


Safety and Tolerability of Intra-Articular Injection of Adipose-Derived Mesenchymal Stem Cells GXCPIC in 11 Subjects With Knee Osteoarthritis: A Nonrandomized Pilot Study Without a Control Arm

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Cheng-Fong Chen^{1,2,3} , Yi-Chung Chen^{1,3}, Yu-Show Fu⁴,
Shang-Wen Tsai^{1,2}, Po-Kuei Wu^{1,2,3}, Chao-Ming Chen^{1,2,3},
Wei-Ming Chen^{1,2,3}, Hung-Ta Hondar Wu^{5,6}, Chia-Hsin Lee⁷,
Chao-Liang Chang⁷, Po-Cheng Lin⁷, Yong-Cheng Kao⁷,
Chun-Hung Chen⁷, and Ming-Hsi Chuang^{8,9}

Abstract

The current study aimed to determine the safety profile of intra-articular-injected allogeneic adipose-derived mesenchymal stem cells (ADSCs) GXCPIC in subjects with knee osteoarthritis (OA) and its preliminary efficacy outcome. The 3 + 3 phase I study was designed with two dose-escalation cohorts: low dose (6.7×10^6 GXCPIC, $N = 5$) and high dose (4×10^7 GXCPIC, $N = 6$). The primary endpoint was safety, which was evaluated by recording adverse events throughout the trial; the secondary endpoints included total, pain, stiffness, and function subscales of the Western Ontario and McMaster Universities Arthritis Index (WOMAC), Visual Analogue Scale (VAS) for pain, and 12-Item Short Form (SF-12) health survey questionnaire. The GXCPIC treatment was found to be safe after 1 year of follow-up with no treatment-related severe adverse events observed. When compared to baseline, subjects in both the low- and high-dose cohorts demonstrated improving trends in pain and knee function after receiving GXCPIC treatment. Generally, the net change in pain (95% confidence interval (CI) = -7.773 to -2.561 at 12 weeks compared to baseline) and knee function (95% CI = -24.297 to -10.036 at 12 weeks compared to baseline) was better in subjects receiving high-dose GXCPIC. Although this study included a limited number of subjects without a placebo arm, it showed that the intra-articular injection of ADSCs was safe and well-tolerated in subjects with therapeutic alternatives to treat knee OA. However, a larger scale study with an appropriate control would be necessary for clinical efficacy in the following study.

Keywords

knee osteoarthritis, allogeneic adipose-derived mesenchymal stem cells (ADSCs), GXCPIC, safety, tolerability

¹ Department of Orthopaedics and Traumatology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

² Department of Surgery, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC

³ Therapeutic and Research Center of Musculoskeletal Tumor, Department of Orthopaedics, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

⁴ Department of Anatomy and Cell Biology, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC

⁵ Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

⁶ Department of Radiology, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC

⁷ Gwo Xi Stem Cell Applied Technology Co., Ltd., Hsinchu, Taiwan, ROC

⁸ Institute of Biopharmaceutical Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC

⁹ College of Management, Chung Hua University, Hsinchu, Taiwan, ROC

Cheng-Fong Chen and Po-Kuei Wu is also affiliated with Department of Exercise and Health Sciences, University of Taipei, Taipei, Taiwan, ROC.

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Corresponding Author:

Cheng-Fong Chen, Department of Orthopaedics and Traumatology, Taipei Veterans General Hospital, 18F, No. 201, Sec. 2, Shi-Pai Rd., Beitou District, Taipei 112201.

Email: cf_chen@vghtpe.gov.tw



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Introduction

Osteoarthritis (OA) is a common chronic degenerative joint disease that affects elderly and obese population^{1,2}. The prevalence of knee OA in females is significantly higher than that in males³ and around the age of 75 years was 16%–17%, of which 10%–12% for men and 18%–20% for women⁴. The most common clinical manifestations of OA are pain, swelling, stiffness, function limitation, limited mobility, and causes to decrease health-related quality of life (HRQOL). Current treatments for knee OA are mostly symptomatic, focusing on pain reduction, inflammation control, and joint function maintenance, including paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and hyaluronic acid (HA). However, the aforementioned treatments can only alleviate and the progression of OA is continuing to aggravate⁵.

Mesenchymal stem cells (MSCs) have multilineage differentiation potential, immunosuppressive properties, and low immunogenicity and are extensively available⁶. Among the others, adipose-derived stem cells (ADSCs) represent a promising source for their abundance, accessibility, and less invasive collection procedure⁷. ADSCs have been proposed as an appealing treatment for knee OA^{8–17}. Many preclinical studies have confirmed intra-articular injection of ADSCs reduced synovitis, osteophyte formation, and cartilage degeneration^{8,9}. Furthermore, clinical studies showed that the autologous ADSCs improved knee function and relieved pain without causing adverse events^{11–17}. A recent study found that using the autologous ADSCs in patients resulted in significant improvements in pain and life quality for up to 12 months when compared to the baseline¹⁶. While most studies have examined the efficacy and safety of the autologous ADSCs, the allogenic ADSCs have the advantage of application accessibility^{19–22}. Only a few clinical trials for the allogenic ADSCs treatment in patients with knee OA were investigated^{19–22}. In addition, different procedures or methodologies of adipose tissue derivation are very important in the application of orthopedics^{23,24}. Different harvest and isolation methods will affect the cell viability and functional phenotype of ADSCs²⁴. Until now, only a few clinical orthopedics-related applications with high-quality and high-concentration cells that meet regulatory requirements have been studied²⁴. Therefore, we conducted a phase I clinical trial in this study to evaluate the safety, tolerability, and efficacy of injecting the allogenic ADSCs that meet regulatory requirements in knee OA patients' knee.

Materials & Methods

GXCPC1 Preparation

The ADSCs in GXCPC1 were obtained from a trial in Hualien Tzu Chi Hospital, Taiwan (IRB number IRB-106-88-A). The inclusion/exclusion criteria for the adipose tissue

donors followed the guideline for donor eligibility by Taiwan Food and Drug Administration and were tested negative for human immunodeficiency virus-1/2, hepatitis B virus, hepatitis C virus, and syphilis infections as well as screened for high risks for transmissible spongiform encephalopathies and Creutzfeldt-Jakob disease. The preparation process of GXCPC1 was modified from reference^{25–27}. To put it briefly, the adipose tissues of eligible donors were collected via liposuction and immediately transferred to a Good Tissue Practice (GTP) lab (Gwo Xi Stem Cell Applied Technology Co., Ltd.). Adipose tissues were dissociated with collagenase and the resultant dispersed cells were collected and cultured at 37°C in a carbon dioxide incubator for the primary culture. GXCPC1-related quality testing was executed by a third-party certification laboratory (accredited in respect of laboratory by Taiwan Accreditation Foundation, Accreditation Criteria: ISO/IEC 17025, Accreditation Number: 2800). In-process and safety testing of GXCPC1 for microbiological assessments (including mycoplasma, sterility, and endotoxin tests) were employed to assure safety. The immunophenotypes (human clusters of differentiation CD34, CD45, CD90 and CD105), the viability, and tri-lineage differentiation properties were also evaluated. The quality tests such as sterility, mycoplasma, identity, purity, potency, and stability were conducted to meet regulatory requirements. GXCPC1 is a turbid white cell suspension containing 6.7×10^6 or 4×10^7 ADSCs in 3 ml of normal saline and packed in sterile glass bottles.

Trial Design

This trial (protocol number GXCPC1-01) was conducted at Taipei Veterans General Hospital in Taiwan. This trial was registered on clinicaltrials.gov (NCT03943576) and was approved by the Institutional Review Board (IRB number 2018-10-005C) in accordance with the Declaration of Helsinki.

The purpose of this 3 + 3 dose-escalation phase I study was to assess the safety, tolerability, and efficacy of allogeneic ADSCs (GXCPC1) in the treatment of knee OA. Two dose levels were tested: 6.7×10^6 (low dose) and 4×10^7 (high dose). Eligible subjects were assigned to one of the two doses according to the chronological order of eligibility confirmation.

A subject was considered evaluable if this subject contributed to the assessment of tolerability. Tolerability assessment contributes when (1) an eligible subject received GXCPC1 injection and experienced dose-limiting toxicity (DLT), or (2) an eligible subject received a successful GXCPC1 injection and no DLT was observed until week 8. The DLT was defined as any adverse event that is equal to or greater than grade 3 (CTCAE v.5.0) and was causally related to GXCPC1.

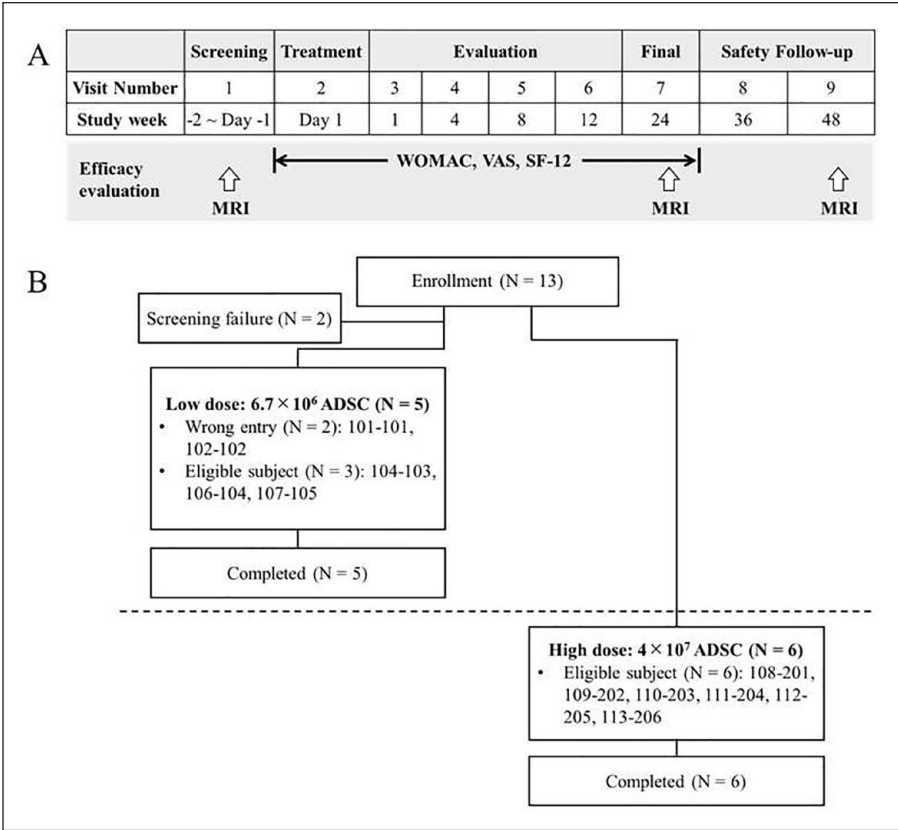


Figure 1. Study schedule and schema of study subject disposition. (A) Study schedule. (B) Schema of study subject disposition. ADSC: adipose-derived mesenchymal stem cells; SF-12: 12-item Short Form; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Subjects

Before enrolling, all subjects provided written informed consent to participate in the study. Adults aged 40 to 80 years old with Kellgren-Lawrence grading II-IV and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score range 7 to 17 in the target knee were enrolled in the study²⁸. The study excluded subjects who had previous surgery for articular fracture, ligament reconstruction, meniscal reconstruction, or knee arthroplasty on the target knee. Subjects who had intra-articular intervention 12 weeks before the screening were also excluded, as were those who had received a systemic or local immunosuppressive agent, an anti-inflammatory drug, steroid, analgesics, opioid, or duloxetine for knee OA 1 week before screening. Acetaminophen and NSAID act as pain relievers when subjects were in need. Subjects should, however, stop taking pain relievers at least 24 h before the pain evaluation.

One of the eligible subject's knees that met the criteria was chosen as the target knee for efficacy evaluation. Each subject received a single intra-articular injection at the target knee on day 1, followed by scheduled visits on weeks 1, 4, 8, 12, 24, 36, and 48 (Fig. 1A).

Outcome Measures

The primary endpoint was the incidence of adverse events (AEs) and serious adverse events (SAEs) up to 48 weeks after administration. The changes in laboratory examination results from baseline to post-treatment visits were included in the safety assessments. Secondary endpoints included net changes in WOMAC total and sub-scores (pain, stiffness, and physical function), Visual Analogue Scale (VAS) for pain, and 12-item Short Form (SF-12) from baseline to post-treatment visits.

Clinical Laboratory Evaluation

Laboratory assessments, including hematology and biochemistry, were performed at the screening, week 1, week 8, week 24, and week 48 visits. The measured items were listed as follows: for hematology: white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, hemoglobin, hematocrit, platelet, and red blood cells; for biochemistry: aspartate aminotransferase, alanine aminotransferase, serum creatinine, blood urea nitrogen, total bilirubin, and albumin.

Table 1. Summary of Demographics Data in ITT Population.

	Low dose (N = 5)	High dose (N = 6)
Age (years), mean (SD)	66.2 (5.89)	64.5 (5.32)
Body weight (kg), mean (SD)	67.8 (12.24)	68.7 (4.55)
Body height (cm), mean (SD)	159.6 (5.22)	153.5 (4.06)
Baseline BMI (kg/m ²), mean (SD)	26.6 (4.68)	29.3 (2.82)
Gender (M/F), n (%)	0/5 (0%/100%)	0/6 (0%/100%)
Disease duration (years), mean (SD)	7.07 (3.130)	4.31 (3.831)
Kellgren–Lawrence grade, n (%)		
II	2 (40.0%)	3 (50.0%)
III	2 (40.0%)	3 (50.0%)
IV	1 (20.0%)	0

Abbreviations: BMI: body mass index; ITT: intend-to-treat.

Table 2. Summary of Adverse Events in ITT Population.

Event: Subject (%)	Low dose (N = 5)	High dose (N = 6)
Subjects with AE	17: 5 (100.0%)	37: 6 (100.0%)
Grade \geq 3	3: 3 (60.0%)	2: 1 (16.7%)
Grade 4	0	1: 1 (16.7%)
Grade 5	0	0
Subjects with treatment-related AE	2: 2 (40.0%)	7: 6 (100.0%)
Grade \geq 3	0	0
Grade 4	0	0
Grade 5	0	0
Subjects with SAE	2: 2 (40.0%)	1: 1 (16.7%)
Requires or prolongs hospitalization	2: 2 (40.0%)	1: 1 (16.7%)
Life-threatening	0	0
Death	0	0
Subjects with treatment-related SAE	0	0
Subjects with SUSAR	0	0

The data are presented as “adverse event number: subject number with adverse events (%).” AE: adverse event; ITT: intend-to-treat; SAE: serious adverse event; SUSAR: suspected unexpected serious adverse reactions.

Statistical Analysis

For statistical analysis, the intend-to-treat (ITT) population was used, which included all subjects who had ever received GXPC1. For the WOMAC, VAS for pain, and SF-12, one-sample *t* test (denoted as *t*) was used to assess the net change from baseline to post-treatment visits within group. If the net changes were not normally distributed, Wilcoxon rank-sum test (denoted as *w*) would be used to analyze the difference. All within-group comparisons were performed educing a 95% confidence interval for difference. Statistical Analysis Software (SAS) version 9.4 was used for all the statistical analyses.

Results

Subjects' Disposition and Baseline Characteristics

A total of 13 subjects were screened in the study; two subjects were screen failures, resulting in five subjects in the low-dose cohort and six subjects in the high-dose cohort (Fig. 1B). Two subjects, who had WOMAC pain scores of

4 and 2, respectively, were mistakenly received GXPC1 at low dose. However, the two subjects still completed the trial for long-term safety monitoring and efficacy evaluation.

The demographic and baseline characteristics of the ITT population are shown in Table 1. In the ITT population, the mean (SD) age of all subjects was 66.2 (5.89) years in the low-dose cohort and 64.5 (5.32) years in the high-dose cohort. All subjects had body weight index (BMI) < 35 kg/m² and the mean (SD) BMI of all subjects was 26.6 (4.68) kg/m² in the low-dose cohort and 29.3 (2.82) in the high-dose cohort. In both cohorts, the subjects were all females with knee OA grades II to IV. The average duration of knee OA since diagnosis was 7.07 years in the low-dose cohort and 4.31 in the high-dose cohort.

Safety

No subjects in the trial experience DLT. AEs were reported by all subjects in both cohorts (Tables 2 and 3). Three (60.0%) subjects in the low-dose cohort and one (16.7%)

Table 3. Summary of Adverse Events by System Organ Class and Preferred Term in ITT Population.

Event: Subject (%)	Low dose (N = 5)	High dose (N = 6)
At least one below	17:5 (100.0%)	37:6 (100.0%)
General disorders and administration site conditions	2:2 (40.0%)	7:6 (100.0%)
Injection site pain	2:2 (40.0%)	6:6 (100.0%)
Pyrexia	0	1:1 (16.7%)
Infections and infestations	5:2 (40.0%)	15:5 (83.3%)
Gastroenteritis	1:1 (20.0%)	3:3 (50.0%)
Nasopharyngitis	1:1 (20.0%)	5:2 (33.3%)
Herpes virus infection	1:1 (20.0%)	2:2 (33.3%)
Conjunctivitis	0	2:2 (33.3%)
Acute hepatitis B	1:1 (20.0%)	0
Groin abscess	1:1 (20.0%)	0
Otitis externa	0	1:1 (16.7%)
Tinea pedis	0	1:1 (16.7%)
Urinary tract infection	0	1:1 (16.7%)
Vaginal infection	0	0
Musculoskeletal and connective tissue disorders	5:4 (80.0%)	2:2 (33.3%)
Osteoarthritis	2:2 (40.0%)	1:1 (16.7%)
Arthralgia	1:1 (20.0%)	0
Back pain	0	1:1 (16.7%)
Musculoskeletal pain	1:1 (20.0%)	0
Rotator cuff syndrome	1:1 (20.0%)	0
Gastrointestinal disorders	1:1 (20.0%)	2:2 (33.3%)
Abdominal distension	0	1:1 (16.7%)
Gastritis	1:1 (20.0%)	0
Mouth ulceration	0	1:1 (16.7%)
Injury, poisoning, and procedural complications	1:1 (20.0%)	1:1 (16.7%)
Procedural pain	1:1 (20.0%)	0
Road traffic accident	0	0
Traumatic arthropathy	0	1:1 (16.7%)
Skin and subcutaneous tissue disorders	0	4:3 (50.0%)
Urticaria	0	2:1 (16.7%)
Acne	0	1:1 (16.7%)
Dermatitis allergic	0	1:1 (16.7%)
Ear and labyrinth disorders	1:1 (20.0%)	1:1 (16.7%)
Vertigo	1:1 (20.0%)	1:1 (16.7%)
Cardiac disorders	1:1 (20.0%)	0
Mitral valve prolapse	1:1 (20.0%)	0
Eye disorders	0	3:1 (16.7%)
Conjunctival oedema	0	1:1 (16.7%)
Conjunctivitis allergic	0	1:1 (16.7%)
Lacrimation decreased	0	1:1 (16.7%)
Reproductive system and breast disorders	0	1:1 (16.7%)
Atrophic vulvovaginitis	0	1:1 (16.7%)
Respiratory, thoracic and mediastinal disorders	0	1:1 (16.7%)
Epistaxis	0	1:1 (16.7%)
Vascular disorders	1:1 (20.0%)	0
Hypertension	1:1 (20.0%)	0

The data are presented as “adverse event number: subject number with adverse events (%).” ITT: intend-to-treat.

subject in the high-dose cohort experienced grade ≥ 3 AEs. Treatment-related AEs were reported by two (40.0%) subjects in the low-dose cohort and six (100.0%) subjects in the high-dose cohort, but none of them were severe. Two (40.0%)

subjects in the low-dose cohort and one (16.7%) subject in the high-dose cohort had SAEs that necessitated or prolonged hospitalization. All SAEs were considered unrelated to treatment. Moreover, no suspected unexpected serious

Table 4. Summary of Treatment-Related AEs in ITT Population.

Event: Subject (%)	Low dose (N = 5)	High dose (N = 6)
At least one below	2:2 (40.0%)	7:6 (100.0%)
General disorders and administration site conditions	2:2 (40.0%)	7:6 (100.0%)
Injection site pain	2:2 (40.0%)	6:6 (100.0%)
Pyrexia	0	1:1 (16.7%)

The data are presented as “adverse event number: subject number with adverse events (%)” AE: adverse event; ITT: intend-to-treat.

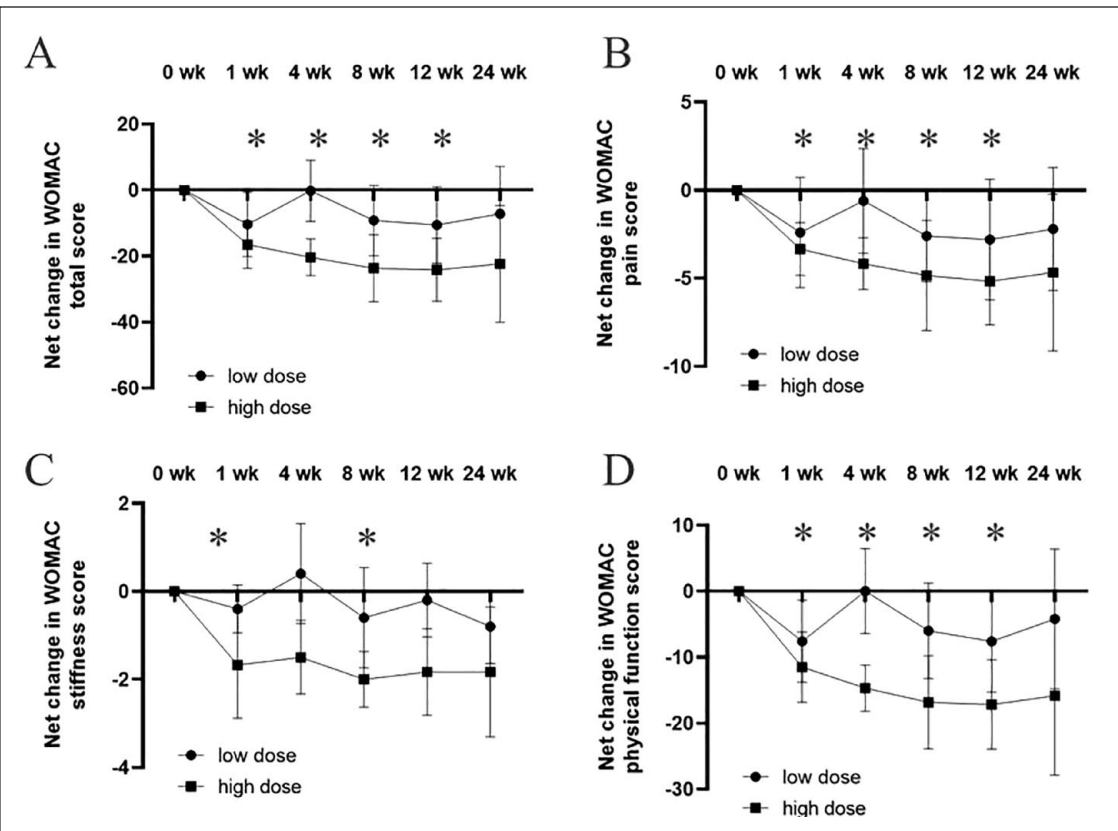


Figure 2. Net changes in WOMAC from baseline to 24 weeks after intra-articular injection of GXCP1. (A) WOMAC total score, (B) WOMAC pain score, (C) WOMAC stiffness score, and (D) WOMAC physical function score. The data are presented by mean and error bars indicate standard deviation. WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. *: Sign of significant difference in the high-dose cohort.

adverse reaction (SUSAR) or death was reported in this study. Table 4 showed that the most common treatment-related AEs were injection site pain in both cohorts.

All subjects had either normal or abnormal without clinically significant (NCS) values in hematology and biochemistry parameters. No clinically significant values were found throughout the study period in both cohorts.

Efficacy

In both cohorts, there was a decreasing trend in WOMAC total and sub-scores (pain, stiffness, and physical function) in the net change from baseline to post-treatment visit (Fig. 2). Over time, the high-dose cohort had greater reductions, which

represented the greater improvement, in WOMAC total and sub-scores than the low-dose cohort. The net change from baseline to post-treatment in high-dose cohort showed significant differences in WOMAC total, pain, and physical function scores at 1, 4, 8, and 12 weeks compared to baseline (Fig. 2A, B, and D). There were also significant differences in WOMAC stiffness scores from baseline to 1 and 8 weeks after administering a high dose of GXCP1 (Fig. 2C). However, the low-dose cohort had no significant difference in WOMAC total, pain, stiffness, and physical function sub-scores.

Consistent with these results, both cohorts had a decreasing trend in the VAS for pain in the net change from baseline to post-treatment visit (Fig. 3). A significant difference in VAS for pain was observed in the low-dose cohort at 12 and

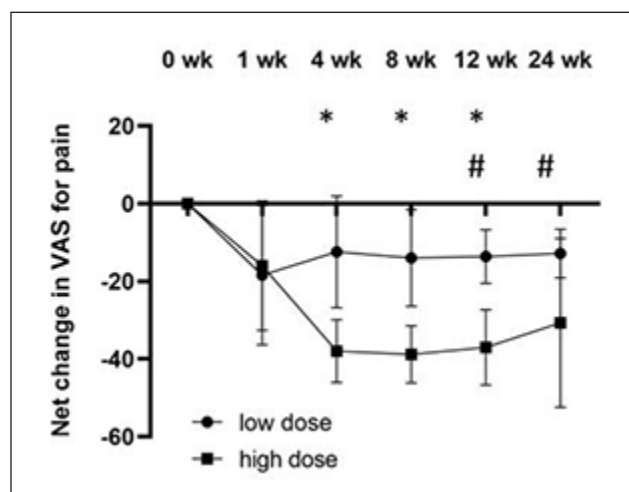


Figure 3. Net changes in VAS for pain from baseline to 24 weeks after intra-articular injection of GXCP1. The data are presented as mean and error bars indicate standard deviation. VAS: Visual Analogue Scale. *, #: Sign of significant difference in the high-dose cohort and low-dose cohort, respectively.

24 weeks. A significant decrease in VAS for pain was observed in the high-dose cohort at 4, 8, and 12 weeks.

The net change in SF-12 physical component summary (PCS) from baseline to post-treatment visit had an increasing trend in both cohorts (Fig. 4A). An increase in SF-12 PCS in the high-dose cohort was observed from 1 week to 24 weeks after GXCP1 administration. On the contrary, we found no statistical differences in SF-12 MCS (mental component summary) over time in either cohort (Fig. 4B).

Discussion

This study preliminarily confirmed that intra-articular injection of GXCP1 was safe and well-tolerated in subjects with knee OA. Based on a phase I clinical trial, this study focused on treatment-related adverse events in subjects. We observed that the most common complication related to the allogeneic ADSCs was injection site pain in 40% subjects in the low-dose cohort and 100% subjects in the high-dose cohort. All the treatment-related adverse events were graded as mild or moderate and they all soon subsided. These transient side effects were also observed in the other reported clinical trials^{19–22}. Perhaps, physiological responses in the joint cavity or anti-histone H2B antibody production were resulted after intra-articular injections with ADSCs^{5,29}. Moreover, the allogeneic ADSCs had already been proven to be safe in numerous clinical trials^{19–22}. A systematic review of literature discovered only four SAEs in 844 intra-articular MSCs procedures, including one infection, one pulmonary embolus, and two unrelated events to the intervention³⁰. In our study, no severe adverse events related to the GXCP1 were reported over the 48-week study period. Overall, this study proved that GXCP1 for knee OA treatment was safe and well-tolerated.

These results of WOMAC scores, VAS score, and SF-12 implied that better results might be achieved with an intra-articular injection at the dose of 4×10^7 GXCP1. The choice of optimal cell numbers for intra-articular injection was challenging and varied across studies. One clinical study used higher cell doses of up to 1×10^8 ADSCs, and the study found that at least 1×10^8 ADSCs per injection was required to reduce cartilage defects through regeneration¹⁶. Chen et al. reported pain significantly decreased using 1.6×10^7 or 3.2×10^7 or 6.4×10^7 ADSCs; especially, 3.2×10^7 ADSCs had the best effect on pain relief among them, but no cartilage regeneration was observed²⁰. Lu et al. indicated two intra-articular injections of 1.0×10^7 , 2.0×10^7 , and 5.0×10^7 ADSCs, and only 5.0×10^7 ADSCs significantly decreased VAS at week 12 and 48, while no significantly decreased WOMAC at week 24 and 48. Interestingly, there was no significant trend toward increased cartilage in 1.0×10^7 ADSCs²². Some reported that the high MSCs injection (1×10^7) generated free bodies of scar tissue in the rat joint which may cause considerable dysfunction of the joints, whereas others reported that sufficient cell density is required for rabbit cartilage production^{8,11}. In our study, significant differences in WOMAC pain score were reported from baseline to week 1, 4, 8, and 12 while the differences in VAS were found at week 4, 8, and 12 in the high-dose cohort. Only VAS at week 12 and 24 showed significant differences from baseline to post-treatment in the low-dose cohort. According to the results of safety and preliminary clinical efficacy, high-dose cohort conferred an improvement in pain and functional scores.

The preliminary clinical efficacy results confirmed that GXCP1 could improve HRQOL in OA patients according to SF-12 results. The SF-12 is a self-reported questionnaire to assess the impact of HRQOL on disease status. Previous studies used SF-12 to assess HRQOL in OA patients^{31–34}. This trial intended to enroll both genders but subjects were all female. The result showed that the population of OA was predominantly female. According to gender differences in the 911 elderly Taiwanese individuals with knee OA, significant differences in SF-12 PCS were reported while no statistical differences in SF-12 MCS were observed in Taiwanese females with knee OA. On the contrary, significant differences in SF-12 MCS were found while no statistical differences in PCS were observed in Taiwanese males with knee OA³⁵. This report indicated the presentation and natural history of condition may be different in male and female groups of Taiwanese. This result aligns with our study. In our study, an increase in SF-12 PCS in the high-dose cohort was observed from 1 week to 24 weeks after GXCP1 administration. On the contrary, we found no statistical differences in SF-12 MCS over time in either cohort (Fig. 4B). By contrast, neither SF-12 PCS nor MCS found significant improvement after bone marrow MSCs treatment in knee OA patients' knee³³. Another study indicated a significant reduction was observed in SF-36 at 6 and 12 months in knee OA patients' knee¹⁷. Therefore, the preliminary clinical efficacy results

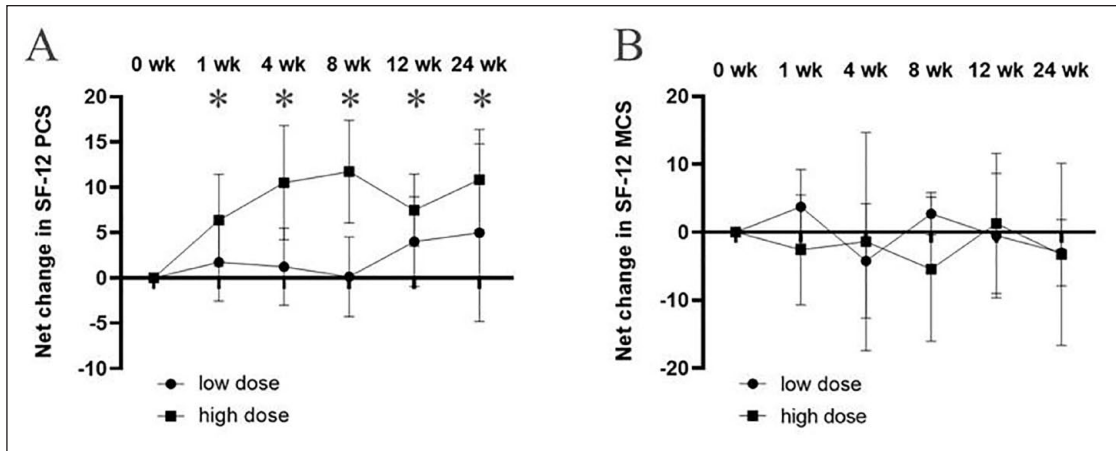


Figure 4. Changes in SF-12 during 24 weeks after intra-articular injection of GXPC1. (A) PCS. (B) MCS. The data are presented as mean and error bars indicate standard deviation. MCS: mental component summary; PCS: physical component summary. *: Sign of significant difference in the high-dose cohort.

confirmed that GXPC1 could improve HRQOL in OA patients. However, due to the small size and gender of clinical trials, more scientific evidence is needed to confirm the therapeutic effect of GXPC1.

Robert et al. indicated that the types of performed procedures and the choice and processing adipose tissue derivatives are high heterogeneity²⁴. Bi et al. also reported that different processing methods of adipose tissue should be explicitly explained with application in orthopaedic²³. GXPC1, an expanded ADSCs product, is dissociated with enzymes and the resultant dispersed cells were collected and cultured according to our published methods. Flow cytometry immunophenotyping analysis revealed that GXPC1 was positive ($\geq 95\%$) for the surface markers CD90, and CD105, but essentially negative ($\leq 2\%$) for CD34 and CD45 (data not shown). Moreover, GXPC1 that meets regulatory requirements was shown to be safe, well-tolerated, and efficient in knee OA patients' knee in our study. However, the main limitation of this study was the small number of subjects (11). In addition, it was not randomized and did not include a control arm (placebo). However, this study showed that intra-articular injection of ADSCs was safe and well-tolerated in subjects with knee OA. Nonetheless, a larger scale study with an appropriate control would be necessary for clinical efficacy in the following study.

Moreover, many studies have reported that ADSCs treatment can improve pain, swelling, stiffness, and function of the knee in patients with KL grading I-III, and even KL grading IV. Both Chahal et al.¹⁴ and Kuwasawa et al.³⁶ showed that MSCs improved pain, stiffness, symptoms, and quality of life relative to baseline in patients with late-stage KL knee OA. In addition, some patients with KL grading IV are unwilling to undergo arthroplasty. Therefore, we would like to know whether GXPC1 can improve symptoms in patients with late-stage KL knee OA or not. In this study, we recruited one patient with KL grading IV and this patient

with KL grading IV in this study was special. According to her X-ray, this patient's knee was diagnosed as KL grading IV. However, the WOMAC pain score and VAS of baseline were 8 and 14, respectively. Perhaps, this patient seems relatively insensitive to pain. Therefore, all pain questionnaire scores are not high. Even though all pain questionnaire scores are not high, after GXPC1 treatment, the improvement of WOMAC total score and VAS from baseline to post-treatment was observed (3 and 14, respectively) at 24 weeks. This patient completely improved painful symptoms from the VAS questionnaire score after GXPC1 treatment. Therefore, GXPC1 has therapeutic potential for OA patients with KL grading IV from these results. In summary, GXPC1 therapy was found to be safe and effective for treating knee OA subjects. GXPC1 groups at low or high doses demonstrated a safety profile with a long duration of the pain relief. GXPC1 administration is low risk, and these findings support the continued development of GXPC1.

Authors' Note

This study was done in Taipei Veterans General Hospital, Taiwan.

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Author Contributions

C.-F.C., S.-W.T., P.-K.W., C.-M.C., W.-M.C. and H.-T.H.W. contributed to the research design and wrote the manuscript; Y.-S.F. drafted and revised the work; Y.-C.C. was responsible for the research execution, data collection, and data analysis. C.-H.L. contributed to the research design, data curation, validation, project administration, investigation, supervision, writing-review and editing. P.-C.L. contributed to the conceptualization, resources, supervision, project

administration, and funding acquisition. C.-L.C., Y.-C.K., and C.-H.C. contributed to the validation. M.-H.C. contributed to the conceptualization and funding acquisition. All authors have read and approved the final manuscript.

Availability of Data and Materials

The data sets used/or analyzed are available by the corresponding author on reasonable request.

Clinical Trial Notation

Allogeneic Adipose Tissue-Derived Mesenchymal Stem Cells (GXPC1) for Knee Osteoarthritis (NCT03943576).

Ethical Approval

Ethical aspects of the study were approved by the Research Ethics Committee of Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (IRB No: IRB106-88-A) and the Institutional Review Board of Taipei Veterans General Hospital (IRB number 2018-10-005C).

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

All the patients provided informed consent for inclusion in the study.

Research Ethics and Patient Consent

All procedures involving human subjects were conducted in accordance with policies adopted by the Research Ethics Committee of Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (IRB No: IRB106-88-A) and the Institutional Review Board of Taipei Veterans General Hospital (IRB number 2018-10-005C).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORCID iD

Cheng-Fong Chen  <https://orcid.org/0000-0002-2485-6159>

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