Diclofenac Sodium Gel in Patients with Primary Hand Osteoarthritis: A Randomized, Double-blind, Placebo-controlled Trial

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ABSTRACT. ***Objective.*** To measure the efficacy and safety of diclofenac sodium gel in patients with primary hand osteoarthritis (OA).

Methods. In a randomized, double-blind, placebo-controlled trial, men and women aged ≥ 40 years diagnosed with primary OA in the dominant hand were randomly assigned to self-apply topical 1% diclofenac sodium gel (Voltaren® Gel) (n = 198) or vehicle (n = 187) to both hands 4 times daily for 8 weeks. Primary outcome measures included OA pain intensity (100-mm visual analog scale), total Australian/Canadian Osteoarthritis Hand Index (AUSCAN) score, and global rating of disease activity at 4 and 6 weeks. Secondary outcomes included onset of efficacy in Weeks 1 and 2, durability of efficacy at 8 weeks, measures of disease activity in the dominant hand, pain intensity in the nondominant hand, AUSCAN subindices, end of study rating of efficacy, and Osteoarthritis Research Society International response criteria.

Results. Diclofenac sodium gel decreased pain intensity scores by 42%–45%, total AUSCAN scores by 35%–40%, and global rating of disease by 36%–40%. Significant differences favoring diclofenac sodium gel over vehicle were observed at Week 4 for pain intensity and AUSCAN, with a trend for global rating of disease activity. At Week 6, diclofenac sodium gel treatment significantly improved each primary outcome measure compared with vehicle. Secondary outcomes generally supported the primary outcomes. The most common treatment-related adverse event (AE) was application-site paresthesia. Most AE were mild. No cardiac events, gastrointestinal bleeding, or ulcers were reported.

Conclusion. Topical diclofenac sodium gel was generally well tolerated and effective in primary hand OA. (NCT ID: NCT00171665) (J Rheumatol First Release Aug 1 2009; doi:10.3899/jrheum.081316)

Key Indexing Terms:
PAIN OSTEOARTHRITIS DICLOFENAC SODIUM
NONSTEROIDAL ANTIINFLAMMATORY AGENTS TOPICAL ADMINISTRATION

Osteoarthritis (OA) is a frequent cause of disability and impaired quality of life[1,2]. Radiographic hand OA is prevalent in 55% of the elderly[3-7]. Symptomatic hand OA has a prevalence of 7% to 26%[8-11], producing pain, stiffness, reduced grip strength, reduced hand mobility, and difficulty performing dextrous tasks[3,11-13]. The hand joints most commonly affected are the distal interphalangeal (DIP), proximal interphalangeal (PIP), and first carpometacarpal (CMC-1)[3,4]. Frequently, both hands are affected[3,4].

Nonsteroidal antiinflammatory drugs (NSAID) reduce pain and improve function in hand OA[14]; however, nonselective NSAID carry dose-related gastrointestinal (GI) risks[15], and nonselective NSAID and cyclooxygenase-2 (COX-2)-selective inhibitors alike bear risks of cardiovascular and renal adverse effects[16-19].

Topical NSAID provide effective analgesia but minimize systemic NSAID exposure, potentially reducing risk of adverse events (AE). Evidence for their efficacy derives primarily from short (e.g., 2 week) trials for knee OA[20]. The Osteoarthritis Research Society International (OARSI) proposes 2 to 4 weeks as adequate for testing NSAID efficacy in hand OA[21]. We examined the efficacy and safety of topi-

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cal 1% diclofenac sodium gel (Voltaren® Gel, Novartis Consumer Health, Inc., Parsippany, NJ, USA) compared with vehicle (placebo) in patients with hand OA. Our study was designed to recognize the variable cyclic course of hand OA by considering primary outcome measurements at both 4 and 6 weeks plus secondary outcome measurements assessing onset over the first 2 weeks and durability to 8 weeks.

MATERIALS AND METHODS

Trial design. This prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter 8-week trial compared the efficacy and safety of topical 1% diclofenac sodium gel with vehicle in patients with symptomatic OA of the dominant hand. The protocol followed the OARSI guidelines for clinical trials of the hand[22]. The trial is registered with ClinicalTrials.gov (NCT00171665, "Efficacy and Safety of Diclofenac Sodium Gel in Hand Osteoarthritis").

The protocol was approved by the institutional review boards of all 65 participating US institutions and carried out in accord with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, European Directive 2001/20/EC, and local ethical and legal requirements. All enrolled patients provided written informed consent.

Patients. Eligible patients were men and women aged ≥ 40 years with a diagnosis at screening of primary OA in their dominant (target) hand. OA was defined following American College of Rheumatology criteria as nodal enlargement in ≥ 2 of 10 joints (CMC-1, DIP, or PIP)[23].

Inclusion criteria required OA pain in the dominant hand for ≥ 12 months and use of an NSAID for ≥ 1 episode of pain. Patients meeting these criteria underwent a washout period (≥ 7 days) of previous OA medications. Randomization to diclofenac sodium gel or placebo required patients to have pain in the dominant hand during the 24 hours before the baseline visit, rated as ≥ 40 mm on a 100-mm visual analog scale (VAS). Pain in the dominant hand had to exceed pain in the nondominant hand by ≥ 20 mm, and patients taking NSAID at screening had to have an increase in pain in the dominant hand of ≥ 15 mm during washout. Posterior-anterior radiographs had to show Kellgren-Lawrence grade 1, 2, or 3 changes[24] in symptomatic joints.

Exclusion criteria included Kellgren-Lawrence grade 4 OA, secondary OA, other rheumatic diseases, other painful nonrheumatic diseases involving the dominant hand or arm, symptomatic OA at additional locations besides the hand(s) requiring treatment, laboratory values indicative of rheumatoid arthritis, history of other inflammatory diseases, or a diagnosis of fibromyalgia. Ambidextrous patients were excluded because the evaluation of treatment outcomes required assessments in dominant versus nondominant hands.

Intervention. Eligible patients were randomized in a 1:1 ratio to receive diclofenac sodium gel (Voltaren® Gel, consisting of diclofenac sodium in a vehicle composed of isopropyl alcohol, propylene glycol, cocoyl caprylocaprate, mineral oil, ammonia solution, perfume cream 45/3, carbomer 980, polyoxyl 20 cetostearyl ether, and purified water) or vehicle (2 g to each hand) 4 times daily for 8 weeks. The vehicle administered to the control group was identical in composition to diclofenac sodium gel, except for the absence of diclofenac sodium. The 2 treatments were also identical in appearance, smell, and texture. The vehicle for diclofenac sodium gel had no counterirritant or other analgesic properties that might confound efficacy assessments. The investigators, site and sponsor personnel, and patients were blinded to treatment assignment until after the study database was locked.

Patients were shown how to apply the gel under supervision and were provided with detailed instructions for the use and application of the gel as well as dosing pads to standardize the application amount. The dose of 2 g was judged sufficient for approximately half the surface of each hand (200 cm^2). Gel was to be applied to the base of the thumb and all 5 digits, with particular attention to affected joints. Application involved gentle massage without rubbing or excessive joint movement, and hands were not washed until ≥ 1 hour after application. Dosing times were to be distributed evenly over waking hours.

Rescue medication (acetaminophen 500-mg tablets) was allowed to a maximum dose of 4 g daily during washout and throughout double-blind treatment, excluding the 36 hours before each evaluation. The same rescue medication was to be used for any other pain experienced during the trial, such as headache.

Efficacy and safety assessments. Primary efficacy outcomes were the 4-week and 6-week measurements of 3 coprimary efficacy indices selected before study initiation: OA pain intensity in the dominant hand during the previous 24 hours (100-mm VAS; 0 = no pain, 100 = unbearable pain); total Australian/Canadian Osteoarthritis Hand Index (AUSCAN) score for the dominant hand; and global rating of disease activity (100-mm VAS; 0 = very good, 100 = very poor). The total AUSCAN score was calculated as the average of scores on 15 questions[25] rating pain, stiffness, or function standardized to range from 0 (no pain/stiffness/difficulty) to 100 (extreme pain/stiffness/difficulty). AUSCAN functional assessments were performed in the dominant hand only. The timepoints for efficacy assessment were based on the recommendations of the OARSI task force for phase III trials, specifying 4 weeks as adequate for testing efficacy of NSAID treatment in the hand[21]; an additional 6-week assessment was added in recognition of the variable cyclic characteristic of hand OA. In response to US Food and Drug Administration request, the duration of the study was extended to determine safety and efficacy at Week 8.

Measurement of the 3 coprimary efficacy indices at Weeks 1, 2, and 8 were included as secondary outcome measures. Other secondary efficacy outcomes included measurements at each visit (Weeks 1, 2, 4, 6, and 8) of the pain, stiffness, and physical function subscales within the AUSCAN index and OARSI response[26]. The OARSI response is defined as an improvement ≥ 50% and an absolute change ≥ 20 mm in either pain or physical function, or as an improvement ≥ 20% and an absolute change ≥ 10 mm in ≥ 2 of the following: pain, patient global rating of disease, and physical function. For this purpose, OA pain intensity in the dominant hand was the measure of pain and the AUSCAN physical function subscale was the measure of physical function. End-of-study global rating of efficacy (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent) was assessed, and use of rescue medication in the 2 treatment groups was compared.

Patients kept a daily diary recording the number of applications of study medication, the number of tablets of rescue medication taken, and the reason for its use. To assess compliance, patients' diaries, used tubes of study medication, and remaining tablets of rescue medication were collected at each visit. Patients with compliance issues were counseled.

Safety assessments included AE, laboratory test results, and vital signs. Treatment-emergent AE were graded for severity, categorized for likely relationship to trial drug, and coded in the *Medical Dictionary for Regulatory Activities,* Version 7.0.

Statistical analysis. The sample size of 180 patients per treatment group was chosen to provide 90% power to detect a statistically significant difference in OA pain intensity (100-mm VAS) if the true difference between diclofenac sodium gel and vehicle was 7 mm with a standard deviation of 20.5 mm. This sample size and power to detect were based on assumptions from a previous 4-week placebo-controlled study comparing an oral NSAID with placebo in hand OA[27]. Use of this sample size and power are supported by results from a 3-week study comparing diclofenac diethylamine 1.16% gel with oral ibuprofen (400 mg 3 times daily) in patients with hand OA[28]. Based on these studies, it was assumed that the standard deviations of the other outcomes would be < 20.5 mm, so the power to detect a difference of 7 mm would exceed 90%. Assuming a correlation of 0.6 among the 3 outcomes, power to detect a statistically significant difference on all 3 outcomes is approximately 80%.

The primary population for the efficacy and safety analyses was all treated patients. Patients with a baseline score ≤ 10 mm on a primary efficacy outcome were excluded from the analysis of that specific outcome (before unblinding) because efficacy would be difficult to demonstrate with such a low baseline value. This applied only to the AUSCAN index and global rating of disease because patients with VAS-rated pain intensity ≤ 10 mm during the previous 24 hours would not have been randomized.

Patients were classified at baseline as either having or not having OA pain in the CMC-1 joint (CMC-1 status). Differences between treatment groups on all efficacy outcomes assessed on a 100-mm VAS were tested with analysis of covariance. For these analyses, the main effects included treatment, study site, and CMC-1 status, with baseline as a covariate. Statistical significance was defined as a 2-sided p value < 0.05.

Differences between treatment groups in OARSI response rates were tested with logistic regression with main effects of treatment and CMC-1 status. Differences between treatment groups on the end-of-study global rating of efficacy were tested with the proportional odds logit model with main effects that included treatment, study site, and CMC-1 status. Interactions of treatment with other main effects were removed from all final models upon determination that they were not statistically significant.

If a patient missed one or more assessments but then continued in the study, missing assessments were imputed as the average of the last preceding and the first following nonmissing assessments, rounded down to the nearest integer. Missing postbaseline efficacy assessments for patients who discontinued were imputed using the last-observation carried-forward approach. This included carrying the baseline assessment forward if there was no subsequent assessment. If a patient discontinued owing to lack of efficacy, the worst of the last observation or the baseline observation was carried forward. If a patient discontinued owing to lack of efficacy and did not assess the global rating of efficacy, that patient's rating was imputed as "Poor." Missing data from hand examinations or safety evaluations were not replaced.

Failed treatment was defined as a series of ≥ 4 consecutive days, starting after Day 7, during which the patient treated hand OA pain with at least 2 g acetaminophen, at least half the maximum daily over-the-counter (OTC) dose of an NSAID, or ≥ 1 single prescription-strength dose of a nonselective or COX-2–selective NSAID. Assessments from all subsequent study visits were replaced by the worst of the latest preceding assessment or the baseline assessment.

Efficacy assessments from a primary efficacy visit (Week 4 or 6) were not used if the patient had not used study medication on the day of the primary efficacy visit and the 2 preceding days or if the patient was using an oral NSAID or opioid for any purpose (other than OA pain in the hands) on the day of the primary efficacy visits. Assessments at the affected visit were replaced by assessments from the latest preceding unaffected visit carried forward.

RESULTS

Patients. A total of 809 patients from 65 centers were enrolled in the study, 385 of whom were randomized (198 in the diclofenac sodium gel group and 187 in the vehicle group; Figure 1). All received ≥ 1 dose of trial drug [intent-to-treat (ITT) population]. Roughly 87% of patients in each group completed the study. The most common reason for premature discontinuation was unsatisfactory therapeutic effect (4.0% diclofenac sodium gel and 7.0% vehicle).

Baseline demographic and background characteristics in the ITT population were similar for the diclofenac sodium gel and vehicle treatment groups (Table 1): about 77% of patients were women, 63% were aged 51 to 70 years, 91% were right-handed, 71% had a painful CMC-1 joint in the dominant hand at randomization, 52% were taking oral NSAID before the screening visit, and 52% had a Kellgren-Lawrence grade of 3.

Four patients were excluded from the analysis of global rating of disease and one from the AUSCAN analysis for having baseline values ≤ 10 mm. Treatment failed in 49 patients (24 diclofenac sodium gel, 25 vehicle), most commonly for excessive use of rescue medication or other OTC or prescription analgesics to relieve hand OA pain. These patients were discontinued from the study, and assessments from all subsequent study visits were replaced by the worst of the latest preceding assessment or the baseline assessment. Most discontinuations (40 of 49) occurred between Weeks 1 and 4. Excluded data from Week 4 or 6 (11 diclofenac sodium gel, 7 vehicle) were due to dosing issues or concurrent use of disallowed medications.

Efficacy. Table 2A and Table 2B summarize primary outcome measures at baseline, and Weeks 4, 6, and 8. At Week 4, diclofenac sodium gel was significantly superior to vehicle on 2 of the 3 primary outcome measures (OA pain intensity and total AUSCAN score), but not on the global rating of disease activity (p = 0.06). Diclofenac sodium gel treatment reduced mean VAS pain intensity by 42.3% (31.1 mm) versus baseline, which was 30.1% greater than the reduction observed with vehicle (23.9 mm). Diclofenac sodium gel produced a 35.0% (23.5 mm) reduction in total AUSCAN score and a 36.1% (20.8 mm) reduction in global rating of disease. In the vehicle group, reductions in total AUSCAN (16.8 mm) and global rating of disease (14.8 mm) were 39.9% and 40.5% lower, respectively, than in the diclofenac sodium gel group.

At Week 6, diclofenac sodium gel was significantly superior to vehicle in all primary outcome measures. Diclofenac sodium gel reduced mean VAS pain intensity by 45.8% (33.7 mm), total AUSCAN score by 38.5% (25.9 mm), and global rating of disease by 40.1% (23.1 mm) compared with baseline. In the vehicle group, reductions from baseline in VAS pain intensity (26.7 mm), total AUSCAN (18.6 mm), and global rating of disease (16.3 mm) were 26.2%, 39.2%, and 41.7% lower, respectively, than in the diclofenac sodium gel group. At Week 8, reductions in VAS pain intensity and global rating of disease were numerically, although not significantly, greater with diclofenac sodium gel than with vehicle. However, diclofenac sodium gel remained significantly superior to vehicle on total AUSCAN score through the end of the study.

Table 2A and Table 2B summarize scores for the AUSCAN pain, stiffness, and functional indices at baseline and Weeks 4, 6, and 8. At Weeks 4 and 6, diclofenac sodium gel was significantly superior to vehicle on each of the 3 AUSCAN indices. At Week 8, diclofenac sodium gel remained significantly superior to vehicle on the AUSCAN stiffness (p < 0.048) and functional (p < 0.017) indices and was numerically superior to vehicle on the pain index (p < 0.09).

Figure 2 displays the time course for each primary out-

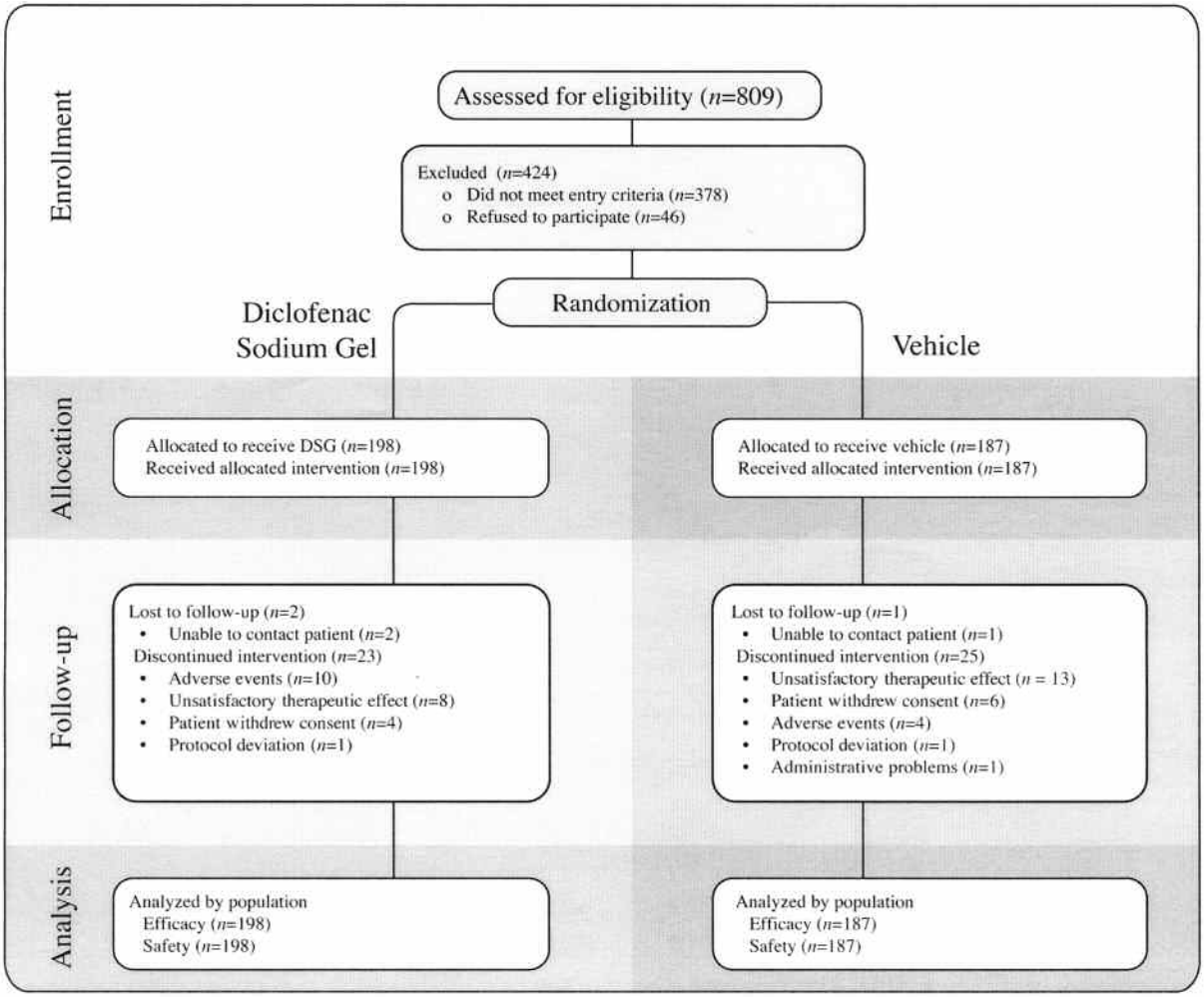

Figure 1. The progress of the study. DSG: diclofenac sodium gel 1%.

come and the 3 AUSCAN subscales. Diclofenac sodium gel produced statistically significant improvement relative to vehicle in VAS pain intensity and total AUSCAN score beginning at Week 1 but did not show significant improvement relative to vehicle on global rating of disease until Week 6. Peak efficacy was observed at Week 6, after which between-group differences diminished as pain levels plateaued in the diclofenac sodium gel group but continued to decline in the vehicle group. Least-squares mean differences at Week 6 were 6.3 mm for OA pain intensity, 7.1 mm for total AUSCAN score, and 6.0 mm for global rating of disease activity. At Week 8, the least-squares mean difference between treatments declined to 5.4 mm for pain intensity, reflecting a nonsignificant trend favoring diclofenac sodium gel (p = 0.06). Least-squares mean differences for total AUSCAN remained statistically significant (6.0 mm; p = 0.028), but the between-group difference in scores on the global rating of disease (4.5 mm; p = 0.11) was no longer significant.

A similar time course was observed for efficacy measured by the 3 subscales of the AUSCAN index. A significant efficacy benefit with diclofenac sodium gel versus vehicle was demonstrated for all 3 subscales by Week 1. Between-group differences peaked at Week 6 and narrowed through Week 8. Least-squares mean differences at Week 6 were 6.1 mm (p = 0.021) for pain, 8.0 mm (p = 0.005) for stiffness, and 7.5 mm (p = 0.005) for function. At Week 8, the least-squares mean difference for pain was not significant (4.7 mm; p = 0.09), but the least-squares mean differences for stiffness (5.8 mm; p = 0.048) and function (6.7 mm; p = 0.017) were significant.

Table 3 summarizes results for additional secondary efficacy outcomes. The proportion of OARSI responders in the diclofenac sodium gel group increased steadily from 55.6% at Week 1 to 65.7% at Week 8 and was typically about 10% higher than the proportion of responders in the vehicle group. For OA pain intensity in the nondominant hand, diclofenac sodium gel was significantly superior to vehicle at Weeks 1 and 6. Diclofenac sodium gel was significantly superior to vehicle in the end-of-study global rating of effi-

Table 1. Baseline demographic characteristics by treatment group (intent-to-treat population).

Characteristic	Diclofenac Sodium Gel, n = 198	Vehicle, n = 187
Men, %	23.2	23.0
Race, %		
White	87.4	90.9
Black	5.6	2.1
Asian	1.5	0
Other	5.6	7.0
Mean age ± SD, yrs	63.6 ± 10.3	64.7 ± 9.6
Range	40–92	40–87
Mean height ± SD, cm*	165.0 ± 9.8	164.7 ± 10.1
Mean weight ± SD, kg†	76.6 ± 18.4	77.8 ± 20.0
Mean BMI ± SD*†, kg/m^2	28.0 ± 6.3	28.6 ± 6.5
Range	17.6–55.0	17.5–49.8
Right-handed, %	92.9	89.3
Kellgren-Lawrence grade, %		
1	19.2	14.4
2	27.8	33.7
3	53.0	51.9
Mean painful joints in dominant hand ± SD, n	5.2 ± 2.5	5.3 ± 3.0
Painful CMC-1 joint, %	67.2	75.9
Painful DIP/PIP (digits 2–3), %	78.8	77.5
Currently treating with NSAID	54.5	48.7

* Baseline height and BMI measurements were not available for 1 patient in the diclofenac sodium gel group. † Baseline weight and BMI measurements were not available for 1 patient in the vehicle group. BMI: body mass index; CMC-1: first carpometacarpal joint; DIP: distal interphalangeal joints; NSAID: nonsteroidal antiinflammatory drug; PIP: proximal interphalangeal joints.

cacy (p = 0.008). A total of 47.7% of patients in the diclofenac sodium gel group rated treatment as Very Good or Excellent versus 36.5% in the vehicle group.

The treatment groups did not differ in patterns of rescue medication use. Most patients used rescue medication at some point during the trial (82.1% diclofenac sodium gel, 82.6% vehicle). The mean number of acetaminophen tablets taken per day (over all days in all patients) was 0.9 in the diclofenac sodium gel group and 1.1 in the vehicle group; the mean number of days patients used acetaminophen was 15.3 in the diclofenac sodium gel group and 16.7 in the vehicle group. The proportion of patients using acetaminophen decreased in each group from roughly 70% at Week 1 to roughly 50% at Week 8.

Compliance and drug exposure. The mean number of doses applied daily was 3.8 in the diclofenac sodium gel group and 3.7 in the vehicle group. The mean number of weeks patients were compliant (applied > 20 doses/week) was similar between groups (7.0 weeks, diclofenac sodium gel; 6.6 weeks, vehicle). Compliance with treatment for > 6 weeks was similar in the diclofenac sodium gel (77.8%) and vehicle (75.9%) groups. The mean level of compliance in each group was > 75% in every week of the study. Most patients (58.6% diclofenac sodium gel, 57.8% vehicle) were compliant for all 8 weeks.

Safety. At least one treatment-emergent AE was reported by 52.0% of patients in the diclofenac sodium gel group and by 43.9% of patients in the vehicle group (Table 4). Most AE were of mild severity. Very few patients (2.5%, diclofenac sodium gel; 2.1%, vehicle) experienced severe treatment-emergent AE. The most frequent treatment-emergent AE was headache (11.1%, diclofenac sodium gel; 10.2%, vehicle). The overall incidence of GI AE was 7.6% in the diclofenac sodium gel group and 3.7% in the vehicle group, and most were of mild severity. The most frequent GI AE was diarrhea (2.0%, diclofenac sodium gel; 1.1%, vehicle). No ulcers or GI bleeding were reported.

Suspected drug-related treatment-emergent AE occurred in 9.1% of the diclofenac sodium gel group and 3.7% of the vehicle group. Application-site reactions occurred in 4.5% of the diclofenac sodium gel group and 2.1% of the vehicle group. The most common application-site reaction was paresthesia (2.5%, diclofenac sodium gel; 1.1%, vehicle). No other application-site reaction was suspected to be treatment-related for more than 2 (1%) patients in either treatment group. Only 2 (1%) patients in the diclofenac sodium

Table 2A. Primary efficacy outcomes at baseline (intent-to-treat population).

Outcome Measure	Diclofenac Sodium Gel, n = 198 Rating		Vehicle, n = 187 Rating		
	Mean ± SD	Range	Mean ± SD	Range	p§
OA pain intensity*	73.6 ± 15.6	40–100	73.6 ± 14.2	41–100	NS
Total AUSCAN score†	67.2 ± 17.4	13–96	66.7 ± 16.8	10–98	NS
Pain index*	66.3 ± 17.9	12–98	66.8 ± 16.2	11–99	NS
Stiffness index†	66.0 ± 22.8	1–98	66.6 ± 23.9	4–100	NS
Functional index††	67.9 ± 18.8	9–99	66.7 ± 18.4	8–99	NS
Global rating of disease††	57.6 ± 19.0	5–97	56.5 ± 19.9	9–97	NS

* 0 = no pain, 100 = extreme pain. † 0 = no pain/stiffness/difficulty, 100 = extreme pain/stiffness/difficulty. †† 0 = very good, 100 = very poor. § Difference in least-squares mean for vehicle minus that for diclofenac sodium gel. AUSCAN: Australian/Canadian Osteoarthritis Hand Index; BL: baseline assessment; NS: not significant.

Table 2B. Primary efficacy outcomes at Weeks 4, 6, and 8 (intent-to-treat population).

Outcome Measure	Diclofenac Sodium Gel, n = 198		Vehicle, n = 187		
	Rating Mean ± SD	Change From BL Mean ± SD %	Rating Mean ± SD	Change From BL Mean ± SD	p[§] (change vs vehicle, %)
Week 4					
OA pain intensity*	42.6 ± 30.5	31.1 ± 25.8 (–42.3)	49.7 ± 28.8	23.9 ± 27.0 (–32.5)	0.018 (+30.1)
Total AUSCAN score[†]	43.7 ± 28.2	23.5 ± 24.4 (–35.0)	50.2 ± 27.3	16.8 ± 25.2 (–25.2)	0.011 (+39.9)
Pain index*	42.2 ± 28.7	24.1 ± 24.8 (–36.3)	48.3 ± 27.4	18.5 ± 25.1 (–27.7)	0.027 (+30.3)
Stiffness index[†]	42.6 ± 30.1	23.4 ± 27.3 (–35.4)	50.4 ± 30.1	16.2 ± 28.7 (–24.3)	0.011 (+44.4)
Functional index[††]	44.7 ± 28.6	23.2 ± 25.4 (–37.4)	50.8 ± 28.3	15.9 ± 26.1 (–23.8)	0.01 (+45.9)
Global rating of disease[††]	37.5 ± 26.8	20.8 ± 27.1 (–36.1)	41.9 ± 25.8	14.8 ± 28.1 (–26.2)	0.06 (+40.5)
Week 6					
OA pain intensity*	39.9 ± 31.6	33.7 ± 27.8 (–45.8)	46.9 ± 29.9	26.7 ± 28.0 (–36.3)	0.023 (+26.2)
Total AUSCAN score[†]	41.4 ± 28.8	25.9 ± 25.1 (–38.5)	48.5 ± 28.1	18.6 ± 26.2 (–27.9)	0.006 (+39.2)
Pain index*	40.2 ± 29.1	26.1 ± 25.6 (–39.4)	46.7 ± 28.7	20.1 ± 26.5 (–30.1)	0.021 (+30.0)
Stiffness index[†]	40.9 ± 31.1	25.2 ± 28.7 (–38.2)	49.5 ± 28.1	17.2 ± 30.0 (–25.8)	0.005 (+46.5)
Functional index[††]	42.0 ± 29.3	25.8 ± 26.1 (–38.0)	48.9 ± 28.7	17.8 ± 26.9 (–26.7)	0.005 (+44.9)
Global rating of disease[††]	35.2 ± 27.3	23.1 ± 27.0 (–40.1)	40.4 ± 26.3	16.3 ± 28.0 (–28.8)	0.023 (+41.7)
Week 8					
OA pain intensity*	38.1 ± 32.7	35.5 ± 28.9 (–48.2)	44.0 ± 30.9	29.6 ± 29.5 (–40.2)	0.06 (+19.9)
Total AUSCAN score[†]	40.5 ± 29.9	26.7 ± 26.6 (–39.7)	46.5 ± 28.7	20.5 ± 27.3 (–30.7)	0.028 (+30.2)
Pain index*	39.2 ± 30.1	27.2 ± 26.9 (–41.0)	44.2 ± 29.5	22.5 ± 27.8 (–33.7)	0.09 (+20.9)
Stiffness index[†]	39.4 ± 32.1	26.6 ± 30.0 (–40.3)	45.5 ± 31.4	21.1 ± 30.5 (–31.7)	0.048 (+26.1)
Functional index[††]	41.4 ± 30.4	26.5 ± 27.6 (–39.0)	47.5 ± 28.3	19.2 ± 28.0 (–28.8)	0.017 (+38.0)
Global rating of disease[††]	34.2 ± 28.2	24.2 ± 28.1 (–42.0)	37.9 ± 27.4	18.8 ± 29.2 (–33.3)	0.11 (+28.7)

* 0 = no pain, 100 = extreme pain. [†] 0 = no pain/stiffness/difficulty, 100 = extreme pain/stiffness/difficulty. [††] 0 = very good, 100 = very poor. [§] Difference in least-squares mean for vehicle minus that for diclofenac sodium gel. AUSCAN: Australian/Canadian Osteoarthritis Hand Index; BL: baseline assessment; NS: not significant.

gel group and none in the vehicle group had a GI AE believed to be drug-related.

Laboratory, physical examination, and vital sign observations were unremarkable. There were no changes in blood pressure.

A total of 14 patients — 10 (5.1%) in the diclofenac sodium gel group and 4 (2.1%) in the vehicle group — experienced AE that led to trial drug discontinuation. Of the 10 patients treated with diclofenac sodium gel, 6 discontinued owing to AE suspected to be related to study medication. These included dermatitis, allergic dermatitis, application-site dermatitis, dry mouth, nausea/swollen tongue, and fungal infection. Only one patient in the vehicle group discontinued because of an AE (application-site dermatitis) suspected to be related to study medication.

DISCUSSION

In this trial, diclofenac sodium gel applied 4 times daily for mild to moderate (Kellgren-Lawrence grade 1–3) hand OA achieved the primary endpoints of reduced pain and improved function relative to vehicle at 4 and 6 weeks and improved patient global rating of disease activity relative to vehicle at 6 weeks. Relative to baseline, diclofenac sodium gel was associated with 42% to 45% reductions in VAS pain intensity, 35% to 40% reductions in total AUSCAN, and 36% to 40% reductions in global rating of disease after 4 and 6 weeks. Secondary outcome measures supported the results of the primary measures. Superiority of diclofenac sodium gel over vehicle on most primary and secondary outcome measures was evident by Week 1, the earliest assessment of efficacy in the protocol, and peaked at Week 6. Thereafter, a decline in between-group efficacy differences reflected stabilization of pain in the diclofenac sodium gel group and a catch-up effect in the placebo group. This catch-up is consistent with the usual time course of pain resolution in an OA flare.

The topical application of both diclofenac sodium gel and vehicle had equal potential for rubefacient effects in the 2 groups. Although the vehicle had no analgesic properties of its own, analgesia in the vehicle group may have been attributable to a beneficial effect of rubbing. In the diclofenac sodium gel group any positive effect of rubbing would be additive to the benefits of the active ingredient, diclofenac sodium. The observation that rubbing alone was

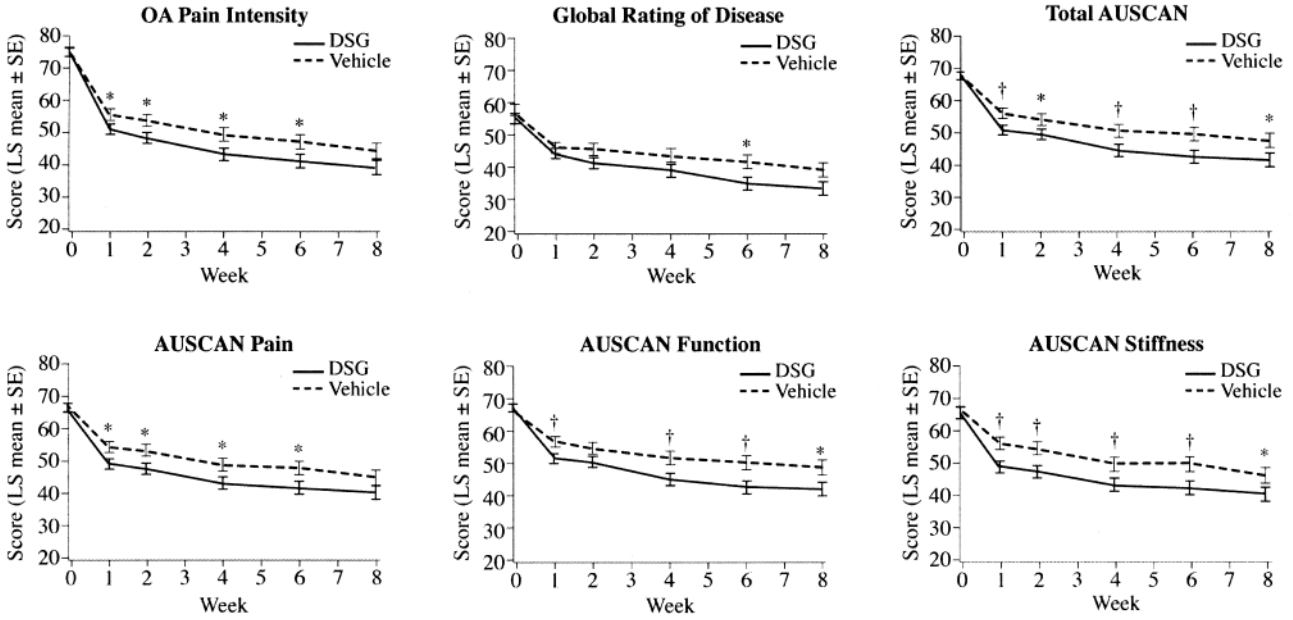

Figure 2. Time profile for primary and secondary outcome measures. AUSCAN: Australian/Canadian Osteoarthritis Hand Index; DSG: diclofenac sodium gel 1%; LS: least-squares. *p < 0.05; †p < 0.01; p values refer to differences between treatment groups for change in score in the dominant hand from baseline at particular timepoints.

Table 3. Secondary efficacy outcomes (intent-to-treat population).

	Diclofenac Sodium Gel, n = 198	Vehicle, n = 187	p
OARSI Response Rate, Dominant Hand, %			
Week			
1	55.6	41.7	0.008
2	59.1	50.3	0.06
4	62.6	50.3	0.013
6	64.1	55.1	0.054
8	65.7	56.7	0.06
	Diclofenac Sodium Gel, n = 198	Vehicle, n = 187	p
OA Pain Intensity, Nondominant Hand, mean ± SD			
Baseline	27.8 ± 17.9	30.2 ± 18.2	
Change from baseline to			
Week 1	4.5 ± 16.7	2.0 ± 18.3	0.014
Week 2	5.3 ± 18.1	3.6 = 19.6	0.06
Week 4	6.4 ± 18.2	4.1 ± 21.1	0.06
Week 6	6.7 ± 18.9	4.3 ± 21.3	0.048
Week 8	6.9 ± 19.7	5.7 ± 21.6	0.20
	Diclofenac Sodium Gel, n = 195	Vehicle, n = 181	p
End-of-Study Global Rating of Efficacy, %			
Rating			
0 = poor	22.6	29.3	
1 = fair	12.3	16.0	
2 = good	17.4	18.2	
3 = very good	28.7	24.9	
4 = excellent	19.0	11.6	
Mean ± SD	2.09 ± 1.44	1.73 ± 1.41	0.008*

* Based on least-squares mean difference from proportional odds logit model. OARSI: Osteoarthritis Research Society International.

Table 4. Treatment-emergent adverse events occurring in ≥ 2% of patients (all patients treated).

Adverse Event, %	Diclofenac Sodium Gel, n = 198	Vehicle, n = 187
Any adverse event	52.0	43.9
Gastrointestinal adverse event	7.6	3.7
Most frequent individual adverse events		
Headache	11.1	10.2
Back pain	6.1	7.5
Arthralgia	3.5	7.0
Pain in extremity	3.5	3.2
Sinusitis	3.0	0.5
Neck pain	3.0	0.5
Application-site paresthesia	2.5	1.1
Pharyngolaryngeal pain	2.5	0
Diarrhea	2.0	1.1
Cough	2.0	1.1
Upper respiratory tract infection	2.0	0.5

less beneficial than rubbing with diclofenac sodium gel is consistent with research showing that physiotherapy with joint massage as a primary component was numerically but not significantly superior to usual care in patients with knee OA[29].

Research in patients with knee OA suggests that reductions of 40% (20 mm) in VAS pain intensity and 39% (18 mm) in clinical global rating of disease relative to baseline constitute clinically meaningful effects[30]. Improvements with diclofenac sodium gel met both thresholds, whereas improvements with vehicle were typically 30% to 40% lower and beneath these thresholds. Even at Week 8, when between-group differences for 2 of the 3 primary outcome

measures were not significant, improvements relative to baseline were of a clinically meaningful magnitude. Although improvement in VAS pain intensity in the nondominant hand was < 40%, baseline pain levels were also much lower, making substantial improvements unlikely. Nonetheless, improvements in the diclofenac sodium gel group (16%–25%) were 47% to 125% greater than the vehicle group at Weeks 1 through 6, and 21% greater at Week 8.

Diclofenac sodium gel was generally well tolerated. The most common treatment-related AE were skin reactions, which occurred in 4.5% of the diclofenac sodium gel group. Most AE in patients treated with topical diclofenac sodium gel were mild. Severe GI (e.g., ulcers, bleeding), cardiac, or renal events reported with oral NSAID did not occur in patients treated with diclofenac sodium gel.

Topical diclofenac produces efficacious levels of drug in local tissue[31] with reduced systemic exposure[32]. Concern about potential GI, renal, and cardiac AE has increased interest in topical administration of NSAID to reduce systemic exposure. European recommendations prefer topical over systemic treatments for OA, especially for mild to moderate pain[33]. OARSI recommendations for the management of hip and knee OA state that topical NSAID are effective as an adjunct or alternative to oral analgesic/antiinflammatory agents[34]. Consistent with these recommendations, data from our trial suggest clinical efficacy and good tolerability with topical diclofenac sodium gel.

Few published randomized controlled trials have evaluated topical nonsalicylate NSAID in patients with hand OA[28,35-38]. In a double-blind trial comparing topical diclofenac (Voltaren® Emulgel®, applied 4 times daily) with oral ibuprofen (1200 mg/day) in patients with symptomatic hand OA, topical diclofenac gel was as effective as oral ibuprofen, based on the proportion achieving ≥ 40% reduction in pain relative to baseline[28]. Moreover, the diclofenac gel was better tolerated than oral ibuprofen, with fewer severe AE (2.4% vs 5.8%, respectively), fewer discontinuations (1.2% vs 8.3%), and fewer withdrawals due to adverse GI events (0.6% vs 5.1%)[28].

In a double-blind equivalence trial comparing topical diclofenac solution with oral diclofenac in patients with knee OA, topical and oral diclofenac showed equivalent efficacy, but oral diclofenac was associated with a higher incidence of GI AE, including severe abdominal pain, dyspepsia, and diarrhea[39]. In our report, the overall incidence of GI AE was 7.6% in the diclofenac sodium gel group and 3.7% in the vehicle group, and most of these AE were of mild severity. Treatment-related application-site paresthesia occurred in only 2.5% of patients treated with diclofenac sodium gel and 1.1% of patients in the vehicle group. No other treatment-related application-site reaction occurred in > 1% of patients in either group.

Most trials assessing topical agents in OA have been of short duration. A 2004 metaanalysis of topical NSAID in patients with chronic musculoskeletal pain concluded that these agents have demonstrated efficacy and safety in trials lasting up to 2 weeks, but additional trials would be required to establish their value during extended treatment[20]. Two studies demonstrating 12-week efficacy of topical diclofenac solution in knee OA have been published[40,41]; however, longterm data on topical NSAID in hand OA are still lacking[37]. Although not a longterm trial, our study provides much needed evidence that diclofenac sodium gel is safe and effective over a clinically relevant period of time. Diclofenac sodium gel showed statistically significant superiority compared with vehicle beginning at 1 week. Between-group differences favoring diclofenac sodium gel peaked at 4 to 6 weeks on most outcome measures and narrowed thereafter, reflecting an increase in efficacy for vehicle, not a reduction in efficacy for diclofenac sodium gel. This catch-up effect in the vehicle group likely represents the natural resolution of pain at the end of an OA flare. Thus, diclofenac sodium gel was effective over a period that has real clinical relevance. Additional research is needed to determine whether diclofenac sodium gel provides effective pain relief as a maintenance therapy over longer periods.

In this trial, diclofenac sodium gel provided sustained symptom reduction (pain relief) in hands affected by OA. Although diclofenac sodium gel also improved measures of function, it is important to note that the US Food and Drug Administration approves diclofenac sodium gel only for the indication of pain relief. These results suggest that this topical diclofenac sodium gel (Voltaren® Gel) should be considered a safe and effective treatment option for patients with hand OA. Future studies are needed to provide information on the potential benefits of multimodal therapy, with topical therapy as a key component.

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