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University of Alberta

ASSESSMENT OF THE EFFICACY OF TOPICAL DICLOFENAC USING THE WOMAC VA3.0 AND SF-36 AS OUTCOME MEASURES

by

DAVID W. GRACE 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Education

Department of Educational Psychology

Edmonton, Alberta

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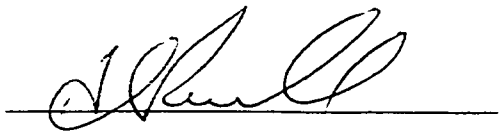

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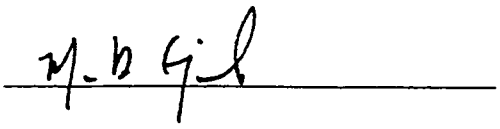

Dr. M. J. Gierl

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ABSTRACT

In a double blind, randomized, parallel groups design clinical trial of patients with mild to moderate osteoarthritis of the knee, a topical formulation of 2% diclofenac (NSAID) lecithin organogel was compared with placebo gel. The WOMAC VA3.0 Osteoarthritis Index, a disease-specific outcome measure, and the SF-36, a generic health status measure, were used to determine treatment efficacy. Gain score analysis revealed a significant difference ($p \leq .05$) in improvement between diclofenac and placebo over the treatment period on the pain subscale of the WOMAC and the physical function subscales of the WOMAC and SF-36. Pearson correlations were moderate to high between the three subscales of the WOMAC and the bodily pain, physical function, and physical role functioning subscales (0.329 to 0.618, all significant at $p \leq .05$). The results indicate that a topical formulation of 2% diclofenac could be an effective alternative to the use of oral NSAIDs in this patient population.

Acknowledgement

I wish to thank the members of my thesis committee, for participating in this arduous ordeal. To Todd Rogers, my thesis advisor, words cannot express how much your patience and encouragement has meant to me. You are an editor and teacher without peer. Thank you for sluggin' it out with me.

I also wish to thank my parents, Michael and Vida, who together, made me what I am today, for better or for worse. Now take a bow.

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Assessment of the Efficacy of Topical Diclofenac using the WOMAC VA3.0 and SF-36 as Outcome Measures

Osteoarthritis (OA) is characterized by progressive degeneration of articular cartilage. Epidemiological data indicate that the presence and severity of OA increases with age, although the disease may not be an inevitable result of aging (Felson, 1990; Moskowitz, 1993; Rosenbloom, Brooks, Bellamy, and Buchanan, 1985). OA is uncommon in adults under the age of 40 and extremely common in those above 60. Lifestyle, occupation and possibly genetic factors may be of etiological importance (Felson, 1990). The relationship between risk factors and OA may differ across joints. For lower extremity joints, obesity and injury either due to acute events or to repetitive impact loading may be the most important preventable causes of the disease.

OA, also known as degenerative joint disease, has traditionally been classified into two main subgroups: primary or idiopathic OA (occurring in the absence of any known underlying factor) and secondary OA. In the latter, predisposing factors include: physical trauma, previous joint diseases, mechanical/anatomical anomalies, endocrine/metabolic disorders, and neurological deficiencies (Rosenbloom et al., 1985). Whether primary or secondary, the disease results in joint pain, joint stiffness, restricted range of motion, and joint crepitus. Joint articular cartilage and subchondral bone are the sites of these abnormalities found in the osteoarthritic process (Moskowitz, 1992). The disease is slow in its evolution, and results in two primary pathological responses. One pathological response is the structural breakdown of cartilage leading to the development of erosions on the cartilage surface. Contrasting with this structural loss is a second response, a joint

space narrowing due to the growth of new cartilage and bone at the joint periphery, resulting in osteophyte spur formation (Moskowitz, 1993).

OA often affects certain joints and spares others. Disease predeliction is for hand joints involved in pincer grip type actions and lower weight bearing joints-joints not designed for these tasks (Moskowitz, 1993). The interphalangeal joints of the hands (distal and proximal), the carpometacarpal joint of the thumb, the cervical and lumbar spines, the first metarsophalangeal joint, and, particularly the hips and knees, are primary target areas for OA. However, OA of the knee is of particular importance due to the increased risk of developing co-morbidities.

Treatment of OA involves a multifaceted approach including patient education, rest, medication, physiotherapy, occupational therapy, and in selected patients, the use of intra-articular steroid injections or, possibly, surgical intervention. However, the mainstay of management is the use of oral non-steroidal anti-inflammatory drugs (NSAIDs) (Badley, 1981; Heyneman, 1995).

Generally, NSAIDs are weak organic acids that demonstrate a tendency to accumulate at inflamed tissue sites. NSAIDs are thought to suppress inflammation by reducing prostaglandin synthesis through the inhibition of cyclo-oxygenase. It is now evident that the inhibition of cyclo-oxygenase2 (COX2), the inducible form of cyclo-oxygenase, is the primary pharmacological instrument responsible for reducing inflammation (Vane, 1994). The inhibition of its constitutive COX1 is the mechanism responsible for many of the adverse effects associated with NSAIDs (Vaile & Davis, 1998). A number of compounds, selective COX2 inhibitors, claiming greater efficacy

and an improved safety profile, are currently in development or have recently received regulatory approval.

The use of oral NSAIDs is associated with a significant adverse event profile. Many sources (Evans et al., 1995; Figueras, Capalle, Castel, and Laorte, 1994; Johnson, Quinn, and O Day, 1995; Zimmerman, Siguencia, and Tsvang, 1995) document an increased risk of peptic ulceration and upper gastrointestinal tract bleeding in persons using oral NSAIDs. The oral NSAID-related morbidity is high, primarily due to gastrointestinal complications including ulceration and bleeding. Gastrointestinal (GI) side effects occur in roughly 25% of those who use oral NSAIDs and treatment of these complications has been found to add 45% to the cost of rheumatic disease care (Figueras et al., 1994; Johnson et al., 1995). Incidences of life-threatening gastric or duodenal perforation and GI bleeding are 2-fold higher in elderly patients treated with oral NSAIDs than in the younger population and the risk of fatal outcome is greater in the elderly (Davies & Anderson, 1997). OA is one of the most frequent diseases encountered in the elderly and they commonly use oral NSAIDs. Consequently, there is an additive effect in patients with OA to present NSAIDs' side effects: increased age and NSAID intake (Smalley, 1995).

Efforts have been made to find solutions to the significant adverse effect profile associated with the use oral NSAIDs. These include the development of safer anti-inflammatory drugs such as targeted COX2 inhibitors and modifications in the manner by which NSAIDs are delivered. Modifications of the oral NSAID formulations include buffered and sustained release products. Alternative routes of delivery include intravenous and rectal administration, however, these are still associated with significant

adverse events due to their reliance upon systemic drug distribution (Vaile et al., 1998). There has also been considerable interest in the development of non-systemic routes of NSAID delivery in recent years. These are applied topically and include sprays, plasters, creams and gels. The rationale for using topical NSAIDs is that while there are generally lower systemic concentrations of the drug, high concentrations can be achieved locally, thus diminishing the risk of systemic side effects such as GI bleeding (McNeill, 1992).

Applied topically, these drugs are formulated to penetrate the *stratum corneum* in significant enough amounts to exert therapeutic activity. Reports of local enhanced topical delivery (LETD) indicate resultant increased tissue to plasma ratios, as well as two tissue concentration peaks. The first peak corresponds to initial local delivery and the second peak corresponds to the drug plasma profile (Radermacher et al., 1991; Singh & Roberts, 1994). LETD for topical NSAIDs has been reported to occur as far as skin, subcutaneous fatty tissue, and muscle. Topical application of NSAIDs has resulted in measureable drug concentrations in soft tissue compartments, enough to inhibit inflammation. However, evidence is inconclusive regarding deeper tissues such as the synovium (Grahame, 1996). Low correlations between plasma levels and therapeutic effect, moderate to high correlations between plasma levels and toxicity, and moderate to high correlations between synovial fluid levels and therapeutic effect all suggest that local depots of NSAIDs may improve the therapeutic window for this class of agents (Davies, 1997).

LETD is largely dependent on the nature of drug and vehicle, as well as skin integrity and hydration. Following topical administration of an emulsion gel or a solution gel of diclofenac, the maximum plasma concentrations were 10% of that reached after an

intramuscular injection. The C_{max} of the solution gel was almost twice that of the emulsion gel and was reached in shorter time (Seth, 1992). A submicron emulsion vehicle (SME) demonstrated a 40% increase in activity compared to conventional topical formulations of diclofenac, attributable to the dual effects of smaller particle size and the penetration enhancement abilities of phospholipids (Friedman, Schwarz, and Weisspapir, 1995). Use of phospholipid systems in topical diclofenac delivery is gaining acceptance due to a good tolerability profile, in addition to enhanced penetration of drug through the *stratum corneum* (Friedman et al.; Kriwet & Muller-Goymann, 1995). Lecithin organogels, which are phospholipid micro-emulsion systems, have been advocated in the topical delivery of diclofenac, although only evidence of *in vitro* testing has been available to predict percutaneous absorption (Dreher, Walde, Walther, and Wehrli, 1997; Willimann, Walde, Luisi, Gazzaniga, and Stroppolo, 1992).

Review of Placebo Controlled Human Trials

Experience with topical NSAIDs has been gained through use in opthamology (Koay, 1996) and acute soft tissue injuries (Campbell, & Dunn, 1994; Heyneman, 1995). Scarce information is available on efficacy and safety in treating OA (Bakshi, Darekar, Langdon, and Rotman, 1991; Dreiser & Tisne-Camus, 1993; Rau & Hockel, 1989; Vaile et al., 1998). Kageyama (1987) conducted a randomized, double-blind, placebo controlled, multicentre study of piroxicam gel in 246 patients with OA of the knee and reported significantly greater improvement than placebo on a number of efficacy parameters which included spontaneous pain, tenderness, pain on movement, swelling, and limitation of movement. In addition, patients and physicians assessed overall improvement (5-level scale) and response to the study drug. It is unclear which efficacy

parameters were analyzed and what the "response to study drug" was. Analysis of changes in individual symptoms and quality of life measurements revealed that piroxicam provided "significantly better and more rapid improvement than placebo" (p. 115). What these symptoms were (efficacy parameters?) and what the Quality of Life (QOL) measures were, is not revealed. Methods of statistical analyses are also not mentioned. While the study seems intriguing, it was published in abstract form only.

Radermacher et al. (1991) conducted a double-blind placebo controlled trial comparing diclofenac gel to placebo gel on ten subjects with bilateral symptomatic involvement (OA of both knees), applying a different treatment to each knee. While the primary research interest was to measure and compare drug concentrations in synovial fluid and plasma, knee flexion and knee joint circumference were also measured. The data were analyzed at pre and post treatment using paired *t*-tests. Improvement was seen in both knees over time on both measures ($p < .05$); however, no significant differences were found between the two treatments.

Sandelin et al. (1997) compared topical NSAID (eltenac), oral diclofenac, and placebo in a randomized, double blind, multi-centre study of 290 patients with OA of the knee. The primary outcome measures, Lequesne's Index (a composite index measuring pain and physical function) and a visual analog pain scale exhibited no significant differences between either of the active treatments and placebo. Subgroup analysis of patients with more severe symptoms at baseline showed statistical significance, at post-treatment, between the active treatments and placebo on these measures. This was a well-designed study, with three parallel groups, allowing simultaneous comparisons of a local (topical) and a systemic (oral) NSAID treatment with placebo. A number of reasonable

explanations for a strong placebo effect were suggested, including poor design of outcome instrument items, making them susceptible to extreme responses. The cooling effect of the gel, due to its alcohol content, and local self-administration (rubbing) were also suggested as explanations for the placebo effect. The authors suggest that, taking into account the characteristics of OA, and the adverse events profile of oral NSAIDs reported in the literature, the NSAID gel could be a safe alternative to oral medication, particularly in patients with more severe pain.

Moore, Tramer, Carroll, Wiffen and McQuay (1998) performed a quantitative meta-analysis by which they examined the efficacy and safety of topical NSAIDs in acute and chronic pain conditions (arthritis, rheumatism). They included all randomized clinical trials in which pain was an outcome and compared topical NSAIDs with placebo, with another topical NSAID, or with an oral NSAID. In the effort to locate reports of these clinical trials, a number of different search strategies were employed: library databases (Medline, Embase, and the Oxford Pain Relief Database) with no restriction to English language, and requests of pharmaceutical companies for unpublished reports. Abstracts and reviews were not sought.

All eligible reports were reviewed independently by each of the 5 authors to assess adequacy of randomization and blinding, and to assess description of withdrawals. All reviewers met for purposes of attaining consensus on trial quality rating. Trials described as randomized were given one point and if the method of randomization was fully described and deemed adequate (e.g., computer-generated or a table of random numbers), an additional point was given. Inadequately randomized or non-randomized trials were excluded from further analysis. Trials described as blinded were given one point and if

the blinding procedure was described and adequate (e.g. identical appearance of treatments), a further point was awarded. Reports describing the reasons for and number of withdrawals were given one point. The minimum trial quality score was one and the maximum was five.

Despite the authors' comprehensive efforts to review all eligible topical NSAID clinical trials, and the relatively minimal standards for trial quality they set, only 12 placebo-controlled clinical trials examining treatment for chronic conditions were retained for further analysis. The mean trial quality score for these 12 trials was 3.15. Of these, only four examined the use of topical NSAIDs with OA subjects (two with OA of the knee). Four of the twelve studies used diclofenac as the active treatment, of these four, two used a plaster (patch) delivery method and two used a topical gel form of delivery. Outcome measures for the 12 trials included: a 4-point pain intensity scale, a single visual analog scale for pain, physician and patient global assessments, a 4-point verbal pain scale, and a 5-point global rating scale.

The authors found that in treating chronic conditions, topical NSAIDs performed significantly better than placebo (ρ=.05) with a "number needed to treat" mean of 3.1 (range of 2.7 to 3.8). The "number needed to treat" represents the number of subjects that would have to be treated with a topical NSAID to achieve a successful outcome who would not have done so treated with placebo. Local and systemic adverse events were rare (3.6% and 0.5%, respectively) and of these, only 0.5% were considered serious enough to withdraw the subject. These incidence rates were similar to those of placebo.

While these meta-analysis results (efficacy and safety) could be viewed as biased, owing to a publication preference for trials with positive findings, this quantitative review

does serve to point out the scarcity of rigorous clinical trials in which the efficacy and safety of topical NSAIDs has been "scientifically" assessed. Specifically, it calls attention to the absence of published placebo controlled clinical trials for OA of the knee using a topical diclofenac gel treatment and employing comprehensive, reliable, and valid patient-driven outcome measurement instruments.

Use of Topical NSAIDs

Topical NSAIDs have been approved for the treatment of OA in Europe and in parts of Asia for approximately 15 years. Clearly, unpublished, proprietary clinical trial reports for the purposes of obtaining regulatory agency approval exist, but are unavailable. In North America, the Health Protection Branch (HPB) in Canada, and the Federal Drug Administration (FDA) in the U.S.A., have yet to approve a topical NSAID for the treatment of OA. This is due, in part, to a more comprehensive set of submission procedures than that required by European and Asian regulatory agencies. This increased requirement is based upon the presence of adverse event profiles associated with this route of delivery. Reviews of clinical trials submitted for regulatory approval have uncovered a 1% to 2% rate of sensitization following topical application, possibly resulting in a serious adverse reaction when a subject is exposed systemically (orally) to the same drug or to another NSAID (Health Canada, 1998).

With other classes of drugs, alternative routes of delivery submissions required chemistry, animal toxicology, and, in some cases, small clinical trials in humans for purposes of determining safety (Phase I). Due to the nature of the adverse effects profile associated with topical NSAIDs, regulatory agencies now require pharmaceutical companies to conduct all phases of investigation required for a New Drug Submission

(Health Canada, 1998). This requires Phase II and III human clinical trials costing hundreds of millions of dollars. This may be viewed as a prohibitively expensive procedure to undertake, when the entry of a topical NSAID into the market would serve to cut into the market share already held by that company's oral NSAID.

While not approved by the regulatory bodies in North America, topical NSAIDs have met with great favor from physicians and patients alike. In Canada, each provincial or territorial department of health is responsible for regulating the prescription and compounding of pharmaceuticals (Health Canada, 1998). Daily, physicians prescribe topical NSAIDs for the treatment of OA. Upon receiving a prescription, pharmacists compound the formulation, mixing the NSAID drug powder into a cream, lotion, or gel base. In Alberta, the most popular of these topical NSAID compounds is 2% diclofenac in PHLOJEL®. Diclofenac is a potent inhibitor of prostaglandin synthesis and exhibits powerful analgesic effects. Therapeutic doses of oral diclofenac have proven to be equi-efficacious as other commonly-used oral NSAIDs in the treatment of OA (Davies, 1997). PHLOJEL® is a lecithin organogel base possessing penetration enhancing qualities manufactured by J.A.R. Pharmaceuticals Ltd. of Edmonton, Alberta, Canada. This gel base was used for both the active drug and placebo topical formulation. This study was sponsored by J.A.R. Pharmaceuticals Ltd., hereinafter, referred to as the sponsor.

Though the potential benefits of a topical NSAID therapy for treatment of OA are enormous, there exists a lack of evidence for its therapeutic efficacy and safety. Reports of clinical trials investigating topical NSAIDs are either unpublished of unacceptable quality, or not specific to OA of the knee. This study will attempt to determine whether a topical NSAID is an effective and safe therapeutic intervention for patients with mild to

moderate OA of the knee. Does a topical NSAID alleviate the pain, stiffness, and physical functioning impairment, symptomatic of osteoarthritis of the knee, significantly better than placebo?

Research Hypothesis

The one-tailed research hypothesis is as follows: Patients with mild to moderate OA of the knee treated with topical 2% diclofenac will indicate a significant improvement in physical functioning and the amount of pain and stiffness experienced and this improvement will be significantly greater than that indicated by patients treated with topical placebo, as determined by their responses to the WOMAC VA3.0 Osteoarthritis Index and the bodily pain and physical function subscales of the SF-36 Health Survey.

The WOMAC, a disease-specific, OA treatment intervention outcome indicator, was chosen over other outcome measures for its reliability, validity, and discriminatory characteristics in assessing clinical efficacy in this study population.

The SF-36 is a generic quality of life measure possessing some subscales relevant to the evaluation of treatment efficacy. However, unlike the WOMAC subscales, the SF-36 subscales lack specificity and are susceptible to the expected demographic and clinical characteristics of the study population: elderly and over-weight, possessing a high degree of bilateral symptomatic involvement, and a high rate of chronic comorbidity. Despite this concern, significant differences in improvement between the treatment groups in favour of topical 2% diclofenac on specific SF-36 subscales assessing bodily pain, and physical function will serve to support the hypothesis.

Method

Measurement Instruments

The outcome measurement instruments used for the determination of treatment efficacy were the WOMAC (Western Ontario and McMaster Universities) VA3.0 Osteoarthritis Index, developed by Bellamy, Buchanan, Goldsmith, Campbell, and Stitt (1988) and the SF-36 (36-Item Short Form Health Survey), developed by Ware and Sherbourne (1992).

Outcome measures used to evaluate the efficacy of treatment interventions include non-clinical measures such as cost or length of stay and clinical measures such as mortality or functional outcomes (Wright & Young, 1997). For drug therapies, such as topical NSAID treatments, the most important outcome measures for patients and physicians are those of health-related quality of life, health status, and functional outcomes.

Health status scales may be disease-specific or generic measures. Disease-specific scales focus on a specific disorder, disease, or patient population and the problems associated with it. They are generally considered to be more powerful instruments in detecting the effects of treatment (Bombardier et al., 1995; Hawker, Melfi, Paul, Green, and Bombardier, 1995; Martin, Engelberg, Agel, and Swiontkowski, 1997). Generic measures, on the other hand, due to their broader perspective, are better able to detect concomitant complications in areas not specifically related to the disease under consideration. They also allow treatment impact to be compared across a variety of populations and medical conditions.

WOMAC VA3.0 Osteoarthritis Index. The WOMAC (Appendix A) is a disease-specific, multi-dimensional, self-administered, health status instrument developed specifically for patients with lower extremity arthritis. It is widely used to evaluate the effectiveness of operative and non-operative therapeutic interventions for the treatment of OA. The WOMAC consists of 24 questions aggregated into 3 separate subscales measuring the following dimensions using a visual analog scale (VAS): pain (5 items), stiffness (2 items), and physical function (17 items). There is no WOMAC cumulative score.

The instructions for completing the WOMAC are presented to the subjects with reference to study joint, that is, "arthritis in your knee". Item response polarity is consistent throughout the three subscales. The left anchor, "no", indicates an absence of a characteristic (e.g., pain) and the right anchor, "extreme", indicates an excessive amount of this characteristic. Subjects are instructed to place an x on a line connecting the two anchors, indicating the degree of pain, stiffness or disability they had experienced in the last 48 hours. The WOMAC can be completed in about ten minutes.

Numerous studies report the WOMAC to be a reliable (Internal Consistency-Cronbach's alpha range from 0.75 to 0.94 and test-re-test reliability-Inter Class Correlations [ICC] range from 0.85 to 0.95) instrument for the assessment of symptoms and physical functioning ability in patients with OA of the knee (Bombardier et al., 1995; Martin et al., 1997; Wright & Young, 1997). Being there is no "gold standard" for purposes of comparison, a number of techniques have been used to investigate the WOMAC's criterion, content, construct, and discriminant validity. These techniques include examination of floor and ceiling effects, physician instrument ratings, and

receiver operating characteristic curve analysis. Without exception, the authors believe the WOMAC to be a valid measurement instrument for use with this specific patient population (Beaton et al.; Bombardier et al.; Martin et al.; Wright et al.).

SF-36 Health Survey. The SF-36 (Appendix B)is the most frequently used health-status measure in North America. It was developed to address general health concepts not specific to any age, disease, or treatment group and to allow for comparisons of the relative burden of different diseases and the relative benefits of different treatments (Ware, 1992). The SF-36 comprises of 36 questions aggregated into 8 subscales measuring the following dimensions: general health perceptions (5 items), physical functioning (10 items), social functioning (2 items), bodily pain (2 items), general mental health (5 items), vitality (4 items), physical role functioning (4 items), and emotional role functioning (3 items). One item not included in any of the subscales, reported health transition, used to measure changes in health status, may be administered as a supplemental question. For the purposes of this study, the health transition item was included and analyzed as an additional subscale. The clinical investigator also chose to remove four of the five items comprising the general health perception subscale. The items were deemed redundant, adding little information to the one remaining item.

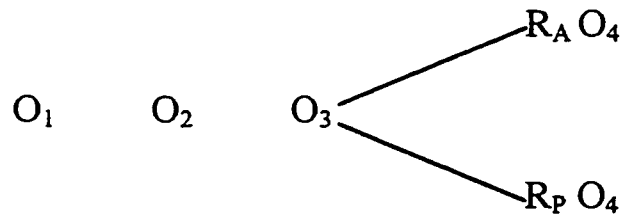
Item response choices range from a dichotomous to a six-level response continuum. A subscale's (physical and emotional role functioning) dichotomous (Yes/No) items were aggregated and quantified, in effect creating a subscale response choice not unlike a multi-level response option. For example, in the case of a three-item dichotomous response subscale, a value (one) was assigned to a "yes" response and a value (two) was assigned to a "no" response, thus making the minimum response score on that subscale a

three, and the maximum response score, a six. Adjustments were made for differing item and subscale response, standardizing them so that the larger the item and subscale response score, the greater the respondent's functioning, health and vitality, and the less pain experienced. As is the case with the WOMAC, the use of a summary SF-36 score is not recommended. It is self-administered and can be completed in approximately 10 minutes.

The SF-36 has also been shown to be a reliable (subscale ICC range 0.31 to 0.91) and valid measure of general health status with patients who have a variety of conditions across a wide range of age, diseases, or treatment groups (Bombardier et al., 1995; Martin et al., 1997; Wright et al., 1997).

Design

The study was of a double-blind, randomized, placebo-controlled parallel groups design. The schematic of this design is:



where,

O_1 - Screening Visit,
O_2 - Washout Period,
O_3 - Final Enrollment Visit,
R_A - Treatment Period (Active Drug),
R_P - Treatment Period (Placebo), and
O_4 - Post-Treatment Visit.

The schedule of the clinical study as it was conducted is presented in Table 1 on page 16.

Table 1

Schedule of Clinical Study

Component	Screening (Visit 1)	Washout Period	Final Enrollment (Visit 2)	Treatment Period	Post-Treatment (Visit 3)
Number of Days	1	3-7	1	14	1
CLINICAL					
Medical History	X				X
Physical Examination	X				X
Laboratory Tests	X				X
Vital Signs	X				X
X-ray Review	X	X			
Adverse Events		X	X	X	X
Eligibility Review	X	X	X	X	
MEDICATIONS					
Acetaminophen Tablets		X		X	
Study Medication				X	
DOCUMENTS & ADMINISTRATION					
Informed Consent Form	X				
Patient Information Sheet	X				
Concomitant Medication Record		X			
Case Report Forms	X	X	X	X	X
Randomization			X		
OUTCOME MEASURES					
WOMAC			X		X
SF-36			X		X

The "independent" or predictor variable in this study was the OA treatment intervention, manipulated by randomly assigning subjects to either the active drug or placebo treatment groups. Dependent variables were the attributes measured by the three subscales of the WOMAC (pain, stiffness, and physical functioning) and the 9 subscales of the SF-36 (general health perceptions, physical functioning, social functioning, bodily pain, general mental health, vitality, physical role functioning, mental role functioning, and health transition). Confounding variables included weight, age, type of symptomatic involvement, presence of chronic co-morbidity, and presence of acute intermittent illness. These variables were controlled for by specification (exclusion criteria) in the design phase of the study and by randomization of subjects to treatment groups.

Subject Selection

The study subjects were recruited primarily through Dr. Kenneth Skeith's (Clinical Investigator) Rheumatology practice at the Allin Clinic and clinics at the University of Alberta Hospital. Additional study subjects were recruited by way of referrals from general practitioners and other rheumatologists in the greater Edmonton, Alberta region. A notice of the study and request for volunteers was posted in the lobby and elevators at the Allin Clinic. Recruitment of potential study subjects (candidates) began March 1997 and was completed October 1997.

During the Screening Visit (Visit 1), each candidate was given a full explanation of the study by the clinical investigator or research nurse. When it was apparent that the candidate understood the Informed Consent Form (Appendix C), Patient Information Sheet (Appendix D), and implications of participating in the study, they were asked to sign and date the Informed Consent Form. The candidate was provided with a copy of

the signed Informed Consent Form and Patient Information Sheet. At this time the candidate was assigned a Screening ID#. They were then evaluated on their general health status and eligibility for study entry was determined.

To be selected candidates had to satisfy the following study inclusion criteria:

- at least 35 years of age
- availability of subject for entire study period
- willingness to adhere to protocol requirements
- symptomatic and radiologic OA of the knee requiring daily drug therapy
- OA disease duration of at least 3 months
- clinically relevant laboratory values within ±10% of normal range.

Subjects were excluded if they possessed any one of the following exclusion criteria:

- Stage 4 OA
- recent history (in the last two years) or presence of alcohol abuse
- women who are pregnant, lactating, or of childbearing potential and not using an effective form of birth control
- significant history of allergies
- corticosteroid or hyaluronic acid injections of target knee within one month prior to enrollment
- hypersensitivity to any NSAID
- local skin disease
- prior joint replacement surgery on target knee
- started physiotherapy in the preceding two weeks or anticipate starting or stopping physiotherapy during the study
- blood donation in previous 56 days
- multiple blood sampling 30 days prior to study onset
- subjects possessing a language or psychological barrier.

A medical history, physical examination, and blood and urine sampling for laboratory tests were then completed for those candidates who met the inclusion criteria and did not possess any of the exclusion criteria. The medical history consisted of an evaluation of past or present cardio-vascular, pulmonary, musculoskeletal, gastrointestinal, genitourinary, neurological, endocrine, psychiatric, lymphatic,

dermatologic, or immunologic disorder or disease, as well as any other medical disorders. The physical examination included vital signs (blood pressure, pulse rate, and respiratory rate), height and weight, an examination of the eyes, ears, nose, throat, and an examination of the cardio-vascular, pulmonary, musculoskeletal, gastrointestinal, genitourinary, neurological, psychiatric, lymphatic, dermatologic, haematologic, and immunologic systems. Blood and urine samples were taken for the following laboratory tests:

- Haematology: leukocytes, erythrocytes, haemoglobin, haematocrit, platelets, lymphocytes, monocytes, neutrophils, eosinophils, and basophils.
- Biochemical: B.U.N., glucose, creatinine, sodium, potassium, chloride, uric acid, calcium, inorganic phosphorous, total protein, albumin, total and conjugated bilirubin, A.S.T., A. L. T., and alkaline phosphate.
- Urinalysis: Specific gravity, pH, W.B.C., albumin, glucose, ketone, bile, R.B.C., nitrate, urobilinogen, and microscopic examination.

Baseline demographic characteristics were recorded and the candidate underwent a series of standard baseline osteoarthritis assessments which included identification of target knee, type of symptomatic involvement, presence of a chronic co-morbidity, presence of an acute intermittent illness, duration of OA symptoms, determination of ACR (American College of Rheumatology) functional grade, and determination of OA radiographic grade. If X-rays of both knees were not current, the candidate was sent to have them taken at this time.

All study candidates were instructed to discontinue their current NSAID therapy for a washout period of between 3 and 7 days, until they met the necessary flare criteria (persistent symptoms of OA requiring daily use of medication). Candidates were sent home with a seven-day supply of acetaminophen 500mg. for pain control and a

Concomitant Medication Record (Appendix E). They were instructed to record the frequency and the amount of acetaminophen and other non-OA drug treatments used daily on this form.

During the Washout Period, the clinical investigator assessed the study candidate's laboratory parameters for any abnormalities and determined whether they were clinically significant. Laboratory values within 10% extended normal values were classified clinically as normal. Those candidates with normal values or abnormal values deemed clinically insignificant were eligible for enrollment. Subject X-rays were also reviewed by the clinical investigator and assigned an OA radiographic grade , if not done previously. If the candidates had met the necessary flare criteria during the Washout Period, had met all other entry criteria, and were willing to remain in the study, their continued participation was confirmed at the Final Enrollment Visit (Visit 2). At this visit, Concomitant Medication Records completed during the Washout Period and unused acetaminophen tablets were collected from the study subjects. At this time, the WOMAC and SF-36 baseline outcome assessments were completed.

Subject Assignment to Treatment

Upon confirmation of eligibility, each subject was assigned a study ID# and the corresponding medication. Eighty medications were randomized (40 each for the placebo treatment and the active drug treatment) and numbered consecutively. As subjects were enrolled they were assigned the next numbered medication, thus serving to randomly assign each subject to either placebo or active treatment group. In order to maintain the blind assignment, replacements were assigned the next numbered medication, not the

treatment of the subject they replaced. The computer-generated randomization scheme was developed using SPSS version 7.0 for Windows (SPSS Inc., 1996).

Seventy subjects were expected to complete the study. Recruitment was done on a continuous basis and replacements were added until a total of 70 subjects completed the study. Both drop-outs and withdrawn subjects were replaced. Drop-outs were classified as those subjects who failed to complete all visits by their choice. Withdrawals were classified as those subjects withdrawn from the study by the clinical investigator for protocol violations or adverse events. Subjects were discontinued and classified as withdrawals if there was significant inter-current illness, an adverse event or surgery, symptoms/signs indicating a possible toxic response, or a failure to comply with the administrative requirements of the protocol. The clinical investigator was to withdraw a subject from the study if it was determined the subject did not follow pre-study directions regarding the use of concomitant medications, correct application of the study medication, or if the subject was otherwise uncooperative during the study. Detailed reasons for removal were recorded and every effort was made to obtain a complete follow-up for any withdrawn patient.

Treatments

The active drug treatment group received 2% diclofenac in PHLOJEL® and the placebo treatment group received PHLOJEL® alone. Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac has exhibited anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known. Its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity. PHLOJEL® is a unique topical base

consisting of lipids and a polymer formulated in a vehicle of water and alcohol. Its enhanced penetration characteristics make it suited to deliver therapeutic agents to sites within the skin or to facilitate their transport through the skin to reach other body tissues and fluids. PHLOJEL®, with or without active drug, applied to the skin has no discernible warming or cooling effect. There is also no discernable difference in appearance between the two treatments.

During the Treatment Period, subjects self-administered the medication assigned to them, either 2% diclofenac in PHLOJEL® (active drug) or placebo PHLOJEL®, three times daily at approximately the same times each day for a period of two weeks. Dosage amount (2.5 grams) was controlled using a level scoop of medication. Subjects were asked to apply this amount to the target knee. They were to rub the medication onto the affected area with two fingers for between 5 and 20 seconds and then wash their hands thoroughly. The target knee was not occluded. Subjects were to maintain their usual amount and quality of physical activity and were instructed that application of the study medication was to be avoided for one hour before and one hour after strenuous activity or bathing.

Subjects were given a supply of acetaminophen 500 mg tablets at the Screening Visit (Visit 1) for use during the Washout Period and at the Final Enrollment Visit (Visit 2) for use during the Treatment Period. They were instructed to use no more than eight 500 mg tablets per day for control of pain. No other concomitant medication for treating OA (for example, cortisones, NSAIDs, and pain killers) was allowed. Each subject was questioned specifically regarding adherence to these restrictions during the Final Enrollment Visit and Post-Treatment Visit. If they admitted prohibited drug ingestion,

the clinical investigator decided whether the subject was permitted to remain in the study, depending on the amount or type of drug used and whether this would have an effect upon the subject's responses on the WOMAC or SF-36. The drug and dosage was noted and reported. Subjects were asked to record the frequency of usage and the amount of, assigned study medication, acetaminophen, and other non-OA drug treatments used daily on the Concomitant Medication Record.

At the Post-Treatment Visit (Visit 3), Concomitant Medication Records completed during the Treatment Period, unused study medication, and unused acetaminophen tablets were collected from the subjects. During this visit, the series of clinical assessments that were administered during the Final Enrollment Visit (Visit 2) were completed (see page 18). The second set of WOMAC and SF-36 outcome instruments were completed by subjects at this time. Blood and urine samples were collected for the haematology, biochemical and urinalysis laboratory tests. Upon receipt of the laboratory results, the clinical investigator assessed each abnormal laboratory value outside of ± 10% of normal values and determined whether it was clinically significant and treatment related. Laboratory values within 10% extended normal values were not assessed as they were assumed to be clinically normal. Treatment related abnormal laboratory values were reported as an adverse event.

Study Administration

Drug Accountability. An inventory record of study drugs dispensed and returned was maintained. Study medication and concomitant medication (acetaminophen) for the purpose of pain control, was provided to study subjects in both treatment groups.

Blinding Procedure. Neither the clinical investigator nor the research nurse in charge of the clinical aspects of the study, in particular of the adverse events, was informed of which study medication (placebo or active drug) the study subjects were given. The subjects were also unaware of which study medication they were given. The employees of J.A.R. Pharmaceuticals Ltd., responsible for the manufacture, packaging, and labeling of study medications, and data input personnel were unaware of the blinding code. Upon coding the medication containers, the principal investigator sealed the randomization scheme in an envelope to be opened after all data had been entered into study database or, in the case of a serious adverse event, it was deemed necessary by the clinical investigator to determine a subject's medication.

Study Sampling. No more than 60ml of blood was drawn from each subject over the duration of the study. Blood and urine samples were collected for laboratory testing during the Screening Visit (Visit 1) and Post-Treatment Visit (Visit 3). These were collected and processed by the Dynacare Kasper Medical Laboratory staff on-site at the Allin Clinic and sent to their central facility for analysis.

Ethics Review. An Application for Ethics Review, the Study Protocol, an Informed Consent Form, and a Patient Information Sheet were submitted to the Institutional Review Board (Caritas Research Steering Committee) for ethics approval. Verbal approval to conduct the study was given pending the incorporation of suggested minor amendments to these documents. These changes were made, reviewed, and written ethics approval was received prior to initiation of the study (Appendix F). Guidelines as drawn up by the Institutional Review Board were followed with regard to the ethical treatment of human subjects in the study.

Adverse Events. Clinical adverse events or serious adverse events were subjective or objective signs or symptoms of illness that appeared during the course of the study regardless of whether they had a causal relationship to study medication. This included all events both expected (known pharmacologic response) and unexpected or unwanted. Moreover, all events that occurred in relation to the clinical study after the last drug administration were estimated as an Adverse Event or Serious Adverse Event.

It was the clinical investigator's responsibility to record and report all adverse events occurring during the study (including all deviations of laboratory values from normal ranges), regardless of their relationship to the study medication. If judged necessary by the clinical investigator, an adverse event was recorded on the HPB 5069 form - Report of an Adverse Reaction or Event Suspected Due to Drugs, Vaccines, Cosmetics, or Food Products (Appendix G).

Information about a serious adverse event was recorded on the HPB 5069 form and was reported to the Sponsor within one working day. This report was to contain a detailed description of the observed symptoms and the contra-active therapy prescribed. The clinical investigator was to judge the possible causal relationship between the event and the study drug. The clinical investigator was to arrange additional examinations at his own discretion to clarify if the event was connected with the study medication and to decide whether or not a specialist should be consulted. All adverse events, serious or not, were followed up and reported regularly to the Sponsor until an outcome was known. The Sponsor or its representative was responsible for notification to regulatory agencies. Definitions of adverse and serious adverse events, guidelines for classification of adverse

events, criteria for determining the relationship of any adverse event to study medication, and requirements for adverse events documentation are found in Appendix H.

Study Documents. Study documents were designed to fulfill regulatory requirements (Study Protocol, Clinical Trial Document Amendment Form, Informed Consent Form and an Adverse Events Table), and to facilitate subject, clinical investigator, and research nurse protocol compliance (Patient Information Sheet, Concomitant Medication Record, Schedule of Clinical Study [Table 1] and Patient Case Report Form [Appendix I]). Other documents, developed by outside agencies, were also used. These included the Caritas Steering Committee Application for Ethics Review, the HPB 5069 form (Report of an Adverse Reaction or Event Suspected Due to Drugs, Vaccines, Cosmetics or Food Products), and the two subject-administered outcome measurement instruments-the WOMAC VA3.0 Osteoarthritis Index and the SF-36 Health Survey.

A Concomitant Medication Record was given to study subjects at Screening (Visit 1), to be completed during the washout period, and at Final Enrollment (Visit 2), to be completed during the two-week treatment period. Subjects were instructed to record the type, dosage amount and frequency of all medications used during the two periods, including all prescription, "over-the-counter" and study medications. The purpose of this was twofold. This "self-record" document served not only to alert the clinical investigator to possible protocol violations (restricted drugs), but, also to increase the likelihood of regular application of study medication.

Data Integrity. Patient Case Report Forms (CRFs) were designed to serve as source documents (patient charts) and to facilitate the chronological, by visit, collection

of study data. Demographic and clinical data were collected in order as outlined in the CRF. Queries and checklists ensured that few steps were missed and all data was collected as required. Pocket pages held subject x-rays, laboratory results, Adverse Events Table (Appendix J), completed Concomitant Medication Records, and completed outcome measurement instruments (WOMAC and SF-36). The clinical investigator and research nurse were queried as to the nature of missing data. Where possible, data was recovered from patient charts.

All information pertinent to the analyses of safety and efficacy was coded and entered into an SPSS database (SPSS Inc., 1996). The entered data was checked for accuracy by two people and then locked, awaiting the entry of the treatment variable and subsequent data analysis. Disagreement between the two checkers was resolved through a mutual review of the study document in question.

Data Analyses

All statistical tests were run with alpha set at .05. This was done in consideration of the conventions existing in the pharmaceutical industry. It could be argued, however, that due to the subjective nature of responses to the WOMAC and SF-36, a lower probability value should be employed. More research has to be done on the use of these outcome measures for making decisions regarding the health of patients. It is a relatively recent concern for the pharmaceutical industry and its regulatory bodies. While the research hypothesis was one-tailed, two-tailed significance tests were used, to provide protection against excessive Type I error.

All sample distributions were assumed to be normal for this population. Levene's test for equality of variance between groups was conducted for all parametric tests.

Statistical analyses were conducted using SPSS version 7.0 for Windows (SPSS Inc., 1996).

Baseline demographic and clinical analysis. Demographic and clinical characteristics can be grouped into three categories of variables as follows. Gender, target knee, type of symptomatic involvement, presence of chronic co-morbidity, and presence of acute intermittent illness are all categorical, nominal variables. With the exception of type of symptomatic involvement they are also dichotomous. ACR grade is a categorical, ordinal variable. The remaining demographic and clinical variables, age, height, weight and duration of OA are continuous or ordered discrete, in that they are measured on a ranked spectrum possessing quantifiable intervals.

Descriptive statistics, frequencies and tests for determining significant differences between treatment groups were conducted for each variable at baseline (pre-treatment). All nominal or ordinal demographic and clinical variables were analyzed for differences between treatment groups at baseline using Chi-square tests for independence for gender, target knee selection, presence of chronic co-morbidity, presence of acute intermittent illness, symptomatic involvement, and ACR grade. Independent samples t-tests (Bolton, 1997, chap. 5) were used to determine if significant differences existed between treatment groups at baseline on the following ratio variables: age, height, weight, and duration of OA.

Correlations among the WOMAC and SF-36 subscales at post-treatment. Bivariate correlations among the subscales of the WOMAC and the SF-36 were calculated using the subscale's post-treatment score aggregated over both treatment groups. This was done to determine if a significant relationship existed among subscales,

giving an indication of whether or not they are measuring similar characteristics of health status. Pearson's correlation coefficients were computed, an appropriate statistical procedure to use for quantitative, normally distributed variables. As mentioned above, two-tailed tests of significance were used for the statistical analysis.

Outcome measures analysis. Though the WOMAC and SF-36 subscales are comprised of items possessing ordinal scale characteristics, there is ample evidence supporting the use of parametric statistical tests for analyses. Bolton (1997) states "the use of parametric methods to analyze rating scale data is considered to be acceptable by many statisticians, including members of the Federal Drug Administration" (p. 540). The WOMAC consists of three discrete subscales or variables, however, owing to the large number of possible item response values along a continuum (Visual Analog Scale) and their ordered nature, they closely resemble continuous, ratio variables and were analyzed as such.

The SF-36 measurement instrument consists of nine subscales, two of which consist of one categorical, ordinal variable (general health and change in health), and two of which consist of multiple dichotomous response items (physical and emotional role functioning) that were consolidated to produce an ordinal variable. The remaining five subscales are classified as ordinal variables. The SF-36 is a robust instrument, in that it works well with the various populations from which its samples are drawn and its design generally precludes the harmful effects of gross systematic errors or outliers. Thus, the nine subscales or variables were statistically analyzed using parametric methods.

Analysis of gain scores was used to determine whether there was a significant difference in the average score gain of the two treatments on the WOMAC and SF-36

subscales. This is an appropriate statistical method to employ when the study subjects are drawn randomly from defined populations and if the purpose of the study is to compare these subjects with respect to average gain, trend, or other intrasubject contrast (Bock, 1975, chap. 7). The difference in scores from baseline to post-treatment for each subject was calculated and the group mean of these changes was then compared between treatments using an independent samples *t*-test.

Adverse events analysis. Adverse events were categorized by type and severity. The analysis was conducted with all randomized subjects (74). A count and incidence rate (%) for each category by treatment group were calculated. These included percent within event, percent within treatment, and percent of total number of subjects randomized.

Results & Discussion

Withdrawals, Drop-outs, and Removals

There were 88 candidates screened for the clinical trial (Table 2). Of this number, 12 candidates did not meet the specified entry criteria. Seven did not meet the necessary OA inclusion criteria, 4 did not want to fulfill the stated study obligations or were unavailable for the length of the study, and one was unable to sufficiently understand the English language. Two candidates met the entry criteria but did not wish to continue after the washout period (withdrawals). Hence, 74 subjects remained and were randomized. Of these, two subjects (both placebo) did not complete all visits (drop-outs), one subject (placebo) was withdrawn from the study due to a protocol violation (applied medication to the wrong location), and one subject (active drug) was withdrawn from the

study after 5 days of treatment due to a skin rash. The final sample sizes (those completing the clinical trial) were 33 placebo and 37 active drug.

One subject (active drug) failed to complete the WOMAC at the Final Enrollment Visit (Visit 2) and three subjects (one placebo and two active drug) failed to complete the WOMAC at the Post-Treatment Visit (Visit 3). After the removal of these 4 cases, 32 cases in the placebo treatment group and 34 cases in the active drug treatment group were included in the statistical analyses of demographic and clinical characteristics and outcome measures (WOMAC and SF-36).

Baseline Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics are given in Table 3. There were no significant differences between treatment groups on baseline characteristics of age, gender, height, weight, type of symptomatic involvement, presence of chronic co-morbidities and acute intermittent illnesses, target knee selection, ACR grade, and duration of OA.

Bilateral symptomatic involvement (OA of both knees) was present in 77% of subjects and chronic co-morbidities were experienced by 50% of subjects. Mean age of the subjects was over 61 years. Obesity was characteristic of the population sample, subjects weighing, on average, over 87 kilograms. While these results may seem extreme, they are characteristic of patients suffering from OA of the lower extremities. It is evident that the sample of subjects for this study was representative of the target population of concern.

Correlations Among the WOMAC and SF-36 Subscales

Pearson's correlations were very high (significant at the $p \leq .01$ level) for all three WOMAC subscales with each another (Table 4). These correlations ranged from 0.715 to 0.867. SF-36 bodily pain, physical function, and physical role function subscales were moderately to highly correlated with the three WOMAC subscales (range -0.329 to -0.618). Negative correlations are due to the opposite polarities of the WOMAC and the adjusted SF-36. These correlations were all significant at $p \leq .01$. The remaining SF-36 subscales exhibited much lower correlations with the WOMAC subscales (range -0.016 to -0.282), none significant at $p \leq .01$. This concurs with findings reported in the literature (Wright, 1997; Martin, 1997). With reference to the WOMAC, the highly correlated SF-36 subscales are likely measuring similar constructs and these constructs are dissimiliar to those being measured by the remaining SF-36 subscales.

WOMAC Gain Score Analysis

As hypothesized, there was a significant difference in gain scores between treatment groups on the pain and physical function subscales of the WOMAC (Table 5). Subjects in the active treatment group experienced a significantly greater degree of pain relief and physical functioning ability than did those subjects in the placebo group over the period of treatment. Repeated measures analysis produced identical results.

Figure 1 presents a graphical representation of this significant difference in improvement between the treatment groups as measured by the pain subscale (the same scenario applies to the physical function subscale). At baseline (pre-treatment), the placebo group experienced less pain than the active treatment group, though not significantly so. At post-treatment, the active group experienced less pain than the

placebo treatment group. This difference between the treatment groups was also not significant. Only the active group experienced a significant decrease in pain over the treatment period (on all WOMAC subscales). Gain score analysis allowed for quantification of this improvement within each group by subtracting the subject's pre-treatment response score from their post-treatment response score. The group mean of these differences were calculated and an independent groups *t*-test was used to compare the difference means.

The difference between pre and post within the active group was significant on all three subscales. However, while the active group experienced a significant decrease in stiffness over the course of the study, this decrease was not significantly different than the decrease in stiffness experienced by the placebo group. A possible explanation for this is that the stiffness subscale consists of only two items and may not be of sufficient sensitivity to discriminate between the two groups. For the same reason, it may be more sensitive to outliers or extreme responses than the other two scales.

Stiffness in OA patients is generally most severe upon arising in the morning. It may not be as great a concern later in the day as the joints are being worked. One of the items in the stiffness scale refers to stiffness in the a.m. and the other refers to stiffness later in the day. Significant differences in responses to the stiffness subscale a.m. item may be mitigated by a more balanced, by group, p.m. item response when item responses are combined into subscale scores. A combined group analysis of the two items (using a paired *t*-test) revealed no significant differences on the responses to the two items at pre and post-treatment. An additional theory, somewhat contradictory to the one presented above, is as follows: is it possible that experiencing less pain is associated with greater

mobility and physical functioning, resulting in increased knee flexion and usage, and that this, in turn, leads to knee fatigue and stiffness. This was not testable as it involves a comprehensive examination of the stiffness domain's utility as an important outcome measure when the primary outcome of interest for a treatment intervention is pain reduction.

SF-36 Gain Score Analysis

SF-36 subscale pre vs. post within group means and gain scores by group are given in Table 6. There was no significant difference between pre and post-treatments observed on any of the subscales for the placebo group. The active group improved significantly on the bodily pain, change in health, physical function, and physical role functioning role subscales. Gain score analysis found the magnitude of gain from pre to post-treatment was significantly greater for the active treatment group than for the placebo group on the physical function and the change in health subscales. On the SF-36, the physical function subscale has the greatest number of items (10), all but one of them dealing with an activity that requires strenuous movement of the knee or walking. It is also highly correlated with the physical function subscale of the WOMAC. This subscale looks to be the most sensitive of the SF-36 subscales to an improvement in OA of the knee due to the number and content of response items.

Hypothesized, a priori, to be an outcome measure supporting our research hypothesis, the bodily pain subscale failed to indicate a significant difference between treatment groups in the magnitude of pain relief experienced from pre to post. Only the active group experienceed a significant degree of pain relief over time. Post-study review of the two bodily pain subscale items finds overly general references to pain. The items

were not designed to detect disease-specific improvement, nor do the situations presented involve activities utilizing the knees.

The change in health scale consists of only one question having five possible responses, ranging from "Much better now than one week ago" to "Much worse now than one week ago". It queries: Compared to one week ago, how would you rate your health in general now? The question asks for a description of general health, orienting the subject to make a comparison to a previous point in time or examine improvement. As patients were asked this question at baseline (after a 3-7 day washout), after they had experienced the "flare" criteria, it is not surprising they would feel worse than a week before, when they were still on a treatment for OA. The subjects were then asked this question after they had been on two weeks of study treatment. Those in the placebo group had been without medication for 3 weeks, while those in the active group had been on active drug therapy for two weeks. In effect, the design of the question and this study serve to exaggerate and moderate the item responses for the active and placebo treatment groups, respectively. This would explain the significant difference in gain over treatment period the active group experienced versus the placebo group.

With the exception of, general health and physical function, all SF-36 subscales are composed of items that include a modifying phrase, "during the past week", similar to that of the change in health subscale. The problems with analysis of these subscales are as presented in the above discussion of the change in health subscale. This confounding "time element" instrument design characteristic was not forseen during selection of outcome measurement instruments, nor during the study design phase.

Adverse Events

All subjects randomized (36 placebo and 38 active) were included in the analysis of safety (Table 7). The active group experienced six adverse events (four rash, one nausea and cramps, and one case of hirsutism) and the placebo group, nine adverse events (five rash, two nausea, one numbness and one complaint of pruritis). All adverse events in both groups were mild in severity and did not require immediate treatment. The nine "rash" and one pruritis events were determined by the clinical investigator to be of "possible" relationship to study medication (active or placebo). All other events were deemed "not related" to study medications (see Appendix H for explanation). 16% of the active treatment group and 25% of the placebo treatment group experienced some type of adverse event. While these rates are high, the fact that the placebo group had a higher incidence rate or one at all, leads one to speculate that a number of "rash" events may have been caused by the gel and not the drug. One subject in the active drug treatment group reporting a rash was withdrawn from the study by the clinical investigator. All other subjects completed the study. All subjects experiencing adverse events had their symptoms disappear, either during the study, or shortly after study completion.

Summary

Physicians and patients express concern with the intake of oral medications, particularly when the area exhibiting pain can be localized. OA of the knee has been treated by a number of methods and interest continues to be generated among physicians and patients for topical treatments. A significant difference was found between the active and placebo treatment groups in the magnitude of change on the WOMAC measures over the course of treatment. Although both groups improved, it is clear that the active

treatment contributed to a more positive change in patient pain and physical functioning. This disease-specific instrument (WOMAC) was designed to detect improvement due a specific intervention. In this study, usefulness of the intervention for a patient's pain and physical functioning due to a particular disease (OA of knee), is confirmed. Lack of significant findings on most subscales in the generic measure (SF-36), as measured by subject's responses to subscale items, reveal that these elderly subjects continue to experience major disabilities due to other co-morbidities and symptomatic involvement, suggesting that addressing one condition (OA of the knee) may not significantly improve overall functioning.

Use of the WOMAC as a criterion of treatment success or failure in OA may be of value relative to the recent trend of the regulatory agencies to increase the emphasis placed upon direct patient impressions (Health Canada, 1998). The direct recording on rating scales of comfort, flexibility, and pain measures encourage the patient to become more conscious of the health domains being measured and the treatment process itself. More research needs to be done, examining the validity, reliability, and responsiveness of outcome measurement instruments, both generic and disease-specific, for use with specific patient populations. This is of particular importance, if these measures are to be used as the primary indicators of treatment efficacy in human clinical trials for the purpose of new drug submissions to regulatory agencies.

Future studies regarding topical delivery of diclofenac should compare it to other topical formulations, evaluate chronic usage, and examine optimal dosage range and intervals. Efficacy of topical diclofenac for the treatment of acute tissue and joint trauma, such as sports-related injuries, is another possible area of research. From results of this

double-blinded, placebo-controlled, randomized study, topical diclofenac delivery appears to have therapeutic value in treatment of OA of the knee as determined by a disease-specific, patient-driven, subjective measure—the WOMAC Osteoarthritis Index.

Table 2

Subject Dropouts, Withdrawals and Removals by Group

Reasons	Placebo n	Active n	N
Screening (Visit 1)			88
Did not meet necessary OA inclusion criteria			-7
Did not want or were unable to fulfill study obligations			-4
Unable to sufficiently understand English			-1
Total			76
Washout Period			76
Did not wish to continue after washout period			-2[w]
Total			74
Final Enrollment (Visit 2)	36	38	74
Randomization			
Total	36	38	74
Treatment Period	36	38	74
Withdrawn from study by clinical investigator due to rash		-1[w]	-1
Total	36	37	73
Post-treatment (Visit 3)	36	37	73
Did not return for Post-Treatment Visit (Visit 3)	-2[d]		-2
Removed from study due to protocol violation	-1[w]		-1
Total	33	37	70
Statistical Analyses of Efficacy	33	37	70
Failed to complete WOMAC at Final Enrollment (Visit 2)		-1[r]	-1
Failed to complete WOMAC at Post-Treatment (Visit 3)	-1[r]	-2[r]	-3
Total	32	34	66

Note. Adverse events analysis conducted with all randomized subjects. [w]Indicates withdrawals. [d]Indicates drop-outs. [r]Indicates removals.

Table 3

Baseline Demographic and Clinical Characteristics by Group

Variable	Placebo	Active	Test
	n	n	χ^2
Gender			
Female	20	20	
Male	12	14	.09
Target Knee			
Left	13	13	
Right	19	20	.01
Symptomatic Involvement			
Bilateral	26	25	
Unilateral Left	2	3	
Unilateral Right	4	6	.56
Chronic Co-morbidity			
Absent	14	18	
Present	17	15	.56
Acute Intermittent Illness			
Absent	28	31	
Present	4	2	.80
ACR Grade			
1	0	1	
2	10	6	
3	19	22	
4	3	3	2.22
	X ± SD, (n)	X ± SD, (n)	t
Age	63.94 ± 10.79, (32)	58.62 ± 14.19, (34)	1.71
Height (cm)	164.33 ± 8.74, (32)	165.78 ± 10.64, (34)	-.60
Weight (kg)	85.53 ± 17.27, (32)	89.75 ± 22.27, (34)	-.86
Duration of OA (months)	143.32 ± 153.14, (31)	127.56 ± 179.87, (34)	.38

Table 4

WOMAC and SF-36 Subscale Correlations at Post-Treatment

Subscale	WOMAC Pain	WOMAC Stiffness	WOMAC Physical Function	SF-36 Bodily Pain	SF-36 Change in Health	SF-36 Physical Function	SF-36 Emotional Role Function	SF-36 General Health	SF-36 Mental Health	SF-36 Physical Role Function	SF-36 Social Function	SF-36 Vitality
WOMAC Pain	1.000											
WOMAC Stiffness	.715**	1.000										
WOMAC Physical Function	.867**	.815**	1.000									
SF-36 Bodily Pain	.-536**	-.618**	-.576**	1.000								
SF-36 Change in Health	-.252*	-.071	-.058	-.198	1.000							
SF-36 Physical Function	-.362**	-.434**	-.544**	-.491**	.247	1.000						
SF-36 Emotional Role Function	-.058	-.060	-.043	-.086	.044	-.167	1.000					
SF-36 General Health	-.036	-.206	-.282*	-.190	-.045	-.354**	-.201	1.000				
SF-36 Mental Health	.051	.063	-.016	-.074	-.093	.154	-.362**	-.365**	1.000			
SF-36 Physical Role Function	-.350**	-.329**	-.365**	-.428**	-.088	-.483**	-.472**	-.238	-.149	1.000		
SF-36 Social Function	-.210	-.140	-.205	-.405**	-.012	-.228	-.460**	-.234	-.593**	-.293*	1.000	
SF-36 Vitality	-.199	-.219	-.212	-.353**	-112	-.176	-.262*	-.566**	-.435**	-.254*	-.494**	1.000

*$p \leq .05$. **$p \leq .01$.

Table 5

WOMAC Subscale Pre vs. Post Within Group Means and Gain Scores by Group

Subscale	Placebo		Active		Gain
	n	X ± SD	n	X ± SD	t
Pain					
Pre-Treatment	32	4.04 ± 1.83	34	4.47 ± 1.75	
Post-Treatment	32	3.43 ± 1.96	34	2.82 ± 1.83	
Gain Score	32	-.61 ± 2.18	34	-1.65 ± 1.52	2.27*
Physical Function					
Pre-Treatment	32	4.15 ± 1.83	34	4.64 ± 1.65	
Post-Treatment	32	3.70 ± 2.02	34	3.44 ± 1.81	
Gain Score	32	-.45 ± 1.61	34	-1.20 ± 1.34	2.07*
Stiffness					
Pre-Treatment	32	4.86 ± 2.08	34	4.91 ± 1.86	
Post-Treatment	32	4.61 ± 2.46	34	4.05 ± 2.21	
Gain Score	32	-.25 ± 1.88	34	-.86 ± 2.01	1.26

* $p \leq .05$.

Table 6

SF-36 Subscale Pre vs. Post Within Group Means and Gain Scores by Group

Subscale	Placebo		Active		Gain
	n	X ± SD	n	X ± SD	t
Bodily Pain					
Pre-Treatment	32	2.86 ± .61	33	2.76 ± .81	
Post-Treatment	32	3.00 ± .71	33	3.02 ± .85	
Gain Score	32	.14 ± .59	33	.26 ± .66	-.75
Change in Health					
Pre-Treatment	32	2.97 ± .54	31	2.77 ± .62	
Post-Treatment	32	3.16 ± .63	31	3.39 ± .67	
Gain Score	32	.19 ± .69	31	.61 ± .92	-2.08*
Emotional Role Functioning					
Pre-Treatment	31	5.48 ± .96	32	5.03 ± 1.33	
Post-Treatment	31	5.45 ± .96	32	5.03 ± 1.28	
Gain Score	31	-.03 ± .75	32	0.00 ± 1.14	-.13
General Health					
Pre-Treatment	32	3.25 ± .88	31	3.06 ± 1.00	
Post-Treatment	32	3.28 ± .96	31	3.16 ± .97	
Gain Score	32	.03 ± .40	31	.10 ± .47	-.59
Mental Health					
Pre-Treatment	31	4.94 ± .84	32	4.70 ± .79	
Post-Treatment	31	5.07 ± .67	32	4.68 ± .98	
Gain Score	31	.12 ± .67	32	-.02 ± .72	.81
Physical Function					
Pre-Treatment	32	1.97 ± .40	34	1.68 ± .35	
Post-Treatment	32	1.98 ± .46	34	1.83 ± .41	
Gain Score	32	0.00 ± .18	34	.15 ± .30	-2.33*
Physical Role Functioning					
Pre-Treatment	28	5.57 ± 1.67	32	5.22 ± 1.48	
Post-Treatment	28	5.79 ± 1.69	32	5.75 ± 1.63	
Gain Score	28	.21 ± 1.13	32	.53 ± 1.22	-1.04
Social Functioning					
Pre-Treatment	32	4.28 ± .75	33	3.77 ± .88	
Post-Treatment	32	4.34 ± .62	33	3.94 ± .96	
Gain Score	32	.06 ± .58	33	.17 ± .79	-.61
Vitality					
Pre-Treatment	31	3.46 ± 1.11	32	3.44 ± 1.01	
Post-Treatment	31	3.56 ± .96	32	3.55 ± .95	
Gain Score	31	.10 ± 1.04	32	.11 ± .64	-.06

*$p \leq .05$.

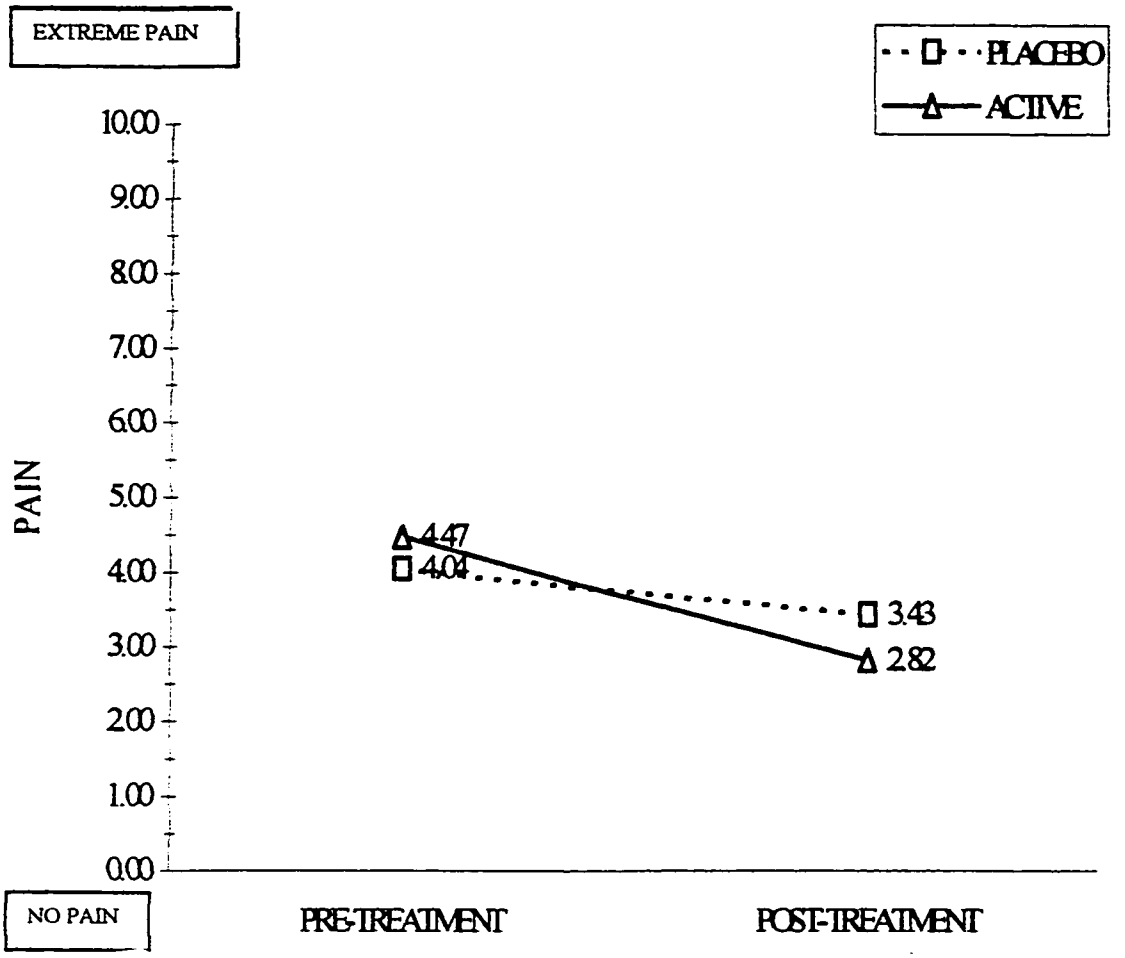
Table 7

Adverse Events by Group

Severity/Event		Placebo	Active	Total
No Event	Count	27	32	59
	% within event	45.8%	54.2%	100.0%
	% within treatment	75.0%	84.2%	79.7%
	% of Total	36.5%	43.2%	79.7%
Mild/Rash	Count	5	4	9
	% within event	55.6%	44.4%	100.0%
	% within treatment	13.9%	10.5%	12.2%
	% of Total	6.8%	5.4%	12.2%
Mild/Nausea & Cramps	Count		1	1
	% within event		100.0%	100.0%
	% within treatment		2.6%	1.4%
	% of Total		1.4%	1.4%
Mild/Nausea	Count	2		2
	% within event	100.0%		100.0%
	% within treatment	5.6%		2.7%
	% of Total	2.7%		2.7%
Mild/Hirsutism	Count		1	1
	% within event		100.0%	100.0%
	% within treatment		2.6%	1.4%
	% of Total		1.4%	1.4%
Mild/Numbness	Count	1		1
	% within event	100.0%		100.0%
	% within treatment	2.8%		1.4%
	% of Total	1.4%		1.4%
Mild/Pruritis	Count	1		1
	% within event	100.0%		100.0%
	% within treatment	2.8%		1.4%
	% of Total	1.4%		1.4%
Total	Count	36	38	74

Figure 1

WOMAC Pain Subscale Gain Score



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Appendix A

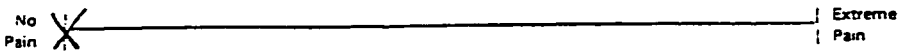
WOMAC OSTEOARTHRITIS INDEX VERSION VA3.0

INSTRUCTIONS TO PATIENTS

In Sections A, B and C questions will be asked in the following format and you should give your answers by putting an "X" on the horizontal line.

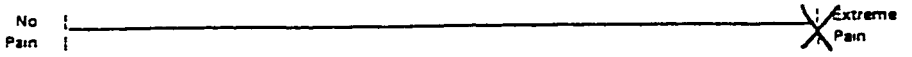
NOTE:

1. If you put your "X" at the left end of the line, i.e.



then you are indicating that you have no pain.

2. If you put your "X" at the right end of the line, i.e.



then your are indicating that your pain is extreme.

3. Please note:
   a) that the further to the right you place your "X" the more pain you are experiencing.

   b) that the further to the left you place your "X" the less pain you are experiencing.

   c) please do not place your "X" outside the end markers.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced in the last 48 hours.

Remember the further you place your "X" to the right, the more pain, stiffness or disability you are indicating that you experienced. Finally, please note that you are to complete the questionnaire with respect to your study joint(s). You should think about your study joint(s) when answering the questionnnaire, i.e., you should indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your study joint(s). Your study joint(s) has been identified for you by your health care professional. If you are unsure which joint(s) is your study joint, please ask before completing the questionnaire.

WOMAC OSTEOARTHRITIS INDEX VERSION VA3.0

Section A

INSTRUCTIONS: The following questions concern the ***amount of pain you have experienced due to arthritis in your knee.*** For each situation, please enter the amount of pain experienced in the last 48 hours. **(Please mark your answers with an "X".)**

QUESTION: How much pain do you have?

1. Walking on a flat surface.
   No Pain |———————————————————————| Extreme Pain
2. Going up or down stairs.
   No Pain |———————————————————————| Extreme Pain
3. At night while in bed.
   No Pain |———————————————————————| Extreme Pain
4. Sitting or lying.
   No Pain |———————————————————————| Extreme Pain
5. Standing upright.
   No Pain |———————————————————————| Extreme Pain

PAIN1 _____

PAIN2 _____

PAIN3 _____

PAIN4 _____

PAIN5 _____

Section B

INSTRUCTIONS: The following questions concern the ***amount of joint stiffness (not pain) you have experienced in the last 48 hours in your knee.*** Stiffness is a sensation of restriction or slowness in the ease with which you move your joints. **(Please mark your answers with an "X".)**

6. How severe is your stiffness after first awakening in the morning?
   No Pain |———————————————————————| Extreme Pain
7. How severe is your stiffness after sitting, lying or resting later in the day?
   No Pain |———————————————————————| Extreme Pain

STIFF6 _____

STIFF7 _____

Section C

INSTRUCTIONS: The following questions concern *your physical function*. By this we mean *your ability to move around and to look after yourself*. For each of the following activities, please indicate the degree of difficulty you have experienced in the last 48 hours due to arthritis in your knee. **(Please mark your answers with an "X".)**

QUESTION: What degree of difficulty did you have with ...

8. Descending stairs.
   No Pain | ——— | Extreme Pain — PFTN8 _____

9. Ascending stairs.
   No Pain | ——— | Extreme Pain — PFTN9 _____

10. Rising from sitting.
    No Pain | ——— | Extreme Pain — PFTN10 _____

11. Standing.
    No Pain | ——— | Extreme Pain — PFTN11 _____

12. Bending to floor.
    No Pain | ——— | Extreme Pain — PFTN12 _____

13. Walking on a flat surface.
    No Pain | ——— | Extreme Pain — PFTN13 _____

14. Getting in/out of car.
    No Pain | ——— | Extreme Pain — PFTN14 _____

15. Going shopping.
    No Pain | ——— | Extreme Pain — PFTN15 _____

16. Putting on socks/stockings.
    No Pain | ——— | Extreme Pain — PFTN16 _____

17. Rising from bed.
    No Pain | ——— | Extreme Pain — PFTN17 _____

18. Taking off socks/stockings.
    No Pain | ——— | Extreme Pain — PFTN18 _____

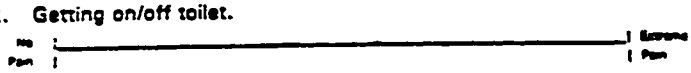
19. Lying in bed.
    No Pain | ——— | Extreme Pain — PFTN19 _____

20. Getting in/out of bath.
    No Pain | ——— | Extreme Pain — PFTN20 _____

21. Sitting.
    No Pain | ——— | Extreme Pain — PFTN21 _____

Section C (cont'd)

22. Getting on/off toilet.



23.. Heavy domestic duties.

24. Light domestic duties.

PFTN22 _____

PFTN23 _____

PFTN24 _____

PARIS SECTOGRAM:

Pain	_____	(degrees)
Stiffness	_____	(degrees)
Physical Function	_____	(degrees)
Total	_____	(degrees)

Appendix B

SF-36 Health Survey

This survey must be completed by the patient and checked for completion by site personnel.

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is: ..... (circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. Compared to one week ago, how would you rate your health in general now? (circle one)

Much better now than one week ago	1
Somewhat better now than one week ago ..	2
About the same as one week ago	3
Somewhat worse now than one week ago .	4
Much worse now than one week ago	5

3. The following items are about acitivities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. Vigorous activities such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking several blocks	1	2	3
i. Walking one block	1	2	3
j. Bathing or dressing yourself	1	2	3

SF-36 HEALTH SURVEY (cont'd)

4. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities carefully as usual	1	2

6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups?

(circle one)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past week?

(circle one)

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very Severe	6

SF-36 HEALTH SURVEY (cont'd)

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

	(circle one)
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week –

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

	(circle one)
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

Appendix C

Informed Consent Form

PHARMACEUTICALS LTD.

INFORMED CONSENT FORM

Title of the Project: A DOUBLE-BLIND, RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL OF TOPICAL DICLOFENAC IN PATIENTS WITH OSTEOARTHRITIS OF THE KNEE.

Investigators: Dr. Kenneth J. Skeith, phone number 482-7551
Dr. James A. Rogers, phone number 492-3478

- I have been told about the above noted study and the possible risks.
- I have read and understood the Patient Information Sheet for this study and have been given the chance to ask any questions I may have.
- I have been given time to think about my taking part and have freely agreed to take part in the study.
- I know that I can, at any time, ask for more information about the study or stop taking part without my decision affecting my medical care.
- I understand that if I have symptoms that make me wish to stop taking part, I will inform the study doctor or nurse immediately.
- I understand that the study doctor may take me off the study at any time if he feels it is in my best interest.
- I understand that my medical records may be reviewed by all parties involved in the study and that any reports from this study will not mention my name.
- I agree to take part in the study and will follow the instructions carefully.

Study Subject Name	Signature	Date
Witness Name	Signature	Date
Investigator Name	Signature	Date

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Appendix D.

Patient Information Sheet

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PATIENT INFORMATION SHEET

Title of the Project: A Double Blind, Randomized Placebo-controlled Trial of Topical Diclofenac in Patients with Osteoarthritis of the Knee.

Investigators: **Dr. Kenneth J. Skeith, phone number 482-7551**
Dr. James A. Rogers, phone number 492-3478

Introduction:

You are being asked to participate in a research study that will involve some 70 rheumatic patients with osteoarthritis of the knee. The information below is to help you to make a decision regarding participation in this study.

Purpose:

Osteoarthritis is one of the most common rheumatic diseases and it frequently involves the knees, producing pain and stiffness and limiting walking. One important approach to treating patients with osteoarthritis is to try and relieve symptoms of pain and stiffness using anti-inflammatory drugs (often known as NSAIDs). Some common NSAIDs that you may have used include diclofenac (Voltaren), naproxen (Naprosyn), indomethacin (Indocid), etc. However, NSAIDs may produce side effects, including stomach and intestinal problems. The current drug under testing would be a topical formulation of diclofenac gel rubbed locally onto the knee. The reason for using this combination is to provide an anti-inflammatory effect and reduce symptoms of pain and stiffness without its stomach side-effects.

Procedures:

In the present study, you will be treated with either 2% diclofenac in PHLOJEL™ or PHLOJEL™ as placebo (an inactive substance). However, the study is double-blind; that is, neither you nor the physician will know which of these 2 treatments you are receiving. The duration of the treatment will be 2 weeks.

The study requires a total of 3 visits. One (a screening visit) is prior to starting to ensure that your osteoarthritis is active and that you are otherwise well. This will involve taking a blood sample. In this visit we will ask you to stop using any oral anti-inflammatory drug.

At the next visit, the topical medication will be started and a clinical assessment will be made of the activity of your arthritis. You will also be asked to fill out two short questionnaires which will tell us how much your arthritis is troubling you. You will be required to give another sample of blood.

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Two weeks after this you will have the third visit and you will be assessed using the same procedures as the second visit. A last blood sample will be drawn at the time of the third visit to measure the level of drug in your system.

Each visit will take approximately 1 hour of your time.

The total amount of blood drawn from you will be no more than 4 tablespoons.

Possible Risks:

Side effects noted with the involved drug include skin effects such as rashes, hives, and itchiness; stomach effects such as peptic ulcer and mild diarrhoea. All of these side effects will be reversible on stopping the drugs, and its reported frequency has been very low. As with any new drug or combination of drugs, however, if unexpected symptoms develop during treatment, it is important to consider whether the symptoms might be drug-related and they should be reported to, and discussed with, the clinical investigator (physician) or his assistant.

Individuals of childbearing potential may not enter the study because of the possible effects of this drug on the fetus.

Voluntary Participation:

Participation in this study is voluntary and a refusal to participate will not otherwise affect your future medical care. Feel free to discuss your participation with your family and/or primary care physician prior to enrolling in this study. In addition, you may withdraw at any time you wish, and equally, the physician may require you to discontinue if he is concerned about a possible side effect. You may be asked to complete a post-study examination which includes: a physical assessment and routine blood and urine samples similar to those taken during the screening visit. By agreeing to participate in the study, you will also agree to not increase or alter any of your medications without discussing it with the study investigators.

Confidentiality:

The records of this study will be confidential, and no mention will be made of your name in any report; however, J.A.R. Pharmaceuticals Ltd., the Canadian Health Protection Branch or other international regulatory agencies have the right to inspect your study records (relating to this study only). All study records will be stored at J.A.R. Pharmaceuticals Ltd. for a period of fifteen years.

Please feel free to ask questions about any aspect of this research, this information sheet, or your rights as a study participant, either now or in the future and you can direct your questions to Dr. Kenneth Skeith at 482-7551.

If you have further concerns about any aspect of this study, you may contact the Patient Concerns Office of the Capital Health Authority at 474-8892. This office has no affiliation with the study investigators.

JAR-97-0202b J.A.R. Pharmaceuticals Ltd. Week 1

Patient Screening ID # __ __ __ Patient Initials __ __ __

CONCOMITANT MEDICATION RECORD

Week 1 _____ to _____
(month/dd/yy) (month/dd/yy)

	DAY 1		DAY 2		DAY 3		DAY 4		DAY 5		DAY 6		DAY 7		DAY 8	
	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time
Acetaminophen																
Acetaminophen																
Acetaminophen																
Acetaminophen																
Acetaminophen																
Acetaminophen																
Acetaminophen																
Acetaminophen																
Other (Specify)																

Please fill out this form as accurately as possible. It is very important that you record any and all medications that you use for the time of the study. This will give the investigators the information they need to determine the safety and effectiveness of the drug (gel) that is being studied.

Appendix E

Concomitant Medication Record

JAR-97-0202b | **J.A.R. Pharmaceuticals Ltd.** | Week 2

Patient Study ID # __ __ __ | Patient Initials __ __ __

CONCOMITANT MEDICATION RECORD

Week 2 _____ (month/dd/yy) **to** _____ (month/dd/yy)

	DAY 1		DAY 2		DAY 3		DAY 4		DAY 5		DAY 6		DAY 7	
	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time
Acetaminophen														
Acetaminophen														
Acetaminophen														
Acetaminophen														
Acetaminophen														
Acetaminophen														
Acetaminophen														
Acetaminophen														
PHLOJEL ™														
PHLOJEL ™														
PHLOJEL ™														
Other (Specify)														

Please fill out this form as accurately as possible. It is very important that you record any and all medications that you use for the time of the study. This will give the investigators the information they need to determine the safety and effectiveness of the drug (gel) that is being studied.

JAR-97-0202b

J.A.R. Pharmaceuticals Ltd.

Week 3

Patient Study ID # __ __ __

Patient Initials __ __ __

CONCOMITANT MEDICATION RECORD

Week 3 _____ (month/dd/yy) **to** _____ (month/dd/yy)

	DAY 1		DAY 2		DAY 3		DAY 4		DAY 5		DAY 6		DAY 7	
	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time
Acetaminophen														
Acetaminophen														
Acetaminophen														
Acetaminophen														
Acetaminophen														
Acetaminophen														
Acetaminophen														
Acetaminophen														
PHLOJEL ™														
PHLOJEL ™														
PHLOJEL ™														
Other (Specify)														

Please fill out this form as accurately as possible. It is very important that you record any and all medications that you use for the time of the study. This will give the investigators the information they need to determine the safety and effectiveness of the drug (gel) that is being studied.

Appendix F

Ethics Approval

CARITAS HEALTH GROUP

16940 - 87 Avenue Edmonton, Alberta T5R 4H5 Tel. (403) 484-8811 Fax. (403) 930-5774

March 19, 1997

Dr. James A. Rogers
JAR Pharmaceuticals Ltd.
Box 60052,
University of Alberta Postal Outlet
Edmonton, Alberta
T6G 2S4

Dear Dr. Rogers:

Re: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial of Topical Diclofenac in Patients with Osteoarthritis of the Knee
Amendment #1 - March 7, 1997

Thank you for presenting this study at the March 7, 1997 meeting of the Caritas Research Steering Committee, and for submitting Amendment #1 to the protocol, dated March 7, 1997.

Amendment #1 makes a change in the dose and application instructions to more closely reflect the common application practices and dose amount currently employed by patients in Alberta using topical diclofenac. This change is acceptable to the Committee.

Amendment #1 also makes the following changes requested by the Committee:

1. A font change to improve readability, in consideration that many participants will be elderly;
2. The sentence with regard to exclusion of individuals of childbearing potential has been underlined for emphasis;
3. The height and weight restrictions have been removed;
4. The reference to the Complaints Office of the Capital Health Authority has been changed to Brenda Waye, Caritas Corporate Manager.

With these changes, the Protocol as amended and the Information/Consent Form have the approval of the Caritas Research Steering Committee from an ethical and scientific viewpoint.

....2

We would appreciate a report to our Committee on completion of this project. It would also be appreciated if credit would be given to Caritas and its Research Steering Committee in publications where appropriate.

If you have any questions, please do not hesitate to contact me. I can be paged at the Grey Nuns Community Hospital and Health Centre, or you may leave a message with the committee secretary, Ms. Peggy Morton, at 930-5924 or fax 930-5961.

Yours sincerely,

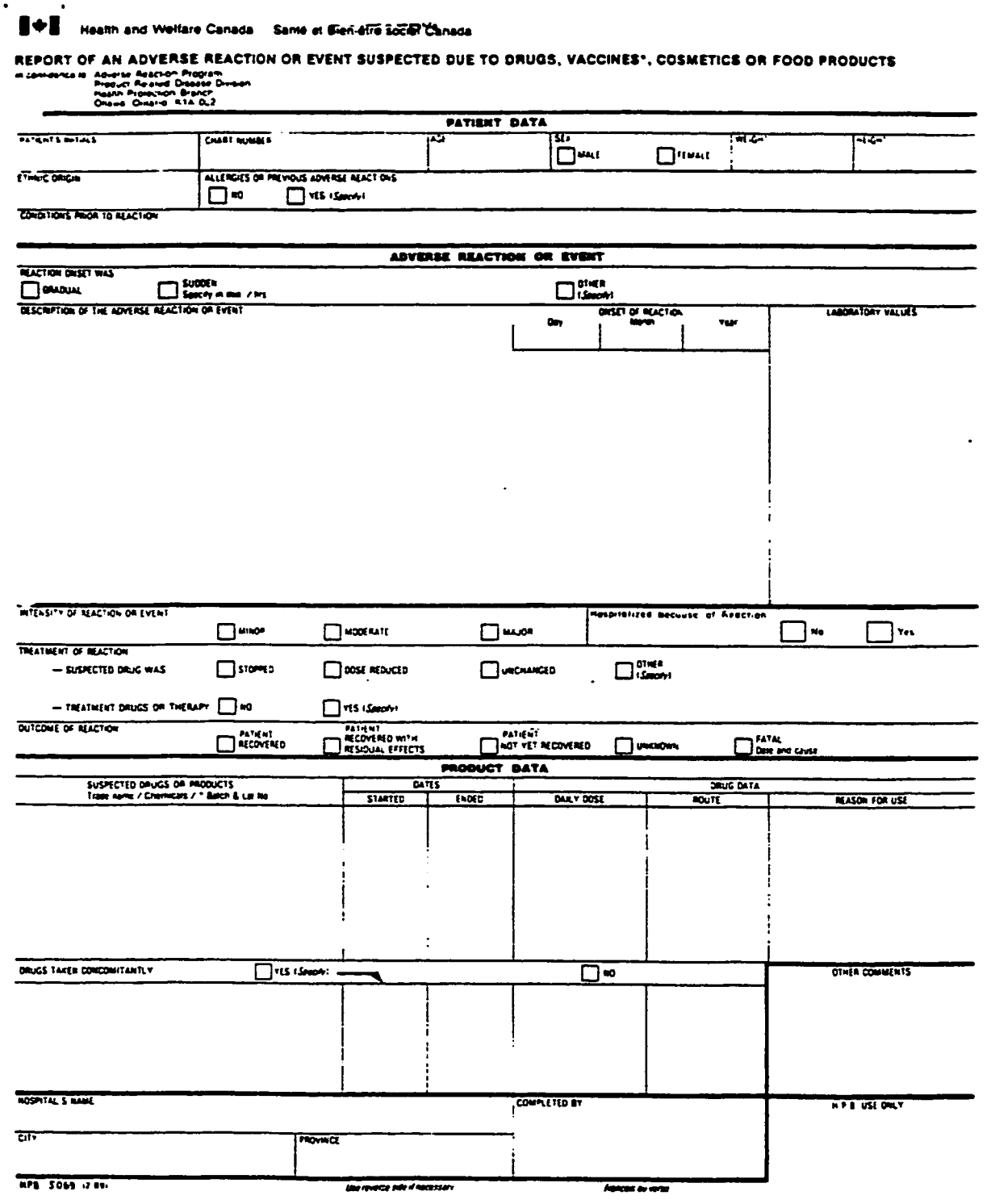
G.F. MacDonald, M.D., FRCP(C)
Chair, Caritas Research Steering Committee

c:\wp61\wpdocs\research\diclofenac.m24
CRSC File

Amendment #1 incorporates all the changes requested by the Committee as follows:

Appendix G

HPB 5069 form-Report of an Adverse Reaction or Event Suspected To Drugs, Vaccines, Cosmetics, or Food Products



Health and Welfare Canada Santé et Bien-être social Canada

REPORT OF AN ADVERSE REACTION OR EVENT SUSPECTED DUE TO DRUGS, VACCINES*, COSMETICS OR FOOD PRODUCTS

In correspondence to: Adverse Reaction Program
Product Related Disease Division
Health Protection Branch
Ottawa Ontario K1A 0L2

PATIENT DATA

PATIENT'S INITIALS | CHART NUMBER | AGE | SEX ☐ MALE ☐ FEMALE | WEIGHT | HEIGHT

ETHNIC ORIGIN | ALLERGIES OR PREVIOUS ADVERSE REACTIONS ☐ NO ☐ YES (Specify)

CONDITIONS PRIOR TO REACTION

ADVERSE REACTION OR EVENT

REACTION ONSET WAS ☐ GRADUAL ☐ SUDDEN Specify in min / hrs ☐ OTHER (Specify)

DESCRIPTION OF THE ADVERSE REACTION OR EVENT | ONSET OF REACTION Day / Month / Year | LABORATORY VALUES

INTENSITY OF REACTION OR EVENT ☐ MINOR ☐ MODERATE ☐ MAJOR | Hospitalized because of Reaction ☐ No ☐ Yes

TREATMENT OF REACTION
— SUSPECTED DRUG WAS ☐ STOPPED ☐ DOSE REDUCED ☐ UNCHANGED ☐ OTHER (Specify)
— TREATMENT DRUGS OR THERAPY ☐ NO ☐ YES (Specify)

OUTCOME OF REACTION ☐ PATIENT RECOVERED ☐ PATIENT RECOVERED WITH RESIDUAL EFFECTS ☐ PATIENT NOT YET RECOVERED ☐ UNKNOWN ☐ FATAL Date and cause

PRODUCT DATA

SUSPECTED DRUGS OR PRODUCTS Trade name / Chemicals / * Batch & Lot No	DATES STARTED	DATES ENDED	DRUG DATA DAILY DOSE	DRUG DATA ROUTE	DRUG DATA REASON FOR USE

DRUGS TAKEN CONCOMITANTLY ☐ YES (Specify): ☐ NO | OTHER COMMENTS

HOSPITAL'S NAME | COMPLETED BY | HPB USE ONLY

CITY | PROVINCE

HPB 5069 (2 89) Use reverse side if necessary Please do write

Appendix H

Adverse Events: Definitions, Guidelines for Classification, and Criteria for Determining Relationship to Study Medication

Definitions

Clinical adverse events or serious adverse events are illness, subjective or objective signs or symptoms that have appeared during the course of a study independently of a causal relationship to study medication. This includes all events both expected (known pharmacologic response) and unexpected or unwanted occurring during the course of the study. Moreover, all events that occur in relation to a clinical study after the last drug administration have to be estimated as an Adverse Event or Serious Adverse Event.

Adverse Events

Event related or non-related to study medications

Intercurrent illnesses

Important abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the Clinical Investigator considers to be clinically important

Serious Adverse Events

Overdose

Results in in-patient hospitalization

Life-threatening

Fatal

Cancer

Permanently Disabling

Classification of Adverse Events

All adverse events will be recorded on an adverse event information sheet and graded as mild, moderate, or severe according to the following definitions:

Mild

Causing no limitations of usual activities; the subject may experience slight discomfort.

Moderate

Causing some limitation of usual activities; the subject may experience annoying discomfort.

Severe

Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

Causality/Drug-Related Assessment

The Clinical Investigator will determine the relationship of any adverse event to study medication according to the following criteria:

Definite

A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by improvement of stopping the drug and by the reappearance of the reaction of repeated exposure and that could not be explained by other known factors.

Probable

A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by improvement of stopping the drug and that could be explained by the administration of the drug.

Possible

A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the drug, but that could readily have been produced by a number of other factors.

Unlikely

A reaction that follows a reasonable temporal sequence from administration of the drug; but that could probably not be explained by the administration of the drug.

Not related

Registration Procedure of Adverse Events

It is the Clinical Investigator's responsibility to record and report all adverse events which occur during the study (including all deviations of laboratory values from normal ranges), regardless of their relationship to the study medication. If judged necessary by the Clinical Investigator, an adverse event will be recorded on the HPB 5069 form, Report of an Adverse Reaction or Event Suspected Due to Drugs, Vaccines, Cosmetics or Food Products.

Information about serious adverse event will be recorded on the HPB 5069 form and will be reported to the Sponsor within one working day. This report will contain a detailed description of the observed symptoms and the contra-active therapy. The Clinical Investigator will judge the possible causal relationship between the event and the study drug.

The Clinical Investigator will arrange additional examinations at his own discretion to clarify if the event is connected with the study medication and will consult a specialist if necessary. All adverse events, serious or not, will be followed up and reported regularly to the Sponsor until an outcome is known.

The Sponsor or its representative will be responsible for notification to regulatory agencies.

Any event that does not meet the above criteria; there is sufficient information that etiology of the event is in no sequence to the study drug.

Not possible to judge

A judgment of the relation to study drug is not possible.

Adverse Events Documentation

The recording of every single Adverse Event and /or Serious Adverse Event has to meet special requirements:

- detailed subject data
- exact documentation of the event
- exact description of temporal sequence following drug administration
- documentation of duration and severity
- documentation of the results of diagnostic and therapeutic measurements
- results of a repeated exposure (re-challenge) if possible
- details to the development and outcome including medical judgment
- as much data as possible have to be obtained which are important for judgment concerning the relationship of the adverse event to study drug
- critical examination of the relationship to study drug

All adverse events will follow this scheme when spontaneously reported by the subject, observed by the Clinical Investigator or elicited by general questioning.

Appendix I

Patient Case Report Form

SCREENING ID# _____ **PATIENT INITIALS** _ _ _

Title: A Double-Blind, Randomized Placebo-Controlled Clinical Trial Of Topical Diclofenac In Patients With Osteoarthritis Of The Knee.

PATIENT CASE REPORT FORM

CLINICAL SCREENING (VISIT 1)

Demographic Data

Date: _____ (month/dd/yy) Screening ID#: ___ ___ Gender: _____ Race: _____

Name: _____

Initials: ___ ___ ___ Age: _____ DOB: _____ (month/dd/yy)

Address: _____

Phone #: H) _____ W) _____ Occupation: _____

Primary Physician: _____ Phone #: _____

Next of Kin: _____ Phone #: _____

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID# _____ **PATIENT INITIALS** _ _ _

Medical History

Osteoarthritis of the knee: Yes No If Yes, date of diagnosis: _____

Corticosteroid or hyaluronic acid injections of the target knee in the last one month:

Yes No If Yes, give date: _____

Prior total joint replacement surgery on target knee:

Yes No If Yes, give date: _____

Have you started physiotherapy in the last two weeks?

Yes No If Yes, give date: _____

Do you anticipate starting or stopping physiotherapy during the duration of the study?

Yes No

Alcohol History (list # of drinks / day, wk or mo): _____	Yes	No
Drug Dependency, Psychological Disease: _____	Yes	No
Cardiovascular Disease: _____	Yes	No
Gastrointestinal Disorders: _____	Yes	No
Musculoskeletal: _____	Yes	No
Neurological: _____	Yes	No
Lymphatic: _____	Yes	No
Dermatologic: _____	Yes	No
Immunologic: _____	Yes	No
Haematological Disease: _____	Yes	No
Diabetes: _____	Yes	No
Glaucoma: _____	Yes	No
Genitourinary: _____	Yes	No
Endocrine: _____	Yes	No
Pulmonary (asthma, bronchitis): _____	Yes	No
Allergies: _____	Yes	No
Allergy to NSAID's or similar drugs: _____	Yes	No
Significant Illness in past 30 days: _____	Yes	No

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID# _____ **PATIENT INITIALS** _ _ _

Title: A Double-Blind, Randomized Placebo-Controlled Clinical Trial Of Topical Diclofenac In Patients With Osteoarthritis Of The Knee.

PATIENT CASE REPORT FORM

REGULATORY

Has the study been explained to the patient and his/her questions answered?	Yes	No
Has the patient read and understood the Patient Information Sheet?	Yes	No
Has the patient read and understood the Informed Consent Form?	Yes	No
Has the patient signed and dated the Informed Consent Form?	Yes	No
Has the witness signed and dated the patient's Informed Consent Form?	Yes	No

CLINICAL SCREENING (VISIT 1)

Demographic Data

Date: _____ Screening ID#: ___ ___ Gender: _____

Age: _____ Race: _____

Medical History / Physical Examination

Is the patient available for the entire study period?	Yes	No	
Is the patient pregnant?	Yes	No	N/A
Is the patient presently breastfeeding?	Yes	No	N/A
Is the patient presently able to bear children?	Yes	No	N/A

If Yes, Is the patient using an effective form of birth control?

Yes (specify type _____) No

Note: Measurements of wt and ht done without shoes

Wt:_____lb. =_____kg. Ht:_____in. =_____cm.

BP (After 5 min of rest): _____ Arm used for BP: _____

TPR:_____ Time of vital signs: _____

Nurse/Physician signature:_____

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID# _____ **PATIENT INITIALS** _ _ _

		Date Of Surgery	Condition Still Present	
Surgeries:	_____	_____	Yes	No
	_____	_____	Yes	No
	_____	_____	Yes	No
	_____	_____	Yes	No
	_____	_____	Yes	No

Current Medications

Identify the medications the patient is currently taking for osteoarthritis or for any other conditions. List by name, daily dose and the condition for which the patient takes them.

Name of medication	Daily Dose	Condition for which medication is taken

Blood donation / Multiple samples in past 56 days: (circle) _____ Yes No

If Yes, give date: _____

History of fainting upon blood sampling: _____ Yes No

Has the patient had x-rays taken of his/her knee recently? Yes No

If Yes, give date and have the x-rays sent to the clinic to be reviewed during washout. Date: _____

If No, send the patient for x-rays of both the right and left knees.

Nurse/Physician signature: _____

Send the patient to the physician with his/her signed Informed Consent Form.

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID# _____ **PATIENT INITIALS** _ _ _

Physician Assessment

General Appearance: _____

Dermatologic: _____

Eyes: _____

Ears, Nose, Throat: _____

Cardiovascular: _____

Pulmonary: _____

Gastrointestinal: _____

Genitourinary: _____

Musculoskeletal: _____

Lymphatic: _____

Neurological: _____

Endocrine: _____

Haematologic: _____

Immunologic: _____

Other: _____

Osteoarthritis Assessment

Disease duration of symptoms in knees: _____

Radiographic Grade: Left Knee: Grade I ☐ Grade II ☐ Grade III ☐ Grade IV ☐

Right Knee: Grade I ☐ Grade II ☐ Grade III ☐ Grade IV ☐

Does this patient have unilateral or bilateral symptomatic involvement (Check One):

Unilateral Left: ☐ Unilateral Right: ☐ Bilateral: ☐

ACR Functional Grade: Grade I ☐ Grade II ☐ Grade III ☐ Grade IV ☐

Chronic comorbidity: Absent ☐ Present ☐ (Specify) _____

_____

Acute Intermittent Illness: Absent ☐ Present ☐ (Specify) _____

_____

Identification of Target Knee: Right ☐ Left ☐

Has Informed Consent Form been signed by physician? Yes No

Physician's Signature: _____ Date: _____

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID# _____ **PATIENT INITIALS** ___

Has patient been instructed to halt the use of current therapies for OA?	Yes	No
Has patient been instructed in the use of acetaminophen for pain control?	Yes	No
Has patient been instructed how to fill out Concomitant Medication Record?	Yes	No
Has patient been provided with a:		
a) Copy of signed Informed Consent Form and Patient Information Sheet?	Yes	No
b) One week supply of acetaminophen (identified with screening ID #)?	Yes	No
c) Concomitant Medication Record (identified with screening ID #)?	Yes	No
Has patient booked an appointment for Visit 2?	Yes	No
Has patient been instructed to return:		
a) Unused acetaminophen on Visit 2?	Yes	No
b) Concomitant Medication Record on Visit 2?	Yes	No

Laboratory

Has patient's laboratory requisition been completed?	Yes	No
Has patient been sent to lab for blood /urine sampling (lab tests)?	Yes	No

Record patient's laboratory identification number: _____

Washout Period

Note: Insert photocopies of laboratory results and x-rays in following pocket page.

Have the laboratory reports and x-rays been reviewed? Yes No

List any significant findings and action taken:

_____

_____

_____

_____

_____

_____

Physician's Signature: _____ Date: _____

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID# _____ **PATIENT INITIALS** __ __ __

PATIENT ELIGIBILITY RECORD (SCREENING TO VISIT 2)

Were there any findings in the clinical screening which precludes patient from continuing in the study? Yes No

Did the laboratory results indicate any reason(s) for which the patient should be excluded from the study? Yes No

List any significant change in the patient's general health status since the last visit?

_____

_____

_____

Do any of the above changes preclude patient from continuing in the study? Yes No

Have any prohibited concomitant medications been taken since Visit 1? Yes No

Specify: _____

Is the patient ineligible or unwilling to continue in the study? Yes No

If any of the above answers are Yes, please complete the following section:

Date of Termination: _____ (month/dd/yy)

Reason for Termination:

- ☐ Patient Withdrawal
- ☐ Significant Intercurrent Illness, Surgery
- ☐ Protocol Violation
- ☐ Adverse Events (please complete adverse event table - page 13)
- ☐ Other (please specify) _____

_____

_____

_____

Clinical Investigator's General Comments

_____

_____

_____

Clinical Investigator's Signature: _____ Date: _____

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID# __ __ STUDY ID # __ __ __ PATIENT INITIALS __ __ __

Insert Concomitant Medication Record from week 1 into the pocket page at the end of this Case Report Form.

FINAL ENROLMENT VISIT (VISIT 2) **Date:** _____ (month/dd/yy)

Has patient experienced the necessary OA flare criteria? Yes No

If No, patient is not eligible to participate in this study at this time. Patient may return after OA flare criteria has been met.

Did patient return acetaminophen and Concomitant Medication Record? Yes No

Has patient been assigned a study ID#? Yes No

Patient Global Assessment of Musculoskeletal Condition
How would you classify how your OA of the knee has been in the last week? (circle):

a) No problem b) Mild c) Moderate d) Severe

Physician Global Assessment of Musculoskeletal Condition
Your overall assessment of the patient's OA of the knee is one of the following (circle):

a) No problem b) Mild c) Moderate d) Severe

Have the following been checked for corresponding **Study ID # and Visit/Week #?**

WOMAC Osteoarthritis Index Version VA3.0	Yes	No
SF-36 Health Survey	Yes	No
Concomitant Medication Record	Yes	No
Study Medication Pots	Yes	No
Acetaminophen Pill Vials	Yes	No

For the following measurements, use the check boxes to indicate completion:

- ☐ Physician Global Assessment of Musculoskeletal Condition
- ☐ Knee Range Of Movement (final page of WOMAC)
- ☐ Patient Global Assessment of Musculoskeletal Condition
- ☐ WOMAC Osteoarthritis Index Version VA3.0
- ☐ SF-36 Health Survey

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID# __ __ STUDY ID # __ __ __ PATIENT INITIALS __ __ __

Has patient been instructed in the use of the PHLOJEL ™ medication?	Yes	No
Has patient been instructed in the use of acetaminophen for pain control?	Yes	No
Has patient been instructed how to fill out Concomitant Medication Record?	Yes	No
Has patient been provided with a:		
a) Two week supply of acetaminophen (identified with Study ID # & Week #)?	Yes	No
b) Two week supply of PHLOJEL ™ medication?	Yes	No
c) Concomitant Medication Record (identified with Study ID # & Week #)?	Yes	No
Has patient booked an appointment for Visit 3?	Yes	No
Has patient been instructed to return:		
a) Unused acetaminophen on Visit 3?	Yes	No
b) Unused PHLOJEL™ medication on Visit 3?	Yes	No
c) Concomitant Medication Record on Visit 3?	Yes	No

Laboratory

Has patient's laboratory requisition been completed?	Yes	No
Has patient been sent to lab for blood sampling(pharmacokinetics)?	Yes	No

Record patient's laboratory identification number: _____

Nurse/Physician's Signature: _____ Date: _____

TREATMENT PERIOD

Has patient been contacted and questioned regarding his/her health status?	Yes	No
Has patient been reminded to return the following on Visit 3:		
a) Unused acetaminophen?	Yes	No
b) Unused PHLOJEL™ medication?	Yes	No
c) Concomitant Medication Record (Weeks 2 and 3)?	Yes	No

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID#___ STUDY ID #____ PATIENT INITIALS ____

PATIENT ELIGIBILITY RECORD (VISIT 2 TO VISIT 3)

List any significant change in the patient's general health status since the last visit?

_____

_____

_____

Do any of the above changes preclude patient from continuing in the study? Yes No

Have any prohibited concomitant medications been taken since Visit 2? Yes No

Specify: _____

Did the patient deviate from his/her normal level of activity since Visit 2? Yes No

Specify: _____

Did the patient receive any additional medical treatment since Visit 2? Yes No

Specify: _____

Did the patient deviate from the instructions regarding the application of PHLOJEL™ medication (dosage and frequency)? Yes No

Specify: _____

Is the patient ineligible or unwilling to continue in the study? Yes No

If any of the above answers are Yes, please complete the following section:

Date of Termination: _____
(month/dd/yy)

Reason for Termination:

- ☐ Patient Withdrawal
- ☐ Significant Intercurrent Illness, Surgery
- ☐ Protocol Violation
- ☐ Adverse Events (please complete adverse event table - page 13)
- ☐ Other (please specify) _____

_____

_____

_____

_____

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID# __ __ **STUDY ID #** __ __ __ **PATIENT INITIALS** __ __ __

Clinical Investigator's General Comments

_____

_____

_____

_____

Clinical Investigator's Signature: _____ Date: _____

POST-TREATMENT VISIT (VISIT 3) **Date:** _____ (month/dd/yy)

Did patient return the:

a) Unused acetaminophen? Yes No

b) Concomitant Medication Record (Weeks 2 and 3)? Yes No

c) Unused PHLOJEL™ medication? Yes No

Insert Concomitant Medication Record from weeks 2 and 3 into the pocket page at the end of this Case Report Form.

Patient Global Assessment of Musculoskeletal Condition
How would you classify how your OA of the knee has been in the last week? (circle):

a) No problem b) Mild c) Moderate d) Severe

Physician Global Assessment of Musculoskeletal Condition
Your overall assessment of the patient's OA of the knee is one of the following (circle):

a) No problem b) Mild c) Moderate d) Severe

Have the following been checked for the corresponding Study **ID# and Visit/Week #**?

WOMAC Osteoarthritis Index Version VA3.0 Yes No

Physician Global Assessment of Musculoskeletal Condition Yes No

Patient Global Assessment of Musculoskeletal Condition Yes No

SF-36 Health Survey Yes No

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID#___ STUDY ID #____ PATIENT INITIALS ___

For the following measurements, use the check boxes to indicate completion:

- ☐ Physician Global Assessment of Musculoskeletal Condition
- ☐ Knee Range Of Movement (final page of WOMAC)
- ☐ Patient Global Assessment of Musculoskeletal Condition
- ☐ WOMAC Osteoarthritis Index Version VA3.0
- ☐ SF-36 Health Survey

Laboratory

Has patient's laboratory requisition been completed? Yes No

Has patient been sent for blood and urine sampling? (pharmacokinetic & lab) Yes No

Record patient's laboratory identification number: _____

Note: Insert photocopies of laboratory results in following pocket page.

Nurse/Physician's Signature: _____ Date: _____

RESEARCH PROTOCOL JAR-97-0202B

SCREENING ID# __ __ STUDY ID # __ __ __ PATIENT INITIALS __ __ __

ADVERSE EVENTS: ☐ NONE

ADVERSE EVENTS TABLE

Symptoms	Start (date and time)	End (date and time)	Intensity 1= Mild 2= Moderate 3= Severe	Drug Relation 0= Unknown 1= Not Related 2= Unlikely 3= Possible 4= Probable 5= Definite	Action Taken 1= None 2= Drug 3= Other

Are any symptoms considered to be serious adverse events: ☐ Yes ☐ No ☐ N/A

If Yes, please complete an HPB form (Report form for AE or event suspected due to Drugs, Vaccines, Cosmetics or food Products) and include it in the CRF. Report to J.A.R. Pharmaceuticals Ltd. Immediately.

Appendix J

Adverse Events Table