| | | |
|---|---|---|
| **Name of Sponsor/Company:**<br>Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier**<br><br>**Volume:**<br><br>**Page:** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>Kék Lukács Ointment | | |
| **Name of Active Ingredient:**<br>Azithromycin<br>Miconazole<br>Sulfamethoxazole | | |

**Title of Study:**
A Phase II/III Adaptive, Seamless, Prospective, Randomised, Controlled, Parallel, Open Multicenter 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. István Juhász, MD, DSc, Dr. med. habil.
2. Lajos Kemény, MD, DSc, Dr. med. habil.
3. Róbert Tamás, MD
4. Péter Geréb, MD

**Study centre(s):**
1. Department of Dermatology, Medical Center of the University of Debrecen, Hungary
2. Department of Dermatology and Allergology, Albert Szent-Györgyi Clinical Center, University of Szeged, Hungary
3. Department of Plastic and Burn Surgery Medical Centre, Hungarian Army Medical Center, Hungary
4. Department of Plastic and Burn Surgery, Aladár Petz County Hospital

**Publication (reference):**
N/A

| | |
|---|---|
| **Studied period (years):** 1<br>(24 June 2014)<br>(11 June 2015) | **Phase of development**: II/III |

**Objectives:**

Primary objective:
To compare the clinical efficacy of Kék Lukács ointment treatment with standard Dermazin® cream (SSD) therapy in wound healing by evaluating the days needed until reaching ≥91% (complete or almost complete) epithelisation quantitatively assessed by three-dimensional (3D) digital photo documentation (planimetry) taken on Day 1 (baseline) and on every second day of the treatment period from Day 2 including all clinical visits as well as on End-of-Treatment (EoT) Visit.[1]

[1] *Study protocol version 02 (SP) wording:* To compare the clinical efficacy of Kék Lukács ointment treatment with standard Dermazin® (SSD) therapy in wound healing; with 3D photo documentary every second day from the first day of treatment till the 22nd day of treatment or till healing of the wound; by evaluating the days needed to the wound healing.

| | | |
|---|---|---|
| **Name of Sponsor/Company:**<br>Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:**<br>Azithromycin<br>Miconazole<br>Sulfamethoxazole | **Page:** | |

Secondary objectives:

1. Investigator‘s semi-quantitative assessment of the degree of epithelisation on every clinical visit during the treatment period (from Day 2) as well as on EoT Visit and on follow-up visit 2 (FU2 Visit, Day 35±3 of the follow-up period).[2]
2. Investigator‘s assessment of signs of wound infection and inflammation: a) oozing, b) erythema, c) warmth, d) oedema, e) pain, and f) odour on every clinical visit during the treatment period as well as on EoT Visit and on FU2 Visit (Day 35±3 of the follow-up period).[3]
3. Investigator’s assessment of wound bed coverage and wound margin inequality and wound margin erythema on every clinical visit during the treatment period as well as on EoT Visit and on FU2 Visit (Day 35±3 of the follow-up period).[4]
4. Investigator’s or Study Nurse’s assessment of wound surface on every treatment day as well as on EoT Visit and on FU2 Visit (Day 35±3 of the follow-up period); in addition, Investigator's or Study Nurse’s assessment of wound secretion on every treatment day.[5]
5. Investigator’s assessment of cosmetic results by evaluation of general wound appearance, crusting and scabbing on clinical visits from visit 3 (Day 8±1) during the treatment and follow-up period.[6]
6. Investigator’s or Study Nurse’s assessment of the ease of application of each study treatment by the evaluation of patient-reported pain associated with target wound care (wound cleaning, study medication application, and dressing application/removal/re-application) after daily wound care sessions during the treatment period. Before-treatment pain scores were also recorded.[7]
7. Incidence of suitability for skin transplantation (if applicable) was planned to be estimated.

[2] *SP wording:* To assess the change in degree of epithelization of wound comparing to day 1 on each clinical visit from the second day of the study till the reaching of a 91% epithelization.
[3] *SP wording:* Investigator‘s assessment of signs of wound infection and inflammation: a) oozing, b) erythema, c) warmth, d) oedema, e) pain, f) odour on each medical visit in treatment and follow up periods of the study (Treatment period: Day 1, 2, 8, 15, 22, 29 and Follow up period 7 and 35 day after last treatment).
[4] *SP wording:* Clinical assessment of the wound bed and wound margin on each medical visit in treatment and follow up periods of the study.
[5] *SP wording:* To monitor the wound surface and wound secretion on the treatment days.
[6] *SP wording:* To evaluate the satisfaction of cosmetic result after Kék Lukács ointment treatment through the evaluation of general wound appearance, crusting and scabbing comparing to Dermazin® (SSD) on the medical visits of the study beginning at visit 3.
[7] *SP wording:* To assess the ease of application of Kék Lukács ointment by the evaluation of pain at each treatment and dressing change.

| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

8. Investigator's or Study Nurse's assessment of the tolerability of local treatment on target wound by evaluation of sensitivity and local irritability (burning, stinging, itching, tightness, tingling) on every treatment day (from Day 2) and on EoT Visit.[8]
9. Collecting pharmacoeconomic information (not performed).

Exploratory objectives:

An attempt was made to identify factors influencing the rate of wound healing and to assess the effect of patient age, gender, anatomical localisation of the wound and centre (investigational site) on wound healing as exploratory analyses.

**Methodology:**

Treatment period

On Visit 1 (Day 1) patients underwent screening for inclusion/exclusion criteria after obtaining their written informed consent. Eligible patients were randomised to either Kék Lukács ointment treatment or Dermazin® cream (SSD) therapy.

Debridement was performed on the target wound before first treatment application. The selected target burn area was cleaned with 0.9% physiological saline solution. Test or control treatment was applied every day after cleaning the wound surface with 0.9% physiological saline solution by the Study Nurse. According to randomisation, either Kék Lukács ointment was applied to a thickness of 1-2 mm with a sterile spatula onto a sterile gauze dressing or Dermazin® cream was applied to a thickness of 2-4 mm with a sterile spatula onto a sterile gauze dressing. This gauze (Vliwasoft®) was applied to the target wound surface as primary layer and an absorbent dressing (Vliwazell®) was applied as secondary layer. Fixation of primary and secondary dressings was done by Mollelast® haft bond securing bandage or Curafix® H self-adhesive tape. During the treatment period, patients received outpatient or home nursing attendance for treatment application on every day (nurse visits).

3D digital photographs were taken on Day 1 (baseline) and on every second day of the treatment period from Day 2 including all clinical visits as well as on EoT Visit and FU1 and FU2 Visits to a) document baseline wound characteristics (inclusion criteria); b) provide quantitative evaluation of the rate of epithelisation; c) document Investigator-performed (semi-quantitative) assessment of the degree of epithelisation on every clinical visit during the treatment period (from Day 2) as well as on EoT Visit and on FU2 Visit (Day 35±3 of the follow-up period); and d) document Investigator- and Investigator-/Study Nurse-assessed wound characteristics (signs of wound infection and inflammation, wound bed coverage and wound margin inequality and wound margin erythema, wound surface and wound secretion, signs of sensitivity and local irritability, cosmetic results) on clinical/nurse visits in the treatment and follow-up period, as applicable. Therefore, some of the days of 3D digital photo

[8] *SP wording:* To assess the tolerability of local therapy of target wound based on sensitivity and local irritability every day during treatment period (from Day 2 till reaching of a 91% epithelization).

| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

documentation for different evaluations coincided.
Analysis and assessment of digital images was performed by a validated Quantificare 3D LifeViz™ system.
When suspected wound healing was observed by the Study Nurse on a day when only a nurse visit but no clinical visit was scheduled, the patient was asked to come to an extra clinical visit on the subsequent day. This extra clinical visit was considered as EoT Visit if the Investigator semi-quantitatively confirmed almost complete or complete epithelisation of the target wound.
Routine haematology and clinical chemistry tests from blood and urine including C-reactive protein (CRP) were performed on Visit 1 (Day 1) and on EoT Visit per protocol as well as at any time when needed.
As per Investigator's judgement, a qualitative microbiology test of the target wound to evaluate bacterial load could be performed at enrolment (Day 1) or at any time when needed.

End-of-Treatment (EoT) Visit[9]
After reaching ≥91% epithelisation of the target wound, the treatment was stopped and EoT Visit was performed on the day after the last treatment day. EoT Visit occurred on Day 29±1 the latest.

Follow-up period
After the treatment period patients were followed on two clinical visits on Day 7±3 and Day 35±3 of the follow-up period. The day of EoT Visit was considered as first day of the follow-up period.
It was possible to use mild antiseptic wash-off solutions (povidone-iodine or octenidine-dihidrochloride) in the follow-up period when needed. During the follow-up period, Unguentum hydrophilicum nonionicum Ph. Hg. VII. Naturland was applied daily for scar care, moisturising, hydrating and (optionally) bandage to provide mechanical and light protection.

**Number of patients (planned and analysed):**
Planned
Phase II: 20 subjects per treatment group (altogether 40 subjects);
Phase III: 16–50 subjects per treatment group (altogether 32–100 subjects)
Analysed
Phase II: 19 subjects in Kék Lukács ointment group); 21 subjects in Dermazin® cream group (altogether 40 subjects)
Phase III: 17 subjects in Kék Lukács ointment group); 16 subjects in Dermazin® cream group (altogether 33 subjects)

**Diagnosis and main criteria for inclusion:**
Partial thickness (second degree) burns requiring local antimicrobial treatment due to infectious

[9] *SP wording:* closure visit

| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

risk, as per Investigator's judgement.

1. Written informed consent of the patient.
2. Male or female patients above 18 years of age.
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 intrauterine device) or abstinence throughout the trial (treatment + follow-up period).
4. Burns of thermal origin.
5. Total burn area for all burns on a single patient should not be greater than 15% of total body surface area (TBSA).
6. Patients with burn injuries confined to the trunk and/or upper and/or lower extremities.
7. Patients' study target burn area (partial thickness) should be greater than 25 $cm^2$ but not greater than 400 $cm^2$ (or 2% of TBSA).
8. Patients with partial thickness (second degree) burns and with the possibility to start study treatment 6–72 hours post-burn.[10]
9. As per Investigator's judgement, local antimicrobial treatment is required due to infectious risk and the target wound is suitable for Dermazin® cream (SSD) treatment.
10. Patients who are 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, 40 g/400 $cm^2$ once daily topically, 513003

**Duration of treatment:**

Maximum 21 days by default, extended by up to 7 additional days (altogether maximum 28 days) in case not achieving complete or almost complete epithelisation until Day 21, as per Investigator's semi-quantitative assessment.

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

Dermazin® cream, 20–40 g/400 $cm^2$ once daily topically, DV6054, DV6056, ED8602, EM4558

**Criteria for evaluation:**

**Efficacy:**

Primary endpoint:

The primary efficacy endpoint in this trial was the number of days until reaching ≥91% epithelisation of the target wound. Wound healing was attained on the first treatment-free day when the unhealed wound area was ≤9% of the baseline (Day 1) wound area[11]. Target wound area was quantitatively assessed by planimetry (3D digital photography imaging and area

[10] *SP wording:* burn therapy started within 6–72 hours

[11] *SP wording:* Wound healing will be attained on the first day when the wound area (as measured by planimetry, taking the mean of the values evaluated by two independent assessors) will be below 10% of the baseline wound area.

| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

calculation), taking the mean of the values evaluated by two independent assessors. 3D digital photographs for planimetric evaluations were taken after cleaning the target wound including the careful removal of all study medication remnant and before the application of the due dose of the study medication. This means that no specific hints that might have indicated treatment group assignment were visible on the photographs. Therefore, assessment of the primary efficacy variable was performed in an evaluator-blinded manner, although the treatment itself was conducted in an open-label fashion.

Wound area was measured on Day 1 (baseline) and on every second treatment day from Day 2 of the treatment period onwards until EoT Visit. No efficacy threshold was defined. On each measurement, current target wound area and accurate percent reduction of target wound area were calculated for each subject. No rounding of unhealed wound area percentage or interpolation for wound area was performed.

For patients by whom the treatment of the target wound was continued by surgery the day of ordering surgery had to be considered as day of wound healing.

If the surgery area exceeded 50% of the original wound area the patient was excluded from the per protocol (PP) analysis. If the surgery area did not exceed 50% of the original wound area the patient remained in the PP analysis set and the healing of the wound area outside the surgical area was taken into account for the analysis.

Secondary endpoints:

1. Investigator‘s semi-quantitative assessment of the degree of epithelisation on every clinical visit during the treatment period (from Day 2) as well as on EoT Visit and on FU2 Visit (Day 35±3 of the follow-up period).[12]
2. Investigator‘s assessment of signs of wound infection and inflammation: a) oozing, b) erythema, c) warmth, d) oedema, e) pain, and f) odour on every clinical visit during the treatment period as well as on EoT Visit and on FU2 Visit (Day 35±3 of the follow-up period).[13]
3. Investigator’s assessment of wound bed coverage and wound margin inequality and wound margin erythema on every clinical visit during the treatment period as well as on EoT Visit and on FU2 Visit (Day 35±3 of the follow-up period).[14]
4. Investigator’s or Study Nurse’s assessment of wound surface on every treatment day as well as on EoT Visit and on FU2 Visit (Day 35±3 of the follow-up period); in addition, Investigator's or Study Nurse’s assessment of wound secretion on every treatment day.[15]

[12] *SP wording:* To assess the change in degree of epithelization of wound comparing to day 1 on each clinical visit from the second day of the study till the reaching of a 91% epithelization.

[13] *SP wording:* Investigator‘s assessment of signs of wound infection and inflammation: a) oozing, b) erythema, c) warmth, d) oedema, e) pain, f) odour on each medical visit in treatment and follow up periods of the study (Treatment period: Day 1, 2, 8, 15, 22, 29 and Follow up period 7 and 35 day after last treatment).

[14] *SP wording:* Clinical assessment of the wound bed and wound margin on each medical visit in treatment and follow up periods of the study.

[15] *SP wording:* To monitor the wound surface and wound secretion on the treatment days.

| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

5. Investigator's assessment of cosmetic results by evaluation of general wound appearance, crusting and scabbing on clinical visits from visit 3 (Day 8±1) during the treatment and follow-up period.[16]
6. Investigator's or Study Nurse's assessment of the ease of application of each study treatment by the evaluation of patient-reported pain associated with target wound care (wound cleaning, study medication application, and dressing application/removal/re-application) after daily wound care sessions during the treatment period. Before-treatment pain scores were also recorded.[17]
7. Incidence of suitability for skin transplantation (if applicable) was planned to be estimated.
8. Collecting pharmacoeconomic information (not performed).

**Safety:**

Safety endpoints:

1. The incidence of adverse events[18] (AEs) during the entire study period.
2. Investigator's or Study Nurse's assessment of the tolerability of local treatment on target wound by evaluation of sensitivity and local irritability (burning, stinging, itching, tightness, tingling) on every treatment day (from Day 2) and on EoT Visit.[19]
3. Changes from baseline (Day 1) to EoT Visit in haematology and clinical chemistry parameters in blood and urine including CRP.

**Exploratory**

Exploratory endpoints

An attempt was made to identify factors influencing the rate of wound healing and to assess the effect of patient age, gender, anatomical localisation of the wound and centre (investigational site) on wound healing as exploratory analyses.

**Statistical methods:**

Analysis sets

*Safety analysis set*

All randomised subjects who received at least one study treatment.

*Intent-to-treat (ITT) analysis set*

All randomised subjects who received at least one study treatment and had at least one post-

[16] *SP wording:* To evaluate the satisfaction of cosmetic result after Kék Lukács ointment treatment through the evaluation of general wound appearance, crusting and scabbing comparing to Dermazin® (SSD) on the medical visits of the study beginning at visit 3.

[17] *SP wording:* To assess the ease of application of Kék Lukács ointment by the evaluation of pain at each treatment and dressing change.

[18] *SP wording:* treatment-related adverse events

[19] *SP wording:* To assess the tolerability of local therapy of target wound based on sensitivity and local irritability every day during treatment period (from Day 2 till reaching of a 91% epithelization).

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

baseline evaluation of the target wound area.

*Per protocol (PP) analysis set*
All randomised subjects who received at least one study treatment and had at least one post-baseline evaluation of the target wound area and did not have any major protocol deviation (protocol violation). Protocol violations included:

- violation of any inclusion/exclusion criterion;
- randomisation error;
- use of any prohibited systemic or topical medication on the test site and/or on other (non-target) burn area(s); or
- missing more than one clinical visits (treatment and/or follow-up).

Patients who experienced deterioration of the target wound due to treatment failure and needed therefore skin transplantation on the target wound were withdrawn from the study. If the surgery area exceeded 50% of the original wound area the patient was excluded from the PP analysis. If the surgery area did not exceed 50% of the original wound area the patient remained in the PP analysis set and the healing of the wound area outside the surgical area was taken into account for the analysis.

Analysis methods
*Primary efficacy analysis:* ITT and PP analysis sets
The primary analysis for the number of days until wound healing was a one-sided t-test comparing the means of the two treatment groups, assuming equal variances and testing the null hypothesis $H_0$: $\mu_1-\mu_2=3$ versus the alternative $H_a$: $\mu_1-\mu_2<3$ at a one-sided 2.5% level (where $\mu_1$ and $\mu_2$ denoted the average number of days until wound healing in Kék Lukács ointment and Dermazin® cream groups, respectively). Decision on non-inferiority was based on this analysis.
In the planning period of the study we assumed that all patients would recover until the end of the treatment period; therefore, no censored data would be present and the t-test can be applied. In case there were any censored data, the time until wound healing would be analysed by Wilcoxon-test (Halperin), generalised for censored data. In the course of this analysis those patients by whom no healing is observed until Day 28 would be censored on Day 28 day and the number of days until wound healing would be considered >28. Patients withdrawn from the study due to wound deterioration would be taken into account as patients not healed until Day 28; therefore, the analysed time until wound healing would be >28.
In case of normally distributed data the asymptotic relative efficiency of the Wilcoxon-test compared to the t-test is $3/\pi(\approx 0.9549)$; therefore, the impact on sample size of switching from t-test to Wilcoxon–test was expected to be small. However, it would have been taken into account (if needed) during the interim analysis when the sample size was re-evaluated.
As a supportive analysis, the same difference between means (95% confidence interval [CI]) was also estimated within a mixed model, accounting for treatment, wound type and wound size at baseline, allowing for different variances in the two treatment groups.

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

If and only if the primary analysis yielded a statistically significant result the null hypothesis $H_0$: $\mu_1-\mu_2=0$ versus the alternative $H_a$: $\mu_1-\mu_2<0$ would also be tested applying a t-test as described above. Decision on superiority would be based on this analysis.

*Secondary efficacy analyses:* ITT analysis set
The scores assigned by the Investigator to the signs of wound infection and inflammation, the pain scores and the cosmetic results were compared across the two treatment groups by a Wilcoxon–Mann–Whitney-test, for each time point separately.
The percent reduction of wound area was planned to be compared between the two treatment groups within a repeated measures ANOVA model, for each time point separately (analysis not included in the *Statistical Report*).
Wound margin, wound bed, wound surface and wound secretion were characterised descriptively.
The proportion (95% CI) of subjects receiving skin transplantation was planned to be estimated for each treatment group separately (if applicable – not done).
Descriptive characterization of pharmacoeconomic information was planned (not done).

*Safety analyses:* Safety analysis set
The incidence (95% CI) of selected AEs which are assumed to be signs of drug intolerance was planned to be estimated (not done).
AEs were coded (Medical Dictionary for Regulatory Activities, MedDRA) and tabulated by system organ class and preferred term.
Changes from baseline (Day 1) to EoT Visit in haematology and clinical chemistry parameters in blood and urine including CRP were characterised descriptively.
The tolerability of local therapy of target wound based on sensitivity and local irritability will be compared across the two treatment groups by a Wilcoxon–Mann–Whitney test, for each time point separately.

*Exploratory analyses:* ITT analysis set
The effect of patient age, gender, anatomical localisation of the wound and centre (investigational site) on wound healing was assessed as exploratory analyses.

**Summary – Conclusions**

**Efficacy Results**

Primary efficacy results

In terms of the primary efficacy endpoint, the non-inferiority of Kék Lukács ointment compared to Dermazin® cream could be demonstrated for both the PP (mean number of days until target wound healing: 8.5 [Kék Lukács ointment group] versus 10.9 [Dermazin cream® group]; $p<0.0001$; combined rejection margin for Fisher's combination=0.0038) and the ITT analysis sets (mean number of days until target wound healing 8.8 [Kék Lukács ointment group] versus 10.9 [Dermazin cream® group]; $p=0.0001$) (combination of phase II and phase III results) (**Tables 1–2**).

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

**Table 1**. Comparison of mean number of days until target wound healing across treatment arms – non-inferiority hypothesis testing (PP dataset)

| Phase | Statistics[a] | Kék Lukács ointment | Dermazin® cream | Kék Lukács ointment + Dermazin® cream |
|---|---|---|---|---|
| Phase II | N (not censored) | 19 | 21 | 40 |
| | Mean | 9.1 | 10.9 | -1.8 |
| | 95% CI (Lower bound to Upper bound) | 7.0 to 11.2 | 8.2 to 13.5 | -5.1 to 1.6 |
| | p-value[b] | NA | NA | 0.0033 |
| Phase III | N (not censored) | 16 | 14 | 30 |
| | Mean | 7.9 | 11.0 | -3.1 |
| | 95% CI (Lower bound to Upper bound) | 6.2 to 9.6 | 7.6 to 14.4 | -6.6 to 0.4 |
| | p-value[c] | NA | NA | 0.0006 |
| Phase II+III | N (not censored) | 35 | 35 | 70 |
| | Mean | 8.5 | 10.9 | -2.4 |
| | 95% CI (Lower bound to Upper bound) | 7.2 to 9.9 | 8.9 to 12.9 | -4.7 to -0.0 |
| | p-value[d] | NA | NA | <0.0001 |

[a] Descriptive statistics are based on subjects with not censored data, while the p-values are based on all subjects
[b] one-sided t-test
[c] Wilcoxon-Halperin one-sided test, comprising the subject(s) with censored data
[d] p-values from phase II and III combined (Fisher's method): significant if ≤0.0038

**Table 2**. Comparison of mean number of days until target wound healing across treatment arms – non-inferiority hypothesis testing (ITT dataset)

| Phase | Statistics[a] | Kék Lukács ointment | Dermazin® cream | Kék Lukács + Dermazin® cream |
|---|---|---|---|---|
| Phase II | N (not censored) | 19 | 21 | 40 |
| | Mean | 9.1 | 10.9 | -1.8 |
| | 95% CI (Lower bound to Upper bound) | 7.0 to 11.2 | 8.2 to 13.5 | -5.1 to 1.6 |
| | p-value[b] | NA | NA | 0.0033 |
| Phase III | N (censored) | 0 | 1 | 1 |
| | N (not censored) | 17 | 15 | 32 |
| | Mean | 8.4 | 10.9 | -2.5 |

| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

| | | | | |
|---|---|---|---|---|
| | 95% CI (Lower bound to Upper bound) | 6.5 to 10.4 | 7.7 to 14.0 | -5.9 to 1.0 |
| | p-value[c] | NA | NA | 0.0377 |
| Phase II+III | N (censored) | 0 | 1 | 1 |
| | N (not censored) | 36 | 36 | 72 |
| | Mean | 8.8 | 10.9 | -2.1 |
| | 95% CI (Lower bound to Upper bound) | 7.4 to 10.2 | 8.9 to 12.8 | -4.4 to 0.2 |
| | p-value[d] | NA | NA | 0.0001 |

[a] Descriptive statistics are based on subjects with not censored data, while the p-values are based on all subjects
[b] one-sided t-test
[c] Wilcoxon-Halperin one-sided test, comprising the subject(s) with censored data
[d] p-values from phase II and III combined (Fisher's method): significant if ≤0.0038

All analysis results indicated the better effect of Kék Lukács ointment versus Dermazin® cream in terms of days until target wound healing (distribution of days until target wound healing was displayed graphically by Kaplan–Meier-method, means and adjusted means were compared by ANOVA, medians were compared by descriptive statistics) (**Tables 3–4**, **Figure 1**), however, superiority hypothesis testing did not attain statistical significance.

**Table 3**. Descriptive statistics of number of days until wound healing (PP dataset)

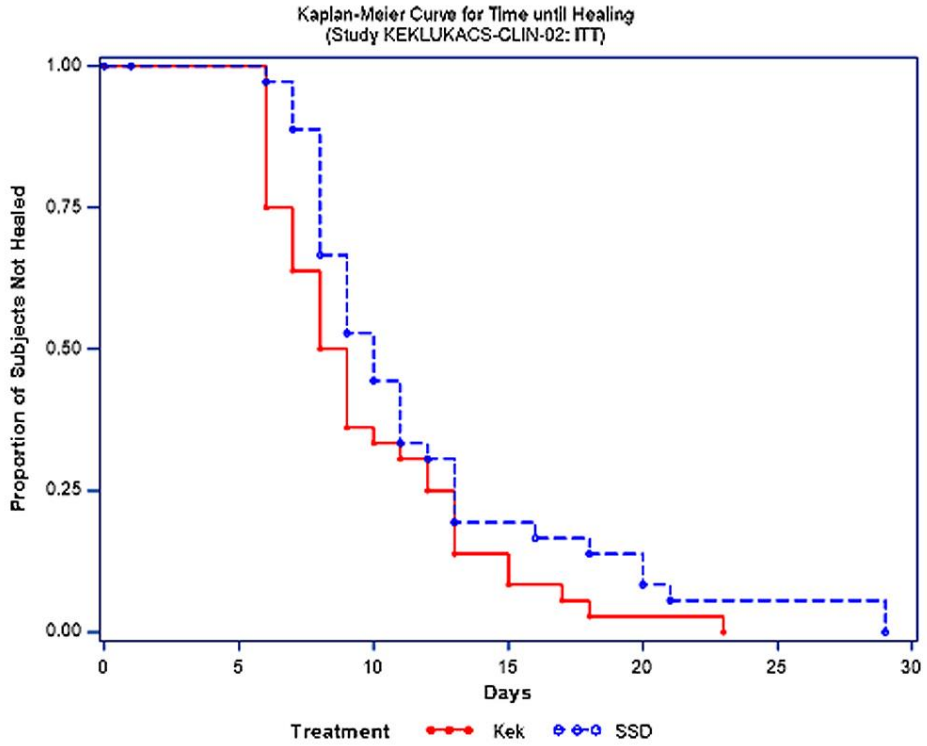
| | **Statistics** | **Kék Lukács ointment** | **Dermazin® cream** |
|---|---|---|---|
| Number of days until wound healing | N | 35 | 35 |
| | Mean | 8.5 | 10.9 |
| | SD | 3.88 | 5.79 |
| | Median | 7.0 | 9.0 |
| | Minimum | 5 | 5 |
| | Maximum | 22 | 28 |

**Table 4**. Descriptive statistics of number of days until wound healing (ITT dataset – non-censored data)

| | **Statistics** | **Kék Lukács ointment** | **Dermazin® cream** |
|---|---|---|---|
| Number of days until wound healing | N | 36 | 36 |
| | Mean | 8.8 | 10.9 |
| | SD | 4.07 | 5.71 |
| | Median | 7.5 | 9.0 |
| | Minimum | 5 | 5 |
| | Maximum | 22 | 28 |

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

**Figure 1.** Proportion of subjects not healed versus treatment day (ITT dataset)

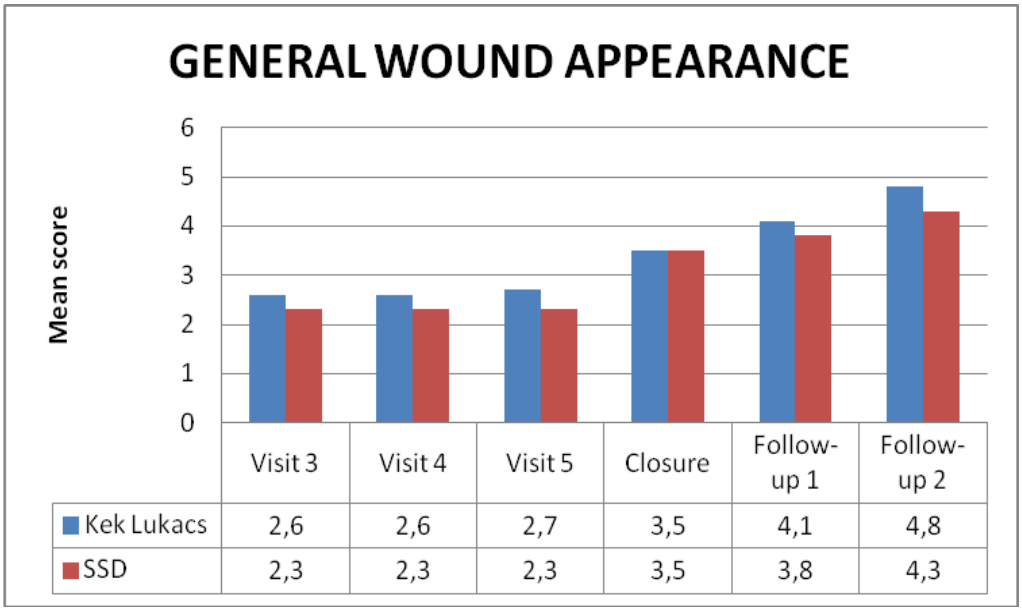



Secondary efficacy and exploratory results

The general wound appearance at FU2 Visit was significantly better after Kék Lukács ointment treatment than after Dermazin® cream treatment (**Figure 2**). Similarly, wound-related mean pain scores after treatment – characterising the ease of application of study treatment according to *Study Protocol* – were significantly lower in the Kék Lukács ointment group than in the Dermazin® cream group on Day 1 (p= 0.037) and Day 2 (p=0.038) of the treatment period.

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

**Figure 2.** Mean scores for general wound appearance per visit and treatment group



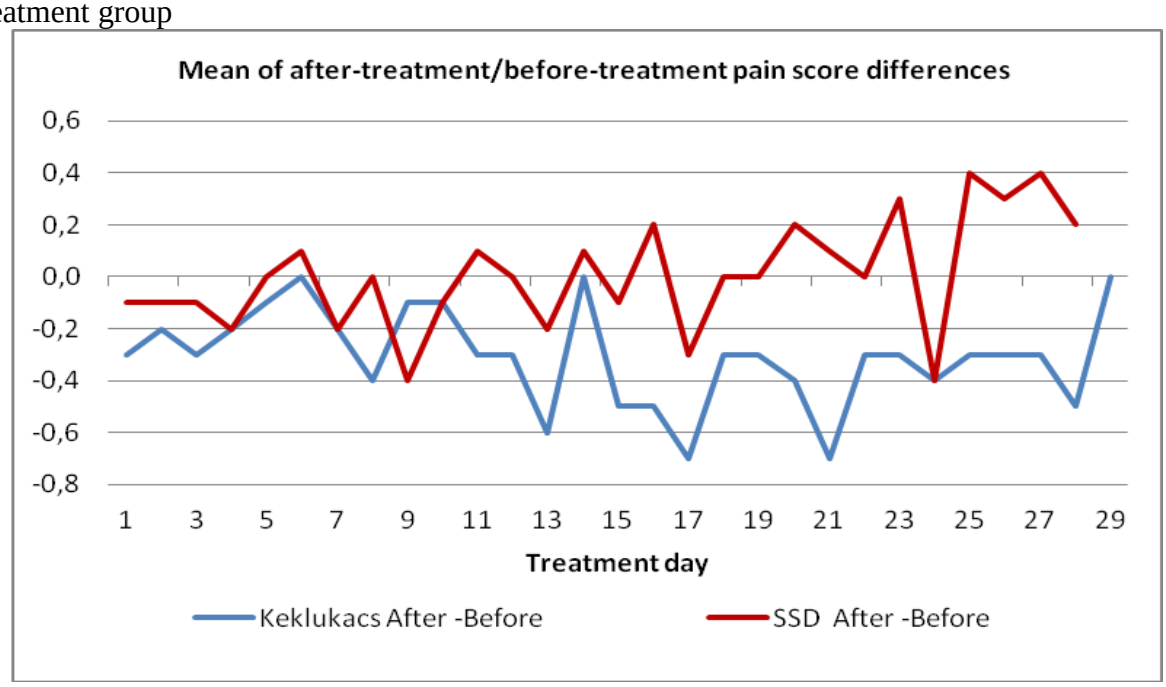

| | Visit 3 | Visit 4 | Visit 5 | Closure | Follow-up 1 | Follow-up 2 |
|---|---|---|---|---|---|---|
| Kek Lukacs | 2,6 | 2,6 | 2,7 | 3,5 | 4,1 | 4,8 |
| SSD | 2,3 | 2,3 | 2,3 | 3,5 | 3,8 | 4,3 |

Scores for clinical assessment were 0–4 and 0–3 vs. scores for statistical analysis were 1–5 and 1–4.

Although the *Study Protocol* and SAP declared the ease of application of study treatment to be characterised by after-treatment pain, this parameter may clinically be better reflected by the difference of after-treatment and before-treatment pain scores. Therefore, an additional analysis was performed (not included in SAP) to assess the after-treatment/before-treatment pain score differences per treatment day and treatment arm. Although this comparison did not allow any statistically significant conclusions, the mean of after-treatment/before-treatment pain score difference showed a tendency to be lower for Kék Lukács ointment than for Dermazin® cream, during almost the entire treatment period (**Figure 3**).

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

**Figure 3**. Mean of after-treatment/before-treatment pain score differences per treatment day and treatment group




Parameter "Wound related pain AFTER treatment" was missing on day 5 for patient 112; on day 5 for patient 429; on day 8 for patient 406; on day 8 for patient 433; on day 9 for patient 209; on day 10 for patient 408; on day 10 for patient 418; on day 13 for patient 215; on day 13 for patient 411; on day 14 for patient 111; on day 20 for patient 211; on day 20 for patient 214.
Parameter "Wound related pain BEFORE treatment" was missing on day 9 for patient 209; on day 13 for patient 215; on day 14 for patient 111; on day 20 for patient 211; on day 20 for patient 214.

Regarding other secondary efficacy parameters, no significant difference between the treatment arms could be demonstrated.

None of the patients in the Kék Lukács ointment group experienced treatment failure/target wound deterioration and required therefore skin transplantation. The only patient who suffered such an outcome was on Dermazin® cream treatment.

Exploratory analyses indicated that patient age (p=0.002) and anatomical localisation (p=0.008) had a statistically significant effect on the mean number of days until wound healing (**Tables 5–6**).

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

**Table 5**. Effect of patient age on wound healing

| Days until target wound healing | | Age (years) | | |
|---|---|---|---|---|
| | | <40 | 40–60 | >60 |
| Kék Lukács ointment | Mean | 10.42 | 8.44 | 11.50 |
| | Standard Error of Mean | 0.973 | 0.713 | 2.220 |
| | Count | 12 | 16 | 8 |
| Dermazin® cream | Mean | 9.14 | 12.40 | 14.58 |
| | Standard Error of Mean | 0.628 | 1.416 | 2.294 |
| | Count | 14 | 10 | 13 |

**Table 6.** Effect of anatomical localisation on wound healing

| Anatomical localisation of the target wound | Treatment | | | | | |
|---|---|---|---|---|---|---|
| | Kék Lukács ointment | | | Dermazin® cream | | |
| | Days until target wound healing | | | Days until target wound healing | | |
| | Mean | SD | Valid N | Mean | SD | Valid N |
| Left lower extremity | 11.14 | 3.939 | 14 | 17.00 | 8.246 | 9 |
| Left upper extremity | 7.00 | 1.195 | 8 | 9.44 | 3.609 | 9 |
| Right lower extremity | 8.86 | 3.625 | 7 | 10.78 | 3.930 | 9 |
| Right upper extremity | 11.14 | 5.521 | 7 | 10.86 | 2.340 | 7 |
| Trunk | | | 0 | 8.00 | 0.000 | 2 |

Additional efficacy considerations (not included in *Study Protocol* and in the Statistical Analysis Plan [SAP])

In addition to analyses included in the *Study Protocol* and SAP, an impressing difference was observed between Kék Lukács ointment and Dermazin® cream when comparing time until wound healing of a specific subset of wounds (localised on leg or foot) with known poorer epithelisation tendency than of other body sites (**Table 7**). This observation further supports the pronounced efficacy of Kék Lukács ointment in facilitating epithelisation process and wound healing after partial thickness (second degree) burn injury.

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:** Kék Lukács Ointment | **Volume:** | |
| **Name of Active Ingredient:** Azithromycin Miconazole Sulfamethoxazole | **Page:** | |

**Table 7**. Descriptive statistics of days until target wound healing per specified anatomical localisation and treatment group (subjects reached 91% epithelisation during treatment period; N=72)

| Treatment | Anatomical localisation of target wound | N | Mean | Median | SD | Min | Max |
|---|---|---|---|---|---|---|---|
| | | 72[a] | 10.819 | 9 | 5.036 | 6 | 29 |
| | Leg or foot | 19[b] | 13.421 | 13 | 5.650 | 6 | 29 |
| | Other | 53[b] | 9.887 | 9 | 4.496 | 6 | 29 |
| Kék Lukács | | 36[c] | 9.778 | 8.5 | 4.072 | 6 | 23 |
| Dermazin® | | 36[c] | 11.861 | 10 | 5.713 | 6 | 29 |
| Kék Lukács | Leg or foot | 14 | 11.357 | 12.5 | 3.650 | 6 | 18 |
| Kék Lukács | Other | 22 | 8.773 | 7.5 | 4.082 | 6 | 23 |
| Dermazin® | Leg or foot | 5 | 19.200 | 20 | 6.611 | 11 | 29 |
| Dermazin® | Other | 31 | 10.677 | 9 | 4.672 | 6 | 29 |

[a] Total number of treatments.

[b] Total number of treatments by anatomical localisation of target wound.

[c] Total number of treatments by treatment arm.

**Safety Results**

Out of the 34 AEs reported in the study, only two events (one event per treatment arm) fulfilled the criteria of a SAE.

One event was considered severe and four events were rated as moderate. The severe event occurred in the Dermazin® cream group while all moderate events were observed in the Kék Lukács ointment group. The remaining AEs were of mild severity.

There was only one AE probably related to the study treatment (Dermazin® cream group). This AE was a SAE and patient was withdrawn from the study due to this event (treatment failure/target wound deterioration and need of skin transplantation). Patient recovered after this SAE.

No death occurred in the trial. No clinically significant laboratory (haematology, clinical chemistry, or urine analysis) abnormalities occurred in any of the treatment groups.

Only one patient was withdrawn from the study due to AE (Dermazin® cream group).

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 or the marketing authorisation of Kék Lukács ointment.

**Conclusion**

It is to conclude that this adaptive, seamless phase II/III clinical trial fulfilled its purposes in proving the efficacy and safety of Kék Lukács ointment and evidencing its place on the market of topical medicinal products for human burn care.

| | | |
|---|---|---|
| **Name of Sponsor/Company:**<br>Lukács és Társa Gyógyszerkereskedelmi Bt. | **Individual Study Table Referring to Part of the Dossier**<br><br>**Volume:**<br><br>**Page:** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>Kék Lukács Ointment | | |
| **Name of Active Ingredient:**<br>Azithromycin<br>Miconazole<br>Sulfamethoxazole | | |
| **Date of Study Report:**<br>22 October 2015 | | |