# Efficacy and Safety of 5% Ibuprofen Cream Treatment in Knee Osteoarthritis. Results of a Randomized, Double-Blind, Placebo-Controlled Study

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*ABSTRACT.* ***Objective.*** To investigate the efficacy and safety of a cream containing 5% ibuprofen (Dolgit® cream) in primary knee osteoarthritis (OA) in a double-blind, randomized, placebo-controlled, parallel-group study using an adaptive sequential design.

***Methods.*** Patients of both sexes aged 40–75 years, with a visual analog scale (VAS) score for pain on motion of ≥ 40 mm, a Lequesne index score of 5–13, and a Kellgren-Lawrence radiographic score grade II–III were enrolled between January 2001 and July 2001. Study medication was applied in a 10-cm strip tid for 7 days on the more painful knee. Each strip of the active treatment contained approximately 200 mg ibuprofen. The primary efficacy variable was the treatment response rate compared between the 2 groups. Response was defined as a reduction of pain on motion, self-assessed on VAS, of ≥ 18 mm or ≥ 23% compared to baseline.

***Results.*** The second interim analysis scheduled post-inclusion of 2 × 25 patients revealed a response rate of 21 patients (84.0%) in the ibuprofen group and of 10 patients (40.0%) in the placebo group ($p = 0.0015$). The study was then terminated. All secondary endpoints such as pain at rest, overall pain, Lequesne index, and global assessment of efficacy also showed the superiority of ibuprofen. No adverse event was recorded.

***Conclusion.*** The efficacy and safety of ibuprofen cream in treatment of primary knee OA were statistically significant and clinically relevant compared to placebo. (J Rheumatol 2004;31:565–72)

*Key Indexing Terms:*
IBUPROFEN TOPICAL TREATMENT KNEE OSTEOARTHRITIS

Pharmacological treatment of rheumatic diseases with oral nonsteroidal antiinflammatory drugs (NSAID) like ibuprofen is a current therapy, while the use of topical NSAID is less well established[1,2]. The efficacy of a cream containing 5% ibuprofen (Dolgit®) in the treatment of rheumatic diseases has been examined in several clinical studies[3-7]. This ibuprofen cream, marketed in many countries, has been in use for 20 years with good success, including use for accidental and sports injuries.

In addition to evidence gathered over many years of experience with the use of this drug, its safety has been assessed in postmarketing surveillance studies, especially in 2 projects[8,9] involving almost 40,000 patients. The rate of side effects has been very low, averaging around 2% and comprising mainly reversible allergic skin reactions. While systemic side effects are extremely rare, gastrointestinal (GI) discomfort and bronchospasm have been described in predisposed patients[8,9].

But the efficacy is still controversial, mainly due to insufficient study data. Apart from the obligation to use a randomized and controlled trial design, international guidelines have now to be taken into account. A new study was therefore planned and conducted in accord with the European Committee for Proprietary Medicinal Products (CPMP) guideline[10] and the guideline of the International Conference on Harmonisation[11].

## MATERIALS AND METHODS

This study investigated the efficacy and safety of a 5% ibuprofen cream (Dolgit®) versus placebo cream in a typical musculoskeletal disease. The study was designed as a prospective, double-blind, randomized, placebo-controlled, parallel-groups trial in primary knee osteoarthritis (OA) with 3 adaptive interim analyses. The study was performed at the Postgraduate Medical School in Prague, Czech Republic.

*Study population.* Patients of both sexes aged ≥ 40 and ≤ 75 years had to meet the following inclusion criteria for enrolment into the study: (1) primary knee OA, unilateral or bilateral (International Classification of Disease-10: M17.0/M17.1); chronic and decompensated, i.e., painful, but nonactivated and without effusion or swelling, diagnosed according to the classification criteria of the American College of Rheumatology[12]: (i) knee pain on most days (> 15 days) of the preceding month, (ii) radiographic osteophytes,

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grade II or III on the Kellgren-Lawrence OA severity score[13]; (2) score for pain on motion of ≥ 40 mm on a 100 mm visual analog scale (VAS); (3) total score ≥ 5 and ≤ 13 (i.e., moderate to severe) on the Lequesne algofunctional index[14]; (4) patients provided signed informed consent.

Patients were not enrolled if they met one of the following exclusion criteria: (1) secondary OA; (2) obesity (body mass index ≥ 30 kg/m$^2$); (3) chronic painful disease of the hip or the ankle joint; (4) allergic diathesis, bronchial asthma, or known hypersensitivity to NSAID; (5) eczematous skin eruption; or (6) any physiotherapy.

The study was conducted in accord with the Declaration of Helsinki[15] and the local legislation. The protocol, information for patients, and the informed consent form were presented for approval to the ethics committee in Prague and accepted.

*Interventions*. Four visits were scheduled (Day 0, Day 1, Day 4, and Day 8). The first 2 visits could be held on the same day provided that no washout period was necessary. When the patient had previously been treated with drugs having a therapeutic effect on the knee joint, a washout period of 1 to 60 days was mandatory, depending on the duration and type of pretreatment. The active treatment phase was scheduled to last 7 days.

Patients fulfilling all inclusion criteria were assigned a 100 g tube of study medication in chronological order. The investigator applied a strip of cream on the more painful knee to demonstrate to the patient the mode of application: one 10-cm strip of cream 3 times daily, always applied on the same knee joint more severely affected at the beginning of treatment (equivalent to 3 × 4 g of cream and 3 × 200 mg ibuprofen for the active sample). The cream had to be massaged in until it had been absorbed completely by the skin. For dose standardization purposes, patients also received a spatula with a 10 cm mark as an application aid. Before the visits on Day 4 and Day 8 patients also had to apply the cream as usual in the morning.

Any concomitant treatment with other topical, intraarticular or systemic steroidal or nonsteroidal antirheumatics, analgesics, or disease modifying antirheumatic drugs was not allowed. However, it was assured that patients received any medically necessary treatment (i.e., antihypertensives). During the washout period, peripherally-acting oral analgesics such as paracetamol were allowed as rescue medication up to 2 days before start of the study treatment.

*Outcome measures*. The primary efficacy variable of the study was the reduction (response) of pain on motion assessed by the patient on a 100 mm VAS. Response was defined as a reduction of ≥ 18 mm or ≥ 23% from baseline to last observation.

Secondary variables of efficacy were: (1) mean changes in pain on motion, pain at rest, and overall pain from baseline to last observation; (2) improvement of algofunctional disability assessed on the Lequesne index; (3) global assessment of efficacy by patient and investigator; (4) frequency, type, and severity of adverse events; and (5) global assessment of safety by patient and investigator.

The outcome measures were recorded as follows:

*Assessment of pain on motion on VAS*. The patient's self-assessment of pain on motion in the knee joint, i.e., the pain experienced on movement in the more painful/treated knee, during the 24 h preceding the visit days, was elicited using a standardized approach and recorded on a VAS. The scale consisted of a 100 mm horizontal line; the left end of the scale (0) represented "no pain" and the right end (100 mm) "unbearable pain."

*Assessment of pain at rest and overall pain on VAS*. The patient's assessment of pain at rest and of overall pain in the more painful/treated knee was recorded on a VAS in the same manner and at the same time as described above for pain on motion. Overall pain was defined as the sum of all pain scores in the more painful knee joint: pain on motion, pain at rest, pain on pressure, pain in standing position, and pain after rising from a resting position.

*Lequesne index*. The Lequesne algofunctional index for knee OA contains questions designed to assess the following symptoms: pain, maximum distance walked, and activities of daily living. The theoretical maximum score is 24. Patients with a score < 5 or ≥ 14, i.e., with minor or extremely severe disability, could not be included in the study.

*Overall assessment of efficacy*. At the final visit (Day 8) the patient and the investigator gave an overall assessment of efficacy of the study medication on a verbal rating scale (VRS) of 5 categories (4 = very good, 3 = good, 2 = moderate, 1 = poor, 0 = none or worse).

*Overall assessment of safety*. At the final visit (Day 8) the patient and investigator gave an overall assessment of safety of treatment with the study medication on a verbal rating scale of 5 categories (4 = very good, 3 = good, 2 = moderate, 1 = poor, 0 = bad).

*Randomization and blinding*. Randomization was performed by the biostatistician of the appointed contract research organization, ClinResearch, using SAS randomization software (v. 6.12). The randomization ratio was 1:1 in blocks of 6.

Patient numbers corresponding to the randomization numbers were printed on the tube labels. Treatments were assigned by the investigator to the patients in strictly ascending order only after enrolment on Day 1.

The study was carried out on a double-blind basis. The data management personnel also remained blinded to group assignment until a blind review was performed before decoding. To ensure blind conditions, the placebo cream was identical to the ibuprofen cream in the quality and quantity of inert ingredients, color, odor and consistency.

*Statistical methods and sample size*. The study was planned with a 4-stage group sequential adaptive design with sample size adjustments after the 3 scheduled interim analyses[16,17]. Adaptive designs have the potential to adjust sample size midstream when the assumed effect was over- or underestimated. This was the reason we decided to use an adaptive design. The study was stopped after 50 patients because the null hypothesis was already rejected. The null hypothesis $H_0$ was that the response rate during treatment with ibuprofen cream is equal to that observed under placebo cream. The alternative hypothesis $H_1$ was that the response rate during treatment with ibuprofen cream is higher than that observed with placebo cream.

At the first interim analysis after observation of a minimum of 12 patients in each treatment group, the null hypothesis could be rejected and the study stopped if the one-sided test for difference between ibuprofen cream and placebo cream yielded a p value < 0.00410. Otherwise the study would be continued with a recalculated sample size, based on the effect size calculation of the interim analysis. At the second confirmatory analysis the null hypothesis could be rejected again if the test statistic based on the inverse normal method exceeded the critical value 2.4121. Analogous test decisions were to be made in the third interim analysis and the final

analysis. This procedure would preserve the overall Type I error rate of $\alpha = 0.025$. For confirmatory hypothesis testing at the interim analysis and the final analysis, Fisher's exact test for comparing rates (one-sided) was used.

All other group comparisons were hypothesis-generating, i.e., p values resulting from statistical tests were to be interpreted in the exploratory sense only. Standard descriptive summary statistics should be used to summarize the demographic and baseline data.

Two data sets were defined for the efficacy analysis, the intention-to-treat sample (ITT) and the adherence-to-protocol sample (ATP). The ITT sample was to include all patients who had been randomized and had received at least one dose of study medication. The ATP sample comprised patients who did not violate the selection, inclusion, and exclusion criteria and who were treated according to the study protocol. The confirmatory test for difference as well as the interim effect size calculations were based on the ITT individual last observation carried forward change from baseline.

The analysis of safety variables was based on all patients treated with study medication.

Statistical analysis was carried out by ClinResearch GmbH, Cologne, Germany, using SAS. The recommendations of the International Conference on Harmonisation guidelines E9 and E10 were followed[18,19].

## RESULTS

Figure 1 shows the flow of patients through each phase of the study. Altogether 50 patients were screened, correctly randomized, and enrolled into the study. The recruitment period lasted from January 2001 until July 2001. All 50 randomized patients were treated with at least one dose of study medication and those who had at least one post-baseline value of VAS assessment of pain on motion could be included in the intent-to-treat population.

The data for one patient showed a major protocol deviation: one female patient receiving ibuprofen had a grade IV radiographic Kellgren-Lawrence OA severity score. This patient's data were therefore excluded from the ATP analysis.

The safety analysis was based on the data of all 50 patients who received at least one application of the study medication.

*Demographic and other baseline characteristics.* The majority of patients, i.e., 39 of the 50 patients included in the ITT analysis, were women (78.0%). The proportion of women in the treatment groups ranged from 23/25 (92.0%) in the ibuprofen group to 16/25 (64.0%) in the placebo group. This variation, however, is considered to be within the range to be expected with random assignment to the groups.

The other demographic data revealed no evidence of systematic differences between treatment groups. Table 1 shows the distributions of sex, age, weight, height, body mass index, and race in the treatment groups.

*Table 1.* Demographic data (ITT population). Data are mean (SD).

| Characteristic | Ibuprofen Group, n = 25 | Placebo Group, n = 25 |
|---|---|---|
| Male, n | 2 | 9 |
| Female, n | 23 | 16 |
| Age, yrs | 67.0 (±6.7) | 66.9 (±7.5) |
| Height, cm | | |
| Male | 181.5 (±4.9) | 179.0 (±4.6) |
| Female | 164.8 (±4.9) | 164.8 (±5.0) |
| Weight, kg | | |
| Male | 79.5 (±0.7) | 83.8 (±5.2) |
| Female | 71.3 (±7.8) | 69.8 (±6.7) |
| Body mass index | 26.1 (±2.6) | 25.9 (±2.2) |

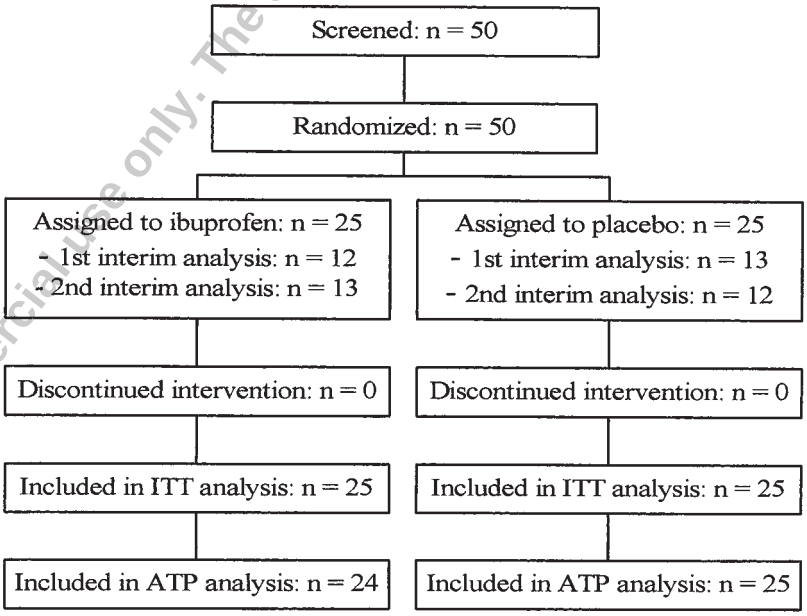


*Figure 1.* Disposition of patients.

The Kellgren-Lawrence radiographic severity score as an objective measure of the severity of OA showed a comparable result in the 2 groups (Table 2).

With one exception, all patients had bilateral knee OA. There were 34% of patients with concomitant diseases (40% in the active group, 28% in the placebo group), arterial hypertension being the most frequent condition. Neither concomitant diseases nor concomitant medication differed markedly between the groups.

Homogeneity of the 2 groups was also assured for all pain assessment measures and the Lequesne index. The corresponding mean baseline scores are given in Tables 3 and 4.

*Primary efficacy variable*. The first interim analysis was performed on 25 patients who completed Day 8. No patient terminated the study prematurely.

All 12 patients who received ibuprofen were responders, in contrast to only 2 of the 13 patients given placebo. As $p < 0.0001$ (Fisher's exact test, one-tailed) was lower than the stopping criterion ($p_1 = 0.0041$), the null hypothesis could have been rejected and the study discontinued. However, the 95% repeated confidence interval was 0.376, 0.970, and thus had a precision of only 59.4%. Since the number of patients included in the first interim analysis was relatively small, the "blind" advisory board (according to ICH E9[18]) decided to continue with the study and to perform a second interim analysis. Further, the rate of male patients (only 2, i.e., less than 10%) was too low, since a rate of at least 25% was required to obtain a more representative study population.

The second interim analysis was performed on 50 patients, 25 treated with ibuprofen and 25 with placebo. Again, no patient terminated the study prematurely.

Treatment compliance was measured by weighing the tubes at each visit. No compliance violations concerning consumption occurred.

At the end of the study period, 21 patients (84.0%) in the ibuprofen group were responders, but only 10 patients (40.0%) in the placebo group. This finding was highly significant ($p < 0.0001$; Fisher's exact test, one-tailed). The 95% RCI was 0.098, 0.690, again with a precision of about 59%, but this time based on a larger sample size. The second objective, a higher proportion of at least 25% of male patients, had also been achieved.

As the confirmatory objective of the study was already reached at the first interim analysis and was further confirmed with a larger sample size, the advisory board decided to terminate the study after the second interim analysis. Table 5 presents the results of the 2 interim analyses.

The results of the ATP analysis of the primary endpoint revealed an almost identical, statistically significant result of $p < 0.0001$ (Fisher's exact test, right), and hence no relevant deviations compared with those of the ITT analysis.

All responses in the ibuprofen group were already obtained at Day 4, whereas at that time only 4 responses were reported for the placebo group (Figure 2).

*Secondary endpoints. Pain assessment on the VAS: pain on motion, pain at rest, overall pain*. In both treatment groups, the mean baseline values of all VAS pain qualities, i.e., pain on motion, pain at rest, and overall pain, were completely comparable: the slight difference of roughly 3.5 mm between the baseline values for pain on motion was not statistically significant.

The development of pain on motion, pain at rest, and overall pain during the course of the study on treatment with

*Table 2*. Kellgren-Lawrence severity scores.

| Grade | Ibuprofen Group, n = 25 n (%) | Placebo Group, n = 25 n (%) |
|---|---|---|
| I | 0 (0.0) | 0 (0.0) |
| II | 14 (58.3) | 18 (72.0) |
| III | 10 (41.7) | 7 (28.0) |
| IV | 1 (2.0) | 0 (0.0) |

*Table 3*. Mean pain on motion, pain at rest, and overall pain, 100 cm VAS (baseline, after 4 days, after 8 days).

| Observation | Ibuprofen Group, n = 25 mean (SD), mm | Placebo Group, n = 25 mean (SD), mm |
|---|---|---|
| | Pain on Motion | |
| Day 1 (baseline) | 63.08 (±7.27) | 59.48 (±7.98) |
| Day 4 | 41.48 (±10.19) | 53.76(±9.55) |
| Day 8 | 31.72 (±15.01) | 52.56 (±13.02) |
| | Pain at Rest | |
| Day 1 (baseline) | 52.52 (±4.40) | 52.48 (±7.28) |
| Day 4 | 31.16 (±9.04) | 47.20 (±13.43) |
| Day 8 | 29.00 (±13.62) | 42.16 (±14.70) |
| | Overall Pain | |
| Day 1 (baseline) | 52.64 (±6.18) | 54.76 (±5.85) |
| Day 4 | 36.28 (±10.48) | 48.84 (±11.82) |
| Day 8 | 30.04 (±12.75) | 42.44 (±13.41) |

*Table 4*. Lequesne index algofunctional impairment score, all visits. Data are mean scores (± SD).

| Baseline Values | Ibuprofen, n = 25 | Placebo, n = 25 | Mean Decrease, %, Ibuprofen vs Placebo | |
|---|---|---|---|---|
| Day 1 | 10.4 ± 1.2 | 10.4 ± 1.6 | | — |
| Day 4 | 8.7 ± 2.0 | 9.7 ± 2.4 | 14.3 | 4.8 baseline/Day 4 |
| Day 8 | 7.5 ± 2.3 | 9.5 ± 2.6 | 28.6 | 0 baseline/Day 8 |

*Table 5*. Summary of the 2 interim analyses (ITT).

| Study Stage | Responder Rates Ibuprofen Group (%) | Placebo Group (%) | 95% RCI |
|---|---|---|---|
| 1st stage, n = 25 | 12/12 (100) | 2/13 (15.4) | 0.376, 0.970 |
| 2nd stage, n = 25 | 9/13 (69.2) | 8/12 (66.6) | 0.098, 0.690 |
| Both stages, n = 50 | 21/25 (84.0) | 10/25 (40.0) | — |

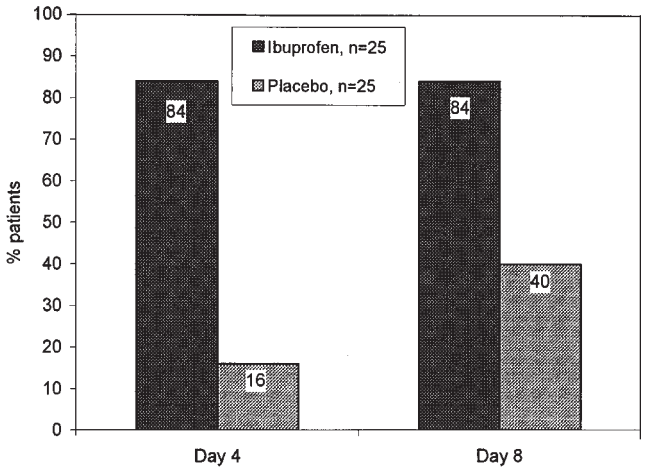


*Figure 2*. Responder rates.

ibuprofen cream and placebo cream (mean values, all visits) is shown in Table 3.

The results show that ibuprofen consistently provided a reduction of all pain qualities: pain relief was most pronounced from baseline to Day 4, and continued, although less prominently, up to Day 8. With placebo, the reduction in pain was slight and almost constant between baseline and Day 4 and to Day 8, respectively.

*Lequesne index*. The Lequesne index for knee OA comprises items for rating functional disability measured by pain, maximum distance walked, and activities of daily living.

The group mean baseline values (Day 1) were almost identical in the ibuprofen group and the placebo group: 10.4 ± 1.2 vs 10.4 ± 1.6 points.

On Day 4, the average index score was 8.7 ± 2.0 in the ibuprofen group versus 9.7 ± 2.4 in the placebo group. This represents an average decrease of 1.7 ± 1.8 versus 0.8 ± 1.2, or 16.6% ± 17.0% versus 8.7% ± 14.7%.

On Day 8, a further difference between the groups was observed. The average index score was 7.5 ± 2.3 points in patients receiving ibuprofen versus 9.5 ± 2.6 using placebo. This represents an average decrease from Day 8 to Day 1 of 2.9 ± 2.2 for ibuprofen versus 1.0 ± 1.5 for placebo. This is a decrease of 27.5% ± 20.7% versus 10.7% ± 17.0%.

The algofunctional mean impairment scores of the Lequesne index classified by severity grades for both treatment groups before, during, and at the end of the treatment are shown in Table 4.

*Global assessment of efficacy by patients and investigator.* The global efficacy of the study treatment was assessed by the investigator on a 5-point VRS as very good in 10/25 patients (40.0%) receiving ibuprofen cream, good in 7/25 (28.0%), moderate in 4/25 (16.0%), and poor in 4/25 (16.0%) patients. In contrast, the investigator's assessment of efficacy in the placebo group was very good in 1/25 (4.0%) patients receiving placebo cream, good in 3/25 (12.0%), moderate in 6/25 (24.0%), and poor in 15/25 (60.0%) patients. The rating "none" was not assigned in any of the cases.

The patients' global assessment of efficacy was exactly the same, and thus no discrepancies occurred between the investigator's and patients' evaluation of treatment benefit (Figure 3).

*Adverse events*. None of the 50 randomized patients experienced any adverse events during the study.

Another safety variable was the overall assessment of safety by the patients and the investigator at the end of the trial. Since adverse events did not occur, the patients and investigator unanimously rated the overall safety of the treatment as very good in all cases.

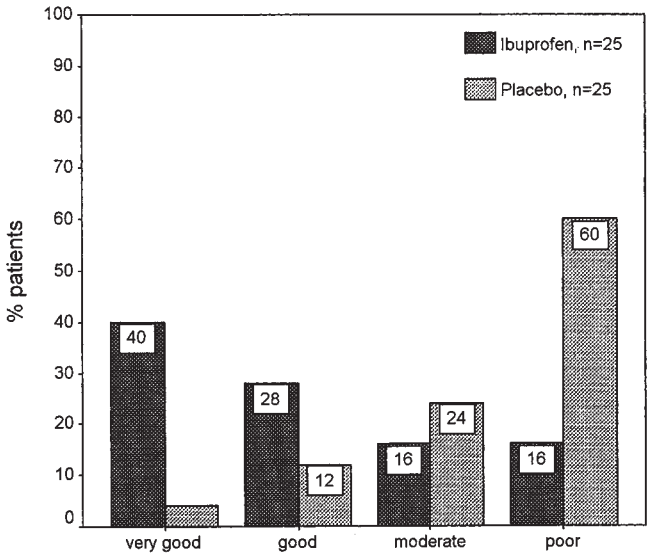


*Figure 3*. Overall assessment of efficacy.

## DISCUSSION

NSAID are extensively prescribed worldwide because of their value in treating disorders of the musculoskeletal system. Ibuprofen has proved to be one of the best-tolerated NSAID: it has a very low risk of adverse drug reactions, especially GI bleeding that is often a concern with these medications[20-23].

The rationale for developing a topical NSAID as gel or cream formulation was to achieve efficacy by direct penetration of the active agent into the painful tissue. A further goal was to reduce the risk of adverse drug reactions by keeping plasma concentrations at a low level, since even with oral ibuprofen GI disorders are frequent.

While topical ibuprofen formulations are regarded as well tolerated, with only infrequent side effects, in most cases manifesting as mild and fully reversible cutaneous reactions and only rarely as GI symptoms[24-26], their efficacy in rheumatic diseases or traumatic disorders has always been doubted[25,27]. In order to show efficacy, requirements have changed fundamentally in recent years[28].

The primary objective of this placebo-controlled clinical trial in primary knee OA was to confirm the efficacy and safety of an ibuprofen cream containing 5% active ingredient. Since a comparable study using an identical cream to treat the same clinical indication had recently been performed[7], and had yielded favorable results for ibuprofen, a secondary objective of the present study was to demonstrate the reproducibility of the study design and its positive outcome.

Primary knee OA, unilateral or bilateral, was therefore chosen again as the study indication. To avoid recruitment errors and ensure that the results would be reproducible, the disease was defined according to the ICD-10 classification criteria M17.0 and M17.1[29].

The CPMP guideline on Clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis[10] was taken into consideration when planning the study.

A placebo arm is generally regarded as state of the art in trials designed to test drug efficacy. Especially in studies assessing pain, a placebo group is considered mandatory as patients with pain are highly susceptible to autosuggestion and to external influences.

To evaluate both the efficacy and the tolerability of ibuprofen cream most effectively, monotherapy was considered essential; the concomitant administration of other medications such as analgesics or antiinflammatories (NSAID) orally or topically was not allowed.

Since the study objective was to confirm efficacy and tolerability of a marketed drug, the treatment regimen corresponded to the recommended and approved daily dose of ibuprofen cream: 4 g cream tid in the active treatment group, i.e., 200 mg ibuprofen tid (= 600 mg).

Not only the statistical significance but also the clinical relevance of the outcome had to be demonstrated. In this study, this is defined as a reduction of pain on motion of ≥ 18 mm or 23% from baseline to the last value assessed on a VAS, based on the recommendations of Todd and Funk[30]. These authors investigated the clinically relevant pain relief when pain is rated using a standardized 100 mm VAS, and found that a response of ≥ 18 mm or ≥ 23% is to be regarded as the minimum clinically relevant change in pain measurement in an individual patient. This definition of individual response must be considered a very demanding endpoint[31–33].

The mandatory baseline value of at least 40 mm allowed the presence of pain sufficiently severe to justify pharmacologic intervention and ensured that a drug effect would be demonstrated.

The clinical trial was found to have a design suitable for distinguishing between the effect of ibuprofen and that of placebo cream. A difference of 20% between the response rates of the 2 groups was estimated to reveal a statistically significant and clinically relevant result. This level was largely surpassed, with a treatment response rate of 84% (21/25 patients) in our ibuprofen group, but only 40% (10/25 patients) in the placebo group.

The statistical ITT analysis confirmed the marked difference in the response rates between the 2 treatment arms: the difference was statistically significant, and efficacy was more pronounced with ibuprofen than placebo. The 2 interim analyses did not show the same response rates: in the first analysis the effect was very pronounced for ibuprofen, while in the second analysis the placebo effect was almost as marked as the ibuprofen effect. Moreover, the sequential adaptive design was found to be appropriate for this kind of study, since it allowed recalculation of the required sample size, making it possible to restrict the number of patients (using placebo) to a minimum.

The ATP analysis confirmed this result, since only one patient of the ibuprofen group was not included in this analysis.

The results show that ibuprofen cream acts rapidly to reduce pain: all the responses in the ibuprofen group were observed as early as Day 4, whereas in the placebo group only 4 responses were observed at this time.

The results were not compromised by any substantial difference in demographic variables or specific baseline values between the groups: the higher proportion of men in the placebo group did not influence the mean demographic characteristics such as body weight or age, or baseline values for pain, radiographic severity, or Lequesne score; the slight disparity of 3.6 mm in the average values for pain on motion was not statistically significant. A similar difference was observed between the 2 treatment arms for all secondary efficacy variables, emphasizing the efficacy of ibuprofen cream and its superiority over placebo.

The Lequesne index to evaluate the algofunctional effect of OA also revealed a major clinical improvement.

No adverse event was observed. This indicates the good

tolerability of topical ibuprofen cream. The patients and the investigator consistently rated the tolerability of the drug as excellent and with no difference compared to placebo.

The results we obtained for efficacy and tolerability are not fully consistent with those reported by Rovensky, *et al*[7], despite minor design modifications.

Recently, 2 studies with topical NSAID have shown consistent outcomes and have demonstrated the value of these agents in rheumatic diseases. Machen and Whitefield[34] evaluated the efficacy of an ibuprofen gel in 81 patients with soft tissue injuries in a placebo-controlled double-blind study. A significant difference in favor of the active treatment was found for the time required to achieve clinically meaningful pain reduction. At the end of treatment after 7 days, 75% of patients treated with ibuprofen gel had a clinically relevant reduction in pain compared to 39% of patients using placebo gel. Zacher, *et al*[35] used a double-dummy technique to compare topical diclofenac with oral ibuprofen. The investigators enrolled 321 patients with activated arthrosis of finger joints (Heberden and/or Bouchard arthritis) and treated them for 3 weeks. The main efficacy variable was ≥ 40% response in pain reduction. Topical treatment was found to be at least as effective as systemic ibuprofen.

Our results demonstrate that this pharmaceutical formulation of ibuprofen cream exhibits good efficacy and safety in the treatment of knee OA. The positive experience with this topical NSAID in the treatment of rheumatologic disorders was confirmed. The study design was found to be suitable to show differences between active and non-active topical treatment and to deliver reproducible test results. Our findings, together with the 3 other randomized, double-blind, controlled clinical studies described recently, have made a major contribution to the benefit-risk assessment of topical NSAID.

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