Review of an exploratory phase II FDA regulated clinical trial of a novel surgical innovation: completion of a prospective, randomized, controlled trial to compare NeoCart with the standard-of-care, microfracture, for articular cartilage repair

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Background: Full thickness articular cartilage lesions cause significant morbidity, and surgical intervention is frequently applied to restore the joint surface. Current approaches of cartilage restoration have not proven to produce hyaline cartilage and have limited clinical longevity. The objective of the current study was to evaluate a novel autologous cartilage tissue implant, NeoCart, at the conclusion of the FDA-regulated exploratory phase II randomized, prospective clinical trial. The primary surgical standard-of-care, microfracture, was set by the FDA as the control. Objectives included parameter setting for the phase III trial while conducting a preliminary long-term evaluation of safety and efficacy.

Methods: Patients were randomized 2:1 to NeoCart (n=21) or microfracture (n=9) surgical intervention at time of arthroscopy. Baseline demographics and patient-reported outcomes were established including: International Knee Documentation Committee (IKDC); Knee Injury and Osteoarthritis Outcome Score (KOOS) components including Pain, Activity of Daily Living, Quality of Life, Symptoms, Sports & Recreation; Short Form 36; and Visual Analog Scale Pain. Adverse events (AEs), range of motion, and patient reported outcomes were assessed annually for 5 years.

Results: The treatment and control groups did not significantly differ in age, gender distribution, symptom duration, lesion size, or baseline patient reported outcomes aside from pre-surgical Visual Analog Scale Pain scores and KOOS Pain and Recreation. AE rates did not differ between treatments. The control group had greater loss to follow-up over a 5-year period. Change from baseline was significantly greater for NeoCart than for microfracture for primary end points; IKDC (1, 2 years) and KOOS Pain (1, 3, 4 years), and secondary end points; KOOS Quality of Life, Symptoms, and Sports & Recreation until 4 years. At 5 years, IKDC, KOOS Pain, Activities of Daily Living, and Quality of Life, and Short Form 36 Physical scores for both treatments improved significantly (P<0.05). Improvements for NeoCart were sustained earlier and throughout the entire study period.

Conclusions: NeoCart implantation has a safety and efficacy profile supporting further consideration of this therapy in a confirmatory phase III trial for establishment as a primary cartilage injury treatment. While clinical trials for surgical interventions depend on comparison with a standard-of-care, the favorability of the control procedure, microfracture, varied over the study duration. The known short duration of microfracture's therapeutic effect was likely associated with high loss to follow-up in the small control group. Although adequate for setting phase III parameters, this study is under-powered to clearly attribute...
Introduction

Cartilage defects represent a clinical and therapeutic challenge as full thickness injury cannot intrinsically heal, leading to significant pain and functional impairment. When left untreated, lesions further progress to degenerative joint conditions. The goal of treatment is to restore a congruent functional joint surface to prevent disease progression. Current primary treatment options for relatively small cartilage injuries include mechanical chondroplasty and/or microfracture (1,2). Microfracture involves drilling or tapping into the subchondral bone to facilitate transposition of marrow cells to fill the defect with a fibrocartilaginous tissue (3,4). However, clinical improvement after microfracture is inconsistently observed, with about 25% of patients reporting minimal relief within the first 12–24 months of treatment (5,6), and a peak in clinical improvement at 24 months (7,8). Despite varied outcomes and short-term efficacy, the FDA established microfracture as the standard in cartilage repair to which any new therapy for cartilage repair is compared in the United States (9).

Alternatives to microfracture, including autologous chondrocyte implantation (ACI), have historically been secondary procedures performed after chondroplasty and microfracture fail. ACI represents the first generation of “regenerative techniques” in which healthy cartilage is used to provide an autogenous cell therapy to produce hyaline-like cartilage tissue within the defect. Chondrocytes are isolated and expanded in a laboratory before surgical application to the defect. Reoperation has been reported in approximately 1/3 of first generation ACI cases; although, second and third generation techniques have improved reoperation rates (10). Failure rates of about 16% after ACI treatment have been reported, with favorable results in 83% of patients after 5–11 years (11), or 69% after 9 years (12). In addition, Zaslav et al. reported a 24% failure rate and significant improvements in all clinical outcome measures in patients receiving ACI implantation for failed articular cartilage treatments (13). Comparing ACI treatment with microfracture, Knutsen et al. reported a 23% failure rate in each cohort and significant, but equal, clinical improvements in both cohorts after 5 years (14). Saris et al. reported equal improvements at 3 years post-operative with second generation characterized chondrocyte implantation or microfracture (15), while others have reported superior clinical outcomes with microfracture (16).

NeoCart® (Histogenics, Waltham, MA), an autologous cartilage tissue-engineered implant, represents a novel approach for primary treatment of articular knee cartilage defects. NeoCart is a laboratory-generated tissue derived from autogenous chondrocytes obtained through arthroscopic biopsy. In NeoCart manufacture, chondrocytes are isolated, embedded in a type I collagen matrix, and incubated in a bioreactor prior to implantation. The bioreactor recreates physiologic pressure and oxygen tension to favor a chondrocyte cell phenotype, which is crucial to proper tissue development (17). At implantation, the approximately 2 mm thick disc consists of autogenous chondrocytes and an average of 10 mg/mL of sulfated glycosaminoglycans—a critical component of hyaline cartilage extracellular matrix. Neither microfracture nor currently available ACI treatments provide both chondrocytes and hyaline specific extracellular matrix molecules at the time of surgery, which may contribute to relatively high failure rates.

The objective of the current study was to assess clinical and patient-reported outcomes acquired at final follow-up from an FDA-regulated exploratory phase II randomized, controlled study comparing NeoCart with microfracture for primary treatment of grade 3 International Cartilage Repair Society (ICRS) cartilage injuries of the distal femoral condyle in adults (18–55 years). We have previously
differences in longer term efficacy. Nonetheless, preliminary results demonstrate that NeoCart may provide an alternative primary surgical option for cartilage injury with a more rapid onset of action than microfracture.

Keywords: Phase II clinical trial; randomized controlled trial; tissue engineering; articular cartilage; knee; microfracture; NeoCart

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reported short-term results from the phase I and phase II trials that demonstrated safety of the NeoCart implant with decreased pain and improved functional outcomes at 6–24 months post-treatment (18,19). The phase II randomized clinical trial (Clinicaltrials.gov, NCT00548119) is now complete with mean final follow-up of 51 months. To further evaluate the safety and efficacy of NeoCart for primary repair of femoral condyle cartilage defects, we evaluated temporal changes in patient reported outcomes in NeoCart-treated patients compared with microfracture controls. As an exploratory study, we used this data to establish parameters for a phase III confirmatory study protocol.

**Methods**

The study was approved by the Institutional Review Board. Inclusion and exclusion criteria for enrollment are in Table S1, and details for randomization and treatment are included in Figure 1.

Forty-nine subjects were consented. Pre-operative MR images were obtained, and patients with one (n=28) or two (n=2) isolated contained articular cartilage lesions of the femoral condyle, confirmed by arthroscopy, were enrolled. Patients were randomized 2:1; two NeoCart per microfracture for the following reasons: (I) accommodating patient preference for a novel therapeutic versus a well-known standard; (II) establishing experience for surgeons learning a new technical procedure; and (III) meeting the defined statistical power for a novel therapeutic in comparison with a procedure of established efficacy (20). Microfracture patients underwent treatment at the index arthroscopy. NeoCart patients underwent arthroscopic cartilage biopsy and implantation approximately 6 weeks later (Figure 2). Neocart was surgically placed during an “ambulatory” procedure via a mini-arthrotomy and secured.
with a proprietary collagen-based bio-adhesive (21). The rehabilitation protocol was the same for both study cohorts. Additional operative and rehabilitative details were reported previously (18).

All patients were assessed for range of motion (ROM) and completed the following patient-reported outcome questionnaires at baseline, 3 months, 6 months, 1 year, and annually thereafter through 5 years: International Knee Documentation Committee (IKDC; subjective), Knee injury and Osteoarthritis Outcome Score (KOOS) Pain, KOOS Activity of Daily Living (ADL), KOOS Quality of Life (QOL), KOOS Symptoms, KOOS Sports & Recreation, Short Form 36 (SF-36) and Visual Analog Scale (VAS) Pain. IKDC and KOOS Pain were established as the primary end points by the FDA. One NeoCart patient was lost to follow-up at 2 years, one withdrew at 3 years, two were lost at 3 years, two were lost at 5 years, and 15 (71%) patients were considered long-term follow-up at 5 years. One microfracture patient was lost to follow-up at 3 years, one withdrew at 5 years, three were lost at 5 years, leaving four (44%) patients considered long-term follow-up at 5 years.

**Statistical analyses**

Objective data was collected and managed by the study sponsor data management services (Synteract, Carlsbad, CA, USA). Descriptive statistics and responder rate were calculated at each time for the intent to treat population with significance set at P<0.05 (two sided). Patients were classified as responders if they achieved a 12-point improvement in the KOOS Pain score and a 20-point improvement in the IKDC subjective score (18). Mean change from baseline was calculated for all outcome measures and time points, in addition to scores at final follow-up for all patients (last observation carried forward) (22). A paired t-test was applied comparing score change from baseline between cohorts. Primary outcomes, IKDC and KOOS scores, and change from baseline to final follow-up were evaluated by an
analysis of covariance (ANCOVA), using the baseline scores as the covariate.

**Results**

**Safety**

AEs were captured by principal investigators and categorized using the definition of the US Department of Health and Human Services Office for Human Research Protections (23). Ninety-nine AEs were reported in the NeoCart cohort and 31 in the microfracture cohort during the study period. There were 21 AEs related specifically to the procedure in the 21 NeoCart patients [moderate procedural pain (n=5), mild arthralgia (n=7), moderate hypoesthesia (n=1), moderate joint effusion (n=1), mild joint effusion (n=1), mild joint stiffness (n=1), mild limb injury (n=1), mild wound secretion (n=1), mild muscle atrophy (n=1), and mild neuralgia (n=1)] and eight AEs related specifically to the procedure in the nine microfracture patients [mild arthralgia (n=6), mild joint swelling (n=1), severe meniscus lesion (n=1)]; these rates did not differ significantly between treatment arms.

There were 7 severe AEs in the NeoCart cohort; arthralgia (n=3) and subsequent joint locking (n=1) in the index knee, and ligamentous rupture (n=1) and septic arthritis (n=1, ultimately treated with knee arthroplasty) in the contralateral knee. Due to temporal relationships and exam findings, these were not considered related to either the NeoCart implant or to the procedure by treating enrolling investigators. There were two severe events in the microfracture cohort; a malignant pelvic neoplasm, and a meniscus lesion in the index knee (treated with debridement) after 4-year follow-up which was the sole severe AE deemed possibly related to the procedure.

The most common AEs in the NeoCart cohort included arthralgia, related to the implant (n=9, mild), and post-operative pain (n=5, moderate) and arthralgia (n=7, mild) related to the procedure itself. The most common AE in the microfracture cohort included arthralgia (n=6, mild). No patients were discontinued because of any AE, and the number, severity, and type of AE were not different in those that were lost to follow-up compared with those that were not.

**Efficacy analysis**

Demographics are summarized in Table 1; only body mass index (BMI) differed significantly between groups. Baseline patient reported outcome scores are also summarized in Table 1. VAS scores were significantly higher in the NeoCart cohort, KOOS Sports & Recreation was higher in the microfracture cohort and all other parameters were similar between cohorts.

Follow-up rates (defined as annually complete patient reported outcome scores) for IKDC measures in the NeoCart cohort were 95%, 86%, 71%, 62%, and 57% at years 1–5, and 100%, 90%, 76%, 71%, and 71% for KOOS measures. Follow-up rates for the IKDC and the KOOS measures were 100%, 100%, 78%, 78%, and 44% at years 1–5 in the microfracture cohort.

Change from baseline through final follow-up is summarized in Table 2. SF-36 Mental score did not change with either treatment at any time point, with the exception of the microfracture cohort at 3 months. Improvement with NeoCart compared to baseline was significant (P<0.05) for all other parameters at all time points, with the exception of ROM and KOOS Sports & Recreation at 3 months. Improvement for the microfracture cohort was limited to IKDC beginning at 6 months, ROM beginning at 3 years, KOOS Pain beginning at 4 years, KOOS ADL and QOL beginning at 1 and 2 years respectively, and SF-36 Physical beginning at 1 year.

Mean change from baseline for IKDC and KOOS Pain (the two primary study outcome measures) is represented graphically in Figure 3. Improvement in mean IKDC score at 1 and 2 years was greater (P<0.05) with NeoCart than with microfracture treatment (Figure 3A). The NeoCart cohort demonstrated greater improvement for KOOS Pain at 6 months and at 1 and 3–4 years (Figure 3B); for KOOS QOL at 3 months and at 1–2 years; for KOOS Symptoms at 6 months and at 3–4 years; and for KOOS Sports & Recreation at 1–4 years. Improvement in the VAS Highest score was greater in the NeoCart cohort at 1, 2, and 4 years, compared with microfracture (Figure 3C). Improvement in the VAS Average (usual) score was greater in the NeoCart cohort at 6 months, at 1–4 years, and at final follow-up, compared with microfracture (Figure 3D). At final follow-up, there were no other significant differences in change from baseline when the NeoCart and microfracture groups were compared.

By 5 years, 100% of non-responders in the microfracture cohort were lost to follow-up (n=3 of 3), whereas only 50% of non-responders were lost to follow-up in the NeoCart cohort (n=2 of 4). Due to the relatively small numbers of patients and to address the potential impact of loss to follow-
up, responder rates in each cohort were calculated using imputed data for all time points with the last observation carried forward method (19). Based on a change from baseline in IKDC score of >20 and a change in KOOS Pain score of >12, significantly more NeoCart patients responded to treatment at 1 year (16/21, 76.2%, \( P=0.046 \)) compared with microfracture patients (1/9, 11.1%). At years 2–5, responder rates for the NeoCart group were 15/18 (83.3%), 12/16 (75.0%), 12/15 (80.0%), and 13/15 (86.7%), respectively. Responder rates for the control group in years 2–5 were 2/9 (22.2%), 1/7 (14.3%), 1/7 (14.3%), and 3/4 (75%), respectively. Responder rates at years 2-5 did not differ significantly between cohorts. At final follow-up (51.6±13.8 months NeoCart; 52.0±8.5 months microfracture), 67% (6/9) of microfracture patients were considered responders while 81% (17/21) of NeoCart patients were responders, although these did not differ significantly.

To adjust for variation in baseline IKDC, KOOS Pain and VAS scores, an ANCOVA was performed using the baseline score as co-variant. The adjusted IKDC and KOOS Pain score changes from baseline differed significantly between the NeoCart and microfracture cohorts at 1 year (\( P=0.028 \) and 0.016, respectively). Baseline scores did not disproportionately influence the change in IKDC and KOOS Pain scores at 1 year. However, by final follow-up, IKDC (Figure 4A) and KOOS Pain (Figure 4B) scores in the NeoCart cohort improved regardless of baseline values, whereas with microfracture, there was less treatment efficacy in those with higher baseline function or pain scores. Of note, this temporal phenomenon for the microfracture cohort was not seen in VAS (Highest and Average/usual) scores at either 1 year (18,19) or final follow-up (Figure 4C,D).

Table 1 Baseline demographics, patient reported outcomes and range of motion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NeoCart (N=21)</th>
<th>Microfracture (N=9)</th>
<th>P value</th>
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<tr>
<td>Age (years)</td>
<td>41.4±9.2</td>
<td>38.8±9.4</td>
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<td>Male, n (%)</td>
<td>19 (90.5)</td>
<td>6 (66.7)</td>
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<td>Duration of symptoms (years)</td>
<td>2.8±5.0</td>
<td>2.2±3.8</td>
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<td>Pre-debridement lesion size [range] (mm(^2))</td>
<td>227±96 [100–440]</td>
<td>173±73 [100–310]</td>
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<td>Post-debridement lesion size [range] (mm(^2))</td>
<td>287±138 [100–540]</td>
<td>252±135 [100–500]</td>
<td>0.535</td>
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<td>KOOS pain</td>
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<td>KOOS sport &amp; recreation</td>
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* statistically significant differences (\( P<0.05 \)). IKDC, International Knee Documentation Committee score; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QOL, quality of life; VAS, Visual Analog Scale; SF-36, Short Form Health Survey 36.
<table>
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<td>20–21</td>
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<td>7</td>
<td>6–7</td>
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<td>VAS average (mean ± SD)</td>
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<td>−28.6±15.3*</td>
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<td>VAS highest (mean ± SD)</td>
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<tr>
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<td>−30.2±32.7*</td>
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<td>−46.6±24.3*</td>
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<td>SF-36 physical (mean ± SD)</td>
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<td>6.6±9.5</td>
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<td>11.7±5.5</td>
<td>8.7±11.0*</td>
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Some number values (n) are variable due to 1–3 patients omitting 1 patient reported outcome at the visit indicated. *, significant change from baseline (P<0.05). IKDC, International Knee Documentation Committee score; KOOS, Knee Injury and Osteoarthritis Outcome score; ADL, activities of daily living; QOL, quality of life; VAS, Visual Analog Scale; SF-36, Short Form Health Survey 36.
Figure 3 Temporal representation of IKDC (A), KOOS pain (B), highest VAS pain (C) and average VAS pain (D) scores mean changes from baseline. Significant cohort differences (P ≤ 0.05) are illustrated by *.

Figure 4 ANCOVA analysis of change in IKDC (A), KOOS pain (B), highest VAS pain (C) and average VAS pain (D) outcome scores as a function of baseline.
Discussion

NeoCart implantation appears safe and efficacious over 5 years, supporting further study as a primary treatment of focal cartilage injuries in the knee. While the NeoCart cohort had significantly improved patient reported outcomes and higher follow-up rate over the 5-year study period, there were more overall AEs compared with microfracture. The procedure-related AE’s, however, were equivalent in the two groups. Only one severe AE was considered possibly related—a meniscus lesion in the microfracture cohort. All other events were mild or moderate and were consistent with the minimally invasive nature of these procedures. Thus, NeoCart appears to be as safe as microfracture, the standard primary surgical treatment for isolated cartilage lesions in the United States.

Both cohorts experienced significantly improved patient reported outcome scores during the 5-year study. Improvements were generally greater, in comparison with baseline, and occurred sooner (from 3–48 months earlier) in the NeoCart cohort. Unlike with microfracture, the NeoCart cohort reported significant improvements in IKDC, KOOS Pain, KOOS Symptoms, KOOS Sports & Recreation, and VAS scores. In addition, both baseline VAS scores and average BMI were higher than in the microfracture cohort. This potentially provides for greater likelihood of improved outcomes in patients with lower BMI in the microfracture cohort (8). However, we observed the opposite; consistently strong positive outcomes were observed in change from baseline data with NeoCart compared to microfracture. The NeoCart cohort also included a significantly higher incidence of positive responders, based on both 20-point improvements in IKDC score and 12-point improvements in KOOS Pain score at 1 year compared with microfracture. By 5 years, all non-responders were lost in the microfracture cohort, while 50% of non-responders in the NeoCart cohort remained. This attrition amongst the microfracture non-responders may well explain the idiosyncratic improvement in outcomes at 5 years in the small cohort reporting at study conclusion.

We previously reported that the adjusted change in outcome scores at 1 year, based on adjusting for differences in baseline values, was significantly higher for the NeoCart group; by 11.6 points for IKDC score and 12.1 points for KOOS Pain score (18). By final follow-up, it became clear that microfracture treatment mostly benefited those who reported the lowest baseline IKDC and KOOS Pain scores, while the outcome for the NeoCart cohort was independent of baseline scores. Consequently, NeoCart patients experienced similar improvements in outcome across the spectrum of baseline pain and function values, but the microfracture cohort outcomes appeared dependent on the baseline values. Microfracture patients improved less than NeoCart patients if their baseline IKDC or KOOS Pain scores were higher, and this difference between cohorts was magnified at later time points. Analysis of baseline-adjusted VAS scores did not demonstrate this distinction between the cohorts. This is of interest, as it may be that an element of the effect of NeoCart in patients with higher scores (higher functioning and potentially earlier disease) reflects improvements in functional capacity to a greater degree than simply reduction in VAS pain score. Thus, NeoCart may represent a better initial treatment option for patients with higher functional capacity in earlier disease states.

Chondroplasty and microfracture are primary therapeutic options for the repair of focal chondral injuries. Microfracture is associated with production of a fibrocartilage fill that is less durable, resilient, and able to withstand biomechanical forces in comparison to native hyaline cartilage. Bony overgrowth has been described in 25% (8), to nearly 50% (24), of microfracture patents, and the benefits plateau after 1–2 years (7,8). The hyaline-like cartilage associated with ACI is a promising alternative to microfracture for these injuries (11). However, in direct comparisons with microfracture, ACI showed no statistically significant improvements at 5 years (14), or 15-year follow-up (25). In contrast to current therapies, NeoCart is implanted with chondrocyte functional matrix, which likely explains earlier efficacy. In a comparison with microfracture, NeoCart led to significantly more positive responders at 1 year (18). With sustained benefit through 5 years, this data confirms the benefits of NeoCart persist and are superior to microfracture. In a separate evaluation of MRI follow-up of the NeoCart group, we found that radiographic measures improved longitudinally until 2 years, with maintenance of the improvement until final follow-up at 5 years (26).

Strengths of our study include its prospective randomized nature, comparison to control current standard, and 5-year follow-up period (27), as a minimum of 2–3-year follow-up is recommended for comparing clinical outcomes after knee cartilage treatment (28,29). We used two common validated measures as “primary” outcomes, IKDC and KOOS, which reliably score knee symptoms and function in patients with articular cartilage lesions (30). We also reported the proportion of responders and AEs based on FDA guidelines (23). For responder
A principal study limitation is the low sample size. This is a function of “exploratory” trial design, to gain and establish parameters for larger confirmatory trials and calculate power (32,33). Thus, we were not able analyze subgroups to better define variables that may influence outcomes, such as BMI and age. Similarly, low numbers, especially in the microfracture cohort, are particularly troubling as loss to follow-up of a few patients potentially affects the statistical power and a type I or II error is at risk (22). The phase II trial was initially statistically powered in favor of the NeoCart cohort through 2:1 unequal randomization because microfracture had already been well defined in the literature, patients expressed a strong preference toward a novel therapeutic over the standard-of-care, and the surgeons performing the operation needed to gain experience with NeoCart implantation in order to facilitate the learning curve necessary for a larger phase III study.

A second limitation was the number of dropouts in the control group during the study period. Our follow-up rate for most outcome measures was generally high through year 4, although the 5-year follow-up for the microfracture cohort dropped to 44%. This high dropout at the final follow-up prompted us to use imputation for final statistical analysis, which has clear and known limitations (34). Specifically, the observations that were carried forward were likely an overestimate of patient response, given that the therapeutic effect of microfracture peaks at 24 months. The data reporting the efficacy of microfracture, however, has accumulated since the original trial design, in which the FDA set the standard-of-care for the control group (9). Aside from these limitations in the longevity of the control procedure through final follow-up, microfracture is not necessarily a fixed standard because its popularity among surgeons and the prevalence of cases have been declining throughout the entire study duration (35). Thus, not coincidentally, we had a large loss to follow-up after the known peak of microfracture longevity with only the control group in this study. This reflects the conundrum of recruiting for long term studies, for which comparison to standard-of-care controls have shorter term clinical benefits than the study duration. A solution to this problem may be a cross-over study design, whereby a patient leaves the control for the treatment group after failure. However, the concern of bias in early clinical response prohibited this method because neither patients nor surgeons were blinded to treatment, so there might have been incentive to seek further intervention in favor of the treatment group. Without the opportunity to cross over, those patients who were lost to follow up may have sought treatment elsewhere after failure.

In this exploratory phase II trial, the outcomes were statistically in favor of NeoCart; however, definitive statements require the statistical power of a phase III trial, which was designed and powered based on this exploratory phase. This process of graduated sample size in trial design methodology is critical to successful FDA-regulated Investigational New Drug (IND) evaluations for surgical procedures and biologic therapeutics. Unfortunately, randomized, controlled trials and the required phases for novel surgical devices are not well known to the orthopaedic audience. On submission of this data to leading orthopaedic journals, reviewers rejected the manuscript, primarily citing the low sample size and loss to follow-up in the control group despite the presentation of this data as long-term follow-up of an exploratory, not a confirmatory, clinical trial. We argue that these limitations provide basis for further investigation into the superiority of NeoCart in a confirmatory trial, and presentation of phase II data elucidates both the importance and the limitations of the exploratory phase of the FDA approval process for a novel surgical therapy.

Conclusions

Now completed, data from this FDA-regulated phase II exploratory clinical trial are allowed for parameter setting and fine tuning of the phase III multicenter confirmatory trial (NCT01066702, clinicaltrials.gov). We established that patients with excessively high baseline IKDC and KOOS Pain scores should be eliminated from inclusion to eliminate the ceiling effect, and that failures in each cohort remain failures over time and will likely leave the study. Using this preliminary data for the power analysis, 245 patients are required to confirm the efficacy of NeoCart treatment over that of microfracture treatment—a study that is currently underway, with a primary end point of one year, and evaluation through 3-years based on these experiences.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


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### Inclusion/exclusion criteria

**Inclusion criteria**

**Initial**
- Patient able and willing to give informed consent
- Age between 18 and 55 years
- Patient presenting with symptomatic knee pain indicative of an articular cartilage injury
- Patient medically able to undergo arthroscopic microfracture or biopsy and subsequent arthrotomy for NeoCart implantation

**At arthroscopy**
- Patient with at least 1 treatable lesion located on either medial or lateral femoral condyle that would be a candidate for microfracture therapy
- ICRS grade III lesion
  - Lesions with a maximum linear dimension of at least 1 cm and no more than 3 cm to healthy cartilage border
  - Lesions with total area less than area of NeoCart (7–8 cm²)

**Exclusion criteria**

*Any previous surgical treatment of lesion other than debridement*
- Body mass index >35 kg/m²
- Joint space narrowing of >1/3 compared with normal knee, or <3 mm of joint space measured on radiographs, osteophytes, sclerosis, or degenerative conditions in treatment knee noted on radiographs
- Malalignment >3° outside mechanical axis of other knee, or need for surgery to correct malalignment
- Other symptomatic pathology of contralateral knee
- Surgery on contralateral knee within 8 weeks prior to scheduled arthroscopy
- Any form of inflammatory arthritis
- Ankylosing spondylitis
- Synoviomia, hemangioma, pigmented villonodular synovitis, or neoplasm in knee
- Patient on chemotherapy
- Patient unable to undergo magnetic resonance imaging (MRI)
- Patient who is pregnant or intends to become pregnant during the year following initial enrollment
- Known history of allergy to bovine products or to collagen or more than a minimal reaction to an intradermal collagen injection challenge
- History of autoimmune disease
- Evidence of HIV or chronic hepatitis-B or C viral infection
- Known allergy to gentamicin
- Current drug or alcohol abuse
- Patient deemed by investigator as unlikely to comply with protocol
- Subchondral bone loss
- Patent requiring a concomitant procedure other than medial or lateral partial meniscectomy, removal of loose bodies, debridement of articular cartilage lesions other than that being treated and synovectomy
- Untreated ACL and/or PCL deficiency or ligamentous instability in involved knee
- Meniscus with rim <50% of normal thickness
- ICRS grade III or IV kissing lesion
- More than slight anterior knee pain referable to patellofemoral joint and ICRS grade-III (B), III (C), or IV trochlear groove or patellar lesion