Executive Summary

Background:

A randomized, double-blind, pilot study was performed to evaluate the effects of 14-days oral supplementation of the anti-inflammatory herbal extract Perluxan™, a standardized supercritical carbon dioxide hops extract containing 30% alpha acids, on individuals with osteoarthritis of the knee.

Method:

A Western Ontario McMasters Osteoarthritis Index (WOMAC) 5-item symptom assessment questionnaire was used to measure improvements of pain relief before (pretest) and after (posttest) 14 days of Perluxan™ (1 g × d^{-1}, n = 12 or 2 g × d^{-1}, n = 12) or placebo (n = 12) intake.

Results:

Walking on a Flat Surface: significant improvement in pain relief with 2 g × d^{-1} Perluxan™ supplementation at hour 2 post-dosing on day 1, day 2 and 4 and with 1 g × d^{-1} Perluxan™ intake at day 2 and 6 in comparison to placebo (mean change from baseline, $p<0.05$). While in Bed: significant improvement in mean pain relief with 2 g × d^{-1} Perluxan™ intake at day 3 and with 1 g × d^{-1} Perluxan™ supplementation at day 3, day 12 and day 13 in comparison to placebo (mean change from baseline, $p<0.05$). Sitting or Lying: low-dose intake (1 g × d^{-1} Perluxan™) significantly improved mean pain relief ($p<0.05$) in comparison to high-dose supplementation (2 g × d^{-1} Perluxan™).

Conclusion:

It is concluded that 14-days of either 1 or 2 g of oral Perluxan™ supplementation significantly improved parameters of Osteoarthritis pain.

Background:

The Western Ontario MacMaster Osteoarthritis Index (WOMAC) is a validated instrument designed specifically for the assessment of lower extremity pain and function in Osteoarthritis (OA) of the knee or hip. The WOMAC is a reliable and sensitive instrument for the detection of clinically important changes in health status following a variety of interventions (pharmacologic, surgical, physiotherapy, etc.). It probes clinically-important symptoms in the areas of pain, stiffness and physical function in patients with osteoarthritis of the hip and/or knee. The index consists of 24 questions (5 pain, 2 stiffness and 17 physical function).

This study investigated the pain relieving effects of short-term Perluxan™ intake, a standardized supercritical carbon dioxide hops extract containing 30% alpha acids, on individuals with osteoarthritis of the knee, using the WOMAC 5-item Symptom Assessment investigating OA pain severity scores during Walking on a Flat Surface, Up and Down Stairs, While in Bed, Sitting or Lying and Standing Upright.

Methods:

Subjects

Thirty-six subjects meeting the criteria of osteoarthritis of the knee according to the American College of Rheumatology [ACR], Class I, II or III, have been included in the study. Inclusion criteria were a VAS pain score of ≥ 30 to ≤ 80 on question 1A of the 5-item WOMAC assessment questionnaire and a Body-Mass-Index (BMI) of < 39.9.

Study Protocol

A randomized, double-blind placebo-controlled study was performed over a period of 15 days. Subjects were required to report twice to the study site. On day one (pre-test), a physical assessment of the knees was conducted, at which the investigator confirmed the target knee selected. A WOMAC 5-item symptom assessment questionnaire (24-hour pain assessment) was completed and the time to perform a 20-meter walk on a flat surface was recorded. Height, weight, BMI and vital signs (blood pressure, heart rate, and body temperature) were measured. A fasting blood sample was collected to analyze blood works.

Subjects, who currently used NSAIDs or any other anti-inflammatory or pain medication, were instructed to discontinue taking any such products during the remainder of the study. Subjects were instructed that, if necessary, up to 2,000 mg of acetaminophen, was allowed to be taken for arthritis and other pain, but for no more than two days per week (rescue medication). The

use of acetaminophen had to be discontinued 48 hours prior to visit 2, and within two hours after intake of the study product.

Subjects were instructed to record any use of acetaminophen, the amount taken, and the reason it was taken in a self-assessment and product use diary. Subjects were instructed to bring all unused study product, the study product containers and the diaries with them to the post-test and were remained to fast at least 10 hours before the post-test and not to take any study product on that day.

The subjects reported back to the study site on day 15 (post-test). Time to perform the 20-meter walk on the flat surface was recorded and vital signs measured. A fasting blood sample was collected to analyze blood works. Study product was collected, checked for compliance, and diaries were reviewed and collected.

Experimental Conditions

Qualified subjects were assigned in random order to either the 1 g × d^{-1} Perluxan™ (n=12), the 2 g × d^{-1} Perluxan™ (n=12) or the placebo (n=12) group. The 14-day supplementation period was started immediately after the pre-test to assess current pain (baseline) and was continued until the day before the post-test. Subjects from the Perluxan™ groups received a standardized supercritical carbon dioxide hops extract containing 30% alpha acids at a rate of 1 or 2 g per day, while the others received corresponding placebo supplements.

Statistics

Between-group comparisons for all efficacy variables were conducted using t-tests. If the between group comparison showed statistic significance, an ANOVA multiple comparison, using Tukey's method was performed.

Results:

Demographic

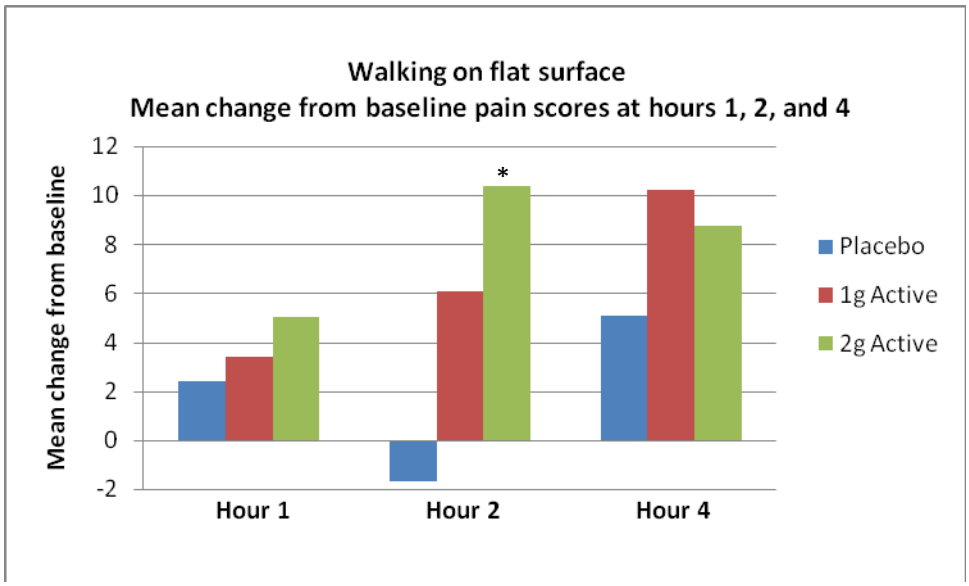
The subjects age ranged from 39 to 74 years, the average age was 57 years. The majority of subjects were Caucasian (92%) and female (78%). There were no significant differences among groups on these demographics.

Rescue Medication

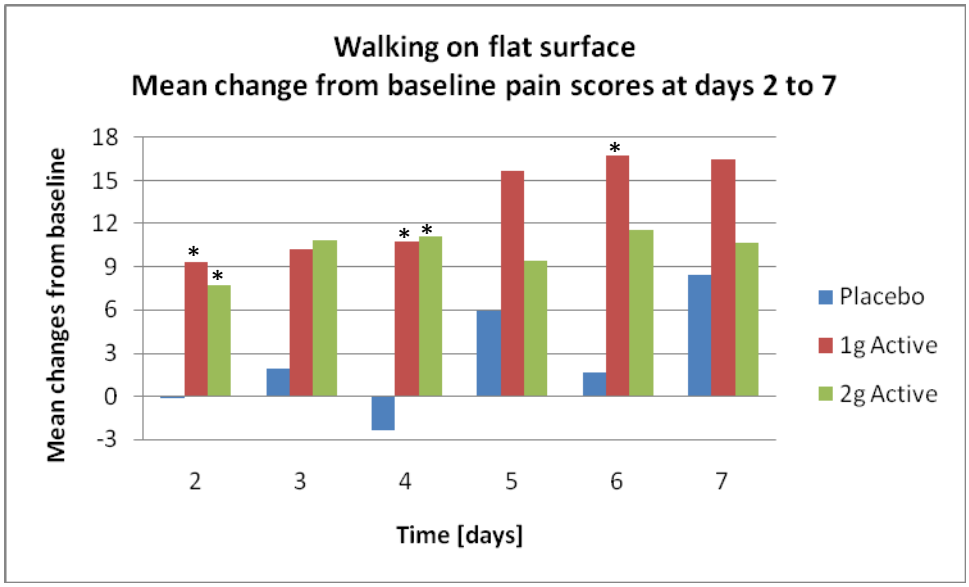
Four subjects used rescue medication (acetaminophen). Three subjects in the placebo group (on days 1, 6, and 14, respectively) and one subject in the 2 g × d^{-1} Perluxan™ group (on days 7 and 11).

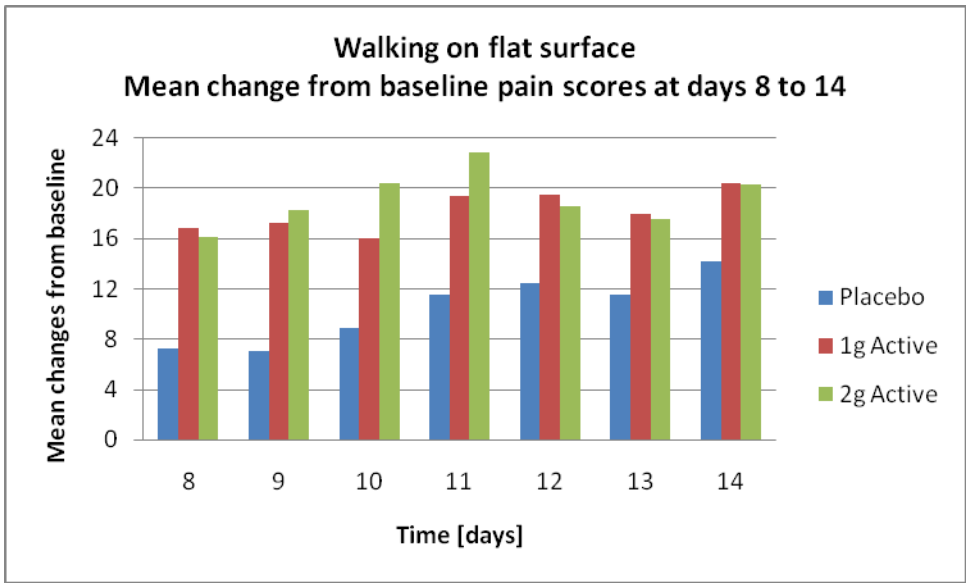
Pain Relief Walking on a Flat Surface

2 g × d^{-1} Perluxan™ intake resulted in a significant ($p<0.05$) improvement of mean pain relief after 2 hours on the first day of supplementation. 1 and 2 g × d^{-1} Perluxan™ supplementation showed an improvement of pain relief after hours 1 and 4 in comparison to placebo; however, the effect was not statistically significant.



1 and 2 g × d^{-1} Perluxan™ intake significantly ($p<0.05$) improved mean pain relief at days 2 and 4 in comparison to placebo. In addition, 1 g × d^{-1} Perluxan™ supplementation resulted in a significant ($p<0.05$) reduction of pain relief on day 6. Both Perluxan™ groups continuously showed greater pain relief than placebo.

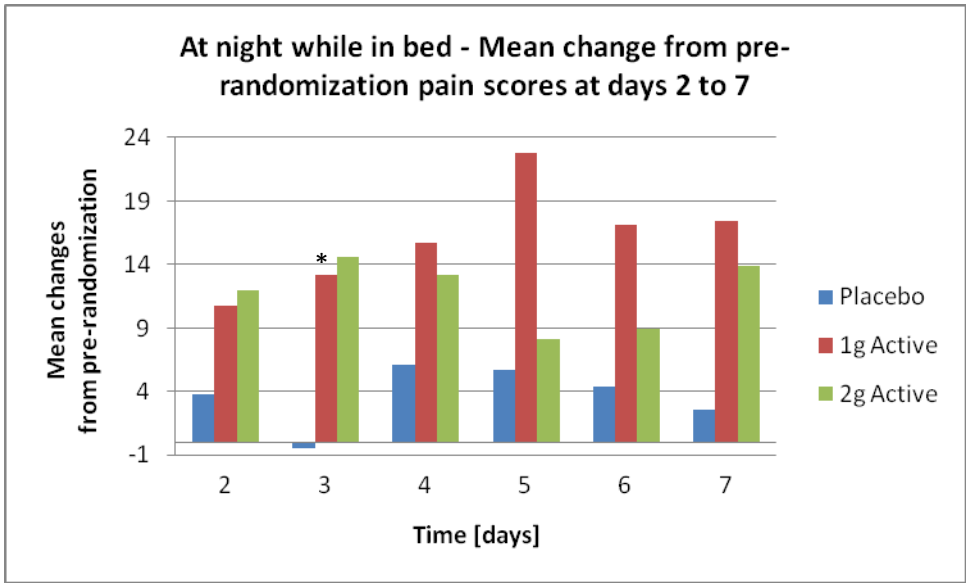


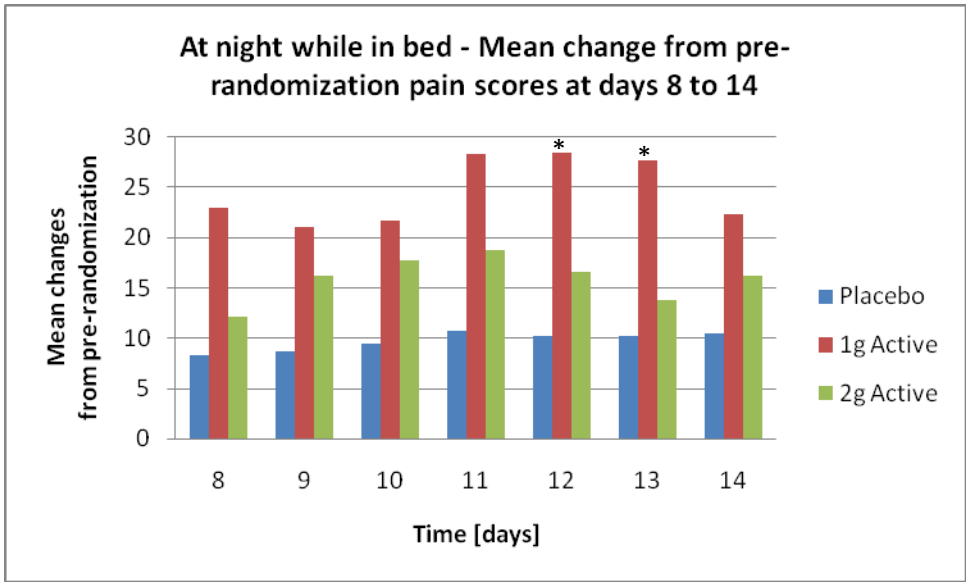


Pain Relief While in Bed

1 g × d^{-1} Perluxan™ supplementation exhibited a quick onset and continued improvement of mean pain relief while in bed in comparison to placebo. The improvements in mean pain relief were significant ($p<0.05$) on days 3, 12 and 13 and a sub analysis of subjects with percent improvement of ≥25% showed significant improvements ($p<0.05$) over placebo on days 4 and 5.

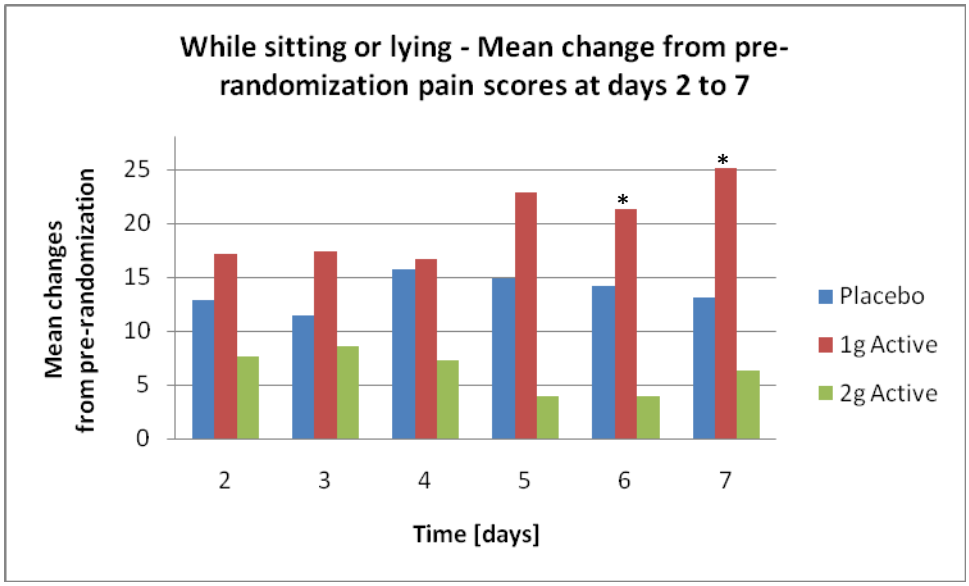
2 g × d^{-1} Perluxan™ intake seemed to have a more immediate effect on mean pain relief while in bed; however, improvement over placebo was not significant. Comparison to 1 g × d^{-1} Perluxan™ showed no additional effect.

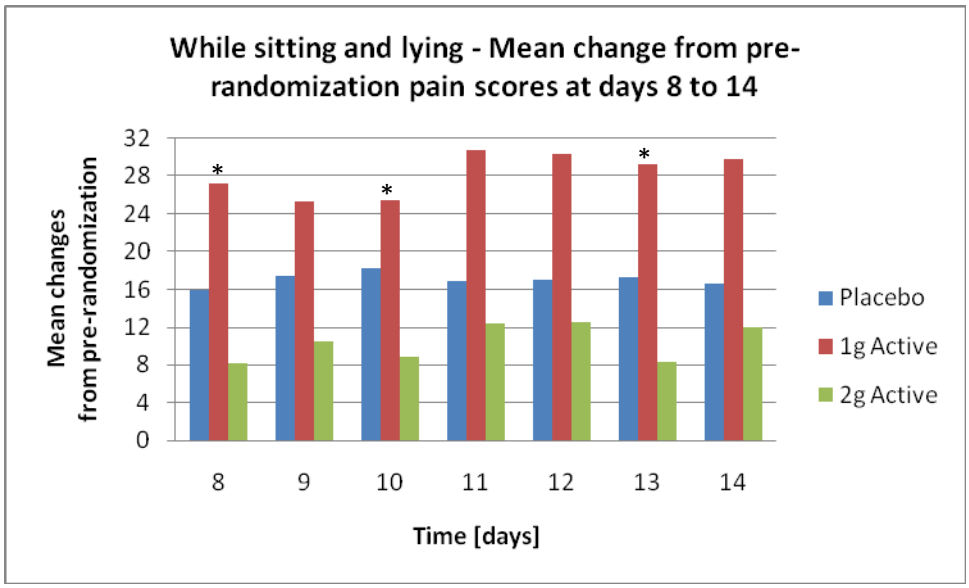




Pain Relief Sitting or Lying

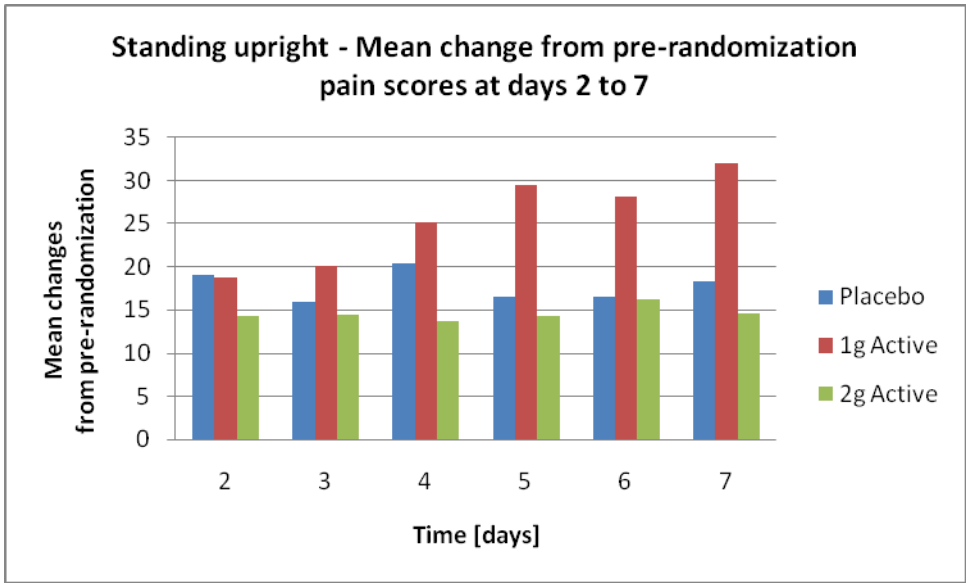
1 g × d^{-1} Perluxan™ intake showed improvements of mean pain relief compared to placebo during all test days. The improvements in the 1 g × d^{-1} Perluxan™ group were significant on days 6, 7, 8, 10 and 12 in comparison to the 2 g × d^{-1} Perluxan™ group.





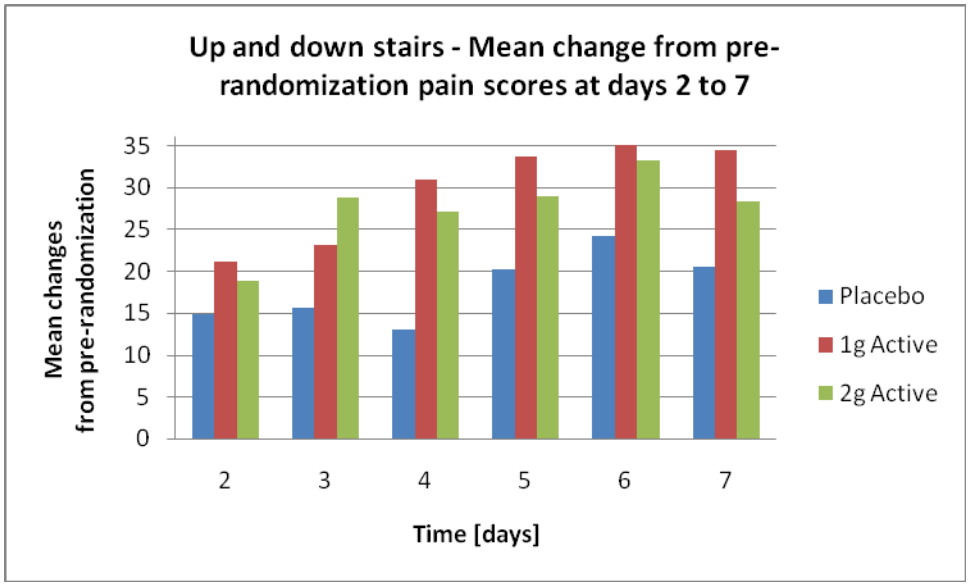
Pain Relief Standing Upright

1 g × d^{-1} Perluxan™ intake showed improvements of mean pain relief compared to 2 g × d^{-1} Perluxan™ and placebo during all test days, however, the effects were not statistically significant.



Pain Relief Up and Down Stairs

1 g × d^{-1} Perluxan™ intake showed improvements of mean pain relief compared to 2 g × d^{-1} Perluxan™ and placebo during all test days, however, the effects were not statistically significant.



Twenty-meter walk

No significant difference could be measured between the placebo (21.33 seconds pre-test, 20.00 seconds post-test), the 1 g × d^{-1} Perluxan™ (19.00 second pre-test, 17.80 seconds post-test) and the 2 g × d^{-1} Perluxan™ group (19.64 seconds pre-test, 19.73 seconds post-test) in the twenty-meter walk test.

Blood works

The analysis of blood works (Na, K, Ca, Cl, CO2, Anion Gap, Glucose, Bun, Creatinine, T Protein, Albumin, T Bilibubin, AST, ALT and ALK Phos) before and after supplementation did not show any differences between groups.

Adverse Events

Four subjects (two in the placebo group and two in the 2 g × d^{-1} Perluxan™ group) experienced eight adverse events during the study. Seven of these adverse events were deemed to have no relationship to the treatment. One adverse event in the 2 g × d^{-1} Perluxan™ group (mild, intermittent belching) was deemed to have a possible relationship to the treatment. All adverse events were resolved by the end of the study.

Discussion:

Standardized carbon dioxide extract of hops (Humulus lupulus L.) has been proven to be an effective strategy targeting inflammatory disorders and/or inflammatory pain in mice by selective COX-2 inhibition (Hougee et al., Planta Med. 2006, 72(3), 228-233). This result is consistent with Lemay et al.'s study, showing that standardized hops extract exhibited equivalent COX-2 inhibition but significant COX-1 sparing activity relative to ibuprofen (Asia Pac J Clin Nutr. 2004, 13(Suppl), S110) in a randomized, double-blind ex vivo design.

The aim of this study was to investigate the efficacy and safety of 1 and 2 g × d^{-1} Perluxan™ supplementation on individuals with osteoarthritis of the knee in a randomized, double-blind, placebo-controlled design.

The critical success factor for treatment of pain is a self-determined fast acting pain relieving effect of the product to motivate the individual to continuously take the supplement. Perluxan™ intake showed a fast acting effect on mean pain relief and significant improvement over placebo could be measured after only 2-hours after the first intake.

1 g × d^{-1} Perluxan™ has been established as an effective dose to improve pain relief in individuals with OA of the knee, significantly improving mean pain relief while in bed, sitting or

lying and walking on a flat surface. High-dose Perluxan™ intake (2 g × d^{-1}) seemed to have no additional long-term benefit.

The effectiveness of Perluxan™ supplementation is supported by the limited use of rescue medication in the treatment groups in comparison to placebo (three in placebo group, none in 1 g × d^{-1} Perluxan™ group, one in 2 g × d^{-1} Perluxan™ group).

The comparison of pre- and post-supplementation blood work and the adverse side effect monitoring showed that Perluxan™ seemed to be well-tolerated.

Perluxan™'s improves pain relief with the ultimate outcome of improved function and quality of life.

Further studies are needed to establish the lowest efficacious dose of Perluxan™ supplementation to improve pain relief in individuals with OA and to investigate the effects of Perluxan™ intake on non-pain related OA parameters (24-question WOMAC).

Conclusion:

It is concluded that 14-days of either 1 or 2 g of oral Perluxan™ supplementation significantly improved parameters of OA pain.

Patients are seeking natural alternatives to non-steroidal anti-inflammatory drugs (NSAIDs) after the realization in recent years that extreme complications, including gastric ulcers, bleeding, heart complications and even deaths have been associated with the use of NSAIDs.

Combining Perluxan™ with dietary supplements (e.g. Glucosamine and Chondroitin) that may bring nutrients to the joints might stop or even repair the damage to the joint. None of the standard pharmaceutical agents can do this. In addition, natural COX-2 alternatives for pain and arthritis relief might offer cost advantages over drugs.

Perluxan™ has been proven to be an effective alternative for pain relief in individuals with osteoarthritis of the knee.