10670/0011

ZACIN CREAM 0.025%

AN ABRIDGED APPLICATION FOR A PRODUCT LICENCE

CLINICAL EXPERT REPORT

VOLUME 1 OF 1

PREPARED BY:-

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CONTENTS

PRODUCT PROFILE - ZACIN CREAM 0.025%

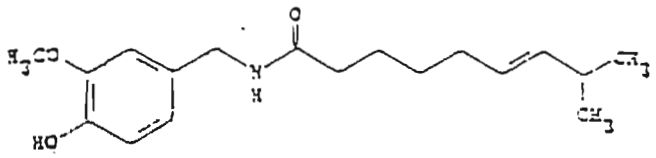
A. TYPE OF APPLICATION

This is an abridged product licence application for marketing authorisation in the United Kingdom for Zacin Cream 0.025% under PL 10670/0011.

Zacin Cream contains 0.025% capsaicin, a naturally occurring substance found in capsicum fruit. The active ingredient, capsaicin, has been licensed by Eurodema (Axsain, PL 10670/0003) for the symptomatic relief of pain associated with post-herpetic neuralgia.

B. CHEMICAL AND PHARMACOKINETIC PROPERTIES

Capsaicin, chemical name trans-8-methyl-N-vanillyl-6-nonenamide, is an alkaloid with the following structure:



Capsaicin has a molecular weight of 305.40 and forms white translucent crystals which melt at 64.5°C.

Absorption after topical application is unknown. Average consumption of dietary spice from capsicum fruit has been estimated as 2.5g/person/day in India and 5.0g/person/day in Thailand. Capsaicin content in capsicum fruit is approximately 1%, therefore daily dietary intake of capsaicin may range from 0.5-1mg/kg/day for a 50kg person. Application of two tubes of Zacin cream 0.025% (90g) each week results in a 3.2mg/day topical exposure. Assuming 100% absorption in a 50kg person, daily exposure would be 0.064mg/kg, which is approximately one-seventh to one-eighth of the above-mentioned dietary intake.

C. INDICATIONS

Zacin Cream 0.025% is indicated for the symptomatic relief of pain associated with osteoarthritis.

Although the precise mechanism of action of capsaicin is not fully understood, evidence suggests that capsaicin provides an analgesic effect by depleting and preventing subsequent reaccumulation of Substance P in peripheral sensory neurons. Substance P is one of the principal chemomediators of pain impulses from the periphery to the central nervous system and also plays a role in inducing inflammatory response.

Adults and elderly should apply Zacin Cream 0.025% to the affected area not more than 4 times daily. Zacin is not suitable for use in children.

D. PRECAUTIONS

Zacin Cream 0.025% is contra-indicated on broken skin or irritated skin. It should be kept away from the eyes. After applying Zacin Cream with the fingers, hands should be washed immediately.

Zacin may cause transient burning on application. This burning is observed more frequently when application schedules of less than 3 to 4 times daily are utilised.

E. MARKETING/POST-MARKETING

Zacin Cream is approved for marketing in the US.

1. PROBLEM STATEMENT

Osteoarthritis, also termed degenerative joint disease, is a chronic, debilitating condition of unknown aetiology. It is well established that the prevalence of the disorder increases with age. In a radiographic survey of women less than 45 years of age, only 2% had osteoarthritis. Between the ages of 45-64, however, the prevalence was 30% while for those older than 65 years it was 68%[1]. The figures are similar in males but somewhat lower in the older age groups. Osteoarthritis is a leading cause of disability; in a 1974 study conducted in the UK, 2.3% of men and 1.3% of women found it necessary to retire from employment due to osteoarthritis or associated conditions and an estimated 4.7 million working days were lost as a result[2].

While the early stages of osteoarthritis are painless, joint pain will eventually cause the patient to seek medical attention. The pain, which is often described as a deep ache localized to the involved joint, is typically aggravated by use and relieved by rest. With disease progression, however, the pain may become persistent. Stiffness of the involved joint may also be evident. Physical examination of the joint may reveal localized tenderness and bony or soft tissue swelling; crepitus is characteristic. Synovial effusions are relatively uncommon, however[1].

At the gross tissue level, osteoarthritis is characterized by progressive deterioration and loss of articular cartilage, accompanied by a proliferation of new bone and soft tissue in and around the involved joint. However, joint pain arising from this process must originate from other structures within the joint since cartilage is absent of innervation. In some patients, pain may be due to activation of nerve endings in the periosteum covering osteophytes. In others, pain may arise from microfractures of subchondral bone or alterations in blood flow caused by hypertrophic subchondral trabeculae. Muscle spasm and stretching of the joint capsule or, in some patients with advanced osteoarthritis, synovitis may be the origin of joint pain[1].

Medical treatment of osteoarthritis includes drug therapy, physical therapy for increasing joint mobility, exercise for muscle strengthening and use of canes and walkers to alleviate abnormal joint loading. For more advanced cases of osteoarthritis, surgical replacement of the affected joint may be required. Historically, the focus of pharmacological therapy for osteoarthritis has been to relieve pain, the primary symptom of the disease, in hopes of increasing joint mobility and function.

Pharmacological agents for the relief of pain associated with osteoarthritis include the use of analgesics (e.g. paracetamol), anti-inflammatory drugs [e.g. salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs)] and intra-articular injection of corticosteroids. Relatively few patients achieve satisfactory pain relief with paracetamol or NSAIDs alone. The use of these agents can be limited by adverse effects, potential interactions with other medications taken by the patient and pre-existing conditions such as liver disease or peptic ulcer for which the drugs are contraindicated. Moreover, these drugs alone often fail to provide sufficient pain relief[3].

Paracetamol is the most commonly used analgesic, however high doses over long periods of time are not without significant adverse effects, particularly liver toxicity. Largely because of their ease of use and broad acceptance, NSAIDs form the basis of osteoarthritis therapy. However, salicylates and NSAIDs often have undesirable adverse effects such as gastric dysfunction and irritation (including ulceration), sodium retention, platelet dysfunction, and exacerbation of allergic rhinitis and asthma. Potentially life threatening adverse effects of NSAIDs such as gastrointestinal bleeding and renal compromise are particularly problematic in the elderly; this age group experiences the highest incidence of serious gastrointestinal bleeding and renal compromise[3,4-7].

Topical therapy for muscle and joint pain is well accepted and this includes the wide use of topical NSAIDs for arthritis pain. Zacin (0.025% capsaicin) represents a novel approach to the topical treatment of pain associated with osteoarthritis by virtue of a mechanism of action distinct from that of other agents, such as topical NSAIDs. Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) produces an analgesic effect, in part, by interfering with the synthesis, storage, transport, and release of Substance P from nociceptive C-fibre neurons[8,9]. C-fibre neurons innervate the joint synovium and are thought to compose over 80% of the sensory nerves arising from the joint[10-12]. Substance P can be released from both the central and peripheral terminals of these fibres and is believed to play a major role in pain perception[12]. Substance P also acts directly on cells involved in the inflammatory response and has been described as a broad-spectrum mediator of inflammation, with effects on lymphocytes, monocytes, neutrophils, mast cells, and synoviocytes[13-15]. It may also affect cartilage destruction by acting directly on cartilage cells to alter their metabolism.

Topical capsaicin cream (0.025% and 0.075%) has been shown to be safe and effective analgesic therapy and has gained wide spread use in the U.S. and Canada as pain management therapy for the treatment of arthritis, painful diabetic neuropathy, and post-herpetic neuralgia. A number of leading experts in the field of rheumatology have suggested that capsaicin is an important therapeutic modality in treating the pain associated with arthritis[3,16,17]. Axsain cream (0.075% capsaicin) was licensed in the UK in 1992 for the symptomatic relief of neuralgia associated with and following herpes zoster infections (post-herpetic neuralgia), after open lesions have healed. Clinical data are presented in this application supporting the safety and effectiveness of Zacin (0.025% capsaicin) for the symptomatic relief of the pain associated with osteoarthritis.

2. CLINICAL PHARMACOLOGY

2.1. Neuropharmacology

Comprehensive reviews on the neuropharmacology of capsaicin principally from *in vitro* assessment and animal experimentation can be found in the medical literature. Full copies of two reviews[8,9] are included in Appendix 1 of this report.

2.1.1. Role of Substance P

Pain is principally mediated by small diameter sensory nerve fibres (nociceptors). Abrupt and sharp injury to the skin, muscle, or articular tissue is transmitted by myelinated A-delta nerve fibres. The other type of pain, often characterized as a burning sensation resulting from prolonged tissue damage, is mediated by unmyelinated nociceptive C-fibres which are polymodal in the sense that they respond to chemical, thermal and mechanical injury. The undecapeptide Substance P is believed to be a key neuromodulator involved in the transmission of pain and is found predominantly in nociceptive C-fibres and to a lesser extent, A-delta fibres[18]. Substance P also causes vasodilatation, plasma extravasation, and release of histamine from mast cells and may contribute to persistence of an inflammatory response within the joint[19]. In animal preparations, locally applied capsaicin appears to preferentially affect nociceptive C-fibres and to a lesser extent A-delta fibres[8,20].

2.1.2. Pharmacological Activity of Capsaicin

Capsaicin has two, apparently contradictory, effects. The first is related to nerve stimulation. Capsaicin has an immediate excitatory effect on afferent neurons and has been shown to produce a depolarization of nociceptive C-fibres when studied using cultured neuronal preparations[21,22]. In man, this activity is exemplified by observations that local applications of capsaicin produce an immediate effect of burning pain and/or marked hyperalgesia presumably by activation of primary afferent C-fibres, and perhaps A-delta fibres, and subsequent release of Substance P[23]. This capsaicin-induced depolarization of nociceptive neurons is likely to be the result of an interaction with a specific membrane receptor. Recent evidence confirming the existence of a capsaicin receptor, localized to mammalian sensory neurons, has been obtained using a novel capsaicin competitive antagonist, capsazepine[25]. It is likely that capsaicin-evoked Substance P release results from calcium and other cation entry via receptor activated ion channels[22].

The second, subsequent effect is that capsaicin can act as an anti-nociceptive and anti-inflammatory agent. The duration of this effect can range from hours to weeks and probably represents several levels of capsaicin action[9]. *In vivo*, the acute anti-nociceptive activity of capsaicin appears to be due to an effect related to receptor activation in the spinal cord dorsal horn. Support for this theory is derived from the observation that low dose systemic administration of capsaicin reversibly blocked C-fibre evoked firing of dorsal horn projection neurons[24].

With repeated exposure to capsaicin, there is desensitization of nociceptive C-fibres to both thermal and mechanical stimulation. The extent of desensitization depends on the concentration of capsaicin and time of exposure. Low concentrations of capsaicin induce a loss of sensitivity to further capsaicin administration without impairing responses to other noxious stimuli[22].

Repeated exposure of peripheral nerves to capsaicin produces a prolonged block of conduction in nociceptive neurons and a loss of chemical sensitivity due to impairment of signal transduction at the nerve terminal[23]. Conceivably, this desensitization process may involve affinity changes in the capsaicin receptor or uncoupling of the receptor-ion channel complex. This nonspecific desensitization is exemplified by a loss of sensitivity to repeated applications of capsaicin and attenuated responses to other chemical and physical noxious stimuli. At higher concentrations desensitization may be the result of selective sensory neurotoxicity brought about by toxic concentrations of capsaicin[9].

Capsaicin is not selective for Substance P depletion. It produces marked reductions in a number of other neuropeptides as well, including somatostatin, calcitonin gene-related peptide, and vasoactive intestinal polypeptide[23].

2.1.3. Pharmacology of Chronic Topical Capsaicin

The anti-nociceptive effects of long-term topical application of capsaicin have been evaluated in animal models and normal human subjects.

In a double-blind clinical investigation, ten normal human volunteers applied 0.025% capsaicin to one arm and a control emollient on the contralateral arm four times daily for a period of two weeks[26]. Skin temperature, skin temperature change and flare generated by histamine and allyl isothiocyanate, tactile threshold, sensitivity to heat, cold, and pinprick intensity, galvanic skin potential amplitudes (GSP), electrical stimulation perception thresholds (ESP), and antidromically-evoked sensory nerve action potentials (SNAPs) were determined at baseline and at three hours, three days and 14 days of application. There were no significant changes in GSP, skin temperatures or to tactile thresholds, ESP or SNAPs. Perceived intensity of grouped hot, cold, and pinprick stimuli was significantly diminished by the repeated application of capsaicin. After 14 days of application, heat sensation was preferentially affected, with only borderline effects on pinprick and cold sensation. Flare responses were not diminished in this study even after repeated applications and despite a small sensory loss.

In another double-blind study conducted with ten normal human subjects, capsaicin (0.075%) was compared to vehicle cream when applied to the forearm four times daily for a period of six weeks[27]. Psychophysical measurements of detection thresholds and suprathreshold magnitude for several cutaneous sensory modalities were made within each treatment area at baseline and one, three and seven days after the first application and once per week thereafter. During the first two to five weeks, capsaicin evoked mild burning pain with each application, but no visible flare. No adverse sensations were reported with the vehicle cream. Neither tactile detection thresholds nor pain sensation induced by pricking or pinching were altered

by capsaicin or vehicle. Warmth sensation thresholds increased significantly during the later stages of the study. A return to baseline was noted within two weeks post-application. Heat pain threshold increased after two weeks of capsaicin application and remained elevated. A maximum increase of 22.8% (vs. 3.5% for vehicle alone) occurred at the end of the study. Within two weeks of post-application, the mean pain threshold began to return to baseline. The sensation of itch produced by histamine was not affected by capsaicin treatment. These results demonstrate that prolonged application of capsaicin selectively diminishes sensations of heat pain. This effect is temporary, but is maintained with repeated capsaicin application.

2.1.4. Role of Substance P in Arthritis: Effect of Capsaicin

Capsaicin appears to have anti-inflammatory properties related to attenuation of Substance P activity. In rats with adjuvant-induced arthritis, subcutaneous capsaicin, at doses sufficient to deplete Substance P stores, significantly reduced both paw tenderness and swelling[28]. This beneficial effect occurred regardless of whether capsaicin was given before or after the onset of inflammation. Others have since confirmed and extended these observations.

2.2. Pharmacological effects of capsaicin *in-vivo*

Study 015-01 was conducted to determine the anti-inflammatory activity of topical capsaicin by measuring the effect of treatment on the concentration of various inflammatory mediators in patients with rheumatoid arthritis. A tabular summary for this study is included in Appendix 4. The study was designed as a six week, vehicle-controlled, double-blind trial evaluating the effects of topical capsaicin cream (0.075%) applied four times daily (qid) for four weeks to the knees of patients with rheumatoid arthritis. Clinical analysis of this study is discussed in section 3. Ten patients who met American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis and had at least one knee joint with synovial effusion and moderate pain participated in the study. Following treatment, the patients were followed for a two-week post-treatment period.

Clinical and laboratory assessments were obtained at baseline, treatment weeks 2 and 4 and post-treatment at week 6. Laboratory assessments of synovial fluid included measurements of Substance P, Prostaglandin E_2 (PGE_2), interleukin 6 (IL-6), interleukin 1-beta (IL-1ß), calcitonin gene-related peptide (CGRP), and neopterin. In addition, analysis was performed for white blood cell count (WBC) and WBC differential.

Synovial fluid determinations of Substance P, PGE_2, IL-6, and neopterin are shown in Table 1. Synovial concentrations of Il-1ß and CGRP were undetectable. After four weeks of treatment, patients treated with capsaicin had a mean reduction of 29% in Substance P levels vs a 3% increase in the vehicle group. PGE_2 levels decreased by a mean of 43% for capsaicin-treated patients vs a 6% increase for vehicle-treated patients. IL-6 levels tended to decrease in both groups. As calculated by percentage change from baseline, a greater decrease was observed in capsaicin-treated patients (49%) compared with vehicle patients (13%) at week 4.

Neopterin, a biochemical marker of immune system activation in inflammatory disease, especially macrophage-monocyte activity, decreased in the capsaicin group by 46% compared with an increase in the vehicle group after four weeks of treatment. Substance P levels continued to decrease in both groups during the two week medication-free period while PGE_2, IL-6, and neopterin levels increased in both groups.

Synovial fluid total WBC counts did not change in either group throughout the six week study. However, an important trend was observed. The percentage of polymorphonuclear leucocytes dropped by 40% in capsaicin group compared with a 10% increase in the vehicle-treated patients at Week 4. No significant differences were noted for total blood WBC counts.

TABLE 1

VARIABLE	(n) BASELINE	TREATMENT PERIOD (n) WEEK 2	TREATMENT PERIOD (n) WEEK 4	POST-TREATMENT (n) WEEK 6
Substance P (pg/ml)				
Capsaicin	(4) 44.3±4.8	(4) 39.5±6.5	(3) 31.3±7.5	(3) 27.7±8.5
Vehicle	(4) 47.5±6.1	(4) 49.5±3.2	(3) 46.0±10.3	(3) 20.0±5.8
Prostaglandin E_2 (pg/ml)				
Capsaicin	(4) 43.0±14.4	(4) 34.5±7.9	(3) 24.7±7.8	(3) 25.7±6.3
Vehicle*	(4) 48.5±18.2	(4) 51.3±18.1	(3) 51.3±22.8	(3)127.0±109
Interleukin-6 (ng/ml)				
Capsaicin	(4) 3.7±1.3	(4) 3.4±1.4	(3) 1.9±1.4	(3) 5.4±2.5
Vehicle	(5) 9.4±2.9	(5) 10.0±3.3	(4) 8.2±4.0	(4) 9.4±2.7
Neopterin (ng/ml)				
Capsaicin**	(4) 2.8±1.6	(3) 1.2±0.2	(3) 1.5±0.4	(3) 12.0±8.1
Vehicle	(5) 1.5±0.3	(5) 2.9±0.9	(4) 8.4±6.5	(3) 10.4±8.4

*** One vehicle patient had values of 764, 925, 633, and 682 ng/ml at each of the visits, respectively. When these values are included the mean Prostaglandin E_2 values are 191.6±144.0, 226.0±175.0, 196.8±146.0, and 265.8±159.0 ng/ml.**

**** One capsaicin-treated patient had a value of 55.6 ng/ml neopterin at Week 2. When this value is included, the mean is 14.8±13.6 ng/ml.**

The trends observed in this study were suggestive of a pharmacological effect of topical capsaicin, however, the small number of subjects precluded the demonstration of significant effects on inflammatory mediators.

2.3. Pharmacokinetics

Systemic absorption following the topical application of 0.025% capsaicin as Zacin has not been studied. However, systemic and distant somatosensory activity has not been observed after local applications implying that systemic absorption from cutaneous vascular beds is low. Moreover, daily exposure from topical therapy is considered to be much less than the amount ingested based on the average consumption of dietary spice from capsaicin fruit. For example, in some parts of Asia, it is estimated that a highly spiced diet could contain 0.5-1.0 mg capsaicin per kilogram body weight per day[29].

No information is available concerning absorption, distribution, metabolism, or elimination following either oral or systemic administration in man. After intravenous administration to rats, capsaicin is concentrated mainly within the spinal cord and the brain, and to a much lesser extent in the liver and blood. At an intravenous dose of 1 mg/kg, the half-life of capsaicin in rats was 7.1±3.2 min (mean±SD, n=4)[30]. When capsaicin was administered orally to rats, about 85% of the dose was absorbed over the course of three hours and was largely converted to dihydrocapsaicin by first pass metabolism[31]. Both capsaicin and the metabolites of capsaicin bind to serum albumin and are metabolized in the liver by the mixed function oxidase system. Dihydrocapsaicin and capsaicin are believed to be excreted in the urine[31,32]. The significance of these findings to absorption, metabolism, distribution, and elimination of capsaicin in man is unknown. Capsaicin has no known drug interactions and the seemingly low systemic levels following topical application further minimizes this potential.

(As no concomitant NSAIDs were allowed in this trial, it does seem strange that the placebo response in 066-04 was so high.)

3. CLINICAL TRIALS

Five double-blind, vehicle-controlled studies (066-04, 109-01, 87-04, 89-12, 015-01) have been carried out as Phase IV studies in the U.S. The objective of the first four studies was to evaluate the safety and efficacy of topically-applied capsaicin cream vs vehicle for the relief of pain associated with arthritis. The fifth double-blind study (015-01) was a clinical pharmacological investigation; the pharmacological results of this study have been discussed in 2.2. Studies 066-04 and 109-01 used only patients suffering from osteoarthritis, while Studies 015-01, 87-04 and 89-12 also included patients suffering from rheumatoid arthritis. Salient characteristics of the studies are summarized in Table 2. Tabulated summaries for all five clinical studies are provided in Appendix 2.

TABLE 2

Study No.	Dose capsaicin	Diagnosis of patients*	Objectives
066-04	0.025%	OA	Safety and efficacy
109-01	0.025%	OA	Safety and efficacy
87-04	0.025%	OA & RA	Safety and efficacy
89-12	0.075%	OA & RA	Safety and efficacy
015-01	0.075%	RA	Clinical pharmacology

*OA: osteoarthritis, RA: rheumatoid arthritis

All studies employed common statistical methodology in the analysis of results and included: Chi Square Test, Student's T-test, or Fischer's Exact Test, Cochran-Mantel-Haenszel, analysis of variance, log transformations, paired T-tests, Wilcoxon rank sum test, stepwise regression, and McNemar's test of correlated proportions. Two-tailed tests were performed in all instances. Statistical significance was established as $p \leq 0.05$. Efficacy parameters utilised are detailed in Appendix 3.

Study 066-04 was a multicentre, randomized, double-blind study which evaluated the safety and efficacy of 0.025% capsaicin as monotherapy in 113 patients with primary or post-traumatic osteoarthritis. Demographic data for this study are presented in Appendix 4. Patients applied 0.025% topical capsaicin or vehicle (qid) for a period of 12 weeks. During the trial, patients were given 12 paracetamol tablets per month to be used for non-arthritis pain. 96 patients completed the study. Efficacy and safety assessments were recorded at baseline and at weeks 1, 2, 4, 8, and 12 of treatment.

Efficacy assessments that were performed included: Physician's Global Evaluation, Patient's Global Evaluation, Categorical Pain Severity, VAS-Pain Severity, Morning Stiffness Questionnaire, and Articular Tenderness. Overall, 28 patients (8 capsaicin 20 vehicle) were considered to be nonresponders by investigators. For purposes of efficacy analysis, these patients had their respective week 4 efficacy values used at week 8 and week 12.

Study 109-01 was a single centre, randomized, double-blind study which evaluated the safety and efficacy of topical capsaicin in 59 patients with active primary osteoarthritis of the hands. Pretreatment patient characteristics and the percentage of patients who used NSAIDs concurrently during the study are listed in Appendix 4.

Patients were administered a two phase dosage regimen over the nine-week study duration. Throughout Phase I, from day 1 to week 3, patients topically applied either 0.025% capsaicin or vehicle (qid). In Phase II, week 4 to week 9, patients received the same treatment as in Phase I, but with application decreased to twice daily (bid). 29 participants received capsaicin and 30 received vehicle with a total of 48 patients completing the study (capsaicin=25, vehicle=23). Efficacy and safety assessments were performed at baseline and following 1, 3, 6, and 9 weeks of treatment.

Efficacy assessments that were performed included: Categorical Pain Assessment, VAS-Pain Severity, Grip Strength, Joint Swelling, Functional Capacity, and Articular Tenderness.

Study 87-04 was a multicentre randomized, double-blind study conducted in 101 patients with rheumatoid arthritis (n=31) or osteoarthritis (n=70) of the knee joints. Sixty-three patients with osteoarthritis (33 capsaicin, 30 placebo) completed the trial. Participants applied 0.025% capsaicin or vehicle topically qid for four weeks. Ninety-two patients completed the study. Patients were allowed to take standard oral arthritis medications during the study provided the dosages were stable prior to and during the study. Efficacy and safety assessments were performed at baseline and following 1, 2, and 4 weeks of treatment.

Pretreatment patient characteristics are listed in Appendix 4. Efficacy assessments that were performed included: Physician's Global Evaluation, Categorical Pain Severity, VAS-Pain Severity, VAS-Pain Relief, VAS-Morning Stiffness, VAS-Morning Stiffness Relief and Functional Capacity.

Study 89-12 was a single centre, randomized, double-blind study to evaluate the safety and efficacy of 0.075% capsaicin in 21 patients for the relief of pain associated with rheumatoid arthritis (n=7) and osteoarthritis (n=14) of the hands. Twenty patients, including all 14 suffering from osteoarthritis, completed the study which involved the application of topical capsaicin or vehicle qid for four weeks. Details of these 14 patients are included in Appendix 4. Patients were allowed to take standard oral arthritis medications during the study provided the dosages were stable prior to and during the study. Efficacy and safety assessments were performed at baseline and following 1, 2, and 4 weeks of treatment.

Efficacy assessments that were performed included: Categorical Pain Severity, VAS-Pain Severity, Grip Strength, Joint Swelling, Morning Stiffness Assessment, Articular Tenderness, and Functional Capacity.

Information from this study is included as supporting data only since 0.075% capsaicin cream was used as active treatment rather than 0.025%, capsaicin which is the proposed dosage strength for osteoarthritis in the UK.

In **Study 015-01** clinical assessments performed included the Physician's Assessment of Knee Joint Tenderness and Joint Swelling, Patient's Assessment on a Visual Analog Scale (VAS), an evaluation of morning stiffness, and a health assessment questionnaire.

Seven patients completed the study. Eight patients (80%; n=4 each group) reported concomitant NSAID use during the study.

3.1. Global analysis of efficacy

Table 3 provides an abbreviated overview and synopsis of the efficacy of topical capsaicin cream in the relief of pain associated with osteoarthritis.

TABLE 3

	Study 066-04	Study 109-01	Study 87-04	Study 89-12
Study Medication and Dosage Regimen	0.025% capsaicin; qid vs placebo	0.025% capsaicin; qid- 3 wks bid- 6 wks vs placebo	0.025% capsaicin; qid vs placebo	0.075% capsaicin bid vs placebo
Number of patients taking part in trial (OA = osteoarthritis, RA = Rheumatoid arthritis)	OA-113	OA-59	OA-70 RA-31	OA-14 RA-7
Patients withdrawing from capsaicin treatment due to lack of efficacy	four	none	one	none
VAS-Pain Severity - % improvement at end of trial vs (placebo)	53* vs (27)	33 vs (15) at 3 wks qid; 28 vs (21) at 6 wks bid	33 vs (16) 38* vs (17)†	55* vs 18
Articular Tenderness Assessment % of patients with relief# or % improvement## at end of trial vs (placebo)	74* vs (50) # passive range of motion, palpation	21.7* vs(1.2) ## dolorimetry	not performed	43* vs (10) ## dolorimetry.

* p<0.05 vs vehicle
† patients using low dose or no NSAIDs

3.1.1. Visual Analogue Scale for pain

3.1.1.1. VAS-Pain Severity

Figures 1-4 overleaf illustrate the VAS-Pain Severity results for Studies 066-04, 109-01, 87-04, and 89-12.

In Study 066-04 (see Figure 1), significant reductions in VAS-Pain Severity were noted for the capsaicin group of 53% (p=0.03), 49% (p=0.011) and 53% (p=0.02) at Weeks 4, 8, and 12, respectively, compared with 21%, 22%, and 27% for vehicle-treated patients at the same time points.

In Study 109-01 (see Figure 2), four times daily applications gave a mean reduction in VAS pain of 25% at week 1 and of 33% at week 3 compared with 13% and 15%, respectively, for vehicle-treated patients. When the dosing regimen was reduced from qid to bid, a transitory reversal in scores occurred in the capsaicin-treated patients. The positive trend had returned by week 9 however, where a 28% decrease was noted for capsaicin-treated patients as opposed to 21% for vehicle-treated patients with bid dosing. Although not statistically significant these results were clinically meaningful (p=0.115 qid and p=0.616 bid).

Osteoarthritic patients in Study 87-04 (see Figure 3) treated with capsaicin displayed significantly greater (p=0.002) VAS-Pain Severity at baseline than vehicle-treated patients. This difference was accounted for in the analysis by calculating the mean percent change from baseline. Capsaicin-treated patients showed a greater reduction in pain than did vehicle-treated patients over the first 2 weeks of the study and, after 4 weeks of treatment, capsaicin had reduced VAS for pain severity by 33% compared to a 16% reduction with vehicle.

A significant effect on efficacy was observed with concomitant NSAID treatment in this study. Those capsaicin-treated patients (n=28) taking no or low dose NSAIDs exhibited a significant reduction in VAS-Pain severity at Week 4 versus vehicle-treated patients (n=26) taking no or low dose NSAIDs (38 vs 17%, p=0.045). The patients on high doses of NSAIDs responded less well to capsaicin treatment. This finding may reflect the more refractory nature of the disease in patients requiring higher doses of NSAIDs. These patients are presumably in greater pain, and may be refractory to all types of analgesic treatment. The group of high-dose NSAID users had the highest baseline VAS-Pain Severity score suggesting a high level of disease symptomatology despite high doses of analgesic/anti-inflammatory drugs. Thus, additional therapeutic agents may also be expected to exert less pronounced effects.

In Study 89-12 (see Figure 4) capsaicin-treated osteoarthritis patients showed a reduction in VAS-Pain Severity of 34% at Week 2 and 55% at Week 4 compared with values of 11% and 18% for vehicle-treated patients. The reduction at Week 4 was significant (p=0.045) in favour of capsaicin.

FIGURE 1: STUDY NO. 066-04
Visual Analogue Scale for Pain Severity

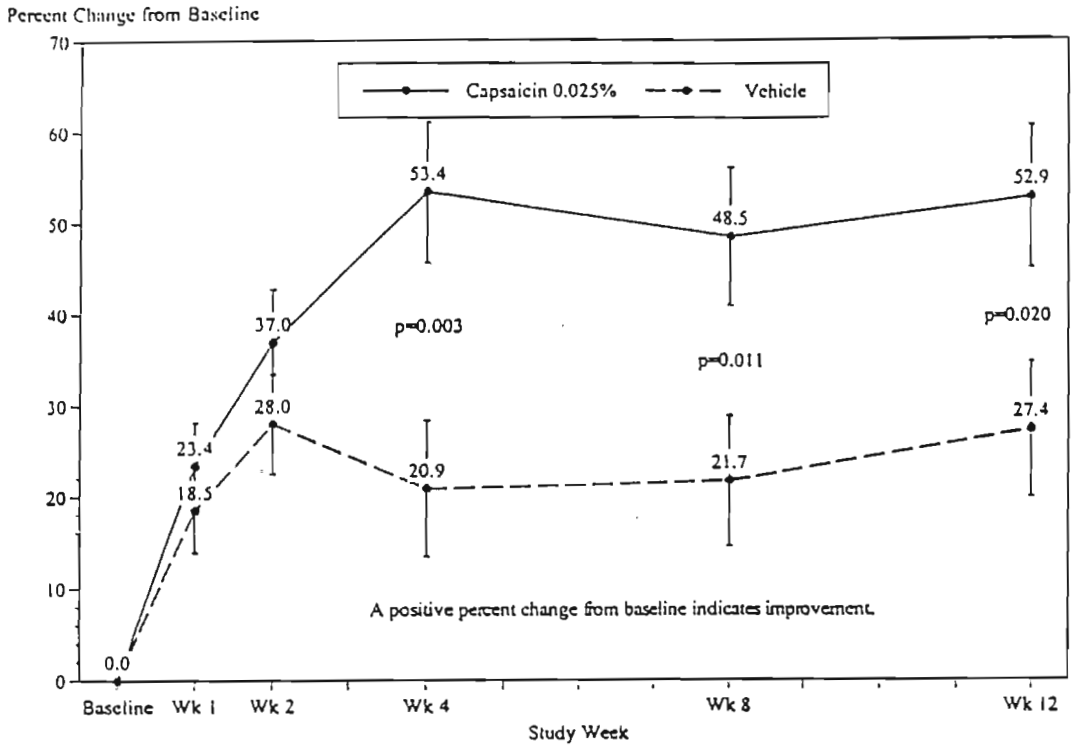
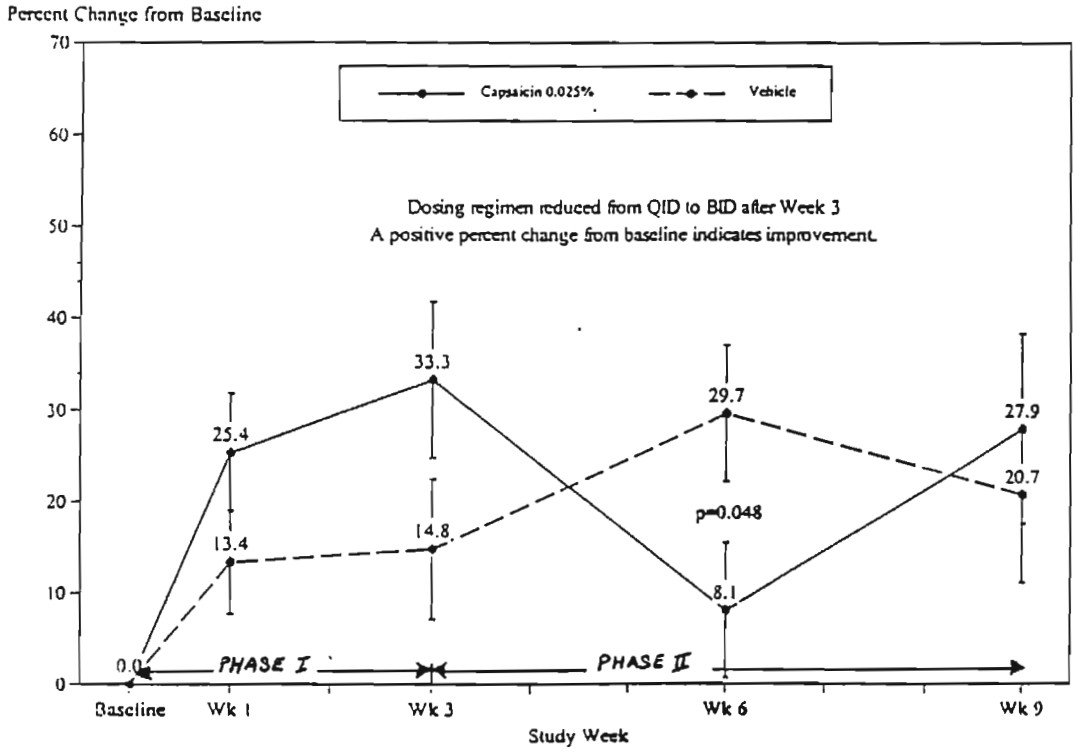


FIGURE 2: STUDY NO. 109-01
Visual Analogue Scale for Pain Severity



PHASE I - QID dosing regimen
PHASE II - BID dosing regimen

FIGURE 3: STUDY NO. 87-04
Visual Analogue Scale for Pain Severity

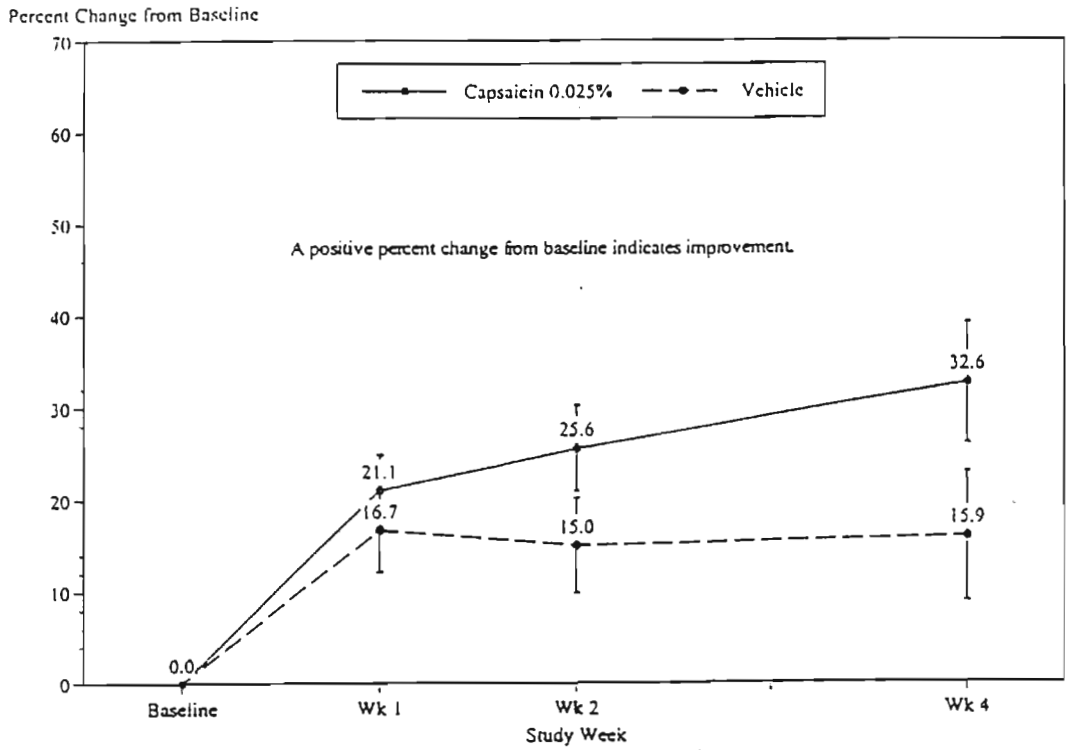
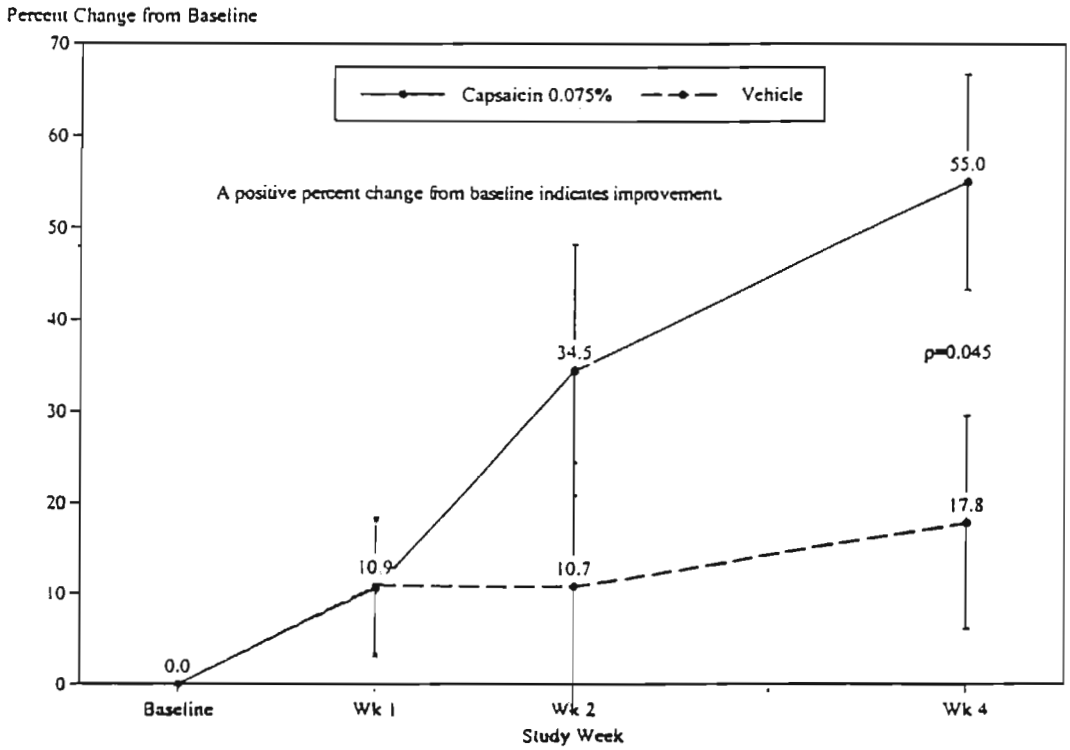


FIGURE 4: STUDY NO. 89-12
Visual Analogue Scale for Pain Severity



3.1.1.2. VAS-Pain Relief

In addition to the VAS-Pain Severity, Study 87-04 also utilized VAS-Pain Relief as a control measure to assess the efficacy of topical capsaicin treatment. For osteoarthritis patients statistically significant differences were not observed, however, there was a trend for greater pain relief in the capsaicin-treated group at the end of the study (45 vs 34%). Percentages of improved patients treated with capsaicin were 70%, 76%, and 72% at weeks 1, 2, and 4, respectively, compared to 50%, 52%, and 52% treated with vehicle treatment.

3.1.2. Categorical Pain Severity Assessment.

Capsaicin-treated patients in Study 109-01 had a greater categorical pain score assessment at baseline compared to vehicle-treated patients (p=0.017), but this was adjusted for in the statistical analysis. Although no statistically significant differences were seen between the treatment groups, results at week 1, 3 and 9 showed greater mean reduction in pain severity for capsaicin vs vehicle treated patients, with significance being approached at Week 3 (p=0.059).

In Study 87-04, mean categorical pain severity decreased at each visit for capsaicin treated osteoarthritis patients; changes from baseline were noted of 48% (Week 1), 56% (Week 2) and 69% (Week 4) in capsaicin-treated patients compared with values in vehicle treated patients of 42%, 41%, and 52%, respectively. While perhaps not clinically meaningful, the changes did reach statistical significance.

No significant differences were observed between treatment groups of osteoarthritis patients in Study 89-12. However, there was trend for greater improvement in the capsaicin-treated patients when compared to the vehicle-treated patients at each week.

3.1.3. Physician's and Patient's Global Evaluation

Study 066-04 employed both Patient's Global Evaluation and Physician's Global Evaluation. More capsaicin-treated patients experienced pain relief at each visit than vehicle-treated patients. A significant difference in the number of patients reporting pain relief was detected at Week 4 (p=0.023) and Week 12 (p=0.029) as shown in Table 4.

TABLE 4

Percent of Patients Improved Compared to Baseline - Patient's Global Evaluation			
Week	**Capsaicin**	**Vehicle**	**p-value**
1	70	66	0.152
2	81	70	0.075
4	85	63	0.023
8	76	56	0.101
12	81	57	0.029

Similarly, more capsaicin-treated patients experienced pain relief, according to Physician's Global Evaluation than vehicle-treated patients. A significant increase was noted at Week 4 (p=0.042) and Week 12 (p=0.026) as shown in Table 5.

TABLE 5

Percent of Patients Improved Compared to Baseline - Physician's Global Evaluation			
Week	**Capsaicin**	**Vehicle**	**p-value**
1	66	58	0.307
2	81	72	0.410
4	81	63	0.042
8	76	58	0.053
12	81	54	0.026

3.1.4. Articular Tenderness Assessment

Articular tenderness as assessed by passive range of motion in Study 066-04 is summarized in Table 6.

TABLE 6

Tenderness by Passive Range of Motion: Percent of Improved Patients Compared to Baseline			
Week	**Capsaicin**	**Vehicle**	**p-value**
1	44	42	0.580
2	58	48	0.420
4	75	51	0.053
8	72	48	0.025
12	74	50	0.026

Patients on capsaicin cream (0.025%) showed significant improvement in tenderness upon passive range of motion by Week 8 which was sustained through Week 12. The percentage of patients noting improvement in passive range of motion in the target joint at Week 8 was 72% (33/45) for capsaicin-treated patients versus 48% (24/50) for vehicle-treated patients. Similar results were observed at Week 12 with 74% (32/43) of capsaicin-treated patients reporting improvement versus 50% (23/46) vehicle-treated patients.

Study 066-04 also assessed articular tenderness by palpation and these results are summarized in Table 7 overleaf.

TABLE 7

Tenderness by Palpation: Percent of Patients Improved Compared to Baseline			
Week	**Capsaicin**	**Vehicle**	**p-value**
1	46	28	0.084
2	48	41	0.354
4	63	43	0.031
8	61	46	0.008
12	63	39	0.007

Significant decreases in tenderness with palpation occurred at Weeks 4, 8, and 12. Improvement was reported by 61% (28/45) of capsaicin-treated patients versus 46% (23/50) vehicle-treated patients at week 8 and 63% (27/43) of capsaicin-treated patients versus 39% (18/46) of vehicle-treated patients at week 12.

Study 109-01 showed statistically significant reductions in articular tenderness determined by calibrated dolorimetry at week 1 (p=0.046), week 3 (p=0.018) and week 9 (p=0.016) as shown in Table 8 below.

TABLE 8

Mean % change from baseline in articular tenderness				
Dosage regimen	**Week**	**Capsaicin**	**Vehicle**	**p-value**
qid	1	12.4	0.2	0.046
	3	25.6	6.2	0.018
bid	6	13.3	7.2	0.551
	9	21.7	1.2	0.013

After 3 weeks of qid therapy, the mean percentage change was greater than four times that for vehicle. At week 6, after 3 weeks of bid therapy, there was still almost double the reduction in articular tenderness with capsaicin treatment; although this difference may be clinically relevant, it was no longer significant when compared to the vehicle-treated group. By week 9, however, following 6 weeks of bid therapy, the mean percentage change had once again risen to be significant in favour of capsaicin.

In Study 89-12, the overall trend showed that capsaicin produced greater reductions in articular tenderness (dolorimetry) compared with vehicle in both hands, whether assessed separately or together, at all time points (weeks 1, 2 and 4). At week 4, this difference was significant. In both hands combined, there was a 43% reduction for capsaicin compared with 10% for vehicle (p=0.22) and in the right hand alone, a reduction of 49% vs 12% (p=0.015) was observed.

3.1.5. Morning Stiffness, Grip Strength, Joint Swelling Assessment and Functional Assessment

No significant differences were observed in morning stiffness in any of the three studies (066-04, 89-12, 87-04) which assessed this parameter. However, 87-04 and 66-04 tended to show greater decrease in morning stiffness in favour of capsaicin-treated patients compared to vehicle.

Grip strength assessment of osteoarthritic patients in Study 89-12 yielded a consistent trend for improvement in capsaicin-treated patients in the right and left hands, both individually and combined. At week 4, grip strength in capsaicin-treated patients had increased by an average of 14% versus 1.3% in the vehicle-treated group, however this difference did not achieve statistical significant. This pattern of response was mirrored in Study 109-01 where mean grip strength in capsaicin-patients increased by 30% at week 3 compared to 16% in vehicle-patients (non-significant), and by 32% at week 9 compared to a 3% change for vehicle group. This latter change was statistically significant (p=0.046).

In Study 109-01, capsaicin-treated patients experienced a greater, but nonsignificant reduction, in joint-swelling compared to vehicle at weeks 3, 6 and 9, approaching significance at week 9 (p=0.057). However, it should be noted that only four capsaicin and three vehicle patients had swelling noted as diagnostic criteria prior to entry into the study.

In Study 89-12, a significant difference in joint swelling between groups in favour of vehicle was noted in osteoarthritis patients at week 4 (p=0.037); no other significant differences in this parameter were noted.

In study 109-01, capsaicin-treated patients exhibited greater improvement in hand function at week 9 as compared with vehicle-treated patients when evaluated by functional assessment.

3.2. Global analysis of safety

3.2.1. Adverse Events

Safety results for Studies 87-04, 89-12, 066-04, 109-01, and 015-01 are summarized in this section and for analysis purposes the adverse experiences recorded for both rheumatoid arthritis and osteoarthritis patients are considered together. Appendix 5 provides an overall summary of adverse experiences reported and Table 9 overleaf summarises the percentage of patients reporting application site adverse events for all studies.

TABLE 9

Percent of Patients Reporting Application Site Reactions		
Study No	**Capsaicin**	**Vehicle**
109-01	41%	13%
066-04	67%	4%
87-04	54%	4%
89-12†	100%	18%
015-01†	40%	0%
†0.075% capsaicin		

Throughout Study 066-04, a total of 304 (177 capsaicin, 127 vehicle) adverse experiences were reported by 97 patients (54 capsaicin, 43 vehicle). The most frequently reported adverse event was headache (31 capsaicin, 23 vehicle) followed by application site reactions (capsaicin 26, vehicle 2).

Of the 26 application site reactions reported in the capsaicin-treated group, 23 were for warmth/stinging/burning following application, one patient reported eye irritation as the result of accidental transference, and there was one report each for tingling, erythema, and itching. Two vehicle-treated patients reported warmth/stinging/burning at the application site. All but one of these application site reactions was classified as mild to moderate in severity and all application site reactions occurring in the capsaicin-treated patients were attributed to study drug. The number of patients reporting warmth/stinging/burning declined over the course of the study (See Figure 5 overleaf); 17% reported burning or stinging at week 1, 9% at week 4, 5% at week 8 and 3% at week 12.

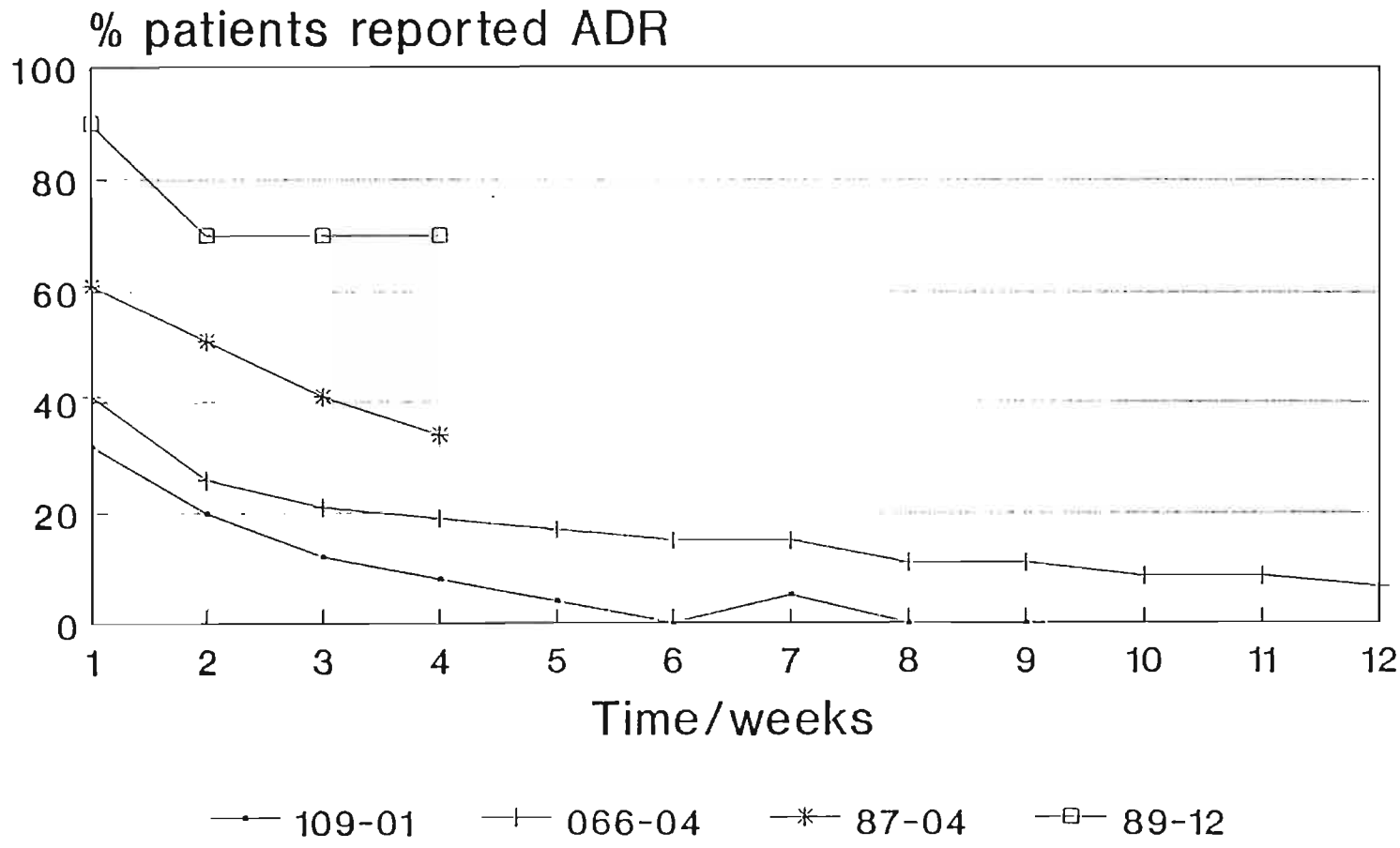
In addition to headache, other systemic adverse events included, back pain reported by 15 patients (9 capsaicin, 6 vehicle) and generalized pain reported by 14 (6 capsaicin, 8 vehicle). No adverse event was considered to be clinically significant by the investigator. None were attributed to study drug, although several were of unknown origin.

In Study 109-01, a total of 62 adverse experiences were reported by 33 (56%) patients throughout the study (21 capsaicin, 12 vehicle).

Application site reactions were the most frequently reported adverse experience with 16 (27%) patients (12 capsaicin and 4 vehicle) reporting 21 reactions and these reactions were most prevalent in Weeks 1 and 2 of treatment. The application site reactions for capsaicin comprised eight reports of warmth/burning, 2 of tingling/stinging and one of stinging only. The majority of the warmth/burning reactions (10/12, 80%) in the capsaicin-treated group were classified as mild to moderate in severity. The incidence of application site reactions declined during the course of therapy (See Figure 5 overleaf). All resolved without further treatment and were attributed to study drug by the investigator.

Figure 5

% Capsaisin patients experiencing ADR at application site



Of the four application site reactions occurring in the vehicle group, two were for dryness and two for burning.

Other adverse experiences that were reported included fever, headache, paraesthesia, hypotension, and nausea. No adverse event was considered to be clinically significant by the investigator. With the exception of rhinitis and conjunctivitis, none of the systemic adverse events were attributed to study drug by the investigator, although three (arthralgia, pain and syncope) were classified as of unknown origin.

In Study 87-04, a total of 68 adverse experiences were reported by 42 patients (30 capsaicin, 12 vehicle) throughout the study. Application site reactions were the most frequent adverse experience; reported by 28 capsaicin-treated patients (12 rheumatoid arthritis, 16 osteoarthritis) and 2 vehicle-treated (rheumatoid arthritis) patients. Twenty-five capsaicin-treated patients reported warmth, burning/stinging, two capsaicin-treated patients reported erythema and four capsaicin-treated patients and one vehicle-treated patient reported other miscellaneous application site reactions. A large percentage of the application site reactions (93%) were classified as mild to moderate in severity. 90% of the application site reactions were attributed to study medication with the remaining 3 of unknown origin.

No adverse event was considered to be clinically significant by the investigator and none of the systemic adverse events were attributed to study drug.

In Study 89-12, patients with rheumatoid and osteoarthritis were treated with 0.075% capsaicin. Thirty six adverse events were reported by 13 patients (10 capsaicin, 3 vehicle). Application site reactions were the most frequently reported adverse experience (capsaicin 10, vehicle 2): 9 capsaicin-treated patients reported burning/stinging at the application site and 1 reported eye irritation following accidental contact with the study drug. One vehicle-treated patient reported burning/stinging and 1 reported facial erythema on accidental facial contact with study drug. The majority of application site reactions in the capsaicin-treated group (77%) were mild to moderate in severity. All of the application site reactions were attributed to study drug and resolved without further treatment.

No adverse event was considered to be clinically significant by the investigator and none of the systemic adverse events were attributed to study drug.

In Study 015-01, six adverse experiences (5 capsaicin, 1 vehicle) were reported by 5 patients (4 capsaicin, 1 vehicle). Application site reactions of moderate severity were reported by two patients receiving capsaicin (one patient reporting warmth, the other reporting erythema and warmth). A joint disorder (swelling) was reported by one capsaicin-treated individual and increased pain was reported by another patient treated with capsaicin. One patient receiving vehicle reported increased swelling of the treated knee. No adverse experience was considered to be clinically significant by the investigator and no adverse experience of a systemic nature was attributed to the study drug. The application site reactions were attributed to study medication by the investigator, the other adverse experiences were not attributed to the study medication or were of unknown origin.

3.2.2. Premature Study Withdrawals

Five out of 51, 2/49, 1/10, and 1/10 capsaicin-treated patients withdrew from Studies 066-04, 87-04, and 89-12, 015-01, respectively, because of adverse experiences. In Study 109-01 only 2 vehicle-treated patients withdrew. All patients recovered upon withdrawal of study medication without further treatment and without sequel. Altogether, only six patients discontinued capsaicin treatment because of a burning/stinging reaction with application of the cream.

The total number of withdrawals for each study is summarised in Table 10.

TABLE 10

Study number	Number of patients enrolled in study	% withdrawal	Number of withdrawals	
			Capsaicin	Vehicle
066-04	113	15	11	6
109-01	59	19	4	7
87-04	101	7	3	4
89-12	21	5	1	0
15-01	10	20	1	1

Table 11 overleaf summarises the reasons for patient withdrawal.

3.2.3. Drug Interactions

None of the studies discussed noted any safety issues caused by drug interactions between capsaicin and concomitant medications. The most commonly used concomitant medications for each are listed in Appendix 6, together with the percentage of osteoarthritis patients from both the capsaicin and the vehicle treatment groups that used these medications.

TABLE 11

Reasons for Study Withdrawal			
Study	**Adverse Event**	**Treat-ment Group**	**Attribu-table to Study Drug**
066-04	Diffuse arthralgia	capsaicin	No
	Back and neck pain	capsaicin	No
	Fractured ankle	capsaicin	No
	Moderate application site burning	capsaicin	Yes
	Severe knee pain	capsaicin	No
87-04	Moderate application site burning	capsaicin	Yes
	Continuous mild burning taste	capsaicin	Unknown
89-12	Severe application site burning	capsaicin	Yes
015-01	Severe application site burning	capsaicin	Yes
109-01	Nausea, vomiting, diaphoresis, disorientation, diminished coordination, tiredness.	vehicle	Unknown
	Slipped disc.	vehicle	

4. POST-MARKETING EXPERIENCE

No serious unexpected adverse events have been reported in the U.S. with capsaicin (0.025%) since the product was introduced in 1987 (approximately 3 million tubes sold). The 2 year post-marketing experience with capsaicin (0.075%) is similar. The most common adverse effect that has been reported with the use of either capsaicin 0.025% or 0.075% is stinging or burning pain at the application site which was anticipated form the results of earlier clinical studies with capsaicin. Erythema and/or rash have been infrequently reported in post-marketing surveillance of capsaicin - approximately 1 incident reported by consumers per 100,000 units sold. On rare occasions (three cases reported to date), there have been reports that capsaicin 0.025% or 0.075% was associated with a respiratory irritant effect resulting in coughing, sneezing, rhinitis, and/or difficulty in breathing. In some instances these conditions have required treatment. Usually, this type of event is the result of over-application of the cream and/or a failure to wash off previous applications before reapplying. As a result, the dried capsaicin becomes airborne and is inhaled. Overall, the U.S. post-marketing experience supports the contention that capsaicin 0.025% or 0.075% are extremely safe products.

5. CONCLUSIONS

5.1. Therapeutic Justification

Osteoarthritis is a common disorder that affects a large percentage of individuals as they become older. The pain associated with osteoarthritis has proven to be a difficult condition to treat. Relatively few patients achieve satisfactory pain relief with paracetamol or NSAIDs alone, which are often associated with unacceptable side effects. As a result, patients are often incapacitated or severely limited by their pain which may limit their ability to conduct routine daily activities resulting in a reduced quality of life.

Zacin cream (0.025% capsaicin) works by a unique mechanism of action distinct from all other drug therapy currently used to manage arthritis pain. Capsaicin is the only agent that provides analgesia by specifically interfering with the activity of articular nociceptive Type C-fibre neurons. Importantly, topical capsaicin therapy does not interfere with the perception of other sensations (touch, vibration, etc.) from the treated area.

Zacin uses a novel pharmacological mechanism to effectively treat arthritis pain and has an advantageous safety profile. These characteristics afford Zacin the attributes to be used either as monotherapy or as adjunctive therapy.

5.2. Efficacy

A total of 256 patients with osteoarthritis were randomized to receive capsaicin. The duration of capsaicin therapy ranged from a minimum of four weeks to a maximum of 12 weeks. Two hundred and twenty patients completed the study in which they participated. Of the 129 patients randomized to receive capsaicin, 102 completed the study in which they were participants. Fifty-seven patients received capsaicin (0.025%) as monotherapy. While the numbers on active treatment were relatively low the benefits as demonstrated by the improvements in the outcome measurements were striking. Capsaicin provided significant relief when given as monotherapy (066-04) or when administered as an adjunct therapy with NSAIDs or paracetamol. The pivotal efficacy and safety studies evaluating capsaicin (0.025%) cream for the pain of osteoarthritis showed substantial benefit with improvement on both categorical rating scales and Visual Analogue Scales (VAS). Both techniques being commonly used in pain studies and are well accepted by researchers in this area.

Based on the results of the longer studies such as 066-04, full efficacy of 0.025% capsaicin does not occur until the fourth week of continuous use. Patients should therefore be informed of the possible delay before results can be seen and instructed to persist with compliance to the dosage schedule. No evidence of tolerance was observed.

Zacin cream (0.025% capsaicin) has been shown to be a novel and effective preparation for the management of the pain associated with osteoarthritis. The results of several well-controlled clinical trials discussed herein demonstrate that

Zacin provides significant pain relief in a majority of patients with moderate to very severe osteoarthritis pain. Moreover, in many instances, pain relief was accompanied by improvements in joint mobility and reduced articular tenderness. Together, these findings may translate to an increase in productivity and quality of life.

The clinical evidence supports that capsaicin (0.025%) is efficacious as monotherapy or adjunctive treatment in combination with other systemic analgesics for the treatment of osteoarthritis pain. Studies which directly compare topical capsaicin therapy with other reference therapies for osteoarthritis, e.g., NSAIDs, have not been conducted and would have been beneficial in confirming the efficacy of capsaicin.

5.3. Safety

Based on evidence in well-controlled clinical trials, Zacin cream poses minimal risk of serious systemic adverse effects to the patient with osteoarthritis. This characteristic is impressive indeed when contrasted to other pharmacological approaches used to manage arthritis pain which expose the patient to a wide range of adverse effects, some potentially serious or even life-threatening. The risk of adverse effects takes on an added measure of importance in the elderly patient, whose health and general well-being may already be compromised by other diseases or treatments. Comparative studies with competitor products would have been valuable in underlining the relative safety profile of capsaicin.

Post-marketing results have indicated that there is some potential for respiratory irritancy if the gel is not correctly applied. A warning within the dosing instructions on the patient leaflet may be appropriate to prevent this from occurring. There are no data on the effects of topical capsaicin in pregnancy although there appear to be no adverse effects of a capsaicin-rich diet.

There are no known drug interactions when Zacin cream is used as concomitant therapy. The concurrent use of medical therapies such as antihypertensives, hormone replacement therapy, oral contraceptives, remittive agents, NSAIDs, and paracetamol did not raise any safety concerns in the clinical trials that have been conducted to date. When necessary, therefore, other medications used to manage osteoarthritis pain or drugs used to treat unrelated conditions can be used concurrently with Zacin with minimal concern for drug interactions.

5.4. Dose and Administration

Conventional dose range and absorption studies have not been performed with topical capsaicin. For osteoarthritis pain, the 0.025% formulation appears to produce results, in terms of efficacy, similar to the 0.075% formulation. Although the 0.075% capsaicin did not raise any significant safety issues, the chronic nature of osteoarthritis necessitates that treatment is long-term, and the lower dose would, therefore, be the most appropriate and desirable choice.

The four times daily dosage regimen appears to be satisfactory. In most cases, efficacy was apparent after one to two weeks of application although the maximum effect is not observed until around four weeks. A twice daily application schedule was also explored as a maintenance dosage regimen (Study 109-01). While significant results were eventually achieved after some weeks, more research is required before this dosage regimen could be systematically recommended.

5.5. Risk/benefit

Zacin, containing 0.025% capsaicin, combines an excellent safety profile with effective treatment of debilitating pain associated with osteoarthritis. These characteristics allow Zacin to be used effectively either as monotherapy or as adjunctive therapy.

Zacin is a safe and effective treatment alternative for providing symptomatic relief of the pain associated with osteoarthritis and represents an important new treatment modality.

6. Signature of the expert

[redacted]

Date [redacted]

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