A Phase 2, Double-Blind, Randomized, Controlled Study to Evaluate the Efficacy and Safety of JointStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Treatment of Osteoarthritis

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Protocol Signature Page

I have carefully read the attached protocol entitled "A Phase 2, Double-Blind, Randomized, Controlled Study to Evaluate the Efficacy and Safety of JointStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Treatment of Osteoarthritis" dated May 14, 2018 and agree to its terms in cluding principles of disclosure and confidentiality.

I agree to submit this protocol to the Institutional Review Board to obtain its approval prior to initiation of the study.

I also agree to comply with the International Conference of Harmonization (ICH) Tripartite Guidelines on good Clinical Practice, and applicable regulations/guidelines set forth in the Code of Federal Regulations (CFR), Title 21, Parts 11, 50, 54, 56, and 312.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of NC.

Signature

Name of Principal Investigator

Date (DD/MMM/YYYY)

Protocol Synopsis

Title: A Phase 2, Double-Blind, Randomized, Controlled Study to Evaluate the Efficacy and Safety of JointStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Treatment of Osteoarthritis

Phase: Phase 2

Indication: Osteoarthritis (Degenerative Arthritis)

Study Objective: To evaluate the efficacy and safety of autologous adipose tissue derived mesenchymal stem cells (AdMSC) for the treatment of osteoarthritis

Study Design: This study is a double-blind, randomized, controlled study with two arms to evaluate JointStem as a treatment for subjects with osteoarthritis. Following a 2-week screening period, approximately 30 subjects will be randomly assigned into one of the following two arms in a 2:1 ratio (2 JointStem : 1 positive control):

- JointStem ($1x10^8$ cells/3mL)
- Positive control: Synvisc-One®

After each subject completes 6-month visit (Visit 6) and the data management team confirms all individual data have no issue, the individual database will be locked and the blinding will be open for the statistical analysis. Only subjects who are randomized to JointStem group will then be scheduled for 9-month and 12-month follow-up visits (Visits 7 and 8).

Long-term follow-up visit will be conducted to collect long-term feedbacks (records of medications and treatments) following 2 years after injection for all subjects who complete 6-month visit and accept the long-term follow-up visit.

Co-Primary Endpoints:
① Change of WOMAC score from baseline at Month 6 (JointStem group)
② Change of VAS score from baseline at Month 6 (JointStem group)
③ MRI improvement evaluation at Month 6 (JointStem group)

Secondary Endpoints:
1) JointStem group vs. positive control group
   ① Change of WOMAC score from baseline at Month 6
   ② Change of VAS score from baseline at Month 6
   ③ Change of KOOS from baseline at Month 6
   ④ Change of Lysholm Knee Scoring Scale from baseline at Month 6
   ⑤ Change of IKDC from baseline at Month 6
   ⑥ Change of RAND-36 Score from baseline at Month 6
2) JointStem group
   ① Change of WOMAC score from baseline at Months 9 and 12
   ② Change of VAS score from baseline at Months 9 and 12
   ③ Comparison of MRI improvement evaluations between at Month 6 and at Month 12
   ④ Change of Lysholm Knee Scoring Scale from baseline at Months 6, 9 and 12
   ⑤ Change of KOOS from baseline at Months 6, 9 and 12

⑥ Change of IKDC from baseline at Months 6, 9 and 12
⑦ Change of RAND-36 Score from baseline at Months 6, 9 and 12

3) Incidence of adverse events and laboratory abnormalities

Exploratory Endpoints: Analysis of all efficacy scales and MRI results and the history of treatments and medications following 2 years after injection for all subjects who are injected and complete 6-month follow-up visit

Inclusion Criteria:

1) Subject who can give written informed consent
2) Male or female of any race, aged 22-60
3) Subject who had osteoarthritis of knee diagnosed at least six months prior to Screening
4) Subject who has joint pain ≥ 40mm on VAS (Visual Analog Scale) at Screening
5) Subject who has swelling, tenderness and active range of motion ≥ Grade I at Screening
6) Subject who seeks invasive interventions of intra-articular injections
7) Subject who is willing to discontinue all pain medications for osteoarthritis except rescue medication (< acetaminophen 3.25 g per day) at least 72 hours prior to screening and throughout the duration of study
8) Subject who has radiographic evidence of grade 3 to 4 osteoarthritis based on the Kellgren and Lawrence radiographic criteria.
9) Female subject who meets one of the following criteria:
   a. Female subject of non-childbearing potential:
      - Post-menopausal for at least 6 months; or
      - Surgically sterile
   b. Female subject of child-bearing potential:
      - Neither pregnant nor lactating; and
      - Abstinent or use adequate contraception (2 forms of birth control, one of which must be a barrier method)
10) Subject who is able to comply with lifestyle guidelines, scheduled visits, treatment plan, laboratory tests, and other study procedures

Exclusion Criteria:

1) Subject who has Body Mass Index (BMI) > 35 kg/m^2
2) Subject who has unstable knees
3) Subject who took any NSAIDs within two weeks from Screening
4) Subject who had any intra-articular injection therapy in any joint within 2 months from Screening
5) Subject who has any clinically significant disease, which is judged by the investigator to affect this clinical trial, including but not limited to diabetes not adequately controlled, bleeding diathesis or hematologic disease, endocrinopathies, cardiovascular disease, renal disease (severe renal impairment), autoimmune disease, inflammatory arthritides, and current infectious disease
6) Subject who has inflammatory arthropathy (rheumatoid, psoriatic, or avascular necrosis), and post traumatic or septic arthritis
7) Subject who has chondrocalcinosis, Paget's disease, Villonodular synovitis, and other non-OA joint diseases
8) Subject who has HIV/viral hepatitis
9) Subject who had knee surgery or radiation therapy in the affected joint within 6 months from Screening
10) Subject who had CVA attack within 6 months from Screening
11) Subject for whom the investigator judges the liposuction can cause any problems

12) Subject who has significant lab abnormalities for the following parameters (If the value is within 10% of the listed laboratory exclusion criterion value and the value is considered not to be clinically significant by the investigator, the subject can be considered for enrollment):
    - Serum ALT and AST > 2 x upper limit of normal
    - Serum creatinine out of normal range
    - PT/INR out of normal range
    - Hemoglobin < 10 g/dL for female subject and hemoglobin < 11 g/dL for male subject
    - Platelets out of normal range
13) Subject who has history of local anesthetic allergy
14) Subject who took immunosuppressants such as Cyclosporin A or azathioprine within 6 weeks from Screening
15) (If a subject uses aspirin or plavix) Subject for whom it is determined that it would not be safe to stop the aspirin/plavix therapy for 2 weeks prior to Visit 2
16) Subject who uses anticoagulants which cannot be stopped or corrected
17) Subject who had oral or intra-muscular corticosteroids within 30 days from Visit 2
18) Subject who had intra-articular corticosteroid injection in any joint within 30 days from Visit 2
19) Subject who had intra-articular hyaluronic acid injection within 30 days from Visit 2
20) Subject who has known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations
21) Subject who has knee joint infections or skin diseases or infections in the area of the injection site
22) Subject who is an active drug/EtOH abuser
23) Subject who was enrolled in any other clinical trials within 2 months from Screening
24) Subject who the principal investigator considers inappropriate for the study due to any other reasons than those listed above
25) Subject whose MRI scan results during the screening period do not demonstrate any sign of cartilage damage.

Investigational Product Dosage and Administration:
One of two treatment groups will receive a single injection of JointStem ($1x10^8$ cells/3mL, autologous adipose tissue derived mesenchymal stem cells) via intra-articular injection.

Control Group:
Positive control (Synvisc-One®) via intra-articular injection

Study Procedures:
Visit 1 (Week -7) – Screening
Visit 2 (Week -5) – Harvest of Adipose Tissue
Visit 3 (Week 0) – Baseline (intra-articular injection)
Visit 4 (Month 1) – 1-month follow-up
Visit 5 (Month 3) – 3-month follow-up
Visit 6 (Month 6) – 6-month follow-up (completion of treatment)
* *Double-blinding will end individually.*
Visit 7 (Month 9) – 9-month follow-up (for only JointStem group)
Visit 8 (Month 12) – 12-month follow-up (for only JointStem group)
Long-term Follow-up (Month 24) – 24-month follow-up

Statistical Analysis:
1. Co-primary Endpoints

Using the following three co-primary efficacy variables, the joint functional improvement of knee joint will be evaluated and gatekeeping procedures will be used for these three hypothesis tests.

1) Change of WOMAC score from baseline at Month 6 (JointStem group)
   It will be tested using paired t-test (one-sided test, α=0.05). If change of WOMAC score from baseline at Month 6 doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.
2) Change of VAS score from baseline at Month 6 (JointStem group)
   It will be tested using paired t-test (one-sided test, α=0.05). If change of VAS score from baseline at Month 6 doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.
3) MRI improvement evaluation at Month 6 (JointStem group)
   The frequency and percentage of subjects whose final PI evaluation is 'improvement' will be calculated (validity criteria: 36%).

2. Secondary Endpoints

The comparison of WOMAC score, VAS score, Lysholm Knee Scoring Scale, KOOS, IKDC and RAND-36 score between study and control groups will be analyzed using Analysis of Covariance (ANCOVA) with factors of treatment and baseline of each variable as a covariate.
Model-based LS Means of the differences between study and control groups along with 95% CI and p-value will be provided.
In addition, the change of secondary efficacy variables within study group shall be tested using paired t-test. If the change of score from baseline at each assessment point doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.
In case of MRI, the frequency and percentage of subjects whose PI evaluation is 'improvement' at Month 6 will be calculated. In addition, MRI improvement evaluation at Month 12 compared to Month 6 will be analyzed using McNemar test or Bowker's test.

Safety variables will be summarized descriptively, by treatment group and visit.

When at least 15 subjects complete 6-month visits (Visit 6, Month 6), one unblinded interim analysis can be performed to evaluate the efficacy and safety of JointStem without the suspension of subject's schedule of assessments. The details of this interim analysis will be presented in the statistical analysis plan.

All efficacy variables and the history of treatments and medications, which are measured at a long-term follow-up visit (24 months after injection) will be analyzed between treatment groups to see any long-term effects of JointStem. Also, MRI results of long-term follow-up visit will be compared to previous MRI results to see any long-term effects of JointStem.

Schedule of Assessments

	Screen.	Harv.	Treat.	1st Follow-up				2nd Follow-Up		Long-term Follow-up
Blinding	**N/A**	**Double Blinding**						**Open [7]**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**ET**	**7**	**8**	**N/A**
Week / Month	**W-7**	**W-5**	**0**	**M1**	**M3**	**M6**	**<M6**	**M9**	**M12 or Final FU[6]**	**M24**
Informed consent	X									
Medical and Medication History	X	X								
Demographic information	X									
Complete physical examination	X		X		X	X	X[4]	X	X	X
Vital signs and weight	X	X	X	X	X	X	X	X	X	X
Hematology, serum chemistry, and urinalysis [1]	X		X	X	X	X	X[4]	X	X	
Pregnancy test [2]	X					X	X[4]		X	
HIV test for Screening	X									
12-lead ECG	X		X			X	X[4]		X	
X-ray	X									
Eligibility confirmation	X	X								
Randomization		X								
Liposuction		X								
Injection of final drug product			X							
AE and concomitant medication assessment			X	X	X	X	X	X	X	
Records of Treatment and Medications										X
MRI scan [3]	X					X	X[5]		X	X
WOMAC			X	X	X	X	X[4]	X	X	X
VAS	X		X	X	X	X	X[4]	X	X	X
Lysholm			X	X	X	X	X[4]	X	X	X
KOOS			X	X	X	X	X[4]	X	X	X
IKDC			X	X	X	X	X[4]	X	X	X
Quality of Life (RAND-36)			X		X	X	X[4]	X	X	X

1. See Appendix 1 for the complete list of laboratory tests
2. Serum pregnancy test is performed for all females of childbearing potential (please refer to the relevant inclusion criteria)
3. May be performed the day of Visit 2 or after due to scheduling or re-scanning.
4. Performed only if the early termination is after V3.
5. Performed only if the early termination is after V4.
6. Performed if the follow-up is discontinued after V6.
7. Only for JointStem group.

Glossary and Abbreviations

AdMSC	Adipose Tissue Derived Mesenchymal Stem Cell
AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
ICH	International Conference of Harmonization
IKDC	International Knee Documentation Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
KOOS	Knee Injury & Osteoarthritis Outcome Score
LOCF	Last Observation Carried Forward
PP	Per Protocol
PT-INR	Prothrombin Time - International Normalized Ratio
SAE	Serious Adverse Event
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Arthritis Index

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APPENDICES

1. PURPOSE OF STUDY

The purpose of this study is to evaluate the efficacy and safety of autologous adipose tissue derived mesenchymal stem cells (AdMSC) for the treatment of osteoarthritis.

2. BACKGROUND AND INDICATION

2.1 What is Osteoarthritis (Degenerative Arthritis)

Osteoarthritis is a group of mechanical abnormalities involving degradation of joints, including articular cartilage and subchondral bone. Symptoms may include joint pain, tenderness, stiffness, locking, and sometimes an effusion. When bone surfaces become less well protected by cartilage, bone may be exposed and damaged. As a result of decreased movement secondary to pain, regional muscles may atrophy, and ligaments may become more lax.[Wei 2002, Conaghan 2008]

Osteoarthritis is the most common form of arthritis, and the leading cause of chronic disability in the United States. It affects about 27 million people in the United States. Eighty percent of Americans develop osteoarthritis by age 65. Twenty-five percent of all patients of osteoarthritis visit to primary care physicians in the US. The total cost of osteoarthritis living with this disease is approximately $5,700 annually per person.[Maetzel 2004] Osteoarthritis costs the US economy nearly $128 billion per year in medical care and indirect expenses, including lost wages and production. As population aging progresses and as more young people start taking up active sports, the size of the target patient group is growing.

2.2 Current Treatment for Osteoarthritis and Their Pitfalls

The cartilage is a unique avascular, aneural tissue that has limited capacity of self-repair once damaged. Despite ongoing research, treatments to manage the disease remain merely symptom-relieving, designed to control pain, and improve function and quality of life limiting adverse events. An effective treatment for cartilage defects is yet to be discovered.

Treatment generally involves a combination of lifestyle modification, analgesics, nonsteroidal anti-inflammatories, and joint injections with steroids or hyaluronan (lubricant). If pain becomes debilitating, joint replacement surgery may be used to improve the quality of life, e.g. partial joint resurfacing (hip and shoulder), and total joint replacement (hip and knee).[Conaghan 2008] Although various treatments are currently in use, none of them is to address the root of cause—cartilage regeneration. In other words, there has been no cure for osteoarthritis till today.

As a way of regenerating the damaged or defective cartilage tissue, treatment of localized damage to articular cartilage using autologous chondrocytes is currently under review. A few studies are marketing this method of treatment named “autologous chondrocyte transplant”.[Wysocka 2010, Hahn 2010] The treatment involves the extraction of healthy cartilage tissue from the patient which is then cultured and transplanted into the damaged site. However, this treatment requires the extraction of

chondrocytes directly from the patient and thus causes new damages in healthy articular cartilage. Also, “autologous chondrocyte transplant” cannot be applied to large lesions. Moreover, the effect is not satisfactory in patients over 40 years old whose cellular regeneration is slowed-down due to aging.

Thus, autologous chondrocyte transplant is rather limited in the number of cells harvested and their activation level and is therefore restricted in terms of treatment site, severity of the condition, and the size of lesion. Generally speaking, there was no therapy available till today to regenerate cartilage for adult.

2.3 Potential Use of Stem Cells in Treatment of Osteoarthritis

Over the last ten years, great progresses have been made worldwide in the adult stem cell field.[Zuk 2010] Because of their unlimited capacity for self-renewal and ability to differentiate into multiple lineages, human stem cells are a potentially powerful and revolutionary tool for repair of cartilage defects. Among different origins of stem cells, marrow-derived stem cells have been considered as pluripotenty of mesenchymal stem cells and proved being successful in many clinical trials.[Jiang 2002]

However, marrow-derived stem cells are limited and not quite easy to access. Recently many groundbreaking articles have been published describing new adult stem cell populations from many tissues which were not expected to find stem cells, such as skin, liver, digestive epithelium, dental pulp and hair follicles and the adipose tissue derived stem cell has become one of the most popular adult stem cell populations being used in the stem cell field.

There are many advantages in using AdMSCs than stem cells isolated from other sources. Firstly, unlike embryonic stem cells, the use of adult AdMSCs in research and therapy is not considered to be controversial as they are derived from adult tissue samples rather than destroyed human embryos. Secondly, adipose tissues represent an abundant and accessible source of adult stem cells, especially with the fact that overweight is a common condition in the United States, 68% of the American adult population is considered either overweight or obese. Even for normal body weight persons and most very lean individuals, 5-20 mL extraction of adipose tissue is not a problem at all. Compared with marrow-derived stem cells, more people accept collecting stem cells via lipoaspirate than bone marrow punctuation. Thirdly, AdMSCs are true stem cells with the capacity of differentiating into multi-lineage mesodermal cells and possible ectodermal and endodermal cells.[Zuk 2010, Stream 2005]

Finally, autologous cells are obtained from the same individual to whom they will be re-implanted. Since the AdMSCs come from the patient's own body, it has no incidence of graft-versus-host rejection and less possibilities of pathogen transmission due to the donor and recipient being the same individual. Moreover, treatments using stem cells do not cause damage as "autologous chondrocyte transplant" would do to healthy articular cartilage, as AdMSC treatment doesn't require the harvesting of healthy cartilage tissues from the patients.

2.4 Current Clinical Trials of Treating Osteoarthritis with Stem Cells

There are no clinical trials to date that have been reported in the USA for humans using AdMSC to treat osteoarthritis. Several trials for osteoarthritis treatment using bone marrow derived stem cells or umbilical cord blood-derived mesenchymal stem cells are currently registered at the NIH clinical trials database. In South Korea, the sponsor completed Phase I and II clinical trials for osteoarthritis treatment with injection of autologous AdMSCs, which was proved as a safe and effective way and actually regenerated healthy cartilage tissue.

Since there is no therapy available today to regenerate cartilage so to effectively treat osteoarthritis, this clinical research has been planned in the USA under the strict regulations required by US FDA and IRB, in order to prove the efficacy and safety of AdMSC in the treatment of osteoarthritis joint and regeneration of cartilage.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a double-blind, randomized, controlled study to evaluate the efficacy and safety of JointStem for the treatment of osteoarthritis. Two or three investigational centers may be utilized in the United States so that a total of approximately 30 subjects will be randomized.

3.2 Selection of Study Population

The study population will be males or females, aged 22 to 60, who have radiographic evidence of grade 3 to 4 osteoarthritis based on the Kellgren and Lawrence radiographic criteria.

3.2.1 Inclusion Criteria

1) Subject who can give written informed consent

2) Male or female of any race, aged 22-60

3) Subject who had osteoarthritis of knee diagnosed at least six months prior to Screening

4) Subject who has joint pain ≥ 40mm on VAS (Visual Analog Scale) at Screening

5) Subject who has swelling, tenderness and active range of motion ≥ Grade I at Screening

6) Subject who seeks invasive interventions of intra-articular injections

7) Subject who is willing to discontinue all pain medications for osteoarthritis except rescue medication (< acetaminophen 3.25 g per day) at least 72 hours prior to screening and throughout the duration of study

8) Subject who has radiographic evidence of grade 3 to 4 osteoarthritis based on the Kellgren and Lawrence radiographic criteria.

9) Female subject who meets one of the following criteria
   a. Female subject of non-childbearing potential:
      - Post-menopausal for at least 6 months; or
      - Surgically sterile

b. Female patients of child-bearing potential:
   - Neither pregnant nor lactating; and
   - Abstinent or use adequate contraception (2 forms of birth control, one of which must be a barrier method)

10) Subject who is able to comply with lifestyle guidelines, scheduled visits, treatment plan, laboratory tests, and other study procedures

3.2.2 Exclusion Criteria

1) Subject who has Body Mass Index (BMI) > 35 kg/m^2

2) Subject who has unstable knees

3) Subject who took any NSAID within two weeks from Screening

4) Subject who had any intra-articular injection therapy in any joint within 2 months from Screening

5) Subject who has any clinically significant disease, which is judged by the investigator to affect this clinical trial, including but not limited to diabetes not adequately controlled, bleeding diathesis or hematologic disease, endocrinopathies, cardiovascular disease, renal disease (severe renal impairment), autoimmune disease, inflammatory arthritides, and current infectious disease

6) Subject who has inflammatory arthropathy (rheumatoid, psoriatic, or avascular necrosis), and post traumatic or septic arthritis

7) Subject who has chondrocalcinosis, Paget's disease, Villonodular synovitis, and other non-OA joint diseases

8) Subject who has HIV/viral hepatitis

9) Subject who had knee surgery or radiation therapy in the affected joint within 6 months from Screening

10) Subject who had CVA attack within 6 months from Screening

11) Subject for whom the investigator judges the liposuction can cause any problem

12) Subject who has significant lab abnormalities for the following parameters (If a value is within 10% of the listed laboratory exclusion criterion value and the value is considered not to be clinically significant by the investigator, the subject can be considered for enrollment):
    - Serum ALT and AST > 2 x upper limit of normal
    - Serum creatinine out of normal range
    - PT/INR out of normal range
    - Hemoglobin < 10 g/dL for female subject and hemoglobin < 11 g/dL for male subject
    - Platelets out of normal range

13) Subject who has history of local anesthetic allergy

14) Subject who took immunosuppressants such as Cyclosporin A or azathioprine within 6 weeks from Screening

15) (If a subject uses aspirin or plavix) Subject for whom it is determined that it would not be safe to stop the aspirin/plavix therapy for 2 weeks prior to Visit 2

16) Subject who uses anticoagulants which cannot be stopped or corrected

17) Subject who had oral or intra-muscular corticosteroids within 30 days from Visit 2

18) Subject who had intra-articular corticosteroid injection in any joint within 30 days from Visit 2

19) Subject who had intra-articular hyaluronic acid injection within 30 days from Visit 2

20) Subject who has known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations

21) Subject who has knee joint infections or skin diseases or infections in the area of the injection site

22) Subject who is an active drug/EtOH abuser

23) Subject who was enrolled in any other clinical trials within 2 months from Screening

24) Subject who the principal investigator considers inappropriate for the study due to any other reasons than those listed above

25) Subject whose MRI scan results during the screening period do not demonstrate any sign of cartilage damage.

3.3 Removal of Subjects from Study

Subjects may be withdrawn from the study for the following reasons:
- At their own request or at the request of their legally acceptable representative
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being
- At the specific request of the sponsor

Also, subjects must be withdrawn for the following reasons:
- A significant violation of the protocol, as determined by the sponsor or the investigator
- Highly significant abnormalities in the laboratory results (Highly significant abnormalities generally follow lab related exclusion criteria, but a PI can determine the high significance on any abnormalities for the safety of subject)
- Use of any other investigational drugs (including placebo)
- Subjects enrolled in the current trial but taking any prohibited medication/therapy stated in the inclusion/exclusion criteria that, in the investigator's opinion, will interfere with the study outcome.
- Subject enrolled in the current trial but having a baby

If a subject prematurely withdraws from the study, the subject must return to the clinical site for the early termination visit. In all cases, the reason for withdrawal must be recorded in the electronic Case Report Form (eCRF) and in the subject's medical records.

Contact will be maintained with subjects who are removed due to an adverse event (AE) until it has been resolved or stabilized, and the information will be documented in the eCRF and in the subject's medical records.

3.4 Premature Termination of Study / Closure of Center

The sponsor has the right to terminate this study, and the investigator/sponsor has the right to close a clinical site, at any time, although this should occur only after consultation between involved

parties; the IRB must be informed in any case. Should the clinical site be closed prematurely, all study materials (equipment, study medication, etc.) must be returned to the sponsor.

This study will discontinue due to medical or administrative reasons such as:

- Serious adverse events probably related to study drug administration so that the use of study drug may no longer be justifiable
- 2 or more deaths are observed during any point in the trial
- 5 or more adverse drug reactions (NCI-CTCAE ≥ Grade 3) on the injected joint are observed during any point in the trial
- Significant change of benefit-risk ratio for the subjects
- Sponsor discontinues the investigation of JointStem for the treatment of osteoarthritis or determines that the doses being studied are no longer justifiable

Possible reasons for closing of a clinical site include the following:

- The investigator feels that the number or severity of adverse events is excessive
- A change of technical, administrative, or personal circumstances occurs and the conduct of the study no longer meets ICH-GCP guidelines
- In case of evident, significant non-compliance to protocol or poor data quality

3.5 Treatment

3.5.1 Treatment to be Administered

At Visit 2 (Week -5), a subject, who is qualified for this study, will be randomized to one of two study groups and the adipose tissue will be harvested via liposuction. At Visit 3 (Week 0, baseline), the randomized subject will receive a single intra-articular injection.

3.5.2 Identity of Investigational Product

JointStem is a 5 ml syringe including AdMSCs as $1x10^8$ cells/3mL and is stable at refrigerated condition up to 1 week. A positive control syringe including hyaluronic acid will be purchased and packed by the aluminum foil pack to be matched with JointStem syringe in appearance to be indistinguishable.

3.5.3 End of Study

The efficacy results will be analyzed when the last subject completes Visit 6 (6-month follow-up) and this study is finished when the last subject completes Visit 8 (12-month follow-up).

Long-term follow-up visit will be conducted to collect long-term feedbacks (records of medications and treatments) following 2 years after injection for all subjects who complete 6-month visit and accept the long-term follow-up visit.

3.5.4 Selection of Dose in Study

The dosage of JointStem was chosen through a phase 1 and 2 study conducted in South Korea.

3.5.5 Choice of Control/Comparator

This study uses hyaluronic acid as a positive control (Synvisc-One®). The purpose of using this control is to compare the efficacy of JointStem with current treatment option based on various endpoints.

3.5.6 Blinding

As this is a double-blinded study, blinding of the drug contents from the subjects, investigators, and other study personnel at each clinical site is necessary. Because two syringes of JointStem and positive control are different, one physician must be only assigned to the role of syringe injection in order to maintain the double-blinding against other site physicians and staffs.

A subject will be assigned with one randomization code on Visit 2 (Week -5). After each subject completes Visit 6 (Month 6) and the data management team confirms all individual data have no issue, the randomization code will be open for the statistical analysis.

A code-break envelope for each subject including the randomization code information will be retained by each site and can be opened, revealing the randomization information, for emergency purposes only. Investigator should note that the occurrence of a SAE should not routinely precipitate immediate unblinding. An attempt to contact the sponsor must be made prior to unblinding. If unblinding occurs, the subject must be early terminated; a written explanation must be prepared immediately.

3.5.7 Prior and Concomitant Treatments

If the use of any concomitant treatment(s) becomes necessary, the treatment(s) must be recorded in the eCRF, including the name of the drug or treatment, dose, route of administration, date and time of the treatment, and indication. In the event that concomitant medication is administered, the

principal investigator or qualified sub-investigator must assess the subject's eligibility of continuing the participation in the study.

The following medications/therapies are not allowed to be taken/used by subjects enrolled in this study during the trial (by 6-month follow-up visit):

- Any pain medication for osteoarthritis except rescue medication (< acetaminophen 3.25 g per day or narcotic pain medications per investigator discretion in the case all other pain control measures have failed. Any pain medication other than acetaminophen 3.25g should only be used as last resort and only for a very limited time until symptoms can be controlled by more conservative methods).
- Any other injections or invasive procedures (including intra-articular injections) in the affected joint
- Any investigational drug (including placebo)
- Any therapy that may affect osteoarthritis, in the judgment of the investigator
- Lidocaine or other numbing agents while making the injection

After the completion of the 6-month follow-up visit, subjects may take pain medication for osteoarthritis and all medications will be tracked and recorded. Until the subjects complete the 12-month follow-up visit, any other treatments/therapies including surgeries (e.g. artificial joint replacement surgery) that, in the judgment of the investigator, affect the assessment of osteoarthritis will be prohibited.

3.5.8 Treatment Compliance

Only subjects who are randomized to JointStem will return on Visits 4, 5, 6, 7 and 8 (Months 1, 3, 6, 9 and 12) or at Early Termination. On the other hand, subjects who are randomized to the positive control group will only return on Visits 4, 5 and 6 (Months 1, 3 and 6) or at Early Termination.

3.6 Study Endpoints and Variables

3.6.1 Study Endpoints

<u>The co-primary endpoints are:</u>

Using the following three co-primary efficacy variables, the joint functional improvement of knee joint will be evaluated and gatekeeping procedures will be used for these three hypothesis tests.

1) Change of WOMAC score from baseline at Month 6 (JointStem group)

2) Change of VAS score from baseline at Month 6 (JointStem group)

3) MRI improvement evaluation at Month 6 (JointStem group)

   MRI improvement evaluation will be finally analyzed through the following two steps:
   - Radiologist will compare and analyze MRI results before and after the administration of IP and write a report for each subject.
   - Principal Investigator will evaluate MRI results of subjects as one of three conditions (a: improvement, b: no change, c: progress) based on the radiologist's report stated above.

<u>The secondary endpoints are:</u>

1) JointStem group vs. positive control group

   ① Change of WOMAC score from baseline at Month 6
   ② Change of VAS score from baseline at Month 6
   ③ Change of KOOS from baseline at Month 6
   ④ Change of Lysholm Knee Scoring Scale from baseline at Month 6
   ⑤ Change of IKDC from baseline at Month 6
   ⑥ Change of RAND-36 Score from baseline at Month 6

2) JointStem group

   ① Change of WOMAC score from baseline at Months 9 and 12
   ② Change of VAS score from baseline at Months 9 and 12
   ③ Comparison of MRI improvement evaluations between at Month 6 and at Months 12
   ④ Change of Lysholm Knee Scoring Scale from baseline at Months 6, 9 and 12
   ⑤ Change of KOOS from baseline at Months 6, 9 and 12
   ⑥ Change of IKDC from baseline at Months 6, 9 and 12
   ⑦ Change of RAND-36 Score from baseline at Months 6, 9 and 12

3) Incidence of adverse events and laboratory abnormalities

Exploratory Endpoint is:

All efficacy variables and the history of treatments and medications, which are measured at a long-term follow-up visit (24 months after injection) will be analyzed between treatment groups to see any long-term effects of JointStem. Also, MRI results of long-term follow-up visit will be compared to previous MRI results to see any long-term effects of JointStem.

3.6.2 Efficacy Variables

- WOMAC score at Visits 3, 4, 5, 6, 7 and 8 (Baseline, M1, M3, M6, M9 and M12) or Early Termination (only if the subject is early terminated after Visit 3) or Final Follow-up Up Visit
- VAS at Visits 3, 4, 5, 6, 7 and 8 (Baseline, M1, M3, M6, M9 and M12) or Early Termination (only if the subject is early terminated after Visit 3) or Final Follow-up Up Visit
- MRI scan at Visits 1, 6 and 8 (Screening, M6 and M12) or Early Termination (only if the subject is early terminated after Visit 4) or Final Follow-up Visit
- KOOS at Visits 3, 4, 5, 6, 7 and 8 (Baseline, M1, M3, M6, M9 and M12) or Early Termination (only if the subject is early terminated after Visit 3) or Final Follow-up Up Visit
- Lysholm Knee Scoring Scale at Visits 3, 4, 5, 6, 7 and 8 (Baseline, M1, M3, M6, M9 and M12) or Early Termination (only if the subject is early terminated after Visit 3) or Final Follow-up Up Visit
- IKDC at Visits 3, 4, 5, 6, 7 and 8 (Baseline, M1, M3, M6, M9 and M12) or Early Termination (only if the subject is early terminated after Visit 3) or Final Follow-up Up Visit
- RAND-36 Score at Visits 3, 5, 6, 7 and 8 (Baseline, M3, M6, M9 and M12) or Early Termination (only if the subject is early terminated after Visit 3) or Final Follow-up Up Visit

3.6.3 Safety Variables

- Hematology, serum chemistry and urinalysis at Visits 1, 3, 4, 5, 6, 7 and 8 (Screening, Baseline, M1, M3, M6, M9 and M12) or Early Termination (only if the subject is early terminated after Visit 3) or Final Follow-up Visit. See Section Appendix 1 for a complete list of laboratory tests to be done.
- ECG evaluation at Visits 1, 3, 6 and 8 (Screening, Baseline, M6 and M12) or Early Termination (only if the subject is early terminated after Visit 3) or Final Follow-up Up Visit
- Complete physical examination at Visits 1, 3, 5, 6, 7 and 8 (Screening, Baseline, M3, M6, M9 and M12) or Early Termination (only if the subject is early terminated after Visit 3) or Final Follow-up Up Visit
- Vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight will be measured at all visits.
- Data regarding AEs and concomitant medications collected at all visits after randomization

3.6.4 Exploratory Variables

The following procedures will be performed at 24-month visit (±2 month):

- WOMAC score
- VAS
- MRI scan
- KOOS
- Lysholm Knee Scoring Scale
- IKDC
- RAND-36 score
- Records of treatments and medications since the last visit

3.6.5 Observation and Measurements

The rating scales used in this study are WOMAC (Western Ontario and McMaster Universities Arthritis Index), VAS (Visual Analog Scale), Lysholm Knee Scoring Scale, KOOS (Knee Injury and Osteoarthritis Outcome Score), IKDC (International Knee Documentation Committee), and RAND-36 questionnaires. All questionnaires are subject-administered and should be completed by the subjects alone at the beginning of each visit to minimize influences from other procedures to be performed at that visit. A short explanation should be given to each subject about the purpose and the necessity of these questionnaires.

4. STUDY PROCEDURES

4.1 Screening Procedures

A signed and dated Institutional Review Board (IRB) approved informed consent must be obtained before any study-specific procedures are performed. Once written informed consent has been obtained, the subject will be screened to determine eligibility and document adherence to the preliminary inclusion/exclusion criteria.

Screening Visit 1 (Week -7)

The following screening assessments/procedures must be performed and the results documented within approximately 7 weeks before Baseline visit unless otherwise indicated:

- Record demographic data (i.e., date of birth, race, height, and weight).
- Measure VAS (see Appendix 4).
- Record medical and medication history.
- Perform a complete physical examination.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature).
- Measure 12-lead ECG.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.
- Perform X-ray for Kellgren-Lawrence scale (see Appendix 2).
- Perform MRI to measure damaged cartilage area (Please follow the instruction separately provided by the sponsor). * MRI may be performed the day of Visit 2 or after due to scheduling or re-scanning, as long as the results are confirmed prior to injection.

4.2 Treatment Period

4.2.1 Visit 2 (Week -5)

For subjects who are preliminarily eligible for this study based on screening procedures, Visit 2 will occur within approximately 2 weeks (± 4 days) after Visit 1. During this visit, the following assessments/procedures should be performed:

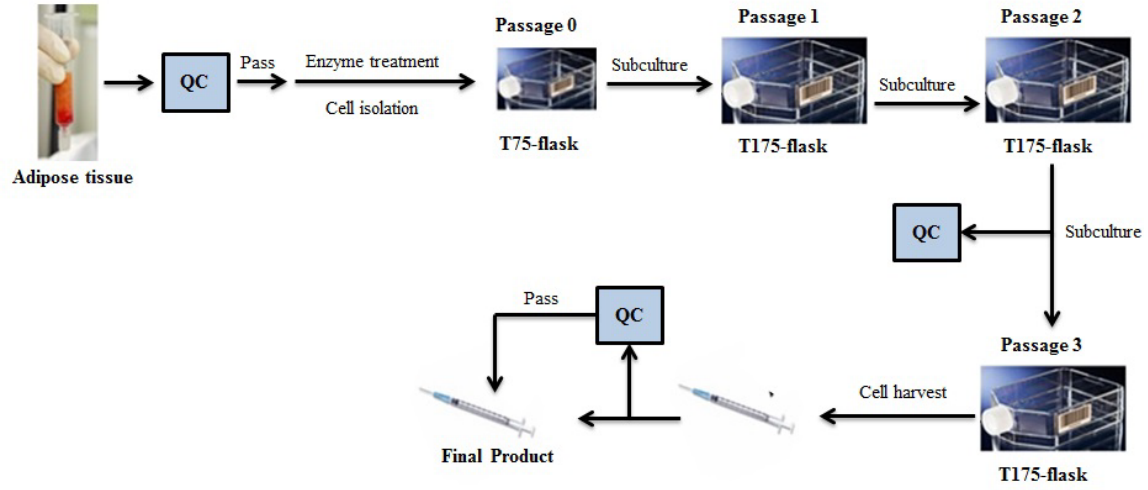
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Confirm medical and medication history.
- Determine the final eligibility.
- Randomize to one of two groups (Please follow the randomization instruction separately provided by the sponsor).

Subjects who are finally eligible will then be taken to the operation room for the procedure of liposuction.

- In sterile conditions, approximately 10 – 40 mL of fat will be harvested using the syringe liposuction technique with Tumescent (or super-wet) local anesthesia (Please follow the liposuction instruction separately provided by the sponsor).
- Ship the packaging box containing the harvested syringe to Biostar SCRI designated by the sponsor (pre-labeled).
- Dispense a concomitant medication note.

4.2.2 Preparation of Final Drug Product in Biostar SCRI

The following procedures for the preparation of final drug product will be performed by well-trained lab technicians at Biostar SCRI. The official package containing the final drug product (syringes) will be shipped to the clinical site.



4.2.3 Visit 3 (Week 0)

Visit 3 will occur within 5 weeks after Visit 2. During this visit, the following assessments/procedures should be performed:

- The following questionnaires/procedures will be completed: WOMAC (see Appendix 3), VAS (see Appendix 4), Lysholm scale (see Appendix 5), KOOS (see Appendix 6), IKDC (see Appendix 7), and RAND-36 (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any adverse event and any change in concomitant medications.

- Perform a complete physical examination.
- Measure 12-lead ECG.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.
- Inject the final drug product into the cavity of knee joint (Please follow the intra-articular injection instruction separately provided by the sponsor).
- Dispense a concomitant medication note.

4.2.4 Visit 4 (Month 1 ± 3 days)

During this visit, the following assessments/procedures should be performed:
- The following questionnaires/procedures will be completed: WOMAC (see Appendix 3), VAS (see Appendix 4), Lysholm scale (see Appendix 5), KOOS (see Appendix 6), and IKDC (see Appendix 7).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any adverse event and any change in concomitant medications.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.
- Dispense a concomitant medication note.

4.2.5 Visit 5 (Month 3 ± 1 week)

During this visit, the following assessments/procedures should be performed:
- The following questionnaires/procedures will be completed: WOMAC (see Appendix 3), VAS (see Appendix 4), Lysholm scale (see Appendix 5), KOOS (see Appendix 6), IKDC (see Appendix 7), and RAND-36 (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any adverse event and any change in concomitant medications.
- Perform a complete physical examination.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.
- Dispense a concomitant medication note.

4.2.6 Visit 6 (Months 6 ± 1 week)

During this visit, the following assessments/procedures should be performed:
- The following questionnaires/procedures will be completed: WOMAC (see Appendix 3), VAS (see Appendix 4), Lysholm scale (see Appendix 5), KOOS (see Appendix 6), IKDC (see Appendix 7), and RAND-36 (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any adverse event and any change in concomitant medications.

- Perform a complete physical examination.
- Measure 12-lead ECG.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.
- Perform MRI measurement (Please follow the collection instruction separately provided by the sponsor).
- Dispense a concomitant medication note.

* *After each subject completes Visit 6 (Month 6) and the data management team confirms all individual data have no issue, the individual database will be locked and the blinding will be open for the statistical analysis.* ***Only subjects who are randomized to JointStem will be scheduled for Visits 7 and 8 (Months 9 and 12).***

4.2.7 Visit 7 (Month 9 ± 1 week)

Only subjects who are randomized to JointStem group will visit the clinical site for the following assessments/procedures:

- The following questionnaires/procedures will be completed: WOMAC (see Appendix 3), VAS (see Appendix 4), Lysholm scale (see Appendix 5), KOOS (see Appendix 6), IKDC (see Appendix 7), and RAND-36 (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any adverse event and any change in concomitant medications.
- Perform a complete physical examination.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.
- Dispense a concomitant medication note.

4.2.8 Visit 8 (Month 12 ± 1 week)

Only subjects who are randomized to JointStem group will visit the clinical site for the following assessments/procedures:

- The following questionnaires/procedures will be completed: WOMAC (see Appendix 3), VAS (see Appendix 4), Lysholm scale (see Appendix 5), KOOS (see Appendix 6), IKDC (see Appendix 7), and RAND-36 (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any adverse event and any change in concomitant medications.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.
- Perform MRI measurement (Please follow the collection instruction separately provided by the sponsor).

4.2.9 Early Termination Visit

If a subject will drop-out the study before Visit 6 (Month 6), the clinical site will try to schedule an early termination visit (one of two types)

1) If a subject will drop-out the study before Visit 4 (Month 1), the following assessments and procedures should be performed for the early termination visit:

- The following questionnaires/procedures will be completed: WOMAC (see Appendix 3), VAS (see Appendix 4), Lysholm scale (see Appendix 5), KOOS (see Appendix 6), IKDC (see Appendix 7), and RAND-36 (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any adverse event and any change in concomitant medications.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.

2) If a subject will drop-out the study after Visit 4 (Month 1), the following assessments and procedures should be performed for the early termination visit:

- The following questionnaires/procedures will be completed: WOMAC (see Appendix 3), VAS (see Appendix 4), Lysholm scale (see Appendix 5), KOOS (see Appendix 6), IKDC (see Appendix 7), and RAND-36 (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any adverse event and any change in concomitant medications.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.
- Perform MRI measurement (Please follow the collection instruction separately provided by the sponsor).

4.2.10 Final Follow-Up Visit

If a subject will discontinue follow-up after Visit 6 (Month 6), the clinical site will try to schedule the final follow-up visit to perform the following assessments and procedures:

- The following questionnaires/procedures will be completed: WOMAC (see Appendix 3), VAS (see Appendix 4), Lysholm scale (see Appendix 5), KOOS (see Appendix 6), IKDC (see Appendix 7), and RAND-36 (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any adverse event and any change in concomitant medications.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis.
- Perform MRI measurement (only if this final follow-up visit is conducted at least 1 month after Visit 6).

4.2.11 Long-term Follow-up Visit (Month 24 ± 2 month)

Subjects who complete 6-month visit and accept the long-term follow-up visit will visit the clinical site for the following assessments/procedures:

- The following questionnaires/procedures will be completed: WOMAC (see Appendix 3), VAS (see Appendix 4), Lysholm scale (see Appendix 5), KOOS (see Appendix 6), IKDC (see Appendix 7), and RAND-36 (see Appendix 8).
- Collect records of treatments and medications since the last visit.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Perform MRI measurement (Please follow the collection instruction separately provided by the sponsor).

4.3 Data Quality

Monitoring and auditing procedures defined/agreed by the sponsor will be followed in compliance with current GCP guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP guideline, and other regulatory aspects. This will include on-site review of the eCRF for completeness and clarity, consistency with source documents, and clarification of administrative matters.

4.4 Documentation

Entries made in the eCRF must be either verifiable against source documents or have been directly entered into the eCRF, in which case the entry in the eCRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be

documented. The study file and all source data should be retained/archived until notification by the sponsor for change of archive site or destruction.

5. ETHICAL AND LEGAL ASPECTS

5.1 Institutional Review Board (IRB)

Documented approval from the IRB will be obtained for all participating trial center(s)/clinic(s) prior to study start, according to GCP and applicable laws and regulations. When necessary, an extension, amendment, or renewal of the IRB approval must be obtained and also forwarded to the sponsor. The IRB must supply to the sponsor, upon request, a list of the IRB members involved in the vote and a statement to confirm that the IRB is organized and operates according to GCP and applicable laws and regulations.

5.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations. This may include an inspection by the sponsor representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives.

Modifications to the study protocol will be implemented by the investigator only after sponsor's approval. However, the investigator may implement a deviation form, or change of the protocol to eliminate any immediate hazard(s) to the trial subjects without prior IRB/sponsor approval. The implemented deviation or change, the reasons for it and, if appropriate, the proposed amendment should be submitted to the IRB/sponsor as soon as possible. Any deviations from the protocol must be fully explained and documented by the investigator.

5.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, will be in place and fully documented prior to the study's start.

5.4 Subject Information Consent

A core information and Informed Consent Form will be provided. Prior to the beginning of the study, the investigator must have the IRB written approval of the Informed Consent Form and any

other written information that will be provided to the subjects. The written approval of the IRB with the approved Informed Consent Form must be in the study files.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files.

5.5 Insurance

All subjects participating in the study will have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.

5.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number and subject initials will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Even if the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects' records to be identified.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical and Analytical Plans

6.1.1 Analytical Populations

6.1.1.1 Intent-to-Treat Population

An intent-to-treat (ITT) population will include subjects who received the intra-articular injection and have at least post-injection efficacy measurements. This cohort will be evaluated for all efficacy variables.

6.1.1.2 Per-Protocol Population

All subjects valid for ITT who completed Visit 6 (Month 6) will be 'valid per protocol' (also called 'valid for efficacy'). Additional criteria may be added prior to unblinding the study database. As with the ITT population, this per-protocol (PP) cohort will also be evaluated for all efficacy variables.

6.1.1.3 Safety Population

Any subject who was randomized and completed Visit 2 (Week -5) will be included in the evaluation of safety. This cohort will be evaluated for all safety variables.

6.1.2 Treatment Group Comparability

Demographic variables, medical history, treatment duration, and efficacy variables at baseline will be summarized by treatment group for the subjects valid for potential safety analysis. Because, in theory, the goal of randomization is to balance out the patient characteristics, statistical tests are not planned for these variables.

6.1.3 Significance Level

The primary efficacy hypothesis tests will be performed using a 5% significance level (but, for the MRI improvement evaluation, it shall meet the validity criteria). For the secondary efficacy endpoints, hypothesis tests will be performed individually at the 5% significance level. All hypothesis tests except for the primary efficacy hypothesis tests will be performed with two-sided alternative hypotheses.

6.1.4 Primary Efficacy Analyses

For primary efficacy endpoints, the joint functional improvement of knee joint will be evaluated using the following three co-primary efficacy variables and gatekeeping procedures will be used for these three hypothesis tests.

Three hypothesis tests will be performed in the following order: 1) Change of WOMAC score within study group, 2) Change of VAS score within study group and 3) MRI improvement evaluation in the study group. If null hypothesis is dismissed at 5% significance level for the first hypothesis test, the second hypothesis will also be tested at 5% significance level. Then, for MRI improvement evaluation, the test will be performed to confirm if the percentage of subjects whose final PI evaluation is 'improvement' meets the validity criteria. If null hypothesis is not dismissed at 5% significance level or it is lower than the validity criteria, the hypothesis test is stopped and it is concluded only previous item of which null hypothesis is dismissed is significant.

1) Change of WOMAC score from baseline at Month 6 (JointStem group)

   Change of WOMAC score from baseline at Month 6 will be tested using paired t-test (one-sided test, α=0.05) with the null hypothesis equal to zero. If change of WOMAC score from baseline at Month 6 doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.

   If null hypothesis is dismissed, the conclusion that the function of knee joint is improved from at least subjects who administer IP can be drawn.

2) Change of VAS score from baseline at Month 6 (JointStem group)

   Change of VAS score from baseline at Month 6 will be tested using paired t-test (one-sided test, α=0.05) with the null hypothesis equal to zero. If change of VAS score from baseline at Month 6 doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.

   If null hypothesis is dismissed, the conclusion that the pain of degenerative arthritis is reduced from at least subjects who administer IP can be drawn.

3) MRI improvement evaluation at Month 6 (JointStem group)

   MRI improvement evaluation will be finally analyzed through the following two steps:

- Radiologist will compare and analyze MRI results before and after the administration of IP and write a report for each subject.
- Principal Investigator will evaluate MRI results of subjects as one of three conditions (a: improvement, b: no change, c: progress) based on the radiologist's report stated above.

→ The frequency and percentage of subjects whose final PI evaluation is 'improvement' will be calculated per group.

If the percentage of subjects whose final PI evaluation is at least 36%, the conclusion that the damaged cartilage of knee joint is improved in the subjects who administer JointStem can be drawn.

6.1.5 Secondary Efficacy Analyses

1) WOMAC Score

① Change of WOMAC score from baseline at Month 6 (JointStem group vs. positive control group)
; This secondary efficacy endpoint will be analyzed with an ANCOVA with factors of treatment and the baseline of WOMAC score as a covariate. Model-based LS Means of the differences between study and control groups, along with 95% CI and p-value will be provided.

② Change of WOMAC score from baseline at Months 9 and 12 (JointStem group)
; Change of WOMAC score from baseline at Months 9 and 12 will be analyzed using paired t-test. If change of WOMAC score from baseline at Months 9 and 12 doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.

2) VAS Score

① Change of VAS score from baseline at Month 6 (JointStem group vs. positive control group)
; This secondary efficacy endpoint will be analyzed with an ANCOVA with factors of treatment and the baseline of VAS score as a covariate. Model-based LS Means of the differences between study and control groups, along with 95% CI and p-value will be provided.

② Change of VAS score from baseline at Months 9 and 12 (JointStem group)
; Change of VAS score from baseline at Months 9 and 12 will be analyzed using paired t-test. If change of VAS score from baseline at Months 9 and 12 doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.

3) MRI

① Comparison of MRI improvement evaluations between at Month 6 and at Month 12 (JointStem group)
; MRI improvement evaluation at Month 12 compared to Month 6 will be analyzed using McNemar test or Bowker's test.

4) Lysholm Knee Scoring Scale

① Change of Lysholm Knee Scoring Scale from baseline at Month 6 (JointStem group vs. positive control group)
; This secondary efficacy endpoint will be analyzed with an ANCOVA with factors of treatment and the baseline of Lysholm Knee Scoring Scale as a covariate. Model-based LS Means of the differences between study and control groups, along with 95% CI and p-value will be provided.

② Change of Lysholm Knee Scoring Scale from baseline at Months 6, 9 and 12 (JointStem group)
; Change of Lysholm Knee Scoring Scale from baseline at Months 6, 9 and 12 will be analyzed using paired t-test. If change of Lysholm Knee Scoring Scale from baseline at Months 6, 9 and 12 doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.

5) KOOS

① Change of KOOS from baseline at Month 6 (JointStem group vs. positive control group)
; This secondary efficacy endpoint will be analyzed with an ANCOVA with factors of treatment and the baseline of KOOS as a covariate. Model-based LS Means of the differences between study and control groups, along with 95% CI and p-value will be provided.

② Change of KOOS from baseline at Months 6, 9 and 12 (JointStem group)

; Change of KOOS from baseline at Months 6, 9 and 12 will be analyzed using paired t-test. If change of KOOS from baseline at Months 6, 9 and 12 doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.

6) IKDC

① Change of IKDC from baseline at Month 6 (JointStem group vs. positive control group)
; This secondary efficacy endpoint will be analyzed with an ANCOVA with factors of treatment and the baseline of IKDC as a covariate. Model-based LS Means of the differences between study and control groups, along with 95% CI and p-value will be provided.

② Change of IKDC from baseline at Months 6, 9 and 12 (JointStem group)
; Change of IKDC from baseline at Months 6, 9 and 12 will be analyzed using paired t-test. If change of IKDC from baseline at Months 6, 9 and 12 doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.

7) RAND-36 Score

① Change of RAND-36 Score from baseline at Month 6 (JointStem group vs. positive control group)
; This secondary efficacy endpoint will be analyzed with an ANCOVA with factors of treatment and the baseline of RAND-36 Score as a covariate. Model-based LS Means of the differences between study and control groups, along with 95% CI and p-value will be provided.

② Change of RAND-36 Score from baseline at Months 6, 9 and 12 (JointStem group)
; Change of RAND-36 Score from baseline at Months 6, 9 and 12 will be analyzed using paired t-test. If change of RAND-36 Score from baseline at Months 6, 9 and 12 doesn't satisfy normal distribution, Wilcoxon signed rank test will be performed.

6.1.6 Safety Analyses

AE rates will be summarized by treatment group and overall, and will be broken down by severity, seriousness and relation to study drug. Statistical tests are not planned for safety variables.

6.1.7 Missing Data

Last observation carried forward (LOCF) imputation method will be used for efficacy variables, but no adjustments for missing data and no imputation methods are planned for safety variables .

6.2 Determination of Sample Size

There was no formal sample size calculation since this is a proof-of-concept study and is not a hypothesis-driven study. The number of enrolled subjects is predefined at n=30, for 20 subjects per study group and 10 subjects per control group.

6.3 Interim Analysis

When at least 15 subjects complete 6-month visits (Visit 6, Month 6), one unblinded interim analysis can be performed to evaluate the efficacy and safety of JointStem without the suspension of subject enrollment. The details of this interim analysis will be presented in the statistical analysis plan. No adjustment on the overall alpha-level will be made, as this is not a statistically powered study.

6.4 Long-term Follow-up Analysis

All efficacy variables and the history of treatments and medications, which are measured at a long-term follow-up visit (24 months after injection) will be analyzed between treatment groups to see any long-term effects of JointStem. Also, MRI results of long-term follow-up visit will be compared to previous MRI results to see any long-term effects of JointStem. The details of this long-term follow-up analysis will be presented in the statistical analysis plan.

7. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

7.1 Definitions

7.1.1 Adverse Events

An adverse event is defined in the 21 CFR 312.32(a) as "Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. Worsening of a pre-existing medical condition (e.g., diabetes, migraine headaches, and gout) after the drug administration should be considered an adverse event if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from baseline values. Abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

Adverse events will be reviewed continuously throughout the study.

7.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

Life threatening: The term life-threatening in the definition of 'serious' refers to an AE in which the subject was at risk of death at the time of the event. It does not see an AE that hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as 'serious', UNLESS at least one of the following exceptions is met:

- the admission results in a hospital stay of less than 12 hours OR
- the admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR
- a medical intervention that requires hospitalization (e.g., blood product transfusion or central line insertion) will be not considered a serious adverse event

However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment.

Disability means a substantial disruption of a person's ability to conduct normal life functions.

Important medical event: Any AE may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. As guidance for determination of important medical events see the 'WHO Adverse Reaction Terminology – Critical Terms List'. These terms either see or might be indicative of a serious disease state.

Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

7.2 Reporting Procedures for All Adverse Events

The investigator is responsible for ensuring that all adverse events (as defined in Section 7.1) observed by the investigator or reported by subjects after the first dose of each subject are properly captured in the subject's medical records and reported on the eCRF.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken, and outcome

7.2.1 Relationship of Adverse Event to Study Drug

The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to study drug and action taken. The investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or eCRFs.

If applicable, the relationship of the adverse event to the study drug will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" The investigator should respond to this question with either Yes or No.

7.2.2 Adverse Event Severity

The severity of adverse events should be graded as follows:

- Mild – Usually transient in nature and generally not interfering with normal activities
- Moderate – Sufficiently discomforting to interfere with normal activities
- Severe – Prevents normal activities

Medically significant adverse events considered related to the study drug by the investigator or Sponsor will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

7.3 Serious Adverse Event Reporting Procedures

Serious adverse events will be collected and recorded from the drug administration to 3-month follow-ups.

Serious Adverse Events, including laboratory test abnormalities fulfilling the definition of serious, after the first dose, and during follow-up period must immediately (within 24 hours of the investigator's awareness) be reported to the person/parties as detailed in the study file. A Serious Adverse Event form must also be completed within 1 day of the investigator's awareness and

forwarded to the designated person/parties as detailed in the study file. Each Serious Adverse Event must be followed up until resolution or stabilization by submission of updated reports to the designated person/parties.

Serious adverse events also will be collected and reported within 1 working day of discovery or notification of the event if it occurs 7 days after the last dose of study drug or after the end of the study and is thought to be possibly related to study drug.

For all deaths, available autopsy reports and relevant medical reports should be faxed to Sponsor or their designee. For this reporting process, subject assessments must be made 7 days after administration of the last dose of study drug.

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the End of Study Case Report Form.

When required, and according to local law and regulations, serious adverse events must be reported to the institutional review board and Regulatory Authorities.

8. USE OF DATA AND PUBLICATION

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, while free to utilize data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution that satisfies both parties.

The investigator is encouraged to participate in the evaluation of the data for scientific purposes but is expected to work with the sponsor in the development of any scientific presentation or publication. Since the sponsor authors will be included, it is expected that all co-authors of the manuscripts will have an opportunity for feedback in the content and conclusions. The technical and editorial resources of the sponsor will be available to assist in the development of abstracts, presentations, and publications regarding this study and it is expected that drafts will be sent to the sponsor with adequate time for input and revisions prior to submission.

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APPENDICES

Appendix 1. Laboratory Parameters

Appendix 2. Kellgren-Lawrence Grading Scale

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Appendix 8. RAND 36 Questionnaires

Appendix 9. MRI Final Evaluation

Appendix 1. Laboratory Parameters

Blood and urine samples for complete laboratory evaluation (hematology, serum chemistry, and urinalysis) at Visits 1, 3, 4, 5, 6, 7 and 8 (Screening, Baseline, M1, M3, M6, M9 and M12) or Early Termination or Final Follow-up Visit.

HEMATOLOGY	CHEMISTRY	URINALYSIS
Hemoglobin	Total bilirubin	Color
Hematocrit	Alkaline phosphatase	Appearance
RBC	ALT (SGPT)	Specific gravity
WBC	AST (SGOT)	pH
MCV	Blood urea nitrogen (BUN)	Protein
MCH	Creatinine	Glucose
MCHC	Glucose	Ketones
Neutrophils (absolute)	Albumin	Bilirubin
Lymphocytes (absolute)	Total protein	Blood
Monocytes (absolute)	Sodium	Leukocyte esterase
Eosinophils (absolute)	Potassium	WBC
Basophils (absolute)	Chloride	RBC
Platelets	Bicarbonate	Epithelial cell
PT-INR	Calcium	Bacteria
	HCG *	Hyaline casts
	HIV **	

* HCG (pregnancy test) only for all females of childbearing potential (please refer to the relevant inclusion criteria) at Visits 1, 6 and 8 or Early Termination or Final Follow-Up Visit.

** Visit 1 only

Appendix 2. Kellgren-Lawrence Grading Scale

Kellgren-Lawrence Grading Scale

The Kellgren-Lawrence grading system is radiological classification of knee osteoarthritis. It is based on x-rays and consists of normal, Grade 1, Grade 2, Grade 3, and Grade 4.

Grade 1: Unlikely narrowing of the joint space, possible osteophytes
Grade 2: Small osteophytes, possible narrowing of the joint
Grade 3: Multiple, moderately sized osteophytes, definite joint space narrowing, some sclerotic areas, possible deformation of bone ends
Grade 4: Multiple large osteophytes, severe joint space narrowing, marked sclerosis and definite bony end deformity.

Appendix 3. WOMAC (Western Ontario and McMaster Universities Arthritis Index)

Section A

PAIN

Think about the pain you felt in your _____ (study joint) caused by your arthritis during the last 48 hours.

(Please mark your answers with an "**x**".)

QUESTION: **How much pain have you had …**	Study Coordinator Use Only
1. when walking on a flat surface? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PAIN1 _____
2. when going up or down stairs? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PAIN2 _____
3. at night while in bed? (that is – pain that disturbs your sleep) none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PAIN3 _____
4. while sitting or lying down? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PAIN4 _____
5. while standing? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PAIN5 _____

Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your _____ (study joint) caused by your arthritis during the last 48 hours.

Stiffness is a sensation of **decreased** ease in moving your joint.

(Please mark your answers with an "**x**".)

	Study Coordinator Use Only
6. How **severe** has your stiffness been **after you first woke up** in the morning? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	STIFF6 _____
7. How **severe** has your stiffness been after sitting or lying down or while resting **later in the day**? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	STIFF7 _____

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself.**

(Please mark your answers with an "**x**".)

QUESTION: **How much difficulty have you had …**	Study Coordinator Use Only
8. when going down the stairs? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN8 _____
9. when going up the stairs? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN9 _____
10. when getting up from a sitting position? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN10 _____
11. while standing? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN11 _____
12. when bending to the floor? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN12 _____
13. when walking on a flat surface? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN13 _____

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself.**

(Please mark your answers with an "**x**".)

QUESTION: **How much difficulty have you had …**	Study Coordinator Use Only
14. getting in or out of a car, or getting on or off a bus?	
none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN14 _____
15. while going shopping?	
none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN15 _____
16. when putting on your socks or panty hose or stockings?	
none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN16 _____
17. when getting out of bed?	
none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN17 _____
18. when taking off your socks or panty hose or stockings?	
none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN18 _____
19. while lying in bed?	
none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN19 _____

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself.**

(Please mark your answers with an "**x**".)

QUESTION: **How much difficulty have you had …**	Study Coordinator Use Only
20. when getting in or out of the bathtub? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN20 _____
21. while sitting? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN21 _____
22. when getting on or off the toilet? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN22 _____
23. while doing heavy household chores? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN23 _____
24. while doing light household chores? none ☐ mild ☐ moderate ☐ severe ☐ extreme ☐	PFTN24 _____

Study Coordinator:

Signature: _____ Date: _____

Appendix 4. VAS (Visual Analogue Scale) for Pain

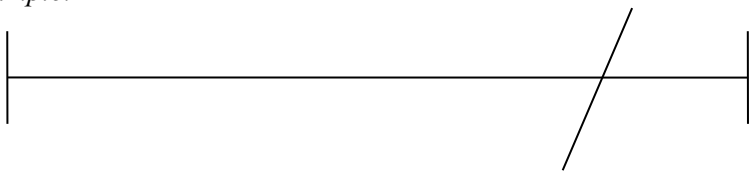
Site No: __ Subject No: __ __ Subject Initials: __ __ __

Visit (circle one): Baseline M1 M3 M6 M9 M12 ET (/ /) Final FU (/ /)

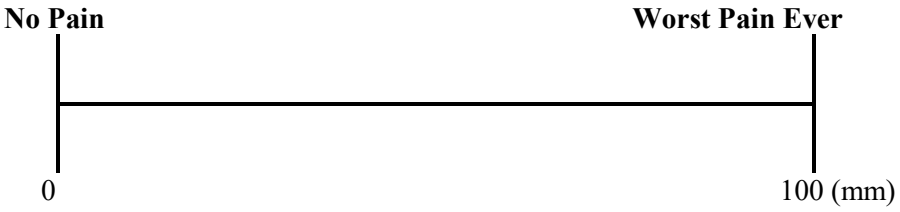
Pain 100mm Visual Analogue Scale

Please mark on the scale below how you feel your pain rates today as the following example:

Example:



No Pain *Worst pain ever*



Marked Length (mm) _____

Study Coordinator:

Signature: _____ Date: _____

Appendix 5. Lysholm Knee Scale

Site No: __ Subject No: __ __ Subject Initials: __ __ __

Visit (circle one): Baseline M1 M3 M6 M9 M12 ET (/ /) Final FU (/ /)

This questionnaire has been designed to give your Physical Therapist information as to how your knee pain has affected your ability to manage everyday life. Below are common complaints that people frequently have with their knee problems. Please answer every section and mark only **ONE** box which best describes your condition at this moment.

I. LIMP:
___ I have no limp when I walk. (5)
___ I have a slight or periodical limp when I walk. (3)
___ I have a severe and constant limp when I walk. (0)

II. USING CANE OR CRUTCHES:
___ I do not use a cane or crutches. (5)
___ I use a cane or crutches with some weight-bearing. (2)
___ Putting weight on my hurt leg is impossible. (0)

III. LOCKING SENSATION IN THE KNEE:
___ I have no locking and no catching sensations in my knee. (15)
___ I have catching sensations but no locking sensations in my knee. (10)
___ My knee locks occasionally. (6)
___ My knee locks frequently. (2)
___ My knee feels locked at this moment. (0)

IV. GIVING WAY SENSATION FROM THE KNEE:
___ My knee never gives way. (25)
___ My knee rarely gives way only during athletics or other vigorous activities. (20)
___ My knee frequently gives way during athletics or other vigorous activities and in turn, I am unable to participate in these activities. (15)
___ My knee often gives way during daily activities. (5)
___ My knee gives way every step I take. (0)

V. PAIN:
___ I have no pain in my knee. (25)
___ I have intermittent or slight pain in my knee during vigorous activities. (20)
___ I have marked pain in my knee during vigorous activities. (15)
___ I have marked pain in my knee during or after walking more than 1 mile. (10)
___ I have marked pain in my knee during or after walking less than 1 mile. (5)
___ I constant pain in my knee. (0)

VI. SWELLING:
___ I have no swelling in my knee. (10)
___ I have swelling in my knee only after vigorous activities. (6)
___ I have swelling in my knee after ordinary activities. (2)
___ I have swelling constantly in my knee. (0)

VII. CLIMBING STAIRS:
___ I have no problems climbing stairs. (10)
___ I have slight problems climbing stairs. (6)
___ I can climb stairs only one at a time. (2)
___ Climbing stairs is impossible for me. (0)

VIII. SQUATTING:
___ I have no problems squatting. (5)
___ I have slight problems squatting. (4)
___ I cannot squat beyond a 90 degree bend in my knee. (2)
___ Squatting is impossible because of my knee(s). (0)

Thank you very much for completing all the questions in this questionnaire.

Score (by Study Coordinator):

TOTAL: _____ (Maximum: 100)

Signature: _____ Date: _____

Appendix 6. KOOS (Knee Injury & Osteoarthritis Outcome Score)

Site No: __ Subject No: __ __ Subject Initials: __ __ __

Visit (circle one): Baseline M1 M3 M6 M9 M12 ET (/ /) Final FU (/ /)

INSTRUCTIONS:
This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities. Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

SYMPTOMS

These questions should be answered thinking of your knee symptoms during the **last week.**

		0	1	2	3	4
S1	Do you have swelling in your knee?	□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
S2	Do you feel grinding, hear clicking or any other type of noise when your knee moves?	□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
S3	Does your knee catch or hang up when moving?	□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
S4	Can you straighten your knee fully?	□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
S5	Can you bend your knee fully?	□ Never	□ Rarely	□ Sometimes	□ Often	□ Always

Stiffness: The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

		0	1	2	3	4
S6	How severe is your knee joint stiffness after first wakening in the morning?	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
S7	How severe is your knee stiffness after sitting, lying or resting later in the day?	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme

PAIN

		0	1	2	3	4
P1	How often do you experience knee pain?	□ Never	□ Monthly	□ Weekly	□ Daily	□ Always

What amount of knee pain have you experienced the last week during the following activities?

		0	1	2	3	4
P2	Twisting/pivoting on your knee	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
P3	Straightening knee fully	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
P4	Bending knee fully	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
P5	Walking on flat surface	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
P6	Going up or down stairs	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
P7	At night while in bed	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
P8	Sitting or lying	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
P9	Standing upright	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme

ADL

Function, daily living: The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

		0	1	2	3	4
A1	Descending stairs	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A2	Ascending stairs	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

		0	1	2	3	4
A3	Rising from sitting	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A4	Standing	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A5	Bending to floor/pick up an object	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A6	Walking on flat surface	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A7	Getting in/out of car	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A8	Going shopping	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A9	Putting on socks/stockings	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A10	Rising from bed	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A11	Taking off socks/stockings	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A12	Lying in bed (turning over, maintaining knee position)	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A13	Getting in/out of bath	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A14	Sitting	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A15	Getting on/off toilet	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

		0	1	2	3	4
A16	Heavy domestic duties (moving heavy boxes, scrubbing floors, etc.)	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
A17	Light domestic duties (cooking, dusting, etc.)	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme

SPORT/REC

Function, sports and recreational activities
The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

		0	1	2	3	4
SP1	Squatting	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
SP2	Running	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
SP3	Jumping	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
SP4	Twisting/pivoting on your injured knee	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme
SP5	Kneeling	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme

QUAITY OF LIFE

		0	1	2	3	4
Q1	How often are you aware of your knee problem?	□ Never	□ Monthly	□ Weekly	□ Daily	□ Constantly
Q2	Have you modified your life style to avoid potentially damaging activities to your knee?	□ Not at all	□ Mildly	□ Moderately	□ Severely	□ Totally
Q3	How much are you troubled with lack of confidence in your knee?	□ Not at all	□ Mildly	□ Moderately	□ Severely	□ Extremely
Q4	In general, how much difficulty do you have with your knee?	□ None	□ Mild	□ Moderate	□ Severe	□ Extreme

Thank you very much for completing all the questions in this questionnaire.

Score (by Study Coordinator):

KOOS Symptoms 100 – (Mean score of S1 to S7 _____ x 25) = _____

KOOS Pain 100 – (Mean score of P1 to P9 _____ x 25) = _____

KOOS ADL 100 – (Mean score of A1 to A17 _____ x 25) = _____

KOOS Sport/Rec 100 – (Mean score of SP1 to SP5 _____ x 25) = _____

KOOS QOL 100 – (Mean score of Q1 to Q4 _____ x 25) = _____

Signature: _____ Date: _____

Appendix 7. International Knee Documentation Committee (IKDC) Subjective Knee Evaluation

Site No: __ Subject No: __ __ Subject Initials: __ __ __

Visit (circle one): Baseline M1 M3 M6 M9 M12 ET (/ /) Final FU (/ /)

SYMPTOMS:

Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?
   - 4 ❑ Very strenuous activities like jumping or pivoting as in basketball or soccer
   - 3 ❑ Strenuous activities like heavy physical work, skiing or tennis
   - 2 ❑ Moderate activities like moderate physical work, running or jogging
   - 1 ❑ Light activities like walking, housework or yard work
   - 0 ❑ Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?

	0	1	2	3	4	5	6	7	8	9	10	
Never	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Constant

3. If you have pain, how severe is it?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Worst pain

4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?
   - 4 ❑ Not at all
   - 3 ❑ Mildly
   - 2 ❑ Moderately
   - 1 ❑ Very
   - 0 ❑ Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?
   - 4 ❑ Very strenuous activities like jumping or pivoting as in basketball or soccer
   - 3 ❑ Strenuous activities like heavy physical work, skiing or tennis
   - 2 ❑ Moderate activities like moderate physical work, running or jogging
   - 1 ❑ Light activities like walking, housework, or yard work
   - 0 ❑ Unable to perform any of the above activities due to knee swelling

6. During the past 4 weeks, or since your injury, did your knee lock or catch?
   - 0 ❑Yes 1 ❑No

7. What is the highest level of activity you can perform without significant giving way in your knee?
   - 4 ❑ Very strenuous activities like jumping or pivoting as in basketball or soccer
   - 3 ❑ Strenuous activities like heavy physical work, skiing or tennis
   - 2 ❑ Moderate activities like moderate physical work, running or jogging
   - 1 ❑ Light activities like walking, housework or yard work
   - 0 ❑ Unable to perform any of the above activities due to giving way of the knee

SPORTS ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis?
   4 ❑ Very strenuous activities like jumping or pivoting as in basketball or soccer
   3 ❑ Strenuous activities like heavy physical work, skiing or tennis
   2 ❑ Moderate activities like moderate physical work, running or jogging
   1 ❑ Light activities like walking, housework or yard work
   0 ❑ Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately Difficult	Extremely difficult	Unable to do
a.	Go up stairs	4 ❑	3 ❑	2 ❑	1 ❑	0 ❑
b.	Go down stairs	4 ❑	3 ❑	2 ❑	1 ❑	0 ❑
c.	Kneel on the front of your knee	4 ❑	3 ❑	2 ❑	1 ❑	0 ❑
d.	Squat	4 ❑	3 ❑	2 ❑	1 ❑	0 ❑
e.	Sit with your knee bent	4 ❑	3 ❑	2 ❑	1 ❑	0 ❑
f.	Rise from a chair	4 ❑	3 ❑	2 ❑	1 ❑	0 ❑
g.	Run straight ahead	4 ❑	3 ❑	2 ❑	1 ❑	0 ❑
h.	Jump and land on your involved leg	4 ❑	3 ❑	2 ❑	1 ❑	0 ❑
i.	Stop and start quickly	4 ❑	3 ❑	2 ❑	1 ❑	0 ❑

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

Cannot perform daily activities **No limitation daily activities**

0	1	2	3	4	5	6	7	8	9	10
❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑

CURRENT FUNCTION OF YOUR KNEE:

Cannot perform daily activities **No limitation daily activities**

0	1	2	3	4	5	6	7	8	9	10
❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑

Thank you very much for completing all the questions in this questionnaire.

Score (by Study Coordinator)

IKDC Score = (Sum of Items: _____) / (Maximum Possible Score: 87) x 100 = _____

** The response to Item 10a is not included in the overall score.*

Signature: _____ Date: _____

Appendix 8. RAND 36 Questionnaires

Site No: __ Subject No: __ __ Subject Initials: __ __ __

Visit (circle one): Baseline M3 M6 M9 M12 ET (/ /) Final FU (/ /)

1. In general, would you say your health is: (circle one)
   Excellent (1) Very good (2) Good (3) Fair (4) Poor (5)

2. **Compared to one year ago**, how would you rate your health in general now? (circle one)
   Much better now than one year ago (1) Somewhat better now than one year ago (2)
   About the same as one year ago (3) Somewhat worse than one year ago (4)
   Much worse than one year ago (5)

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much? (circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
3. **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing **several** flights of stairs	1	2	3
7. Climbing **one** flight of stairs	1	2	3
8. Bending, kneeling or stooping	1	2	3
9. Walking **more than a mile**	1	2	3
10. Walking **several blocks**	1	2	3
11. Walking **one block**	1	2	3
12. Bathing or dressing yourself	1	2	3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**? (circle one number on each line)

	Yes	No
13. Cut down on the **amount of time** you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During **the past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)? (circle one number on each line)

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2

18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During **the past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups? (circle one)
Not at all (1) Slightly (2) Moderately (3) Quite a bit (4) Extremely (5)

21. How much **bodily** pain have you had during the **past 4 weeks**? (circle one)
None (1) Very mild (2) Mild (3) Moderate (4) Severe (5) Very severe (6)

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?
Not at all (1) A little bit (2) Moderately (3) Quite a bit (4) Extremely (5)

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks…** (circle one number on each line)

	All of the Time	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)? (circle one)
All of the time (1) Most of the time (2) Some of the time (3) A little of the time (4) None of the time (5)

How TRUE or FALSE is each of the following statements for you? (circle one number on each line)

	Definitely True	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Thank you very much for completing all the questions in this questionnaire.

Scores (by Study Coordinator):

Item Numbers	Response	Score		Item Numbers	Response	Score
1, 2, 20, 22, 34, 36	1	100		32, 33, 35	1	0
	2	75			2	25
	3	50			3	50
	4	25			4	75
	5	0			5	100
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1	0		13, 14, 15, 16, 17, 18, 19	1	0
	2	50			2	100
	3	100				
21, 23, 26, 27, 30	1	100		24, 25, 28, 29, 31	1	0
	2	80			2	20
	3	60			3	40
	4	40			4	60
	5	20			5	80
	6	0			6	100

	Items	Score (Mean)
Physical Functioning	3, 4, 5, 6, 7, 8, 9, 10, 11, 12	Total: _____ / 10 = _____
Role Limitation (Physical)	13, 14, 15, 16	Total: _____ / 4 = _____
Role Limitation (Emotional)	17, 18, 19	Total: _____ / 3 = _____
Energy/fatigue	23, 27, 29, 31	Total: _____ / 4 = _____
Emotional well-being	24, 25, 26, 28, 30	Total: _____ / 5 = _____
Social Functioning	20, 32	Total: _____ / 2 = _____
Pain	21, 22	Total: _____ / 2 = _____
General Health	1, 2, 33, 34, 35, 36	Total: _____ / 6 = _____

Signature: _____ Date: _____

Appendix 9. MRI Improvement Evaluation

MRI Improvement Evaluation Form

Protocol Number: JS-OAP2-US01

Site No.	Subject No.	Subject Initials

- **The time of Evaluation (from Baseline):**

☐	**From baseline at Month 6**
☐	**From baseline at Month 12**

- **Principal Investigator's MRI Final Evaluation:**

▸ **Please select one of 3 followings for MRI result at above checked time.**

☐ **ⓐ Improvement**

☐ **ⓑ No change**

☐ **ⓒ Progress**

- **Evaluated by:**

Principal Investigator

Name / Signature Date (DD-MMM-YYYY)