PREDATOR Pain Cream:
Product Safety and Efficacy

INTRODUCTION

This study was performed to assemble scientific evidence that demonstrates the safety and efficacy of the active ingredients in Predator Pain Cream. The study is organized into four parts:

1. Lidocaine
2. Glucosamine and Chondroitin
3. Methylsulfonul Methane (MSM)
4. Ethoxydiglycol

PART 1. LIDOCAINE

Topical lidocaine is a common form of anesthesia that is used for a wide variety of medical purposes covering many disciplines. Topical application is considered by many practitioners to be a safer and more readily acceptable method of delivering anesthetic than hypodermic injections, when used in accordance with recommended limitations. Since the inception of topical lidocaine, researchers and healthcare professionals have been investigating and reporting on their research into its safe and effective administration.

This section summarizes the published results of two independent studies that were conducted specifically to further assess the safety and effectiveness of topical lidocaine in the treatment of mid-level pain. These studies focused on the everyday use of lidocaine by pain sufferers to relieve pain in muscles and joints. These studies addressed the everyday use of lidocaine to relieve pain in muscles and joints. Not included in this paper were studies that addressed the use of lidocaine to treat post-operative patients or to treat patients undergoing medical procedures for which lidocaine is commonly used, such as tube insertion, venipuncture, laser treatments or skin grafting.

1A. LIDOCAINE STUDY 1: Oni, Brown, et al, 2010. University of Texas Southwest Medical Center, Dallas. [1]

Lidocaine Study 1 Overview

Topical lidocaine has been used safely and successfully by patients who adhere to the listed usage recommendations. Applications that exceed the recommended limits, however, can cause excessive lidocaine buildup in the patient's blood serum, leading to resulting complications and injury. This study quantifies this effect in a cross-section of subjects and helps to reinforce previously established safe usage limits. Specifically, the study data documents the variability of lidocaine serum levels in the blood after topical facial application of 4% lidocaine over varying time periods, with and without occlusive dressing.

The variables in this study were: lidocaine dosage, application duration and the use of an occlusive dressing over the application area. For all tests, recommended usage limits were observed. Following the topical lidocaine application, the researchers monitored the lidocaine levels in the test subjects' blood serum to

assess the influence of each of the test variables. The study concluded that a 4% concentration of topical lidocaine can be applied both safely and effectively in treating mid-level pain when used as directed.

Lidocaine Study 1 Objectives

The study was conducted to quantify how each of three test variables (dosage, application duration, and use of occlusion) affected the buildup of lidocaine serum in patients' bloodstream following application of 4% topical lidocaine.

Lidocaine Study 1 Methods

Twenty-five healthy volunteers were each assigned to one of four groups (A, B, C, and D). For all tests, 4% topical lidocaine anesthetic cream was applied. Group C represents the test baseline.

Lower Lidocaine Dosage:	Group A had 2.5 g applied to the face for one hour without occlusion.
Shorter Application Duration:	Group B had 5 g applied to the face for one half-hour without occlusion.
Test Baseline:	**Group C had 5 g applied to the face for one hour without occlusion.**
Occlusion Added:	Group D had 5 g applied to the face for one hour with occlusion.

To evaluate serum concentrations, blood was drawn every 30 minutes for four hours.

Lidocaine Study 1 Results

The experimental results indicated that:

1. Doubling the dose of 4% lidocaine for identical application periods increased then serum level in the blood by 50%. **(Group A *vs.* Group C)**

2. Doubling the application interval caused lidocaine serum level to peak more quickly and at a higher level. **(Group B *vs.* Group C)**

3. Adding occlusion caused a three-times increase in the lidocaine level in the patients' blood serum. Occlusion also caused the lidocaine level in the blood serum to peak more quickly than when occlusion was not applied. **(Group D *vs.* Group C)**

Lidocaine Study 1 Conclusions

This study suggests that topical lidocaine can be used safely and effectively when applied according to safety instructions, though metabolism differences among users will cause pronounced variations in individual tolerances to the application. Nonetheless, topical lidocaine was found to be safe and effective when used as directed.

1B. LIDOCAINE STUDY 2: "Herberger, Krause, et al, University Clinics of Hamburg, Hamburg, Germany" [2]

Lidocaine Study 2 Overview

Topical anesthesia is used for a broad spectrum of surgical procedures in dermatology, e.g., electrodessication of superficial skin lesions, cryotherapy, wound debridement, laser epilation and chemical peelings. The major considerations for local anesthetics are effectiveness, rapid action and low toxicity and sensitization. 4% lidocaine and EMLA cream (lidocaine–prilocaine 2.5%) are topicals commonly used for superficial anesthesia.

This study compared the effectiveness of 4% lidocaine cream and lidocaine-prilocaine 2.5% cream, both commercially available as OTC topical pain creams. The study results indicated that both products are safe and approximately equally effective in treating superficial pain.

Lidocaine Study 2 Objectives

The study had two objectives:

1. To compare the analgesic efficacy of lidocaine cream to lidocaine–prilocaine cream and a placebo
2. To assess the safety and tolerability of these two products

Lidocaine Study 2 Methods

This monocentric, intra-individual comparison study was performed at the Dept. of Dermatology, University Hospital of Freiburg on healthy volunteers. The study consisted of a randomized, three-arm, double-blind trial in 40 healthy volunteers comparing the anesthetic effectiveness of the tested products to the placebo at various time points (0–120 min).

A standardized pain was induced by lancet pricks and measured by a visual analog scale. Intra-individual comparison between the test areas was performed in a cross-over design.

Test areas were treated with the three test substances occlusively at one forearm and non-occlusively at the other. The three test sites and the forearm under occlusion were randomly assigned. In 20 volunteers, the preparations were applied for 30 minutes, while in the other 20 test subjects, they were applied for 60 minutes. The application consisted of massaging a small amount of test substance into the skin of the test area at the volar forearms. Immediately afterward, the tester completely covered the respective area with an even layer of the substance.

The lancet pain was determined separately (one test area after the other) at all three test sites at each of the two forearms at 30 and 60 min of occlusion, and – after removal of cream – at seven further measurement times (0 min, 15 min, 30 min, 45 min, 60 min, 90 min and 120 min).

Mean age of the volunteers was 30 years (range 19–59 years), and average body mass index was 22.2 ±2.5; 45% of the participants were male, 55% female. Four of the participants were smokers. None of the volunteers suffered from a skin disease or a type-IV hypersensitivity.

Lidocaine Study 2 Results

In the tests, lidocaine significantly reduced pain compared to the placebo at all assessment points. Pain reduction was achieved significantly earlier using lidocaine occlusively (30 min) (Figures 1). No significant differences were found concerning the anesthetic efficacy of lidocaine *vs.* lidocaine–prilocaine cream. There were no relevant adverse events. There were marked differences in pain values between different application time periods and occlusive or non-occlusive treatment.

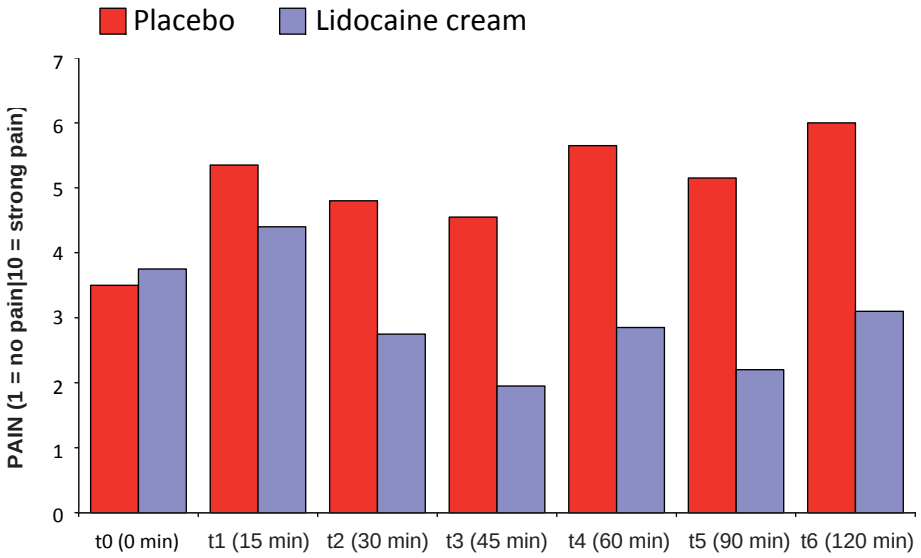

Figure 1. Induced pain after 30 minutes of occlusive application with lidocaine. Time points indicate the intervals after removal of cream.

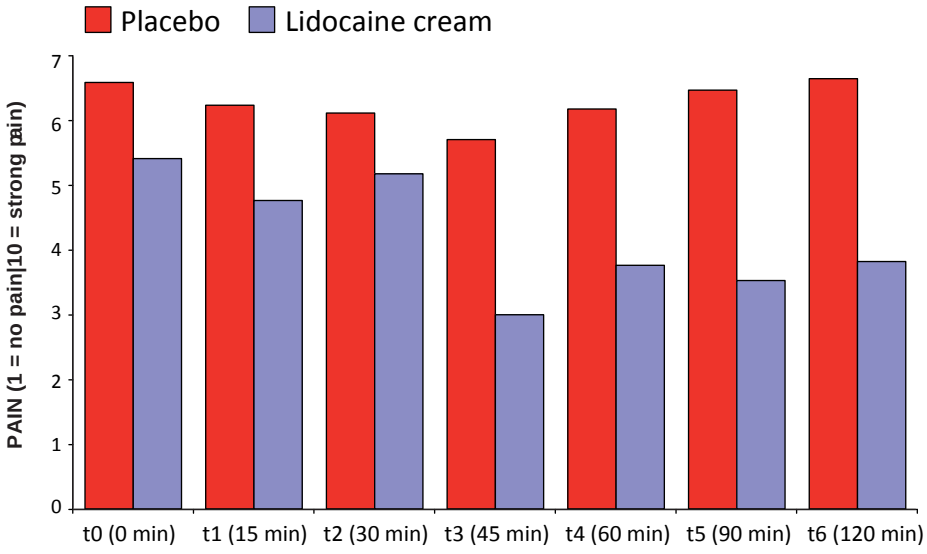

Figure 2. Induced pain after 30 minutes of non-occlusive application with lidocaine. Time points indicate the intervals after removal of cream.

a) In the test areas pretreated for 30 min with 4% lidocaine cream, the induced pain was clearly reduced compared to placebo at all assessment points from 15 to 120 min, both under non-occlusive application (Figure 2) and under occlusion (Figure 1). Differences between lidocaine and placebo were statistically significant at 30, 60 and 120 min in the non-occlusive areas and at 60 and 120 min in the occlusive areas.

b) The same effects, but with higher pain reductions, were observed in the test areas pretreated for 60 min (Figure 3, occlusive, and Figure 4, non-occlusive).

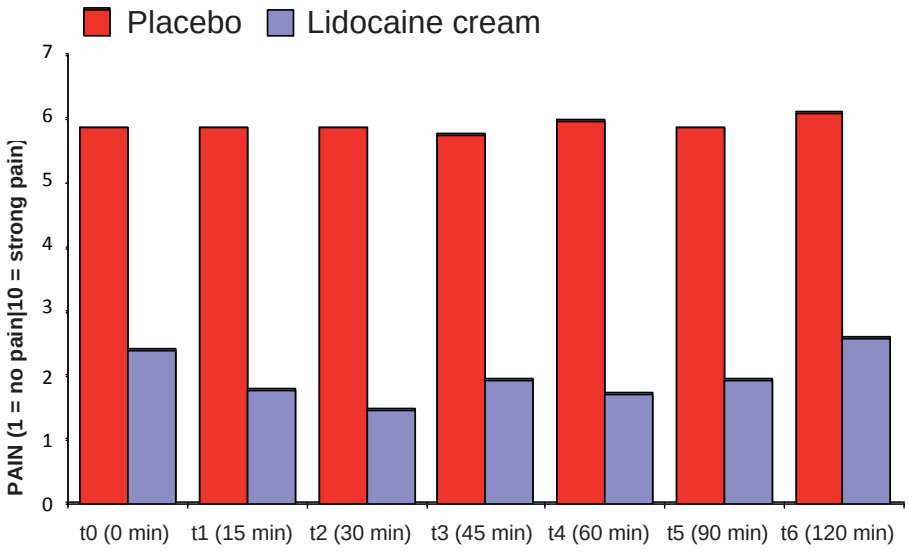

Figure 3. Induced pain after 60 minutes of occlusive application with lidocaine. Time points indicate the intervals after removal of cream.

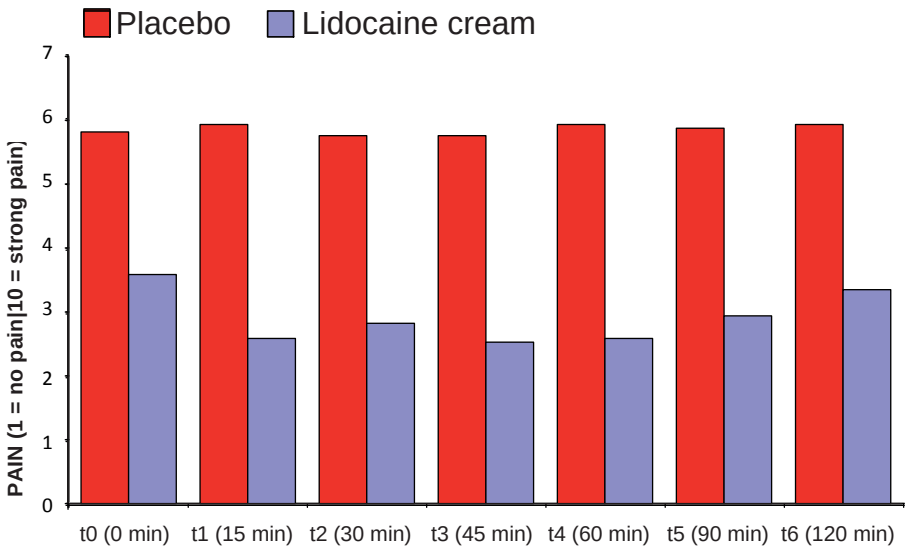

Figure 4. Induced pain after 60 minutes of non--occlusive application with lidocaine. Time points indicate the intervals after removal of cream.

All differences between lidocaine and placebo were statistically significant.

Regardless of occlusion, application of both topical anesthetics for 60 min was more effective than the application for 30 min. All preparations were well tolerated in the majority of volunteers. Four non-serious adverse events (AEs) were reported in four volunteers. The AEs were of mild severity, showing pallor at the pain cream test sites, which disappeared immediately in three cases and in one case after half an hour. The investigator considered the events in three cases to be related probably to study medication. In one case, the causality of the AE was missing. The volunteers recovered without consequence. There was only one case of itching reported at the lidocaine–prilocaine test site and at the placebo test site.

Lidocaine Study 2 Conclusions

This study confirms that a topical preparation with 4% lidocaine is an effective and safe treatment option for superficial anesthesia. It supports the claim that an occlusive application yields more rapid action. 4% lidocaine is useful as a quick-acting local anesthetic for the treatment of minor surgical procedures.

PART 2. GLUCOSAMINE and CHONDROITIN

2A. Glucosamine and Chondroitin Study 1: McAlindon, LaValley, et al, 2000. Arthritis Center, Boston University School of Medicine, Boston. [3]

Glucosamine and chondroitin preparations are widely touted in the lay press as remedies for osteoarthritis (OA), but members of the medical community are still evaluating their effectiveness.

Glucosamine and Chondroitin Study 1 Overview

Osteoarthritis (OA) is a major public health problem for which there are few effective medical remedies. Nonsteroidal anti-inflammatory agents are the most commonly prescribed agents for this disorder but are a frequent cause of serious adverse effects. Glucosamine and chondroitin are compounds extracted from animal products that have been used in various forms for OA in Europe for more than a decade and have recently acquired substantial popularity because of several lay publications. Because of their safety, these remedies would have great utility in the treatment of OA even if they were only modestly effective.

Glucosamine and Chondroitin Study 1 Objectives

This study was conducted to evaluate the benefit of glucosamine and chondroitin preparations for OA symptoms using meta-analysis combined with systematic quality assessment of clinical trials of these preparations in knee and/or hip OA.

Glucosamine and Chondroitin Study 1 Methods

The authors searched for human clinical trials in MEDLINE (1966 to June 1999) and the Cochrane Controlled Trials Register using the terms osteoarthritis, osteoarthrosis, degenerative arthritis, glucosamine, chondroitin, and glycosaminoglycans. They also manually searched review articles, manuscripts, and supplements from rheumatology and OA journals and sought unpublished data by contacting content experts, study authors, and manufacturers of glucosamine or chondroitin.

Studies were included if they were published or unpublished double-blind, randomized, placebo-controlled trials of four or more weeks' duration that tested glucosamine or chondroitin for knee or hip OA and reported extractable data on the effect of treatment on symptoms. Fifteen of 37 studies were included in the analysis.

The authors appraised the evidence provided by clinical trials of glucosamine and chondroitin preparations in OA by combining a systematic quality assessment with a meta-analysis. Because of evidence that these compounds may take several weeks to exert any therapeutic effect, they included only controlled trials that were at least four weeks in duration and trials that tested oral or parenteral glucosamine sulfate, glucosamine hydrochloride, or chondroitin sulfate against placebo among individuals with knee or hip OA. Only trials clearly stated to be double-blind and that had randomized treatment assignments were included in their meta-analysis. They also required that each trial include at least 1 of the outcome measures currently recommended for OA clinical trials.

Glucosamine and Chondroitin Study 1 Results

Trials of glucosamine and chondroitin preparations for OA collectively demonstrate moderate to large treatment effects on symptoms. The efficacy was smaller when measured after only four weeks of treatment, suggesting that induction of full therapeutic benefit may take longer than one month. Nevertheless, even modest efficacy could have clinical utility, given the safety of these preparations.

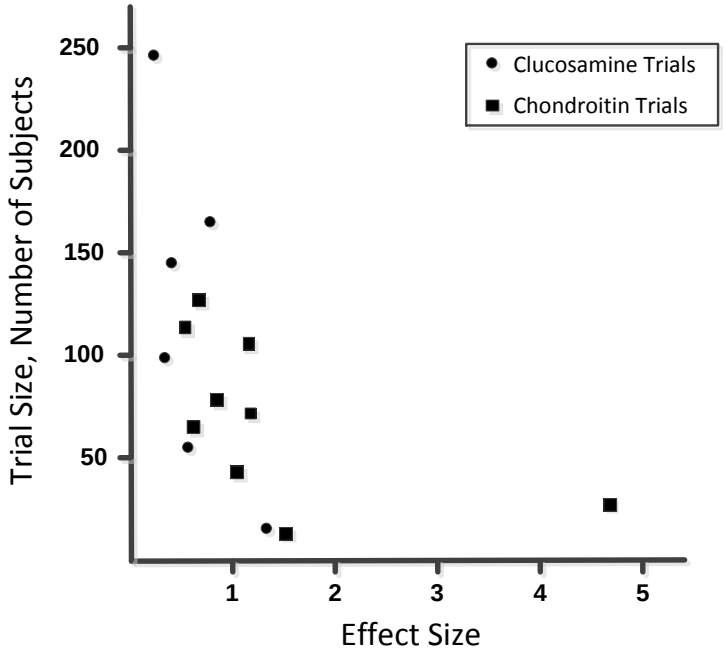

Figure 5. Summary results of clinical trial survey and treatment effects

Glucosamine and Chondroitin Study 1 Conclusions

Though these compounds appear to have considerable utility in OA treatment, the authors recommend further high-quality, independent studies to determine more precisely the actual efficacy and utility of these preparations.

2B. Glucosamine and Chondroitin Study 2: Cohen, Wolfe, et al, 2003, Faculty of Life Sciences, RMIT University, Bundoora, Australia. [4]

Glucosamine and Chondroitin Study 2 Overview

This study examines the use of a topical glucosamine/chondroitin sulfate preparation containing camphor and peppermint oil in relieving pain from OA of the knee.

Glucosamine and Chondroitin Study 2 Objective

This study was conducted to both assess the ability of a topical preparation of glucosamine sulfate and chondroitin sulfate to reduce pain related to OA of the knee and to compare the relative effectiveness of topical *vs.* oral application of these substances.

Glucosamine and Chondroitin Study 2 Methods

Sixty-three patients were randomized to receive either a topical glucosamine and chondroitin preparation or a placebo, which they were instructed to use as required over an eight-week period. Efficacy was assessed using a visual analog scale (VAS) for pain, as well as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The primary outcome measure was participant pain rating based on a 100 mm VAS that was assessed in the clinic at zero, four, and eight weeks. Secondary outcome measures included the WOMAC, a validated, disease-specific questionnaire addressing severity of joint pain, stiffness, and limitation of physical function. A higher WOMAC score indicates a worse symptom severity, with 96 representing the worst possible score.

Glucosamine and Chondroitin Study 2 Results

After 8 weeks, the VAS scores indicated a greater mean reduction in pain for the glucosamine/chondroitin preparation group compared to the placebo group. After four weeks, the difference between active and placebo groups in terms of mean pain reduction from baseline was slightly less than after eight weeks.

Although rapidly absorbed from the gastrointestinal tract, pharmacokinetic data show that when administered orally, glucosamine is subject to uptake and degradation by the liver and uptake into non-joint tissues, so that the dose reaching the articular cartilage is a fraction of a percentage of the oral dose.

While glucosamine has been shown to be active when given intramuscularly, direct topical application into the dermis surrounding an affected joint may potentially deliver a more concentrated dose to the affected area. Chondroitin sulfate has also been shown to be effective in reducing OA pain and to enhance the pain relieving action of glucosamine, despite poor gastrointestinal bioavailability when administered orally. Chondroitin sulfate may further act as a carrier substance to enhance dermal penetration of topical substances.

Glucosamine and Chondroitin Study 2 Conclusions

Topical application of glucosamine and chondroitin sulfate is effective in relieving the pain from OA of the knee and improvement is evidenced after 4 weeks of use. Glucosamine and chondroitin sulfate have been consistently shown to be agents of low toxicity that may relieve the pain and joint stiffness associated with OA. Long-term use of glucosamine may reduce radiographic progression of OA of the knee.

PART 3. METHYL SULFONYL METHANE

Methyl Sulfonyl Methane (MSM) is an organosulfur molecule that can be synthesized commercially from dimethylsulfoxide (DMSO). MSM can be bought at health food stores and on the internet in products such as creams and capsules. It is naturally present in the human body as it is metabolized from ingested DMSO. It can be found in cerebrospinal fluid and plasma at 0-25 µmol/l concentrations. Many properties have been attributed to MSM, some of which include chemopreventive properties, anti-inflammatory activities, anti-atherosclerotic action, prostacyclin (PGI2) synthesis inhibition and free radical scavenging activity.

A study by Usha and Naidu found that patients with knee osteoarthritis (OA) treated with MSM showed a 33% pain reduction on the visual-analogue-scale (VAS) for pain. This section describes the results of two other studies that evaluated the safety and efficacy of MSM in the treatment of pain associated with knee OA.

3A. MSM STUDY 1: Kim, Axelrod, et al, 2005. Southwest College Research Institute, Southwest College of Naturopathic Medicine and Health Sciences, Tempe, AZ. [5]

MSM Study 1 Overview

MSM is a dietary supplement that is being used increasingly for a variety of purposes, one of which is to treat arthritic and rheumatic pain. Because of MSM's sulfur content, it is used by the body to maintain normal connective tissues. MSM may have anti-inflammatory activities, chemopreventive properties, prostacyclin (PGI2) synthesis inhibition, anti-atherosclerotic action, salutary effect on eicosanoid metabolism, and free radical scavenging activity

Osteoarthritis (OA) is the most common form of arthritis and the second most common cause of long-term disability among middle-aged and older adults in the United States. Topically applied MSM is commonly used to relieve pain in older patients suffering from knee osteoarthritis pain.

MSM Study 1 Objectives

A study was conducted to investigate efficacy and safety of MSM in the oral dosages commonly used by practitioners and consumers to treat OA. More specifically, the study was intended to advise practitioners and patients in the appropriate use of MSM for arthritis pain management.

MSM Study 1 Methods

A randomized, double-blind, placebo-controlled trial was conducted. Fifty men and women, 40-76 years of age with knee OA pain were enrolled in an outpatient medical center. Intervention was MSM 3g or placebo twice a day for 12 weeks (6g/day total). Outcomes included the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) visual analogue scale, patient and physician global assessments (disease status, response to therapy), and SF-36 (overall health-related quality of life).

MSM Study 1 Results

The study results are presented in Table 1. Of the fifty original study participants, ten did not complete the trial for various reasons and were not included in the tabulation. Of those who completed the study, 21 received the MSM treatment and 19 received a placebo. At the end of the 12 week trial, the patients treated with MSM reported an average pain level improvement of 15 points on the WOMAC scale (0 = no pain,

100 = worst pain) and an average 16 point improvement in overall physical function. In comparison, participants treated with the placebo reported 7 and 9 point improvements in pain and overall physical function, respectively. MSM treatment produced no significant improvement in either patient or physician global assessment (GA) of health-related quality of life.

In summary, compared to the placebo, MSM produced significant decreases in WOMAC pain and physical function impairment. No notable changes were found in WOMAC stiffness and aggregated total symptoms scores. MSM also produced improvement in performing activities of daily living when compared to placebo on the SF-36 evaluation.

Table 1. Pain Evaluation: WOMAC, patient and physician Global Assessments

	MSM (n = 21)			Placebo (n = 19)			Between group difference at 12 weeks *P* values
	Baseline mean ± s.e.m.	12 weeks mean ± s.e.m.	Change ± s.e.m.	Baseline mean ± s.e.m.	12 weeks mean ± s.e.m.	Change ± s.e.m.	
WOMAC (0–100 mm, VAS)							
Pain	58.0 ± 5.5	43.4 ± 4.6	−14.6 ± 1.3	55.1 ± 5.8	47.9 ± 4.8	−7.3 ± 3.3	0.041*
Stiffness	51.2 ± 5.4	41.1 ± 4.8	−10.1 ± 2.6	55.2 ± 6.2	48.7 ± 6.8	−6.5 ± 2.4	0.320
Physical function	51.5 ± 4.5	35.8 ± 3.2	−15.7 ± 2.0	52.9 ± 5.9	44.1 ± 5.1	−8.8 ± 2.7	0.045*
Total symptoms	53.6 ± 4.9	40.1 ± 3.9	−13.4 ± 1.7	54.4 ± 5.6	46.9 ± 5.2	−7.5 ± 2.5	0.054
Patient Global Assessment (0–4, Likert scale)							
Disease status	3.0 ± 0.1	2.5 ± 0.2	−0.5 ± 0.2	2.8 ± 0.2	2.5 ± 0.2	−0.3 ± 0.2	0.549
Physician GA (0–4, Likert scale)							
Disease status	2.8 ± 0.2	2.5 ± 0.1	−0.3 ± 0.1	2.5 ± 0.1	2.3 ± 0.2	−0.2 ± 0.2	0.447

*Between group differences in the MSM and placebo evaluated using the Student's *t* test. The changes were considered significant for $P < 0.05$. The changes in the primary endpoints WOMAC pain and physical function at 12 weeks were significant between the MSM and placebo groups.

ACRONYMS

SEM = standard error of measurement
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
VAS = visual analog scale

MSM Study 1 Conclusions

MSM (3g twice a day) improved symptoms of pain and physical function during this short intervention without major adverse events. The benefits and safety of MSM in managing OA on a long-term basis cannot be confirmed without further investigation.

3B. MSM STUDY 2: Debbi, Agar, et al, 2011. Assaf Hrofeh Medical Center, Zerifin, Israel. [6]

MSM Study 2 Overview

Osteoarthritis (OA) is the primary cause of disability in the elderly, affecting nearly 27 million individuals in the United States alone. Knee OA is the most common type of OA, with an estimated 12.1% of adults in the United States suffering from pain and functional limitations. Patients with osteoarthritis (OA) take a variety of health supplements in an attempt to reduce pain and improve function.. The purpose of this study was to evaluate the efficacy and safety of MSM in treating patients with OA of the knee at a dosage of 3.375 g/d for 12 weeks. This dosage falls between those used by the studies of Usha and Naidu and Kim, et al, (MSM Study 1, summarized above).

MSM Study 2 Methods

The study was a 12-week randomized, double-blind, placebo-controlled trial using random numbers, assigned according to the order in which the patients were enrolled in the study and given pill bottles containing either the MSM or the placebo. The placebo was comparable in all characteristics to the MSM. The patients were scored at baseline, five weeks and 12 weeks at the outpatient clinic.

In patients suffering from bilateral knee OA, the more symptomatic knee during the initial examination was chosen for efficacy evaluation.

The primary outcomes of the study were the WOMAC questionnaire, the Aggregated Locomotor Function (ALF) score, the SF-36 health survey score and the VAS for pain. The WOMAC includes pain, stiffness, physical function and aggregated total symptoms subscales that were scored from 0 mm to 100 mm (0 = no pain, 100 = worst pain). A Hebrew version of the WOMAC was used in the study, which was shown by Wigler, et al, to be a reliable and valid instrument for evaluating the severity of knee OA in Israeli patients. The ALF score is a sum of the mean timed scores (seconds) on three locomotor functions: time taken to walk 8 meters, time taken to ascend and descend seven stairs, and time taken to transfer from a sitting to standing position. The SF-36 is a health survey on pain and quality of life that is scored from 0-100 (0 = worst pain and quality of life, 100 = no pain and the best quality of life). The VAS is a subjective measurement that the patient reports on a 10 cm horizontal line, where 0 indicates no pain and 10 the worst pain. The VAS is particularly useful in assessing changes in pain for individuals receiving therapy.

At each follow-up patient compliance and safety was evaluated. For compliance, patients were asked directly if they were taking their medication as they were instructed. The number of pills left in the pill bottle was also counted at each follow-up. For safety, patients were asked if there were any side effects or symptoms they were experiencing that they hadn't experienced before the study.

MSM Study 2 Results

For the primary outcomes there was a significant difference between the changes in the WOMAC physical function and aggregated total symptoms in the experimental group compared to the control group after 12 weeks. The results are presented in Table 2.

From baseline to the 12-week endpoint, physical function decreased by 17% in the MSM group and increased by 15% in the placebo group, corresponding to a difference of 14.6 mm between groups. Total symptoms decreased by 20% in the MSM group and increased by 14% in the placebo group, corresponding to a difference of 15.0 mm between groups. No significant difference was found between treatment groups over time in the WOMAC pain or stiffness subscales. Pain decreased by 21% in the MSM group and increased by 9% in the placebo group. The difference in pain improvement was 12.4 mm between the groups. Stiffness decreased by 26% in the MSM group and increased by 37% in the placebo group, corresponding to a difference of 27.2 mm between groups.

The MSM group showed a significant reduction in pain on the VAS. There was a reduction of 6% on the VAS in the MSM group, while there was an increase of 12% on the VAS in the placebo group. This corresponded to a 0.7 cm difference between the changes in each group.

With regard to safety analysis, no adverse events or side effects were recorded. None of the patients reported any side effects or symptoms that they hadn't experienced before the study.

MSM Study 2 Conclusions

The preset study found that patients with OA of the knee treated with 3.375 g/d MSM for 12 weeks show a significant improvement in the function and total score scales of the WOMAC and in the VAS for pain compared to a placebo-controlled group. The results suggest that larger and long-term studies may find additional and greater improvements in knee OA symptoms.

Table 2. Primary outcomes over the 12-week treatment period

	MSM			Placebo				Significance for between group differences at follow-ups	
	6 weeks	12 weeks	Difference 0-12 wk [CI]	6 weeks	12 weeks	Difference 0-12 wk [CI]	Between group differences [CI]	0-6 weeks	0-12 weeks
WOMAC									
Pain	35.5 ±26.1	34.0 ±24.5	-9.0 ±24.0 [-18.9, 0.9]	47.1 ±26.6	49.4 ±20.8	3.5 ±19.3 [-4.5, 11.5]	12.4 [0.0, 24.8]	0.20	0.05*
Stiffness	39.2 ± 31.0	36.0 ± 26.2	-11.7 ± 30.7 [-24.3, 1.0]	52.9 ± 30.4	58.5 ± 24.2	15.5 ± 35.8 [0.7, 30.3]	27.2 [8.2, 46.2]	0.03*	0.01*
Function	36.6 ± 23.7	33.1 ± 23.1	-7.7 ± 19.3 [-15.8, 0.3]	46.2 ± 25.1	54.3 ± 21.1	6.9 ± 17.0 [0.1, 13.9]	14.6 [4.3, 25.0]	0.51	0.01*
Total	36.6 ± 23.9	33.3 ± 22.5	-8.4 ± 17.8 [-15.8, -1.1]	47.2 ± 24.5	53.5 ± 20.3	6.5 ± 17.0 [0.5, 13.5]	15.0 [5.1, 24.9]	0.26	0.00*
ALF	36.5 ± 16.6	36.9 ± 20.7	-6.8 ± 10.3 [-11.0, -2.5]	32.2 ± 10.6	33.9 ± 10.9	0.8 ± 4.9 [-1.2, 2.8]	7.6 [2.9, 12.2]	0.02*	0.00*
SF-36	59.8 ± 19.7	62.2 ± 20.3	8.1 ± 21.8 [-0.8, 17.1]	61.1 ± 16.2	54.5 ± 15.4	-3.4 ± 14.6 [-9.5, 2.6]	-11.6 [-22.1, -1.0]	0.52	0.03*
VAS	3.30 ± 2.8	3.61 ± 2.9	-0.2 ± 3.2 [-1.5, 1.1]	5.22 ± 2.9	5.16 ± 2.2	0.6 ± 2.7 [-0.6, 1.7]	0.7 [-0.9, 2.4]	0.18	0.38

*The significance threshold was set at $p \leq 0.05$

CI = 95% confidence interval
MSM = methylsulfonylmethane
WOMAC = Western Ontario and McMaster Osteoarthritis Index graded from 0-100 mm, with 100 mm being the worst symptoms
ALF = Aggregated locomotor function in seconds
SF-36 = 36-item short-form health survey graded from 0-100, with 0 being the worst pain and quality of life
VAS = Visual-analogue-scale graded from 0-10 cm for pain, with 10 cm being the worst pain

PART 4. ETHOXYDIGLYCOL

The solvent ethoxydiglycol (EG) is currently used in over 500 cosmetic products. The Environmental Working Group's "Skin Deep" cosmetic safety database (cosmeticsdatabase.com) listed 509 products that contain ethoxydiglycol when accessed during the summer 2011. It is anticipated that this common cosmetic ingredient will be a component in numerous future prescription topical products approved for the US market. Dermatologists are already treating patients that apply products containing 5–40% of this solvent multiple times each day. The first FDA-approved prescription drug product to contain ethoxydiglycol was 5% dapsone topical gel. Other prescription topical products that contain ethoxydiglycol either have been approved or are currently under development.

4A. ETHOXYDIGLYCOL STUDY 1: Osborne, DW, J. Cosmetic Dermatology, December 2010. [7]

EG is commonly used as a solvent for topical products, with pharmaceutical formulators taking advantage of its ability to modify skin penetration and the cosmetic industry using it to alter product rub-in and feel. Ethoxydiglycol has been a favorite excipient for formulators of sunless tanning products because it spreads easily without streaking. These products often contain high concentrations of ethoxydiglycol (20–40%) and can be applied frequently to large skin surface areas. Ethoxydiglycol is also contained in a wide range of hair coloring products that are rinse-off applications. Although some of these products are known to be irritating, ethoxydiglycol itself is not considered the source of irritation. However, ethoxydiglycol by virtue of its solvent properties may promote the delivery of other excipients that are contained in the product that are irritating to the skin.

Ethoxydiglycol Study 1 Overview

Many studies evaluating ethoxydiglycol as a skin penetration modifier have shown that ethoxydiglycol enhances a permeant's solubility in the skin without significantly influencing the diffusivity of the permeant in the skin. For the permeants dexamethasone and hydrocortisone, the presence of ethoxydiglycol resulted in enhanced skin retention although the permeability and therefore the systemic uptake were significantly decreased. This effect has been called the intracutaneous depot and can be conceptualized as ethoxydiglycol increasing the reservoir capacity of the stratum corneum. Thus, although ethoxydiglycol is a skin penetration modifier, it is not accurate to describe ethoxydiglycol as a skin penetration enhancer.

Ethoxydiglycol Study 1 Objectives

The objective of this study was to assess the safety and effectiveness of ethoxydiglycol as a transdermal permeation agent.

Ethoxydiglycol Study 1 Methods

This study consisted of a review of technical and patent literature applicable to this objective.

Ethoxydiglycol Study 1 Results

EG when used in a 99.9+% pure pharmaceutical grade is safe and well tolerated. Up to half of the applied solvent crosses the skin's barrier and becomes systemic. For certain drug actives, this solvent provides for an

intracutaneous depot. This solvent has not demonstrated any inherent antimicrobial properties but was found to be mildly inhibitory toward Propionibacterium acnes.

A series of Gatteffosse reports cited in the Scientific Committee on Consumer Products (SCCP) review indicate that:

a. Neat ethoxydiglycol dosed at 0.020 mL per about 50 mm^2 of human volunteer skin (occluded for 48 h) was well tolerated.

b. Use of Marzulli and Maibach's method with 24 adult volunteers concluded that no pathological irritation or sensitization reaction significant to a cutaneous intolerance was noted.

Ethoxydiglycol Study 1 Conclusions

This safe, well-tolerated solvent is already used in many cosmetics and will become an ingredient in an increasing number of prescription products. Its ability to modify the skin delivery of actives it is formulated with (or formulation components that are applied just shortly before or after) make it important for dermatologists to have an understanding of this emerging solvent.

4B. ETHOXYDIGLYCOL STUDY 2. Literature Search

The following citations describe study results and findings available in the trade literature for ethoxydiglycol, also known as diethylene glycol monoethyl ether ("Degee"). Each of these papers addresses ethoxydiglycol's safety and/or effectiveness as a transdermal permeation agent.

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3. Scientific Committee on Consumer Safety, "Opinion on Diethylene Glycol Monoethyl Ether (Degee)" Eighth Plenary Meeting, 21 Sep 2010.

4. "Final report on the safety assessment of butylene glycol, hexylene glycol, ethoxydiglycol, and dipropylene glycol" International Journal of Toxicology. *1985* Sep/Oct 4(5): 223-248.

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2. Herberger K, Krause, K, Maier K, Zschocke I, Radtke M, Augustin M, "Local anesthetic effects of lidocaine cream: randomized controlled trial using a standardized prick pain" J Dermatological Treatment. 2011; Early Online: 1–6

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