A Multicenter, Double-Blind, Phase III Clinical Trial to Evaluate the Efficacy and Safety of a Cell and Gene Therapy in Knee Osteoarthritis Patients

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The aim of this study was to test the clinical efficacy of TissueGene-C (TG-C), a cell and gene therapeutic for osteoarthritis consisting of non-transformed and transduced chondrocytes (3:1) retrovirally transduced to overexpress transforming growth factor- β 1. A total of 163 Kellgren–Lawrence grade 3 patients with knee osteoarthritis were randomly assigned to receive intra-articular TG-C or placebo. Primary efficacy measures included criteria for subjective assessment by International Knee Documentation Committee (IKDC) and pain severity by Visual Analog Scale (VAS) for 52 weeks. Secondary efficacy measures included IKDC and VAS at 26 and 39 weeks; pain, stiffness, and physical function by the Western Ontario and McMaster Universities Arthritis Index (WOMAC); and pain, symptoms, daily activities, function in sports and recreation, and quality of life by the Knee Injury and Osteoarthritis Outcome Score (KOOS), X-ray, magnetic resonance imaging, and soluble urine and blood biomarkers. TG-C was associated with statistically significant improvement over placebo in the total IKDC score and individual categories, and in the VAS score at 26, 39, and 52 weeks. WOMAC and KOOS scores also improved with TG-C over placebo. Patients treated with TG-C showed trends directed toward thicker cartilage and slower growing rates of subchondral bone surface area in the medial tibia, lateral tibia, lateral patella, and lateral patella femoral regions, although these were not statistically significant ($p > 0.05$). Serum C-terminal telopeptide of type I collagen (CTX-I) and urine CTX-II levels were lower over 1 year in TG-C than placebo-treated patients, with CTX-I level reaching statistical significance. These tendencies supported TG-C as holding great potential as a disease-modifying osteoarthritis drug. The most frequent adverse events in the TG-C group were peripheral edema (9%), arthralgia (8%), joint swelling (6%), and injection site pain (5%). TG-C was associated with statistically significant improvements in function and pain in patients with knee osteoarthritis. The unexpected adverse events were not observed.

Keywords: TissueGene-C, osteoarthritis, gene therapy, Phase III

INTRODUCTION

OSTEOARTHRITIS IS A PROGRESSIVE, degenerative disease that affects more than 250 million people worldwide, and in the absence of efficacious new disease-modifying osteoarthritis drugs (DMOADs), the prevalence of osteoarthritis is expected to increase rapidly as the global population ages and

obesity rates increase.^{1,2} Moreover, as a leading cause of physical disability around the world, osteoarthritis places a heavy burden on global health-care expenditure.³ Treatment of osteoarthritis, which most often afflicts weight-bearing knee and hip joints, predominantly entails symptom relief, with nonsteroidal anti-inflammatory drugs being

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the most commonly prescribed agents. However, these treatments are often ineffective at relieving pain and can produce unwanted side effects and fail to halt disease progression, especially for the patient demographic groups in which osteoarthritis is prevalent.⁴ Therefore, a growing unmet need exists for DMOADs to slow or reverse the course of disease progression and provide long-lasting benefits to osteoarthritis patients.

Chondrocytes maintain the integrity of articular cartilage by controlling the production and degradation of extracellular matrix components, including proteoglycans and collagens.⁵ In osteoarthritis, this equilibrium is disrupted such that a net degradation of articular cartilage occurs with increased production of inflammatory cytokines and matrix-degrading enzymes. Many ongoing drug-development strategies for osteoarthritis aim to slow or reverse cartilage degeneration by regulating chondrocyte function. Transforming growth factor- β (TGF- β), which is an anti-inflammatory cytokine, plays a key role in maintaining metabolic homeostasis and the structural integrity of articular cartilage by controlling chondrocyte proliferation and differentiation, as well as extracellular matrix deposition.^{6–8} TGF- β has therefore been considered a primary candidate for restoring damaged cartilage in the articular joints of osteoarthritis patients. Fibroblast growth factor 18 (FGF-18), acting via FGF receptor-3, promotes chondrocyte proliferation, extracellular matrix formation, and cartilage regeneration.⁹ A recombinant form of human FGF-18 has shown promise as a DMOAD in early clinical trials.^{10,11} Cell-based strategies are being developed to overcome problems associated with growth factor pharmacokinetics. Mesenchymal stem cells are multipotent and can develop into cartilage and bone, possess anti-inflammatory and immunosuppressive activities, and have shown promise for osteoarthritis treatment in early clinical studies.^{12,13} Autologous chondrocyte transplantation has shown some promise in initial clinical studies for full-thickness chondral defects of the knee, despite concerns regarding the potential for chondrocyte dedifferentiation.^{12,14}

TissueGene-C (TG-C) was developed as a cell-based growth factor expression strategy and involves a 3:1 ratio of human allogeneic chondrocytes and genetically modified chondrocytes engineered to express TGF- β 1. TGF- β 1 expressing cells were irradiated with a low dose of gamma-ray so that they could not proliferate within the knee joint after injection. TG-C was administered by a single intra-articular injection.^{15,16} In Phase II trials of TG-C in patients with knee osteoarthritis, the intra-articular injection was well tolerated and was

shown to improve functionality, pain, and quality of life when compared to patients either at the start of treatment or given a placebo.^{17,18} Here, the results are reported of a placebo-controlled, double-blind, randomized, parallel group, 12 site, Phase 3 trial with TG-C in patients with osteoarthritis of the knee.

MATERIALS AND METHODS

Study population

Eligible patients aged ≥ 19 years were enrolled who had osteoarthritis of the knee diagnosed by an International Knee Documentation Committee (IKDC),¹⁹ with a subjective score of ≤ 60 (100-point scale), a 100 mm Visual Analog Scale (VAS)²⁰ pain score of ≥ 40 mm, radiographic confirmation of grade 3 osteoarthritis on the Kellgren–Lawrence scale,²¹ and International Cartilage Repair Society (ICRS)²² grade 3 or 4 cartilage damage in major lesions, as confirmed by magnetic resonance imaging (MRI; per the inclusion/exclusion criteria shown in Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/humc). Four patients were withdrawn from this study prior to receiving any treatment: three due to withdrawal of consent and one due to not meeting the inclusion/exclusion criteria; Fig. 1). The study adheres to the CONSORT statement, and a flow diagram is outlined in Fig. 1.

To avoid bias, an independent person prepared a randomization table using a random permuted block design. Random allocation numbers were assigned to investigational agents before they were shipped to the study site. A randomization number was assigned to each patient, and a drug with the same serial number was administered. Investigator blinding was achieved by an independent person who administered TG-C or placebo as per the assigned randomization number. Patient blinding was achieved by filling investigational agents in the same color syringes.

Study-eligible patients were treated with a single 3 mL injection of TG-C, which was pooled into one syringe from two components of non-transduced human allogeneic chondrocytes (hChonJ; 1.35×10^7 cells/2 mL) and transduced human allogeneic chondrocytes (hChonJb#7; 4.5×10^6 cells/1 mL) or a placebo (saline). The injection method used was identical to standard knee injection treatments, such as with hyaluronic acid and/or steroids.

Efficacy evaluations

Primary endpoints. The effect of TG-C on the subjective IKDC assessment score was assessed,

Figure 1. Flow diagram of patient enrollment and analysis. The full analysis set (FAS) was used for analyzing both the efficacy and safety endpoints.

with the outcomes transformed to a 100-point score (higher scores corresponded to better function/fewer symptoms), and changes in pain severity represented by a 100 mm VAS score (0–100 points; lower scores corresponded to less pain) at 52 weeks (12 months) post injection compared to baseline.

Secondary endpoints. The effect of TG-C on IKDC and 100 mm VAS scores at 26 (6 months) and 39 weeks (9 months) post injection were assessed compared to baseline. The effect of TG-C on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score²³ (measuring pain,

stiffness, and physical function), the Knee Injury and Osteoarthritis Outcome Score (KOOS) score²⁴ (100-point scale measuring pain, symptoms, and activities in daily living [ADL], knee function in sport and recreation, and knee-related quality of life) was also assessed at 26, 39, and 52 weeks post injection. Changes in joint space narrowing were measured by X-ray imaging in the posteroanterior view using a SynaFlexer™ positioning frame²⁵ (Synarc, Newark, CA). Whole-organ MRI scoring (WORMS) was used to incorporate changes in edema lesion scoring, cartilage thickness defect depths, cartilage defect surface areas, osteophytes,

joint fluids, meniscus structures, meniscus signals, periarticular inflammation, and synovial thickening and inflammation. Finally, the ICRS grade at 26 and 52 weeks was used to assess cartilage improvement based on the size of the major lesion.

Additional quantitative evaluations of MRI changes were conducted in cartilage thickness and subchondral bone areas. Quantitative changes were evaluated by measuring the bone area of all anatomical regions in the femur, tibia, and patella²⁶ and by automated segmentation of the hyaline cartilage in Double Echo Steady State (DESS) images (or similar images).²⁷ Consistent measurements of thickness were then taken using the active appearance model (AAM; a type of shape model designed for examining fat-saturated, high-resolution images such as the Siemens DESS-weighted sequence). AAM imaging produces detailed and consistent maps of cartilage thicknesses for the entire femur, tibia, and patella cartilage surfaces, subdivided into anatomical masks, which was previously accomplished by manual segmentation.^{28,29}

Changes in the central medial femur (cMF) region and the central medial tibia (cMT) region were measured. These regions have been identified by various investigators (including some at Imorphics) as the most responsive regions for detecting OA progression.³⁰ The average cartilage thickness was measured from the subchondral bone³¹ within a defined anatomical bone region, and is reported here as an average over the region in millimeters.

The effect of TG-C was assessed on serum C-terminal telopeptide of type I collagen (CTX-I, a subchondral bone resorption marker), serum cartilage oligomeric matrix protein (COMP), procollagen type II N-terminal propeptide (PIIANP), markers of cartilage joint metabolism, matrix metalloproteinase 3 (MMP-3), C1M and C3M (markers of tissue inflammation at the synovial membrane), C2M, CS846, urine biomarkers carboxy-terminal of cross-linked fragment type II collagen (CTX-II), and the CTX-II/creatinine ratio at 26, 39, and 52 weeks post injection.

Safety evaluations

The onset, nature, duration, severity, relationship to the study treatment, and outcome of all adverse events were determined and documented during each visit (4, 12, 26, 39, 52 weeks). Safety evaluations included physical examination (vital signs, pulse, temperature, systolic blood pressure, and diastolic blood pressure), laboratory test results (normal/abnormal changes in hematology,

serum chemistry, and urine testing), allergic reactions (common terminology criteria for adverse events [CTCAE v4.02] grade 4 or higher), injection site reaction and infection at the injection site, fibrosis-cosmesis, fibrosis in deep connective tissue, muscular/skeletal hypoplasia (all CTCAE grade 3 or higher), and TGF- β 1 enzyme-linked immunosorbent assay (ELISA) test results (above the normal range of ~ 65 ng/mL) during screening and at 52 weeks.

Statistical analysis

To maintain the overall statistical power for the two common endpoints (IKDC and 100 mm VAS) at $\geq 80\%$ or above, the test power for each endpoint was set at 90%. The number of patients calculated was 78 per group for the IKDC endpoint and 31 per group for the 100 mm VAS endpoint. Therefore, the plan was to enroll 78 patients per group, using the larger number needed to achieve significance for the IKDC endpoint.

Two-sample *t*-testing or Wilcoxon's rank-sum testing was performed per the normality test result to compare the level of improvement in primary endpoints of the IKDC total score and 100 mm VAS score in the TG-C and placebo groups. Analysis of covariance testing was conducted using the TG-C group and the pre-dose baseline IKDC or 100 mm VAS score as covariates, and regression analysis was performed for the endpoints showing statistically significant differences in the intergroup tests for demographic and medical history data. In addition, an intergroup test was performed using a method of analyzing data repeatedly measured through normality evaluation (repeated-measures analysis of variance [ANOVA] testing), and the significance level was set at 5%.

For the secondary efficacy endpoints, the continuous data were compared by the two-sample *t*-test or Wilcoxon's rank-sum test per the normality test result, and repeatedly measured data were tested using a repeated-measures ANOVA test. Categorical data were tested by the chi-square test or Fisher's exact test, depending on the expected frequency of each cell. The chi-square test or Fisher's exact test was also used for intergroup comparisons of normal and abnormal results following physical examination and for laboratory tests. The incidence, confidence interval (CI), and incidence frequency of adverse events, treatment-related events, and serious adverse events were calculated, and intergroup comparisons of incidences were performed using the chi-square test or Fisher's exact test, depending on the expected frequency of cells. Allergic reaction (CTCAE grade 4 or higher), injection site reaction

(CTCAE grade 3 or higher), infection (CTCAE grade 3 or higher), fibrosis–cosmesis (CTCAE grade 3 or higher), fibrosis–deep connective tissue (CTCAE grade 3 or higher), and muscular/skeletal hypoplasia (CTCAE grade 3 or higher) were confirmed by presenting the incidence rate and number of cases occurring per system organ class/preferred term (SOC/PT), based on the severity of adverse events. Patients deviating from the normal range (TGF- β 1 ELISA test score of ~ 65 /mL) were confirmed by performing intra- and intergroup comparisons for each visit.

Imorphics performed additional image analysis for various bone area regions and cartilage thickness-measurement regions. Statistical significance between the TG-C and placebo groups was evaluated using Student's *t*-test. Graphs of the results were produced, with error bars representing the CIs. Bone area changes were normalized to knee widths to correct for differences in patient size.

Study approval

The study protocol, informed consent form, patient information sheet, and other study-related documents were pre-approved by Ministry of Food and Drug Safety and the Institutional Review Board of each study center. Written informed consent was received from participants prior to inclusion in the study. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki.

RESULTS

Patient disposition, demographics, and baseline characteristics

Of the 269 patients screened, 163 were randomized for this study, of which 159 were included in the full analysis set (four patients were excluded due to failure to take the investigational product; Fig. 1). Patients were 18% male and 82% female, with a mean age of 61.5 ± 7.9 years and a mean body mass index (BMI) of 25.6 ± 2.6 kg/m². The mean duration of osteoarthritis in the patients was 5.4 years, with the main lesion sites being the left knee (52%) and the right knee (48%). The TG-C and placebo groups were not different with respect to the target disease, main lesion sites, medical history, and present illnesses (Supplementary Table S2).

Efficacy

Primary efficacy endpoints. Compared to the placebo, TG-C treatment was associated with a

significantly greater improvement in IKDC score (+15 vs. +5 points; $p < 0.001$) and 100 mm VAS score (–25 vs. –10 points; $p < 0.001$) at 52 weeks versus baseline (Fig. 2).

Secondary efficacy endpoints. Compared to the placebo, TG-C treatment showed significant improvements in IKDC and VAS scores at 26 weeks (IKDC: $p = 0.01$; VAS: $p = 0.02$) and 39 weeks (IKDC: $p = 0.02$; VAS: $p = 0.004$) versus baseline. Improvements in the total WOMAC score were greater in the TG-C group than in the placebo group at 26 and 39 weeks, and significantly greater at 52 weeks ($p = 0.003$). TG-C treatment showed greater improvement in each WOMAC category of pain, stiffness, and physical function than did the placebo at each time point. Statistically significant differences were seen in all categories at 52 weeks (pain: $p < 0.001$; stiffness: $p = 0.003$; physical function: $p = 0.008$) and in pain at 26 weeks ($p = 0.02$) and 39 weeks ($p = 0.02$). A statistically significant improvement in the total KOOS score was noted with TG-C treatment compared to placebo at 26 weeks ($p = 0.003$), 39 weeks ($p = 0.03$), and 52 weeks ($p < 0.001$; Fig. 2). TG-C treatment showed a higher level of improvement in each KOOS category of pain, symptoms, ADL function, function in sports and recreation, and knee-related quality of life than did the placebo at each time point. Statistically significant differences were observed in pain ($p = 0.002$), symptoms ($p = 0.005$), ADL functions ($p = 0.02$), and functions in sports and recreation ($p = 0.03$) at 26 weeks, although a statistically significant difference was only observed in pain ($p = 0.003$) at 39 weeks. Significant differences were observed again in all categories at 52 weeks (pain: $p < 0.001$; symptoms: $p < 0.001$; ADL function: $p = 0.002$; function in sports and recreation: $p = 0.004$; quality of life: $p < 0.001$).

Changes in joint space narrowing were measured by X-ray image analysis at 26 and 52 weeks, and were not significantly different between groups. Changes in bone marrow edema lesions, cartilage defect surface areas, joint fluids, meniscus structures, meniscus signals, periarticular inflammation, synovial thickening and inflammation, and sizes of major lesions were measured by MRI analysis using WOMS scoring at 26 and 52 weeks. Results showed that they were not significantly different between groups. However, osteophytes in the trochlea and patella regions in the placebo group showed a significant increase from baseline compared to those in the TG-C-treated group (Supplementary Table S3). Additional quantitative analysis with MRI data showed that the medial and lateral

Figure 2. Improvements in efficacy endpoints with TissueGene-C.

tibial regions underwent a reduction in the rate of bone area change in TG-C group (Fig. 3). The lateral patella and lateral patella femoral regions showed clear trends toward reduced changes from 26 to 52 weeks, and in all regions, less change (but not statistically significant) occurred in patients treated with TG-C than the placebo (Fig. 4). At 52 weeks, both the mean tibia and femur cartilage thicknesses increased after TG-C treatment, although the differences were not statistically significant, while the placebo were not different from baseline (Fig. 4).

The levels of serum CTX-I were lower in the TG-C group than in the placebo at all time points, with a significant decrease ($p=0.05$) observed at 39 weeks. The levels of serum C1M ($p=0.03$) and C3M ($p=0.02$) were transiently significantly higher in

the TG-C group than in the placebo group at 26 weeks, but not at later time points. The urine CTX-II/creatinine ratio was lower in the TG-C group than in the placebo group at all time points, but the differences were not statistically significant. Other biomarkers, such as serum CS846, MMP-3 (placebo < baseline), C2M, and PIIANP showed nonstatistical differences (both groups at 26 weeks < baseline; Fig. 5). The frequency of rescue drug use was not significantly different between the groups, and no patients withdrew during the study for arthroplasty.

Safety

The rates of adverse events were 63% and 44% in the TG-C and placebo groups, respectively. The

Figure 3. Primary bone area analysis. Medial femoral, medial tibial, lateral femoral, and lateral tibial regions. These figures show normalized changes from the baseline in the placebo and TissueGene-C groups. Both the medial and lateral tibial regions showed a slowing rate of bone area changes in the TissueGene-C group.

most common adverse events were arthralgia (occurring in 8% of patients in the TG-C group and 9% in the placebo group), peripheral edema (in 9% of patients in the TG-C and 1% in the placebo group), joint swelling (in 6% of patients in both groups), and injection site pain (in 5% of patients in the TG-C group; Table 1). Adverse events were resolved during the study period, except for three cases (joint swelling; one in the TG-C group and two in the placebo group), which were grade 1 adverse events. No categories other than injection site adverse events were reported as CTCAE grade 3 (severe) or higher. Six cases of adverse events at injection sites occurring in three patients in the TG-C group were assessed to be possibly related or related to TG-C and were resolved during the study period.

Serious adverse events occurred in 11 patients in the TG-C group: one patient each reported bladder cancer, carotid artery stenosis, multiple fractures, a mass of the right parotid, a suicide attempt, right knee medial meniscus tearing, nasal bone fracture,

cerebral hemorrhage and left arm fracture, left knee swelling and pain (arthralgia), clavicle fracture, and itching on the trunk. Only the patient who attempted suicide was withdrawn from the study. All serious adverse events were resolved during the study period (either through surgery or medication), and two cases of serious adverse events (joint swelling and pain) that occurred in the same patient were considered possibly treatment related (Table 1).

Clinically important changes were not observed in electrocardiogram findings, pulse rates, or body temperatures. From baseline to week 52, significant decreases occurred in systolic blood pressure in the TG-C ($p=0.02$) and placebo groups ($p=0.04$), and a decrease in diastolic blood pressure occurred in the TG-C group ($p=0.004$). However, the change in systolic and diastolic blood pressure was not clinically significant. No statistically significant differences were noted in the laboratory test measurements at week 52 compared to baseline, except for one patient who reported clinically

Figure 4. Secondary bone area changes and changes in cartilage thickness. Lateral patella and lateral patella femoral groups showed a clear trend for reduced changes from 26 (6 months) to 52 weeks (12 months) in the TissueGene-C group. At 52 weeks (12 months), changes in both tibia and femur mean cartilage thicknesses in the TissueGene-C treatment group were positive, but these differences were not significantly different.

significant abnormal hyperglycemia at week 52 compared to baseline. However, the investigator considered this event to be unrelated to treatment, as the patient had a high fasting blood sugar value at screening.

DISCUSSION

Injection of TG-C into the knee joints of osteoarthritis patients resulted in clinically significant improvements in the IKDC and VAS when compared to patients receiving a placebo in terms of the

Figure 5. Serum and urine biomarkers. Serum CTX-I levels were statistically significantly lower ($p=0.05$) with TissueGene-C treatment than with the placebo at 39 weeks. Serum C1M ($p=0.03$) and C3M ($p=0.02$) levels were transiently significantly higher in the TissueGene-C group than in the placebo group at 26 weeks but not at later time points. The urine CTX-II/creatinine ratio was lower in the TissueGene-C group than in the placebo group at all time points. The data shown are the least-squares geometric mean ± 1 standard error.

overall subjective assessments of functions, symptoms, and pain after 26, 39, and 52 weeks. Clinically significant improvements were also observed in the WOMAC and KOOS scores. A set of responder criteria for treatment with osteoarthritis drugs has been proposed based on meta-analysis of data from several clinical studies, wherein pain reduction of at least 20% is clinically meaningful in the context of additional functional improvements.³² For symptoms and functions, the primary

and most of the secondary efficacy endpoints in this trial were met, with a reduction in pain of 25% with TG-C treatment after 52 weeks compared to 10% with the placebo group. These results represent clinically meaningful improvements. Besides, the amount, frequency, and use of rescue drugs did not show any statistically significant difference between the two groups.

The safety of osteoarthritis drugs is of especially high priority because of the high prevalence and

Figure 5. (Continued)

chronic nature of the disease and the frequent presence of comorbidities. The incidences of adverse- and treatment-related events were significantly higher in the TG-C group than in the placebo group. These incidences were mostly related to pain and edema at the injection site, and were largely expected from the TG-C treatment itself. The one case of joint swelling and pain that occurred in the same patient was considered to be possibly treatment related, and these conditions all resolved within the study period.

While the primary goals of this study were to assess patient responses to TG-C, in terms of function and pain, the study was also designed to provide an initial assessment of disease modification by measuring changes in joint space widths (with radiographic evaluation), bone area and cartilage thicknesses (with MRI assessment), and soluble biomarkers. There was a clear trend toward slower bone area progression in the TG-C group, although the difference was not statistically significant due to the limited image quality and statistical power. Interestingly, there was an indication of slower bone area progression in the

medial and lateral tibial regions in the TG-C group between 26 and 52 weeks, suggesting the possibility of increasing efficacy over time. Although cartilage thicknesses in the femoral and tibial regions were consistently greater at 52 weeks with TG-C treatment than with the placebo, no statistically significant difference was observed. The lack of statistical significance may stem in part from the observation that many patients had no measurable baseline cartilage.

The observations of lower levels of serum CTX-I and urine CTX-II/creatinine ratios indicated less subchondral bone and cartilage degradation, respectively, in patients treated with TG-C. The transient increase in C1M and C3M levels at the earlier time point may have been due to cartilage regeneration, leading to the release of the 32-mer aggrecan, which binds to Toll-like receptors and can then induce cartilage turnover/inflammation. The 32-mer is the fragment of aggrecan that is generated by MMPs and ADAMTS (a disintegrin and metalloprotease with thrombospondin motifs) proteins.³³ However, the sample size in this study was not sufficiently large to be conclusive. Hence,

Table 1. Frequency of adverse and severe adverse events

Variable	TissueGene-C, N = 78		Placebo, N = 81		p-Value
	n (%)	Cases	n (%)	Cases	
Any adverse event	49 (63)	102	36 (44)	78	0.0202 ^a
Treatment-related adverse events	27 (35)	39	10 (12)	14	0.0009 ^a
Serious adverse events	11 (14)	13	0 (0)	0	0.0003 ^b
Injury, poisoning and procedural complications	5	5	0	0	
Clavicle fracture	1	1	0	0	
Facial bones fracture	1	1	0	0	
Meniscus injury	1	1	0	0	
Multiple fractures	1	1	0	0	
Upper limb fracture	1	1	0	0	
Nervous system disorders	2	2	0	0	
Carotid artery stenosis	1	1	0	0	
Cerebral hemorrhage	1	1	0	0	
Musculoskeletal and connective tissue disorders	1	2	0	0	
Arthralgia	1	1	0	0	
Joint swelling	1	1	0	0	
Gastrointestinal disorders	1	1	0	0	
Salivary gland mass	1	1	0	0	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1	1	0	0	
Bladder cancer	1	1	0	0	
Psychiatric disorders	1	1	0	0	
Suicide attempt	1	1	0	0	
Skin and subcutaneous tissue disorders	1	1	0	0	
Pruritus	1	1	0	0	
Serious adverse drug reactions					
Musculoskeletal and connective tissue disorders	1	2	0	0	
Arthralgia	1	1	0	0	
Joint swelling	1	1	0	0	
Serious treatment-related adverse events	1 (1)	2	0 (0)	0	0.4906 ^b
Adverse events occurring in ≥2% of TissueGene-C-treated patients					
Arthralgia	6 (8)	7	7 (9)	7	
Joint swelling	5 (6)	5	5 (6)	5	
Back pain	3 (4)	4	2 (3)	3	
Edema peripheral	7 (9)	7	1 (1)	1	
Injection-site joint pain	4 (5)	4	0 (0)	0	
Injection-site joint swelling	3 (4)	3	0 (0)	0	
Injection-site edema	2 (3)	2	0 (0)	0	
Nasopharyngitis	3 (4)	3	3 (4)	3	
Headache	2 (3)	2	4 (5)	11	
Pruritus	2 (3)	4	2 (3)	2	

Dictionary: MedDRA v18.1.

A serious adverse event was one that resulted in death, threatened the life of a patient, resulted in disability/incapability or a congenital anomaly or birth defect, required hospitalization or extension of a hospital stay, or a major medical event requiring treatment. No serious adverse events were reported in the placebo group.

^aPearson's chi-square test.

^bFisher's exact test.

another Phase III study has been planned for the United States with sufficient statistical power to evaluate the DMOAD activity of TG-C.

TG-C was associated with non-statistical but potential structural improvements as much as could be expected from surgically implanted chondrocyte treatment (e.g., Chondron),³⁴ which is not expected from the treatment with hyaluronic acid.³⁵ Therefore, TG-C is a novel treatment offering sustained improvement of pain and functions for >1 year with a single injection and holds for great potential for DMOAD.

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AUTHOR DISCLOSURE

No competing financial interests exist.

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