

## RESEARCH PAPER

### **A Natural Mineral Supplement Provides Relief from Knee Osteoarthritis Symptoms: A Randomized Controlled Pilot Trial**

(Running Header: OA of the knee)

#### Study Authors

Joy L. Frestedt, PhD<sup>1</sup>, Melanie Walsh PhD\*<sup>2</sup>, Michael A. Kuskowski, PhD<sup>3</sup>, John L. Zenk, MD<sup>1</sup>

#### Addresses

<sup>1</sup>Clinical Affairs Department, Minnesota Applied Research Center, 564 Southdale Medical Building, 6545 France Avenue South, Edina, MN, USA 55435

<sup>2</sup>Marigot Ltd., Strand Farm, Currabinny, Carrigaline, Co. Cork

<sup>3</sup>Department of Psychiatry, Geriatric Research Education and Clinical Center, Veterans Administration Medical Center, Minneapolis, MN USA 55417

#### Emails

Dr. Melanie Walsh\* – [info@marigot.ie](mailto:info@marigot.ie); Dr. Joy Frestedt – [frest001@umn.edu](mailto:frest001@umn.edu); Dr. Mike Kuskowski - [mike@james.psych.umn.edu](mailto:mike@james.psych.umn.edu);  
Dr. John Zenk - [jzenk@humaneticscorp.com](mailto:jzenk@humaneticscorp.com)

\*Corresponding Author

## Abstract

**Background:** This study evaluated the impact of treatment with a natural multi-mineral supplement from seaweed (Aquamin) compared to a positive control (glucosamine sulfate) on walking distance, pain and joint mobility in subjects with moderate to severe osteoarthritis of the knee.

**Methods:** Subjects (n = 70) with moderate to severe osteoarthritis of the knee were randomized to four treatments for 12 weeks: (a) Glucosamine sulfate (1500 mg/d); (b) Aquamin (2400 mg/d – equaling 100% EU RDA Calcium); (c) Combined treatment composed of Glucosamine sulfate (1500 mg/d) plus Aquamin (2400 mg/d) and (d) Placebo. Treatment was double blinded. Primary outcome measures were WOMAC scores and 6 Minute Walking Distances (6MWD). Laboratory based blood tests were used as safety measures.

**Results:** Fifty patients successfully completed the protocol. Using an Intent To Treat-Last Observation Carried Forward (ITT-LOCF) statistical analysis, all treatment groups showed differences in WOMAC pain scores at the end of the study (ANCOVA  $p < 0.009$ ), although only the Aquamin and glucosamine groups demonstrated significant improvements over the course of 12 weeks of treatment. For WOMAC pain, activity and composite scores, these two groups demonstrated significant improvements over placebo whereas for the stiffness score, only the Aquamin group demonstrated a significant improvement from baseline (ITT-LOCF  $p < 0.002$ , paired T-test). In reference to baseline for the 6 minute walking distance test both the Aquamin group and Glucosamine sulfate group demonstrated a significant improvement ( $p < 0.001$ , 0.003 respectively) with the Aquamin group walking on average 101 feet further and the Glucosamine sulfate group walking 56 feet. All treatments were well tolerated and the adverse events profiles were not significantly different between the groups.

**Conclusions:** Aquamin and glucosamine sulfate offered subjects comparable improvements in joint health and function over 12 weeks on treatment with significant improvements in WOMAC scores and 6 minute walking distances. [ClinicalTrials.gov number: NCT00452101]

## Introduction

Osteoarthritis (OA), also called degenerative joint disease, is a slow destructive process of the joint affecting millions of people worldwide. Although the exact biochemical cause of OA remains unknown, the process usually begins when the joint structures are abnormal or the stress placed on the joint surfaces is unusually high. The secondary inflammation due to progressive articular destruction appears to be localized to the particular joint being affected. Current anti-inflammatory treatments for OA while providing some relief from symptoms are suboptimal and the side effects associated with these treatments; in particular the COX-2 specific NSAID's are becoming increasingly recognized [1, 2]. As a result of this, use of alternative treatments and complementary medicines are gaining popularity among OA sufferers.

A nutraceutical approach to OA either through supplements or functional food ingredients may support an alternative to conventional pharmacological interventions. Glucosamine, a structural component of cartilage and a popular nutraceutical has been the subject of a number of trials [3, 4]. The recent NIH funded Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) tested the efficacy of glucosamine in providing relief for patients with symptomatic knee osteoarthritis [5]. In this multi-centre study, glucosamine hydrochloride was tested either alone or in combination with chondroitin sulfate, a glycosaminoglycan that is also a structural component of cartilage and a popular alternative therapy for OA. In this study, the overall group of patients failed to demonstrate an improvement in symptoms for both the individual and combined treatments possibly as a result of the large (60%) placebo effect observed. Some benefit was observed in a subset of patients with moderate to severe knee osteoarthritis suggesting that the benefits of these nutraceuticals may be limited to this group.

In addition to glucosamine and chondroitin, other nutraceutical products have been reported to provide relief from OA [6-9]. Cat's claw extract has recently been combined with a mineral based treatment (Sierrasil®) to provide symptomatic relief for a group of mild to moderate OA sufferers. While initially demonstrating some benefit with the cats claw/mineral supplement, Miller and co-workers observed that this benefit was at best temporary for a 1-2 week period [10]. Even though the positive effects were short lived in this subset of OA patients, growing evidence suggests that minerals may play a beneficial role in joint health. Naturally occurring minerals such as magnesium, copper, manganese, selenium and zinc have shown anti-inflammatory effects in both animal and human studies. In a rat model of osteoarthritis, a deficiency of dietary magnesium was demonstrated to enhance the amount of cartilage damage [11]. Furthermore, increased magnesium in the diet may influence inflammation through reducing the serum level of the pro-inflammatory protein C-reactive protein [12]. The trace element copper is an essential cofactor in enzymes such as the collagen cross-linker lysyl oxidase and the anti-oxidant enzyme super oxide dismutase (SOD) that also requires zinc and manganese as cofactors. Recent evidence has suggested a role for oxidative stress in the pathogenesis of OA whereby an excess of reactive oxygen species arising from an imbalance in the antioxidant status of the joint (such as reduced levels of SOD) may result in cartilage degradation and joint remodeling [13]. Selenium is also an essential co-factor for glutathione peroxidase may have a role in reducing the incidence of osteoarthritic lesion [14, 15] Positive roles have also been suggested for trace minerals such as boron and manganese in reducing the symptoms and slowing the pathogenesis of OA [16].

The present study was designed to evaluate the potential for a seaweed-derived multi-mineral supplement to alleviate OA symptoms. The mineral supplement (Aquamin) is derived

from the red algae *Lithothamnion corallioides*. *Lithothamnion corallioides* is rich in calcium and magnesium in the form of carbonate salts (34% and 3% by weight respectively) as well as having trace minerals (Table 1).

The goal of this trial was to determine if consumption of Aquamin either alone or in combination with Glucosamine sulfate would confer less joint pain, stiffness and immobility compared to placebo or glucosamine sulfate alone.

## **Materials and Methods**

### Study Design

This study was a randomized, double blind, placebo controlled clinical trial with four parallel treatment groups: Aquamin, Glucosamine Sulfate, Aquamin plus Glucosamine Sulfate and Placebo. This trial was performed in compliance with all applicable regulations and guidelines (e.g. International Conference on Harmonization Good Clinical Practices, ICH-GCP, the Declaration of Helsinki, 21CFR50-Protection of Human Subjects, and 21CFR56-Institutional Review Boards) and was approved and continuously reviewed by the Quorum Institutional Review Board (Seattle, WA).

### Subjects

Subjects were recruited by advertising in the Minneapolis, Minnesota area. Subjects of either gender were included if they voluntarily gave informed consent, were ambulatory, 25-75 years old, with normal digestion and absorption, able to restrict calcium to ~600 mg (e.g. two dairy servings) per day and diagnosed with moderate to severe OA of the knee according to the modified clinical criteria of the American College of Rheumatology [17, 18] and had a Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index [19, 20] score  $\leq 75$ . Exclusion criteria were rheumatoid arthritis, gout, pseudogout, Paget's disease, seizure disorder, insulin dependent diabetes mellitus, uncontrolled hypertension, unstable cardiovascular disease, active hepatic or renal disease, active cancer and/or HIV infection or if they required prescription drugs to control pain; had other clinical trial or experimental treatments in the past 3 months; were pregnant, lactating, or at risk of becoming pregnant; or if they received NSAIDS within 48 hours; intramuscular/systemic corticosteroid injection within 4 weeks; intra-articular corticosteroid injection within 2 months; or inter-articular hyaluronic acid injection within 4 months prior to enrollment.

A total of 70 subjects were given study medication. The number of participants was determined from previous experimentation using hyperimmune milk [6]. Each subject received one bottle of 350 two-piece hard shell test article capsules each month. Each bottle (and the capsules inside) appeared identical. Subjects were randomized in blocks of 4 using sequential treatment assignments prepared by the independent consulting statistician. The clinical investigator, statistician, clinic staff and subjects remained blinded throughout the trial to avoid bias. The sequence of the study began with a two week period when subjects were asked to discontinue any prescription or over-the-counter or alternative therapy treatments for osteoarthritis. At the baseline visit, vital signs were assessed and laboratory tests were

performed. Subjects were assessed for WOMAC parameters and a 6 minute walking test was performed. After each month of treatment (at 4, 8 and 12 weeks) the subject's diaries, WOMAC questionnaires, and unused pills were collected, medications/supplements were reviewed, adverse events investigated, vital signs measured, blood was drawn and 6MWD and WOMAC were measured. Active treatment was completed at week 12 when laboratory tests were repeated. Each subject returned to the clinic at 16, 20 and 24 weeks after their treatment began for monitoring of blood chemistry only.

#### Treatments:

The duration of treatment was 12 weeks, administered as three capsules taken with a glass of water, three times per day. The capsules contained Aquamin (267 mg Aquamin + 167 mg maltodextrin) designated A in the results section; Glucosamine sulfate (167 mg glucosamine sulfate + 267 mg maltodextrin) designated GS, Aquamin F and Glucosamine (267 mg Aquamin + 167 mg glucosamine sulfate) designated G+A, or Placebo (434 mg maltodextran) designated the PBO in the results section.. The rescue medication was acetaminophen, 325 mg, 1-2 tablets every 4-6 hours as needed for intractable pain.

#### Study Measurements and Statistical Analysis:

Joint symptoms were assessed using the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, a validated questionnaire [17] The WOMAC Osteoarthritis Index includes scores for pain, stiffness and activities as well as a composite (total) score. The WOMAC scores were transformed according to the standard orthopedic formula [18]

$$\text{Transformed Score} = 100 - (\text{Actual Raw Score} \times 100 / \text{Possible Raw Score})$$

The values represent "percentage of normal," such that increasing scores reflect improvement and decreasing scores reflect worsening of symptoms. The six minute walking distance (6MWD) was conducted by marking off a 100-foot distance in an interior hallway and asking subjects to walk as far as they can as quickly as they can over 6 minutes. The total distance was measured and recorded. Adverse effects were assessed by a questionnaire and vital signs/laboratory measurements respectively.

This study was conducted, monitored and audited in compliance with ICH-GCP guidelines and according to the Minnesota Applied Research Center Standard Operating Procedures (SOP's) and the SOP's of certified vendors (e.g. for WOMAC scoring). Subject compliance was assessed at each visit by pill count, interview, and review of the medication diary. Subject data was kept confidential and study records were stored in a locked and secure storage area. An independent statistician used ANOVA for between group comparisons at baseline. ANCOVA (with baseline score as co-variate) were used to assess between-group differences in change over time. Matched pair T-tests were used for within group comparisons of change over time. Data was analyzed under Intent To Treat Last Observation Carried Forward (ITT-LOCF) case condition and statistical significance was set at  $p < 0.05$ .

## Results

### Baseline Characteristics of subjects.

All four groups were comparable for the number (15-20), gender (6-11 male and 7-11 female) and age (58.5 to 60.3 years) per group (Table 2) indicating that randomization was effective for these parameters. No significant differences were found between groups at baseline for WOMAC (activity and composite scores) 6MWD (ITT; one way ANOVA, NS). However, significant differences were observed between groups for pain and stiffness WOMAC scores ( $p=0.039$  and  $0.013$  respectively).

### WOMAC

All four groups displayed an improvement from baseline for WOMAC scores (Table 3 and Figure 1). Using an ITT-LOCF analysis, only the pain score differed significantly between the groups over the course of the study ( $p=0.009$  ANCOVA). Specifically, at the end of treatment, all pain scores were increased to 52.9, 74.3, 72.9 and 69.1 for PBO, A, GS and G+A respectively (a higher score indicated less pain). Of interest, the rank order of the pain scores changed from baseline:  $PBO < A < GS < G+A$  to  $PBO < G+A < GS < A$  and PBO (52.9) and G+A (69.1) had the lowest while GS (72.9) and A (74.3) the highest scores. These results indicated that the pain scores were significantly improved by 17.5 for A and 12.6 for GS compared to 2.9 for PBO and 1.9 for G+A. This improvement was also reflected in the within group analysis over time where only the Aquamin and Glucosamine groups showed significant improvements. Within the Aquamin and Glucosamine groups, a significant improvement was also observed for the activity and composite (total) WOMAC measurements (Table 3, Figure 1). Of interest the Aquamin group also displayed an improvement for stiffness ( $p=0.002$ ). No significant improvements were demonstrated by the placebo group and the combined treatment group.

### Six minute walking distance (6MWD)

The distance covered during a 6 minute timed walk was significantly improved over time on treatment within the Aquamin group ( $p = 0.001$ , Table 4). The glucosamine group also demonstrated a significant improvement over time on treatment ( $p = 0.03$ ). Subjects on Aquamin walked an additional 101 feet in 6 minutes ( $p=0.001$ ) and the subjects in the glucosamine group walked an additional 56 feet ( $p=0.03$ ) as compared to their average baseline distances.

### Adverse effects.

All treatments were well tolerated. A total of 51 of the 70 subjects given test product (TA) reported eighty-eight (88) adverse effects (AE) but only 7 of the 88 AE (8%) were considered at least possibly related to the TA treatment. These were distributed somewhat evenly across the groups: 1 on PBO, 3 on A, 2 on GS and 1 on G+A and none were considered

definitely related to the TA. Most of the adverse effects (31/88; 35%) were related to musculoskeletal complaints and these were mainly reports of increased knee pain (n=19/88; 22%). All AE have completely resolved or returned to baseline.

## Discussion

This trial was designed to test the efficacy of a marine derived multi-mineral supplement at reducing the symptoms of moderate to severe knee osteoarthritis. The dose of the mineral supplement Aquamin was determined based on previous anecdotal experience and a rigorous Intent to Treat statistical analysis was used to determine if it was more or less efficacious than placebo, glucosamine sulfate or a combination of glucosamine sulfate and Aquamin. The analysis of WOMAC pain, stiffness, activity and composite (total) scores indicated that this mineral supplement may be efficacious at reducing the joint symptoms associated with moderate to severe osteoarthritis. Aquamin significantly improved WOMAC pain, stiffness, activities and composite WOMAC scores compared over the course of the treatment. The glucosamine sulfate treatment group also showed significant improvements over time on treatment for the pain, activities and composite scores. No improvement in stiffness scores was seen with glucosamine sulfate. Given that the pain scores were different between the groups at baseline; these improvements need to be viewed with caution, although the improvement seen with the Aquamin mineral complex may be significant given the change in rank order of the groups from baseline to the end of the study. At baseline, the Aquamin and Placebo groups were in most pain but while only a slight improvement was observed with the placebo group, the Aquamin group was markedly improved over the course of treatment. This improvement was also reflected in the within group analysis over time where only the Aquamin and Glucosamine sulfate groups showed significant improvements.

No baseline differences were observed for the timed walk outcome. Over time on treatment, the Aquamin and glucosamine groups demonstrated significant improvements in walking distance ( $p = 0.001, 0.03$  respectively). On average both groups walked a further 101 and 56 feet respectively when compared to their average distances at the baseline visit, 12 weeks earlier. No significant improvement in walking distance was observed for the combined and placebo groups. The main limitation of this study was its short duration. Furthermore glucosamine sulfate has been proposed to provide a benefit over a longer course of treatment [19] and as such its efficacy may have been under demonstrated within the 12 week study period. Of interest would be an investigation of the longer term effects of the mineral complex compared to glucosamine. Furthermore, it needs to be stated that even though this was a randomized controlled trial, it was nonetheless an exploratory study performed on a group of moderate to severe OA sufferers. An investigation into the effect of this mineral complex compared to glucosamine sulfate in a broader group of OA patients would also be of interest. Why the combined treatment group did not show any additive benefit compared to Aquamin or Glucosamine sulfate alone is also of interest and a possible dietary interaction cannot be ruled out. However, this would need to be further investigated as both individual treatments were efficacious.

As Aquamin is composed of multiple minerals, it is difficult to determine an 'active ingredient' for the complex. A number of minerals may have anti-inflammatory and anti-oxidant

properties which would directly and indirectly influence the efficacy of this unique complex [13, 14, 16]. While the prominent mineral present in Aquamin is calcium (dosage = 80% Ca U.S RDA), its role in joint health is unclear. Magnesium was given at the daily dosage providing 14% (male) to 18% (female) U.S. RDA [12]. Over the course of this study, the increase in consumption of magnesium may have influenced OA symptoms through reducing inflammation around the affected joint. Both manganese and selenium were given at the daily dosage providing up to 16% and 4% of their RDA respectfully. Both of these trace minerals have been reported to reduce the appearance of osteoarthritic lesions and reduce the severity of symptoms in OA [14, 16]. Taken together, the data in this trial suggest that the marine derived multimineral complex in Aquamin may be efficacious in reducing the symptoms and increasing mobility in moderate to severe OA sufferers and that these benefits are at least comparable to glucosamine sulfate over 12 weeks of treatment.

### **Declaration of Competing Interests**

Marigot Ltd. provided funding for this clinical trial and the article processing charges to publish this work. Melanie Walsh is a paid employee of Marigot Ltd., the sponsor of this work and provided only medical writing support for this manuscript. The other authors declare that they have no other competing interests. Marigot Ltd approved the protocol and reviewed the manuscript before submission for publication and can be reached at: Strand Farm, Currabinny, Carrigaline, Co. Cork, Ireland; Phone: 353-21-437-8727; Fax: 353-21-437-8588. Marigot Ltd did not participate in any of the data collection or statistical analyses reported herein.

### **Author's Contributions**

JLF and MW co-authored the manuscript. JLF co-authored the protocol and directed the research team at MARC during the conduct of this trial. JLZ provided critical review of the manuscript, co-authored the protocol and provided medical monitoring services during the trial. MAK provided critical review of the manuscript and the protocol and provided statistical services for the design, execution and analysis of the data in this trial. All authors have read and approved the final manuscript.

### **Acknowledgements**

The authors would like to thank the clinical team members at MARC for their careful care of the subjects in this trial.

## References

1. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, Boyce SW, Verburg KM: **Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery.** *The New England journal of medicine* 2005, **352**(11):1081-1091.
2. Ray WA, Griffin MR, Stein CM: **Cardiovascular toxicity of valdecoxib.** *The New England journal of medicine* 2004, **351**(26):2767.
3. Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Wells G: **Glucosamine therapy for treating osteoarthritis.** *Cochrane database of systematic reviews (Online)* 2005(2):CD002946.
4. Poolsup N, Suthisisang C, Channark P, Kittikuluth W: **Glucosamine long-term treatment and the progression of knee osteoarthritis: systematic review of randomized controlled trials.** *The Annals of pharmacotherapy* 2005, **39**(6):1080-1087.
5. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, Bradley JD, Bingham CO, 3rd, Weisman MH, Jackson CG *et al*: **Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis.** *The New England journal of medicine* 2006, **354**(8):795-808.
6. Zenk JL HT, Kuskowski MA: **The effects of milk protein concentrate on the symptoms of osteoarthritis in adults: an exploratory, randomised, double-blinded, placebo-controlled trial.** *Curr Ther Res* 2002, **63**:430-442.
7. Kim LS, Axelrod LJ, Howard P, Buratovich N, Waters RF: **Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial.** *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2006, **14**(3):286-294.
8. Cho SH, Jung YB, Seong SC, Park HB, Byun KY, Lee DC, Song EK, Son JH: **Clinical efficacy and safety of Lyprinol, a patented extract from New Zealand green-lipped mussel (*Perna Canaliculus*) in patients with osteoarthritis of the hip and knee: a multicenter 2-month clinical trial.** *Allergie et immunologie* 2003, **35**(6):212-216.
9. Biegert C, Wagner I, Ludtke R, Kotter I, Lohmuller C, Gunaydin I, Taxis K, Heide L: **Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: results of 2 randomized double-blind controlled trials.** *The Journal of rheumatology* 2004, **31**(11):2121-2130.
10. Miller MJ, Mehta K, Kunte S, Raut V, Gala J, Dhumale R, Shukla A, Tupalli H, Parikh H, Bobrowski P *et al*: **Early relief of osteoarthritis symptoms with a natural mineral supplement and a herbomineral combination: a randomized controlled trial [ISRCTN38432711].** *Journal of inflammation (London, England)* 2005, **2**:11.
11. Shakibaei M, Kociok K, Forster C, Vormann J, Gunther T, Stahlmann R, Merker HJ: **Comparative evaluation of ultrastructural changes in articular cartilage of ofloxacin-treated and magnesium-deficient immature rats.** *Toxicologic pathology* 1996, **24**(5):580-587.
12. King DE, Mainous AG, 3rd, Geesey ME, Woolson RF: **Dietary magnesium and C-reactive protein levels.** *Journal of the American College of Nutrition* 2005, **24**(3):166-171.
13. Henrotin Y, Kurz B, Aigner T: **Oxygen and reactive oxygen species in cartilage degradation: friends or foes?** *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2005, **13**(8):643-654.

14. Kurz B, Jost B, Schunke M: **Dietary vitamins and selenium diminish the development of mechanically induced osteoarthritis and increase the expression of antioxidative enzymes in the knee joint of STR/1N mice.** *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2002, **10**(2):119-126.
15. Sasaki S, Iwata H, Ishiguro N, Habuchi O, Miura T: **Low-selenium diet, bone, and articular cartilage in rats.** *Nutrition (Burbank, Los Angeles County, Calif)* 1994, **10**(6):538-543.
16. Gaby AR: **Natural treatments for osteoarthritis.** *Altern Med Rev* 1999, **4**(5):330-341.
17. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW: **Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee.** *The Journal of rheumatology* 1988, **15**(12):1833-1840.
18. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD: **Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure.** *The Journal of orthopaedic and sports physical therapy* 1998, **28**(2):88-96.
19. Muller-Fassbender H, Bach GL, Haase W, Rovati LC, Setnikar I: **Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee.** *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 1994, **2**(1):61-69.

#### Tables/Figure:

Table 1: Typical mineral composition of Aquamin.

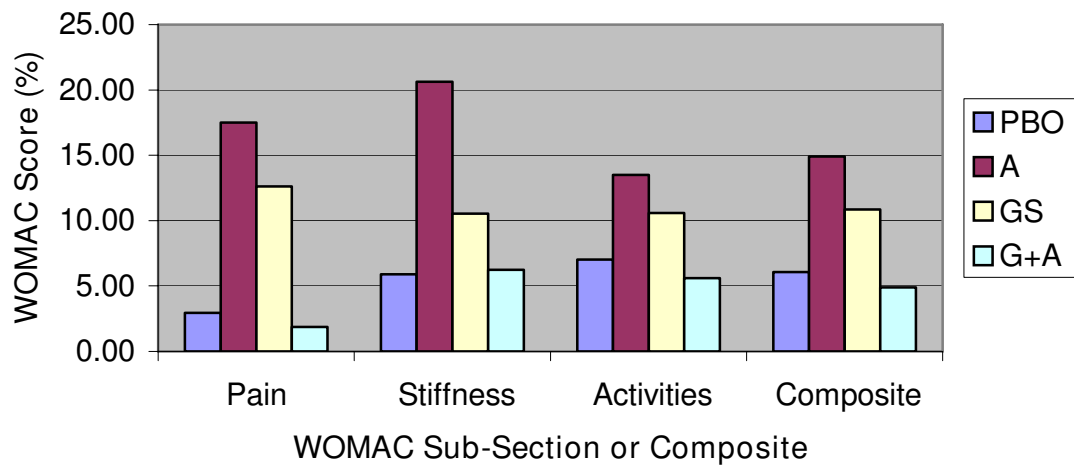
Table 2: Baseline characteristics.

Table 3: Changes in WOMAC scores between and within groups over 12 weeks of treatment (ITT-LOCF).

Table 4: Changes in 6MWD between and within groups over 12 weeks of treatment.

Figure 1: Percent change in WOMAC scores from baseline over 12 weeks of treatment.

Figure 1: Percent Change in WOMAC scores from baseline over 12 weeks of treatment.



**Additional files provided with this submission:**

Additional file 1: frestedt et al -table 1.pdf, 13K

<http://www.nutritionj.com/imedia/1451016554153990/supp1.pdf>

Additional file 2: frestedt et al - table 2.pdf, 19K

<http://www.nutritionj.com/imedia/1876112668153990/supp2.pdf>

Additional file 3: frestedt et al -table 3.pdf, 26K

<http://www.nutritionj.com/imedia/1321384215153990/supp3.pdf>

Additional file 4: frestedt et al -table 4.pdf, 20K

<http://www.nutritionj.com/imedia/9608508011539903/supp4.pdf>