Name of Sponsor/Company: Lukács és Társa Gyógyszerkereskedelmi Betéti Társaság	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of Study:

A Phase II Randomised, Controlled Parallel-Group Pilot Study to Assess the Safety and Efficacy of Kék Lukács Ointment Compared to Standard Silver Sulfadiazine (Dermazin®, SSD) Therapy in the Wound-healing of Patients With Partial Thickness (Second-Degree) Burns.

Investigators:

1. Prof. Dr. med. habil. István Juhász
2. Prof. Dr. Lajos Kemény
3. Dr. Róbert Tamás

Study centre(s):

1. Department of Dermatology, Medical Center of the University of Debrecen, Hungary
2. Department of Dermatology and Allergology, University of Szeged, Hungary
3. Department of Plastic and Burn Surgery, Hungarian Army Medical Center, Hungary

Publication (reference):

N/A

Studied period (years): 1+ (12 September 2012) (31 October 2013)	**Phase of development**: II

Objectives:

Primary objective:

1. To compare the clinical efficacy of Kék Lukács ointment treatment with standard silver sulfadiazine (SSD; Dermazin® cream) therapy in wound healing; degree of epithelisation of wound until Day 22 of treatment compared to Day 1.

Secondary objectives:

1. Investigator‘s assessment of signs of wound infection and inflammation: a) oozing, b) erythema, c) warmth, d) oedema, e) pain, f) odour on Day 1, 2, 8, 15, 22, 29 and 57 of treatment.
2. To assess the wound bed and wound margin on Day 1, 2, 8, 15, 22, 29 and 57 of treatment.
3. To compare the effect of Kék Lukács ointment treatment and SSD (Dermazin® cream) therapy on bacterial load.
4. To assess the degree of epithelisation of wound on Day 2, 8, 15, 22, 29 and 57 of treatment compared to Day 1.
5. To assess the tolerability of local therapy of target wound based on sensitivity and local irritability on every day during treatment period (from Day 2 to Day 22).
6. To evaluate the satisfaction with cosmetic results: general wound appearance and effect on crusting and scabbing after Kék Lukács ointment treatment compared to SSD treatment on Day 8, 15, 22, 29 and 57.
7. To reach eligibility to skin transplantation if needed.
8. To assess the ease of application of Kék Lukács ointment; evaluating pain at application and at dressing changes at every visit.

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9. Pharmacokinetic (PK) analysis performed in patients treated with Kék Lukács ointment to assess the plasma levels of sulfamethoxazole, azithromycin, and miconazole.
10. To collect pharmacoeconomic information (not performed).

Exploratory objective:

1. An attempt was made to identify factors influencing the rate of wound healing (potential stratification factors in a confirmatory study) and to assess the effect of age, gender, and site of the wound area as an exploratory analysis.

Methodology:

Treatment period:

At Visit 1 patients underwent screening for inclusion/exclusion criteria after having provided a written Informed Consent (IC). Eligible patients were randomised to either Kék Lukács ointment or Dermazin® cream treatment for a maximum of 21 days.

Debridement was performed on the target wound before first treatment. The selected burn area was cleaned with 0.9% saline solution. Test or control treatment was applied every day after cleaning the wound surface by the Study Nurse. The study medication (maximum 20 g/200 cm^2 Kék Lukács ointment or maximum 10–20 g/200 cm^2 Dermazine® cream) was spread with a sterile spatula on a sterile gauze dressing. This gauze was applied to the wound surface as a primary layer and then an absorbent dressing (Mesorb®/Zetuvit®) as a secondary layer. Primary and secondary dressing fixation was done by adhesive tape or self-adhesive bandage (Mefix®/Peha-haft®). During treatment period, patients could receive home nurse visits but had to come to the clinic for each numbered visit: Visits 2, 8, 15, 22, 23 and 24 (on Days 2, 8, 15, 22, 29 and 57).

At each clinical visit the burn area was inspected to assess the wound bed and wound margin healing as well as signs of epithelisation, signs of wound infection, and signs of sensitivity and local irritability. Accurate surface area and depth measurement was performed by 3D digital photography at Visits 1, 2, 8, 15, 22, 23 and 24 (Days 1, 2, 8, 15, 22, 29 and 57).

Swabs were taken on Days 1, 8, 15 and 22 or when suspicious secretion occurred or at that day when Kék Lukács ointment or Dermazin® cream treatment was finished, or any time when needed.

The maximum length of active treatment was 21 days.

Follow-up period:

After treatment period patients were followed until Day 57, controlled on Day 29±3 and Day 57±3.

For patients with pre-term (earlier than 21 days) full epithelisation of the target wound, follow-up started from End of Treatment (EOT) Visit day and included follow-up visits 7±3 and 28±3 days thereafter.

After Day 22, Ung. emolliens FoNo was applied daily for scar care, moisturising, hydrating and dry gauze bandage (optional) to obtain mechanical and light protection until Day 57.

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Pharmacokinetics (PK):

In patients treated with Kék Lukács ointment blood samples were collected before dressing changes to determine the plasma level of active ingredients azithromycin, sulfamethoxazole, and miconazole on Day 1, 2, 8 and 22 or on day of discontinuation/withdrawal.

Number of patients (planned and analysed):

Planned: 44 subjects
Analysed: 22 subjects

Diagnosis and main criteria for inclusion:

Deep or mixed deep and superficial partial thickness (second-degree) burns requiring standard care due to suspicion of infection

1. Written informed consent by the patient.
2. Male and female patients aged between 18 and 70 years.
3. Female patients of childbearing potential with a negative result from pregnancy test at inclusion who agree to use an acceptable birth control method (hormonal or IUD) or abstinence throughout the trial.
4. Thermal origin burns.
5. Total burn area for all burns on a single patient should not be greater than 10% of total body surface area (TBSA).
6. Patients with burn injuries confined to the trunk and/or upper and lower extremities.
7. Patients' total study target burn area (second-degree) should be greater than 25 cm^2 but not greater than 200 cm^2.
8. Patients with fresh (burn therapy started less than 24 hours post-burn) deep or mixed deep and superficial partial thickness (second-degree) burns.
9. Patients with non-recent (burn therapy started later than 24 but not later than 48 hours post-burn) deep or mixed deep and superficial partial thickness (second-degree) burns.
10. Due to infectious risk, local treatment is required according to the Investigator's opinion.
11. Patient is able to communicate well with the Investigator and comply with the study requirements.

Test product, dose and mode of administration, batch number:

Kék Lukács ointment; 20 g/200 cm2 once daily, topical; 512001

Duration of treatment:

Maximum of 21 days

Reference therapy, dose and mode of administration, batch number:

Dermazin® cream; 10–20 g/200 cm2 once daily, topical; BR7758

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Criteria for evaluation:

Efficacy:

Primary endpoint:

1. Percent reduction of wound surface area from Day 1 to Day 22 (3 weeks after treatment start).

Secondary endpoints:

1. Incidence of complete (100%) or almost complete (91-99%) wound healing with full epithelisation within 22 days.
2. Time to complete (100%) or almost complete (91-99%) wound healing if full epithelisation occurs within 22 days.
3. Percent reduction of wound surface area on Days 8, 15 and 22 from Day 1.
4. Incidence of treatment failure defined as less than 30% decrease in wound size after 21 days of treatment.
5. Incidence of eligibility to skin transplantation after treatment with Kék Lukács ointment if needed.
6. To assess the ease of application of Kék Lukács ointment; evaluating pain at application and at dressing changes at every visit.

Safety:

Safety endpoints:

1. Incidence of adverse events (AEs) during the whole study period.
2. To assess the tolerability of local therapy of target wound based on sensitivity and local irritability (burning, stinging, itching, tightness, tingling) on every day during the treatment period (from Day 2 to Day 22).
3. Changes in haematology and clinical chemistry parameters in blood and urine including CRP on Days 1, 8, 15 and 22 or earlier on that day when treatment was finished.
4. Investigator‘s assessment of signs of wound infection and inflammation: oozing, erythema, warmth, oedema, pain, odour on Days 1, 2, 8, 15, 22, 29 and 57.
5. Changes in bacterial load qualitative microbiology test (cotton swab) on Days 8, 15 and 22 (or on that day when Kék Lukács ointment or Dermazin® cream treatment finished), compared to Day 1.

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Statistical methods:

Analysis sets

Safety analysis set

All subjects randomised and receiving at least one treatment were included in the safety analysis set.

Intent-to-treat (ITT) analysis set

All subjects randomised, receiving at least one treatment and having at least one post-baseline evaluation of the wound healing area were included in the ITT analysis set.

Per protocol (PP) analysis set

All subjects randomised, receiving at least 1 day of treatment and having at least one post-baseline evaluation of the wound healing area and having no major protocol deviations were included in the PP analysis set.

Safety analysis will be performed on the safety analysis set.

Analysis methods

Primary analysis: ITT and PP analysis sets

The primary efficacy variable was the percent reduction of wound area (compared to the baseline area) over the first 21 treatment days. A random coefficient model was fitted accounting for the fixed effects of treatment group, day (as a continuous covariate) and treatment-by-day interaction, and a random slope for each subject.

The null hypothesis of no treatment-by-day interaction was tested within this mixed model.

Secondary analyses: ITT analysis set

The mean percentages of wound area were compared between the two treatment groups within a repeated measures ANOVA model, for each time point separately.

The scores assigned by the Investigator to the signs of wound infection and inflammation were compared across the two treatment groups by a Wilcoxon–Mann–Whitney test, for each timepoint separately.

Due to the insufficient number of samples, the treatment groups were not compared in terms of bacterial load distribution by a Wilcoxon–Mann–Whitney test.

The distributions of times until complete wound healing in the two treatment groups were compared by a logrank test.

The two treatment groups were compared in terms of pain (before and after treatment) scores by a Wilcoxon–Mann–Whitney test, for each time point separately.

The two treatment groups were compared in terms of satisfaction with cosmetic results by a Wilcoxon–Mann–Whitney test, for each time point separately.

As no skin transplantation was necessary, the proportion (95% confidence interval, CI) of subjects eligible for skin transplantation if needed were not estimated for each treatment group separately.

As there were no treatment failures, the proportion (95% CI) of treatment failures were not estimated for each treatment group separately.

Descriptive characterisation of pharmacoeconomic information was not done.

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PK analysis: PP analysis set
As all measured values for azythromycin and miconazole were below the lower limit of quantification, the geometric means (95% CI) of fold increases from baseline were estimated only for concentration values of sulfamethoxazole at each timepoint.
Exploratory analyses: ITT analysis set
The effect of age, gender, and site of the wound area were not assessed as an exploratory analysis.
Safety analysis: Safety analysis set

The incidence (95% CI) of selected AEs assumed to be signs of drug intolerance were estimated. AEs were coded and tabulated by system organ class and preferred term. Changes from baseline in haematology and clinical chemistry parameters in blood and urine were estimated at each analysis time point.

Summary - Conclusions

Efficacy Results:

On Day 22, the random coefficient model could not show a significant difference in the efficacy of the two treatment arms (treatment-by-day interaction p=0.5645, primary efficacy endpoint). However, it can be seen from the calculated empirical mean differences that the mean percentage of baseline wound area values were consequently lower in the Kék Lukács ointment group than in the comparator arm at each assessment time point (secondary efficacy endpoints). This tendency of wound area reduction was detectable as early as on Day 2 (96.6% vs. 91.2% baseline wound area for Dermazin® cream and Kék Lukács ointment, respectively) with a mean difference of 5.38 (CI -2.09;12.85) and continued on Days 8, 15 and 22. Difference between mean percentage values was the highest with 16.9% (-13.12;47.04) on Day 8 when most of the patients were still in the study (46.3% vs. 29.4% baseline wound area for Dermazin® cream and Kék Lukács ointment, respectively). By Day 22, a considerable proportion of patients (10 of 12 patients in the Dermazin® cream group and 9 of 10 patients in the Kék Lukács Ointment group) achieved complete or almost complete wound healing. Therefore, between-group differences in percentage of baseline wound surface area tended to decrease by time (Day 15: 3.88 [-9.63;17.4]); Day 22: 3.62 [-3.97;11.22]) but Kék Lukács ointment group showed better results at later visits as well (Day 15: 8.3% vs. 4.4%; Day 22: 4.3% vs. 0.7%) (**Fig. 1–3**).

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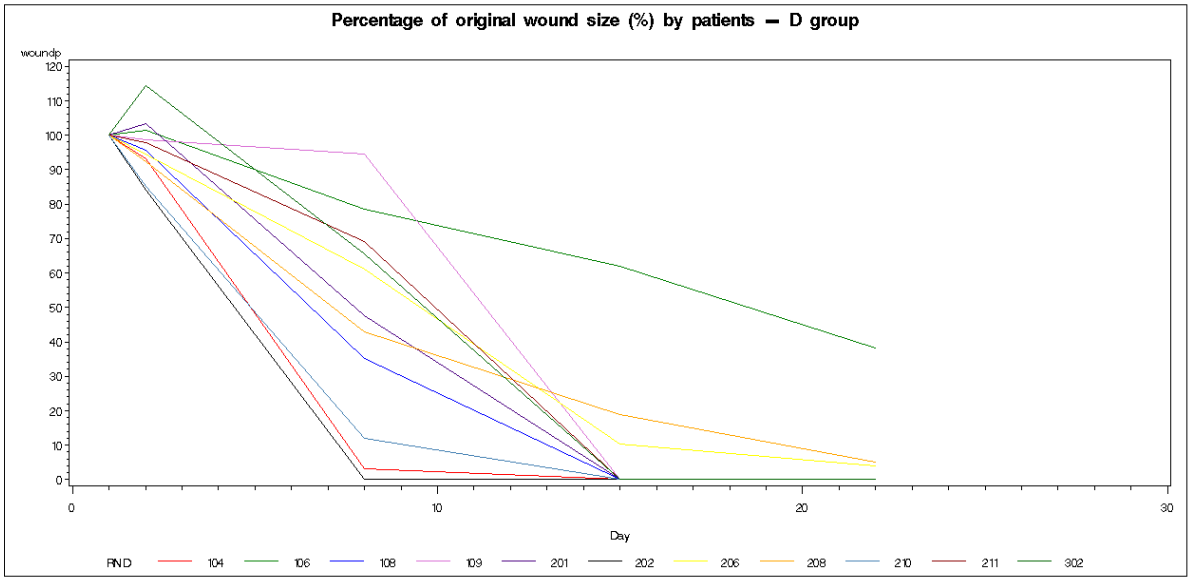

Figure 1 Percentage of original wound size by patients – Dermazin® cream group

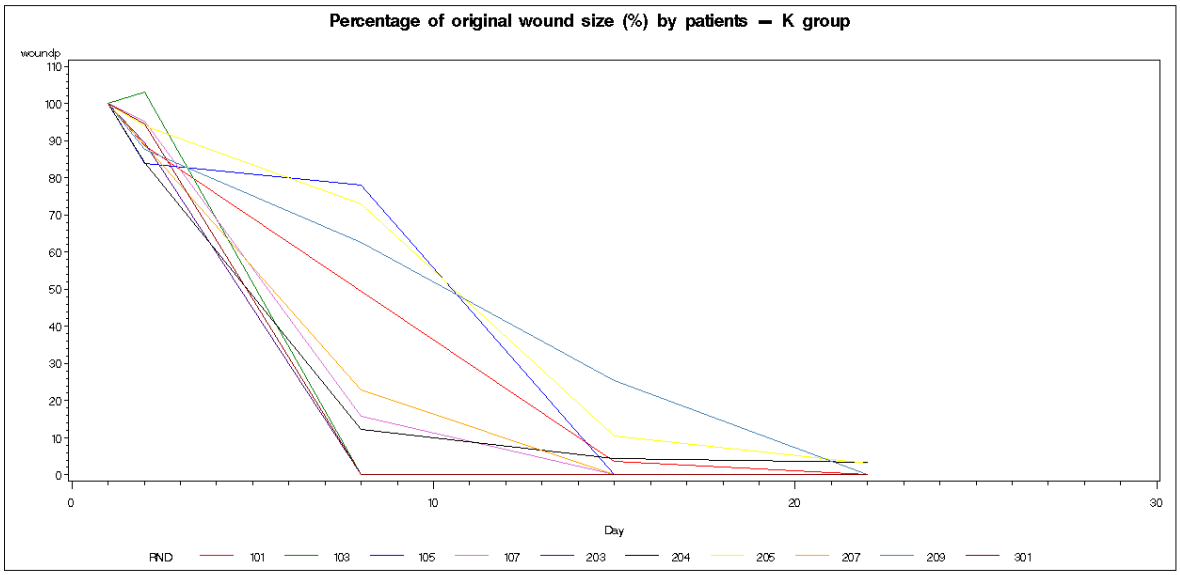

Figure 2 Percentage of original wound size by patients – Kék Lukács ointment group

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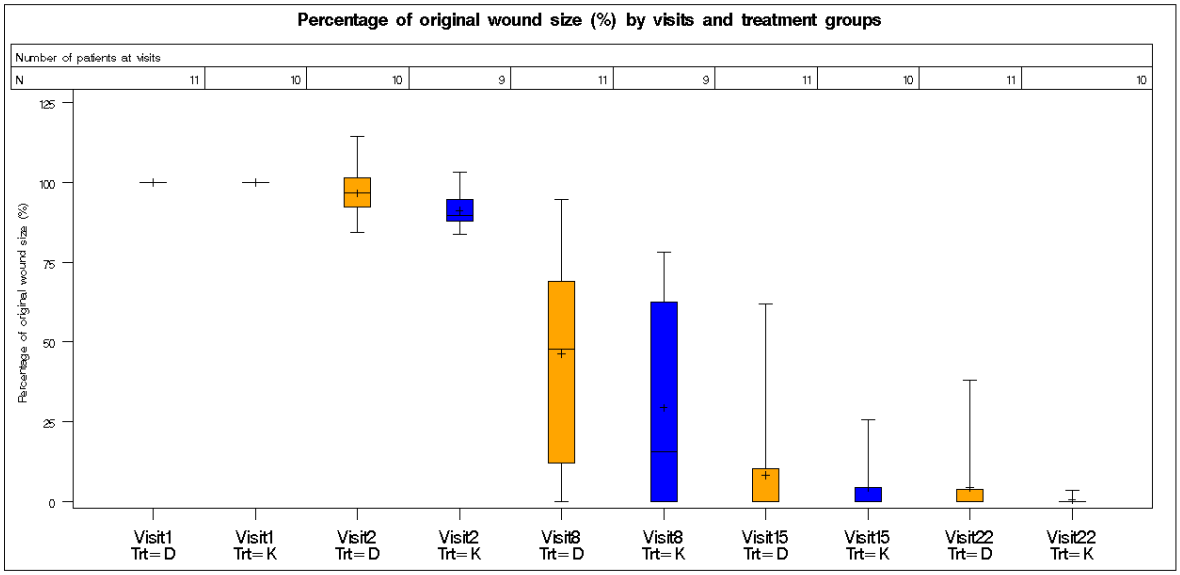

Figure 3 Percentage of original wound size (%) by visits and treatment groups

The distribution of times until complete or almost complete wound healing (secondary efficacy endpoint) did not differ significantly between the two treatment groups (p=0.3455).

Wilcoxon–Mann–Whitney test did not show significant difference between treatment arms at any visits (Days 1–15, 22, 29 and 57) assessed for pain before or after treatment. For Days 16–21, due to the high healing rate and therefore the low number of available data, no statistics were performed.

Regarding other secondary efficacy endpoints, all patients in both treatment arms achieved complete or almost complete wound healing and no treatment failure occurred until Day 57. Therefore, no skin transplantation was performed.

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Safety Results:

A total of 25 AEs in 10 patients (45.45%) were reported during the study and only one event experienced in the Kék Lukács ointment group fulfilled the criteria of a serious adverse event (SAE). Adverse events of special interest occurred in 3 patients (13.64%) and 8 cases, respectively. AEs were mild to severe in the Dermazin® cream group while only mild in severity in the Kék Lukács ointment group.

Pain-related AE occurred in 3 out of 12 patients (25.0%) in the Dermazin® cream group and in 1 out of 10 patients (10.0%) in the Kék Lukács ointment group.

No death occurred in this trial. No dose change or withdrawal was necessary because of AEs.

There were no significant between-group differences in the signs of infection and inflammation at any visit expect for erythema scores at Day 22 which were significantly better in the Kék Lukács ointment group (p=0.0239) and oedema scores at Day 1 with a borderline significant difference favouring the Kék Lukács ointment group.

Bacterial load results were only listed as there were only two non-negative results.

Regarding tolerability symptoms, burning decreased in its intensity during the study in both treatment groups and no severe burning occurred after Visit 11. Other tolerability symptoms also gradually improved over the course of the treatment period except for one patient in the Dermazin® cream group experiencing severe itching until Day 22 of the study.

No clinically relevant changes in vital signs were observed. No consistent changes in any laboratory parameters were observed.

Overall, it can be concluded that both treatments were safe and well tolerated and no safety concerns have arisen that would negatively affect the further stages of the clinical development of Kék Lukács ointment.

Conclusion:

Although statistics for the primary efficacy variable did not significantly favour Kék Lukács ointment over Dermazin® cream treatment, calculated empirical means clearly indicated that patients in the Kék Lukács ointment group performed better at each time point of the treatment period. In summary, this active controlled phase II pilot study has fulfilled its purposes in showing possible paths and next steps of the human clinical development program of Kék Lukács ointment. Concluded from results of the trial and the challenges *experienced during* patient enrolment, a large phase II/III non-inferiority study is proposed – and already approved – in patients with up to third-degree burns and with a greater wound size.

Date of the report: 12 May 2014