Equivalence Study of a Topical Diclofenac Solution (Pennsaid®) Compared with Oral Diclofenac in Symptomatic Treatment of Osteoarthritis of the Knee: A Randomized Controlled Trial

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ABSTRACT. ***Objective***. To compare the safety and efficacy of a topical diclofenac solution versus oral diclofenac in relieving the symptoms of primary osteoarthritis (OA) of the knee, in a randomized, double-blind, double-dummy equivalence trial.

Methods. A total of 622 men and women with radiological evidence of primary knee OA and mild to severe symptoms were randomly assigned to treatment with a topical diclofenac solution plus placebo oral capsules, or placebo topical solution plus oral diclofenac (50 mg) capsules. Patients applied 50 drops of study solution and took 1 study capsule 3 times daily for 12 weeks. Efficacy variables were pain and physical function, measured by the Western Ontario and McMaster Universities (WOMAC) VA 3.1 OA Index, and patient global assessment (PGA). Equivalence in the per-protocol group was based on previously defined ranges of clinically significant difference. Safety was assessed by evaluation of adverse events, vital signs, and laboratory data.

Results. The difference in mean (95% CI) change scores (final minus baseline) between treatments was 13.3 mm (–8.6 to 35.2) for pain (total scale 500 mm), 71.0 mm (–2.4 to 144.5) for physical function (total scale 1700 mm), and 4.3 mm (–1.2 to 9.8) for PGA (total scale 100 mm). The CI for each efficacy variable fell within the predefined equivalence ranges (pain, ± 75 mm; physical function, ± 255 mm; PGA, ± 20 mm), indicating that no clinically relevant difference was found between the 2 treatment arms. Safety analyses of patients applying topical diclofenac solution revealed some minor skin irritation at the application site — mostly skin dryness in 83/311 (27%) patients — but a significantly reduced incidence, relative to oral diclofenac, of total and severe gastrointestinal (GI) adverse events, including dyspepsia, abdominal pain, diarrhea, and nausea. The number of patients developing abnormal liver function tests (including clinically significant elevation), hemoglobin, and creatinine clearance was significantly higher in the oral diclofenac group.

Conclusion. Application of this topical diclofenac solution to the knee of patients with OA produced relief of symptoms equivalent to oral diclofenac, with minor local skin irritation, but significantly reduced incidence of diclofenac-related GI complaints and abnormal laboratory values. (J Rheumatol 2004;31:2002–12)

Key Indexing Terms:
TOPICAL DICLOFENAC NONSTEROIDAL ANTIINFLAMMATORY DRUGS
OSTEOARTHRITIS EQUIVALENCE STUDY WOMAC INDEX

Osteoarthritis (OA) is the most common arthritic condition[1], with the incidence and prevalence projected to rise as the elderly proportion of the population increases[2,3]. Currently recommended nonpharmacological and pharmacological treatment of OA aims to control pain and physical dysfunction while avoiding therapeutic adverse effects[4–7]. Nonsteroidal antiinflammatory drugs (NSAID) are commonly used for management of OA and are effective in relieving the pain and physical dysfunction. However, their use is associated with deleterious gastrointestinal (GI) effects, which range from mild heartburn and bloating to serious ulceration, perforation, obstruction, and bleeding, and with hepatic and renal toxic effects[8–10]. The newer cyclooxygenase-2 selective NSAID report efficacious results with a diminished risk of GI toxicity[11–14]. However, their reported safety profile has come under scrutiny with suggestion of other serious harmful effects, including increased incidence of thrombotic cardiovascular events[15,16].

Topical NSAID offer an attractive alternative to oral

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therapy in relieving the symptoms of OA, with minimal adverse side effects, presumably due to less systemic absorption of the active drug. NSAID applied to the skin as gels, creams, sprays, and foams (several have been approved in Europe) have been reviewed and are thought to reduce the pain associated with rheumatic disorders and soft tissue injuries[17–19]. Despite published reports of their efficacy, the British Society for Rheumatology describes the current evidence for topical NSAID as insufficient[5], while the American College of Rheumatology recommends the use of topical analgesics in the treatment of OA only in patients not responding to acetaminophen and wishing to avoid systemic therapy[4]. Recently, a topical diclofenac solution (Pennsaid®, Dimethaid Health Care Ltd., Markham, Ontario, Canada) was approved in several European countries and in Canada for the treatment of symptomatic OA. Previous superiority trials using this topical diclofenac solution showed it decreased pain and stiffness and improved the physical function and global assessment of patients with primary OA of the knee, with minimal systemic side effects and only minor skin irritation (predominantly dry skin) at the application site[20–22].

Only a few published studies have compared topical versus oral NSAID therapy[17–19]. Recent reviews on equivalence trials have stressed 2 important methodological principles: the efficacy of the study drug should first be demonstrated in a placebo-controlled superiority trial, and the equivalence trial should be adequately powered, with prior definition of the equivalence range[23,24].

We describe the results of a 12-week equivalence study of a topical diclofenac solution compared with oral diclofenac in the treatment of the symptoms of primary OA of the knee.

MATERIALS AND METHODS

Patients and inclusion criteria. This randomized, double-blinded study was conducted at 41 physician outpatient practices in Canada between September 2001 and September 2002, following approval by the appropriate institutional review boards. Eligible patients, who were identified by study investigators at a screening visit, included men and nonpregnant women between 40 and 85 years old, with symptomatic primary OA of the knee and a recent (within 3 mo) radiographic examination showing "osteoarthritis." All radiographs were then sent to a central radiologist (for practical reasons this occasionally occurred after randomization) for confirmation and staging of deterioration and abrasion of articular cartilage and/or formation of new bone at the joint space, based on standard criteria for OA[25]. All patients signed an informed consent statement. During the washout period, all NSAID, narcotic analgesics, acetaminophen, and other prohibited medications/therapies were discontinued for 3–10 days. At baseline, patients were to be enrolled if they had at least mild symptoms of OA in the study knee, based on a Western Ontario and McMaster Universities (WOMAC) VA3.1 OA Index[26] pain subscale total score of at least 125 mm (flare of pain following washout was not required), a WOMAC physical function subscale total score of at least 425 mm and a patient global assessment (PGA) score of at least 25 mm (see "Efficacy Assessments" for further explanation of the WOMAC). All case report forms were sent to the sponsor for remeasurement and data input (for practical reasons this occurred after randomization).

Exclusion criteria. Patients were excluded if they had secondary arthritis related to syphilitic neuropathy, ochronosis, psoriasis, metabolic bone disease, or acute trauma; chondrocalcinosis with a history of pseudogout; fibromyalgia; previous major surgery to the knee or recommendation for knee replacement/reconstruction; recent intraarticular viscosupplementation; current or recent corticosteroid use (orally, intramuscularly, or topically); topical product use at the application site; history of sensitivity to any of the study drugs, acetylsalicylic acid (ASA), or other NSAID; severe, uncontrolled cardiac, renal, hepatic, or other systemic disease; documented recent gastroduodenal ulcer or GI bleeding; history of alcohol or drug abuse; lactation; concomitant skin diseases at the application site; clinically significant elevation of serum creatinine (≥ 176.8 µmol/l) or of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (≥ 3 times upper limit of normal); or involvement within the previous 30 days in another investigational drug trial. Concomitant medications, including NSAID, ASA, acetaminophen, and other analgesic medications, were prohibited during the study, but patients were allowed to continue stable ASA therapy (up to 325 mg/day) for cardiovascular prophylactic purposes.

Interventions. Following the screening and washout periods, each eligible patient attending the baseline visit was assigned the next numbered study kit at that clinic. Study kits were manufactured to contain one of 2 randomly assigned treatments: (1) topical diclofenac solution, Pennsaid® [consisting of 1.5% (w/w) diclofenac sodium in a patented carrier including 45.5% (w/w) dimethyl sulfoxide (DMSO)] plus oral placebo capsules; or (2) oral diclofenac (50 mg) capsules plus topical placebo solution [a modified carrier including 2.3% (w/w) DMSO, but no diclofenac]. Patients were instructed to apply 50 drops of study solution (about 1.55 ml of active solution) around the affected knee — 20 drops to the front and 10 drops to each side and the back, without massage (the first dose was applied under observation) — and take one study capsule orally, 3 times daily for up to 12 weeks. Planned total daily dose for active treatments was about 4.6 ml of topical diclofenac (containing about 75 mg diclofenac) or 150 mg oral diclofenac. Compliance with the dosing regime was verified by weighing bottles at clinic visits. Patients with pain in the opposite knee were allowed to treat it with study solution as patients using oral diclofenac would automatically be treating both knees. However, only one knee — the one with the greater pain score at baseline — was evaluated for efficacy.

Randomization and blinding. Study kits were assembled according to a computer-generated randomization schedule created by an external statistician, using a block size of 4. To ensure complete blinding, the randomization sequence was concealed from investigators, support staff, patients, and the sponsor's clinical research personnel until final data lock and transfer of the data to the external statistician. Masking of the active treatments was achieved via the use of clear and colorless active and placebo solutions in identical bottles, identical capsules for oral diclofenac and placebo, identical bottle labels differing only in the kit number and the addition to the placebo solution of a small quantity of DMSO, which could impart the typical garlic odor/taste following topical administration.

Efficacy assessments. Efficacy assessment was conducted at the baseline visit and 12 weeks later at the final visit or whenever a patient dropped out of the study. There were no intermediate assessments. Primary efficacy variables were as follows: (1) pain and physical function, as measured by the WOMAC VA3.1 OA Index[26], which is a validated questionnaire[27,28] consisting of 24 items in 3 dimensions (pain: 5 items; physical function: 17 items; stiffness: 2 items), each scored on a 100 mm visual analog scale (VAS), anchored from none (0 mm) to extreme (100 mm); and (2) PGA, scored on a 100 mm VAS anchored from very good (0 mm) to very poor (100 mm). This core set of outcome measures follow the recommendations of Outcome Measures in Arthritis Clinical Trials (OMERACT) III[29] and the Osteoarthritis Research Society (OARSI) guidelines[30,31]. The secondary variable was stiffness as measured by the WOMAC stiffness dimension subscale. Missing item scores were imputed with the average of the other items in that dimension to obtain the total dimension score. Change scores

for these efficacy variables were calculated by subtracting the baseline score from the final score.

Safety assessments. Safety analyses were conducted on all patients randomized into the trial. At baseline and final visits, vital signs were recorded and blood and urine samples were obtained for laboratory analysis. Adverse events (AE) were recorded at clinic visits or from telephone reporting and categorized according to Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART)[32]. A severe AE was defined as one that produced significant impairment of function or incapacitation and was a definite hazard to the patient's health[33]. Diclofenac-related AE were defined based on the *Compendium of Pharmaceuticals and Specialties*[34].

Physician-assessed dermatological evaluation of the study knee was done at 1, 6, and 12 weeks or final visit following the baseline visit. Any abnormality was recorded as an AE.

Statistical analysis. Baseline demographic and clinical variables were analyzed by chi-square or Student's t test. Mean change from baseline in efficacy variables and laboratory parameters were analyzed by analysis of variance. AE incidence and number of patients with change in laboratory value from normal to abnormal were analyzed by chi-square or Fisher's exact test. All statistical tests were 2-sided at the 0.05 level of significance. The equivalence ranges for the primary efficacy variables, as specified in the statistical analysis plan a priori, were based on those established by Bellamy, *et al*[35] [± 15 mm per item in the WOMAC (–75 to 75 mm for pain and –255 to 255 mm for physical function) and –20 to 20 mm for PGA]. To demonstrate that the treatment effects between arms were equivalent, 2-sided 95% confidence intervals (CI) were computed for the difference between treatments in the mean change score for each primary efficacy variable. The 2 treatments would be considered equivalent if the CI of the primary efficacy variables were within the predefined equivalence ranges.

To ensure an adequate number of patients were recruited to demonstrate equivalence, sample size was calculated using the formula suggested by Jones, *et al*[36], specifying a power of 90% and delta (± 8.5 mm per item in the WOMAC and ± 8.75 mm for PGA) and standard deviation estimates based on the difference between topical diclofenac solution and placebo found in previous trials that used a Likert version of the WOMAC. Calculations indicated that 183, 176, and 212 evaluable patients [defined as per-protocol (PP) patients; see below] per treatment group would be required to power for equivalence for pain, physical function, and patient global assessment, respectively.

An intent-to-treat (ITT) and a PP group were defined a priori in the statistical analysis plan, according to International Conference on Harmonisation guidelines[37]. Patients were eliminated from the ITT group if the history and radiographic interpretation by the central radiologist did not confirm primary OA, or if they did not take at least one dose of both solution and capsules. It was planned to perform the primary efficacy analysis on the PP data set, as per accepted statistical principles for equivalence studies[23,24]. Patients in the ITT group were then eliminated from the PP group if they had < 28 days of treatment (see exception, below), < 50% of the planned dose of study drugs, fibromyalgia, or no final assessment (Figure 1). To avoid potential masking of a true difference introduced by eliminating early dropouts (< 28 days of treatment), this criterion was waived for any patient who discontinued treatment because of lack of efficacy or an AE deemed possibly or probably related to the study drug. The criterion of at least 50% of the planned dose of study drugs was still applied.

Role of the funding source. The coauthors along with the sponsor designed this study. The sponsor monitored study conduct at the investigator sites for good clinical practices, performed data entry and secondary analyses, and in collaboration with the coauthors, prepared the draft and final manuscript (according to CONSORT guidelines)[38].

RESULTS

Patients. A total of 1057 patients were screened for this study, of whom 435 were excluded, leaving 622 patients

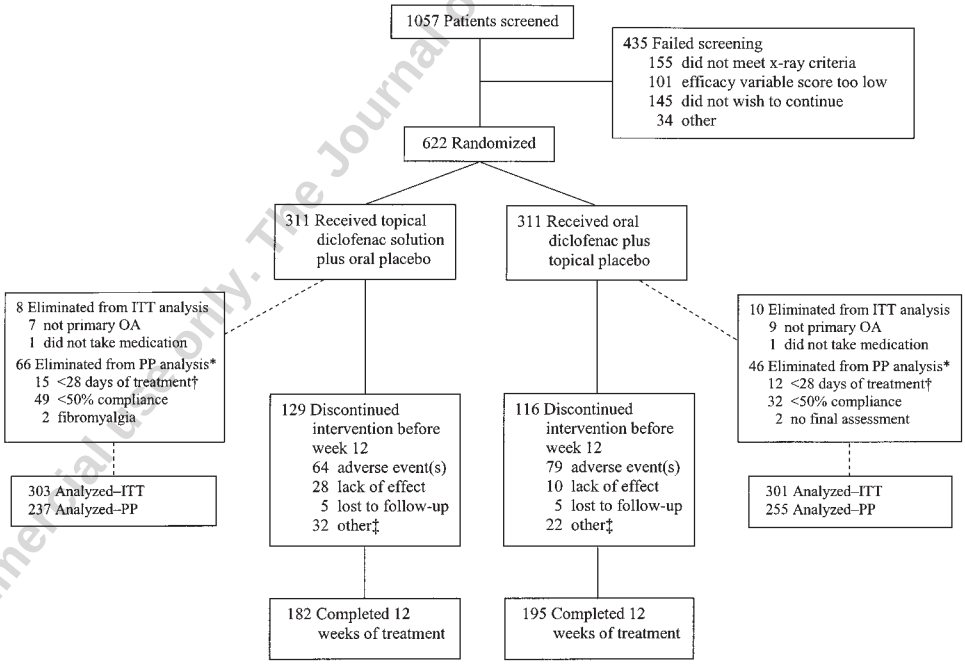

Figure 1. Flow of patients. *For the analysis of equivalence (PP group) of patient global assessment, 3 and 6 patients in the topical diclofenac and oral diclofenac groups, respectively, were excluded because they had no final assessment data for this variable. †A patient who discontinued treatment because of lack of efficacy, or an adverse event deemed possibly or probably related to the study drug, was added back into the per-protocol analysis. ‡Other reasons for discontinuation in the topical diclofenac and oral diclofenac groups included protocol violations (10 and 2 patients), patient noncompliance (8 and 3 patients), and final visit scheduling conflicts (14 and 17 patients).

randomized to active treatment with either topical diclofenac (n = 311) or oral diclofenac (n = 311; Figure 1). There were 377 patients (182 topical diclofenac and 195 oral diclofenac) who completed the full 12 weeks of treatment (Figure 1). The most common reason for discontinuation in both the topical diclofenac and oral diclofenac groups was an AE [64 (21%) and 79 (25%) patients, respectively], followed by lack of efficacy [28 (9%) and 10 (3%) patients, respectively]. Patients treated with topical diclofenac, compared to oral diclofenac, had significantly fewer withdrawals due to GI AE [18 (6%) vs 49 (16%); $p < 0.0001$] and more due to skin-related AE [31 (10%) vs 1 (0.3%); $p < 0.0001$]. Only 10 patients (5 patients per group) were lost to followup.

The randomized treatment groups were comparable ($p > 0.05$) in age, sex, race, other baseline demographics, and baseline efficacy scores (Table 1). Mean age of the patients was 64 years, 101 (16%) were ≥ 75 years, and 356 (57%) patients were women. A total of 239 (77%) topical diclofenac patients and 232 (75%) oral diclofenac patients had pain in the non-study knee and treated it with topical solution.

The mean duration of exposure to active treatment was not significantly different between treatment groups (66 days for topical diclofenac vs 68 days for oral diclofenac; $p = 0.55$). Compliance data indicated that patients on average took 94% (4.4 ml/day) and 91% (2.7 capsules/day) of the planned dose of active topical diclofenac solution and oral diclofenac, respectively. Prophylactic use of ASA was comparable between groups, 44 (14%) and 48 (15%) patients in the topical diclofenac and oral diclofenac groups, respectively. These baseline and other patient characteristics were comparable in the PP treatment groups (data not shown).

Table 1. Baseline demographic and clinical characteristics of treatment groups. Data are presented as mean (SD) unless otherwise indicated.

	Topical Diclofenac Solution, n = 311	Oral Diclofenac, n = 311
Age, yrs	64 (10)	63 (10)
Age ≥ 75, No. (%)	52 (17)	49 (16)
Women, No. (%)	178 (57)	178 (57)
Race/ethnicity, No. (%)		
White	299 (96)	286 (92)
Oriental	2 (1)	3 (1)
Black	4 (0.6)	3 (1)
Hispanic	0 (0)	1 (0.3)
Other	6 (2)	18 (6)
Weight, kg	88 (18)	88 (21)
Height, cm	166 (10)	166 (10)
Heart rate, bpm	74 (9)	75 (10)
Systolic blood pressure, mm Hg	133 (14)	134 (15)
Diastolic blood pressure, mm Hg	79 (8)	80 (9)
Total x-ray score*	6.4 (3.7)	6.2 (3.7)
WOMAC composite index†		
Pain, mm	288 (89)	289 (98)
Physical function, mm	979 (299)	983 (333)
Stiffness, mm	123 (42)	124 (48)
Patient global assessment‡, mm	70 (19)	70 (21)

* Total score of joint space narrowing, marginal osteophytes formation and subchondrial sclerosis for each knee compartment (medial, lateral, patellofemoral); maximum score possible was 27. † WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, visual analog scale; pain scale ranged from 0 (no pain) to 500 (extreme pain); physical function scale ranged from 0 (no difficulty) to 1700 (extreme difficulty); stiffness scale ranged from 0 (no stiffness) to 200 (extreme stiffness). ‡ Patient global assessment scale ranged from 0 (very good) to 100 (very poor).

Efficacy. Sixteen patients did not have primary OA (5 with knee trauma; 5 osteochondritis dissecans; 3 normal radiographs; 2 rheumatoid arthritis; 1 recent knee surgery) and 2 patients missed at least one dose of both solution and capsules. All 18 patients were eliminated from the ITT analysis, leaving 604 patients analyzed for this data set (Figure 1). For the PP data set, further elimination of patients for other predefined reasons (see Figure 1) yielded 492 patients for the analysis of equivalence based on the WOMAC efficacy variables, and 485 patients using PGA (7 patients did not answer the final PGA question. There was no imputation of last observed value in the PP group). Included in the PP group are 6, 5, and 2 patients that did not meet the minimum baseline score requirement for pain (≥ 125 mm), physical function (≥ 425 mm), or PGA (≥ 25 mm), respectively. All but one of these baseline scores were just below the cutoff level. There were 15 and 2 patients in the topical diclofenac and oral diclofenac groups, respectively, that dropped out with < 28 days of treatment, citing lack of efficacy. Of these, 10 patients and 1, respectively, had at least 50% compliance and were put back into the PP group (as per the planned statistical analysis).

Mean baseline, final, and change (final minus baseline) scores for all efficacy variables for patients included in the PP and ITT data sets are given in Table 2. There was no significant difference in the change scores between treatment groups in the PP data set analysis, nor in the ITT data set analysis except for physical function. Patients treated with topical diclofenac showed improvements in all variables of 36–44% over baseline values, while patients treated with oral diclofenac showed slightly greater improvements of 42–49%.

Table 3 shows the results of the equivalence analysis. For the PP data set, the difference in mean change scores (95% CI) between treatments was: pain 13.3 mm (–8.6 to 35.2); physical function 71.0 mm (–2.4 to 144.5); and PGA 4.3 mm (–1.2 to 9.8). The CI for all efficacy variables fit within their corresponding equivalence range. For the ITT data set, the difference in mean change scores (95% CI) was: pain 16.4 mm (–3.4 to 36.1); physical function 90.0 mm (24.0 to 156.0); and PGA 4.5 mm (–0.5 to 9.6). The CI for all efficacy variables fit within their corresponding equivalence range.

Analysis of results for pain on walking, the first item in the WOMAC pain dimension, revealed similar improve-

Table 2. Baseline and change scores with percent improvement following treatment. Data are presented as mean (SD) unless otherwise indicated.

Variable	Diclofenac Treatment Group	n	Baseline, mm	Change from Baseline, mm	% Improvement	p*
Per protocol data set						
WOMAC composite index						
Pain, 0–500 mm	Topical	237	286 (88)	–127 (120)	44	0.23
	Oral	255	286 (100)	–140 (127)	49	
Physical function, 0–1700 mm	Topical	237	968 (291)	–380 (396)	39	0.06
	Oral	255	975 (332)	–451 (431)	46	
Stiffness, 0–200 mm	Topical	237	123 (42)	–48 (59)	39	0.24
	Oral	255	123 (49)	–55 (61)	45	
PGA, 0–100 mm	Topical	234	69 (19)	–30 (31)	43	0.13
	Oral	251	69 (21)	–34 (31)	49	
Intent to treat data set						
WOMAC composite index						
Pain, 0–500 mm	Topical	303	286 (88)	–118 (121)	41	0.10
	Oral	301	289 (98)	–134 (127)	46	
Physical function, 0–1700 mm	Topical	303	971 (295)	–348 (400)	36	0.008
	Oral	301	984 (331)	–438 (426)	45	
Stiffness, 0–200 mm	Topical	303	123 (42)	–45 (58)	37	0.14
	Oral	301	124 (47)	–52 (61)	42	
PGA, 0–100 mm	Topical	303	69 (19)	–27 (31)	39	0.08
	Oral	301	70 (21)	–32 (32)	46	

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, visual analog scale. PGA: patient global assessment. * Analysis of variance.

Table 3. Analysis of equivalence: primary efficacy variables. Data for change scores are mean values.

Variable	Treatment Group	n	Change Score, mm	Difference in Change Score (95% CI) Between Treatments, mm	Equivalence Range*, mm
Per protocol data set					
WOMAC Pain	Topical diclofenac	237	–126.8	13.3 (–8.6 to 35.2)	–75 to 75
	Oral diclofenac	255	–140.1		
WOMAC Physical function	Topical diclofenac	237	–380.4	71.0 (–2.4 to 144.5)	–255 to 255
	Oral diclofenac	255	–451.4		
Patient global assessment	Topical diclofenac	234	–29.5	4.3 (–1.2 to 9.8)	–20 to 20
	Oral diclofenac	251	–33.8		
Intent to treat data set					
WOMAC Pain	Topical diclofenac	303	–118.0	16.4 (–3.4 to 36.1)	–75 to 75
	Oral diclofenac	301	–134.4		
WOMAC Physical function	Topical diclofenac	303	–347.8	90.0 (24.0 to 156.0)	–255 to 255
	Oral diclofenac	301	–437.8		
Patient global assessment	Topical diclofenac	303	–27.1	4.5 (–0.5 to 9.6)	–20 to 20
	Oral diclofenac	301	–31.6		

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, visual analog scale. * Equivalence ranges defined a priori based on Bellamy, *et al* [35] : ± 15 mm per item for pain and physical function, ± 20 mm for patient global assessment. The 95% CI for the difference in mean change scores for each variable fell within these equivalence ranges.

ments in score regardless of data set analyzed. The difference in mean change score (95% CI) between treatments was only 1.0 mm (–4.3 to 6.3) for the PP data set and 1.7 mm (–2.9 to 6.4) for the ITT data set, falling well within the equivalence range (–15 to 15 mm; Table 4).

The number of patients with a clinically-relevant response to treatment was investigated a posteriori using the recently published OMERACT-OARSI set of responder criteria[39]. These criteria (derived from a consensus opinion of international experts using data from oral NSAID trials) take into account the individual patient's absolute and relative change in pain or physical function following treatment, to determine if there is a clinically-relevant "response" to treatment. The results of this analysis show that in both the PP and ITT data sets, there was no significant difference between treatment groups in the number of patients considered "responders" to treatment (Table 5).

Safety. There was no significant difference between treat-

Table 4. Analysis of equivalence: pain on walking. Data for change scores are presented as mean (SD).

Diclofenac Treatment Group	n	Change Score, mm	% Improvement	Difference in Change Score (95% CI) Between Treatments, mm	Equivalence range*, mm
Per protocol data set					
Topical	237	–25.9 (29.4)	45	1.0 (–4.3 to 6.3)	–15 to 15
Oral	253†	–26.9 (29.8)	47		
Intent to treat data set					
Topical	303	–23.6 (28.8)	41	1.7 (–2.9 to 6.4)	–15 to 15
Oral	301	–25.3 (29.6)	44		

Pain on walking score relates to the first question of the Western Ontario and McMaster Universities Osteoarthritis Index pain subscale. * Equivalence ranges defined a priori based on Bellamy, *et al* [35]. The 95% CI for the difference in mean change scores fell within this equivalence range. † Two patients, who had no final data for pain on walking, are excluded from the per protocol analysis.

Table 5. Number of responders to treatment according to the OMERACT-OARSI set of responder criteria. Data are presented as the number of responders to treatment out of the total for that data set; OMERACT-OARSI set of responder criteria[39] were established at OMERACT VI, Australia, 2002. A responder is defined as a patient with ≥ 50% improvement in pain or function that was ≥ 20 mm on a 100 mm VAS, or ≥ 20% improvement in at least two of pain, function, or patient global assessment that was ≥ 10 mm on a 100 mm VAS.

Diclofenac Treatment Group	n	No. (%) of Responders	p*
Per protocol data set			
Topical	236†	167 (71%)	0.68
Oral	254†	184 (72%)	
Intent to treat data set			
Topical	303	201 (66%)	0.37
Oral	301	210 (70%)	

* Analysis by chi-square test. † One patient from each treatment group, missing final patient global assessment data, was excluded from the per protocol analysis since assessment of their "response" could not be determined.

ment groups in change in the vital sign measurements. The number of patients with an increase from baseline in mean blood pressure [defined as (2 × diastolic + systolic)/3][40,41] of 5 mm Hg or greater was not significantly different between the topical diclofenac group (24% of patients) and the oral diclofenac group (28% of patients; p = 0.30).

The incidence of important drug-related AE is shown in Table 6. The AE exhibiting the greatest incidence were application-site dry skin in the topical diclofenac group and dyspepsia in the oral diclofenac group. Patients treated with topical diclofenac experienced significantly fewer GI AE, including dyspepsia, diarrhea, nausea, flatulence, and abdominal pain, compared to oral diclofenac-treated patients (Table 6). In addition, the percentage of these patients whose diclofenac-related GI event was classified as severe was lower in the topical diclofenac group compared to the oral diclofenac-treated group (Figure 2). Regarding other diclofenac-related AE, the incidence of asthma and dizziness was significantly higher in oral diclofenac-treated patients, but there was no significant difference between treatment groups in the occurrence of edema or headache (Table 6).

Patients treated with topical diclofenac solution had significantly more application-site, skin-related AE, including dry skin, rash, pruritus, and vesiculobullous rash (Table 6). The greatest incidence was found for dry skin [83 (27%) patients], which was deemed mild in 96% of these patients, followed by rash [36 (12%) patients]. Fifteen (5%) patients developed vesiculobullous rash (i.e., small blisters ≤ 5 mm diameter), with the investigators deeming 4 cases as mild, 10 moderate, and 1 severe[33]. All cases of vesiculobullous rash resolved upon withdrawal of treatment.

Changes in laboratory measurements following treatment were determined for all patients that had both baseline and final data available for that parameter, regardless of duration of treatment (Table 7). The mean change in liver enzymes, hemoglobin, creatinine, and creatinine clearance was significantly greater in patients treated with oral diclofenac. The number of patients whose liver enzymes became elevated was significantly greater in the oral diclofenac group (10–17% of patients), compared to the topical diclofenac group (2–5% of patients). The oral diclofenac group also had a significantly greater number of patients developing abnormal hemoglobin and creatinine clearance compared to topical diclofenac patients (Table 7). Clinically significant elevation of liver enzymes (≥ 3.0 × upper limit of normal) occurred with greater frequency in oral diclofenac patients. In the oral diclofenac group, 4 (1.4%) and 13 (4.7%)

Table 6. Incidence of adverse events. Data are number (%) of patients experiencing at least one episode of that event.

Adverse Event	Topical Diclofenac Solution, n = 311	Oral Diclofenac, n = 311	p*
Gastointestinal (GI)			
All GI events†	108 (35)	150 (48)	0.0006
Abdominal pain	36 (12)	67 (22)	0.0008
Constipation	25 (8)	31 (10)	0.40
Diarrhea	27 (9)	54 (17)	0.001
Dyspepsia	48 (15)	81 (26)	0.001
Flatulence	30 (10)	52 (17)	0.009
Melena	4 (1)	7 (2)	0.36
Nausea	25 (8)	41 (13)	0.04
Vomiting	5 (2)	7 (2)	0.56
Application site			
Dry skin	83 (27)	4 (1)	< 0.0001
Rash	36 (12)	5 (2)	< 0.0001
Paresthesia	2 (0.6)	2 (0.6)	1.0
Pruritus	20 (6)	2 (0.6)	< 0.0001
Urticaria	1 (0.3)	1 (0.3)	1.0
Vesiculobullous rash	15 (5)	0 (0)	< 0.0001
Other			
Asthma	2 (0.6)	10 (3)	0.02
Dizziness	2 (0.6)	11 (4)	0.002
Dyspnea	0 (0)	7 (2)	0.01
Edema	22 (7)	25 (8)	0.65
Halitosis	4 (1)	1 (0.3)	0.37
Headache	14 (5)	20 (6)	0.29
Hypertension	3 (1)	7 (2)	0.20
Pharyngitis	13 (4)	2 (0.6)	0.004
Taste perversion	6 (2)	2 (0.6)	0.29

* Analysis by chi-square or Fisher's exact test. † Includes all diclofenac-related gastrointestinal adverse events[34].

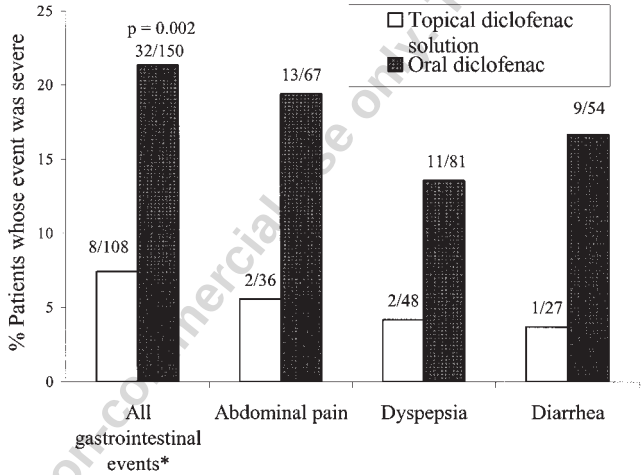

Figure 2. Incidence of severe gastrointestinal (GI) events. *Includes all diclofenac-related GI adverse events[34]. Severe adverse events were defined as events that produced significant impairment of functioning or incapacitation and were a definite hazard to the patient's health[33].

patients developed clinically significant elevation of AST and ALT, respectively, compared to only 1 (0.4%) and 3 (1.1%) patients in the topical diclofenac group (Table 8).

DISCUSSION

Our study demonstrates that this topical diclofenac solution produces efficacy equivalent to oral diclofenac in the symptomatic treatment of OA knee, namely reduction in pain, physical dysfunction, and patient global disability from the disease. The design for this trial adhered to recommended principles of an equivalence study, the key features being setting the equivalence range a priori, calculating an adequate sample size required to test for equivalence, and analyzing the PP data set[23,24,42].

A typical superiority trial begins with the null hypothesis, i.e., the presumption that 2 interventions are the same (i.e., an active drug versus placebo, or active 1 versus active 2). If the data from the 2 treatment groups do not overlap, one

Table 7. Change in laboratory measurements with treatment. Data are presented as mean (SD) unless otherwise indicated; includes only patients with both baseline and final data for that parameter. Number (%) changing from normal at baseline to abnormal at final represent increases (AST, ALT, GGT, creatinine) or decreases (hemoglobin, creatinine clearance) from normal range. Normal ranges were: AST, < 31 (female, F) or < 37 (male, M); ALT < 31 (F), < 41 (M); GGT 7–32 (F), 11–49 (M); hemoglobin, 120–160 (F), 129–173 (M); creatinine, 54–97 (F), 54–124 (M); creatinine clearance, 88–128 (F), 97–137 (M).

Laboratory Test	Diclofenac Treatment Group	n	Baseline	Change from Baseline	p*	No. (%) of Patients Changing from Normal to Abnormal	p†
AST (U/l)	Topical	280	23 (11)	0.2 (8)	0.0002	6 (2%)	0.0001
	Oral	276	21 (8)	5.7 (23)		27 (10%)	
ALT (U/l)	Topical	277	23 (12)	1.2 (15)	0.0003	13 (5%)	< 0.0001
	Oral	276	23 (11)	15 (60)		46 (17%)	
GGT (U/l)	Topical	279	34 (38)	2.7 (21)	0.0004	13 (5%)	< 0.0001
	Oral	276	32 (24)	14 (49)		41 (15%)	
Hemoglobin (g/l)	Topical	274	137 (13)	0.9 (8)	< 0.0001	6 (2%)	< 0.0001
	Oral	273	137 (13)	–2.2 (9)		28 (10%)	
Creatinine (µmol/l)	Topical	281	75 (18)	0.3 (11)	0.003	3 (1%)	0.08
	Oral	277	73 (17)	3.3 (13)		9 (3%)	
Creatinine clearance (ml/min)	Topical	281	73 (21)	0.6 (16)	0.006	12 (4%)	0.01
	Oral	277	76 (22)	–2.7 (12)		27 (10%)	

* Analysis of variance. † Analysis by chi-square test.

Table 8. Clinically significant elevation in liver enzymes. Data are number of patients developing a clinically significant elevation (≥ 3.0 × upper limit normal) in liver enzyme whether baseline was normal or elevated; includes only patients with both baseline and final data for that parameter.

Laboratory Test	Diclofenac Treatment Group	n	No. of Patients Developing Clinically Significant Elevation			
			Baseline Normal	Baseline Elevated	Total (%)	p*
AST	Topical	280	0	1	1 (0.4)	0.21
	Oral	276	3	1	4 (1.4)	
ALT	Topical	277	2	1	3 (1.1)	0.01
	Oral	276	8	5	13 (4.7)	
GGT	Topical	279	1	3	4 (1.4)	0.06
	Oral	276	3	8	11 (4.0)	

* Analysis by chi-square or Fisher's exact test.

concludes there is a difference between the treatments (i.e., active drug is superior to placebo or active 1 is superior to active 2). In this trial, although the absolute numbers were slightly higher for oral diclofenac, there was no statistically significant difference between treatment groups, except for the variable physical function in the ITT group (Table 2). Failure to demonstrate superiority of active drug 1 over active drug 2, however, does not prove them equivalent[43].

If 2 active drugs accepted by convention as equivalent are compared in a clinical trial, the laws of chance and biological variability tell us that the data will not be identical. An equivalence trial begins with the null hypothesis that a difference, with a magnitude of at least delta, does exist between 2 treatments (usually a new active and a standard active comparator)[36]. If the trial then demonstrates that the CI for the observed difference between treatments falls within the range of delta, the null hypothesis is rejected and the 2 treatments are declared "not different by more than the delta" — hence equivalent. The key to a valid equivalence study is the choice of delta — that acceptable, minimal amount of difference between the 2 groups that is not clinically important. For our study, the equivalence ranges chosen are based on the minimal clinically important difference to be sought in OA trials established by Bellamy, *et al*[35]. In the Medical Officer Review of the new drug application for rofecoxib, the US Food and Drug Administration acknowledged these equivalence ranges as being "determined by a panel of expert rheumatologists as representing clinically meaningful differences"[44]. In this study, the CI for the difference in mean change score for each efficacy variable fell within the Bellamy, *et al*[35] equivalence ranges for both the PP and ITT analyses, confirming the 2 treatments were equivalent.

A more recent report by Ehrich, *et al*[45] describes a substantially narrower equivalence range as the minimally perceptible difference between 2 interventions in treating OA [pain, ± 9.7 mm per item (–48.5 to 48.5 mm); physical function, ± 9.3 mm per item (–158.1 to 158.1 mm); PGA, –11.7 to 11.7 mm]. The CI for the difference in mean change score for each primary efficacy variable fell within this set of narrower equivalence ranges and, as Ehrich, *et al* state[45], "provide a more conservative or stringent test of equivalence."

If an equivalence trial is too small, there is an inherent tendency for the 2 interventions (the new drug and the standard comparator) to appear the same. To reduce this potential bias, an adequate sample size was calculated using ß of 0.1 (90% power), to yield greater certainty of the conclusion than the usual ß of 0.2 (80% power) used in superiority trials. An ITT analysis group includes "noise," i.e., dropouts, imputed data, or protocol violators, which may bias towards no difference. As such, the primary analysis was performed on the PP data set as per accepted statistical principles for an equivalence study[23,24,42]. In addition, a conclusion of equivalence was derived from the ITT analysis, enhancing the trustworthiness and robustness of the conclusion.

The percentage of improvement in pain, physical function, and PGA experienced by patients using the topical diclofenac solution was comparable to patients using oral diclofenac (Table 2). Applying the newly published OMERACT-OARSI set of responder criteria[39] provides additional confirmation that the treatment effects of topical diclofenac and oral diclofenac were similar (Table 5). The results for "pain on walking," the first item in the WOMAC pain dimension and often used in other trials as a primary efficacy variable, also point towards equivalence of the 2 treatments (Table 4).

Topical NSAID have been skeptically reviewed since their approval in Europe for the treatment of pain due to soft tissue injuries and arthritic conditions[17-19]. Most studies suffered from inadequate trial design, with short duration (up to 28 days) and outcome measures of unreliable or undefined validity and responsiveness. The conclusion of their efficacy over placebo has been described as weak and insufficient[5,46]. Most topical NSAID preparations are gel or cream formulations that require massage during application, potentially contributing to a placebo effect. This topical preparation is a solution containing the absorption enhancer DMSO, which has been shown to enhance the *in vitro* and *in vivo* penetration of diclofenac through skin[47,48]. Our protocol included instruction to the patient on how to apply study solution without massage.

There have been only a few published studies that compared topical versus oral NSAID therapy of OA or other rheumatic conditions[49–51]. When these studies found no statistically significant difference between treatment arms in patient's assessment of pain, the authors concluded that the topical treatments were as effective as, and a useful alternative to, oral NSAID therapy. As noted above, failure to prove that 2 treatments are different does not establish that they are equivalent[36,42,52]. In their review of topical versus oral NSAID, Heyneman, *et al*[19] criticized these studies for their design and concluded that equal efficacy was not proven.

The present trial, as were previous superiority trials with this topical diclofenac solution[20–22], was designed and conducted according to the recommendations of OARSI[30,31] for clinical trials in OA: longer duration, radiological and clinical symptom entry criteria, and assessment of the essential outcome measures recommended by OMERACT III[29] — pain, physical function and PGA — using a validated assessment questionnaire, i.e., the WOMAC Index[26,28]. DMSO from the topical carrier is rapidly absorbed and metabolized to dimethyl sulfone and dimethyl sulfide, a volatile gas that the patient may perceive as a garlic-like taste or odor. To maintain the blind, topical placebo solution contained 2.3% w/w of DMSO. The success of the blinding is evidenced by the similar incidence of halitosis and taste perversion (COSTART terminology) in the 2 treatment groups.

This dose of oral diclofenac has been shown to be effective when previously compared with placebo or other active drugs in trials of design similar to this one, using the same efficacy variables in a similar patient group with radiological and clinical OA of the knee[53,54]. The magnitude of the response to oral diclofenac observed in this trial, as well as the withdrawal rate due to AE, particularly GI events, was similar to those observed in a comparable trial by Bellamy, *et al*[53].

Patients treated with topical diclofenac exhibited an overall better safety profile compared to patients receiving oral diclofenac. The reduced incidence and severity of GI side effects observed with topical diclofenac is probably related to the reduced peak systemic level of diclofenac when applied topically. Risk of serious GI complications associated with NSAID, such as upper GI bleeding and perforation, appears to be lower with topical NSAID[55]. Although some GI side effects were observed with topical diclofenac solution in this study, earlier, controlled superiority studies found the incidence of these events to be much lower and not significantly different than topical placebo[20–22]. The double-dummy design of this trial with an oral placebo (the large capsule was size "0": length 17.4 mm, diameter 9.8 mm) in the topical diclofenac group might have contributed to a higher anticipation, incidence, and reporting of these events. A systematic review of oral NSAID trials concluded there was a greater reporting of GI adverse events in active comparative trials compared to placebo-controlled trials[56].

In addition to GI bleeding, other reported diclofenac-related adverse effects involve the hepatic and renal systems[54,57,58]. In this study, patients in the oral diclofenac group developed an increase of liver enzymes and creatinine and decreased hemoglobin of similar magnitude and incidence (Table 7, 8) as in previous reports[54,57]. In patients using topical diclofenac solution, the incidence and magnitude of the change in these parameters were significantly lower.

The main safety concerns with the use of topical diclofenac solution are application-site reactions. The

majority of these reactions were minor dry skin or rash, with incidence similar to that reported in earlier superiority trials[20–22]. In a clinical setting, skin reactions may be alleviated through the use of emollients (such products were not permitted in this trial).

We have shown in this study, using an appropriate trial design, that the same NSAID applied topically as taken orally has equivalent efficacy in the symptomatic treatment of knee OA. The main safety concerns following treatment with this topical diclofenac solution were application-site reactions, while incidence of systemic AE associated with oral diclofenac was significantly reduced. The combination of efficacy and safety makes this topical diclofenac solution (Pennsaid®) a viable alternative in the treatment of OA of the knee.

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