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# Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial

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SUMMARY

*Objective:* Evaluate the efficacy and safety/tolerability of cryoneurolysis for reduction of pain and symptoms associated with knee osteoarthritis (OA).
*Design:* Randomized, double-blind, sham-controlled, multicenter trial with a 6-month follow-up in patients with mild-to-moderate knee OA. Patients were randomized 2:1 to cryoneurolysis targeting the infrapatellar branch of the saphenous nerve (IPBSN) or sham treatment. The primary endpoint was the change from baseline to Day 30 in the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score adjusted by the baseline score and site. Secondary endpoints, including visual analogue scale (VAS) pain score and total WOMAC score, were tested in a pre-defined order.
*Results:* The intent-to-treat (ITT) population consisted of 180 patients ($n = 121$ active treatment, $n = 59$ sham treatment). Compared to the sham group, patients who received active treatment had a statistically significant greater change from baseline in the WOMAC pain subscale score at Day 30 ($P = 0.0004$), Day 60 ($P = 0.0176$), and Day 90 ($P = 0.0061$). Patients deemed WOMAC pain responders at Day 120 continued to experience a statistically significant treatment effect at Day 150. Most expected side effects were mild in severity and resolved within 30 days. The incidence of device- or procedure-related adverse events was similar in the two treatment groups with no occurrence of serious or unanticipated adverse device effects (ADE).
*Conclusions:* Cryoneurolysis of the IPBSN resulted in statistically significant decreased knee pain and improved symptoms compared to sham treatment for up to 150 days, and appeared safe and well tolerated.


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## Introduction

Knee osteoarthritis (OA) patients spend 50% of post-diagnosis time (~26 years) receiving conservative, nonsurgical treatments, as total knee arthroplasty (TKA) is typically reserved for patients with end-stage disease due to the limited lifespan of implants and associated risks and high cost of surgery[1]. The most common nonsurgical knee OA interventions, which include physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), bracing, opioids, intra-articular (IA) corticosteroid injections, and viscosupplementation, can alleviate OA knee pain; however, most do not provide satisfactory long-term relief and many are associated with side effects.[1]

Based on the limited efficacy and potential risks associated with current chronic pain treatments, a variety of organizations have recommended multimodal individualized treatment plans that incorporate non-pharmacological therapies and promote the use of non-opioid pharmacological therapies[2–5]. This shift towards emphasizing the use of low-risk minimally invasive therapies to treat chronic pain coincides with advances in the field of cryoneurolysis that have made it possible to target superficial sensory nerves without damaging the dermis to create immediate, localized, and long-lasting nerve blockade[6]. Cryoneurolysis, a nonsurgical minimally-invasive therapy with a well-established mechanism of action[7], may be an excellent addition to a multimodal regimen for the treatment of pain and symptoms of knee OA.

Percutaneous application of low temperatures (−20°C to −100°C) to peripheral nerves causes Wallerian degeneration, in which the nerve structure and conduction are disrupted while the structural elements of the nerve bundle remain intact, allowing for complete regeneration and functional recovery of the nerve[8–10]. The nerve axon is able to regenerate along the previously established path to eventually reinnervate the sensory receptor[11]. There is a growing literature showing that cryoneurolysis of sensory peripheral nerves can provide pain relief for a variety of chronic pain conditions[12–19,7,20], but most of these studies were not randomized controlled trials (RCTs).

The infrapatellar branch of the saphenous nerve (IPBSN), a sensory nerve that innervates the anterior and inferior part of the knee capsule as well as the skin over the antero-medial knee[21], is a prime target for nerve blockade to reduce knee pain. Several studies (including two RCTs) have examined the efficacy of a selective nerve block of the IPBSN for treatment of post-operative knee pain[22–25]. Trescot was the first to propose targeting the IPBSN with cryoneurolysis to treat knee pain[7] and Dasa conducted the first clinical study evaluating cryoneurolysis of the IPBSN prior to TKA as part of a multimodal pain plan to improve postoperative pain relief[23]. The present study is the first clinical trial to examine whether cryoneurolysis of the IPBSN can reduce pain in patients with knee OA.

## Methods

This was a multicenter, randomized, double-blind, sham-controlled trial with up to 6 months of follow-up to evaluate the efficacy and safety/tolerability of cryoneurolysis in patients with pain associated with knee OA (Trial Registry NCT02260921). The study was conducted at 17 sites in the U.S. from April 2013 to June 2016. A central institutional review board (IRB) approved the study, sites were approved by their local IRBs and written informed consent from participating patients was obtained. The study was conducted in accordance with all applicable laws and regulations as specified in the International Conference on Harmonization Guideline for Good Clinical Practice, the Code of Federal Regulations, and the Declaration of Helsinki.

### *Patients*

Patients were aged 33–75 years who met American College of Rheumatology (ACR) combined clinical and radiographic criteria for knee OA[26]. Major inclusion criteria were ambulatory without an assistive device; Grade II or III radiographic changes according to the Kellgren–Lawrence classification system; knee pain ≥40 mm on a 100 mm visual analogue scale (VAS) when performing one of two movements (standing from a seated position or walking up/down stairs) that elicited the worst pain; and ≥50% reduction in VAS pain when performing the activity that elicited the worst pain following a diagnostic lidocaine block of the IPBSN. Major exclusion criteria were gross deformity of the knee, including varus or valgus (<15°) and body mass index (BMI) ≥35 kg/m$^2$. Complete inclusion and exclusion criteria are shown in Table S1.

### *Study duration*

All patients were followed to Day 120 post treatment. Patients who demonstrated a durable benefit from treatment, as defined by a Day 120 Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain subscale score less than their respective baseline scores, were followed to Day 150, and those with a durable response at Day 150 were followed to Day 180.

### *Treatment*

Eligible patients were randomized 2:1 to either cryoneurolysis or sham treatment. Randomization was stratified by study site with randomly chosen block sizes of six or nine to preserve treatment assignment balance within sites while maintaining assignment unpredictability. The randomization sequence was generated by a computer algorithm developed by an independent statistician, who wrote the serial number of the cryoneurolysis device tip to be used for each patient on a piece of paper placed in a sealed envelope; sealed envelopes were provided to the site coordinators who were responsible for enrolling patients and assigning them to interventions. The treating investigators, site staff, and patients were blinded to the patient's group assignment until the final data were locked and sent to the independent statistician for analysis.

Cryoneurolysis was administered using the iovera° device (Myoscience, Inc., Fremont, CA, USA) with a functioning Smart Tip. The iovera° device employs the well-established principle that localized exposure to controlled, moderately low temperature conditions can alter nerve function[27,11,10]. Cryogen (nitrous oxide) flows from the disposable cartridge through the handpiece to the Smart Tip, an assembly of three 27-gauge closed-end needles. As the nitrous oxide enters the needles a highly localized cold zone is formed via the Joule-Thompson effect. Nothing is injected in the body and the nitrous oxide gas is vented safely out of the handpiece.

Sham treatment consisted of cryoneurolysis using the iovera° device with a sham Smart Tip, which was identical in appearance to the tip used for active treatment but did not allow a freezing zone to form and had no therapeutic effect. All patients had lidocaine administered subcutaneously and cutaneously prior to treatment to further blind patients to their group assignment. During treatment, sham Smart Tips displayed the same lights and activation features as an active Smart Tip to ensure blinding of the investigator to the patient's group assignment.

Cryoneurolysis or sham treatment was administered to conscious patients following local anesthesia. The treatment target was the IPBSN [Fig. 1(A)]. Investigators and study staff received training on the treatment procedure. Treatment was performed unilaterally along a treatment line, the location of which was

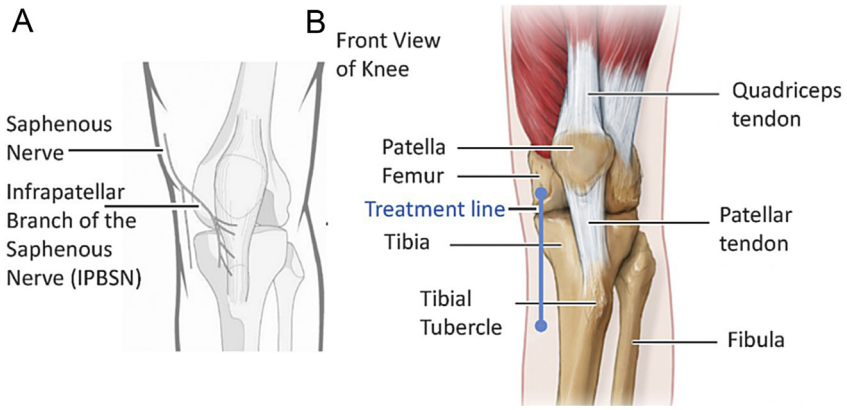


**Fig. 1.** Iovera device (A) infrapatellar branch of the saphenous nerve (B) and treatment line in relation to anatomical landmarks (C).

guided by visualization and palpation of anatomical landmarks [Fig. 1(B)]. Adjacent insertions were placed along the treatment line until the entire line was treated.

*Prior and concomitant medications and therapies*

Patients discontinued all prescription and over-the-counter (OTC) pain medications, herbal supplements, and all other treatments for knee OA for a duration of 5× the half-life of the medication, and discontinued adjunctive therapies for knee pain for 72 h, prior to the screening/baseline visit.

During follow-up, patients were prohibited from undergoing any adjunctive treatment for knee OA, including steroid injections, viscosupplementation, and TKA, and from taking prescription and OTC pain medications other than acetaminophen for rescue medication (maximum of 4 g/day). Use of acetaminophen was monitored by dispensing bottles of medication prior to treatment and counting pills at follow-up visits. Use of prohibited medications/treatments was recorded as a protocol deviation and patients were permitted to continue in the study until Day 120.

Patients were instructed to wash out of pain medications (both prohibited and acetaminophen rescue) for a duration of 5× the half-life of the medication prior to follow-up assessments. For acetaminophen, the washout period was 24 h.

*Measures*

The study included a screening visit to determine eligibility, baseline visit, treatment visit, and up to eight follow-up visits (Day 1, Day 7, Day 30, Day 60, Day 90, and Day 120; Days 150 and 180 were included if there was a continued effect reported at the previous visit as determined by WOMAC pain subscale score).

Several patient-reported outcome measures were collected at baseline and each follow-up visit. The WOMAC is a 24-item disease-specific patient-reported outcome measure with five questions assessing pain (range 0–50), two assessing stiffness (range 0–20), and 17 assessing function (range 0–170)[28]. Patients were assessed on a 100 mm VAS for pain (0 = no pain, 100 = pain as bad as it could possibly be) during one of two activities (standing from a seated position or walking up/down stairs) that elicited the most pain. The 36-item Short Form Health Survey (SF-36) is a generic quality of life instrument with eight health domains. The Patient Global Impression of Change (PGIC) asks patients to assess the extent to which they feel improved following treatment on a 7-point scale (1 = very much improved, 7 = very much worse). PGIC responders were patients who indicated that they were either “very much improved” or “much improved” at each follow-up assessment.

Adverse events (AEs) were mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities. Adverse device effects (ADE) were AEs that the investigator considered related to study treatment, device, or procedure. Expected side effects and complications (e.g., bruising, swelling, inflammation and/or erythema) involving percutaneous access to subcutaneous tissue using a needle and use of dermal anesthesia were assessed at each follow-up visit and documented independently of AEs, except for loss of motor function outside the treatment area. Expected side effects or complications that occurred outside a 3-cm radius elliptical region around the linear grouping of needle insertions, or that persisted ≥30 days, were classified as AEs.

*Statistical analyses*

Statistical analyses were performed using SAS® Version 9.2 (SAS Institute, Cary, NC, USA). The intent-to-treat (ITT) population included all patients who were randomized and underwent the assigned treatment. For the primary and secondary endpoints, missing data were replaced by baseline values.

The primary endpoint was the least squares (LS) mean change from baseline (average of the mean changes from baseline) to Day 30 in WOMAC pain subscale score. To control the family wise type 1 error, secondary endpoints were tested in a pre-defined order (see Supplementary Appendix) if the null hypothesis of the primary endpoint was rejected. WOMAC pain responders, WOMAC total responders, and VAS responders were defined as patients who experienced a ≥30% reduction from baseline on each respective outcome.

Analysis of covariance (ANCOVA) for primary and secondary endpoints evaluating change from baseline included the study site and baseline score as covariates. The Fisher's exact test compared responder rates between the active treatment and sham groups. Sensitivity analyses were conducted which included the VAS activity type as a second covariate for analysis of change from VAS baseline scores; for responder analyses, the Cochran-Mantel-Haenszel test was performed stratified by activity type.

The study was powered to demonstrate a statistically significant difference (one-sided, $\alpha = 0.025$) between the treatment and sham groups on the primary efficacy endpoint. A one-sided test of statistical significance is justified because the only outcome of interest is whether the active treatment is better than the sham treatment, and is not worth distinguishing between the case in which the active treatment is worse than sham treatment and the case in which it is the same because the active treatment would be determined to be inefficacious in both cases. The final sample size was determined by an adaptive design that allowed for interim looks at the data to

enable an early stop for success or futility based upon the primary efficacy endpoint. After 80 patients were enrolled, and every 20 subjects thereafter, interim analyses were conducted and a Bayesian stopping rule resulted in one of three decisions: (1) stop for success, (2) stop for futility, or (3) proceed to next interim (see Supplementary Appendix for details). The adaptive sample size design provides comparable power to a fixed design and has a maximum type 1 error of 2.5%. The maximum sample size of 180 patients (2:1 randomization) was determined based on results of an unpublished clinical trial (http://www.clinicaltrials.gov; NCT01704157; Myoscience, data on file).With 180 enrolled patients, under the best-case scenario (mean change from baseline to Day 30 for the active treatment group relative to the sham group of 10), the adaptive design has a power of 0.995. The adaptive design has a power 0.765 to detect a modest effect (mean change from baseline to Day 30 for the active treatment group relative to sham of six).

## Results

### *Patients*

A total of 180 patients were enrolled and constituted the ITT population (active treatment $n = 121$, sham treatment $n = 59$) (Fig. 2). All randomized patients received their assigned treatment. As shown in Table I, there were no statistically significant differences between treatment groups with respect to these demographic and clinical characteristics. Of the 180 enrolled patients, 141 (93/121 in the active treatment group and 48/59 in the sham treatment group) continued to experience a benefit from treatment at Day 120, and 127 (87/121 in the active treatment group and 40/59 in the sham treat group) continued to experience a benefit from treatment at Day 150.

### *Use of concomitant medications/therapies*

Use of prohibited medications was documented 85 times during the treatment phase of the study. Of these 85 events, 52 (61%) were taken for other than knee pain; these events were reported by 48 patients (32 active, 16 sham) for an indication other than target knee pain. The remaining 33 events in 15 patients (10 active, five sham) were for pain in the target knee.

Acetaminophen was used as rescue medication by 68% (82/121) of active treatment patients and 80% (47/59) of the sham treatment patients during the study ($P = 0.114$). The difference in mean cumulative number of acetaminophen pills used during the study was not statistically significant between groups (active: 48 ± 77, sham: 61 ± 100, $P = 0.382$).

### *Treatment*

The mean standard deviation (SD) exposure per treatment was 23 (8) minutes. Seven device malfunctions were reported. Four of the malfunctions occurred during the preparation or prime cycle; the device was put into standby, placed into the dock, and then successfully prepared for treatment. Three malfunctions occurred during the exchange of cartridges and were resolved without any delay in treatment. All procedures were completed and none were terminated early due to device malfunction.

### *Allocation concealment*

In response to the question, "Which treatment do you think you received?" most patients in both the active and sham groups thought they had received the active treatment early during follow-up (Day 1: 80.8% vs 75.9%, $P = 0.439$; Day 7: 74.6% vs 63.2%, $P = 0.155$). Over time, some patients became aware of their group assignment based on their response to treatment, such that there was a non-significant trend for a greater proportion of patients in the active treatment group who believed they had received the active treatment on Day 30 (69.5% vs 53.4%, $P = 0.045$) and Day 60 (71.4% vs 53.4%, $P = 0.027$). For all remaining visits, there were no statistically significant differences between treatment groups.

### *WOMAC pain subscale score*

The active treatment group had a statistically significant greater change from baseline to Day 30 (primary endpoint), Day 60, and Day 90 than the sham treatment group (Table II). The LS mean difference between groups in WOMAC pain subscale score at Day 30 was −7.12 (95% confidence interval [CI] −11.01 to −3.32, $P = 0.0004$). Among patients who continued to have a benefit at Day 120 and Day 150, respectively, those who received active treatment had statistically significant lower WOMAC pain score at Day 150 but not Day 180 than those who received sham treatment (Table III). As shown in Fig. 3, the active treatment group had a statistically significant greater proportion of WOMAC pain responders at Day 30 ($P = 0.0015$), and a nonsignificant trend towards a greater proportion of WOMAC responders on Day 60 ($P = 0.0430$) and Day 90 ($P = 0.0285$), compared to the sham group; the responder rate was not statistically significant different between the groups at Day 120 ($P = 0.400$).

### *WOMAC stiffness subscale, physical function subscale, and total scale score*

As shown in Table II, the LS mean difference vs the sham group for the WOMAC physical function and stiffness subscales and the WOMAC total scale was statistically significant at Day 30. At Day 60, there were nonsignificant trends for improvement in the stiffness and physical function subscales and total WOMAC score compared to the sham group. At Day 90, both the physical function subscale and WOMAC total score were statistically significantly improved in the active treatment vs sham group, with a nonsignificant trend towards greater improvement in stiffness in the active treatment group. Among patients who continued to have a benefit at Day 120, those who received active treatment had statistically significant lower WOMAC stiffness, physical function, and total scores at Day 150 compared to those who received sham treatment (Table III). As shown in Fig. 3, a statistically significant greater proportion of patients in the active treatment group were WOMAC total score responders at Day 30 ($P = 0.0003$) and Day 90 ($P = 0.0069$) compared to the sham group; the responder rate was not statistically significant different between the groups at Day 60 ($P = 0.0332$) and Day 120 ($P = 0.400$).

### *VAS*

The LS mean difference vs the sham group for the VAS was statistically significant at Day 30 ($P = 0.0073$) but not at Day 60, Day 90, or Day 120. Among patients eligible for follow-up past Day 120, those in the active treatment group had a statistically significant LS mean difference in VAS score at Day 150 compared to sham-treated patients (Table III). Sensitivity analyses, which accounted for the type of activity used to assess VAS, produced similar results to the primary analyses.

As shown in Fig. 3, a statistically significant greater proportion of patients in the active treatment group were VAS responders at Day 30 ($P = 0.0124$) compared to the sham group; there were no statistically significant differences in response rates between the groups at Day 60 ($P = 0.180$), Day 90 ($P = 0.400$), and Day 120 ($P = 0.5060$).

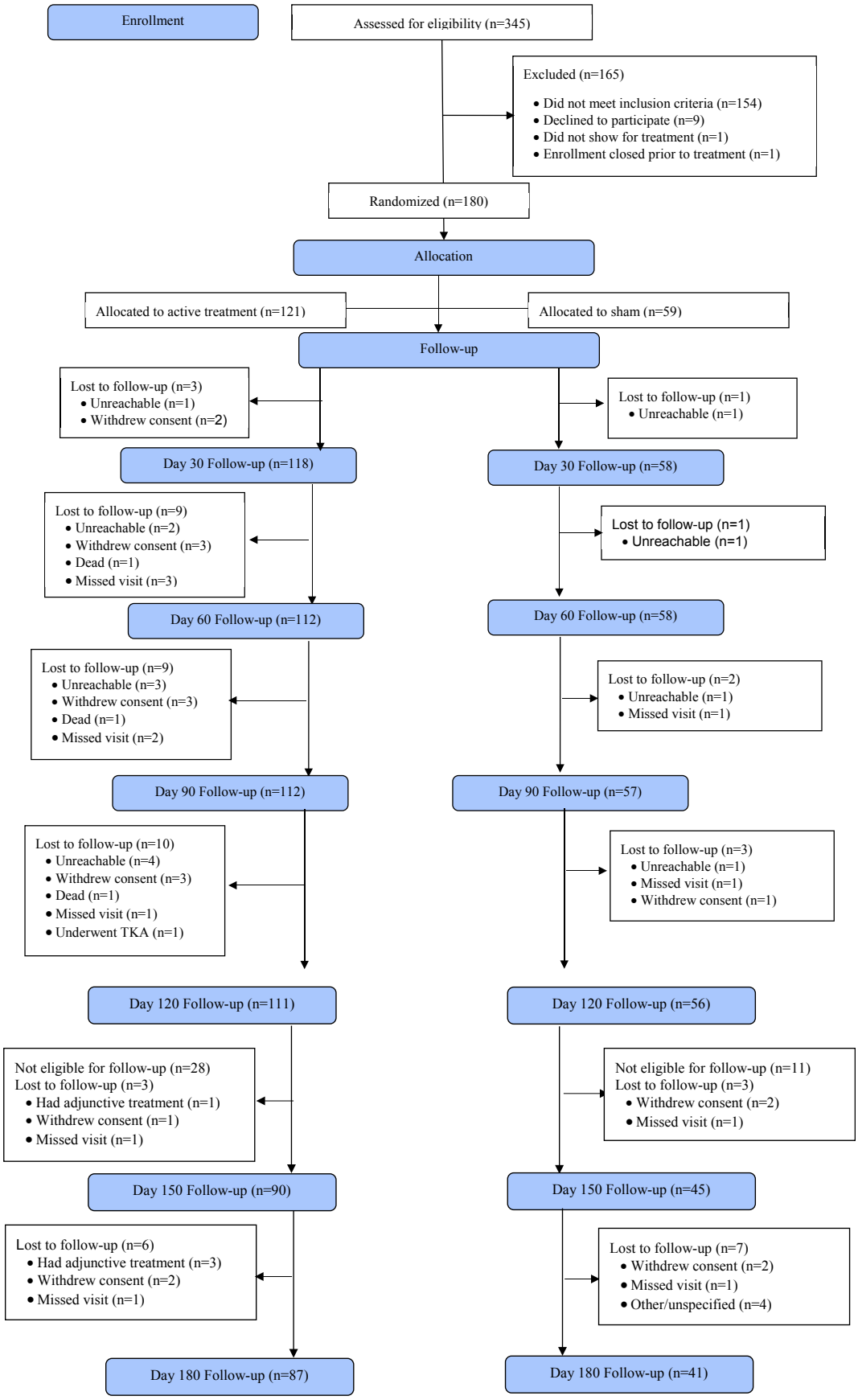


**Fig. 2.** Patient study flowchart.

**Table I**
Demographic and clinical characteristics

| Variable | Treatment ($n = 121$) | Sham ($n = 59$) |
|---|---|---|
| Age (years) | | |
| Mean (SD) | 60.6 (8.98) | 61.3 (8.17) |
| Median | 61.5 | 61.3 |
| Range | 36.5–75.3 | 40.3–74.7 |
| Gender, *n* (%) | | |
| Male | 42 (34.7) | 19 (32.2) |
| Female | 79 (65.3) | 40 (67.8) |
| Race, *n* (%) | | |
| White | 110 (90.9) | 50 (84.8) |
| Black or African American | 8 (6.6) | 8 (13.6) |
| Asian | 2 (1.7) | 0 (0.0) |
| American Indian or Alaska Native | 2 (1.7) | 0 (0.0) |
| Native Hawaiian or Pacific Islander | 0 (0.0) | 1 (1.7) |
| Other | 1 (0.8) | 0 (0.0) |
| BMI ($kg/m^2$) | | |
| Mean (SD) | 29.1 (3.97) | 30.0 (3.54) |
| Median | 29 | 30 |
| Range | 18.6–41.4 | 20.3–35.5 |
| Kellgren–Lawrence classification, *n* (%) | | |
| Grade 2 | 69 (57.0) | 25 (42.4) |
| Grade 3 | 52 (43.0) | 34 (57.6) |
| Time since diagnosis (months) | | |
| Mean (SD) | 77.4 (80.7) | 66.1 (69.1) |
| Median | 51.8 | 36.9 |
| Range | 0–425.4 | 0–271.8 |
| Treated knee, *n* (%) | | |
| Left | 64 (52.9) | 29 (49.2) |
| Right | 57 (47.1) | 30 (50.9) |
| Treated knee circumference (cm) | | |
| Mean (SD) | 38.0 (3.8) | 38.4 (3.4) |
| Median | 38 | 38 |
| Range | 39.5–52.0 | 32.0–47.0 |
| Baseline WOMAC, mean (SD) | | |
| Pain score | 30.6 (7.9) | 31.0 (7.1) |
| Stiffness score | 12.9 (3.9) | 14.0 (3.8) |
| Function score | 102.1 (31.2) | 106.1 (28.0) |
| Total score | 145.6 (41.1) | 151.1 (36.9) |
| Baseline VAS, mean (SD) | 66.2 (15.7) | 70.9 (15.6) |

*SF-36*

There were no statistically significant differences between groups on the SF-36 at any time during the study (Table S2). Though patients in the active treatment group experienced statistically significant improvements in knee pain and function vs the sham group, these did not translate into statistically significant changes in overall health-related quality of life.

*Patient global impression of change*

As shown in Table S3, there were no statistically significant differences between groups in the proportion of PGIC responders at any of the follow-up assessments.

*Expected side effects*

The most commonly reported expected side effects were bruising, numbness, redness, tenderness upon palpation, and swelling (Table IV). Most expected side effects were mild in severity and resolved within 30 days. The severities for three reported side effects (bruising, altered sensation and local pain) were not recorded.

*Adverse events*

A total of 243 AEs in 113 patients occurred during the course of the study, four of which were serious adverse events (SAEs). All four SAEs were unrelated to the device or procedure. One active treatment group patient experienced two myocardial infarctions (counted as separate events), with the second resulting in death. One sham treatment group patient had a pulmonary embolism and one active treatment group patient was diagnosed with malignant lung neoplasm.

Eighty-four AEs were deemed possibly or probably related to the device or procedure (Table V). The incidence of device- or

**Table II**
LS mean change from baseline and difference in LS mean change from sham for WOMAC and VAS

| | Active treatment ($n = 121$) | Sham treatment ($n = 59$) | LS mean difference from sham (95% CI)* | *P*-value |
|---|---|---|---|---|
| | LS mean (SE) change from baseline | LS mean (SE) change from baseline | | |
| **WOMAC pain** | | | | |
| Day 30 (Primary endpoint) | −16.65 (1.26) | −9.54 (1.63) | −7.12 (−11.01 to −3.22) | 0.0004 |
| Day 60 | −16.64 (1.24) | −11.98 (1.60) | −4.65 (−8.48 to −01.82) | 0.0176 |
| Day 90 | −17.03 (1.30) | −11.37 (1.68) | −5.67 (−9.69 to −1.64) | 0.0061 |
| Day 120 | −15.27 (1.28) | −12.45 (1.65) | −2.82 (−6.77 to 1.13) | 0.161 |
| **WOMAC stiffness** | | | | |
| Day 30 | −6.70 (0.53) | −4.38 (0.69) | −2.32 (−3.97 to −0.68) | 0.0060 |
| Day 60 | −6.51 (0.55) | −4.87 (0.72) | −1.64 (−3.36 to 0.08) | 0.0615 |
| Day 90 | −6.79 (0.54) | −4.97 (0.70) | −1.83 (−3.50 to −0.15 | 0.0325 |
| Day 120 | −6.28 (0.56) | −5.01 (0.72) | −1.27 (−3.00 to 0.47) | 0.152 |
| **WOMAC physical function** | | | | |
| Day 30 | −55.48 (4.11) | −34.18 (5.31) | −21.30 (−34.02 to −8.57) | 0.0012 |
| Day 60 | −52.64 (4.21) | −39.23 (5.43) | −13.14 (−26.43 to −0.39) | 0.0436 |
| Day 90 | −56.00 (4.21) | −40.11 (5.44) | −15.89 (−28.93 to −2.86) | 0.0172 |
| Day 120 | −51.82 (4.16) | −42.66 (5.37) | −9.16 (−22.04 to 3.72) | 0.162 |
| **WOMAC total** | | | | |
| Day 30 | −78.78 (5.81) | −48.26 (7.51) | −30.52 (−48.52 to −12.53) | 0.0010 |
| Day 60 | −75.75 (5.87) | −56.28 (7.58) | −19.47 (−37.64 to −1.30) | 0.0359 |
| Day 90 | −80.31 (5.89) | −56.51 (7.60) | −23.80 (−42.02 to −5.57) | 0.0108 |
| Day 120 | −73.33 (5.91) | −60.32 (7.64) | −13.01 (−31.32 to 5.31) | 0.163 |
| VAS | | | | |
| Day 30 | −40.09 (2.87) | −27.83 (3.68) | −12.25 (−21.16 to −3.35) | 0.0073 |
| Day 60 | −38.53 (2.91) | −32.44 (3.73) | −6.09 (−15.11 to 2.94) | 0.185 |
| Day 90 | −37.90 (3.01) | −31.58 (3.86) | −6.32 (−15.66 to 3.01) | 0.183 |
| Day 120 | −35.49 (2.93) | −30.59 (3.76) | −4.90 (−13.99 to 4.20) | 0.289 |

SE = standard error.
* Based on ANCOVA with baseline score and site as covariates.

**Table III**
LS mean change from baseline and difference in LS mean change from sham for WOMAC and VAS for responders at day 150 and 180

| | Active treatment | | Sham treatment | | LS mean difference from sham (95% CI)* | *P*-value |
|---|---|---|---|---|---|---|
| | N | LS mean (SE) change from baseline | N | LS mean change from baseline | | |
| **WOMAC pain** | | | | | | |
| Day 150 | 93 | −20.58 (1.30) | 48 | −14.19 (1.65) | −6.40 (−10.28 to −2.51) | 0.0015 |
| Day 180 | 87 | −20.75 (1.28) | 40 | −17.61 (1.65) | −3.14 (−6.87 to 0.59) | 0.0984 |
| **WOMAC stiffness** | | | | | | |
| Day 150 | 93 | −8.42 (0.54) | 48 | −5.70 (0.70) | −2.72 (−4.39 to −1.05) | 0.0016 |
| Day 180 | 87 | −8.51 (0.60) | 40 | −7.22 (0.80) | −1.30 (−3.11 to 0.52) | 0.159 |
| **WOMAC physical function** | | | | | | |
| Day 150 | 93 | −66.32 (4.35) | 48 | −46.41 (5.55) | −19.91 (−32.98 to −6.83) | 0.0031 |
| Day 180 | 87 | −66.72 (4.36) | 40 | −58.10 (5.65) | −8.61 (−21.37 to 4.15) | 0.184 |
| **WOMAC total** | | | | | | |
| Day 150 | 93 | −95.08 (6.13) | 48 | −66.50 (7.83) | −28.58 (−47.03 to −10.13) | 0.0027 |
| Day 180 | 87 | −94.75 (6.23) | 40 | −83.74 (8.09) | −11.02 (−29.28 to 7.25) | 0.234 |
| **VAS** | | | | | | |
| Day 150 | 93 | −48.88 (2.86) | 48 | −34.28 (3.60) | −14.60 (−23.20 to −6.00) | 0.0010 |
| Day 180 | 87 | −45.40 (3.22) | 40 | −37.41 (4.15) | −7.99 (−17.43 to 1.46) | 0.0965 |

SE = standard error.
* Based on ANCOVA with baseline score as a covariate.

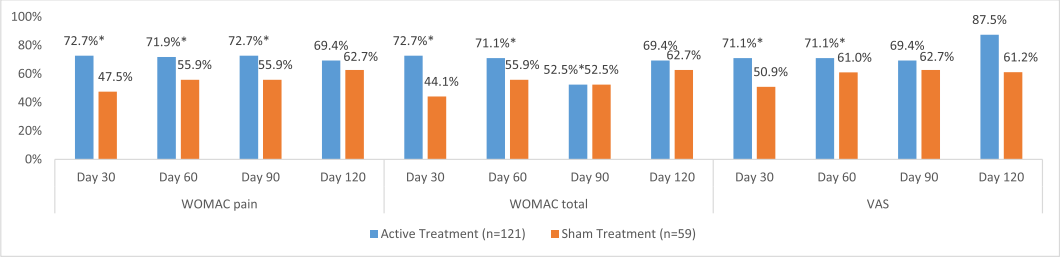


**Fig. 3.** Responder rates for WOMAC and VAS.

**Table IV**
Incidence and severity of expected side effects

| Side effect | Total population ($n = 180$) | Treatment ($n = 121$) | Sham ($n = 59$) | Severity | | |
|---|---|---|---|---|---|---|
| | | | | Mild | Moderate | Severe |
| Altered sensation, *n* (%) | 36 (20) | 25 (21) | 11 (19) | 30 (83) | 5 (14) | 0 (0) |
| Bruising, *n* (%) | 124 (69) | 93 (77) | 31 (52) | 108 (87) | 15 (12) | 0 (0) |
| Crusting, *n* (%) | 9 (5) | 6 (5) | 3 (5) | 9 (100) | 0 (0) | 0 (0) |
| Hyperpigmentation, *n* (%) | 1 (0.5) | 1 (1) | 0 (0) | 1 (100) | 0 (0) | 0 (0) |
| Itching, *n* (%) | 9 (5) | 7 (6) | 2 (3) | 9 (100) | 0 (0) | 0 (0) |
| Local pain, *n* (%) | 37 (21) | 26 (22) | 11 (19) | 30 (81) | 4 (11) | 2 (5) |
| Numbness, *n* (%) | 95 (53) | 63 (52) | 32 (54) | 73 (77) | 18 (19) | 3 (3) |
| Redness, *n* (%) | 74 (41) | 50 (41) | 24 (41) | 1 (100) | 0 (0) | 0 (0) |
| Swelling, *n* (%) | 65 (36) | 49 (40) | 16 (27) | 58 (89) | 7 (11) | 0 (0) |
| Tenderness on palpation, *n* (%) | 69 (17.8) | 46 (38) | 23 (39) | 62 (90) | 7 (10) | 0 (0) |
| Tingling, *n* (%) | 19 (11) | 17 (14) | 2 (3) | 18 (95) | 1 (5) | 0 (0) |

procedure-related AEs was similar in the two treatment groups, and most (90%) events were mild in severity. Only one device- or procedure-related AE was rated as severe (administration site altered sensation in a sham treatment patient). No serious ADE or unanticipated ADE were reported.

## Discussion

Results of the present study provide support for the efficacy and safety of cryoneurolysis for the treatment of the pain and symptoms of knee OA. At Day 30, the relative magnitude of improvement in WOMAC function score (−54%) and VAS (−61%) in the active treatment group far exceeded the established minimal clinically important improvement thresholds in patients with knee OA (−32% and −21%, respectively)[29]. Because large placebo responses have been documented in OA clinical trials[30], it is important to compare the relative improvement of cryoneurolysis over sham treatment with differences between active and placebo groups in other trials of non-surgical OA interventions. The relative post treatment reduction of 7.1 points (Day 30 WOMAC pain) and 4.7 points (Day 60 WOMAC pain) and 12 mm (Day 30 VAS) and 6 mm (Day 60 VAS) in the active vs sham treatment groups compares favorably to the effect sizes observed with oral NSAIDs[31,32], opioids[31,33], and viscosupplementation[34] in placebo-controlled trials. Although IA corticosteroids provide a similar degree of immediate pain reduction[31], the effect wanes after 4 weeks and does not appear to be as durable as cryoneurolysis.

Cryoneurolysis appeared safe and well tolerated with expected side effects that were mostly mild in severity, transient, and did not require intervention. The higher incidence of swelling in the active

**Table V**
Adverse events* related to study device or procedure

| Adverse event, *n* (%) | Treatment ($n = 121$) | Sham ($n = 59$) | Severity | | |
|---|---|---|---|---|---|
| | | | Mild | Moderate | Severe |
| Any adverse event | 57 (47) | 27 (46) | 76 (90) | 7 (8) | 1 (2) |
| Bruising | 4 (3) | 2 (3) | 6 (100) | 0 (0) | 0 (0) |
| Altered sensation | 3 (2) | 2 (3) | 4 (80) | 0 (0) | 1 (20) |
| Local pain | 9 (7) | 4 (6) | 10 (77) | 3 (23) | 0 (0) |
| Tingling | 3 (2) | 1 (2) | 4 (100) | 0 (0) | 0 (0) |
| Swelling | 3 (2) | 3 (5) | 6 (100) | 0 (0) | 0 (0) |
| Numbness | 18 (15) | 1 (1) | 19 (100) | 0 (0) | 0 (0) |
| Tenderness upon palpation | 14 (12) | 8 (14) | 18 (82) | 4 (18) | 0 (0) |
| Itching | 2 (2) | 0 (0) | 2 (100) | 0 (0) | 0 (0) |
| Redness | 0 (0) | 2 (3) | 2 (100) | 0 (0) | 0 (0) |
| Knee pain | 0 (0) | 3 (5) | 3 (100) | 0 (0) | 0 (0) |
| Pain aggravated | 0 (0) | 1 (2) | 1 (100) | 0 (0) | 0 (0) |
| Vasovagal reaction | 1 (1) | 0 (0) | 1 (100) | 0 (0) | 0 (0) |

* Expected side effects, including altered sensation, bruising, crusting, hyperpigmentation, itching, local pain, numbness, redness, swelling, tenderness on palpation, and tingling, were considered adverse events only if the event occurred outside of a 3 cm radius elliptical region around the linear grouping of needle insertions or persisted for 30 days or longer.

treatment group is expected because ablation of the target sensory nerve triggers a healing process beginning with an inflammatory phase that causes localized swelling[35]. Together, these findings indicate that cryoneurolysis may provide equivalent or superior pain relief with relatively low risks compared with currently available pharmacological treatments for knee OA.

Although many study patients experienced a durable benefit of treatment, cryoneurolysis is not expected to have a permanent effect as the targeted sensory nerve will regenerate and regain function. Multiple cryoneurolysis treatments with the device used in this trial results in nerve regeneration that is predictable and repeatable[36]. As treatment loses effectiveness, patients may undergo repeated cryoneurolysis treatments as needed, extending the potential clinical benefits of this therapy and enabling activities that may slow joint deterioration. Unlike pharmacological treatments, which have increased safety risks with greater treatment duration (e.g., NSAIDs, opioids) or limitations in the frequency of administration (e.g., IA injections of corticosteroids or hyaluronic acid), the excellent safety profile of cryoneurolysis could allow for repeated treatments without increasing risks. Studies have demonstrated that cryoneurolysis is safe both for the affected nerve and the surrounding tissue structures (e.g., blood vessels and muscle)[6,7]. In 50 years of commercial cryoneurolysis use, there have been no published cases of permanent nerve damage and only a single case of neuritis.[7,37]

Several limitations should be noted. Although allocation to treatment group was initially well concealed, patients began to more accurately guess their treatment group assignment based on their response to treatment over time, which may have affected patient-reported outcomes and biased results in favor of active treatment. There is a lack of consensus about how OA treatment responders should be defined[38–40]. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) suggested that, in evaluating interventions for chronic pain, a 10–20% decrease in pain intensity was minimally important, ≥30% moderately important, and ≥50% substantial[39]. Per these recommendations, the criterion used to define WOMAC pain and VAS responders in the present study (≥30% decrease in pain intensity) is consistent with a moderate level of pain relief; utilization of a higher threshold (≥50% reduction) for defining responders would have resulted in smaller proportions in both study groups. The reduction in knee pain and symptoms experienced by actively treated patients did not translate to improved generic health-related quality of life, possibly because improvement in function in patients with OA is better detected by the WOMAC than the SF-36[41] and the WOMAC better discriminates among individuals with knee problems whereas the SF-36 better discriminates among individuals with varying levels of self-reported general health status and comorbidities[42]. The reduction of ~30% in pain observed in the sham group is consistent with the size of the sham effect in studies utilizing sham acupuncture[43,44], and may be attributable to patient expectations or the placebo effects of participating in a research study with frequent clinical contact. Lastly, although the study was conducted at multiple sites with different investigators applying treatment, lending greater weight to the robustness and generalizability of results, the trial should be replicated to ensure reproducibility of findings.

In patients with mild to moderate knee OA, cryoneurolysis of the IPBSN resulted in statistically significant decreased knee pain and improved symptoms compared to sham treatment at Day 30, Day 60, and Day 90 compared to sham treatment. Among patients who evidenced a continued benefit of treatment at Day 120, those in the active treatment group maintained statistically significant improved WOMAC pain subscale scores at Day 150 compared to the sham treatment group. Both the magnitude and duration of benefit associated with cryoneurolysis compared favorably to the therapeutic effect of alternative treatments for knee OA. The clinical evidence presented herein highlights the promising therapeutic impact that cryoneurolysis may offer for the treatment of pain and symptoms associated with knee OA, particularly as part of a changing healthcare landscape that seeks to identify effective and safe non-pharmacological options to treat chronic pain.

## Contribution of authors

All listed authors substantially contributed to this work by acquiring data, critically revising the article, and approving the final article. Dr. Radnovich (dr.radnovich@injurycaremedical.com) takes responsibility for the integrity of the work as a whole, from inception to finished article.

## Competing interest statement

All authors were investigators in the study and their institutions received research grants from Myoscience to support their participation as investigators. Drs. Choo, Darr, Harrell, Lane, Metyas, Naranjo, Olson, Patel, Scott, Segal, Shock, Surowitz, and Wei have no competing interests. Drs. Dasa and Radnovich are paid consultants to Myoscience. Dr. Dasa also is a paid speaker for and owns stock options in Myoscience. Dr. Valadie is a paid consultant to and has received royalties from Arthrex.

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Myoscience, Inc. provided funding to support the conduct of this study and assisted in the study design, analysis of data, and decision to submit the manuscript for publication. The study sponsor played no role in interpreting the study data and writing the manuscript, which the authors completed independently of the sponsor.

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**Supplementary data**

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