS for FAS3 at Screening / Baseline (V1) was comparable between the treatment groups with mean values of 11.2 (SD± 2.4, median 11.0) for LAS41003, 11.0 (SD± 2.6, median 11.0) for OCT and 10.9
(SD ± 2.8, median 10.0) for PRED.

Comparable values were seen for FAS2.

The highest median change from Screening / Baseline (V1) until EoT (V5) in the FAS3 was seen for the LAS41003 group (-9.0), followed by the PRED group (-8.0) and the OCT group (-7.0), suggesting that LAS41003 treatment may be the most effective in the reduction of clinical signs of infected eczema.

Comparable values were seen for FAS2.

At the follow up period visit (EoS) the median change from baseline of the IESS continued to improve in the OCT group (being -8 at EoS). By contrast some loss of improvement was noted in the LAS41003 group (change from baseline -8) and an even greater loss was noted in the PRED group (change from baseline -6.5).

Almost comparable results were also obtained for the analysis of the FAS2.

Change in scores for the individual signs of superficial infected eczema incorporated in the IESS from Baseline to EoS:

Regarding the FAS3 the most frequent and most prominent sign, which was persisting at EoT as well as at EoS was erythema (median value of 1.0) in each of the treatment groups. As all individual scores with a value of 1 (mild intensity) or above were rated as a lack of clinical success, erythema was the most frequent reason for lack of success. Whereas erythema was the only sign in the PRED group which was obviously contributing to the failure to achieve clinical success, persistent scaling in both of the other treatment groups and persistent edema/indurations in the OCT group, with a median score of 1.0 each, also contributed to failure to achieve clinical success in the LAS41003 group and to a greater lack of clinical success in the OCT group. Consequently the trend was for PRED treatment to be regarded the most effective at EoT, followed by LAS41003 treatment and OCT treatment.

At EoS the median scores for each of the infection signs (exudation / crusting, oozing and papulo-vesicles) remained unchanged in the OCT group and the LAS41003 group, whereas the median score for exudation and crusting increased to 1.0 in the PRED group, suggestive of a higher rate of recurrent infection, possibly due to a less efficient elimination of bacteria in the PRED group and equally effective elimination of bacteria in the LAS41003 and the OCT treatment group.

Again almost comparable results were obtained with respect to the analysis of the FAS2.

Patient's assessment of itching and pain at each visit:

Comparable values of pain reduction were obtained at the EoT as well as at EoS for each of the treatment groups of the FAS3, showing no statistical significant differences.

Due to the inflammatory action of steroidal treatment, a comparable relief of itching was obtained under treatment with LAS41003 and under treatment with PRED, whereas a statistically significant lower reduction of itching was seen for the OCT treatment group until EoT (p=0.0069). Regarding the EoS no statistically significant differences were obtained in any case.

Investigator's Global Improvement Index$_{\text{related to BASELINE}}$ (IGII$_{\text{related to BASELINE}}$) at V2 to V5:

The Investigator's Global Improvement Index (IGII$_{\text{related to BASELINE}}$) at EoT (V5), assessed in comparison to Screening / Baseline (V1) revealed no difference between LAS41003 and PRED treatment (median score of 2.0 = significantly improved at EoT in both treatment groups). The median IGII$_{\text{related to BASELINE}}$ in the OCT group (1.0 =improved) was significantly lower (p=0.0071, Wilcoxon-Mann-Whitney test) and indicated a less pronounced improvement of infected eczema compared to treatment with LAS41003 or PRED.

The improvement after treatment with LAS41003 and PRED also showed a comparable time course. The same level of improvement, which was reached at Visit 3 (day 7) in the LAS41003 group and the PRED group, was reached later, at Visit 4 (day 10), for the OCT group. This indicates a trend to an earlier onset of action under LAS41003 treatment and PRED treatment compared to OCT treatment.

Investigator's Global Improvement Index$_{\text{related to EoT}}$ (IGII$_{\text{related to EoT}}$) at V6:

The median scores of the IGII at EoS assessed in comparison to EoT, indicated either no change (OCT group) or improvement (PRED group and LAS41003 group), but the differences detected were not of statistical significance.

Patient's Global Improvement Index (PGII) at V2 to V5:

The results seen for the PGII were comparable to the investigator's improvement assessment. The lowest improvement was reported for the OCT group at each time point up to EoT, whereas comparable values of improvement were seen for the PRED and the LAS41003 groups.

At EoT the median score of PGII was 2.0 in both the LAS41003 and the PRED groups, indicating a significant improvement of infected eczema at EoT. A statistically significantly lower median value was obtained for the OCT compared to the LAS41003 treatment (median PGII=1.0, p=0.0004).

Investigator's Assessment of Overall Efficacy:

The overall efficacy at EoT was rated as good for the LAS41003 group and the PRED group (median score of 3.0, each) and as only moderate (median score of 2.0) for the OCT group, which was statistically significantly lower compared to the LAS41003 group (p=0.0015).

At EoS no change in the median score compared to EoT was seen for the LAS41003 group, whereas the median score in the PRED group fell from 3.0 at EoT to 2.0 at EoS. The median score for the OCT group increased by 1 point from EoT until EoS, and so reached the same median score as seen for the LAS41003 group (median score of 3.0). The differences between treatment groups seen at EoS were not of statistical significance.

Overall the results are in line with the rankings obtained for the IGII and the PGII as well as with the results regarding clinical success.

Summary of Safety:

Overview of AEs:

12.7% of all patients in the SS experienced an AE during the course of the study. Of these, most patients could be found in the LAS41003 treatment group (LAS41003=16.2%, OCT=12.0%, PRED=10.4%).

3.2% of all patients suffered from AEs that were assessed as related to the IMP. The number was slightly higher in the OCT treatment group: 4.0% of the patients in this group experienced an IMP-related AE. In the LAS41003 treatment group, the incidence rate was 2.9%, and in the PRED treatment group 2.6%.

0.9% of all patients suffered from AEs that were considered related to the study procedure.

The most frequent AEs were 'General Disorders and Administration Site Conditions" and 'Infections and

Infestations' (5% of all patients, respectively). 2.3% of all patients experienced AEs that were specified as 'Skin and Subcutaneous Tissue Disorders'.

More patients in the LAS41003 treatment group experienced AEs that were classified as 'Infections and Infestations' compared to the 2 other treatment groups (LAS41003=10.3%, OCT=2.7%, PRED=2.6%), whereas in the OCT treatment group, more patients suffered from AEs classified as 'Skin and Subcutaneous Tissue Disorders' (LAS41003=0.0%, OCT=4.0%, PRED=2.6%). In the PRED treatment group, more patients were documented with AEs of the MedDRA SOC 'General Disorders and Administration Site Conditions' (LAS41003=4.4%, OCT=4.0%, PRED=6.5%).

AEs that were classified in other MedDRA SOCs occurred in less than 1% of all patients, respectively.

2.7% patients experienced AEs that led to a premature discontinuation of the study. None of these AEs was considered as related to the IMP. No major differences could be detected between the respective treatment groups.

Details of AEs:

Most AEs were of mild intensity. Only four AEs were of severe intensity. None of them were considered related to the IMP.

Most AEs occurred once and were unrelated to the IMP. AEs that occurred after each treatment were rare but were all related to the IMP.

Most of IMP-related AEs did not require a change in treatment.

2.7% of all patients were withdrawn from the study due to an AE. None of these were considered related to the IMP. 7.7% of all patients experienced AEs that needed drug treatment; again, none of these were related to the IMP. One patient suffered from one AE that needed non-drug treatment and was considered related to the IMP. One patient was admitted to hospital because of a preplanned investigation of a pre-existing condition ('Coronary Artery Disease'). This was therefore not regarded as SAE. It was not related to the IMP.

20 patients suffering from 27 AEs recovered without sequelae from their respective AEs already during the study period (LAS41003=13, OCT=6, PRED=8). Two additional ones were improved but not yet recovered at EoS. Eight AEs were continuing at V6/EoS, of which only 1 was considered related to the IMP. No patient experienced an AE that recovered with sequelae, led to death or where the outcome remained unknown.

Overall, 7.7% of all patients experienced AEs that were judged 'dermatological reactions'. In 3.2% of all patients, these AEs were regarded as related to the IMP.

As expected, most AEs occurred in the treatment phase (until V5/EoT), whereas 12 AEs occurred in the post-treatment phase (between V5/EoT and V6/EoS).

In conclusion, with respect to the above discussed different details of AEs no major differences between the treatment groups could be detected.

'Common AEs':

Most 'common AEs' were related to the skin or were infections/infestations: The incidence rate of AEs of the MedDRA SOC 'General Disorders and Administration Site Conditions' was slightly higher in the PRED treatment group (6.5%) than in the LAS41003 treatment group (4.4%) and the OCT treatment group (4.0%). The incidence rate within the MedDRA SOC 'Infections and Infestations' was highest in the LAS41003 treatment group (10.3%) and lower in the OCT treatment group (2.7%) and the PRED treatment group (2.6%). The highest incidence rate with respect to the MedDRA SOC 'Skin and Subcutaneous Tissue Disorders' was found in the OCT treatment group (4.0%), followed by the PRED treatment group (2.6%) and the LAS41003 treatment group (0.0%). However, as the preferred terms within these MedDRA SOCs overlap in some cases and the symptoms sometimes resemble each other, the differences between the respective treatment groups can be considered negligible.

IMP-related AEs:

Most IMP-related AEs were application site reactions and classified as 'General Disorders and Administration Site Conditions', 'Infections and Infestations' and 'Skin and Subcutaneous Tissue Disorders'. Most of them were already known and are listed in the SmPCs of prednicarbate cream (e.g. Prednitop®) and octenidine (e.g. Octenisept®). No relevant differences in the 3 treatment groups were

seen.

SAEs:
No serious adverse event (SAE) occurred during the course of the study.

Worsening of signs incorporated in the IESS:
The sign that worsened most often was 'Scaling' (17.3% of all patients) Most of these deteriorations were recorded on V3/D7 with a decrease towards the end of the study. Scaling is often seen when skin heals and is therefore an expected sign after eczema.

'Edema/Induration' (9.1% of all patients) and 'Papulo-vesicles (8.2% of all patients) were the signs most often named as having worsened. Deterioration in the signs 'Erythema', 'Exudation/Crusting', 'Oozing' and 'Pustules' were reported less frequently (<5% of all patients, respectively).

In the PRED treatment group, the frequency of worsening tended to be slightly higher in most of signs when compared to the other groups. One possibility might be that infections tend to worsen when treated with topical corticosteroid without applying anti-microbial therapy.

Vital parameters:
No significant changes in the mean systolic and diastolic blood pressure and the pulse rate were found between the respective study visits in all 3 treatment groups.

Overall conclusions:

The clinical study showed that LAS41003 is an effective medication in the treatment of superficial infected eczema.

Infection with fungi made only a minor contribution to infected eczema, as infection caused solely by fungi was seen in only 3.6% (8 out of 220 patients) of all patients with this clinical diagnosis, respectively in 4.7% (8 out of 169 patients) of all patients for whom the clinical diagnosis was confirmed by the results of the microbial analysis at Screening / Baseline. Thus the emphasis of the treatment of infected eczema must concentrate on bacteria.

The clinical study showed that bacteria, which were regarded as relevant for infected eczema and which have been found on the infected eczema site before treatment were eliminated or, if present, were without clinical relevance at the end of the treatment period in about 80% of the patients after treatment with LAS41003.

These elimination rates were comparable with the elimination rates which were achieved after treatment with OCT, and they were more than 25% higher than those achieved after treatment with PRED. The statistical analyses of this key efficacy variable showed the superiority of LAS41003 compared to the PRED treatment.

The elimination rate at the end of treatment with LAS41003 was about 48% if all bacteria were taken into consideration, irrespective whether they had been found on the infected eczema site before. Also here, the antibacterial activity was comparable to that of OCT and about 20% higher than that of PRED.

About 70% of the patients showed clinical success at the end of the treatment period with LAS41003. In comparison to the treatment with OCT, a small advantage was seen for LAS41003 after 14 days of treatment. In addition, clinical success rates for LAS41003 at the visits 2, 3 and 4 were higher than for OCT which suggested the possibility that healing might be quicker after treatment with the combinational product. However, no statistically significant differences could be detected during the study.

The clinical success rate for PRED was slightly higher at the end of treatment and at all visits during treatment, though the difference was not statistically significant. This situation changed at the end of the follow up phase, where a more pronounced decrease in the rate of clinical success was obtained for the PRED treatment group, raising the possibility of a less efficient elimination of bacteria at the end of the study, with clinical signs having been masked by the steroid, although the bacteria had continued to be present. When both endpoints were combined in the composite endpoint of the therapeutic success, the success rates for PRED and the LAS41003 and OCT groups became closer.

The analyses of the therapeutic success at EoT, the composite of clinical and bacteriological success, which was also the primary efficacy variable of the study, did not support superiority of LAS41003 compared to either of the mono-preparations. Although the highest rates of therapeutic success were

obtained for the LAS41003 treatment group, irrespective of different evaluation strategies and variably stringent evaluation criteria, superiority could not be statistically proven. As the treatment differences between LAS41003 and both of the mono-preparations were lower than the expected treatment difference (25% at an error probability of 5%), it may be that superiority would only have been proven by a higher number of treated patients.

The analysis of the secondary efficacy variables such as Patient's Assessment of Itching, Investigator's and Patient's Global Improvement Index (IGII and PGII) as well as by the Investigator's Assessment of Overall Efficacy gave support for superiority of LAS41003 compared to OCT treatment at EoT. For each of these variables statistically significant differences between LAS41003 treatment and OCT treatment were obtained at EoT. Moreover it was seen that the onset of action seemed to be faster in the LAS41003 treatment group when compared to the OCT treatment. This can be seen as a further benefit for the LAS41003 treatment, as a faster onset of action and therefore earlier disappearance of clinical signs associated with infected eczema, might result in a higher compliance of patients treated with LAS41003.

The possibility of more pronounced long term efficacy of the LAS41003 treatment compared to PRED was suggested by trends in the IESS, the Investigator's Global Improvement Index (IGII) and the Investigator's Assessment of Overall Efficacy, as assessed at EoS, even if none of these differences were statistically significant. The recurrence of exudation and crusting at EoS was most prominent in the PRED treatment group, indicating a higher rate of relapse, possibly due to a less efficient elimination of bacteria. Accordingly a more evident shift towards deterioration was seen with respect to the individual rating scores of the IGII at EoS, resulting in overall a less pronounced improvement in comparison to LAS41003 treatment. Moreover the overall efficacy at EoS was rated as good for the LAS41003 treatment group and as moderate only, regarding the PRED treatment.

Comparing the occurrence of the safety parameters in the different treatment groups lead to the following conclusions regarding the treatments safety profile:

The numbers of AEs leading to discontinuation as well as the numbers of severe AEs were very low and evenly distributed over the 3 treatment groups.

AEs that were considered related to the IMP, such as 'Application Site Reactions' (e.g. 'Pain', 'Pruritus') and 'Pustules' were already known and are listed in the SmPC of prednicarbate (e.g. Prednitop®) and octenidine (e.g. Octenisept®).

In the PRED treatment group, the frequency of worsening tended to be slightly higher in most of signs when compared to the other groups. The reason might be that infections tend to worsen when treated with topical corticosteroid without applying anti-infectious therapy.

The treatment with octenidine/prednicarbate combination as well as octenidine and prednicarbate mono-preparation produced no unexpected adverse events either relating to the MedDRA SOC allocation or to the AE details, or to the relation to the IMP. The distribution and the frequency of AEs were low and previously expected.

Overall, although slight differences between treatment groups could be documented, no significantly relevant differences of the AE profile in the 3 treatment groups was seen. Most of AEs assessed as related to the study drug were already known and did not reveal any unsuspected safety concerns. Only in terms of worsening of signs, prednicarbate mono-therapy revealed a slightly more unfavorable safety outcome when compared with the 2 other treatment groups.