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SYNOPSIS

Name of Sponsor/Company:	Name of Finished Product:	Name of Active Ingredient:
Merck Selbstmedikation GmbH	Kytta-Balsam® f	Comfrey root extract plus methyl nicotinate

Title of study

Double-blind, randomised, multi-centre, placebo-controlled clinical trial to investigate the efficacy and safety of a combination of comfrey root extract plus methyl nicotinate versus a preparation containing methyl nicotinate alone or placebo in patients with conditions of acute upper or low back pain.

Investigators

Co-ordinating Investigator:

[redacted]
Germany

Other investigators:

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Germany

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Study centres

Six active centres in Germany.

Publication

Planned.

Studied period (Date of first enrolment - Date of last completed)

29 January 2010 – 04 May 2011.

Phase of development

III

Objectives

The primary objective of this trial was to show that Kytta-Balsam® f (a combination of comfrey extract plus methyl nicotinate) is superior to the single preparation of methyl nicotinate or placebo cream. The primary efficacy variable was the area-under-the-curve (AUC) of the Visual Analogue Scale (VAS) on active standardised movement values at Visits 1 to 4 (at actual measurement times).

Secondary objectives of the study were the investigation of the following secondary efficacy variables:

- Back pain at rest, assessment by patient on Visual Analogue Scale (VAS).
- Pressure algometry (pain-time curve; AUC over 5 days).
- Global assessment of efficacy by patient.
- Global assessment of efficacy by investigator.
- Functional impairment measured with the Oswestry Disability Index.
- Consumption of analgesic medication.

Moreover, the safety was assessed by means of general physical examinations, vital signs, and the occurrence of AEs and SAEs, respectively.

Methodology

The trial was performed as a randomised, double-blind, multi-centre, three-arms, placebo-controlled, clinical Phase III parallel group trial over a treatment period of 5 ± 1 days.

Number of patients

Planned			Analysed (FAS-ITT/PP)		
Kytta-Balsam® f	Methyl nicotinate	Placebo	Kytta-Balsam® f	Methyl nicotinate	Placebo
150	150	50	163/156	164/156	52/50

Name of Sponsor/Company:	Name of Finished Product:	Name of Active Ingredient:
Merck Selbstmedikation GmbH	Kytta-Balsam® f	Comfrey root extract plus methyl nicotinate

Patient population

Patients with acute upper or low back pain.

Diagnosis and main criteria for inclusion

At Visit 1 (Day 1, 0 h) male or female patients had to fulfil the following inclusion criteria:

- Age range 18-45 years.
- Good general condition.
- Written informed consent.
- Acute back pain (either upper or low back pain), not in combination.
- Sensitivity to algometric pressure on the site contralateral to the painful trigger point at least 2.5 N/cm².
- Back pain on active standardised movement of at least 50 mm on a 100 mm Visual Analogue Scale (VAS).
- Basic value of the pressure algometry on the trigger point should not exceed 50 % of the respective value of the site contralateral to the painful trigger point.

Exclusion criteria were:

- Upper or low back pain that was attributable to any identifiable cause (e. g. disc prolapse, spondylolisthesis, osteomalacia, or inflammatory arthritis).
- Any recent trauma.
- Any recent strains of the back muscles documented by the clinical evaluation and anamnesis.
- Chronic back pain.
- Likelihood of prolapsed spinal disc documented by clinical symptoms (pain irradiation to peripheral areas, paraesthesia, clinically detectable impairment of muscle strength of related areas).
- Back pain caused by metabolic or neurological diseases documented by anamnesis (i.e. toxic neuropathy).
- Diabetes Mellitus.
- Risk factors for spinal infection.
- Recent onset of bladder dysfunction or severe or progressive neurological deficit in the low extremity (as a possible indication of prolapsed disk).
- Concomitant use of any anti-inflammatory drugs, heparinoids or analgesics including herbal preparations (glucocorticosteroids, NSAIDs, etc.) for the same indication or other indications (e.g. rheumatoid arthritis).
- Analgesics or NSAIDs applied by any route of administration within 10 days before study entry or corticoid drugs applied by any route of administration within 60 days before study entry.
- Any other concomitant treatment (e.g. cosmetics, ointments at the treated area) or medication that interferes with the conduct of the trial.
- Known intolerance or hypersensitivity (allergy) to comfrey extract, peanut, soya,

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Merck Selbstmedikation GmbH	Kytta-Balsam® f	Comfrey root extract plus methyl nicotinate

methyl nicotinate, parabenes or one of the other ingredients of the trial treatments, including known toxic reactions.
- Local skin affections that do not allow the application of the test cream.
- Participation in a clinical trial within the previous 30 days before enrolment in the trial, participation in this study before or simultaneous participation in another clinical trial.
- Pregnancy or lactation period.
- Women with childbearing potential without an effective contraceptive method.
- Abuse of alcohol, medicaments or illicit drugs.
- Any patient in the investigator's opinion not considered suitable for enrolment.
- Legal incapacity or limited legal capacity to give informed consent.

Test product, dose and mode of administration, batch number
Kytta-Balsam® f. A total of 100 g cream contained: comfrey root liquid extract (1:2) 35.0 g, Extractant: Ethanol 60 % (v/v) and methyl nicotinate 1.2 g for topical application. The batch numbers of randomised IMPs used were [redacted] and [redacted]. 12 cm of cream layer (approximately 4g) had to be applied topically, three times daily.

Duration of treatment

5 ± 1 days.

Reference therapy, dose and mode of administration

- Methyl nicotinate. A total of 100 g cream contained: Methyl nicotinate 1.2 g for topical application.
- Placebo for topical application.

Criteria for evaluation
Efficacy
All randomised patients were assessed in the FAS/ITT population. Moreover, a per protocol analysis (PP) was carried out. The per protocol population included all patients, who met the inclusion and exclusion criteria and showed no major protocol violations. The FAS/ITT-evaluation was the primary analysis in this superiority trial.

Safety
All patients treated at least one time with one of the study drugs were assessed for safety.

Statistical methods
A multiple and a priori ordered testing strategy was carried out confirmatorily with a stipulated multiple α-level of 5 % in the FAS (ITT) population. Four hierarchical two-sided null hypotheses are stipulated.

H_{01}: There are no differences between the three treatment groups regarding the AUC of the VAS sum values on active standardised movement.

Name of Sponsor/Company:	Name of Finished Product:	Name of Active Ingredient:
Merck Selbstmedikation GmbH	Kytta-Balsam® f	Comfrey root extract plus methyl nicotinate

H_{02a}: There are no differences between the treatment groups regarding the AUC of the VAS sum values on active standardised movement between Kytta-Balsam® f and placebo.

H_{02b}: There are no differences between the treatment groups regarding the AUC of the VAS sum values on active standardised movement between methyl nicotinate and placebo.

H_{02c}: There are no differences between the treatment groups regarding the AUC of the VAS sum values on active standardised movement between Kytta-Balsam® f and methyl nicotinate.

The first null hypothesis was tested by means of an ANOVA with the factors "treatment", "centre", and "treatment * centre interaction". Only if the treatment difference was significant to an α-level of 5 % the three elementary null hypotheses were tested by means of corresponding t-tests to the same α-level of 5 %. This multiple testing procedure controls the multiple α-level of 5 % (closed-test procedure).

The treatment effect was estimated by mean differences between the pairs of two treatments. Additionally, 95 % confidence intervals were determined.

All secondary efficacy and safety variables were analysed descriptively.

Summary – conclusions

Efficacy results

A total of 379 patients with conditions of acute upper or low back pain were randomly assigned to the double-blind treatment (Kytta-Balsam® f: n=163, methyl nicotinate: n=164, placebo: n=52). For efficacy, all enrolled patients were evaluated as the Full Analysis Set/intention-to-treat (FAS/ITT) population. After exclusion of 17 patients due to major protocol violations, a total of 362 patients (Kytta-Balsam® f: n=156, methyl nicotinate: n=156, placebo: n=50) were evaluated as Per-Protocol (PP) population.

Primary response criterion: The area-under-the-curve (AUC) of the Visual Analogue Scale (VAS) on active standardised movement values at Visits 1 to 4 (at actual measurement times) was markedly smaller in the Kytta-Balsam® f treatment group than in the methyl nicotinate and in the placebo group (ANOVA: $p<0.0001$). The pairwise comparisons of the mean AUCs of VAS sums on active standardised movement showed 27 % smaller values in favour of Kytta-Balsam® f compared to methyl nicotinate (6548.65 mm x h versus 8975.32 mm x h, i.e. a mean treatment effect of -2426.7 mm x h), and 50 % smaller values in favour of Kytta-Balsam® f compared to placebo (6548.65 mm x h versus 13052.40 mm x h, mean treatment effect -6503.8 mm x h). Methyl nicotinate alone reached a reduction of this variable of 31 % compared to placebo (8975.32 mm x h versus 13052.40 mm x h, mean treatment effect -4077.1 mm x h). All pairwise comparisons were statistically significant (t-test: $p<0.0001$). Kytta-Balsam® f proved superiority to the two other treatment arms.

Name of Sponsor/Company:	Name of Finished Product:	Name of Active Ingredient:
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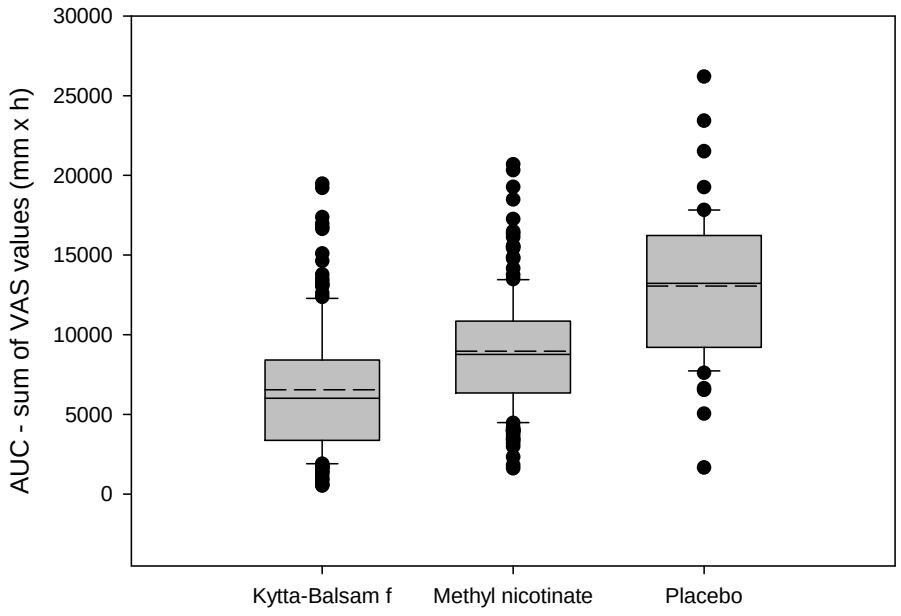
Figure 1: AUC of VAS sum on active standardised movement at actual measurement times (FAS/ITT)



Secondary response criteria: The pairwise comparisons of the AUC of VAS values on pain at rest at actual measurement times were 27 % lower, comparing Kytta-Balsam® f with methyl nicotinate (1782.60 mm x h versus 2457.32 mm x h, mean treatment effect -674.7 mm x h), and 54 % lower comparing Kytta-Balsam® f to placebo (1782.60 mm x h versus 3910.66 mm x h, mean treatment effect -2128.1 mm x h); all pairwise comparisons were again statistically significant (t-test: p=0.0005, p<0.0001). The AUC of the pressure algometry values in the trigger point was much higher in the Kytta-Balsam® f group, which means significantly less inducible pressure pain than in both comparator groups (64 % more compared to placebo and 19 % more compared to methyl nicotinate respectively, t-test: p<0.0001). Regarding the global assessment of efficacy by the patients, 94 % of patients in the Kytta-Balsam® f group considered the treatment effect after 5 days as "good" or "excellent", compared to 50 % in the methyl nicotinate and only 8 % in the placebo group.

Moreover, 17.3 % of patients in the placebo group needed to take paracetamol at least once as rescue medication, which was markedly more than in the treatment groups (Kytta-Balsam® f group: 9.2 %, methyl nicotinate group: 5.5 %). The average total dose of rescue medication was higher in the placebo group (9929 mg) than in the active treatment groups (Kytta-Balsam® f: 7400 mg, methyl nicotinate: 8889 mg) in the subgroup of patients who took rescue medications at least once.

The Oswestry Disability Index between Visit 1 and Visit 4 (FAS/ITT) improved by 80 % in

Name of Sponsor/Company:	Name of Finished Product:	Name of Active Ingredient:
Merck Selbstmedikation GmbH	Kytta-Balsam® f	Comfrey root extract plus methyl nicotinate

the Kytta-Balsam® f group (V1 24.85, V4 4.96) compared to 54 % in the methyl nicotinate group (V1 24.38, V4 11.3) and 22 % in the placebo group (V1 25.63, V4 20.06).

The Kytta-Balsam® f ointment was thus consistently more effective in the treatment of acute upper or low back pain than both comparators, while methyl nicotinate displayed a non-negligible effect as well. The results are clear-cut over the primary and all secondary variables in this clinical trial. Patients treated with the Kytta-Balsam® f had significant reductions in pain scores and were more satisfied with the treatment effect than those receiving only methyl nicotinate. A clear benefit of the combination product compared to the mono substance methyl nicotinate could thus be proven. Methyl nicotinate alone, however, proved to have a noticeable effect on the disease under investigation as well.

Safety results

All 379 patients enrolled, who received at least one dose of study medication, were included in the safety population (SAF). A total of 327 patients received at least one dose of one of the nicotinate-containing preparations (Kytta-Balsam® f: n=163, methyl nicotinate: n=164). Fifty-two patients received placebo. Adverse events (AEs) reports which included multiple descriptions were splitted into single AEs for analysis purposes and counted separately. Four drug related AEs were recurrent, meaning they were recorded more than once in the same patient.

AEs: A total of 19 patients (5 %) (Kytta-Balsam® f: n=10 (6.1 %), methyl nicotinate: n=9 (5.5 %), placebo: n=0) showed at least one AE during the course of the clinical trial (33 AEs in total).

Drug related AEs: 9 patients (2.4 %) showed at least one AE, which was classified as drug-related (Kytta-Balsam® f: n=3 (1.8 %), methyl nicotinate: n=6 (3.7 %), placebo: n=0). In total, 22 drug-related AEs were recorded.
The affected System Organ Classes (SOC) were “General disorders and administration site conditions” (n=17), Skin and subcutaneous tissue disorders (n=3) and Vascular disorders (n=2).

15 out of the 22 drug-related AEs were located at the application site (application site redness, application site itching, application site pruritus, application site allergy, application site reaction, application site swelling), and may reflect typical sensations caused by the topical application form of the treatments. It is remarkable that the majority of these drug related AEs occurred in the methyl nicotinate group (14 events), not in the Kytta-Balsam® f group (one event).

The 22 drug-related AEs (certain or probable) included also five recurrent events, and did all occur in the two treatment groups, none in the placebo-group (Kytta-Balsam® f: n=7, methyl nicotinate: n=15). The causality of the 7 drug-related AEs in the Kytta-Balsam® f group was assessed as “probably” drug-related. The 15 drug-related AEs in the methyl nicotinate group were classified as “certainly” drug-related. All above drug-related AEs were assessed as mild or moderate by the investigators.

Name of Sponsor/Company:	Name of Finished Product:	Name of Active Ingredient:
Merck Selbstmedikation GmbH	Kytta-Balsam® f	Comfrey root extract plus methyl nicotinate

SAEs: Two unrelated AEs were classified as serious: recurrent depressive disorder and pancreatic insufficiency. Both of these cases occurred in the Kytta-Balsam® f treatment group.

Conclusions

This report presents the data collected during a Phase III study to show superior efficacy of Kytta-Balsam® f ointment in patients with conditions of acute upper or low back pain in comparison to placebo. Measurements for pain were obtained by VAS evaluation of pain on movement and pain-at-rest values, pressure algometry, global assessment scores, Oswestry Disability Index, and finally by the amount of use of rescue medication.

A total of 379 patients were included and passed five days of treatment with trial medication of Kytta-Balsam® f, methyl nicotinate, and placebo, respectively. VAS values differed significantly between Kytta-Balsam® f, methyl nicotinate, and placebo.

The results strikingly demonstrate that Kytta-Balsam® f has a clinically relevant, favourable impact on the outcomes of patients suffering from acute upper or low back pain. Patients treated with Kytta-Balsam® f had statistically significant and clinically relevant reductions in pain scores and increases in tenderness, respectively. Significantly more patients in the Kytta-Balsam® f group reached a virtually pain-free status at Visit 4 compared to the placebo group as well as compared to the methyl nicotinate group, as documented by the results of the global assessment of efficacy by the patients and by the investigators. The results of this clinical trial are clear-cut and consistent across all primary and secondary efficacy variables.

Moreover, the results of this clinical trial show that methyl nicotinate contributes a good deal to the efficacy of the combination product Kytta-Balsam® f.

Overall, the safety evaluation did not reveal any additional risks and confirmed the good safety profile of Kytta-Balsam® f.

Kytta-Balsam® f proved to be a safe option for the treatment of patients with conditions of acute upper or low back pain.

Date of report

27 September 2011