Efficacy of Topical Diclofenac Diethylamine Gel in Osteoarthritis of the Knee

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ABSTRACT. ***Objective***. To assess the efficacy and safety of topical diclofenac diethylamine gel, 1.16%, 4 g applied qid for 3 weeks to relieve the symptoms of osteoarthritis (OA) of the knee.

Methods. Patients with OA of the knee washed out their OA medications for at least 5 drug half-lives. Patients with adequately high baseline pain scores were randomized to apply either double-blind active or placebo gel for 3 weeks. Acetaminophen (up to 2 g/day) was supplied as rescue medication. In a diary, patients recorded compliance to dosing and use of rescue medication and assessed daily pain on movement, spontaneous pain, and pain relief. At weekly site visits, patients completed the Western Ontario and McMaster (WOMAC) Osteoarthritis Index Questionnaire, which includes assessment of pain, stiffness, and physical function, and assessed pain intensity "right now." At the final visit, a global assessment of treatment efficacy was completed.

Results. Of 238 randomized patients, 237 were included in the intent to treat efficacy analysis. Treatments differed significantly for daily pain on movement at Day 5, and continued on most days through end of study. Peak differences were achieved in the second week. On the primary outcome, average pain on movement over Days 1–14, diclofenac gel was significantly superior to placebo gel. Scores for all 3 WOMAC indices for diclofenac gel treatment were significantly superior to placebo at Weeks 2 and 3. A significant difference was achieved on pain intensity "right now" at all 3 weeks. At the end of the study, patients rated diclofenac gel as significantly more effective in treating the pain of OA of the knee ($p = 0.03$) compared to placebo. There were no safety issues concerning adverse events or laboratory values.

Conclusion. Diclofenac gel was effective and safe for relief of symptoms of OA of the knee over 3 weeks of dosing. (J Rheumatol 2005;32:2384–92)

Key Indexing Terms:
DICLOFENAC TOPICAL KNEE NONSTEROIDAL ANTIINFLAMMATORY DRUG WESTERN ONTARIO AND McMASTER OSTEOARTHRITIS INDEX OSTEOARTHRITIS

Osteoarthritis (OA) is the most common form of arthritis, and most frequently affects the knees. Radiographic OA of the tibiofemoral compartment occurs in 5%–15% of people aged 35–74 years[1]. If nonpharmacological treatments do not adequately manage the pain and physical disability associated with the disease, the European League Against Rheumatism (EULAR) guidelines recommend acetaminophen (paracetamol) as first-line treatment for OA pain and either oral or topical nonsteroidal antiinflammatory drugs (NSAID) for those who do not respond adequately to the former[1]. The American College of Rheumatology (ACR) guidelines offer similar advice, noting that in patients with knee OA and moderate to severe pain, and in whom signs of joint inflammation are present, topical NSAID may be considered as either adjunct or monotherapy[2]. The ACR guidelines cite the review of Moore, *et al*[3], which supports the efficacy of topical NSAID in both acute and chronic conditions.

Diclofenac diethylamine (DEA) gel (1.16%; Voltaren® Emulgel®, Novartis, Nyon, Switzerland) has been used extensively in Europe since 1985 to relieve the symptoms of OA of the knee, as well as other painful, inflammatory tendon, ligament, muscle, and joint conditions. As a topical NSAID, it may be an attractive alternative to either oral NSAID or acetaminophen. Both the ACR and EULAR guidelines note the well known gastrointestinal (GI) toxicity of oral NSAID, while a recent study suggests that daily use of acetaminophen for symptoms of OA of the knee does not improve overall levels of pain, stiffness, or physical

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function[4]. In contrast, the existing epidemiological literature on topical NSAID supports their excellent safety[5], and pharmacokinetic studies have shown that systemic exposure from topical NSAID is typically 10% or less of the exposure from the same dose administered orally[5]. Therefore, a study was conducted to assess the proposition that diclofenac gel is safe and effective as first-line therapy for the symptoms of OA of the knee.

MATERIALS AND METHODS

This was a randomized, double blind, placebo controlled, multicenter study of 3 week duration comparing the efficacy and safety of 1.16% diclofenac gel to placebo in the treatment of pain in patients with OA of the knee. Placebo gel, identical in color, feel, and smell, was used to blind the study. The study was conducted in 22 centers in Germany in accord with ethical standards for the treatment of human subjects outlined in the Declaration of Helsinki. The protocol and informed consent were approved by an appropriate ethical committee for each center. Each patient gave written informed consent before undergoing any study procedure.

Patients. Male and female patients were recruited if they were 45 years of age or older, with clinically diagnosed, symptomatic, unilateral OA of the knee for at least 6 months. OA was confirmed at screening by radiographic observation of osteophytes and at least one of joint space narrowing, sclerosis, or subchondral cysts. Patients were excluded at the screening visit if they had clinically significant abnormalities in blood chemistry, hematology or urinalysis, radiographic evidence of severe OA (almost complete loss of joint space, large cysts, severe osteophytic changes, severe malformation of the joint), secondary OA, history of rheumatoid arthritis (RA) or of any other chronic inflammatory disease such as colitis, history of fibromyalgia, current GI bleeding or history of bleeding over the last 3 years, significant injury to the target joint within 6 months prior to screening, or major knee surgery of the target joint within one year of screening. Further requirements assessed at the baseline visit are described below.

Methods. The study consisted of a washout phase of one day to 2 weeks, depending on patients' individual premedication, and a 3 week treatment phase. Patients were asked to keep a daily diary with pain assessment and to attend the study center for pain and functional ability assessments (Table 1) on a weekly basis.

Washout phase. Patients satisfying the inclusion criteria at the screening visit entered a washout phase in which they discontinued their usual analgesic medication for a period of at least 5 half-lives. They were supplied with acetaminophen 500 mg tablets as rescue medication and were allowed to use up to 4 tablets per day for all pain they experienced. They recorded the time and number of tablets taken in a daily washout-phase diary. At the end of each day or at the time of first use of rescue medication, patients assessed daily pain on movement on a 100 mm visual analog scale (VAS; 0 = no pain and 100 = unbearable pain), and daily spontaneous pain, defined as pain in general during the day, on a 4 point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) and recorded the result in the diary.

Baseline assessment. At the end of the specified washout period, patients returned to the study center for the baseline visit. After sitting for 30 minutes, they assessed pain intensity in the target knee "right now" on both a 100 mm VAS and a 4 point severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Those scoring ≥ 50 mm on the VAS and at least "moderate" pain on the 4 point scale were then assigned to the lowest available randomization number allocated to the site and asked to complete the Western Ontario and McMaster (WOMAC) Osteoarthritis Index Questionnaire (version VA 3.0[6]; each question was answered as 0 = none, 1 = mild, 2 = moderate, 3 = severe, or 4 = extreme).

Treatment phase. Kits containing tubes of blinded active or placebo study medication bearing the patient number were prepackaged according to a computer generated randomization schedule. The treatments assigned to the patient numbers were unknown to all personnel involved in the study until the clinical phase was completed and the data were clean. Each site was assigned a series of consecutive randomization numbers from the schedule and corresponding kits. As a patient qualified to be randomized, the patient was assigned the lowest randomization number available at the site. The medication kit corresponding to the randomization number was supplied to the patient with a treatment-phase diary and a fresh supply of rescue medication. Patients were instructed to apply 4 g of the gel to the front of the knee 4 times daily and rub in for no more than 1 minute until the gel vanished, paying specific attention to the medial (internal) area. A measuring device was supplied to standardize the application. Patients were permitted to use up to 4 tablets of rescue medication per day for all pains they experienced regardless of origin. Use of any other analgesics, systemic steroids, or antidepressant medications was prohibited and nonpharmacologic therapy could not be introduced, changed, or discontinued during the treatment phase.

The treatment-phase diary was completed daily for the duration of participation in the study. Patients continued to record all use of rescue medication and daily assessments of pain on movement and spontaneous pain as in the washout phase (Table 1). Additionally, they recorded the times of all doses of study medication applied and also assessed daily pain relief at the end of the day or at time of first use of rescue medication.

Table 1. Efficacy assessments.

Diary-based efficacy assessments (daily at the end of each day or before the intake of rescue medication)
- Pain on movement: "How do you estimate the amount of your knee pain while you are moving during your daily activities?"
  - Visual analog scale (VAS): 100 mm; 0 = no pain, 100 = unbearable pain
- Spontaneous pain: "How do you describe the pain that you experienced in your treated knee today?"
  - 4 point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe
- Pain relief: "How much pain relief did you experience in your treated knee today?"
  - 5 point scale: 0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete

Study center-based efficacy assessment (every 7 days)
- Pain intensity in the target knee "right now": "How would you describe your knee pain right now?"
  - After sitting for 30 minutes
  - VAS: 100 mm; 0 = no pain, 100 = unbearable pain
  - 4 point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe (baseline visit only)
- WOMAC Questionnaire:
  - Pain (5 questions), stiffness (2 questions), and physical function (17 questions)
  - 5 point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme
- End of study global evaluation of treatment: "How do you rate this medication as a treatment of the pain of osteoarthritis of the knee?"
  - 5 point scale: 0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent

Patients were scheduled to return to the study center every 7 days over the treatment phase for pain and functional ability assessments. These included pain intensity on a 100 mm VAS and the pain, stiffness, and physical function indices of the WOMAC (Table 1). At each visit, compliance to dosing, use of rescue medication, and diary completion were checked and use of concomitant medications and incidence of adverse events were updated. At the end of study visit, patients assessed global treatment efficacy.

End of study blood and urine samples were collected for laboratory assessments.

Statistical methods. The primary efficacy outcome was the diary assessment of daily pain on movement averaged over Days 1–14. A sample size of 120 per group was planned to provide 80% power to declare a statistically significant difference if the average pain on movement over Days 1–14 for active gel was 7.5 mm lower than for placebo gel, assuming a standard deviation of 20 mm.

The intent-to-treat efficacy analysis included all randomized patients who used any study medication and provided any post-baseline efficacy data. However, one patient was randomized to placebo despite reporting no pain in the diary over the final 3 days of the washout period and no pain at the baseline visit. Therefore, this patient was excluded from the intent-to-treat efficacy analysis. Other patients were excluded from analyses of specific outcomes when imputation procedures specified below did not yield an outcome value for the analysis.

For the 3 daily diary assessments (Table 1), pain on movement, spontaneous pain, and pain relief, the treatments were compared daily and also averaged over Days 1–7, 8–21, and 1–14 using ANOVA with main effects of center and treatment. For pain on movement and spontaneous pain, a baseline covariate term was also included, defined as the average of all daily assessments during the washout. Supplementary comparisons of the treatments each day on each of the 3 daily diary assessments were conducted using the same ANOVA models. When computing the averages over the various day ranges, gaps in the daily diary assessment record of up to 3 days were imputed by averaging the 2 surrounding non-missing assessments. Subjects with gaps > 3 days were excluded from the analyses of averages over any day range that coincided with the gap. If subjects completed diaries for at least the first 3 days, but stopped completing diaries before Day 21, the missing diaries were imputed by carrying the last non-missing diary record forward.

Percentage of days using rescue medication and average number of tablets used per day were compared using the Cochran-Mantel-Haenszel comparison of treatment means, stratified by center.

For the assessments at the weekly visits to the study site, the WOMAC indices, and pain intensity (Table 1), the treatments were compared using ANOVA, with main effects of center and treatment and the value assessed at the baseline visit as covariate. Each WOMAC index was computed by adding together the responses to the relevant questions and each index total was multiplied by a scale factor to be defined on a 0–100 scale. Missing assessments after premature discontinuation were imputed by carrying forward results from the last visit.

After the study was unblinded, it was decided to calculate the OARSI/OMERACT response rate (Osteoarthritis Research Society/Outcome Measures in Rheumatology). An OARSI/OMERACT task force determined that 3 symptomatic domains should be included in phase III clinical OA trials — pain, physical function, and patient global assessment — and that response should be defined in terms of both an absolute change and a relative change from baseline levels[7]. However, a global rating of disease was not assessed in this study so the definition was modified.

Treatment was considered successful if (1) the WOMAC index of pain or of physical function declined by 50% or more and by at least 20 points on a 0–100 scale, or (2) the WOMAC indices of pain and physical function both declined by 20% or more and by at least 10 points on a 0–100 scale at the end of the study. Success rates were compared between treatment groups with the Cochran-Mantel-Haenszel test stratified by center.

Safety was summarized as frequency of adverse events and incidence of clinically relevant changes in laboratory parameters from baseline to the end of the study.

RESULTS

Between November 2001 and August 2002, 267 patients were screened, of whom 238 completed the washout and were randomized, 117 to diclofenac gel and 121 to placebo gel (Figure 1). A total of 15 (13%) diclofenac gel patients and 23 (19%) placebo patients discontinued prematurely. Of these 38 patients, 26 were discontinued for protocol violations, primarily of inclusion and exclusion criteria. One center, which had randomized 3 patients, was found to be noncompliant with the protocol. The 3 patients were discontinued from the study and the center was closed.

There were no statistically significant differences between treatment groups in important demographic and background disease characteristics (intent-to-treat efficacy population, Table 2). Study patients were all Caucasian; almost 2/3 were female and the mean age was 66 years. Few (< 10%) were receiving physical therapy and < 30% in either group had periarticular pain, caused by OA in all instances. Just below 30% in either group had moderate or severe swelling of the joint capsule. About 15% in either group had joint effusion. Almost all patients had osteophytes, joint space narrowing, and sclerosis, and a few had subchondral cysts.

Assessments provided by the patients in the intent-to-treat efficacy population during the washout and at the baseline visit are summarized in Table 3. Mean duration of washout was roughly 5 days. About 1/3 of patients in either group used rescue medication during the washout, with a mean of 0.5 tablets of rescue medication used per day. For most patients the score recorded for the various measures during the washout phase and baseline visit were consistent with a moderate level of OA pain.

Diary-based efficacy assessments. Seven patients (3 active gel, 4 placebo) in the intent-to-treat efficacy population were excluded from the intent-to-treat analysis of the primary outcome (end of day pain on movement averaged over Days 1–14) because they provided either no pain on movement assessments over the washout period or at most one assessment during the treatment phase, or because of a gap of > 3 days in their diary record during the first 14 days, which was not imputed. In the remaining 230 patients (114 using diclofenac gel and 116 placebo), diclofenac gel was significantly superior to placebo, with a difference of 4 mm averaged over Days 1–14 ($p = 0.02$; Table 4). Separation of the diclofenac gel and placebo pain curves developed steadily over the first 2 weeks, and was generally maintained over the third week (Figure 2). Using the same ANOVA model as for the primary outcome, diclofenac gel was significantly superior to placebo in daily end of day pain on movement at Days 5, 6, 11–16, and 18–21. Diclofenac gel was not signif-

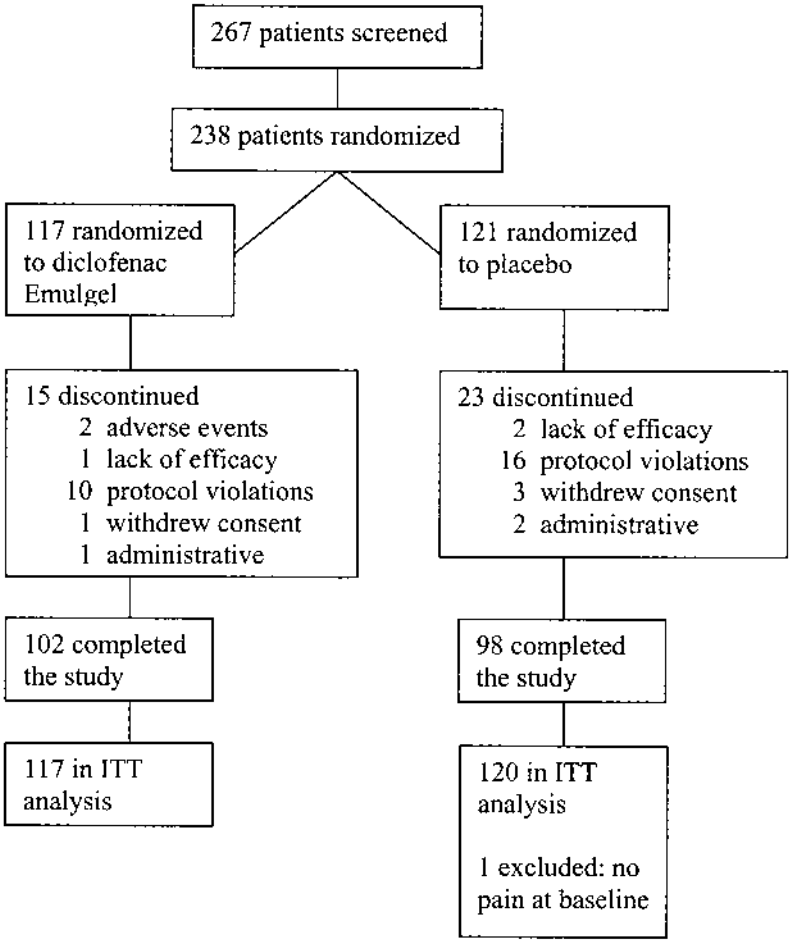

Figure 1. Patient disposition. ITT: intent-to-treat.

icantly superior in pain on movement averaged over Days 1–7, representing the period over which differences between treatment groups gradually developed, but was significantly superior in pain on movement averaged over Days 8–21, the period in which a difference was already evident, with an average difference of 6 mm ($p = 0.005$; Table 4).

A lesser degree of difference between treatment groups was found in the analysis of spontaneous pain, with a statistically significant difference in the average over Days 8–21 ($p = 0.02$; Table 4). No significant difference was noted in the comparison of end of day pain relief over any timeframe.

A slow but steady reduction in use of rescue medication was seen over the 3 weeks of dosing, but there were no differences between diclofenac gel and placebo in patterns of use of rescue medication (Table 4).

Study center-based efficacy assessments. One active-treatment patient was excluded from the analyses of WOMAC and pain intensity and one placebo patient was excluded from the analysis of pain intensity because they did not supply baseline values. In the remaining patients, diclofenac gel was significantly superior to placebo on the assessment of pain intensity at all 3 weekly visits, with a difference of 6 mm at the Week 1 visit ($p = 0.03$) and peak difference of 11 mm ($p = 0.0002$) at the Week 2 visit (Table 5). Significant superiority of diclofenac gel over placebo on the WOMAC indices developed over 2 weeks, with a mean difference of roughly 7–9 points on the 100 point scale for all 3 indices at Weeks 2 and 3.

The end of study OARSI/OMERACT response rate for diclofenac gel was significantly superior to the placebo rate, 62% versus 46% ($p = 0.01$; Table 5). At the end of the study, patients rated diclofenac gel as significantly more effective in treating the pain of OA of the knee ($p = 0.03$; Table 5) with 69% rating it as "good", "very good," or "excellent" compared to only 58% for placebo.

Defining duration of the washout as either 1–4 days or > 4 days split the study population into 2 groups of roughly equal size (Table 2). In an exploratory analysis not prespecified in the protocol, efficacy of diclofenac gel, as assessed by end of day pain on movement recorded in the daily diaries, was found to be dramatically different in those with the longer washout compared to those with the shorter washout. In patients with washout of > 4 days, the difference between treatments in pain on movement at Day 2 was

Table 2. Demographic/background disease characteristics.

ITT Efficacy Population	Diclofenac Gel, n = 117	Placebo, n = 120
Age, yrs, mean (SD)	66 (9)	66 (9)
BMI		
Male, mean (SD)	29 (6)	28 (5)
Female, mean (SD)	28 (4)	28 (5)
Female, %	62	65
Caucasian, %	100	100
Receiving physiotherapy, %	7	8
Has periarticular pain, %	29	29
Has moderate or severe tenderness on pressure†, %		
Joint space medially	92	94
Joint space laterally	30	21
Patella medially	47	34
Patella laterally	15	13
Has moderate or severe swelling of	27	28
Joint capsule†, %		
Has joint effusion, %	15	14
Has		
Osteophytes, %	99	99
Sclerosis, %	90	92
Subchondral cysts, %	16	12
Joint space narrowing, %	96	97

† Measurement scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe. ITT: intent-to-treat, BMI: body mass index.

Table 3. Washout and baseline visit symptom assessments.

ITT Efficacy Population	Diclofenac Gel, n = 117	Placebo, n = 120
Washout		
Duration ≤ 4 days, %	46	49
Duration (days), mean (SD)	5.3 (3.0)	5.0 (3.0)
Used any rescue medication, %	35	31
Tablets/day, mean (SD)	0.5 (0.8)	0.5 (0.9)
Daily pain on movement*, mean (SD)	66 (15)	67 (14)
Daily spontaneous pain†, mean (SD)	2.1 (0.4)	2.1 (0.5)
Baseline symptom assessments		
Pain intensity††, mean (SD)	69 (10)	66 (12)
% Moderate/% severe	77/20	73/19
WOMAC, mean (SD)		
Pain score	48 (16)	47 (16)
Physical function score	53 (15)	51 (15)
Stiffness score	48 (21)	46 (17)

* Pain on movement measured daily on VAS (0 = no pain, 100 = unbearable pain), averaged over washout. † Spontaneous pain (i.e., pain in general) measured daily. †† Pain intensity "right now," measured at the baseline visit (0 = none, 1 = mild, 2 = moderate, 3 = severe); also on VAS (0 = no pain, 100 = unbearable pain) at all visits.

already 7 mm, climbing to 14 mm by the end of Week 2 (Figure 3).

Safety. Adverse events were infrequent in both treatment groups. In each group there were 11 patients (9%) with one or more adverse events. Two patients, both in the placebo group, experienced GI adverse events (dry mouth and nausea). Four patients in the diclofenac gel group experienced adverse events of the skin or subcutaneous tissue (one Quincke's edema, one allergic contact dermatitis, and 2 application site reactions), versus 3 placebo patients (application site irritation and inflammation, application site burning, and allergic contact dermatitis). One serious adverse event, a brain tumor, occurred in one placebo patient.

There were no changes of note in hematology, serum chemistry, or urinary laboratory measures in the active or placebo group from the baseline visit to the end of the study. Mean values of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), total bilirubin, and alkaline phosphatase changed by 3% or less over the 3 weeks of the study in either treatment group. No patient in the diclofenac gel group had SGOT or SGPT elevated to twice the upper limit of normal (2x ULN) at either the baseline or final visit. In contrast, 3 placebo patients had SGPT elevated to 2x ULN and 2 other placebo patients had SGOT elevated to 2x ULN at the final visit. None of these abnormalities was considered clinically significant.

DISCUSSION

The objective of this well powered study of modern clinical design was to demonstrate the efficacy and safety of diclofenac DEA gel to relieve the symptoms of OA of the knee. Efficacy developed over the course of the first week, reached a peak during the second week, and was maintained over the third week. With the active gel significantly greater rates of response, based on OARSI/OMERACT criteria, were seen at the end of the study. Improvement was shown in all measures of pain (spontaneous pain, pain intensity "right now," pain on movement, WOMAC pain index), as well as in the WOMAC physical function index, indicating that treatment with diclofenac gel increased the ability of these patients to follow their daily routine. The WOMAC physical function index includes questions regarding the degree of difficulty going up and down stairs, standing, bending, walking, and performing many other routine daily activities. There were no safety issues; both the adverse event experience and the laboratory profiles were identical comparing the active gel and placebo groups.

The finding of greater efficacy in patients with a longer washout period (> 4 days) suggests that a longer washout may be necessary to establish a real baseline, and that washing out for the traditional 5 half-lives of the previous therapy may not always suffice. No definitive conclusion can be drawn from this analysis, which was specified after the data were unblinded. Nonetheless, if reproducible, the finding above would have important consequences in the design of future studies.

Statistically significant separation from placebo was not seen until Day 5. This differs from oral NSAID, which typically demonstrate first-dose efficacy, possibly reflecting an

Table 4. Diary-based efficacy assessments.

Day Range	Diclofenac Gel, n = 117	Placebo, n = 120	Difference	p
Decline from baseline* in pain on movement*** averaged over days, mean (SD)				
1–14**	14 (16)	10 (13)	4	0.02
1–7	10 (15)	7 (13)	3	0.10
8–21	20 (19)	14 (17)	6	0.005
Decline from baseline* in spontaneous pain*** averaged over days, mean (SD)				
1–7	0.28 (0.43)	0.20 (0.43)	0.08	0.14
8–21	0.52 (0.55)	0.36 (0.54)	0.16	0.02
Pain relief*** averaged over days, mean (SD)				
1–7	1.10 (0.82)	1.04 (0.71)	0.06	0.49
8–21	1.51 (0.93)	1.34 (0.79)	0.17	0.10
N; Used any rescue medication, %; average no. tablets/day†				
Overall	117;39;0.4	120;39;0.4		> 0.80††
Week 1	117;33;0.4	120;33;0.4		> 0.80††
Week 2	114;32;0.4	114;30;0.4		> 0.80††
Week 3	111;29;0.4	107;23;0.3		> 0.50††

* Baseline was average of assessment over washout, see statistical methods. ** Protocol-specified primary efficacy outcome. *** Pain on movement measured daily on VAS (0 = no pain, 100 = unbearable pain); spontaneous pain (i.e., pain in general) measured daily (0 = none, 1 = mild, 2 = moderate, 3 = severe); pain relief measured daily (0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete). † N: number of subjects with any diary records in period, number of tablets per day is averaged over N. †† Describes p values for both percentage used any rescue medication and number of tablets per day.

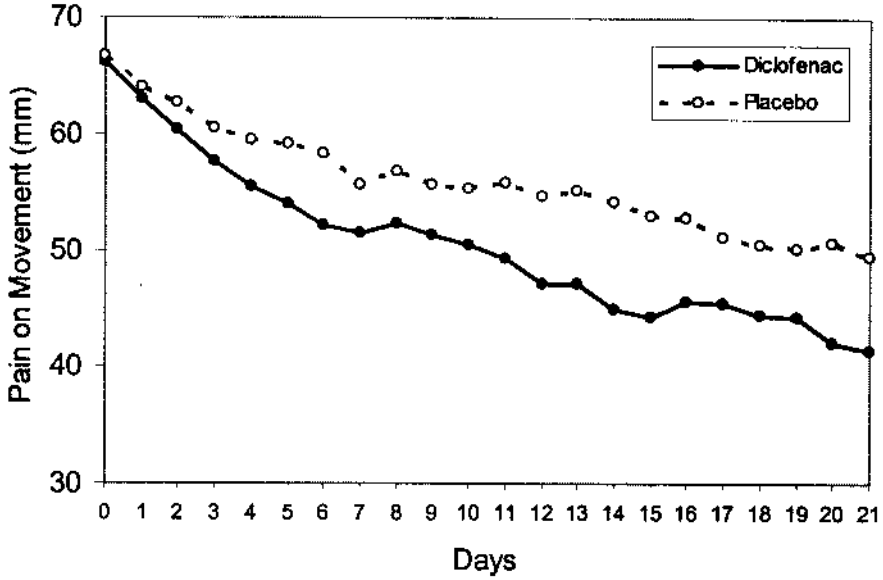

Figure 2. Daily end-of-day pain on movement scores over 3 weeks. 0 = no pain, 100 = unbearable pain.

effect on pain of systemic origin. The delay in onset of efficacy did not result in intolerable pain in most patients; only a third of patients used acetaminophen rescue medication during the first week, and those patients used, on average, less than half a tablet per day. Patients did not generally consider the delay an important negative attribute of diclofenac gel. On the global assessment of treatment provided by the patients after 3 weeks of dosing, a substantial majority of patients were satisfied with diclofenac gel as a treatment for OA of the knee.

It is not clear why use of rescue medication during the treatment period in the active gel group was comparable to use in the placebo group. It may be that acetaminophen as rescue medication was used to treat occasional OA knee pain of systemic origin that would not be addressed by a locally acting topical NSAID. Alternatively, it must be noted

Table 5. Study center-based efficacy assessments.

Week	Diclofenac Gel, n = 117	Placebo, n = 120	Difference	p
Decline from baseline visit in pain intensity, mean (SD)				
1	18 (20)	12 (18)	6	0.03
2	27 (23)	17 (21)	11	0.0002
3	34 (26)	25 (24)	9	0.006
Decline from baseline visit in WOMAC pain score, mean (SD)				
1	11 (14)	8 (14)	3	0.22
2	17 (18)	9 (18)	8	< 0.0001
3	22 (21)	14 (23)	9	0.0002
Physical function score, mean (SD)				
1	11 (13)	8 (12)	3	0.12
2	18 (17)	11 (15)	7	0.0002
3	23 (21)	16 (22)	8	0.001
Stiffness score, mean (SD)				
1	11 (18)	8 (15)	3	0.30
2	17 (21)	11 (20)	7	0.002
3	22 (23)	14 (24)	9	0.0004
End of study global treatment efficacy, %				
Poor	5	7		0.03
Fair	25	35		
Good	39	38		
Very good	22	14		
Excellent	9	6		
OARSI/OMERACT response rate at final visit, %				
	62	46		0.01

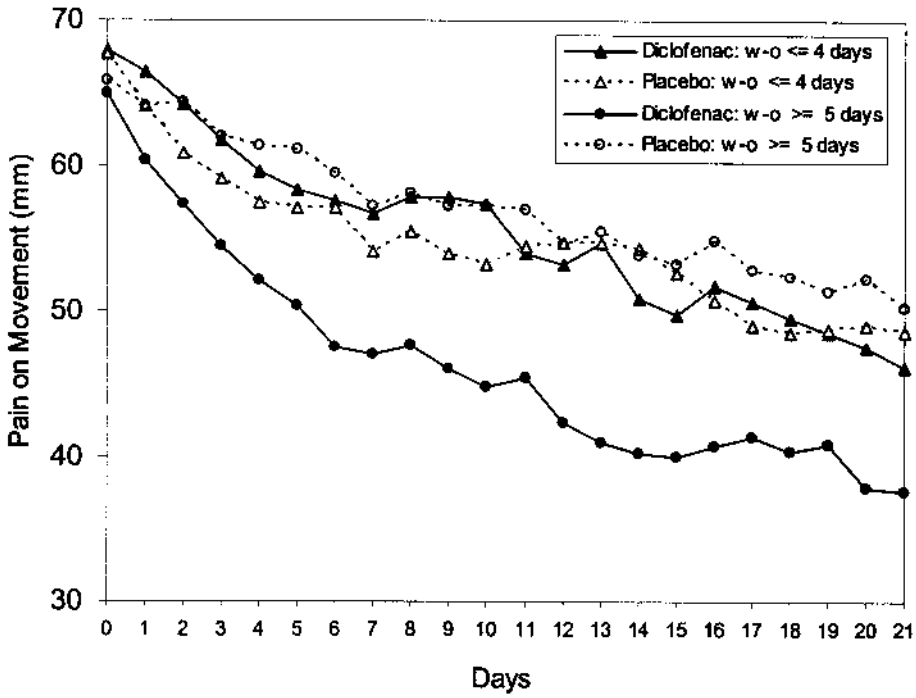

Figure 3. Daily end-of-day pain on movement scores over 3 weeks by duration of washout period. 0 = no pain, 100 = unbearable pain.

that patients used rescue medication in this study for all aches and pains they experienced, and not only for pain of OA of the knee. In a study comparing a systemic NSAID to a placebo, one could expect less use of rescue medication in the active group, even for conditions other than OA of the knee. However, in this study of a topical NSAID, one would

expect comparable use of rescue medication for conditions other than OA of the knee. In the end, only 39% of patients required rescue medication at any time during the study, and those patients averaged 0.4 tablets/day even in the placebo group.

A recently published metaanalysis of topical NSAID[8] questions their efficacy in the longterm treatment of OA. It concludes from the available data that topical NSAID are effective in the first 2 weeks of use, but there is no evidence of efficacy in Weeks 3 or 4. The negative results at Weeks 3 and 4 in the metaanalysis came from studies of other topical NSAID that were not effective in Weeks 1 and 2 either. It would therefore seem that the efficacy of each topical NSAID must be considered separately from all others. Two recent systematic reviews on topical NSAID conclude that there is a body of evidence to support the efficacy in treating acute painful conditions for one week[9] and chronic musculoskeletal conditions for 2 weeks[10].

Mason, *et al*[9] analyzed the outcome close to 7 days and found an average placebo response of 39% compared to a NSAID response of 65% in treating acute painful conditions. For chronic musculoskeletal pain Mason, *et al*[10] focused on outcomes close to 2 weeks, but at least a week, and reported a mean placebo response of 26% compared to an NSAID response of 48%.

Studies with a duration of either 4 weeks or 12 weeks were conducted with a topical 1.5% diclofenac solution containing dimethyl sulfoxide (DMSO) to enhance penetration through the skin[11-13]. Treatment resulted in high efficacy rates, but a substantial incidence of skin-related adverse events was reported, with 27%–41% of patients in the topical diclofenac groups reporting adverse events, apparently caused by DMSO.

Our study documents a significant treatment effect at Week 3 combined with favorable tolerability and further adds to the favorable efficacy and tolerability profile of diclofenac gel in the topical treatment of rheumatic diseases of the joints. Further, the topical treatment with diclofenac gel has proven to be superior with regard to GI events and at least as effective as the oral NSAID. This has been observed in a recent double blind, randomized study of topical diclofenac gel versus oral ibuprofen over 3 weeks in patients with active OA of the finger joints (Heberden and/or Bouchard arthritis)[14].

A key issue to consider is the clinical relevance of the effect of diclofenac gel. For proof of efficacy in OA pain, evaluations of the target joint supported by functional evaluations are requested[15]. Only limited information is available from the literature on pain evaluation regarding the minimum clinically perceptible difference and the minimum clinically important improvement[16]. The conclusions of these reports relate exclusively to the change from baseline that a patient would consider relevant, rather than the difference between active treatment and placebo in change from baseline, e.g., the treatment effect in our study. However, the results of those studies are relevant if one thinks of the results in our placebo group as a baseline and treats the results in our active group as if they are a change from that baseline.

With regard to the literature, a pain difference of 9 to 10 mm on a 100 mm VAS pain scale can be regarded as the minimum clinically relevant difference between active gel and placebo vehicle. Eberle and Ottillinger[17] analyzed 3 clinical studies to establish the minimum clinically important change scores in knee OA. For VAS pain measures, a mean difference of 8.4 mm was considered the minimal clinically important change from baseline. Ehrich, *et al*[18] analyzed 2 clinical studies of OA of the knee or hip and determined the minimal perceptible clinical improvements as 9.7 mm for the WOMAC pain scale. Other authors report clinically relevant pain differences of 13 mm[19], 9 mm[20], or 6.2 mm[21], depending on the pain condition and the underlying disease. In our study, differences between diclofenac gel and placebo vehicle after the first week were in the range of 6–10 mm depending on the assessment (pain intensity, pain on movement, WOMAC). Thus, the results are consistent with the range of values that have been proposed as defining a clinically relevant difference. The clinical relevance of the observed changes with diclofenac gel is further documented by the superior results of the WOMAC subscore evaluations at Weeks 2 and 3. The WOMAC pain score improved by 35% and 47%, respectively, for active gel compared to only 20% and 29% for the placebo vehicle.

These results can be explained by therapeutically effective concentrations in the tissue below the site of application, as found in earlier studies of diclofenac DEA, especially in the periarticular tissue[22] and intraarticular compartment[23,24]. In a well designed study Rolf, *et al*[24] showed that high intraarticular concentrations, with limited systemic exposure, can be achieved with topical ketoprofen, and concluded that less-vascularized tissue may act as reservoirs. Theoretical consideration allows bridging these results to diclofenac[25]. A recent review acknowledges that locally applied NSAID do reach the synovial fluid compartment and can concentrate in the intraarticular tissue[5].

Given the favorable tolerability profile of topical diclofenac gel and the risk of NSAID-mediated GI events on oral treatment, it seems rational to give patients with rheumatic joint pain a trial of topical treatment prior to institution of oral NSAID. With the additional evidence of efficacy and safety of diclofenac gel that has now been demonstrated, it should be considered as an appropriate first-line option for the treatment of pain in OA of small and large joints.

In summary, diclofenac DEA gel applied 4 times daily has been shown to effectively relieve the pain of OA of the knee in a large, placebo controlled study with well accepted clinical pain measurements. Therefore diclofenac DEA gel

can be recommended as first-line therapy for the treatment of the pain of OA of the knee.

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REFERENCES

1. Pendleton A, Arden N, Dougados M, et al. EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2000;59:936-44.
2. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43:1905-15.
3. Moore RA, Tramer MR, Carroll D, Wiffen PJ, McQuay HJ. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. BMJ 1998;316:333-8.
4. Case JP, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis. Arch Intern Med 2003;163:169-78.
5. Heyneman CA, Lawless-Liddy C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases. Drugs 2000;60:555-74.
6. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
7. Pham T, van der Heijde D, Lassere M, et al. Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria. J Rheumatol 2003;30:1648-54.
8. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. BMJ 2004;329:324. Epub 2004 July 30.
9. Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for acute pain: a meta-analysis. BMC Fam Pract 2004;5:10.
10. Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. BMC Musculoskeletal Disorders 2004;5:28. doi: 10.1186/1471-2474-5-28.
11. Bookman AAM, Williams KSA, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled study. Can Med Assoc J 2004;171:333-8.
12. Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution (Pennsaid) in the treatment of primary osteoarthritis of the knee. Arch Intern Med 2004;164:2017-23.
13. Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (Pennsaid) compared with oral diclofenac in the symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. J Rheumatol 2004;31:2002-12.
14. Zacher H, Burger KJ, Färber L, et al. 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 2001;26:7-14.
15. Reiter S. Topische nichtstereoidale antirheumatika. Aspekte zur planung und auswertung klinischer studien und ergebniss-bewertung im zulassungsverfahren. Bundesgesundheitsbl-Gesundheitsforsch-Gesundheitsschutz 2000;43:950-9.
16. Bellamy N, Carr A, Dougados M, Shea B, Wells G. Towards a definition of difference in osteoarthritis. J Rheumatol 2001; 28:427-30.
17. Eberle E, Ottillinger B. Clinically relevant change and clinically relevant difference in knee osteoarthritis. Osteoarthritis Cartilage 1999;7:502-3.
18. Ehrich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities Osteoarthritis Index questionnaire and global assessment in patients with osteoarthritis. J Rheumatol 2000;27:2635-41.
19. Todd KH, Funk KG, Funk JP, Bonacci R. The clinical significance of reported changes in pain severity [abstract]. Acad Emerg Med 1995;2:369-70.
20. Kelly AM. Does the clinically significant difference in visual analog pain scores vary with gender, age, or cause of pain? Acad Emerg Med 1998;5:1086-90.
21. Wells GA, Tugwell P, Kraag GR, et al. Minimum important difference between patients with rheumatoid arthritis: The patient's perspective. J Rheumatol 1993;20:557-60.
22. Gondolph-Zink B, Gronwald U. Active substance concentration in articular and periarticular tissues of the knee joint after cutaneous application of diclofenac-diethylammonium emulgel. Akt Rheumatol 1996;21:298-304.
23. Rademacher J, Jentsch D, Scholl MA, Lustinetz T, et al. Diclofenac concentration in synovial fluid in inflammation and degenerative joint disease. Br J Pharmacol 1991;31:537-41.
24. Rolf C, Engström B, Beauchard C, Jacobs D, Le Libour A. Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. Rheumatology Oxford 1999;38:564-7.
25. Cordero JA, Camacho M, Obach R, Domenech J, Vila L. In vitro based index of topical anti-inflammatory activity to compare a series of NSAIDs. Eur J Pharmaceutics Biopharmaceuticals 2001;51:135-42.