This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1543953X. To subscribe, visit imjournal.com

ORIGINAL RESEARCH

# Evaluating Clinical Response and Activity of Cyplexinol Osteoinductive Proteins in Osteoarthritis of the Hip and Knee: A Randomized, Controlled Trial

*Richard Garian, DC, CCSP; James J. Scaffidi, BS*

**Abstract**

**Context:** Osteoarthritis (OA) is the most common form of arthritis, and it affects more than 20 million people in the United States. The most commonly affected joints are the hips and knees, and OA-related complications are the main reasons for total knee and hip replacements. The proteins in Cyplexinol have been used for the past 25 years by orthopedic surgeons to promote bone and cartilage growth.

**Objective:** The study intended to investigate the efficacy and safety of a novel protein complex that contains bone morphogenetic protein (150 mg of Cyplexinol, Nature's BMP-complex), for relieving pain and stiffness in participants with moderate to severe osteoarthritis (OA) of the hip or knee.

**Design:** The study was a randomized, double-blind, placebo-controlled clinical trial.

**Setting:** The author's office and the study questionnaires were administered via phone.

**Participants:** Participants were individuals 55 years and older who had been diagnosed with moderate-to-severe, osteoarthritis joint pain in the hip or knee (weight-bearing joints) and who had been symptomatic for at least 5 days a week for a minimum of 3 months.

**Intervention:** The participants received either a single daily dose of 150 mg of Cyplexinol or of a placebo for a 12-week duration.

**Outcome Measures:** Three primary endpoints—pain, stiffness, and quality of life (QOL)—were evaluated using the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index 3.1. Primary efficacy analyses were based on a one-way analysis of variance (ANOVA). Secondary endpoints were treatment compliance and adverse events.

**Results:** Eighty-seven participants enrolled in the study. Treatment with 150 mg of Cyplexinol resulted in a significant decrease in pain and stiffness, together with an increase in QOL by week 12 in comparison to placebo treatment, which showed no significant improvement in symptoms. The α level was set at $P < .0001$ for the treatment group and $P > .05$ for the placebo group. For the WOMAC pain subscale, a significant effect of a 3.35 point increase (95% CI, 2.58-4.13; $P < .0001$) was observed for 150 mg of Cyplexinol at week 12 in comparison to a negative effect of -0.35 points (95% CI, -1.40-0.71; $P > .05$) for the placebo. The mean changes at week 12 for WOMAC stiffness were 2.95 points (95% CI, 1.94-3.97; $P < .0001$) for 150 mg of Cyplexinol and 0.18 points (95% CI, -0.82-1.19; $P > .05$) for the placebo. The mean changes at week 12 for WOMAC QOL were 3.12 points (95% CI, 2.38-3.86; $P < .0001$) for 150 mg of Cyplexinol and -0.40 points (95% CI, -2.034-1.24; $P > .05$) for the placebo.

**Conclusions:** Cyplexinol treatment at 150 mg was statistically more effective than the placebo in treating the signs and symptoms of osteoarthritis in a weight-bearing joint (hip or knee). Treatment with 150 mg of Cyplexinol was shown to be a natural, safe, and effective way to increase QOL by decreasing common symptoms such as pain and stiffness.

**Richard Garian, DC, CCSP, is a chiropractor in Framingham, Massachusetts. James J. Scaffidi, BS, is president of ZyCal Bioceuticals in Shrewsbury, Massachusetts.**

*Corresponding author: Richard Garian, DC, CCSP*
*E-mail address: drgarian@yahoo.com*

Osteoarthritis (OA) is the most common form of arthritis, and it affects more than 20 million people in the United States.[1,2] OA is often classified as a degenerative joint disease that is characterized by the progressive deterioration and eventual loss of cartilage in the hands, feet, knees, hips, and spine.[3] However, this disease is not simply the cause of gradual cartilage degradation, but also is the result of proinflammatory cytokines and collagen cross-linking, which can cause bone abnormalities, inflammation, and stiffness. Risk factors that are involved in the development of OA include

This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1543953X. To subscribe, visit imjournal.com

age, gender, genetic predisposition, prior joint injury, hormonal deficiencies, abnormal joint shape, and obesity.[1]

The most commonly affected joints are the hips and knees, and OA-related complications are the main reasons for total knee and hip replacements. According to recent studies, one in two people develop OA in the knees by age 85; two out of three people who are overweight develop knee OA in their lifetimes[4]; and one person out of four develops hip OA in their lifetime.[5] Epidemiologic studies also show that this form of arthritis becomes more prevalent with age and is gender-specific. More specifically, the prevalence of OA is higher in men than women before the age of 50, but women show a higher incidence of OA in the hands, feet, and knees after the age of 50.[6,7] Despite the multifaceted nature of OA, this disease displays common features such as pain, loss of function, stiffness, and deformity.

Pathological changes that typically occur with the onset of OA include the gradual degradation of articular cartilage with concomitant alterations in the bone lying directly under the cartilage. In addition, the thickening of subchondral bone occurs, together with joint-capsule hypertrophy and the formation of osteophytes. Structures associated with the joint that are also affected include (1) the menisci in knee OA; (2) the synovium, which becomes inflamed; and (3) ligaments that undergo degeneration.[3,8] A serious joint injury can lead to OA, but this disease is often the result of both local injury and systemic factors such as heredity.

Previous studies have shown that bone morphogenetic proteins (BMPs), which are growth factors that belong to the transforming growth factor β (TGF-β) superfamily, can stimulate bone and cartilage growth.[9,10] Studies have also shown that insulin-like growth factor (IGF), basic fibroblast growth factor (bFGF), and transforming growth factor beta (TFG-β) have therapeutic effects on OA.[11-13] Cyplexinol (Ostinol, ZyCal Bioceuticals, Inc) is a protein complex that stimulates bone and cartilage and contains osteoinductive proteins, the BMPs, as well as key growth factors for cellular maturation, including TGF-β, IGF, and bFGF. All of those proteins are naturally found in bone and cartilage. Due to Cyplexinol's protein composition, this complex is among the first to improve complications that are associated with cartilage loss and degeneration as well as structural deterioration that causes pain and inflammation.[14,15] Unique to this protein complex are the BMPs and the principle of osteoinductivity. This term was first described by Urist (1965) in his seminal work, *Bone Formation by Autoinduction*.[16] Urist defined osteoinductivity as the ability of a protein complex to activate, stimulate, and differentiate mesenchymal stem cells into osteoblasts and chondrocytes to produce bone and cartilage tissue, respectively.

The proteins in Cyplexinol have been used for the past 25 years by orthopedic surgeons to promote bone and cartilage growth.[10] The purpose of this study is to investigate the effectiveness of 150 mg of Cyplexinol orally in decreasing pain and improving joint flexibility, in comparison to a placebo tablet, in people suffering from OA in their hip or knee joints.

## Participants and Methods

### Design

All participants signed an informed consent form prior to enrolling in the study. Participants were alphabetized and assigned to either a treatment group or a placebo group by selecting odd and even numbers from a random-number table. The treatment product was a tablet that consisted of 150 mg of Cyplexinol. The placebo tablet was identical in appearance and composition but did not include the active ingredient. Participants took a single daily dose of the treatment supplement or the placebo. No rescue analgesic or pain medication was used throughout the trial.

This 12-week, randomized, double-blind, placebo-controlled clinical trial required the completion of questionnaires for the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index 3.1. An independent investigator assessed the effectiveness of the 150 mg of Cyplexinol using the questionnaires. That investigator collected the data during the screening phase and at baseline, week 1, week 6, and week 12 (exit questionnaire) by contacting each participant via telephone.[17] Both the participants and the investigator collecting the data were blinded to the group assignment.

If any intermediate WOMAC questionnaire was not completed within 3 days of the scheduled time, that week's data were eliminated, and the participant had to complete all of the subsequent questionnaires. If a second intermediate questionnaire was not completed within 3 days of the scheduled time, the participant could continue the trial if they agreed to complete all subsequent questionnaires. If a participant did not comply with the protocol, that person was considered to be a withdrawal; however, their results were still included in the intended-to-treat data set for analysis. If the final questionnaire was not completed within 1 week of the scheduled time, the participant was given the option to complete the questionnaire within the next 2 weeks.

### Participants

Individuals aged 55 years and older who met the inclusion criteria for osteoarthritis were enrolled in the study. To be eligible for the study, participants must have been diagnosed with moderate-to-severe, osteoarthritis joint pain in the hip or knee (weight-bearing joints) and must have been symptomatic for at least 5 days a week for a minimum of 3 months. Participants who gave written consent were informed of the potential risks and health benefits of participating in the study as well as their responsibilities. Participants' responsibilities included

This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1543953X. To subscribe, visit imjournal.com

compliance with the study's protocol and with the questionnaire schedule at baseline and at 1, 6, and 12 weeks.

An assessment and diagnosis of osteoarthritis or degenerative joint disease in a specific joint was conducted for each participant by the research team. Documentation of the diagnosis was kept on file. After the diagnosis, each participant completed an initial WOMAC questionnaire to document the specific joint that was affected. Based on the inclusion criteria, 87 participants with affected knee or hip joints were enrolled in this study.

Individuals were excluded who (1) were 54 years of age or younger on the study's starting date; (2) were women who were pregnant or nursing mothers; (3) had a body mass index (BMI) of less than 18.5 (underweight) or more than 40.0 (morbidly obese), with BMI defined as weight (lb) x 703/in$^2$; (4) were currently using glucosamine, chondroitin, methylsulfonylmethane (MSM), S-adenosylmethionine (SAMe), omega-3, or any other herbal product or supplement for pain and inflammation of joints; (5) were currently using nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX-2) inhibitors, disease-modifying antirheumatic drugs (DMARDs), steroids or corticosteroids, tumor necrosis factor (TNF) blockers, narcotics, or other controlled substances for pain as prescribed by a medical physician for any other condition; (6) were unwilling to interrupt the intake of supplements or medications for at least 1 month prior to beginning the study; (7) had rheumatoid or other forms of arthritis and joint pain that were the result of nerve or muscle damage, accidents, falls, or trauma; and (8) withdrew from the study. No additional participants were recruited as replacements for people who withdrew, and an exit questionnaire was administered to understand the reason or cause for the discontinuation.

### Assessment of Safety

No adverse events were anticipated. An adverse event was defined as any symptom, sign, illness, or injury that developed or worsened in severity in the course of the study. Abnormal experiences that resulted in withdrawal from the study, clinical symptoms, or the need for additional treatment were also considered to be adverse events. Serious adverse events were classified as symptoms that were life-threatening or fatal, required or extended a hospital stay, or resulted in a significant disability. Participants were asked to report adverse events from the study's beginning to the end of the study's follow-up period. The follow-up period was defined as 30 days following the last administration of the treatment drug or placebo.

### Statistical Analysis

Efficacy analyses were based on the intent-to-treat (ITT) population, which included all of the randomized participants. ANOVA was computed for each of the three endpoints—pain, stiffness, and QOL, with the mean change from baseline to week 12 as the dependent variable. The treatment and placebo groups were factors, and the baseline value for each primary endpoint was the covariate. If a participant withdrew from the study, the last set of WOMAC data that was collected for the participant was carried forward for statistical analyses. A two-sided significance test was conducted for each variable to compare treatment with 150 mg of Cyplexinol to treatment with the placebo. *P* values that were ≤.05 were considered statistically significant.

## Results

### Participants

A total of 87 participants were randomized to receive treatment with 150 mg of Cyplexinol (n=43) or a placebo (n=44), once per day. Eighty-three participants completed the study and four participants withdrew, two from the placebo group, one from the treatment group due to an incomplete follow-up, and one from the treatment group due to noncompliance with the protocol. No withdrawals occurred due to adverse side effects. Furthermore, none of the remaining participants failed to complete the questionnaire at week 6. The last set of WOMAC data that was collected for the withdrawals was carried forward for statistical analyses.

### Efficacy Analyses

In comparison to the placebo, treatment with 150 mg of Cyplexinol resulted in a statistically significant improvement in pain, stiffness, and QOL according to the WOMAC index. The α level was set at .05 for the placebo group to ensure that an effect would be detected for the placebo if one occurred. The α level was set at .0001 for the treatment group to reduce type I errors (false positives). For the scoring of the WOMAC subscales a numerical range of 0 to 10 is used. For pain, 0 means no pain and 10 means the worst pain. For stiffness, the same 0 to 10 scale is used, with 0 meaning no stiffness and 10 meaning the worst stiffness. For QOL, the scale is inverted so 0 means the lowest or worst QOL and 10 means the highest or best QOL.

Table 1 and Figure 1 show that a significant improvement in pain, stiffness, and QOL was observed on the WOMAC subscales for the treatment group. The change in the group's mean scores reached significance: (1) as early as week 1, decrease in pain of 1.57 points (95% CI, 0.74-2.39; $P < .0001$); (2) at week 6, decrease in stiffness of 2.14 points (95% CI, 1.14-3.14; $P < .0001$); and (3) at week 6, an increase in QOL of 2.40 points (95% CI, 1.61-3.18; $P < .0001$). Gradual improvement continued to week 12. In comparison, the placebo group's mean scores: (1) at week 1, deteriorated with a slight increase in pain of 0.01 points (95% CI, -1.02-1.00; $P > .05$); (2) at week 6, improved slightly with a decrease in stiffness of 0.53 points (95% CI, -0.43-1.50; $P > .05$); and (3) at week 6, deteriorated with a

This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1543953X. To subscribe, visit imjournal.com

**Table 1.** Demographics and Mean Changes From Baseline to Weeks 1, 6, and 12

| | 150 mg of Cyplexinol (n = 43) | | Placebo (n = 44) | |
|---|---|---|---|---|
| **Mean Age, y** | 67.9 ± 9.94 | | 67.7 ± 11.62 | |
| **Gender** | | | | |
| Male | 18 | | 20 | |
| Female | 25 | | 24 | |
| | **Mean ± SD** | **95% CI** | **Mean ± SD** | **95% CI** |
| **WOMAC change from baseline to week 1**[a] | | | | |
| Pain subscale score | 1.57 ± 0.42 | 0.74-2.39 | -0.01 ± 0.51 | -1.02-1.00 |
| Stiffness subscale score | 1.18 ± 0.51 | 0.17-2.19 | 0.52 ± 0.49 | -0.46-1.50 |
| QOL subscale score | 1.11 ± 0.40 | 0.33-1.90 | 0.10 ± 0.76 | -1.41-1.60 |
| **WOMAC change from baseline to week 6**[a] | | | | |
| Pain subscale score | 2.63 ± 0.40[b] | 1.84-3.45 | -0.13 ± 0.56 | -1.26-0.99 |
| Stiffness subscale score | 2.14 ± 0.50[b] | 1.14-3.14 | 0.53 ± 0.49 | -0.43-1.50 |
| QOL subscale score | 2.40 ± 0.40[b] | 1.61-3.18 | -0.11 ± 0.91 | -1.92-1.70 |
| **WOMAC change from baseline to week 12**[a] | | | | |
| Pain subscale score | 3.35 ± 0.39[b] | 2.58-4.13 | -0.35 ± 0.53 | -1.40-0.71 |
| Stiffness subscale score | 2.95 ± 0.51[b] | 1.94-3.97 | 0.18 ± 0.51 | -0.82-1.19 |
| QOL subscale score, mean ± SD | 3.12 ± 0.37[b] | 2.38-3.86 | -0.40 ± 0.82 | -2.034-1.24 |

[a]All scores represent the mean change from baseline to weeks 1, 6, and 12. For the WOMAC pain, function, and QOL subscales, a positive change represents an improvement. Treatment drug and placebo were administered once daily.
[b]Represents a statistically significant difference with $P < .0001$.

Abbreviations: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; QOL, quality of life; 95% CI, 95% confidence interval.

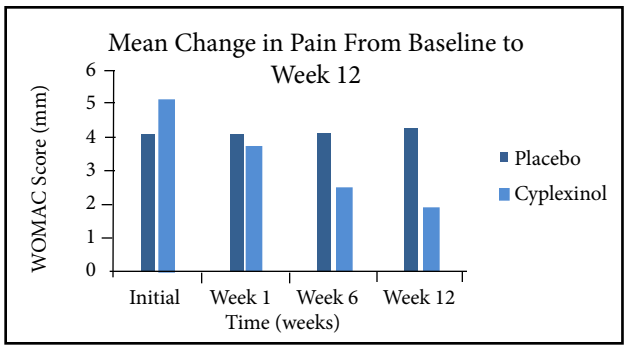
slight decrease in QOL of 0.11 points (95% CI, -1.92-1.70; $P > .05$).

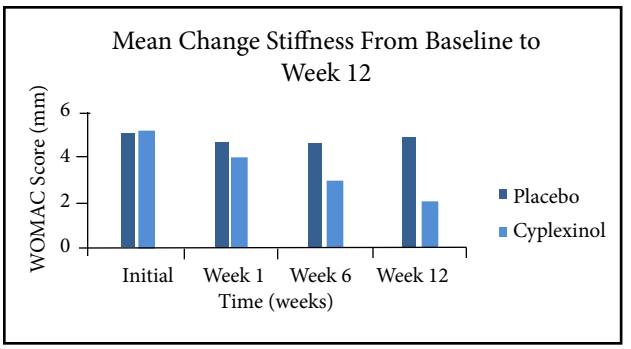
The most significant effect, an improvement (decrease) in pain, by 3.35 points (95% CI, 2.58-4.13; $P < .0001$), was observed for the WOMAC subscale at week 12 for the treatment group in comparison to the placebo group, which had an increase in pain of 0.35 points (95% CI, -1.40-0.71; $P > .05$) at week 12 (Table 1). A significant effect was seen with a decrease of 2.95 points (95% CI, 1.94-3.97; $P < .0001$) was observed for the WOMAC stiffness subscale at week 12 for the treatment group in comparison to a slight improvement with a decrease in stiffness of 0.18 points (95% CI, -0.82-1.19; $P > .05$) for the placebo group. A significant effect (increase) of 3.12 points (95% CI, 2.38-3.86; $P < .0001$) was also observed for the WOMAC QOL subscale at week 12 for the treatment group in comparison to a decrease of 0.40 points (95% CI, -2.034-1.24; $P > .05$) for the placebo group.

Percent population analyses also showed that 48.78% of the sample population that was treated with 150 mg of Cyplexinol experienced a significant decrease in OA-related pain (at least 25% improvement) at week 1; at 6 weeks, 87.80% experienced less pain; and at 12 weeks, 90.24% experienced less pain (Figure 2). A decrease in pain as well as an increase in QOL was defined as at least 25% improvement in symptoms. Similar percentages were observed for the QOL endpoint. At week 1, 36.59% began to experience a significant overall improvement in QOL (at least 25% improvement); at 6 weeks, 75.61% reported an increase in their QOL; and at 12 weeks, 90.24% reported an improvement in QOL. A gradual improvement in stiffness was also observed for the treatment group. At week 1, 42.50% experienced significantly less stiffness and improved mobility (at least 25% improvement) in the affected joint; at 6 weeks, 67.50% reported a decrease in stiffness; and at 12 weeks, 82.50% reported less stiffness.

This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1543953X. To subscribe, visit imjournal.com

**Figure 1.** Mean change from baseline to week 12 for the Western Ontario and McMaster Universities (WOMAC) pain, stiffness, and QOL subscales for treatment with 150 mg of Cyplexinol or a placebo. A decrease in WOMAC score represents an improvement ($P < .0001$). QOL = quality of life.



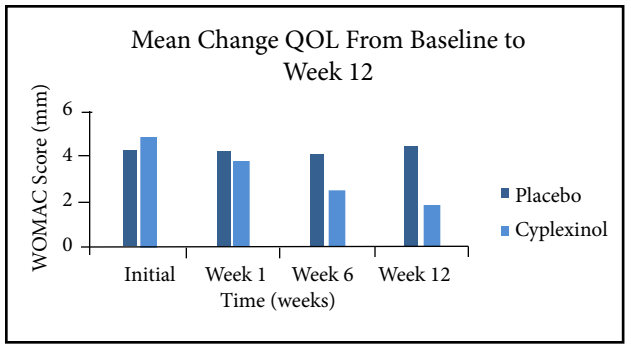
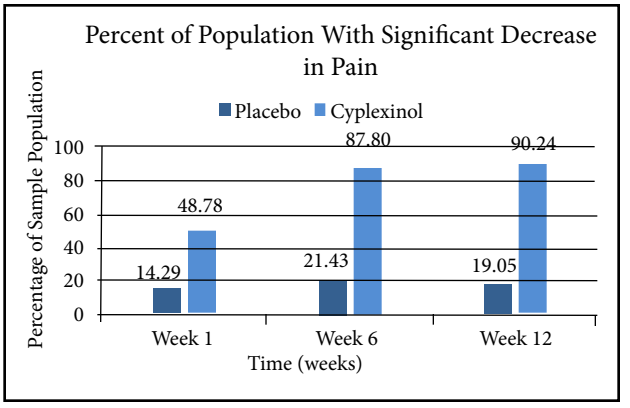
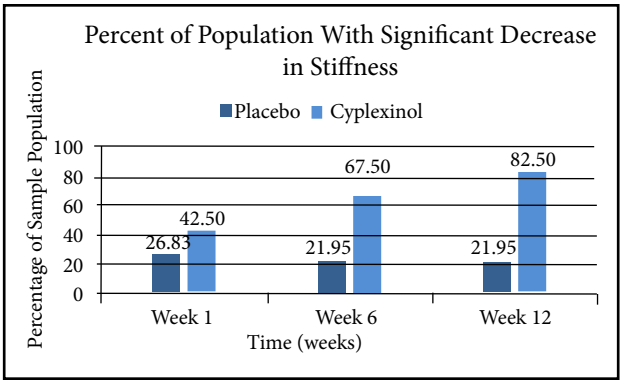
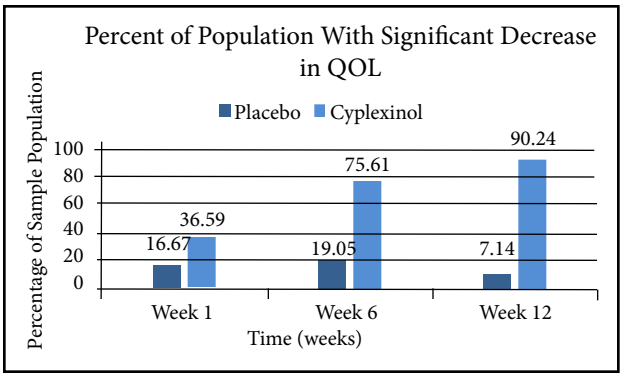




**Figure 2.** Percentage of the sample population that experienced a decrease in symptoms after being treated with 150 mg of Cyplexinol. A postive increase in percentage represents an improvement. Similar percentages for the placebo group represent no change in symptoms.




Of the sample population of placebo participants, 21.43% reported slight improvements in pain at week 6, but this percentage decreased to 19.05% by week 12. Significant improvement (decreases) in stiffness was not observed for the placebo group; 26.83% reported a decrease in stiffness during week 1, but this percentage decreased to 21.95% at week 6, and at week 12, remained the same. Figure 2 shows that QOL decreased dramatically for the placebo group for week 1 (16.67%), week 6 (19.05%), and week 12 (7.14%).

ITT *t* test analyses showed no significant difference for pain, stiffness, or QOL between the ITT participants and the withdrawals.

## Discussion

The results of this clinical trial showed that 150 mg of Cyplexinol treatment decreased stiffness and improved mobility over a 12-week period in OA-affected, weight-bearing joints in comparison to the placebo, which did not produce a significant difference in symptoms after 12

This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1543953X. To subscribe, visit imjournal.com

weeks. The QOL endpoint, which involved assessing a participant's ability to carry out daily activities—going up stairs, standing, getting out of bed, and bending with ease—also improved upon treatment of OA with Cyplexinol. The effect was not immediate, but a marked decrease in OA-related complications was observed by week 6 for each of the endpoints that were evaluated. The earliest effect that was experienced by participants was a decrease in pain after taking 150 mg of Cyplexinol once a day for 1 week (Figure 1). Proinflammatory cytokines such as tumor necrosis factor α (TNF-α), IL-1, and IL-6 are often detected around OA-affected joints and are believed to be one of the causes of chronic pain and inflammation.[18] The acidic environment that develops as a result of proinflammatory cytokines as well as proteolytic fragments that accumulate around the OA-affected joint, lead to the activation of growth factors such as BMPs. Once activated, BMPs (eg, BMP-7) begin to down-regulate both basal and TNF-induced expression of cytokines such as IL-1 and IL-6.[19,20] Therefore, BMPs act upon inflammatory processes, and the rapid decrease in pain that was observed for participants who were treated with 150 mg of Cyplexinol is attributable to the immunoprotective BMP activity.

Improvements that were observed in relation to joint stiffness and QOL may also be attributable to BMP activity (particularly BMP-7), which has been shown to improve the amount and quality of OA-affected cartilage while it shortens the amount of time it takes for damaged cartilage to heal.[21-23] BMP-7 strengthens cartilage by stimulating proteoglycan synthesis in human osteoarthritic chondrocytes.[24] Furthermore, BMP-7 acts upon articular tissues by upregulating chondrocyte metabolism and increasing the survival of chondrocytes, which are cells that play a major role in the cartilage-repair process. Enhanced chondrogenic activity that is mediated by BMP-7 results in an increase in cartilage, synovial membrane, and surrounding tissue.[25] Similarly, BMP-6 has a stimulatory effect on chondrocytes that leads to an increase in proteoglycan synthesis,[26] indicating that both BMP-6 and BMP-7 play a vital role in the maintenance of joint integrity.

During the current clinical trial, participants who were treated with 150 mg of Cyplexinol experienced less stiffness (Figures 1 and 2) together with increased mobility and a heightened ability to conduct daily activities with ease as cartilage began to heal. In general, the increase in the overall QOL in combination with the decrease in stiffness that was observed implies that 150 mg of Cyplexinol had a positive and timely effect on OA-affected joints by activating cells that stimulate proteoglycan synthesis and cartilage repair. In particular, proteins contained within 150 mg of Cyplexinol, such as IGF and BMPs, have been shown to promote cartilage regeneration and increased joint mobility, which gives a glimpse of the role that these proteins may play in treating OA.[11]

The association between consistent use of 150 mg of Cyplexinol and a steady improvement of OA-related complications was clearly demonstrated in the treatment group because the percentage of participants who experienced an improvement in symptoms gradually increased throughout the trial (Figure 2). Furthermore, 150 mg of Cyplexinol was markedly more effective than the placebo as symptoms continued to persist in the placebo group throughout the 12-week trial. A small percentage of the placebo population (7.14%) even experienced a decrease in their QOL during the trial period. These findings may be attributable to an inadequate level of growth factors in the body; Otsuki et al propose that the abnormal regulation of osteoinductive proteins (BMPs) may result in degenerative diseases such as OA.[27] Previous research, which revealed a significant decrease in BMP-4 and BMP-5 in the synovial fluid of participants with OA and rheumatoid arthritis (RA), supports this notion and indicates the important role that BMPs play in joint homeostasis.[28]

In general, the results of this clinical trial support previous studies that suggest that BMPs, which are found in Cyplexinol (150 mg), are effective targets for OA therapy as these growth factors play a central role in joint homeostasis and cartilage formation through regulation of osteoblasts and chondrocytes.[14,25] BMPs are one of the main active constituents of the 150 mg of Cyplexinol, and in the current study, the treatment of OA with this natural complex led to a rapid decrease in pain, which is one of the main symptoms of OA. However, growth factors such as BMPs not only treat pain by acting upon inflammatory process but also by activating critical stem cells called *mesenchymal stem cells* that in are found in the synovial membrane.[29] In particular, both BMP-6 and BMP-7 have been shown to stimulate mesenchymal stem cells, causing them to differentiate into chondrocytes that migrate out of the synovium and into the hyaline cartilage where increased proteoglycan synthesis occurs.[24,26] Furthermore, previous studies have shown that increasing the survival of chondrocytes promotes cartilage repair.[25,30]

## Conclusion

The information that was gathered from the current study can help health care professionals better understand the role that BMPs play in degenerative joint conditions, such as OA, and how such proteins may treat or prevent degeneration and cartilage loss in people who are currently afflicted with or at risk of developing this disease.[25] One of the main advantages of using this osteoinductive complex to treat OA is that it naturally stimulates cartilage growth while it down-regulates the inflammatory cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6), without causing the potential health problems (eg, cardiovascular problems) that may develop from taking nonsteroidal, anti-inflammatory drugs (NSAIDs).[19,20,31] This research supports Cyplexinol in becoming one of the key

This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1543953X. To subscribe, visit imjournal.com

components in the future for supplements that promote optimal joint health. Long-term clinical trials with a larger sample population are needed to further evaluate the efficacy and safety of using 150 mg of Cyplexinol to treat OA.

**Acknowledgements**

ZyCal Bioceuticals, Inc. sponsored the study by providing all product free of cost; the study received no grants. Manuscript was edited by Adam Perlman, MD – Director of Integrative Medicine, Duke University.

**References**

1. Issa SN, Sharma L. Epidemiology of osteoarthritis: an update. (review). *Curr Rheumatol Rep.* 2006;8:7-15.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* 2008;58:26-35.
3. Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med.* 2000;133:635-646.
4. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum.* 2008;59:1207-1213.
5. Murphy LB, Helmick CG, Schwartz TA, et al. One in four people may develop symptomatic hip osteoarthritis in his or her lifetime. *Osteoarthr Cartil.* 2010;18:1372-1379.
6. Lawrence RC, Hochberg MC, Kelsey JL, et al. Estimates of the prevalence of selected arthritis and musculoskeletal diseases in the United States. *J Rheumatol.* 1989;16:427-441.
7. Verbrugge LM. Women, men, and osteoarthritis. *Arthritis Care Res.* 1995;8:212-220.
8. Loeser RF, Goldring SR, Scanzello CR, et al. Osteoarthritis: a disease of the joint as an organ. (review). *Arthritis Rheum.* 2012;64:1697-1707.
9. Reddi AH. BMPs: from bone morphogenetic proteins to body morphogenetic proteins. *Cytokine Growth Factor Rev.* 2005;16:249-250.
10. Reddi AH, Reddi A. Bone morphogenetic proteins (BMPs): from morphogens to metabologens. (editorial). *Cytokine Growth Factor Rev.* 2009;20:341-320.
11. Chen L, Jiang W, Huang J, et al. Insulin-like growth factor 2 (IGF-2) potentiates BMP-9-induced osteogenic differentiation and bone formation. *J Bone Miner Res.* 2010;25:2447-2459.
12. Inoue A, Takahashi KA, Arai Y, et al. The therapeutic effects of basic fibroblast growth factor contained in gelatin hydrogel microspheres on experimental osteoarthritis in the rabbit knee. *Arthritis Rheum.* 2006;54:264-270.
13. Caplan AI, Correa D. PDGF in bone formation and regeneration: new insights into a novel mechanism involving MSCs. *J Orthop Res.* 2011;29:1795-1803.
14. Li B. Bone morphogenetic protein-Smad pathway as drug targets for osteoporosis and cancer therapy. *Endocr Metab Immune Disord Drug Targets.* 2008;8:208-219.
15. Mundy GR. Nutritional modulators of bone remodeling during aging. *Am J Clin Nutr.* 2006,83:427S-430S.
16. Urist MR. Bone: formation by autoinduction. *Science.*1965;150:893-899.
17. Bellamy N. WOMAC Osteoarthritis Index User Guide. Version V. Brisbane, Australia; 2002.
18. Orita S, Koshi T, Mitsuka T, et al. Associations between proinflammatory cytokines in the synovial fluid and radiographic grading and pain-related scores in 47 consecutive patients with osteoarthritis of the knee. *BMC Musculoskelet Disord.* 2011;12:144.
19. Gould SE, Day M, Jones SS, et al. BMP-7 regulates chemokine, cytokine, and hemodynamic gene expression in proximal tubule cells. *Kidney Int.* 2002;61:51-60.
20. Lee MJ , Yang CW, Jin DC, et al. Bone morphogenetic protein-7 inhibits constitutive and interleukin-1 beta-induced monocyte chemoattractant protein-1 expression in human mesangial cells: role for JNK/AP-1 pathway. *J Immunol.* 2003;170:2557-2563.
21. Cook SD , Patron LP , Salkeld SL, et al. Repair of articular cartilage defects with osteogenic protein-1 (BMP-7) in dogs. *J Bone Joint Surg Am.* 2003;85-A:116-123.
22. Jelic M, Pecina M, Haspl M, et al. Regeneration of articular cartilage chondral defects by osteogenic protein-1 (bone morphogenetic protein-7) in sheep. *Growth Factors.* 2001;19:101-113.
23. Louwerse RT, Heyligers IC, Klein-Nulend J, et al. Use of recombinant human osteogenic protein-1 for the repair of subchondral defects in articular cartilage in goats. *J Biomed Mater Res.* 2000;49:506-516.
24. Stove J , Schneider-Wald B, Scharf HP, et al. Bone morphogenetic protein 7 (bmp-7) stimulates proteoglycan synthesis in human osteoarthritic chondrocytes in vitro. *Biomed Pharmacother.* 2006;60:639-643.
25. Hurtig M, Chubinskaya S, Dickey J, et al. BMP-7 protects against progression of cartilage degeneration after impact injury. *J Orthop Res.* 2009;27:602-611.
26. Bobacz K, Gruber R, Soleimanm A, et al. Expression of bone morphogenetic protein 6 in healthy and osteoarthritic human articular chondrocytes and stimulation of matrix synthesis in vitro. *Arthritis Rheum.* 2003;48:2501-2508.
27. Otsuki S, Hanson SR, Miyaki S, et al. Extracellular sulfatases support cartilage homeostasis by regulating BMP and FGF signaling pathways. *Proc Natl Acad Sci USA.* 2010;107:10202-10207.
28. Bramlage CP, Haupl T, Kaps C, et al. Decrease in expression of bone morphogenetic proteins 4 and 5 in synovial tissue of patients with osteoarthritis and rheumatoid arthritis. *Arthritis Res Ther.* 2006;8:R58.
29. Sykaras N, Opperman LA. Bone morphogenetic proteins (BMPs): how do they function and what can they offer the clinician? (review). *J Oral Sci.* 2003;45:57-73.
30. Chubinskaya S, Hurtig M, Rueger DC. OP-1/BMP-7 in cartilage repair. *Int Orthop.* 2007;31:773-781.
31. García-Rodríguez L, González-Pérez A: Long-term use of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population. *BMC Med.* 2005;3:17.