Oral Cetylated Fatty Acids for the Improvement of Functional Ability and Pain in Patients with Knee Osteoarthritis

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Running Title: Celadrin® Improves Walking Performance

Abstract

Objective: To determine the benefit of low dose oral cetylated fatty acids (Celadrin®) on function and pain in subjects with moderate osteoarthritis (OA) of the knee.

Methods: 93 subjects were evaluated at baseline, and again at 4 and 8 weeks after consuming either placebo (n=46) or Celadrin® (n=47). Evaluations included the 6-minute timed walk, VAS pain scales, WOMAC, the Lequesne Algofunctional Index (LAI) and other measures of knee function.

Results: All 93 subjects completed the study, and between-group comparisons indicated a statistically significant improvement in the distance walked in 6 minutes in the Celadrin® treated group at 2 weeks (+232.57 ft v. -119.01 ft, $p=0.0002$), 4 weeks (+330.09 ft v. -113.76ft, $p<0.0001$), and 8 weeks (+537.42 ft v. -105.57ft, $p<0.0001$). Average pain severity decreased significantly in the Celadrin® group on all 4 VAS items after 2 weeks and was statistically superior across all VAS items at 8 weeks compared to the subjects who received placebo ($p<0.02$ to $p<0.0003$). All other pain and function scores showed significant changes from baseline to end of treatment in both groups but no significant between-group differences were found. No adverse events were reported.

Conclusion: Subjects with moderate OA of the knee who received Celadrin® achieved significant improvements in their functional self-efficacy coupled with a significant reduction in their knee pain compared with those who received placebo.

Introduction

Osteoarthritis (OA) of the knee is the final common pathway of multiple risk factors including injury, genetics, aging, obesity, mechanical forces, and inflammation. Once the process has begun, the joint begins to remodel in ways that lead to abnormalities of the joint surface as well as in the juxtaarticular bone marrow (1). As OA of the knee progresses, it can lead to tendino-muscular abnormalities such as quadriceps weakness as the body attempts to compensate (2,3). Since this is a weight bearing joint, the combination of the pain in the knee and the weakness of the surrounding muscles can lead to functional deficiencies that significantly decrease the quality of life of the patient.

For the practicing clinician, the choice of treatment for this disorder is becoming more difficult. NSAIDs (including COX-2 inhibitors), once-standard therapies for OA, have been identified by the American Heart Association as risky in certain populations, ironically the same populations who are most likely to require treatment (including the elderly and those with heart disease or at risk for heart disease) (4). Invasive therapies such as intra-articular glucocorticoids and hyaluronans carry procedural risks and only offer temporary relief. Very few dietary supplements have been subjected to the scrutiny of randomized double-blind clinical trials and even fewer still have been able to demonstrate consistent pain relief efficacy across multiple trials (5-13). One exception to this group is Celadrin®, a proprietary cetylated fatty acid (CFA) which has demonstrated significant improvements in function and pain reduction in patients with OA of the knee in 3 different published randomized clinical trials (14-17).

The current protocol is designed to evaluate a reduced dose version of previously tested and marketed oral Celadrin® for improvement of functional performance and quality of life, and reduction of pain in individuals suffering from knee osteoarthritis.

Materials and Methods

The supplement (Celadrin®) is a proprietary blend of cetylated fatty acids with a range of carbon lengths from 10 to 20. The manufacturing process is highly specific to produce a compound that has a narrow range for each cetylated fatty acid within the blend. The product used in the current study contained 52% of the blend and 48% tapioca powder as a carrier. Four 400mg capsules were consumed per day resulting in a daily consumption of 1600mg of total powder and 832mg of Celadrin®. The placebo was composed of magnesium stearate in visually identical hard-shell capsules.

Functional measurements

Six-minute walk distance test: Subjects were instructed to "Walk as rapidly as possible without putting yourself at risk for injury" and were followed up along a marked flat surface path, 147 feet long by a study coordinator with a rolling pedometer (Road Runner Outdoor Run Wheel) while being timed for 6 minutes with a stopwatch. Subjects would walk the length of the path, turn around and walk back to their starting point continuing this cycle until stopping due to fatigue or discomfort. The total distance walked was recorded.

Knee range of motion (ROM): Range of motion of the knee was measured using an inclinometer (Baseline Bubble Inclinometer, Fabrication Enterprises Inc, NY) The axis of the inclinometer was placed at the intersection of the thigh and shank at the knee joint.

For knee flexion the subject was placed in the prone position with their feet off the table (knee fully extended), then the subject was asked to actively flex their knee to the full flexion position. For knee extension the subject was placed in the sitting position at the end of the table, keeping their back straight. The subject started with knee flexion at 90°, then they fully extended their knee without changing the position of their pelvis and lumbar spine.

Timed "up and go" from chair(18): The subject was instructed to ascend from a seated position (without using their hands to assist) and walk to a marked point on the floor located 3m away. The test was repeated 3 times, and the shortest time interval was used.

Unilateral anterior reach(17): Subjects stood with hands on their hips and extended their non-painful leg out so as to induce flexion on the painful knee. The displacement (distance that the heel of the non-painful leg traveled) was measured. The test was repeated 3 times, and the largest displacement was used.

Scales and Questionnaires

Visual Analog Scale – The four questions were asked at each study time point using an 11-point Likert scale. The questions included "How severe is your pain now?", "What is the least severe that your knee pain has been in the last week?", "What is the most severe that your knee pain has been in the last week?", and "How much is pain interfering with your activities?"

WOMAC(19) – The WOMAC Osteoarthritis Index is a validated patient reported health status questionnaire that evaluates pain, stiffness, and physical disability in patients who

suffer from osteoarthritis of the knee or hip. It has been used extensively in the published OA research literature and was evaluated at each study time point in the current study.

Lequesne Algofunctional Indices for Knee Osteoarthritis(20). Algofunctional indices for osteoarthritis of the knee were evaluated for each subject at each study time point. This validated evaluation includes questions regarding pain or discomfort during bed rest, morning, after standing for 30 minutes, while ambulating, and during prolonged sitting.

Subjects and Study Design

Two hundred fifteen (215) subjects with a history of knee osteoarthritis were screened between the two research facilities (Medicus Research facility in Northridge, CA and BRCG in Ellicott City, MD). Ninety three subjects (54% men and 46% women) were eligible and entered into this randomized double-blind, placebo-controlled 8-week trial. There were no significant differences between groups regarding gender, age, or number of years since diagnosis of osteoarthritis (see Table 1). All 93 subjects who started the study completed all the study visits for a 0% drop-out rate.

IRB approval was obtained from the Copernicus Group IRB (Cary, NC) prior to any study related procedures. Good Clinical Practices (GCP) was followed throughout the study. All subjects gave informed consent according to GCP guidelines prior to initiating any study procedures.

Subjects were screened for osteoarthritis of the knee using the ACR Criteria (21) including pain in the knee for greater than 6 months, a knee x-ray with Kellgren and Lawrence (K&L)

grade of 2 (effacing) or 3 (significant loss), and one of the following: age greater than 40, morning stiffness lasting 30 minutes or less, or demonstration of crepitus on knee range of motion.

Subjects with any other rheumatologic or autoimmune disorders or who were taking corticosteroids or other immunosuppresants were excluded as were any subjects who had a severe hip or back disability which could interfere with their ability to perform the functional measures. Subjects who had received any injections in the knee (glucocorticoid or hyaluronic acid) were required to wait for admission into the study until 3 months had passed since the last injection of either product.

Subjects underwent a history and physical examination by a board certified physician, all women of child bearing potential were given a urine pregnancy test, and all subjects of child bearing potential were required to use appropriate methods of contraception during the active study.

Subjects were seen at a screening visit and underwent a 2-week single-blind placebo run-in period to assess compliance and to allow time to washout any anti-inflammatory or pain reducing medications. Subjects were given rescue medication (acetaminophen) and rescue usage was recorded. After the washout/run-in period, subjects were randomized to receive four capsules per day (two with breakfast and two with dinner) of the investigational product or sensory identical placebo. Subjects were evaluated at baseline, 2 weeks, 4 weeks, and 8 weeks during which they underwent functional evaluations and were given the standardized scales and questionnaire items.

The clinical safety profile of the product was assessed by questioning the subjects at each visit concerning any changes in their medical condition, any visits to their physician, consumption of any new prescription or over the counter medications or dietary supplements. In addition, events of clinical interest (including gastritis, easy bruising, or bleeding diatheses based on the anti-inflammatory mechanism of the product) were queried at each visit.

Statistical Analysis

Between-group analyses were performed on the change from baseline data in each group. The two-way ANOVA model included terms for group, week, and group-week interaction. Within group analyses were conducted using a two-sided paired samples t-test (SPSS, Version 9.1, Cary, NC).

Results

Functional Measures

The primary outcome measure was the six-minute timed walk. The Celadrin® group demonstrated significant improvement at all time points compared to their baseline evaluation, while the placebo group was slightly worse than baseline for the remainder of the study (Figure 1). Based on a paired samples t-test, there was a significant, within-group improvement from baseline for the Celadrin® group to Week 2 ($p<0.001$), to Week 4 ($p<0.001$), and to Week 8 ($p<0.001$). The placebo group demonstrated a significant reduction in total walk distance from baseline to Week 2 ($p=0.028$) and to Week 4 ($p=0.029$). The placebo group change from baseline to Week 8 trended toward significant worsening as well ($p=0.059$). The ANOVA (between-group) assessment was statistically significant in favor of the Celadrin® group at 2 weeks (+232.57 ft v. -119.01

ft, p=0.0002), 4 weeks (+330.09 ft v. -113.76ft, p<0.0001), and 8 weeks (+537.42 ft v. -105.57ft, p<0.0001).

Other functional measures did not demonstrate any significant improvements from baseline in either group and there were no significant differences between the two groups.

(FIGURE 1 HERE)

Scales and Questionnaires

Visual Analog Scales: Average pain severity decreased significantly in the Celadrin® group starting at 2 weeks for "What is the least severe your pain has been in the last week" and "How much is pain interfering with your activities" and by 4 weeks for the remaining questions "How severe is your pain now" and "What is the most severe that your pain has been in the last week" (Figure 2). The placebo group did not manifest any significant improvements from baseline in any of the four questions. Paired t-test between-group analyses revealed that improvements from baseline were significantly better in the Celadrin® group compared with the placebo group across all four VAS questions by 8 weeks, with p values ranging from 0.0003 to 0.02.

(FIGURE 2 HERE)

WOMAC: Both groups demonstrated significant improvements from baseline on the total WOMAC and on each of the WOMAC subscales (pain, physical functioning, stiffness) at all time points. The difference between groups was not significant at any time point. When the data were analyzed separately based on the degree of severity of the knee OA (by K&L grade), no significant between group differences were seen.

LAI: Based on the paired samples t-test there was a significant within group improvement from baseline for both the Celadrin® ($p<0.001$) and placebo ($p=0.003$) groups after 2 weeks. At weeks 4 and 8, the amount of improvement compared with baseline was no longer significant for either group. When LAI scores were analyzed separately based on the degree of severity of the knee OA (by K&L grade), there was a statistically significant difference ($p=0.0465$) in change from baseline to week eight in mean LAI score in favor of the Celadrin® group for the subset of subjects whose K&L grade was less severe (K&L=2). In this less severe subgroup, the mean change from baseline to week eight decreased by 2.24 for the Celadrin® group, but increased by 1.82 for the placebo group. The subjects whose K&L grade was more severe (K&L =3) showed no difference between groups.

Rescue Medication Usage: 63% of the placebo group and 55.8% of the Celadrin® group used rescue medication during study. The incidence of usage and amount of usage was not statistically significantly different between groups.

Safety

No clinically significant, study medication associated adverse events, or serious adverse events were observed or reported during the study. There was no difference in the rate of clinically non-significant or non-study medication related adverse events between groups. In addition, no events of clinical interest were identified in either group.

Discussion

The present study demonstrates the clinical significance of a cetylated fatty acid compound (Celadrin®) for improving physical activity and reducing pain in individuals suffering from knee osteoarthritis. Osteoarthritis (OA) is a chronic and debilitating disease that affects over 20 million people in the US alone and millions more worldwide. Individuals suffering from all forms of arthritis and knee OA in particular report reduced physical activity and energy expenditure. Fontaine and colleagues report that nearly 61% of adults with arthritis do not meet the physical activity recommendation (22). This alarming trend does not offer great promise for these individuals, their families, and society in general. The tendency for obesity is high in people who have low energy expenditure (23) and this is true for individuals with arthritis (24). In addition, individuals with low physical activity have increased health costs attributed to the arthritis and pending obesity (25). While reduction of pain is foremost with any malady, for the arthritis patient it is paramount to increase their physical activity and energy expenditure.

The decision to utilize functional measures as the primary outcome in the present study is based on the subjects' ability to measure self-efficacy (confidence in one's ability to perform a particular task) and physical performance which are both clinically relevant measures of mobility (26,27). In the present study those individuals consuming Celadrin® experienced a 42% increase in their 6-minute walking distance compared to no improvement in the placebo group. After 8 weeks, the Celadrin® group improved by 130% compared to no improvement in the placebo group. This finding is important as the OASIS study had previously determined that the 6-minute timed walk contributes to satisfaction with function scores in men and women living with knee pain (28). The ability to improve the 6-minute walking distance by such a large amount is even more

impressive when compared with the small relative increases seen by other interventions in the literature.

An open-label single-arm study of 30 subjects with knee OA showed that the use of an oleoresin of the Ayurvedic herb Commiphora mukul increased the 6-minute walk time by only 4% compared with baseline after 8 weeks (29). Mangani et al investigated the influence of an aerobic exercise program versus a weight training program in individuals suffering from knee osteoarthritis (30). After 3 months the aerobic exercise group showed a 10% improvement in the 6-minute walk test which remained unchanged over the next 15 months of the study. In comparison, the weight training group remained unchanged throughout the study period.

The Arthritis, Diet, and Activity Promotion Trial (ADAPT) compared exercise alone, dietary weight loss alone, both together, or health education alone in overweight and obese subjects with knee OA (31). After 18 months, the exercise and diet group produced significant improvements in the 6-minute walk time of 134 feet (+9.5%) compared with the health education group which decreased by 11 feet (-.7%). Another randomized trial of 83 subjects compared a twice weekly physical therapy regimen with sham control (sub-therapeutic ultrasound to the knee) over an 8-week period (32). At the end of this time, the physical therapy group had increased their 6-minute walk distance by 13.1%. The same author later compared twice weekly physical therapy with a home based exercise program and found an increase in the 6-minute walk distance by about 10% in both groups (33). In another fitness study, 38 subjects were randomized to receive 12 weeks of aquatic exercise or a non-exercise control. The aquatic exercise program was shown to significantly improve the 6-minute walk distance but did not have any effect on

self-reported physical functioning and pain. While there are clearly many health benefits to increasing exercise and losing weight, the amount of effort required to attend twice weekly physical therapy sessions or to adhere to an exercise and diet regimen is much greater for a much smaller walk distance impact than was seen in the current study with the use of the Celadrin® product.

It is noteworthy that improvements in walking may be directly linked to muscle strength in patients afflicted with knee osteoarthritis (34). These authors show improvement in the 100-meter walk test for individuals having better muscle strength and proprioception. It can be suggested that the improvements found in the current study may in fact relate to improved vastus lateralis strength and reduced pain allowing the individuals to increase their physical activity on a daily basis. The use of daily activity monitoring would have better evaluated the link between acute pain in presence or absence of increased daily physical activity. Future studies on this and other compounds should include activity monitoring through such electronic patient reported outcome (ePRO) systems ranging from simple pedometers to the multi-sensor armbands (35-37) and others which can accurately measure the daily physical activity time and energy expenditure.

The importance of increased daily ambulation has been explained above. However, what is the perception of the subject as they ambulate and does it matter whether they experience pain while ambulating? In the present study, subjects completed a standard VAS pain scale in response to pre-selected questions. For the Celadrin® group, subjects experienced reduced pain for all four major questions pertaining to how they felt at the moment and during the preceding week. In contrast, the placebo group tended to have minimal improvements. This may help explain why the Celadrin® subjects had improved

walking distances—they were able to increase their daily activity level due to less pain. Prior work has shown that perceived discomfort and pain significantly reduce 6-minute walk distances in obese women (38). The Celadrin® product's ability to significantly improve the 6-minute walk distance may be related to reductions in pain and in the perception of pain which is also supported by the fact that a lower, but not significant, percentage of the Celadrin® group used rescue medication over the course of the study.

When the current Celadrin® VAS data is compared with the aforementioned Commiphora mukul study (29), the improvements from baseline are comparable. The difference in this study is that the presence of a placebo arm which demonstrates the superiority of Celadrin® with the control. Other knee OA studies of dietary supplements which utilized VAS measurements have also demonstrated similar reductions to Celadrin®. Celadrin® in the current study decreased the VAS by 35% at 8 weeks. Comfrey root ointment reduced total VAS by 54.7% at 3 weeks (39). A standardized white willow bark extract (standardized to 240mg of salicin/day) demonstrated a 15% reduction in total VAS by 6 weeks (40). An Ayurvedic product containing Withania somnifera, Boswellia serrata, Zingiber officinale, and Curcuma longa) was evaluated in 90 subjects who were randomized to receive the Ayurvedic formula or placebo for 32 weeks(41). The reductions VAS were (active = 2.7, placebo = 1.3) at 16 weeks and (active = 2.8, placebo = 1.8) at 32 weeks.

When comparing the current study with the prior data on the Celadrin® product, one sees a pattern of consistency. Another study of the Celadrin® product in an oral formulation (14) was a randomized double-blind, placebo controlled study of 66 subjects in which a higher dose (1575 mg/day) was used. Significant improvements were seen in knee

flexion and function as measured by the LAI when compared to placebo at days 30 and 60. In addition, Kraemer et al. studied Celadrin® in a topical formulation in 2 separate studies (15-17). The subjects applied either Celadrin® (110 mg per application) or placebo cream twice per day for 30 days. The authors reported significant reductions in pain and improvements in functional performance (15,17), as well as improvement in postural stability (16) within 30 minutes of application with continued improvement throughout the 30-day study.

It appears that the present data support the results of the previous studies and provides additional foundational material for the overall understanding of the clinical efficacy and safety profile of the Celadrin®. However, the mechanism of action is still undefined. It seems intuitive that Celadrin® may impact the arachidonic acid pathway as it is comprised of fatty acids. And, in fact unpublished research indicates that Celadrin® affects thromboxane A2 production via thromboxane synthase inhibition of prostaglandin H2.. The reduction of thromboxane A2 may influence the inflammatory cascade throughout a number of physiological pathways that could impact pain receptors, ancillary cytokine production and other agonists associated with osteoarthritis. However, the reported speed of efficacy for the topical Celadrin® cream seems incongruent with arachidonic acid pathway involvement. Given the known dermal penetration capabilities of fatty acids, it is plausible that the topical Celadrin® application has some effect at the cell membrane level near the site of application or at the nerve endings themselves around the joint capsule and musculature. Further research seems warranted given the promising results of the current study and published research.

In summary, subjects with moderate OA of the knee who received Celadrin® achieved significant improvements in their functional self-efficacy coupled with a significant reduction in their knee pain compared with those who received placebo.

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Table 1 – Baseline demographic characteristics

	Active	Placebo
N	47	46
Male	54%	42%
Female	46%	58%
Age	63.05	59.62
Years since diagnosis of OA	6.6	5.3
Kellgren & Lawrence Grade 2	21	20
Kellgren & Lawrence Grade 3	26	26

Figure 1

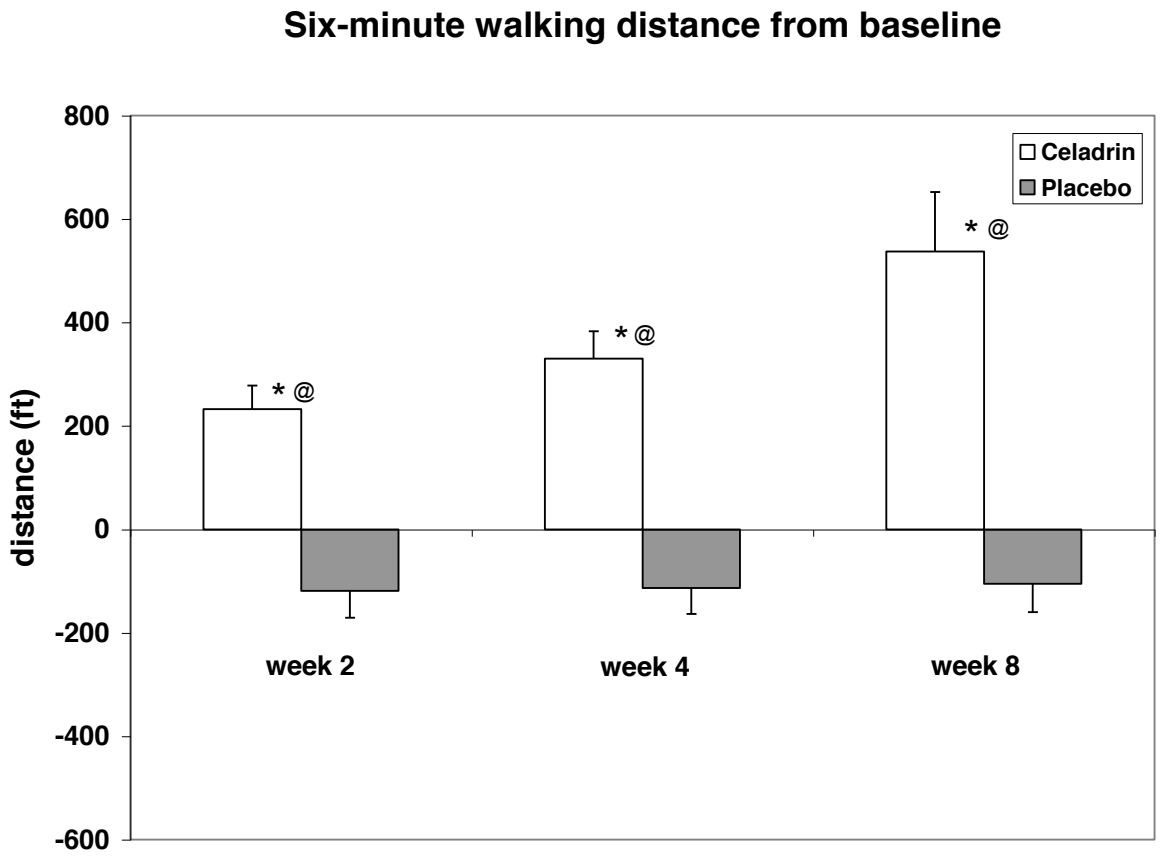
Six-minute walking distance from baseline
800
600
400
200
0
-200
-400
-600
distance (ft)
Celadrin
Placebo
* @
* @
* @
week 2
week 4
week 8

Figure 2

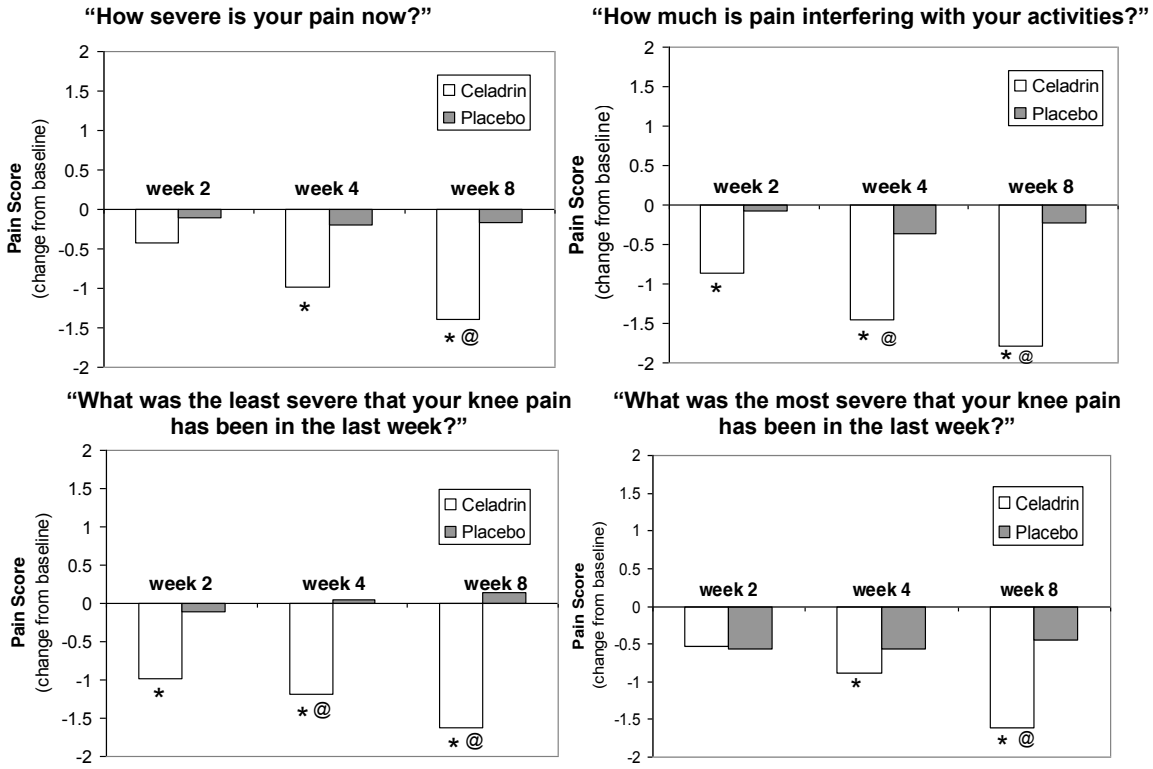
"How severe is your pain now?"
"How much is pain interfering with your activities?"
"What was the least severe that your knee pain has been in the last week?"
"What was the most severe that your knee pain has been in the last week?"
Pain Score
(change from baseline)
Celadrin
Placebo
week 2
week 4
week 8
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
*
* @

Figure Legends

Figure 1—The change in walking distance from baseline (Week 0) for the 6-minute walk test at two-week intervals. * Significant ($p<0.05$) change from baseline. @Significant ($p<0.05$) difference between groups.

Figure 2—The change in response from baseline for each VAS question at two-week intervals for each group. * Significant ($p<0.05$) change from baseline. @Significant ($p<0.05$) difference between groups.

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