LMWF-5A for the Treatment of Severe Osteoarthritis of the Knee: Integrated Analysis of Safety and Efficacy

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abstract

The low-molecular-weight fraction of 5% human serum albumin (LMWF-5A) is being developed to treat the signs and symptoms of severe osteoarthritis of the knee. This study was a post hoc pooled analysis of 3 randomized placebo-controlled trials of a single intra-articular injection of LMWF-5A, focusing on the subset of patients with severe osteoarthritis of the knee (Kellgren–Lawrence grade 4). Patients were randomized 1:1 to receive a single 4-mL intra-articular knee injection of either LMWF-5A or saline. Safety was assessed as the incidence and severity of adverse events. Efficacy was assessed as the change from baseline to week 12 on the Western Ontario and McMaster Universities Osteoarthritis Index pain (primary outcome), stiffness, and physical function subscores and on patient global assessment scores and was presented as the least squares mean difference and 95% confidence interval. The proportion of responders was defined with the Outcome Measures in Rheumatology-Osteoarthritis Research Society International criteria for scenario D and examined with Pearson’s chi-square test. For 417 patients with severe osteoarthritis of the knee, treatment with LMWF-5A resulted in a significant decrease in pain at 12 weeks compared with saline (mean difference, -0.19; 95% confidence interval, -0.34 to -0.04; \( P = .016 \)), with improvements in function (mean difference, -0.15; 95% confidence interval, -0.31 to 0.01) and patient global assessment (mean difference, -0.30; 95% confidence interval, -0.49 to -0.12) and higher responder rates (64.25% vs 50.90%, \( P = .006 \)). No drug-related serious adverse events and no deaths occurred, and the incidence and severity of adverse events were similar across treatment groups. This pooled analysis supports the use of LMWF-5A as a safe therapeutic agent for relief of the signs and symptoms of severe osteoarthritis of the knee. [Orthopedics. 201x; xx(x):xx-xx.]

Osteoarthritis is caused by inflammation of the soft tissue and bony structures of the joint that worsens over time and leads to decreased thickness of the articular cartilage, increased density of the subchondral bone, narrowing of the joint space, thickening of the synovial membrane, and the formation of osteophytes.\(^1\)\(^2\) Disease severity is classified by the Kellgren–Lawrence grading system, ranging from grade 0 (normal knee, with...
no osteophytes or narrowing of the joint space) to grade 4 (large osteophytes, with marked narrowing of the joint space, severe sclerosis, and definite deformity of the bone ends). \(^1\) The primary clinical symptoms are pain and loss of mobility, with significant functional impairment. \(^1\) Osteoarthritis is a leading contributor to global disability. \(^4\) In a study of more than 1000 patients with osteoarthritis, both the presence of frequent knee pain and the severity of knee pain increased with Kellgren–Lawrence grade in a dose-response relationship. \(^5\)

In the past, Kellgren–Lawrence grade 4 osteoarthritis was considered end-stage disease, with total knee arthroplasty as the only remaining option. However, recent studies suggest that synovitis in patients with Kellgren–Lawrence grade 4 osteoarthritis indicates a chronic active “inflammatory” disease process. \(^6\) Additionally, patients with Kellgren–Lawrence grade 4 osteoarthritis have lesions that fluctuate with pain (ie, fluctuating bone marrow lesions and synovitis). \(^5\) Thus, it is possible to examine patients by disease severity and to evaluate treatment options for patients with Kellgren–Lawrence grade 4 osteoarthritis. There is an unmet therapeutic need for patients with severe osteoarthritis who live with debilitating pain and limitations to function and activity.

The low-molecular-weight fraction of 5% human serum albumin (LMWF-5A), the less than 5-kDa ultrafiltrate of 5% human serum albumin, is being developed to provide relief for the signs and symptoms of severe osteoarthritis of the knee. Human serum albumin has been used clinically as a colloid replacement therapy for more than 50 years and has several pharmacologic effects, including decreased inflammation \(^7\) and decreased vascular permeability. \(^8\) In vitro studies of LMWF-5A show both anti-inflammatory activity and anti-neurogenic activity. \(^8\) A pivotal randomized clinical trial in patients with osteoarthritis (Kellgren–Lawrence grades 2, 3, and 4) showed that a single intra-articular injection of LMWF-5A reduced pain among adults with osteoarthritis of the knee and was safe and well tolerated \(^1\); the treatment effect appeared to be greatest in patients with more severe osteoarthritis. The current study examined, through an integrated analysis, the safety and efficacy of an intra-articular injection of LMWF-5A compared with saline for patients with severe osteoarthritis of the knee.

**MATERIALS AND METHODS**

**Study Design and Setting**

This study was a pooled analysis of safety and efficacy data from 3 randomized controlled trials comparing a single injection of LMWF-5A with saline to evaluate the treatment effect and safety in a subset of patients with Kellgren–Lawrence grade 4 osteoarthritis. The randomized controlled trials were performed in accordance with the principles of good clinical practice guidelines, received institutional review board approval, and were registered before patient recruitment occurred. Trial identifiers on ClinicalTrials.gov are as follows: AP-003-A (NCT01839331); AP-003-B (NCT02556710); and AP-004 (NCT02024529). The results of study AP-003-A have been published, \(^12\) and the results of studies AP-003-B and AP-004 have not been published. The 3 trials had uniform design, selection criteria, end points, randomization and blinding, and study drug product. Primary differences were that the studies were performed at different study sites across different time periods (AP-003-A, 2013; AP-004, 2014; AP-003-B, 2015–2016), and AP-003-A was a dose-finding study, with 4 mL and 10 mL of drug product administered. No differences were found between doses, and 4 mL was selected for subsequent studies AP-004 and AP-003-B.

Three additional trials were excluded from the current pooled analysis because the study design, administration, and efficacy end points differed substantially from the single-injection trials examined. Studies AP-007 (NCT02184156) and AP-008 (NCT02242435) were multiple-injection trials (3 injections administered 2 weeks apart). Study AIK (Therapeutic Goods Association identifier 2011/0284) assessed the administration of LMWF-5A alone or in solution with betamethasone and/or lidocaine and/or saline and evaluated the 10-point pain numeric rating scale as the primary end point. The results of study AP-007 have been published. \(^13\)

**Study Participants**

Subject eligibility was identical across all 3 single-injection trials; details have been published. \(^12\) Briefly, eligible patients had radiographic findings of osteoarthritis (Kellgren–Lawrence grade 2, 3, or 4), had symptoms for longer than 6 months with at least moderate pain at baseline (defined as a score of at least 1.5 on the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] version 3.1 5-point Likert pain subscale), were fully ambulatory, and were 40 to 85 years old. Excluded were patients who had a previous injection with LMWF-5A; a history of allergic reactions to albumin and its excipients; any human albumin treatment 3 months before randomization; known clinically significant liver abnormality; concurrent arthritic conditions or any other condition interfering with the free use and evaluation of the index knee; severe osteoarthritis of the hip ipsilateral to the index knee; treatment targeting osteoarthritis that was started or changed 4 weeks before randomization; or use of other intra-articularly injected medications, opioids, significant anticoagulants, immunosuppressants, systemic treatments, or corticosteroids of 10 mg or greater of prednisolone equivalent per day.

**Treatment, Randomization, and Blinding**

Treatment, randomization, and blinding were consistent across all trials. The sponsor, investigators, and study staff who had a role in the day-to-day conduct of the study remained blinded to treatment. Randomization was developed and maintained by an independent statistician, and
patients were randomized 1:1 to receive either LMWF-5A or saline. Patients in the active arm received LMWF-5A, which is the less than 5-kDa fraction of 5% human serum albumin that is produced through ultrafiltration followed by aseptic filling. Those in the control arm received saline. Study drugs were provided in vials labeled with double-panel labels that were blinded for drug content. The only allowed analgesic was a 500-mg acetaminophen tablet every 4 hours as required.

Assessment and End Points

Measurements of safety and efficacy were identical across trials. Measurements of safety included physical examination, vital signs, and clinical laboratory tests (hematology and chemistry). Measurements of efficacy included the WOMAC version 3.1 5-point Likert scale and patient global assessment of disease severity. The patient global assessment of disease severity asked about the overall status of the target knee with respect to the patient’s osteoarthritis: “Considering all the ways in which your arthritis affects you, please indicate how you are doing.” Responses were assessed on a 5-point Likert scale, with 0 indicating very well and 4 indicating very poorly. Evaluations occurred at baseline (day 0) and at weeks 2, 4, 6, 8, 10, and 12. No cellular, tissue, or joint structural changes were measured in the 3 trials.

For all trials, the primary end point was the change in WOMAC pain subscore between baseline and week 12. Secondary end points included the incidence and severity of adverse events through week 12; the change from baseline to week 12 on patient global assessment scores and WOMAC subscores for stiffness, physical function, pain with movement (questions 1 to 2), and pain at rest (questions 3 to 5); and the Outcome Measures in Rheumatology (OMERACT)-Osteoarthritis Research Society International (OARSI) criteria.14 The OMERACT-OARSI response is a composite outcome calculated using the change in WOMAC pain and function and patient global assessment scores. This response was examined according to scenario D, as follows:

1. Significant improvement of pain or function score of 50% or greater and absolute change of 1 point or greater.
2. Improvement of at least 2 of the following 3: (1) change in pain score of 20% or greater and absolute change of 0.5 points or greater; (2) change in function score of 20% or greater and absolute change of 0.5 points or greater; and (3) change in patient global assessment score of 20% or greater and absolute change of 0.5 points or greater.

Statistical Analysis

Statistical analyses were performed using SAS version 9.3 software (SAS Institute, Cary, North Carolina). All studies enrolled patients with Kellgren–Lawrence grade 4 osteoarthritis, which is the focus of this study. Analysis of the subgroup of patients with Kellgren–Lawrence grade 4 osteoarthritis was defined a priori in the protocol and statistical analysis plan for all trials. Patients were analyzed as randomized (intent-to-treat). No adjustment was made for multiple comparison testing; the change in WOMAC pain score from baseline to week 12 was the primary end point. Statistical significance was set at P<.05 for all analyses.

Data are presented as the least squares mean change (95% confidence interval) from baseline to week 12 for WOMAC subscores (pain, pain with movement, pain at rest, stiffness, and physical function) and patient global assessment scores. Differences between treatment groups were analyzed with analysis of covariance adjusted for baseline value. The proportion of OMERACT-OARSI responders was analyzed for differences between treatment groups with Pearson’s chi-square test. Adverse events were examined for all patients who were randomized. Those with missing or incomplete adverse event data were assumed to have a severe related adverse event. Treatment-emergent adverse events were tabulated for incidence and severity; severity was defined as mild (barely noticeable to the subject), moderate (causing discomfort), and severe (causing severe discomfort and significantly impairing or preventing daily activities). Serious adverse events were defined as untoward medical occurrences resulting in death, inpatient hospitalization, or persistent or significant disability or incapacity or were life-threatening.

RESULTS

A total of 1347 patients were enrolled at 40 sites within the United States, including 417 (31%) patients with Kellgren–Lawrence grade 4 osteoarthritis of the knee who were enrolled in aggregate in 3 single intra-articular injection trials. Of these patients, 223 received saline and 194 received LMWF-5A. Baseline data are presented in Table 1. No differences were noted between treatment groups for demographics, WOMAC scores, or patient global assessment scores.

Pain

Patients who were treated with LMWF-5A had significantly greater improvement in WOMAC pain score from baseline to week 12 compared with patients receiving saline (-0.813 vs -0.625; P=.016; Table 2). This equated to a 33.2% reduction in pain with LMWF-5A compared with a 24.7% reduction in pain with saline. A significant reduction in pain with movement (P=.012) and pain at rest (P=.031) from baseline to week 12 was noted for patients treated with LMWF-5A compared with those receiving saline (Table 2).

Function and Response to Treatment

A significant reduction in patient global assessment score (P=.001) was noted for LMWF-5A compared with saline, with borderline significant improvements in function (P=.060; Table 2). The proportion of OMERACT-OARSI responders was significantly greater for patients
A greater duration of response was seen with LMWF-5A compared with saline. The percentage of patients categorized as responders was 62.2% with LMWF-5A vs 47.8% with saline ($P=0.004$) for at least 4 of 6 time points after baseline; 51.3% with LMWF-5A vs 39.6% with saline ($P=0.02$) for 5 of 6 time points after baseline; and 34.2% with LMWF-5A vs 26.1% with saline ($P=0.09$) for all 6 time points after baseline.

**Safety**

No clinically relevant differences were noted for the incidence of treatment-emergent adverse events or serious adverse events between patients receiving LMWF-5A and those receiving saline (Table 3). Treatment-emergent adverse events were reported for 71 (36.6%) of patients treated with LMWF-5A and 82 (36.8%) of patients treated with saline. The most common treatment-emergent adverse event was arthralgia, reported among 18 (9.3%) patients treated with LMWF-5A and 16 (7.2%) patients treated with saline. No other treatment-emergent adverse events occurred among at least 5% of patients. Most adverse events were of minor or moderate severity and were unrelated to treatment. All 3 serious adverse events reported were unrelated to the study drug. Of these, 2 (1%) occurred among patients treated with LMWF-5A. These included 1 patient with intussusception of the intestine (unrelated, resolved) and 1 patient with pneumonia (unrelated, resolved). In addition, 1 (0.4%) patient in the saline group had septic arthritis (unrelated, resolved). No deaths occurred.

**Discussion**

The multifactorial nature of the pain of osteoarthritis may make pain control more difficult, particularly in patients with severe osteoarthritis. Patients with Kellgren–Lawrence grade 4 osteoarthritis are commonly excluded from clinical trials evaluating treatments for osteoarthritis. The current 417 patients with severe osteoarthritis are believed to constitute the largest study of treatment for Kellgren–Lawrence grade 4 published. This pooled analysis showed that a single injection of LMWF-5A was

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### Table 1

Demographics and Baseline Characteristics for the Pooled Population With Kellgren–Lawrence Grade 4 Osteoarthritis of the Knee

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LMWF-5A (n=194)</th>
<th>Saline (n=223)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (No.)</td>
<td>58.3% (113)</td>
<td>51.6% (113)</td>
<td>.17</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>63.6 (8.6)</td>
<td>63.1 (8.6)</td>
<td>.54</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>35.3 (8.1)</td>
<td>34.5 (8.1)</td>
<td>.39</td>
</tr>
<tr>
<td>Patient global assessment, mean (SD)</td>
<td>3.6 (0.9)</td>
<td>3.6 (0.8)</td>
<td>.83</td>
</tr>
<tr>
<td>Western Ontario and McMaster Universities Osteoarthritis Index, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain subscore</td>
<td>2.4 (0.5)</td>
<td>2.3 (0.6)</td>
<td>.52</td>
</tr>
<tr>
<td>Stiffness subscore</td>
<td>2.5 (0.6)</td>
<td>2.5 (0.7)</td>
<td>.38</td>
</tr>
<tr>
<td>Function subscore</td>
<td>2.4 (0.6)</td>
<td>2.4 (0.6)</td>
<td>.26</td>
</tr>
</tbody>
</table>

*Abbreviation: LMWF-5A, low-molecular-weight fraction of 5% human serum albumin.*

### Table 2

Summary of Efficacy: Least Squares Mean Change From Baseline to Week 12 for Primary and Secondary End Points for the Pooled Population With Kellgren–Lawrence Grade 4 Osteoarthritis of the Knee

<table>
<thead>
<tr>
<th>End Point</th>
<th>LMWF-5A (n=194)</th>
<th>Saline (n=223)</th>
<th>$P$</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC pain (primary end point)</td>
<td>-0.813</td>
<td>-0.625</td>
<td>.016$^b$</td>
<td>-0.19  (-0.34 to -0.04)</td>
</tr>
<tr>
<td>WOMAC pain with movement</td>
<td>-0.808</td>
<td>-0.597</td>
<td>.012$^b$</td>
<td>-0.21  (-0.38 to -0.05)</td>
</tr>
<tr>
<td>WOMAC pain at rest</td>
<td>-0.815</td>
<td>-0.641</td>
<td>.031$^b$</td>
<td>-0.17  (-0.33 to -0.02)</td>
</tr>
<tr>
<td>WOMAC stiffness</td>
<td>-0.778</td>
<td>-0.678</td>
<td>.265</td>
<td>-0.10  (-0.28 to 0.08)</td>
</tr>
<tr>
<td>WOMAC function</td>
<td>-0.811</td>
<td>-0.660</td>
<td>.060</td>
<td>-0.15  (-0.31 to 0.01)</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>-0.949</td>
<td>-0.646</td>
<td>.001$^b$</td>
<td>-0.30  (-0.49 to -0.12)</td>
</tr>
</tbody>
</table>

*Abbreviations: CI, confidence interval; LMWF-5A, low-molecular-weight fraction of 5% human serum albumin; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

$^a$WOMAC and patient global assessment were analyzed with analysis of covariance, adjusted for baseline score.

$^b$Statistically significant.
safe and well tolerated across all trials, and these findings suggest important improvements in pain compared with saline. There is no uniformly accepted threshold to determine whether reductions in pain of this magnitude are clinically important. Provisional benchmarks advocated by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials are 10% to 20% for minimally important improvement and 30% or greater for moderately important response to treatment with chronic pain. With a 33% reduction in pain, the current study showed that treatment with LMWF-5A exceeded this threshold, whereas treatment with saline did not.

Patients treated with LMWF-5A also were significantly more likely to respond to treatment and to show a longer duration of response. Patient-level response to treatment, as defined by the OMERACT-OARSI criteria, addresses clinically important improvements, not just statistically significant improvements in outcomes. Although the component measures are often reported, few studies report OMERACT-OARSI responder rates. Several other trials evaluating OMERACT-OARSI responder status in patients with osteoarthritis report rates of 50% to 70% for active treatment; in the current study, the OMERACT-OARSI responder rate was 64% for patients with Kellgren–Lawrence grade 4 osteoarthritis who were treated with LMWF-5A. This response rate may be notable, as patients with a higher Kellgren–Lawrence grade have shown lower OARSI response to treatment and lower change in WOMAC pain scores than patients with a lower Kellgren–Lawrence grade. In addition, LMWF-5A was safe and well tolerated across all trials.

Because patients with severe disease usually are excluded from efficacy trials, no drugs have been approved by the US Food and Drug Administration for pain associated with severe (Kellgren–Lawrence grade 4) osteoarthritis of the knee. Practice guidelines recommend the use of nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, or acetaminophen for control of pain for patients with osteoarthritis. However, all of these have questionable efficacy for severe osteoarthritis. To relieve pain associated with mild to moderate osteoarthritis, intra-articular knee injections have been

![Figure: Responder rates defined according to the Outcome Measures in Rheumatology (OMERACT)-Osteoarthritis Research Society International (OARSI) criteria for scenario D were analyzed with the Pearson chi-square test. Responder rates are presented by treatment arm for a pooled population with Kellgren–Lawrence grade 4 osteoarthritis of the knee. Abbreviation: LMWF-5A, low-molecular-weight fraction of 5% human serum albumin.](image)

![Table 3: Summary of Adverse Events for the Pooled Population With Kellgren–Lawrence Grade 4 Osteoarthritis of the Knee](table)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>LMWF-5A (n=194)</th>
<th>Saline (n=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 adverse event</td>
<td>71 (36.6)</td>
<td>82 (36.8)</td>
</tr>
<tr>
<td>At least 1 related adverse event</td>
<td>2 (1.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Adverse event by severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>48 (24.7)</td>
<td>50 (22.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>28 (14.4)</td>
<td>41 (18.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>6 (3.1)</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>2 (1.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Adverse event leading to withdrawal</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Adverse event leading to death</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Abbreviation: LMWF-5A, low-molecular-weight fraction of 5% human serum albumin.
used, particularly hyaluronate preparations, which appear to have modest (if any) effect only for patients with the least severe disease (Kellgren–Lawrence grade 2 or 3). Opioids are often used to manage the pain of osteoarthritis for patients who have not responded to other pharmacologic interventions; however, opioid use for the treatment of chronic musculoskeletal pain and opioid abuse are significant public health issues because of the US opioid epidemic. Many patients who have pain associated with osteoarthritis believe that they need to live with their pain until they can undergo total knee replacement surgery. Unfortunately, 25% to 30% of patients have persistent postoperative pain, even after total knee replacement surgery. The current authors believe that LMWF-5A is a new treatment option for patients who have severe osteoarthritis of the knee. This treatment showed significant reductions in pain and improvements in response to treatment compared with saline in patients with Kellgren–Lawrence grade 4 osteoarthritis, a group with few treatment options. Several defined molecular components in LMWF-5A, including diketopiperazine and molecule stabilizers (N-acetylated glycosaminoglycans and sodium caprylate), have known biologic activities in vitro and/or in vivo that may contribute to the effectiveness of LMWF-5A. The in vitro pharmacologic activity of LMWF-5A includes anti-inflammatory effects through reduction of proinflammatory cytokine release (tumor necrosis factor-α and interferon-γ), vascular permeability in human retinal endothelial cells, mobilization and differentiation of mesenchymal stem cells derived from bone marrow to tissue-specific cells, protection of cells from apoptosis and autophagy, and upregulation of both cyclooxygenase-2 messenger ribonucleic acid and cyclooxygenase-2 protein in human synovial fibroblasts, human normal and osteoarthritic chondrocytes, and peripheral blood monocytes, including the production of the anti-inflammatory prostaglandin D2 and its metabolite 15d-prostaglandin J2. These mechanisms occur to a greater degree among patients with severe osteoarthritis and account for the observed benefit in this population of patients with Kellgren–Lawrence grade 4 osteoarthritis. The anti-inflammatory activity of LMWF-5A on macrophages also suggests greater relief of symptoms for patients with greater macrophage-mediated inflammation. Other authors have shown that the quantity of knee-related activated macrophages is associated with more severe knee pain and greater radiographic severity of osteoarthritis of the knee.

**Limitations**

This study had several limitations. First, the study was a post hoc analysis of a subgroup of patients who were enrolled across 3 randomized controlled trials. In some circumstances, this type of statistical analysis of efficacy is appropriate and sufficient, as outlined by the International Conference on Harmonisation statistical principles for clinical trials (ICH E9), such as evaluating whether overall positive results also are seen in specified subgroups of patients and evaluating an additional efficacy outcome that requires more power than individual trials provide. Second, historically, saline has been used as a placebo for comparison in superiority trials for osteoarthritis of the knee; however, because intra-articular saline has significant analgesic effects, it should be considered a questionable comparator in superiority trials for osteoarthritis of the knee. Third, outcome measures were limited to patient-reported questions. No imaging or biomarker data were collected and evaluated as part of the single-injection studies. Finally, the primary end point was 12 weeks postinjection. Additional studies with longer observation periods are needed to determine the maximum treatment effect. The maximum treatment effect is 8 weeks for intra-articular hyaluronan products and 2 to 3 weeks for intra-articular corticosteroids. **CONCLUSION**

When administered as a single intraarticular injection into the knee, LMWF-5A appears to safely and effectively reduce pain among patients with severe osteoarthritis of the knee, as shown through the pooled analysis of data from 417 patients with Kellgren–Lawrence grade 4 osteoarthritis of the knee from 3 randomized controlled trials. These data suggest that LMWF-5A can satisfy an unmet medical need for a population with few therapeutic treatment options and debilitating symptomatic disease.

**REFERENCES**


