Available online at www.sciencedirect.com
ScienceDirect
Phytomedicine 14 (2007) 2–10
Phytomedicine
www.elsevier.de/phymed

Efficacy of a comfrey root (Symphyti offic. radix) extract ointment in the treatment of patients with painful osteoarthritis of the knee: Results of a double-blind, randomised, bicenter, placebo-controlled trial

B. Grube, J. Grünwald, L. Krug, C. Staiger*

Merck Selbstmedikation GmbH, Rößlerstrasse 96, 64293 Darmstadt, Germany

Abstract

This randomised, double-blind, bicenter, placebo-controlled clinical trial investigated the effect of a daily application of 6 g Kytta-Salbe® f (3×2 g) over a 3 week period with patients suffering from painful osteoarthritis of the knee.

The two hundred and twenty patients examined consisted of 153 women and 67 men of an average age of 57.9 years. On average, the complaints relating to osteoarthritis of the knee had persisted for 6.5 years. Two hundred and twenty patients were included in the Full Analysis Set (FAS) and safety collective, 186 (84.5%) in the Valid Case Analysis Set (VCAS) collective.

In the course of the trial, the visual analog scale (VAS) total score (primary target value) in the verum group dropped by 51.6 mm (54.7%) and in the placebo group by 10.1 mm (10.7%). The average difference between the groups of 41.5 mm (95% confidence interval = 34.8 to 48.2 mm) or 44.0% is significant ($p < 0.001$). The significance is confirmed through the evaluation of the diary, the VCAS evaluation and the separate assessment of the two centres. This also applies to the separate assessment of the VAS total score following pain at rest and on movement.

The WOMAC (Western Ontario and McMaster Universities) total score (secondary target value) also improved similar to the VAS total score. At the end of the trial, a reduction by 60.4 mm (58.0%) was recorded for the verum group and a reduction of 14.7 mm (14.1%) for the placebo group. The average group difference of 45.7 mm (95% confidence interval = 37.1 to 54.3 mm) or 43.9% is significant ($p < 0.001$).

The difference between the treatment groups increased systematically and significantly, in parallel with the duration of the treatment. Thus, the superiority of the treatment with Kytta-Salbe® f over that with the placebo is proven, even by means of the multi-factorial multivariate analysis for repetitive measurements.

In respect of the explorative secondary target values SF-36 (quality of life), angle measurement (mobility of the knee), CGI (clinical global impression) and global assessment of efficacy by the physician and the patient, a significant superiority ($p < 0.001$ each) of the verum group over the placebo group was also proven.

The results suggest that the comfrey root extract ointment is well suited for the treatment of osteoarthritis of the knee. Pain is reduced, mobility of the knee improved and quality of life increased.

Keywords: Comfrey; Symphytum officinale; Double blind; Randomised; Placebo-controlled clinical trial; Osteoarthritis of the knee; Efficacy; Knee; Pain

*Corresponding author. Tel.: +6151 856 260; fax: +6151 856 203.
E-mail address: christiane.staiger@merck.de (C. Staiger).

0944-7113/$ - see front matter © 2006 Elsevier GmbH. All rights reserved.
doi:10.1016/j.phymed.2006.11.006

Introduction

Rheumatic disorders have different causes (inflammatory, infectious, degenerative, metabolic), are located at different parts of the body (joints, tendons, muscles, spine) and have different symptoms. Among them are several chronic tissue diseases and painful disorders of the locomotor system, including osteoarthritis of the joints.

Osteoarthritis characterises a primarily non-inflammatory, degenerative change of the structure of the cartilage and bones of one or more joints, involving an increasing deformation of the joint. On principle, all joints can be affected; frequently knee and hip joints, hands and the spine are affected. The frequency of osteoarthritis rises with age, approximately 80% of people over 75 are affected (Cooper, 1998). Osteoarthritis of the knee is described by the Deutsche Gesellschaft für Rheumatologie (German Rheumatology Association) as a disease primarily of the joint cartilage which coincides clinically with pain (pain upon walking, pain on exercise), limited movement and walking impairment, and can result in instability, false position and concomitant synovialitis (active athrosis) (Deutsche Gesellschaft für Rheumatologie, 2000).

The multitude of diseases and complaints is faced by an equally large number of therapeutic drug-based and non-drug based treatment options (Walker-Bone et al., 2000, Hunter and Felson, 2006). Due, in particular, to the symptoms: pain, joint stiffness and restriction of movement, patients seek therapeutical advice. As a result, symptomatic improvement represents an important therapeutic objective. The reduction of pain, the preservation and the restoration of the joint's function and thus the restoration of quality of life are therefore important target parameters in clinical trial (Förster, 2005).

The phytopharmaceutical drugs used in Germany are made, for instance, from willow bark and comfrey root. Since antiquity, the medicinal plant comfrey has been used both internally and externally in different forms of administration, for the treatment of a variety of diseases, e.g. bone fractures, wounds and ulcers (Englert et al., 2005).

In recent times, several clinical trials have proven the efficacy of comfrey in the treatment of distorsions, strains and sprains and other muscle and joint complaints (Koll et al., 2004; Predel et al., 2005; Kucera et al., 2005, Staiger, 2005).

In recent observation studies a reduction of pain of approx. 50% in respect of joint pain and a virtually complete decline of morning stiffness was observed after approximately two weeks of treatment with preparations containing comfrey root extract (Klingenburg, 2004; Tschaikin, 2004).

The efficacy of comfrey is essentially due to its anti-inflammatory, analgesic, granulation promoting and antiexsudative properties (Kommission E, 1990, Schmidtke-Schrezenmeier et al., 1992). Allantoin, rosmarinic acid and other hydroxycinamon acid derivatives as well as muco-polysaccharides are likely to be of critical importance for the pharmacodynamics of the root drug (Andres et al., 1989; Gracza et al., 1985).

Patients and methods

The clinical trial was performed in accordance with the ICH-GCP guidelines and the Declaration of Helsinki. The patients were informed prior to commencement of the trial and provided written confirmation of their participation in the trial.

This double-blind, randomised, bicenter, placebo-controlled trial involved a total of 220 patients with painful osteoarthritis of the knee. Both ambulatory centres were located in Berlin, Germany. Principal investigator was Barbara Grube, Kurfürstendamm 157/158, further investigator was Regina Busch, Weißenseer Weg 111. The CRO was Dr. Jörg Grünwald, Waldseeweg 6, Berlin, Germany. Biometry was done by Prof. Dr. Klaus-Dieter Wernecke, Wildensteiner Str. 27, Berlin, Germany.

The patients were randomly allocated to one of two treatment groups and received either the commercially available Kytta-Salbe® f or a placebo. Kytta Salbe® f contains comfrey root liquid extract (1:2, ethanol 60% V/V, 35%), the holder of the marketing authorisation is Merck Selbstmedikation GmbH, Darmstadt, Germany (Fachinformation Kytta-Salbe® f 2006). The extract specification allows an Allantoin content of 0.2–0.5% (m/m). A special procedure is applied to remove over 99% of the pyrrolizidine alkaloids contained in Symphytum officinale (specification: <0.35 ppm in the proprietary medicinal product).

The criteria for inclusion and exclusion are listed in Table 1. The patients applied a 6 cm long thread of verum or placebo ointment on the skin covering the knee joint three times a day and massaged this in. In the event of osteoarthritis of both knees, both knee joints were treated but only the knee that was more severely affected on admission to the trial was assessed. Treatment continued for a period of 21 days. Following a thorough initial examination during the first visit, clinical controls were performed after 6–8, 13–15 and 20–22 days (visits 2–4). In addition to the visits, patients logged the course of pain in a diary.

Primary and secondary target criterion

The primary target criterion was pain relief, namely the reduction of the total score from pain at rest and on movement, assessed by the patient using a 100 mm Visual Analogue Scale (VAS). The patient scores were

Table 1. Inclusion and exclusion criteria

Inclusion criteria

1. Age $\geqslant$18 years (women of reproductive potential should use effective contraceptive measures throughout the trial)
2. Patients provide their written agreement of their participation in the trial, understand the objective of the trial and agree to comply
3. Pain intensity of at least 40 mm on the 100 mm visual analogue scale (VAS) on inclusion

Exclusion criteria

1. Intake of steroids within the last 4 weeks prior to the start of the study
2. Intake of analgesics
3. Intake of systemic and/or local anti-inflammatory drugs prior to the start of the trial ($\leqslant$double the half-life)
4. Known hypersensitivity reaction to any of the components of the treatment
5. Severe systemic and organ disorder
6. Cancer as well as AIDS (HIV-positive)
7. Pregnancy and lactation
8. Alcohol abuse, addiction to therapeutic drugs and drugs of abuse
9. Currently participating or having participated in another clinical trial in the preceding 6 weeks
10. Compliance with and adherence to the protocol cannot be guaranteed due to language problems

measured in millimetres. Their estimations were rounded up/down to 5 mm.

The secondary target criterion was the improvement of the pain, stiffness and function symptoms, determined by means of the WOMAC test (Western Ontario and McMaster Universities). It is recognised as a reliable and valid tool for the recording of the symptoms and physical function restrictions of patients suffering from osteoarthritis of the hip and knee and comprises a total of 24 questions. Each question is presented as an analogue scale and answered by the patient through ticks. (Stucki et al., 1996; EMEA, 1998 CPMP/EWP/787/97).

Further concomitant variables

The restriction of movement of the knee joint was recorded at all visits through angle measurement (neutral-zero method). Excessive stretching and bending of the knee joint were measured using a plastic protractor (Hess, 1992; Meinecke and Gräfe, 2002).

To determine the quality of life, the patients answered the German version of the SF-36 questionnaire at visits 1 and 4 (Bullinger, 1995).

The investigators assessed the severity of the disease using the CGI questionnaire. On the basis of the Clinical Global Impression (CGI), the investigator can execute a benefit-risk assessment of the therapeutic treatment and determine the severity of the disease, the global change of condition and the efficacy index (ratio of effect and adverse drug reactions) (Guy, 1976).

In addition, the vital parameters (heart rate, blood pressure) and adverse events (AE) were registered. All AEs and their possible link with the trial medication were recorded. Compliance was tested by means of the amount of trial drug not used. At the end of the study a global assessment of efficacy and tolerance was made.

The exploratory analysis of the trial was scheduled prospectively, the patient collective determined prior to unblinding. The assessment was effected descriptively. The primary endpoint was the pre–post difference in VAS pain scores. A difference in the comparative branches of the trial (Kytta-Salbe® f versus Placebo) was analysed using the non-parametric two-sample test in accordance with the Mann–Whitney. The diary and the secondary target value were subjected to the same procedure.

Possible changes of clinical parameters when comparing individual visits were tested using the Wilcoxon test for related samples. All tests were performed with a type 1 error $\alpha = 5\%$ two-tailed or 2.5% one-tailed. The evaluation of results for the primary and secondary target value was effected both in accordance with the Full Analysis Set (FAS) principle and in accordance with the Valid Case Analysis Set (VCAS) principle. All patients for whom a signed informed consent form was available and who had received the investigational therapy were included in the FAS collective. The VCAS collective includes all patients treated per protocol.

Results

General information

A total of 220 patients (153 female, 67 male) were randomised and received trial medication after

providing written agreement of their participation in the trial (FAS and Safety population). The patients were of an average age of 57.9 years. The complaints relating to osteoarthritis of the knee had on an average persisted for 6.5 years.

There was no significant group difference with regard to distribution of sex, age, height, and body weight. 44 of the 220 patients (20%) suffered from osteoarthritis of the right knee, while in 33 the left knee was affected. A total of 143 patients (65.0%) suffered from osteoarthritis of both knees, while the right knee was more severely affected in 89 cases and the left knee in 54 cases. There was no significant difference between the groups.

A total of 34 patients, who did not observe the trial's term of 20–22 days or used 25% more or less of the trial medication, were excluded from the VCAS collective.

Efficacy

With regard to *total pain* (total of pain at rest and pain on movement), no significant difference ($p = 0.972$) between the groups in the FAS collective was discernible at the outset of the trial. A continual decline of pain was achieved in both groups; a decline of 51.6 mm (54.7%) in the verum group but only 10.1 mm (10.7%) in the placebo group by the end of the trial. In the verum group the reduction of pain was therefore five times that of the placebo group. The average group difference of 41.5 mm (95% confidence interval = 34.8 to 48.2 mm) corresponds with 44% and is significant ($p < 0.001$). In accordance with the primary target value the intensity of pain was reduced considerably in the verum group from an initial average of "moderate pain" (47.1%) to "mild pain" (21.3%). The difference between the treatment groups increased systematically, in parallel with the term of the treatment (Fig. 1).

With regard to *pain at rest*, again no significant difference ($p = 0.715$) between the groups in the FAS collective was observed at the outset of the trial. In the course of the trial, however, a significant decline of pain of 20.9 mm (56.6%) was recorded in the verum group, while the placebo group recorded a decline of only 4.6 mm (12.2%). The difference between the groups of 44.4% is significant ($p < 0.001$). The development during the clinical trial is depicted in Fig. 2.

With regard to *pain on movement*, the two groups in the FAS collective again did not vary significantly ($p = 0.734$) at the outset of the study. At the end of the trial, however, the verum group had undergone a reduction of pain on movement of 30.7 mm (53.5%) while the placebo group had only undergone a reduction of 5.6 mm (9.9%) (Fig. 3). The group difference to the baseline was significant ($p < 0.001$).

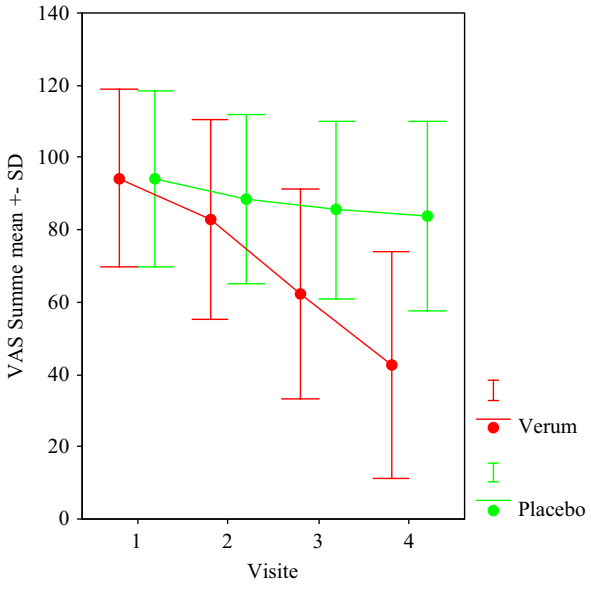

Fig. 1. VAS total score (Pain at rest and on movement).

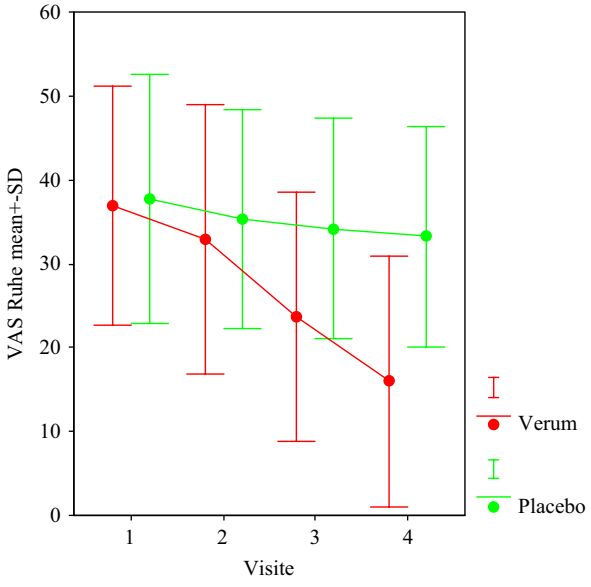

Fig. 2. VAS pain at rest.

The significant differences are always confirmed by the evaluation of the diary, the VCAS collective and the separate assessments of the two centres.

WOMAC and SF-36

With regard to the *WOMAC total score* (secondary target value), an improvement was found similar to the

VAS total score: At the end of the trial, a reduction of 60.4 mm (58.0%) was recorded for the verum group and a reduction of 14.7 mm (14.1%) for the placebo group. The average group difference amounted to 45.7 mm (95% confidence interval for the average value 37.1 to 54.3 mm) or 43.9% and is significant ($p<0.001$). The significance is also confirmed by the VCAS assessment and the separate assessment of the two centres. The division of the WOMAC by pain, stiffness and physical function also resulted in a significant superiority ($p<0.001$ each) of the verum over the placebo.

In the course of treatment a considerable improvement of the *quality of life* (SF-36) of the verum group over the placebo group was observed. The significant group difference was 33.9% ($p<0.001$) for physical function and 7% ($p = 0.006$) for mental function.

Mobility and CGI

With regard to the *restriction of movement*, patients in the verum group experienced a significant improvement ($p<0.001$) of knee flexion — on an average by 7.5 °C (7.0%). In the VCAS collective the group difference was 7.8 °. The *neutral-zero scaling* of the knee showed that patients, on an average, were unable to fully extend their knee (upper and lower leg form a straight line) at the outset of the trial. At the end of the trial, the verum group had undergone an average improvement of 2.0 °, while the placebo group had undergone an average deterioration of 0.4 °. The group difference is significant ($p<0.001$), in the VCAS collective as well.

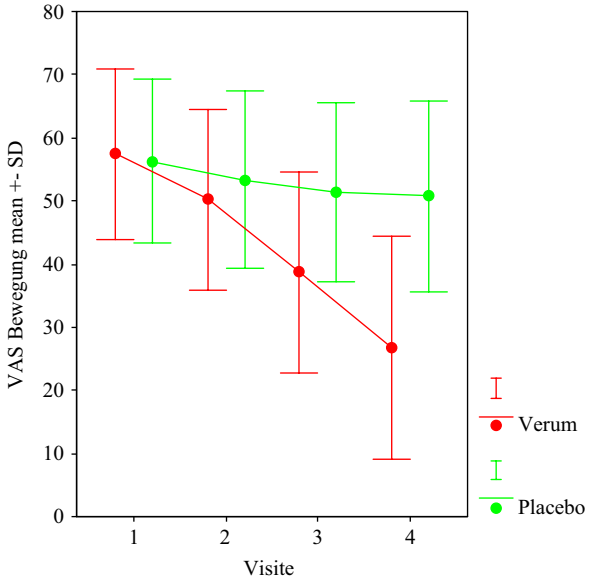

Fig. 3. VAS pain on movement.

The Clinical Global Impression (CGI) on the *severity of the disease* and on the change of the condition also resulted from the significant superiority ($p<0.001$) of the verum over the placebo. In the verum group 29.1% of patients exhibited a "slight", 52.7% a "clear" and 10.9% a "comprehensive" improvement, in compliance with the change of the condition, as expected. 7 patients no longer required treatment. In the placebo group 82.6% did not experience any improvement.

The assessments of the investigators and patients on *global efficacy* complied well with this. In the placebo group no effect was observed in respect of 85.5% (patient view) or 90.9% (physician's view) of patients, while 77.3% or 80.0% of patients in the verum group experienced a good effect (Table 2). At the end of the trial, 8 patients of the verum group were free from symptoms.

In summary, it can be noted that a highly significant superiority of the comfrey root extract ointment could be proven over the placebo (Table 3) in respect of both the primary and the secondary target value (VAS, WOMAC) and all concomitant variables (SF-36, angle measurement, CGI, global assessment of efficacy).

Safety

In the course of the clinical trial 22 patients (10.0%) experienced a total of 22 AEs. These related to 7 patients (6.4%) in the verum group and 15 patients (13.6%) in the placebo group. One patient in the placebo group discontinued the clinical trial at the third visit at her/his own request, due to ineffectiveness. All AEs were not

Table 2. Global assessment of efficacy (FAS collective)

	Verum ($n = 110$) n (%)	Placebo ($n = 110$) n (%)
Physician's judgement		
Symptom-free	8 (7.3)	0
Good effect	88 (80.0)	10 (9.1)
No effect	14 (12.7)	100 (90.9)
Patient's judgement		
Symptom-free	8 (7.3)	1 (0.9)
Good effect	85 (77.3)	15 (13.6)
No effect	17 (15.5)	94 (85.5)

Table 3. Summary of the changes achieved after three weeks and the group difference

Efficacy variable	Verum group		Placebo group		Group difference	
	Absolute	Relative (%)	Absolute	Relative (%)	Absolute	%
VAS (mm)						
Total score	51.6	54.7	10.1	10.7	41.5	44.0
Pain at rest score	20.9	56.6	4.6	12.2	16.4	44.4
Pain on movement score	30.7	53.5	5.6	9.9	25.1	43.6
WOMAC (mm)						
Total score	60.4	58.0	14.7	14.1	45.7	43.9
Pain score	12.1	58.2	2.7	12.9	9.4	45.3
Stiffness score	4.8	55.8	1.2	13.2	3.6	42.6
Function score	43.4	58.2	10.7	14.4	32.7	43.8
SF-36 (points)						
Physical function score	11.9	38.1	1.3	4.2	10.6	33.9
Mental function score	4.2	9.5	1.1	2.5	3.1	7.0
Angle measurement (°)						
Knee flexion	7.5	7.0	0	0	7.5	7.0
Extension of the knee (neutral-zero)	−2.0	−65.8	0.4	19.6	2.4	85.4

serious and did not represent an adverse drug reaction (ADE). There was no significant difference between the groups ($p = 0.072$).

At the end of the trial (visit 4), a global assessment of tolerance was performed by the physician and the patient using a scale. Values ranging from "very good", "good", "moderate" and "bad" could be given. Only "good" and "very good" ratings were issued: In the verum group the "very good" ratings predominated (73.6%, physician and patient) and in the placebo group, the "good" ratings (50.9% physician and 53.6% patient).

Discussion

Osteoarthritis of the knee is among the most frequent degenerative joint diseases within the rheumatic disorders. This is due primarily to the complexity of the knee's structure, the high level of stress it is under from body weight but also to the increasing age of the population of industrialised countries. The primary, conservative treatment of osteoarthritis of the knee is symptomatic, as monotherapy or in combination with physical, physiotherapeutical and drug-based measures.

The most important pillars of drug therapy are pain-relieving and anti-inflammatory drugs, i.e. non-steroidal anti-inflammatory drugs (NSAID) and, as a new variant of NSAID the COX-2 inhibitors, which are considered to be more easily tolerated by the stomach (Sweetman, 2004; Hardman and Limbird, 1996). In severe cases cortisone with a strong antiphlogistic action is injected directly into the knee. Phytopharmaceuticals such as comfrey root extract ointment, which are applied topically, have the benefit that they are applied targetedly and have fewer to no adverse drug reactions. The fact that the active substance actually reaches the target area when applied topically was proven e.g. for diclofenac-diethylammonium emulgel (Gondolph-Zink and Gronwald, 1996).

This clinical trial was characterised by the careful selection of patients (strict observance of the inclusion and exclusion criteria), a high patient number, good patient management, management of a pain diary and good compliance. For a good assessment of efficacy of the trial drug in comparison to the placebo, a homogeneous initial situation in the two groups is important. This condition was fully met with 220 trial participants with painful osteoarthritis of the knee in this comparative trial.

The primary target criterion was fully met. In the pre/post comparison (1st/4th visit), the VAS total score for the verum group dropped by an average of 54.7% over three weeks. In observational studies with Kytta-Salbe® f or Kytta-Balsam® f, involving patients with painful joints and muscles, Tschaikin (2004) and Klingenburg (2004) noticed a reduction of pain of approximately 46% (patient query) after an average treatment time of 12 days. In a clinical trial with diclofenac emulgel (over Ibuprofen oral) that is comparable with this clinical trial with regard to patient age, duration of therapy and VAS initial situation, patients from the diclofenac group with an activated osteoarthritis of the finger joints achieved a reduction of pain (VAS total score) of 41.6% (Zacher et al., 2001).

The result achieved in this clinical trial relating to the primary target value is at least comparable with the above results.

In the pre/post comparison (1st/4th visit) an average group difference of 16.4 mm (44.4%) was determined in respect of pain at rest and a value of 25.1 mm (43.6%) in respect of pain on movement. A change of $\geqslant 20$ mm is considered to be clinically relevant (Biegert, 2003). With an average change of 20.8 mm (an average of pain at rest and on movement or VAS total score divided by 2) this criterion is met, i.e. not only has a statistically relevant trial result been achieved but one that is also clinically relevant (Kelly, 1998).

The extent of pain reduction is, on top of that, at least comparable with the results of other trials. In a clinical trial with orally administered willow bark dry extract and diclofenac (daily dose 1.36 g or 100 mg) to patients with osteoarthritis of the hip and knee (Biegert, 2003), an average difference between diclofenac and the placebo of 18.4 mm (patient assessment) or 7.6 mm (physician assessment) was achieved over a trial period of 42 days; the effect of willow bark dry extract was not different to that of the placebo. In a clinical trial in which comfrey root extract was compared with diclofenac in the treatment of ankle distortions, the clear reduction of pain under topical therapy was again confirmed (Predel et al., 2005). It was additionally proven that the plant-based active substance was at least as effective as the chemical substance; there were even clear indications of the superior efficacy of the phytotherapeutic topical agent.

In this trial, the percentage of change of the WOMAC total score (secondary target value) was analogue to that of the primary target value. In the pre/post comparison the verum group experienced a reduction of 58.0%, while the placebo group experienced a reduction by 14.1%. The group difference (43.9%) is significant ($p<0.001$). Thus, the secondary target criterion is fully met.

In the Biegert trial (Biegert, 2003) a reduction of pain of 16.3% was achieved with willow bark dry extract after 28 days of the trial, of 44.0% with diclofenac and of 10.0% with the placebo, while only the difference between diclofenac and the placebo was significant ($p<0.001$). Although, the application in this clinical trial was topical and not oral, a result was achieved that was at least comparable with that achieved by diclofenac. On division of the WOMAC total score into the sub-scores pain, stiffness and physical function it was additionally proven that the sub-scores changed equally.

With regard to the primary and secondary target value, particular attention should be paid to the fact that a continual pain reduction was achieved in the course of the trial. As early as from the second visit onwards there was a significant group difference ($p<0.001$) of the verum group to the baseline. At the end of the trial, the level of pain reduction achieved in the verum group was 5 times (in respect of VAS) or 4 times (in respect of WOMAC) higher than the level of pain reduction achieved in the placebo group. With regard to the primary and secondary target value, a multivariate covariance analysis and a VCAS assessment were performed additionally and checked for centre effect. In all cases the statements on the significance of the results did not change.

Regarding SF-36, the patients of the verum group displayed a significant improvement of quality of life over the placebo group at the end of the trial. The group difference with regard to "physical function" and "mental function" of 33.9% or 7.0% is significant ($p<0.001$ or $=0.006$). In respect of "physical function", Biegert (2003) describes the following group differences in comparison with the placebo (in %) after 42 days: willow bark dry extract 7.6 ($p=0.236$), diclofenac 25.8 ($p<0.001$). With regard to "mental function" no therapeutic effect was proven. The results of this clinical trial in respect of SF-36 are thus at least comparable with those of the Biegert trial concerning diclofenac.

In this clinical trial the Clinical Global Impressions (CGI) and the global assessments of the investigators and patients underscore the VAS, WOMAC and SF-36 results on efficacy. In all cases a significant superiority ($p<0.001$ each) of the verum over the placebo was proven: with regard to the improvement of the level of severity and the condition of the disease, with regard to the efficacy index and in the view of both the investigator and the patient. Eight patients of the verum group were symptom-free at the end of the trial, seven no longer required treatment. These results must be rated highly as osteoarthritis of the knee is a chronic disease (Towheed and Hochberg, 1997).

The comfrey root extract ointment proved to be very well tolerated and free of adverse effects; the application of Kytta-Salbe® f did not result in any adverse drug reactions. This confirms the results of previous studies (Predel et al., 2005; Koll et al., 2004; Tschaikin, 2004; Klingenburg, 2004; Staiger, 2005). There was only one discontinuation of the trial due to ineffectiveness among the 22 AEs (7 VG, 15 PG) that occurred and this occurred in the placebo group. Clinical parameters (vital parameters) were not affected by the clinical trial. On the basis of the results achieved, it can be deduced that Kytta-Salbe® f is well suited for the therapy of osteoarthritis of the knee. Such therapy reduces pain, improves mobility of the knee and increases quality of life.

Conclusions

The fact that the verum medication is significantly superior to the placebo medication with regard to all target values proves the therapeutic efficacy of the

comfrey root extract ointment in the treatment of painful osteoarthritis of the knee.

At the end of the trial, pain in the verum group had, on an average, reduced five times more than in the placebo group. The primary target value (VAS total score) improved by 54.7% in the verum group, but only by 10.7% in the placebo group.

With regard to the secondary target value (WOMAC total score) verum proved to be four times more effective than the placebo. In the verum group the improvement was 58.0%, in the placebo group, however, it was only 14.7%.

The intensity of pain, when applying Kytta-Salbe® f, on an average reduced from "moderate pain" initially to "mild pain" at the end of the trial. This related both to pain at rest and pain on movement.

Compared to information and clinical trials described in literature, the trial results achieved are of clinical relevance. In comparison with the results of this clinical trial, clinical trials with willow bark dry extract and diclofenac showed that the results achieved by comfrey root extract were at least as good if not better than those with diclofenac and clearly superior to the results achieved with willow bark dry extract.

The good benefit-risk ratio also bears particular emphasis, as not only the excellent and high-level of efficacy are of particular importance to users but also the lack of adverse drug reactions.

This clinical trial has proven that the application of topical comfrey root extract is a sensible treatment option in osteoarthritis of the knee.

References

Andres, P., Brenneisen, R., Clerc, J.T., 1989. Relating antiphlogistic efficacy of dermatics containing extracts of symphytum-officinale to chemical profiles. Planta Med. 55, 66–67.

Biegert, C., 2003. Eine randomisierte, kontrollierte klinische Studie zur Wirksamkeit und Verträglichkeit eines standardisierten Weidenrindenextraktes in der Behandlung von Cox- und Gonarthrosen. Ph.D. Thesis. Faculty of Chemistry and Pharmacy, University of Tübingen, Germany.

Bullinger, M., 1995. German Translation and psychometric testing of the SF-36 health survey: preliminary results from the IQOLA project. Soc. Sci. Med. 41, 1359–1366.

Cooper, C., 1998. Osteoarthritis: Epidemiology. In: Klippel, J., Dieppe, P., Mosby (Eds.), Rheumatology. London, pp. 2.1–2.8.

Deutsche Gesellschaft für Rheumatologie, 2000. Qualitätssicherung in der Rheumatologie—Coxarthrose—Gonarthrose. 〈http://www.rheumanet.org/qs_dgrh/default.htm〉.

EMEA, 1998. CPMP/EWP/784/97. Points to consider on clinical investigation of medicinal products used in the treatment of osteoarthritis.

Englert, K., Mayer, J.G., Staiger, C., 2005. Symphytum officinale L. Der "Beinwell" in der europäischen Pharmazie- und Medizingeschichte. Z. Phytother. 26, 158–168.

Fachinformation, 2006. Kytta-Salbe®f. Merck Selbstmedikation GmbH. January 2006.

Förster, K.K., 2005. Planung, Durchführung und Publikation klinischer Studien bei Arthrose—eine kritische Betrachtung. Orthopädische Praxis 41 (3), 107–114.

Gondolph-Zink, B., Gronwald, U., 1996. Wirkstoffkonzentrationen in artikulären und periartikulären Geweben des Kniegelenkes nach kutaner Anwendung von Diclofenac-Diethylammonium Emulgel. Akt. Rheumatol. 21, 298–304.

Gracza, L., Koch, H., Löffler, E., 1985. Isolierung von Rosmarinsäure aus Symphytum officinale und ihre antiinflammatorische Wirksamkeit in einem In-vitro-Modell. Über biochemisch-pharmakologische Untersuchungen pflanzlicher Arzneistoffe. Arch. Pharm. 318, 1090–1095.

Guy, W. (Ed.), 1976. Clinical Global Impressions. ECDEU Assessment Manual for Psychopharmacology. National Institute of Mental Health, Rockville, MD.

Hardman, J.G., Limbird, L.E. (Eds.), 1996. Goodman & Gilman's The Pharmacological Basis of Therapeutics. McGraw-Hill, New York.

Hess, H., 1992. In: Begutachtung der Haltungs- und Bewegungsorgane. Hrsg.: G. Rompe u. A. Erlenkämper, 2. überarbeitete und erweiterte Auflage. Georg-Thieme-Verlag, Stuttgart.

Hunter, D.J., Felson, D.T., 2006. Osteoarthritis. BMJ 332, 639–642.

Kelly, A.M., 1998. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Academic Emergency Medicine 5, 1086–1090.

Klingenburg, S., 2004. Wärmendes Topikum mit Symphytum officinale. Erfahrungsheilkunde 6, 350–354.

Koll, R., Buhr, M., Dieter, R., Pabst, H., Predel, H.G., Petrowicz, O., Giannetti, B., Klingenburg, S., Staiger, C., 2004. Efficacy and tolerance of a comfrey root extract (Extr. Rad. Symphyti) in the treatment of ankle distorsions: results of a multicenter, randomized, placebo-controlled, double-blind study. Phytomedicine 11, 470–477.

Kommission E, 1990. Monographie Symphyti radix (Beinwellwurzel). Bundesanzeiger 318.

Kucera, M., Barna, M., Horácek, O., Kovarikova, J., Kucera, A., 2005. Topical symphytum herb concentrate cream against myalgia: a randomized controlled double blind clinical study. Adv. Ther. 22, 681–692.

Meinecke, R., Gräfe, K., 2002. Bewegungs-, Längen- und Umfangsmessungen. Neutral-Null-Durchgangsmethode. Lau-Verlag GmbH, 4.überarbeitete Auflage, Reinbeck.

Predel, H.G., Giannetti, B., Koll, R., Bulitta, M., Staiger, C., 2005. Efficacy of a comfrey root extract ointment in comparison to diclofenac in the treatment of ankle distortions: results of an observer-blind, randomized, multicenter study. Phytomedicine 12, 707–715.

Schmidtke-Schrezenmeier, G., Reck, R., Gerster, G., 1992. Behandlung der nichtaktivierten Gonarthrose. Besserung durch ein Phytotherapeutikum. Therapiewoche 42, 1322–1325.

Staiger, C., 2005. Beinwell – eine moderne Arzneipflanze. Z. Phytother. 26, 169–173.

Stucki, G., Meier, D., Stucki, S., Michel, B.A., Tyndall, A.G., Dick, W., Theiler, R., 1996. Evaluation einer deutschen Version des WOMAC (Western Ontario und McMaster Universities) Arthroseindex. Z. Rheumatol. 55, 40–49.

Sweetman, S.C. (Ed.), 2004. Martindale – The Complete Drug Reference, 34th ed. Pharmaceutical Press, London.

Towheed, T.E., Hochberg, M.C., 1997. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology. Semin. Arthritis Rheum. 26, 755–770.

Tschaikin, M., 2004. Extrakt aus Symphytum officinale. Wirksamkeit und Verträglichkeit bei topischer Anwendung. Naturheilpraxis 57, 576–578.

Walker-Bone, K., Javaid, K., Arden, N., Cooper, C., 2000. Medical management of osteoarthritis. BMJ 321, 936–940.

Zacher, J., Burger, K.J., Färber, L., Gräve, M., Abberger, H., Bertsch, K., 2001. Topisches Diclofenac Emulgel versus orales Ibuprofen in der Therapie der aktivierten Arthrose der Fingergelenke (Heberden- und/oder Bouchard-Arthrose). Doppelblinde, kontrollierte, randomisierte Studie. Akt. Rheumatol. 26, 7–14.