Preliminary Trial of Intra-articular LMWF-5A for Osteoarthritis of the Knee

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abstract

This study was conducted to investigate the safety and efficacy of 3 intra-articular injections of the low–molecular-weight fraction of 5% human serum albumin (LMWF-5A) administered every 2 weeks for knee pain as a result of osteoarthritis. This single-center, randomized, vehicle-controlled, double-blind, phase II study was designed to ensure the safety of multiple intra-articular injections of LMWF-5A and to explore its efficacy in reducing pain as a result of knee osteoarthritis. Patients were randomized 1:1 to receive 3 biweekly intra-articular knee injections of either 4 mL LMWF-5A or vehicle control (saline), administered at weeks 0 (baseline), 2, and 4. Safety was examined as the incidence and severity of adverse events. Efficacy was assessed by the mean (SD) change between treatment groups in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score from baseline to week 20. A total of 40 patients were randomized and received treatment. No drug-related serious adverse events and no deaths were reported. Adverse events were similar in patients who received saline (18, 90%) and LMWF-5A (19, 95%). Those treated with LMWF-5A had a significant decrease in pain at 20 weeks compared with the saline group (-1.41 [SD, 0.81] vs -0.85 [SD, 0.64], *P*=.02), corresponding to improvement in pain at week 20 of 64% with LMWF-5A compared with 40% with saline. This preliminary clinical trial showed that repeated intra-articular injections of LMWF-5A are safe when administered at 2-week intervals and are effective in providing relief of the pain of osteoarthritis of the knee at 20 weeks. [*Orthopedics*. 201x; xx(x):exx-exx.]

Osteoarthritis, the most common form of arthritis, affects approximately 25 to 35 million Americans.[1] Pharmacologic treatment for pain as a result of osteoarthritis of the knee includes analgesics, nonsteroidal anti-inflammatory drugs, intra-articular corticosteroids, and intra-articular hyaluronan products. Despite these medical treatments, chronic osteoarthritis of the knee often causes progressive disability and joint deterioration that requires total joint replacement.[2] The increasing prevalence of osteoarthritis of the knee as a result of aging and obesity suggests a growing clinical need for safe and effective local knee treatments.[3]

The low–molecular-weight fraction of 5% human serum albumin (LMWF-5A) is in development to provide relief of pain caused by osteoarthritis of the knee. This agent is produced from the low–molecular-weight fraction (<5000

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Da) of pharmaceutical human serum albumin, which has a long history of clinical use as colloid replacement therapy. Commercial human serum albumin contains the anti-inflammatory and immunemodulating compound aspartyl-alanyl diketopiperazine, which is formed after the dipeptide aspartate-alanine is cleaved from the N-terminus of albumin and cyclizes into a diketopiperazine.[4-7]

A pivotal phase III randomized controlled trial showed that a single intra-articular injection of LMWF-5A was effective in reducing pain in adults with osteoarthritis of the knee and was safe and well tolerated.[8] This study investigated the safety and efficacy of 3 biweekly intra-articular injections of LMWF-5A in osteoarthritis of the knee.

Materials and Methods

A preliminary randomized, vehicle-controlled, double-blind study was designed to evaluate the safety and exploratory efficacy of LMWF-5A vs saline vehicle control. These agents were administered as 3 intra-articular injections of 4 mL each delivered every 2 weeks (at baseline day 0 and weeks 2 and 4) in patients who had symptomatic knee osteoarthritis for at least 6 months before screening. The study, which was conducted at the Denver Metro Orthopedics clinic, consisted of a 28-day screening period and a 52-week participation period that included 8 in-clinic visits and 3 telephone interviews conducted 24 hours postinjection.

The study was performed in accordance with the principles consistent with the International Conference on Harmonisation Guidelines on Good Clinical Practice. The study received approval from the Liberty institutional review board, and written informed consent was obtained. Registration on ClinicalTrials.gov was initiated on July 2, 2014, and preceded patient recruitment (Identifier: NCT02184156). Patients were recruited between August 1, 2014, and October 19, 2014, and follow-up was conducted through October 12, 2015.

Patient Selection

Study subjects were recruited from the population seen by the investigator at the clinical site (J.S.). Eligible patients were 40 to 85 years old and fully ambulatory, with symptomatic index osteoarthritis of the knee for at least 6 months and a clinical diagnosis of osteoarthritis supported by radiologic evidence acquired at screening (Kellgren-Lawrence grades II-IV). Patients were required to have moderate to severe osteoarthritis pain in the index knee (baseline pain rating ≥1.5 on the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC], version 3.1, 5-point Likert pain subscale) after abstaining from analgesia for at least 24 hours.[9] Patients with Kellgren-Lawrence grade II osteoarthritis were limited to 25% of the total enrollment.

Exclusion criteria included previous injection with LMWF-5A; a history of allergic reactions to albumin and its excipients; treatment with human albumin 3 months before randomization; known clinically significant liver abnormality; concurrent arthritic conditions or other conditions interfering with free use and evaluation of the index knee for the duration of the trial; severe hip osteoarthritis ipsilateral to the index knee; treatment of osteoarthritis started or changed during the 4 weeks before randomization; and use of the following medications during the study: intra-articular injection of pain medication or topical treatment in the index knee, analgesics containing opioids, significant anticoagulant therapy, immunosuppressants, systemic treatment, or treatment with corticosteroids of greater than 10 mg prednisolone equivalent per day.

Study Treatments

The building block of LMWF-5A, 5% human serum albumin, obtained from Octapharma USA (Hoboken, New Jersey), is regulated and licensed by the US Food and Drug Administration; the fraction of less than 5 kDa is produced through ultrafiltration followed by aseptic filling. The ultrafiltrate contains aspartyl-alanyl diketopiperazine (approximately 50-200 μM) and excipients (ie, sodium caprylate and sodium acetyltryptophanate). The control arm in this study received treatment with saline vehicle control.

Randomization and Blinding

Patients were randomized 1:1 to receive 3 injections of either 4 mL LMWF-5A or 4 mL saline at weeks 0, 2, and 4. Subjects were randomized sequentially, starting at the lowest number. Randomization was developed and maintained by an independent statistician.

Treatments were provided in study vials with double-panel labels that were blinded for drug content and packed into subject kits (3 vials/kit). Subject kits also contained 3 syringes (5 mL) and 3 needles (20 gauge, 1.5 in long) for each 4-mL injection. The sponsor, the investigator, and all study staff who had a role in the day-to-day conduct of the study were blinded to treatment.

Assessments and End Points

Measures of safety and efficacy were obtained during clinic visits at baseline (day 0) and at weeks 2, 4, 6, 12, 20, 24, and 52. Safety measures included physical examination, vital signs, and clinical laboratory testing (hematology and chemistry). Adverse events were evaluated and recorded from the time that the subject received the study drug through the final visit. Measures of efficacy consisted of the WOMAC, version 3.1, 5-point Likert score.

The primary end point was the change in average WOMAC pain subscore between baseline and week 20. Secondary end points included the incidence and severity of adverse events through week 52, the change in the WOMAC pain subscore between baseline and week 12, and the change in WOMAC stiffness and physical function subscores between baseline and week 20.

Statistical Analysis

This preliminary study evaluated the safety and efficacy of 3 intra-articular

injections of LMWF-5A to design a larger multicenter study of repeat injections of LMWF-5A. The sample size used in the study was not based on formal power calculations, but was chosen for clinical and administrative reasons. Screening of a sufficient number of patients was performed to enroll 40 eligible patients.

Statistical analysis was performed by a biomedical statistician with SAS version 9.3 or later software (SAS Institute, Cary, North Carolina). All analyses were defined a priori and performed in accordance with the study protocol and the plan for statistical analysis. Patients were analyzed as randomized (intent to treat). No adjustment was made for multiple comparison testing, and the change from baseline to week 20 was considered the primary end point. Statistical significance was set at $P<.05$ for all analyses.

Adverse events were examined in all patients who were randomized, and no safety data were imputed. For missing or incomplete data on adverse events, the greatest relationship to the study drug or severity was assumed. Treatment-emergent adverse events were tabulated and analyzed for incidence and severity.

For primary analysis of effectiveness at week 20, imputation with the last observation carried forward was used to assign a value to cases with missing data. Change in any WOMAC subscore (pain, stiffness, physical function) was summarized as mean change (95% confidence interval) from baseline and analyzed for differences between treatment arms with 2-sample Student's *t* test. Responders were considered to have a change in the WOMAC pain subscore of 1 or more points at week 20. Response rates were analyzed for differences between treatment groups with Pearson's chi-square tests.

Table

Baseline Characteristics and Summary of Safety and Efficacy End Points

Baseline Characteristics and Study End Points	LMWF-5A (n=20)	Saline (n=20)	*P*
Baseline characteristics			
Female, No.	12 (60%)	13 (65%)	1.00
White, No.	17 (85%)	20 (100%)	.23
Hispanic, No.	2 (10%)	1 (95%)	1.00
Age, mean (SD), y	63.65 (10.33)	61.35 (9.40)	.35
Body mass index, mean (SD), kg/m^2	30.80 (5.18)	28.70 (3.81)	.23
Kellgren-Lawrence grade II, No.	2 (10%)	0 (0%)	.58
Kellgren-Lawrence grade III, No.	11 (55%)	12 (60%)	
Kellgren-Lawrence grade IV, No.	7 (35%)	8 (40%)	
WOMAC pain subscore, mean (SD)	2.23 (0.47)	2.17 (0.44)	.66
WOMAC stiffness subscore, mean (SD)	2.25 (0.79)	2.33 (0.65)	.74
WOMAC function subscore, mean (SD)	2.17 (0.50)	2.30 (0.52)	.42
Safety end points, No.			
Any adverse event	19 (95%)	18 (90%)	
Mild adverse event	3 (15%)	6 (30%)	
Moderate adverse event	12 (60%)	10 (50%)	
Severe adverse event	4 (20%)	2 (10%)	
Any treatment-emergent adverse event	4 (20%)	1 (5%)	
Any serious adverse event	3 (0%)	0 (0%)	
Any related serious adverse event	0 (0%)	0 (0%)	
Efficacy end points, mean change from baseline (SD)			
Primary: WOMAC pain subscore, week 20	-1.41 (0.81)	-0.85 (0.64)	.02
Secondary: WOMAC pain subscore, week 12	-0.96 (0.72)	-0.84 (0.83)	.62
Secondary: WOMAC stiffness subscore, week 20	-1.11 (1.09)	-1.08 (1.07)	.94
Secondary: WOMAC function subscore, week 20	-1.27 (0.81)	-0.98 (0.69)	.25

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

RESULTS

A total of 55 patients were assessed for eligibility, and 40 patients were enrolled and received treatment with 4 mL LMWF-5A (n=20) or 4 mL saline (n=20). Baseline data are shown in the **Table**. No differences were found between treatment groups in demographic characteristics or WOMAC scores. Two subjects discontinued participation by week 20 because they received an alternative intra-articular injection in the study knee (1 in each study arm) (**Figure 1**).

Safety

An overview of all adverse events is shown in the **Table**. No clinically relevant differences in the incidence of adverse events, treatment-emergent adverse events, or serious adverse events were noted between subjects receiving LMWF-5A and subjects receiving saline.

Treatment-emergent adverse events were reported for 4 (20%) subjects treat-

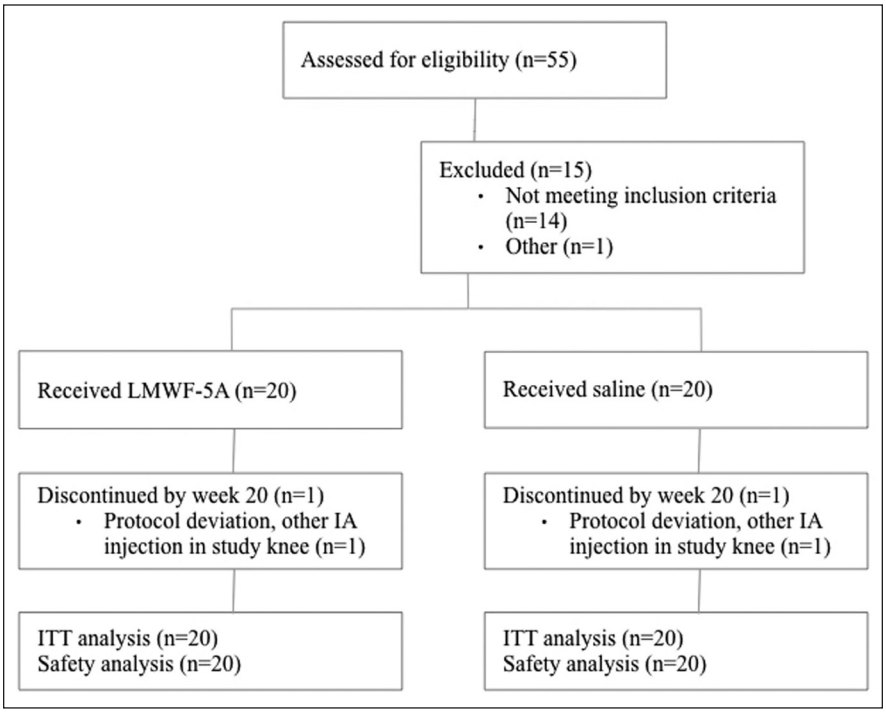
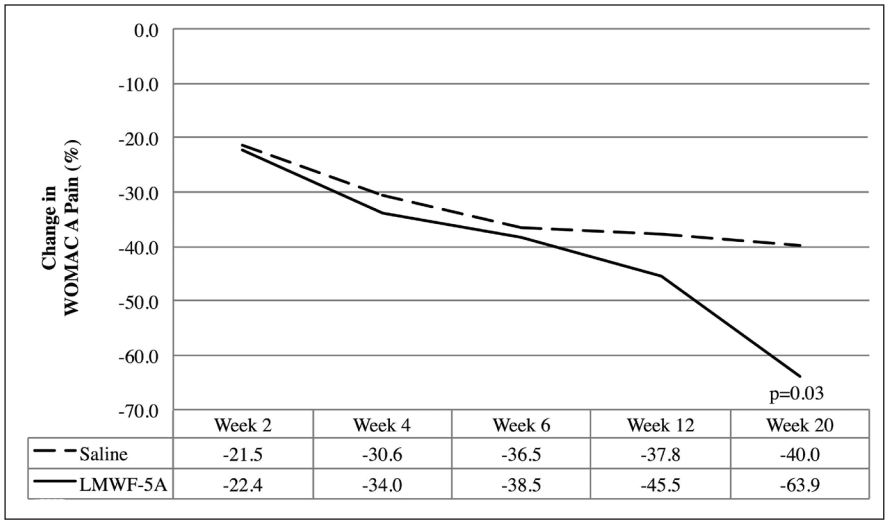


Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Abbreviations: IA, intra-articular; ITT, intent to treat; LMWF-5A, low–molecular-weight fraction of 5% human serum albumin.



	Week 2	Week 4	Week 6	Week 12	Week 20
Saline	-21.5	-30.6	-36.5	-37.8	-40.0
LMWF-5A	-22.4	-34.0	-38.5	-45.5	-63.9

Figure 2: Summary of percentage of improvement in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscore over time, through week 20 (primary end point). Abbreviation: LMWF-5A, low–molecular-weight fraction of 5% human serum albumin.

ed with LMWF-5A and 1 (5%) subject treated with saline. No specific treatment-emergent adverse event occurred in more than 1 subject per arm, and these events included nausea, pain at the injection site, arthralgia, and joint swelling in the LMWF-5A arm and arthralgia in the saline arm. No subject discontinued participation as a result of adverse events, and no deaths occurred.

Overall adverse events were reported in 19 of 20 patients treated with LMWF-5A and in 18 of 20 of those treated with saline. The most common adverse event by system organ class was musculoskeletal and connective tissue disorder, which occurred in 11 (55%) subjects in each treatment arm. Adverse events that occurred in 3 or more subjects in either treatment arm were joint swelling (n=5, LMWF-5A arm; n=3, saline arm), joint stiffness (n=3, LMWF-5A arm; n=3, saline arm), joint injury (n=4; LMWF-5A arm), injection site hematoma (n=3; LMWF-5A arm), and pain at the injection site (n=3, saline arm).

Efficacy

At the primary end point, subjects receiving LMWF-5A showed significantly greater improvement in the WOMAC pain subscore from baseline to week 20 compared with those receiving saline (-1.41 vs -0.85, respectively; *P*=.02) (**Table**). The corresponding percentage of reduction in pain in the LMWF-5A group vs the saline group across study weeks is shown in **Figure 2** (64% vs 40% at week 20, *P*=.03). At week 20, the response rate was significantly higher with LMWF-5A than with saline (79% vs 47%, *P*=.045). No significant differences were noted in secondary end points (**Table**).

Discussion

This preliminary randomized controlled trial showed that 3 biweekly (2-week interval) intra-articular injections of LMWF-5A were well tolerated and efficacious for the treatment of knee pain caused by osteoarthritis. This study supports the findings of the earlier pivotal randomized controlled trial that showed that a single intra-articular injection of LMWF-5A was safe and effective. At the study end point, 3 biweekly injections of LMWF-5A caused a significant decrease in the WOMAC pain subscore compared with saline (-1.41 vs -0.85, *P*=.02). A previous trial showed a similar result with a single injection (-0.93 vs -0.72, *P*=.004).[8] The authors believe that LMWF-5A is an

alternative intra-articular treatment that provides pain relief for patients with moderate to severe osteoarthritis of the knee.

Hyaluronic acid therapies are commonly used for patients who cannot be treated with analgesics, despite recommendations against their use by the American Academy of Orthopaedic Surgeons.[10] Treatment with repeated weekly intra-articular injections of hyaluronic acid into the knee joint for the treatment of pain as a result of osteoarthritis is common and well tolerated. Even with repeated injections, however, patients treated with intra-articular hyaluronic acid do not appear to achieve clinically important benefits in efficacy outcomes.[10-12]

Limitations

The primary limitation of this study is that it was conducted as a preliminary trial and included 40 patients enrolled at a single center. These findings must be confirmed in a larger, multicenter study to establish the efficacy of LMWF-5A in the treatment of knee pain when delivered as a repeat injection. Second, enrollment of patients with less severe osteoarthritis, defined radiologically as Kellgren-Lawrence grade II, was limited.[13] The pathologic findings on presentation differ with disease severity and may result in a different treatment effect at each severity grade. Finally, according to guidance by the US Food and Drug Administration, saline was used as the control arm in this study, yet saline repeatedly has been shown to have active analgesic effects as a standalone injection.[14,15]

Conclusion

This preliminary randomized controlled trial showed that 3 intra-articular injections of LMWF-5A given at 2-week intervals is safe and well tolerated and is effective in reducing pain caused by osteoarthritis at 20 weeks. These findings support previous findings that showed that a single intra-articular injection of LMWF-5A is safe and efficacious in the treatment of pain caused by osteoarthritis. These findings also support the design of a larger, multicenter, phase III randomized controlled clinical trial to establish the safety and efficacy of repeat injections of LMWF-5A in patients with pain as a result of osteoarthritis of the knee.

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