CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Repeated Intra-Articular Injection of SI-613 in Patients with Osteoarthritis of the Knee

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SPONSOR'S SIGNATURE

Declaration of Sponsor

Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Repeated Intra-Articular Injection of SI-613 in Patients with Osteoarthritis of the Knee

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational drug (SI-613 or placebo), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice.

[redacted]
General Manager, Clinical Development Department
Research and Development Division
Seikagaku Corporation

[redacted]

Sep 01, 2017
Date

INVESTIGATOR'S SIGNATURE

I have received and read the investigator's brochure for SI-613. I have read protocol 613/1121 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Study project manager	[redacted]	[redacted]
Medical monitor	[redacted]	[redacted]

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2. LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation	Explanation
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	anteroposterior
AST	aspartate aminotransferase
BMI	body mass index
COX	cyclooxygenase
CBC	complete blood count
CGIC	Clinical Global Impression of Change
CFR	Code of Federal Regulations
DF	diclofenac
eCRF	electronic case report form
FDA	Food and Drug Administration
FTA	femoral-tibial angle
GCP	Good Clinical Practice
GEE	generalized estimating equations
HA	hyaluronate or hyaluronic acid
IA	intra-articular
ICH	International Conference on Harmonisation
IRB	institutional review board
ITT	intention-to-treat
K-L	Kellgren-Lawrence
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
OMERACT-OARSI	Outcome Measures in Rheumatology - Osteoarthritis Research Society International
PASE	Physical Activity Scale for the Elderly
PGIC	Patient Global Impression of Change
PP	per-protocol

SAE	serious adverse event
SAR	suspected adverse reaction
SF-36	36-Item Short Form Health Survey (SF-36)
SKK	Seikagaku Corporation
SOP	standard operating procedure
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

3. INTRODUCTION

3.1. Background

Osteoarthritis (OA) is by far the most common joint disorder in the United States (US) and throughout the world, and it is one of the leading causes of disability in the elderly.[1,2] Osteoarthritis is characterized by damage to joint structures such as hyaline cartilage and subchondral bone, and increases in prevalence with age. Primary symptoms include joint pain and impairment of physical function. The main clinical features are bony swelling, joint effusion, limitation of range of motion, malalignment, and deformation. Treatment for OA aims to relieve pain and improve function. Main treatment options for knee OA are conservative therapies such as exercise, physical therapy, and pharmacotherapy. Pharmacotherapy includes use of oral or topical agents, such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), or intra-articular (IA) injections such as hyaluronic acid (HA) or corticosteroids. Surgery is an option for patients when conservative therapy fails to improve symptoms and joint destruction progresses.

Oral NSAIDs are among the most commonly used medications for mild or moderate knee OA pain. Nonsteroidal anti-inflammatory drugs have a fast-acting analgesic and anti-inflammatory effect and are considered to be effective for improving OA symptoms, but individual patient response varies widely. An increase in upper gastrointestinal tract disorders has been reported in patients on long-term use.[3] In the 1990s, numerous selective cyclooxygenase (COX)-2 inhibitors were developed to reduce upper gastrointestinal tract disorders, but most of them were withdrawn from the market or their development was halted by 2004 due to concerns about cardiovascular adverse reactions.[4] The same concerns with selective COX 2 inhibitors have also been reported with oral NSAIDs.[5]

Intra-articular injection therapies also play an important role in the conservative therapy of knee OA. Corticosteroids and HA formulations are typical examples. Corticosteroids have strong anti-inflammatory effects and are given by IA knee injection to patients with moderate to severe knee OA. However, it is generally recommended that corticosteroid injections be limited to 3 or 4 times per year in most cases because of concern over potential progressive joint destruction through repeated injections into the knee joint.[6] Although the mechanisms of action of IA HA injections are not fully understood, an array of research suggests that HA exerts anti-inflammatory, analgesic, and possibly chondroprotective effects on the joint cartilage.[7] Due to their viscoelastic properties, IA HA injections also function as a lubricant and a shock absorber. As a result of these effects, IA HA injections exert long-lasting pain relief for some patients with OA of the knee.[8]

Seikagaku Corporation (SKK) has developed and evaluated various HA derivatives that are chemically linked with various NSAIDs and possess the advantages of both IA HA injections and NSAIDs. SI-613, an HA derivative chemically linked with diclofenac (DF), was identified through a series of animal arthritis model studies. As the result of data obtained from the nonclinical studies, a single IA injection of SI-613 is expected to provide analgesic effect for OA pain and to remain in joint tissues for a prolonged period of time to provide potent, sustained analgesia, and could be a highly effective and safe treatment for OA pain.

A phase 1 clinical study performed in healthy Caucasian and Japanese male subjects showed that single IA knee injections of SI-613 were safe and well tolerated. A phase 2 study in 121 Japanese subjects with knee OA was then conducted to explore the efficacy and safety of single IA knee injections of 15 mg SI-613 drug solution, 30 mg SI-613 drug solution, and placebo. SI-613 was well tolerated, resulting in no major safety signals. While the differences between treatment groups for the primary efficacy measurement, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscore, were not statistically significant, significant improvement compared with

placebo treatment was found for SI-613 treatment for some individual questions in WOMAC stiffness and WOMAC physical function subscores, which were secondary efficacy measurements. Also, the number of individual WOMAC questions with significant improvements for SI-613 over placebo was larger for the 30 mg SI-613-treated group than for the 15 mg SI-613-treated group. After a single IA injection of SI-613 drug solution or placebo, the estimated difference between the SI-613 and placebo groups in the WOMAC subscores tended to be larger for 30 mg SI-613 treatment than for 15 mg SI-613 treatment from Weeks 1 through 8.

A second phase 2 study in 176 Japanese subjects with knee OA was then conducted to explore the efficacy and safety of repeated IA knee injections (1 injection every 4 weeks, total of 3 injections) of 30 mg SI-613 drug solution and placebo. The repeated IA injections of 30 mg SI-613 drug solution showed significantly greater improvements than placebo in the primary endpoints of the WOMAC pain subscore and the subject daily pain score during Week 1 through Week 12. As in the prior study, SI-613 was well tolerated, resulting in no major safety signals.

Based on these results, SKK begins the US clinical program with this phase 2 study, which is designed to evaluate the efficacy and safety of repeated IA injections (1 injection every 4 weeks, with a total of 3 injections) of 30 mg SI-613 drug solution compared with placebo in subjects with symptomatic knee OA.

3.2. Risks and Benefits

For summary of the known and potential risks and benefits to human subjects, please see Sections 6.3 of the SI-613 Investigator's Brochure.

3.3. Rationale for Route of Administration, Dosage, and Dosing Regimen

3.3.1. Route of Administration and Rationale

The route of administration of SI-613 is via IA injection into the knee joint.

Intra-articular injection is a common route of administration in medical practice, with many similar injectable HA medical devices approved in the US for the treatment of OA knee pain. Intra-articular injection makes it possible to place SI-613 drug substance directly into the joint cavity without diffusing it into other tissues, which contributes to low systemic exposure.

3.3.2. Dosage and Rationale

The volume of injection to be used for this study is 3 mL. [redacted]

The dosage to be used for this study is 30 mg. In the single-dose phase 2 study in Japanese patients with knee OA, it was suggested that a single injection of SI-613 was effective and that efficacy was higher with 30 mg SI-613 than with 15 mg SI-613. The study also suggested that there were no major safety concerns with either dose of SI-613. Based on the above results, 30 mg was selected as the final clinical dose.

3.3.3. Dosing Regimen and Rationale

The dosing regimen of SI-613 will be repeated IA injections of 30 mg SI-613 administered once every 4 weeks for a total of 3 IA injections at Weeks 0, 4, and 8. In the nonclinical study in antigen-induced rabbit arthritis models, a single IA knee injection of SI-613 significantly inhibited knee joint swelling compared with injections in the control group up to 28 days after the injection. In the repeat-dose phase 2 clinical study in Japanese patients with knee OA, IA knee injections of 30 mg SI-613 at 28-day intervals resulted in statistically significant improvement in pain compared with placebo. Therefore, a 28-day (4-week) dosing interval was selected.

4. OBJECTIVES

4.1. Primary Efficacy Objective

The primary efficacy objective of the study is to investigate the efficacy of SI-613 for the treatment of OA knee pain by showing a greater reduction in pain as measured by the WOMAC visual analog scale (VAS) pain subscore over a 12-week evaluation period in subjects treated with SI-613 compared with subjects treated with placebo. The primary efficacy objective will be tested using the null hypothesis that there is no difference in the mean change from the pretreatment measure of pain relief (WOMAC VAS pain subscore) between SI-613 and placebo over 12 weeks.

4.2. Secondary Efficacy Objectives

The secondary efficacy objectives are to investigate the effect of SI-613 on signs and symptoms of OA of the knee versus placebo as assessed by the following:

- WOMAC VAS pain subscore
- WOMAC VAS physical function subscore
- Patient Global Impression of Change (PGIC)
- Proportion of subjects experiencing a >30% or >50% improvement in WOMAC VAS pain subscore
- Outcome Measures in Rheumatology - Osteoarthritis Research Society International (OMERACT-OARSI) responder rate
- WOMAC VAS total score
- WOMAC VAS stiffness subscore
- 36-Item Short Form Health Survey (SF-36) physical component score
- Amount of acetaminophen rescue medication consumed for the target knee
- Clinical Global Impression of Change (CGIC)
- Weekly average of daily pain scores
- Physical Activity Scale for the Elderly (PASE)

4.3. Safety Objective

The safety objective of the study is to support the overall safety of SI-613 by examining the following:

- Incidence of treatment-emergent adverse events (AEs)
- Vital signs readings
- Laboratory tests
- Target knee examinations
- Synovial assessment in the target knee by magnetic resonance imaging (MRI)

5. INVESTIGATIONAL PLAN

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of a 3 mL IA knee injection of 30 mg SI-613 given every 4 weeks for the treatment of OA knee pain over 12 weeks. The subject will be followed up for 26 weeks after randomization.

Following screening, approximately 80 subjects will be randomized in a 1:1 ratio to treatment with SI-613 or placebo. Randomization will be balanced based on baseline WOMAC VAS pain subscore, Kellgren-Lawrence (K-L) score, sex, and investigational site. Screening may occur 1 to 2 weeks prior to injection (Week 0). As part of the eligibility assessments, subjects will complete the WOMAC (with the VAS pain subscore being used as part of the eligibility assessment) and report their pain on a 100-mm VAS after a 50-foot walk test at Screening and at Week 0 prior to injection. Subjects will be randomized to receive an injection every 4 weeks, a total of 3 injections of either 1% SI-613 or placebo and followed up for 26 weeks after randomization. Subjects will have clinic visits at Weeks 0, 1, 2, 4, 6, 8, 10, 12, 18 and 26. Subjects will receive injections at Weeks 0, 4, and 8. Because the SI-613 and placebo preparations might be visually distinguished in the syringe caused by the difference of the viscosity, the injections will be administered by an unblinded injecting physician who is experienced in IA injection of the knee. The unblinded injecting physician will be instructed on how to maintain blinding of other study team members and subjects from the treatment, and will be otherwise uninvolved with conducting the study, including outcome assessment. At all visits, a blinded evaluating physician or a back-up blinded evaluating physician will conduct the assessments. Subjects will report their signs and symptoms of knee OA through the WOMAC at all visits and PGIC at all follow-up visits. Subjects will also complete a daily diary recording their pain on the 11-point Numeric Rating Scale (NRS) before bed each evening. In addition, the SF-36 will be completed at Weeks 0, 4, 8, 12, and 26 and the PASE will be completed at all visits. The physician will complete the CGIC at all follow-up visits and an examination of the target knee at all visits. MRI will be taken at screening, Weeks 12 and 26 to monitor synovial changes of the target knee and assessed by an independent central imaging evaluator. Subjects must switch to using acetaminophen as a rescue pain medication if they are currently using other pain medications. Acetaminophen will be provided, and pill counts will be used to assess consumption between visits.

The primary endpoint is the change in target knee pain from baseline (average of scores at Visits 1 and 2) to post-treatment (defined as the repeated-measures model estimated average of post-treatment time points over Weeks 1 through 12), as measured on the WOMAC VAS. Secondary efficacy analyses will include evaluations of the difference between the SI-613 and placebo groups in changes in the WOMAC VAS subscores for physical function, stiffness, and total score; proportion of subjects experiencing a >30% or >50% improvement in pain; OMERACT-OARSI responder rates; PGIC; CGIC; SF-36 physical component score; daily pain score; PASE; and acetaminophen consumption.

The incidence of treatment-emergent AEs and the results of vital signs readings, laboratory tests, target knee examinations, and the synovial assessment of the target knee by MRI will be used to assess safety.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Subject Inclusion Criteria

A subject must meet all of the following inclusion criteria to be eligible to enroll in the clinical trial:

1. Provides their written informed consent.
2. Is willing and able to complete efficacy and safety questionnaires and is able to read and understand study instructions.
3. Is a male or female aged 40 to 75 years (inclusive) at the time of informed consent.
4. Has a diagnosis at the time of screening of OA of the knee according to American College of Rheumatology (ACR) criteria:
    - Knee pain
    - Plus osteophytes
    - Plus at least 1 of 3 of the following criteria:
        - Age >50 years
        - Morning stiffness <30 minutes
        - Crepitus on active motion
5. Has had OA pain in the target knee during at least the full 12 months (1 year) immediately preceding the screening visit.
6. Has a grade 2 or 3 score on the K-L grading scale based on a bilateral standing anteroposterior (AP) x-ray of the target knee taken no longer than 6 months prior to Screening. Kellegren-Lawrence grading will be assessed based on the following definitions:
    - Grade 2: definite osteophytes and possible narrowing of the joint space
    - Grade 3: moderate multiple osteophytes and definite narrowing of the joint space, some sclerosis and possible deformity of bone ends
7. Has a pain score for the target knee of 50 to 90 mm (inclusive) on a 100-mm VAS at Screening and Day 1 before injection 1) for the mean of the 5 questions on the WOMAC VAS pain subscale prior to the 50-foot walk test and 2) on the pain assessment following a 50-foot walk test, which has no time constraint but must be completed without assistance of walking aids or other assistive devices or supports.
8. Has a pain score for the contralateral knee of ≤30 mm on a 100-mm VAS at Screening and Day 1 before injection 1) for the mean of the 5 questions on the WOMAC VAS pain subscale prior to the 50-foot walk test and 2) on the pain assessment following a 50-foot walk test, which has no time constraint but must be completed without assistance of walking aids or other assistive devices or supports.
9. Is willing to switch to using acetaminophen as a rescue medication if currently using other pain medications.
    - Acetaminophen will be provided for the treatment of breakthrough pain in the target knee. This will be the only pain medication permitted for target knee pain.

- Use of over-the-counter acetaminophen will be permitted for AEs, but the use will be limited to up to 3 days total between each visit for Visits 1 through 4 and up to 5 days total between each visit for Visits 5 through 9.

A maximum of 3000 mg/day total of acetaminophen will be permitted. The use of low-dose aspirin (one to two 81 mg doses/day) for thrombosis prophylaxis is permitted.

10. Is willing to suspend the use of combination over-the-counter medications that may contain prohibited medications or acetaminophen.
11. Is willing to suspend the use of rescue medication (acetaminophen), for both the target knee and any AEs, from the 2 days before to the end of each study visit.
12. Failed at least one pharmacologic treatment (e.g., NSAID) in the management of the target knee OA.

6.2. Subject Exclusion Criteria

The presence of any of the following exclusion criteria excludes a subject from study enrollment:

1. Has a body mass index (BMI) greater than or equal to 40 kg/m^2 at Screening.
2. Has any of the following:
    - Grade 1 or grade 4 score on the K-L grading scale for the target knee.
        - Grade 1: doubtful narrowing of the joint space and possible osteophytic lipping
        - Grade 4: large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends
    - Grade 3 score on the K-L grading scale for the target knee and exhibits at least 1 characteristic of a grade 4 on the radiograph (large osteophytes, marked narrowing of joint space, severe sclerosis, or definite deformity of bone contour)
    - Current or healing fracture of either leg
    - Medical history of severe bone disease that could affect the lower limbs, either generalized (e.g., osteoporosis) or localized (e.g., osteonecrosis, joint deformity, or meniscal instability affecting either leg)
3. Has any of the following in the target knee:
    - Secondary OA resulting from trauma or other diseases
    - History of chondrocyte transplantation
    - History of ligament reconstruction
    - Skin disorder or infection in the injection area of the target knee
4. Has had joint replacement of the target knee at any time or a joint replacement of the contralateral knee in 1 year prior to Screening.
5. Has diagnosed and treated OA of the hips, spine, or ankle within 2 years or has symptomatic OA of the hips, spine, or ankle at Screening or Week 0 pre-injection.
6. Has any of the following, which may affect pain in 1 or both knees:
    - Pain in either lower extremity that is sufficient to interfere with evaluation of the knees

- Inflammatory disease other than OA or septic arthritis of either knee (e.g., joint infection) within 1 year prior to Screening or at Week 0 before injection
- Surgical procedure or invasive procedure (e.g., arthroscopy, joint lavage) in either lower extremity within 1 year prior to Screening
- IA HA injection(s) for the treatment of OA of either knee within 6 months prior to Screening

7. Has received an IA injection(s) into any joint other than IA HA (e.g., corticosteroids, chondroitin sulfate, or glucosamine) within 90 days prior to Screening.
8. Had IA fluid aspirated from either knee within 7 days prior to the start date of screening.
9. Has taken any of the following prohibited medications within 7 days prior to Screening. Unless noted, these medications are prohibited in oral, injectable, and suppository forms, but they can be used in inhaled, nasal, or ophthalmic formulations. Topical administration is permitted except for the lower extremity of the ipsilateral side of the target knee.
    - NSAIDs (DF is prohibited by any route of administration)
    - Medicines for neuropathic pain (e.g., pregabalin, gabepentin)
    - Topical capsaicins
    - Duloxetine (serotonin-norepinephrine reuptake inhibitors)
    - Local anesthesia to either knee (local anesthesia to target knee during SI-613 injection procedure is permitted)
    - Anticonvulsant drugs, herbal medicines with analgesic properties

    Subjects who agree to discontinue use of these medications and for whom discontinuation of these medications is medically appropriate may return 7 days after discontinuation to complete screening.
10. Has taken any of the following prohibited medications within 28 days prior to Screening. Unless noted, oral, injectable, or suppository administration is prohibited, but topical administration is prohibited only for the lower extremity of the ipsilateral side of the target knee.
    - Opioids (prohibited by any route of administration)
    - Corticosteroids (note that IA administration is excluded within 90 days prior to screening per exclusion criterion #7)
    - Antidepressant medications, antianxiety medications, antipsychotic medications, mood stabilizers, and sleeping drugs

    Subjects who agree to discontinue use of these medications, and for whom discontinuation of these medications is medically appropriate, may return 28 days after discontinuation to complete screening.
11. Has had any block procedure (e.g., nerve block, epidural block, or facet block) within 28 days prior to the start date of screening.
12. Has begun taking an oral chondroprotective agent (chondroitin sulfate or glucosamine) for 14 days prior to Screening. Subjects who have been taking a stable dose on a stable regimen for ≥15 days prior to the start date of screening can continue the stable dose

during the study. Subjects who agree to stabilize their dose of these medications or to discontinue use of these medications, and for whom the adjustment made is medically appropriate, may return after ≥15 days to complete screening.

13. Has begun treatment with any physical therapy (exercise therapy, Tai Chi, massage, balneotherapy, taping, insoles, knee braces, thermal agent, and/or transcutaneous electrical stimulation) for OA of the target knee for 28 days prior to the start date of screening. Subjects who have continued at stable regime for ≥29 days prior to the start date of screening can continue during the study. Subjects who agree to stabilize their therapy regimen or to discontinue therapy, and for whom the adjustment made is medically appropriate, may return after ≥29 days to complete screening. Acupuncture is prohibited for either knee for 7 days prior to the start date of screening.
14. Is a female subject who is pregnant or lactating.
15. Is a female subject of childbearing potential who is not willing to use adequate contraceptive measures to avoid pregnancy. All sexually active subjects must agree to practice an adequate method of birth control during the study. Adequate methods of birth control include the following:

    - Hormonal contraception
    - Use of at least 1 acceptable barrier method; acceptable barrier methods include diaphragm plus a spermicidal agent or condoms (male or female) plus a spermicidal agent
    - Vasectomy, hysterectomy, bilateral tubal ligation, intrauterine device, and/or an exclusive sexual partner for whom 1 of these methods applies

    Female subjects who have not menstruated within the past 2 years are considered postmenopausal and do not need to practice birth control.
16. Has a history of aspirin-induced asthma (asthma attacks triggered by NSAIDs, etc.).
17. Has a known allergy or contraindication to sodium HA products, any DF preparation, or acetaminophen.
18. Has another disease that has been associated with any joint symptoms in the past 2 years (e.g., chondrocalcinosis, gout, psoriasis).
19. Has the following exclusionary laboratory test results at Screening:

    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN)
    - Creatinine >1.5 times the ULN
    - Positive hepatitis C antibodies or hepatitis B surface antigen
20. Has a current malignancy or has received treatment for malignancy within the past 5 years prior to informed consent.
21. Has a history of recurrent, severe allergic or immune-mediated reactions or other autoimmune disorders.
22. Has any of the following medical conditions that would interfere with safety or efficacy evaluation: uncontrolled diabetes; immunodeficiency syndrome; significant cardiovascular, renal, or liver disease; severe anemia; clotting disorder or other blood diseases; serious infectious disease; fibromyalgia or other systemic chronic pain

disorder; rheumatoid arthritis; anserine bursa; lumbar radiculopathy; neurogenic or vascular claudication; vascular insufficiency of lower limbs; peripheral neuropathy severe enough to interfere with the study evaluations; seizure disorder; dementia; psychosis (or history thereof); current anxiety, depression, or other neuropsychiatric symptoms.

23. Has presence or history of alcohol or drug abuse, or tests positive on urine drug screen or for blood alcohol. Subjects should be advised not to drink alcohol within 24 hours of Screening. Positive drug or alcohol tests cannot be repeated.
24. Has any other psychiatric, medical, or social condition or situation that, in the opinion of the investigator, is likely to interfere with study conduct, confound interpretation of study results, or adversely affect the balance of benefits and risks of study participation.
25. Has a contraindication to receiving an MRI of the target knee or is unwilling to have MRI performed.
26. Is currently hospitalized or has a planned hospitalization during the life of the study.
27. Is receiving worker's compensation or is currently involved in litigation.
28. Has participated in a clinical study of an investigational drug, device, or biologic within 90 days prior to informed consent.
29. Any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

6.3. Subject Withdrawal Criteria

Subjects will be encouraged to adhere to the protocol and complete all required assessments. A subject will be discontinued from the study for any of the following medical or administrative reasons:

- A treatment-emergent AE or considerable worsening of an AE that, in the judgment of the investigator or medical monitor, represents an unacceptable risk to the subject and warrants stopping the subject's participation in the investigational study. The investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
- Pregnancy.
- Death of subject.
- Poor response of a subject to the investigational product such that the investigator determines that the subject needs treatment that excludes them from the protocol.
- A critical deviation from the inclusion or exclusion criteria that leads the investigator or medical monitor to determine that continued injections of SI-613 or placebo are not appropriate for ethical or safety reasons.
- Having joint replacement of the target knee
- Receiving an IA injection into the target knee joint (e.g., HA, corticosteroids, or chondroprotective agents) during the study.
- Participation in another clinical study.
- Development of human immunodeficiency virus infection (as assessed by a positive test for human immunodeficiency virus) or active hepatitis.

- Development or diagnosis of alcohol or other substance abuse.
- If the investigator judges it impossible to continue the study for a subject because
    - The subject does not comply with protocol requirements
    - The subject is lost to follow up
    - There are technical issues at the site
- Investigator discretion at any time.
- Subject's request.
- Sponsor's discontinuation of the study at a site.
- Premature termination of the study by the sponsor.

Any enrolled subjects desiring to discontinue prior to study completion should be encouraged to continue in the study and adhere to the protocol and subsequent regularly scheduled safety and efficacy evaluations. Subjects who are discontinued outside of any scheduled visit will be encouraged to complete the early termination visit at the time of withdrawal. Subjects who are discontinued during a scheduled visit will be encouraged to complete all assessments for both that study visit and the early termination visit at the time of withdrawal. A subject who withdraws following the injection will not be replaced.

7. STUDY SCHEDULE AND PROCEDURES

7.1. Study Schedule

The study schedule can be found in Table 2.

7.2. Study Procedures

7.2.1. Screening / Visit 1 (Week -2 to -1; Day -14 to -7)

Screening (Week -2 to -1) will occur 7 to 14 days prior to Visit 2 (Week 0).

The following procedures will be performed at Screening / Visit 1:

- Prior to any study-specific procedures, obtain written informed consent for this study.
- Perform screening inclusion/exclusion criteria eligibility assessments, which include the following:
    - Confirm that the subject has not used any prohibited medications or therapies within the protocol-defined washout windows. If a subject has used prohibited or restricted medications or therapies within the washout window, the subject may remain in the study and return after the appropriate washout period to continue the Screening visit.
    - Record the use of prior and current concomitant medications and therapies, confirming that the subject has been on a stable dose and regimens of chondroitin sulfate or glucosamine for at least 15 days and a stable regimen of physical therapy for at least 29 days. If a subject has used varied doses of chondroitin sulfate or glucosamine within the past 15 days inclusive or a varied regimen of physical therapy within the past 29 days inclusive, the subject may begin a period of stable dosing/regimen and return after ≥15 days or ≥29 days, respectively, to recomplete the activities in the Screening visit.
    - Collect demographic data and medical history information, including diagnosis and history of OA.
    - Collect vital signs.
    - Measure the subject's height and weight and use these data to calculate the subject's BMI.
    - If no x-rays are available from the preceding 6 months, obtain an AP x-ray of the target knee joint with the subject in the standing position.
    - Assess K-L score.
    - Assess femoral-tibial angle (FTA).
    - Collect urine sample for a urine drug screen and for laboratory tests (qualitative urinalysis regarding glucose, protein and urobilinogen).
    - Collect blood sample for laboratory tests (complete blood count, complete metabolic profile, blood alcohol content, and hepatitis screening).
    - For females of childbearing potential, collect a blood sample to perform a serum pregnancy test.

- Record baseline signs and symptoms as baseline for future potential AEs.
- Perform examination of the target knee.
- Assess patellar grinding via Clarke's test.
- Administer the WOMAC.
- Conduct the 50-foot walk test and measure pain immediately following using a 100-mm VAS.
- Confirm that the subject meets all of the inclusion criteria and none of the exclusion criteria and is therefore eligible for the study.
- Obtain MRI of the target knee joint (MRI may be scheduled at another day within Day -14 to -3 (from 3 to 14 days prior to Visit 2).
- Record AEs that have occurred during the study visit.
- Distribute subject daily diary.
- Distribute acetaminophen.

7.2.2. Randomization / Visit 2 (Week 0; Day 1)

Visit 2 must occur in a 7- to 14-day window following the Screening visit.

The following procedures will be performed at Visit 2:

- Confirm no use of rescue acetaminophen in the previous 2 days and before the visit at the visit date.
- Review the medical history information.
- Review and update the use of prior and current concomitant medications and concomitant therapies, confirming that the subject has not used any prohibited medications or therapies and has not changed the dose and/or regimen of restricted medications or therapies since the previous visit.
- Collect vital signs.
- Collect urine and perform a dipstick urine pregnancy test.
- Collect the acetaminophen container from the previous visit and count acetaminophen usage.
- Collect the subject daily diary and assess compliance.
- Record AEs.
- Perform examination of the target knee.
- Administer the WOMAC.
- Administer the SF-36.
- Administer the PASE.
- Conduct the 50-foot walk test and measure pain immediately following using a 100-mm VAS.
- Confirm that the subject meets all of the inclusion criteria and none of the exclusion criteria and is therefore eligible for the study.

- Randomize the subject.
- Perform the first injection.
    - The subject will be instructed to avoid any strenuous activities (such as jogging, tennis, and other active sports or heavy lifting) and prolonged weight-bearing activities (such as standing for more than 1 hour) for 48 hours following the IA injection.
- Record AEs that have occurred during the study visit.
- Distribute new subject daily diary.
- Distribute new acetaminophen tablets.

7.2.3. Follow-up Visits 3 (Week 1; Day 8 ± 2), 4 (Week 2; Day 15 ± 2), 6 (Week 6; Day 43 ± 6), 8 (Week 10; Day 71 ± 6), and 10 (Week 18; Day 127 ± 14)

The following procedures will be performed at Visits 3, 4, 6, 8 and 10:

- Confirm no use of rescue acetaminophen in the previous 2 days and before the visit at the visit date.
- Review and update the use of concomitant medications and therapies, confirming that the subject has not used any prohibited medications or therapies and has not changed the dose and/or regimen of restricted medications or therapies since the previous visit.
- Collect vital signs.
- Record AEs.
- Collect the acetaminophen container from the previous visit and count acetaminophen usage.
- Collect the subject daily diary and assess compliance.
- Perform examination of the target knee.
- Administer the WOMAC.
- Record the PGIC.
- Administer the PASE.
- Record the CGIC.
- Record AEs that have occurred during the study visit.
- Distribute new subject daily diary.
- Distribute new acetaminophen tablets.

7.2.4. Additional Injection Visits 5 (Week 4; Day 29 ± 7) and 7 (Week 8; Day 57 ± 7)

The following procedures will be performed at Visits 5 and 7:

- Confirm no use of rescue acetaminophen in the previous 2 days and before the visit at the visit date.
- Review and update the use of concomitant medications and therapies, confirming that the subject has not used any prohibited medications or therapies and has not changed the dose and/or regimen of restricted medications or therapies since the previous visit.

- Collect vital signs.
- Collect urine and perform a dipstick urine pregnancy test.
- Collect urine sample for laboratory tests (qualitative urinalysis regarding glucose, protein and urobilinogen).
- Collect blood sample for laboratory tests (complete blood count and complete metabolic profile).
- Record AEs.
- Collect the acetaminophen container from the previous visit and count acetaminophen usage.
- Collect the subject daily diary and assess compliance.
- Perform examination of the target knee.
- Administer the WOMAC.
- Record the PGIC.
- Administer the SF-36.
- Administer the PASE.
- Record the CGIC.
- Perform the injection.
    - The subject will be instructed to avoid any strenuous activities (such as jogging, tennis, and other active sports or heavy lifting) and prolonged weight-bearing activities (such as standing for more than one hour) for 48 hours following the IA injection.
- Record AEs that have occurred during the study visit.
- Distribute new subject daily diary.
- Distribute new acetaminophen tablets.

7.2.5. Visit 9 (Week 12; Day 85 ± 7)

The following procedures will be performed at Visit 9:

- Confirm no use of rescue acetaminophen in the previous 2 days and before the visit at the visit date.
- Review and update the use of concomitant medications and therapies, confirming that the subject has not used any prohibited medications or therapies and has not changed the dose and/or regimen of restricted medications or therapies since the previous visit.
- Collect vital signs.
- Collect urine sample for laboratory tests (qualitative urinalysis regarding glucose, protein and urobilinogen).
- Collect blood sample for laboratory tests (complete blood count and complete metabolic profile).
- Record AEs.

- Collect the acetaminophen container from the previous visit and count acetaminophen usage.
- Collect the subject daily diary and assess compliance.
- Perform examination of the target knee.
- Administer the WOMAC.
- Record the PGIC.
- Administer the SF-36.
- Administer the PASE.
- Record the CGIC.
- Obtain MRI of the target knee joint (MRI may be scheduled at another day within the window of this visit).
- Record AEs that have occurred during the study visit.
- Distribute new subject daily diary.
- Distribute new acetaminophen tablets.

7.2.6. Visit 11 (Week 26; Day 183 ± 14)

The following procedures will be performed at Visit 11:

- Confirm no use of rescue acetaminophen in the previous 2 days and before the visit at the visit date.
- Review and update the use of concomitant medications and therapies, confirming that the subject has not used any prohibited medications or therapies and has not changed the dose and/or regimen of restricted medications or therapies since the previous visit.
- Collect vital signs.
- Collect urine and perform a dipstick urine pregnancy test.
- Collect urine sample for laboratory tests (qualitative urinalysis regarding glucose, protein and urobilinogen).
- Collect blood sample for laboratory tests (complete blood count and complete metabolic profile).
- Record AEs.
- Collect the acetaminophen container from the previous visit and count acetaminophen usage.
- Collect the subject daily diary and assess compliance.
- Perform examination of the target knee.
- Administer the WOMAC.
- Record the PGIC.
- Administer the SF-36.

- Administer the PASE.
- Record the CGIC.
- Obtain MRI of the target knee joint (MRI may be scheduled at another day within the window of this visit).
- Record AEs that have occurred during the study visit.
- Record the end of study form.

7.2.7. Early Termination Visit

If a subject must withdraw early from the study, all procedures normally included in the last visit of the study (i.e., Visit 11) will be performed. In addition, the reason(s) for withdrawal from the study will be collected.

7.2.8. Unscheduled Visits

There may be situations in which the investigator decides to have a subject return for an unscheduled visit after the subject contacts them about an AE or other health information. Therefore, additional examinations may be conducted as necessary to ensure the safety and well-being of subjects during the study. Electronic case report forms (eCRFs) should be completed for each unscheduled visit. The AE and all required information should be recorded on the appropriate eCRF, and the subject's record should include all relevant information.

Table 2: Study Schedule

	Screening	Randomization / Baseline		Follow-up									
Visit	1	2		3	4	5		6	7		8	9	10	11
Week	-2 to -1	0		1	2	4		6	8		10	12	18	26/ Early Termination
Day	Day -14 to -7	Day 1		Day 8	Day 15	Day 29		Day 43	Day 57		Day 71	Day 85	Day 127	Day 183
Window (days)				± 2	± 2	± 7		± 6	± 7		± 6	± 7	± 14	± 14
		Before Injection	Injection			Before Injection	Injection		Before Injection	Injection				
Informed Consent*	X													
Confirm Rescue Acetaminophen Washout[1]	X	X		X	X	X		X	X		X	X	X	X
Wash Out Prohibited Medications/Therapies[2]	X													
Concomitant Medications and Therapies[3]	X	X		X	X	X		X	X		X	X	X	X
Prior Medications	X													
Medical History	X	X												
Vital signs[4]	X	X		X	X	X		X	X		X	X	X	X
BMI (Height, Weight)	X													
X-ray[5]	X													
Assess K-L Score	X													
Assess femoral-tibial angle	X													
Urine Drug Screen	X													
Laboratory Tests[6]	X					X			X			X		X
Pregnancy Test[7]	X	X				X			X					X
Acetaminophen Consumption Assessment		X		X	X	X		X	X		X	X	X	X
Subject Daily Diary Collection and Compliance Assessment		X		X	X	X		X	X		X	X	X	X
Adverse Events[8]	X	X		X	X	X		X	X		X	X	X	X
Target Knee Examination	X	X		X	X	X		X	X		X	X	X	X
Assess Patellar Grinding via Clarke's test	X													
WOMAC Osteoarthritis	X	X		X	X	X		X	X		X	X	X	X

	Screening	Randomization	Follow-up								
	Baseline										
Visit	1	2	3	4	5	6	7	8	9	10	11
Week	-2 to -1	0	1	2	4	6	8	10	12	18	26/ Early Termination
Day	Day -14 to -7	Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 127	Day 183
Index[9]											
PGIC			X	X	X	X	X	X	X	X	X
SF-36		X			X		X		X		X
PASE		X	X	X	X	X	X	X	X	X	X
CGIC			X	X	X	X	X	X	X	X	X
50-foot Walk Test[9]	X	X									
Inclusion/Exclusion Criteria	X	X									
MRI	X[10]								X[11]		X[11]
Randomization		X									
Injection		X			X		X				
Distribute Subject Daily Diary	X	X	X	X	X	X	X	X	X	X	
Distribute Acetaminophen	X	X	X	X	X	X	X	X	X	X	X[12]
End of Study Form											X

BMI = body mass index; CGIC = Clinical Global Impression of Change; FTA = femoral-tibial angle; K-L = Kellgren-Lawrence; PASE = Physical Activity Scale for the Elderly; PGIC = Patient Global Impression of Change; SF-36 = 36-Item Short Form Health Survey ; WOMAC =Western Ontario and McMaster Universities Osteoarthritis Index

* In principle, subjects are injected within 50 days after informed consent.

[1] Subject need to be suspend the use of rescue medication from the 2 days before to the end of the each clinic visit.

[2] Subjects who agree to discontinue use of the prohibited medications and therapies may return to complete screening after the described washout periods, as described in Section 9.3.

[3] Subject cannot have used any prohibited medications or therapies and has not changed the dose and/or regimen of restricted medications or therapies since the previous visit.

[4] Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature.

[5] X-ray is required if subject has not had an x-ray within 6 months of Visit 1 (Screening).

[6] Laboratory tests at Screening will include complete blood count (CBC), complete metabolic profile, qualitative urinalysis, blood alcohol content, and hepatitis screening. Laboratory tests at other visits will include CBC, complete metabolic profile and qualitative urinalysis. Qualitative urinalysis is for glucose, protein and urobilinogen.

[7] Women of childbearing potential only. A serum test will be performed at Screening, and a dipstick urine test will be performed prior to each injection and at the final study visit/early termination.

[8] Adverse events (AEs) will be assessed twice at each in-person study visit: once at the beginning to capture AEs that have occurred since the last study visit, and once at the end to capture any AEs resulting from the study procedures.

[9] WOMAC visual analog scale; pain subscore and pain following a 50-foot walk test are assessed for the target and contralateral knees at the Screening visit and before injection on Day 1. Other visits will include WOMAC assessment of the target knee only.

[10] MRI at the screening visit will be conducted between Day -14 to Day -3.

[11] If repeat MRI is needed after Visit 9 or Visit 11, the permissible lag time for repeat MRI ONLY will be extended by a maximum of an additional 14 days.

[12] Only if MRI is conducted on the separate date after Visit 11, acetaminophen will be provided as rescue medication.

8. INVESTIGATIONAL PRODUCT INFORMATION AND MANAGEMENT

8.1. Investigational Product

Subjects will be randomized to treatment with SI-613 or placebo. SI-613 combination product contains a drug component—a sterile, transparent, viscoelastic HA-DF hydrogel (fermented HA covalently linked to DF)—in a prefilled syringe (device component) to be administered by IA injection. Each prefilled syringe contains 3 mL of 1% SI-613, which is a dose of 30 mg SI-613. Placebo is vehicle, a citric acid- and sodium citrate-buffered (pH 4.8 - 5.4) solution, in a pre-filled syringe; each prefilled syringe contains 3 mL of placebo. The prefilled syringe is composed of a rubber piston (butyl rubber), rubber tip cap (butyl rubber), adapter grip, and plunger rod and is packaged in a molded plastic amorphous polyethylene terephthalate film blister with a Tyvek® lid.

8.2. Investigational Product Packaging and Labeling

All investigational products used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures (SOPs) of SKK or those of its designee, Good Manufacturing Practice guidelines, International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and applicable regulations.

Investigational products will be supplied by SKK, Japan. These products will be labeled according to US requirements and the established randomization plan. Prefilled syringes of 3.0 mL of SI-613 or 3.0 mL of placebo will be packed into blinded treatment kits containing 3 cartons, each containing a single syringe, 1 for each injection in the study for a single subject. The kits for the 2 treatment groups will be identical and will not reveal whether the syringes inside contain SI-613 or placebo. Investigational product kits will be forwarded to participating sites once all regulatory requirements have been met.

8.3. Investigational Product Storage

Current ICH GCP guidelines require the investigator to ensure that investigational product deliveries from the designated vendor are received by a responsible person at the site. The site will record that the investigational products are handled and stored safely and properly, and that the investigational products are used only to treat study subjects in accordance with the protocol.

The investigational products will be stored securely at each site at the appropriate temperature (between 35.6°F and 46.4°F. DO NOT FREEZE. Protect from light.) until used for treatment of a subject.

Investigational products must be used before the package expiration date. Any unused investigational products beyond the package expiration date must be returned to the designated vendor.

8.4. Investigational Product Administration

At Visit 2 (Week 0), Visit 5 (Week 4), and Visit 7 (Week 8), randomized study subjects will receive a single IA injection of either SI-613 or placebo. Both the unblinded injecting physician and the blinded evaluating physician must be present at these visits. All subject evaluations must be performed by the blinded evaluating physician at all visits. The same blinded evaluating physician will perform evaluations at all the visits for a subject whenever possible.

Because the SI-613 and placebo preparations might be visually distinguished in the syringe caused by the difference of the viscosity, the injections will be administered by an unblinded injecting physician who is experienced in IA injection of the knee. The unblinded injecting physician will be instructed on how to maintain blinding of other study team members and subjects from the treatment. The unblinded injecting physician will administer the injections of SI-613 and placebo in an identical manner, taking appropriate measures to mask the treatment identity from the subject.

The basic procedure for administration is as follows:

One syringe carton will be removed from the treatment kit, which is stored in the refrigerator, approximately 30 to 60 minutes before injection so that it can reach room temperature. Any syringes that will not be used for the current study visit should remain in the refrigerator. Opening the syringe carton and removing the syringe must be conducted by the unblinded injecting physician. The contents of the syringe must be used immediately after the blister packaging is opened.

Warning: Do not concomitantly use disinfectants containing quaternary ammonium salts or chlorhexidine for skin preparation because sodium HA, a component of SI-613, can precipitate in their presence.

1. Strict aseptic administration technique must be followed. Prior to injection, the injecting physician must prepare the injection site with disinfectants.
2. Shield the subject from seeing the syringe containing the investigational product.
3. Injection of subcutaneous lidocaine or similar local anesthetic may be performed prior to injection of the investigational product. Injection of anesthesia into the knee joint is prohibited.
4. At the second (Week 4) and third (Week 8) injections, aspiration of synovial fluid from the target knee immediately prior to injecting the investigational product is allowed if the investigator determines a clinical need. Aspiration at the time of the first injection (Week 0) is prohibited. When aspiration is conducted immediately prior to the second or third injection, the injector will maintain needle placement in the joint while disconnecting the syringe used to relieve joint effusion. Discard the syringe containing the removed joint effusion. The same syringe should not be used for both removing effusion and injecting the investigational product.
5. Peel off the blister Tyvek lid from the blister package and remove the syringe. The contents of the syringe must be used immediately after the blister packaging is opened.
6. Carefully remove the tip cap of the syringe and aseptically attach the syringe to a 20- to 23-gauge needle. To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer lock. If aspiration of synovial fluid was conducted immediately prior injecting the investigational product (at the second or third injection), keep the original needle used for aspiration in the joint and connect the investigational product syringe to the needle already placed in the joint. A thicker than 20-gauge needle may be used for both aspiration and administration if a thick needle is required for aspiration of the joint fluid. Twist the tip cap before pulling it off to minimize leakage.
7. Inject the investigational product into the knee joint through the needle using aseptic injection technique. Place the injection exactly into the knee joint because leakage of investigational product out of the joint cavity may cause pain. Use of guidance for the injection, such as ultrasound guidance, per standard medical practice is allowed.

8. Inject the full 3.0 mL of the investigational product into knee.
9. After the injection, a sterile swab or gauze will be applied, followed by a sterile bandage to cover the injection site.

The subject will be instructed to keep the injected site clean following injection and to avoid any strenuous activities (such as jogging, tennis, and other active sports or heavy lifting) and prolonged weight-bearing activities (such as standing for more than 1 hour) for 48 hours following the IA injection.

8.5. Investigational Product Accountability, Handling, and Disposal

Following injection, the empty syringe should be returned to the empty carton and the carton should be resealed and returned to the subject's treatment kit to allow reconciliation of the product accountability records. These procedures will be conducted by the unblinded injecting physician to prevent unblinding of the treatment assignment at the site. Between injections, kits for subjects who have injections remaining for the study will be stored under the storage conditions between 35.6°F and 46.4°F and protected from light. At the conclusion of the study, all surplus or unused products, empty treatment kits, and resealed syringe cartons containing used syringes will be returned to SKK or its designee per the Returns Protocol devised by the product packaging and labeling vendor.

Inventory and accountability records for the investigational products will be kept by the investigator or designee. The following guidelines are therefore pertinent:

- The investigator agrees not to supply investigational products for treatment of any person except the subjects in this study.
- The investigator will keep the investigational products in a locked and secure storage facility. Access will be permitted only to those authorized by the investigator to dispense these investigational products.
- An investigational product inventory will be maintained by the investigator or appropriate designee. The inventory will include details of materials received and a clear record of when they were dispensed and to which subjects.
- Deliveries will be recorded.
- Investigational products will be handled and stored safely and properly.
- Investigational products will be dispensed only to study subjects in accordance with the protocol.
- Any unused investigational product is to be returned per the instructions in the Returns Protocol.

9. TREATMENT OF SUBJECT

9.1. Description of Investigational Product

Subjects will be randomized to treatment with the SI-613 product, prefilled with HA-DF, or an identical investigational product prefilled with placebo (citric acid- and sodium citrate-buffered [pH 4.8 - 5.4] solution). Please see the full description of the investigational product in Section 8.

9.2. Rescue Medication

Subjects will be provided with acetaminophen at each clinic visit to use as a rescue medication for breakthrough pain in the target knee, and subjects will be instructed to use the acetaminophen only if the pain in the target knee is of sufficient severity to require use of the rescue medication. No acetaminophen use is permitted from the 2 days before to the end of each study visit. Subjects will be asked to bring the acetaminophen container(s) with any remaining tablets to the next visit.

Temporary use of over-the-counter acetaminophen is allowed for the treatment of other AEs, except for the periods from the 2 days before to the end of each study visit. The use of over-the-counter acetaminophen should be limited to up to 3 days between each visit for Visits 1 through 4, up to 5 days between each visit for Visits 4 through 9, and up to 20 days between each visit for Visit 9 through 11. Subjects should report all over-the-counter acetaminophen use to the investigator at each visit.

Subjects will be advised to limit their total acetaminophen use, from both the study-provided acetaminophen and over-the-counter sources, to 3000 mg/day. Subjects will be required to abstain from all use of acetaminophen from the 2 days before to the end of each study visit.

9.3. Concomitant Medications and Therapies

Starting at the Screening visit, the following information use of all concomitant medications and concomitant therapies (concomitant therapies will be recorded only for the therapies conducted for the target knee), including any changes since the last visit, will be recorded in the subject's eCRF, including all prescription drugs, over-the-counter medications, nutritional supplements, vitamins, minerals, herbal products, physical therapy, chiropractic care, etc. The use of acetaminophen as a rescue medication will be recorded separately. Information recorded for each concomitant medication or therapy will include the indication, dosage/regimen, route of administration, and start and stop dates, if applicable. Upon entering the study, each subject will be instructed to report the use of any medication or other therapy to the investigator. Subjects will also be instructed about the importance of not taking any prohibited medication or new medication during the study without first consulting the investigator, unless needed immediately for subject safety.

Prohibited medications and therapies for this study are listed below and with the exclusion criteria in Section 6.2.

9.3.1. Prohibited Medications

The following medications are prohibited for the periods specified prior to Screening and through study completion. Unless noted, the medications are prohibited in oral, injectable, and suppository forms, but

they can be used in inhaled, nasal, or ophthalmic formulations. Topical administration is permitted except for the lower extremity of the ipsilateral side of the target knee.

- 7 days: NSAIDs (diclofenac is prohibited by any route of administration), medicines for neuropathic pain (e.g., pregabalin, gabapentin), topical capsaicins, duloxetine (serotonin-norepinephrine reuptake inhibitors), local anesthesia to either knee (local anesthesia to target knee during SI-613 injection procedure is permitted), and anticonvulsant drugs or herbal medicines with analgesic properties
- 28 days: opioids (prohibited by any route of administration), corticosteroids (IA administration is prohibited within 90 days prior to screening), antidepressant medications, antianxiety medications, antipsychotic medications, mood stabilizers, and sleeping drugs
- 90 days: IA injection(s) into any joint other than IA HA (e.g., corticosteroids, chondroitin sulfate, or glucosamine)
- 6 months: IA HA injection in either knee

The subject should also suspend the use of combination over-the-counter medications that may contain prohibited medications or acetaminophen for the prohibited period of those medications.

9.3.2. Prohibited Therapies

The following therapies are prohibited from the following specified prior to Screening and through study completion.

- 7 days: Acupuncture in either knee
- 28 days: Block procedure (ex; nerve block, epidural block, or facet block)
- 1 year: Surgical procedure or invasive procedure (e.g., arthroscopy, joint lavage) in lower extremity

9.3.3. Restricted Medications and Therapies

Subjects who had been taking stable doses and/or regimens of oral chondroprotective agent (chondroitin sulfate or glucosamine), or physical therapy (exercise therapy, taping, insoles, knee braces, thermal agent, and/or transcutaneous electrical stimulation) for OA of the target knee, for the following specified days prior to the start date of screening can continue during the study.

- ≥15 days: oral chondroprotective agents (chondroitin sulfate or glucosamine)
- ≥29 days: physical therapy for OA of the target knee

Removing joint effusion from either knee is prohibited within 7 days before Screening and through study completion. Removing joint effusion from the target knee as part of the second or third injecting procedure is allowed if the investigator judges the need using a patellar tap test during the target knee examination. Removal of joint effusion during the first injection procedure is prohibited.

9.4. Physical Exercise During the Study

Subjects will be instructed not to change their pattern of regular physical exercise (strength or frequency) from the time of signing the informed consent through study completion.

9.5. Compliance

Compliance issues are not applicable to the product use in this study because the treatment consists only of injections performed by study personnel.

The use of acetaminophen as a rescue medication will be assessed as described in Section 10.7.

Subjects will be instructed to comply with the restrictions regarding the use of new and prohibited concomitant medications and to accurately communicate any use or changes in use to the study site personnel.

9.6. Randomization and Blinding Procedures

A web-based central randomization system will assign subjects to a treatment group. This system will include components for emergency blind break and study drug tracking and will allow users to request reports summarizing system data. If the blind of a subject's treatment must be broken to determine the cause of an illness and proper treatment for the subject, as in the event of a medical emergency, an authorized individual will be able to determine the treatment assignment through the randomization system. When possible, SKK or its designee should be notified prior to breaking the blind. A notification of the unblinding, without revealing the treatment assignment of the individual, will then be communicated to other study staff members.

Blinded treatment kits, each containing 3 prefilled syringes packaged in individual cartons, and individual syringe cartons will be labeled with unique identification numbers. At Visit 2, each subject will be randomized to a treatment, and a kit of the appropriate treatment will be assigned to the subject from the available stock at the site. Both the unblinded injecting physician and the blinded evaluating physician must be present at Randomization / Visit 2 (Day 1/Week 0), Visit 5 (Day 29/Week 4), and Visit 7 (Day 57/Week 8). All subject evaluations must be performed by the blinded evaluating physician at all visits. The same blinded evaluating physician should perform the evaluation for all visits of a subject whenever possible. The unblinded injecting physician must administer the injection and not communicate the treatment allocation to other site staff, the blinded evaluating physician, or subjects. The unblinded injecting physician must be a different individual from the blinded evaluating physician.

All study site personnel will be blinded to the treatment assignment of all subjects except for the unblinded injecting physician, who will perform the injection procedures. The blind for the treatment assignment will be maintained for the entire length of the study.

10. ASSESSMENTS OF EFFICACY

10.1. WOMAC

Subjects will complete the WOMAC version 3.1 with VAS scores at all clinic visits. The WOMAC consists of 3 subscores. Five questions contribute to the pain subscore, 2 questions contribute to the stiffness subscore, and 17 questions contribute to the physical function subscore.

10.2. PGIC

The subject will complete the PGIC at all follow-up visits. A sample can be found in Section 19.1.

10.3. CGIC

The blinded evaluating physician will complete the CGIC at all follow-up visits. A sample can be found in Section 19.2.

10.4. SF-36

Subjects will complete the SF-36 at the indicated visits (Table 2). A sample can be found in Section19.3.

10.5. PASE

Subjects will complete the PASE at the indicated visits (Table 2). A sample can be found in Section 19.4.

10.6. Daily Pain Diary

Subjects will be provided a daily diary in which they will be asked to record their pain each day on the 11-point NRS. A new diary will be provided to study subjects at each clinic visit except for Visit 11. The diary will be collected at the next visit, and the subject's compliance with the completion of the diary assessed. Retraining will be provided to the subject if compliance issues are identified. A sample of the daily diary can be found in Section19.5.

10.7. Acetaminophen Consumption

Acetaminophen will be provided to subjects so that consumption of this rescue medication can be accurately assessed. A new supply of acetaminophen will be provided to study subjects at each clinic visit except Visit 11. The supply container will be collected at the next visit, and the remaining acetaminophen will be counted to record the total number of acetaminophen tablets used since the previous visit.

11. SCREENING ASSESSMENTS

11.1. 50-foot Walk Test

The subject will walk 50 feet on a straight, unobstructed, level course at Visits 1 and 2. The subject will be allowed as much time as needed to complete the 50-foot walk without the assistance of walking aids or other assistive devices or supports. Following completion of the walk, the subject will sit and will be asked to indicate the levels of pain in the target knee and the contralateral knee on a 100-mm VAS.

A sample of the VAS pain scale for use following the 50-foot walk test can be found in Section 19.6.

11.2. X-rays

If a subject has no knee x-rays available from the preceding 6 months, an AP x-ray of the target knee joint with the subject in the standing position will be obtained. The x-rays will be evaluated by the evaluating physician at the site for radiographic evidence and the K-L score assessed using the following scale:

Score	Radiological findings
0	Normal
1	Doubtful narrowing of the joint space and possible osteophytic lipping
2	Definite osteophytes and possible narrowing of the joint space
3	Moderate multiple osteophytes and definite narrowing of the joint space some sclerosis and possible deformity of bone ends
4	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends

Subjects with a K-L score of grade 0, 1, or 4 will be excluded from the study. Subjects with a K-L score of grade 3 who exhibit at least one characteristic of a grade 4 on the radiograph (large osteophytes, marked narrowing of joint space, severe sclerosis, or definite deformity of bone contour) will be also excluded.

11.3. History of Target Knee Osteoarthritis

The following information from the target knee will be recorded:

- Target knee (left or right)
- K-L score and the level of each characteristic: osteophytes, joint space narrowing, osteosclerosis, and bony deformity
- Date of diagnosis
- Start date of current knee pain
- FTA assessment from the X-rays
- Patella Grinding Test (Clarke's test; negative or positive): The purpose of this test is to detect the presence of patellofemoral joint disorder. The subject is positioned in a supine or long sitting position with the target knee extended. The evaluating physician places the web space

of his hand on top of the patella and provides pressure while moving the patella to see if the action causes discomfort or sensitivity (pain = positive). A positive on this test is indicative of pain in the patellofemoral joint.

11.4. Vital Signs

Systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature will be recorded.

11.5. Body Mass Index

The height and weight of the subject will be recorded at Screening and used to calculate a BMI. Any subject with a BMI greater than or equal to 40 kg/m^2 will be excluded from the study.

11.6. Medical History

11.6.1. General Medical History

A brief medical history will be recorded, including the following:

- All concomitant diseases that the subject is experiencing at the time of informed consent;
- Musculoskeletal diseases of the lower extremities that required surgery;
- Other musculoskeletal diseases of the lower extremities in the 1 year prior to Screening; and
- Other diseases that the investigator considers to be important.

11.6.2. Knee Osteoarthritis Treatment History

A brief history of the following treatments, if they have been used, will be recorded, including:

- Medications (name of medication, dosage and dose regimen, periods of usage, intended use, and whether it is the most recent medication) used for the target knee in the 12 weeks prior to Screening or at Screening;
- Physical therapies (name of therapy, frequency, and periods of conduct) used for the target knee in the 12 weeks prior to Screening or at Screening; and
- Intra-articular injections (HA, corticosteroid, etc.) into knee(s) (name of medication, date of final injection, and injection site [left/right])

11.7. Prohibited Medications

Each subject will be asked whether they have taken any of the prohibited medications for this study, listed in Section 9.3, in the 7 or 28 days preceding screening, depending on the medication. If a subject fails this criterion but is willing to discontinue use of the prohibited medication(s), he or she can return after the protocol-defined washout window to complete the screening process.

11.8. Concomitant Medications

Each subject will be asked whether they have been on a stable dose of a chondroprotective agent (chondroitin sulfate or glucosamine) for at least 15 days prior to screening. If a subject fails this criterion

but is willing to stabilize the dose/regimen, he or she can return after 15 days to recomplete the screening process.

11.9. Prohibited Therapies

Each subject will be asked whether they have used or are currently using any of the prohibited therapies for this study, listed in Section 9.3. If a subject fails these criteria but is willing to discontinue use of the prohibited therapy(s), he or she can return after the protocol-defined washout window to complete the Screening process

11.10. Concomitant Physical Therapies

Each subject will be asked whether they have been on a stable regimen of any of the therapies listed in Section 6.2 for at least 29 days prior to screening. If a subject fails this criterion but is willing to stabilize the regimen, he or she can return after 29 days to recomplete the screening process.

11.11. Pregnancy Test

At Screening, blood will be collected from any female subject of childbearing potential to perform a serum pregnancy test to confirm that the subject is not pregnant. At visits when an injection will be given and at the last follow-up visit or an early termination visit, urine will be collected and a dipstick pregnancy test performed for these subjects to confirm that the subject is not pregnant.

11.12. Laboratory Tests

Urine will be collected from each subject to perform a drug screen and for qualitative urinalysis regarding glucose, protein and urobilinogen.

Blood will be collected from each subject to perform a complete blood count, complete metabolic profile, blood alcohol content, and hepatitis screening. The results of the laboratory tests will be reviewed before randomization at Visit 2 to confirm that the subject meets eligibility criteria. In particular, a subject will be excluded if any of the following results are obtained from the laboratory tests:

- AST or ALT >2.5 times the ULN
- Creatinine >1.5 times the ULN
- Positive hepatitis C antibodies or hepatitis B surface antigen

12. ASSESSMENTS OF SAFETY

12.1. Target Knee Examination

At each clinic visit, the target knee will be examined by the blinded evaluating physician for observations of swelling, redness, effusion, or warmth. A result of negative, borderline, or positive will be recorded. Changes in the overall condition of the target knee that, in the investigator's opinion, are associated with or considered an untoward or unfavorable medical occurrence should be reported as an AE.

12.2. Synovial Assessment by MRI

T2 fat-saturated image in the sagittal and axial views by MRI for the target knee will be taken at Visit 1, Visit 9, and Visit 11 (or early termination). The independent central imaging evaluator will conduct the synovial assessment of each subject based on the following imaging criteria:

- Hoffa's synovitis score and the synovitis-effusion score according to the semi-quantitative scoring methods of the MOAKS (MRI Osteoarthritis Knee Score)[9]
- Qualitative assessment for the knee joint synovial thickening

The detailed method for MRI assessments will be defined in the separate independent review manual.

Significant aggravations in the synovial assessments for Visit 9 and/or Visit 11 compared to Visit 1 detected by the independent central imaging evaluator will be reported as an AE.

12.3. Vital Signs

Systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature will be recorded at all clinic visits.

Any abnormal results and changes that, in the investigator's opinion, are associated with or considered an untoward or unfavorable medical occurrence should be reported as an AE.

12.4. Laboratory Tests

Blood will be collected from each subject at Visit 1 (Screening), Visit 5 (Day 29/Week 4), Visit 7 (Day 57/Week8), Visit 9 (Day 85/Week 12), and Visit 11 (Day 183/Week 26 or early termination) to perform a complete blood count (CBC) and complete metabolic profile. Urine will be collected from each subject at Visit 1 (Screening), Visit 5 (Day 29/Week 4), Visit 7 (Day 57/Week8), Visit 9 (Day 85/Week 12), and Visit 11 (Day 183/Week 26 or early termination) for qualitative urinalysis regarding glucose, protein and urobilinogen.

Any abnormal results for these tests will be noted, and changes in the test results that, in the investigator's opinion, are associated with or considered an untoward or unfavorable medical occurrence should be reported as an AE.

12.5. Adverse and Serious Adverse Events

Adverse events will be assessed twice at each study visit: once at the beginning of the visit to record any AEs since the last study visit, and once after all assessments and injections have been performed to

capture any AEs that occur as the result of these activities. At the Screening visit, baseline signs and symptoms will be collected to serve as a baseline for possible future AEs.

This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with 21 Code of Federal Regulations (CFR) 312; ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; and ICH Guideline E6: Guideline for Good Clinical Practice.

Adverse events will be recorded throughout the study and at early termination, and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The investigator is responsible for the detection and documentation of AEs, regardless of treatment group or suspected causal relationship to the investigational product. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to SKK or its designated representative

12.5.1. Definitions of Adverse Events/Effects

12.5.1.1. Adverse Event

An AE is defined as any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (ICH Guideline E6: Guideline for Good Clinical Practice). Any medical condition that is present at the time that the subject is screened will be considered as medical history and not recorded as an AE; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

12.5.1.2. Serious Adverse Event

An AE is considered "serious" if, in the view of either the investigator or SKK, it results in any of the following outcomes (21 CFR 312.32(a)):

- Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to SKK or its designee whether it is considered treatment related or not.
- A life-threatening event: An AE or suspected adverse reaction (SAR) is considered "life-threatening" if, in the view of either the investigator or SKK, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of investigational product dependency or abuse.

- Congenital anomaly or birth defect.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study product, the event must be reported to SKK or its designee as described in Section 12.5.5.1. Any malignancy will be considered "an important medical event."

Adverse events reported from clinical studies associated with hospitalization or prolongation of hospitalization are considered serious. Any hospitalization except observational admissions of less than 24 hours for logistical reasons meets these criteria. This category also includes transfer within the hospital to an acute/intensive care unit (e.g., from a standard-of-care unit to an acute/intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities, or respite care (e.g., caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same-day surgeries (as outpatient/same day/ambulatory procedures)
- <24-hour admissions for observation or evaluation for logistical reasons

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
    - Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual subject
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual subject

12.5.1.3. Adverse Drug Reaction and Suspected Adverse Reaction

An adverse drug reaction means any AE caused by a drug.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than an adverse drug reaction (21 CFR 312.32(a)).

12.5.1.4. Unexpected Adverse Reaction

Seikagaku Corporation is responsible for assessing AEs for expectedness. With regards to reporting to the health authority, an AE is considered "unexpected" when its nature (specificity), severity, or rate of occurrence is not consistent with applicable product information as described in the safety information provided in the protocol and investigator's brochure for SI-613. "Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the investigator's brochure as occurring with a class of

drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)).

12.5.2. Severity of Adverse Events/Serious Adverse Events

The study site will grade the severity of AEs experienced by study participants on a 3-point severity scale (mild, moderate, or severe), as follows:

- Mild: causes no limitation of usual activities; causes slight limitation of usual activities without medication intervention or with only a brief medical intervention
- Moderate: causes some limitation of usual activities and requires medical intervention
- Severe: prevents or severely limits usual activities, or requires systemic intervention

Note: The terms serious and severe are not synonymous. Serious criteria as defined in Section 12.5.1.2 above serve as a guide for defining regulatory reporting obligations. The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache); the event itself, however, may be of relatively minor medical significance. This is not the same as serious, which is based on patient/adverse outcome. Therefore, an AE of severe headache might not be considered serious, but a moderate infection for which a subject is hospitalized should be reported as an SAE.

12.5.3. Relationship to Investigational Treatment

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE and must be provided for all AEs (serious and non-serious).

Seikagaku Corporation's determination of attribution will be used for reporting to the appropriate health authorities. The relation of an AE to study participation will be determined using the descriptors and definitions provided in Table 3.

Table 3: Attribution of Adverse Events

Not Related	The AE is clearly/most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention or concomitant therapy, or the delay between administration and the onset of the AE is incompatible with a causal relation, or the AE started before administration (screening phase). Therefore, there is not a reasonable possibility that the AE was caused by the investigational product.
Related	There is a reasonable possibility that the AE was caused by the investigational product. The expression "reasonable possibility" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship (21 CFR 312.32(a)).

The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. Any AE that is suspected to be related to the investigational product will be classified as an adverse drug reaction.

12.5.4. Collecting and Recording Adverse Events

12.5.4.1. Period of Collection

All AEs, regardless of severity and/or the time of occurrence during the study, are to be recorded on the appropriate AE pages (either "serious" or "non-serious") in the eCRF. Recording of AEs will begin immediately upon a subject's signing the informed consent form and continue through the final study visit. Recording of any adverse drug reaction will continue until the event resolves or stabilizes. The investigator should complete all the details requested, including dates of onset, severity, action taken, outcome, and relationship to investigational product. Each event should be recorded separately.

All AEs and SAEs should be treated as medically appropriate. Adverse events should be followed until stabilization or the final study visit; adverse drug reactions should be followed until resolution or stabilization; and SAEs (regardless of suspected relationship to the investigational product) should be followed until the event resolves, stabilizes, or becomes non-serious.

12.5.4.2. Methods of Collection

Adverse events may be collected as follows:

- Observing the participant
- Questioning the participant in an unbiased and non-leading manner
- Receiving an unsolicited complaint from the participant

An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE if it is determined by the investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

12.5.4.3. Recording Method

12.5.4.3.1. Adverse Events

All AEs occurring during this clinical study will be recorded by the investigator on the appropriate eCRF in precise medical terms, along with the date of onset and the date of resolution. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the investigator should combine signs and symptoms into a single term that constitutes a single diagnosis. Each AE is to be evaluated for duration, severity, seriousness, and relatedness to the investigational product. The severity of the AE and its relationship to the investigational product will be assessed by the investigator.

The investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes. If any medication is administered in response to the AE, this medication should be noted on the concomitant medication eCRF as a concomitant medication administered. The action taken and the outcome must also be recorded. The terms of AE resolution (i.e., recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, fatal, unknown) should also be recorded.

12.5.4.3.2. Serious Adverse Events

Serious adverse events will be recorded on the AE and SAE eCRFs, and health authorities will be notified as outlined in Section 12.5.5.2.

12.5.5. Reporting Adverse Events

12.5.5.1. Reporting Serious Adverse Events to the Sponsor

The following process for reporting an SAE ensures compliance with 21 CFR 312 and ICH guidelines. After learning that a participant has experienced an SAE, the investigator or designee is responsible for reporting the SAE, regardless of relationship or expectedness, within 24 hours of becoming aware of the event. The initial SAE report should include as much information as possible, but at a minimum must include the following:

- Reporter
- Subject identification number
- Study product or intervention
- Serious adverse event term
- Relationship to investigational product
- Reason why the event is serious

Supplemental eCRF pages should be current at the time of SAE reporting: medical history, concomitant medications, demographics, investigational product administration, and death, as applicable.

Unavailable details of the event should not delay submission of the known information. As additional details become available, the SAE eCRF should be updated and re-submitted.

In the event that the eCRF is unavailable, a paper SAE Report Form should be completed and submitted via email or efax within 24 hours of becoming aware of the event. Once the eCRF becomes available, the SAE information should be entered as soon as possible.

SAE Reporting Contact Information:

email: [redacted]

efax: [redacted]

12.5.5.2. Reporting Serious Adverse Events to Health Authorities

Seikagaku Corporation or its designated representative will provide Investigational New Drug safety reports to the Food and Drug Administration (FDA) and investigators in accordance with the FDA regulations detailed in 21 CFR 312.32.

12.5.5.3. Reporting Serious Adverse Events to Institutional Review Boards

It is the responsibility of the investigators to promptly notify their respective institutional review board (IRB) of Investigational New Drug safety reports or other matters involving risk to subjects as mandated by the IRB.

12.6. Pregnancy

During the study, all female subjects should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, the subject will be withdrawn from the study and followed until the pregnancy comes to term.

The investigator is responsible for reporting all available pregnancy information to SKK or its designee within 24 hours of becoming aware of the event, although pregnancy itself if not considered an AE. Monitoring of the participant should continue until the conclusion of the pregnancy. Follow-up information detailing the outcome of the pregnancy and the health of the newborn should be reported as it becomes available.

Partner pregnancies of a male subject do not need to be reported.

12.7. Potential Device Malfunctions

SI-613 investigational product is categorized as a combination product that contains HA-DF (drug component) in a pre-filled syringe (device component). If any malfunction of the device components occurs, the following procedure is required.

12.7.1. Malfunction

A malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device [21 CFR 803.3]. If any malfunction of the investigational product occurs, the investigational product must not be used. It must be placed back in the original kit and kept until the site receives instructions from SKK or its designee. The investigator or designee will report the details of the malfunction to SKK.

12.7.2. Injuries Caused by Device Malfunctions

After learning that a subject, injecting physician, or the other user has experienced any of the following events caused by a device malfunction, the investigator or designee is responsible for reporting the event(s) to SKK within 24 hours of becoming aware of the event.

- Device malfunction associated with a death or serious injury

  A serious injury means an injury or illness that:
  - Is life-threatening
  - Results in permanent impairment of a body function or permanent damage to a body structure, or
  - Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

- This includes any adverse event resulting from insufficiencies or inadequacies in the labeling and the directions specified in the Investigational Product & Rescue Medication Manual, or any malfunction of the device component and any malfunction that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. This includes any event that is a result of a user error or intentional misuse of the medical device.

The investigator or designee will report all the injuries caused by a device malfunction on the appropriate AE pages (either “serious” or “non-serious”) in the eCRF.

Seikagaku Corporation or its designated representative will provide a summary of any reportable device malfunctions associated with a death or serious injury as an Investigational New Drug safety report to the FDA and investigators in accordance with the FDA regulations detailed in 21 CFR 312.32. Any malfunctions leading to death or malfunctions resulting in serious injuries that are considered life-threatening will be submitted to the FDA within 7 calendar days of receipt of the information from the investigator or designee. All other malfunctions leading to a serious injury will be submitted to the FDA within 15 calendar days of receipt of the information from the investigator or designee. Malfunctions not leading to a SAE will be included in the annual report.

13. STATISTICS

13.1. Power and Sample Size Determination

Approximately 80 subjects with symptomatic primary OA of the knee will be randomized. Forty subjects per group (80 total subjects) were calculated to provide an 80% probability that a 3 mm (or greater) treatment difference point effect for the primary endpoint will be observed, but not necessarily at a statistically significant level. This assumes that the true treatment difference is 7.5 mm and standard deviation is 23 mm based on the previous Japanese 613/1022 study.

13.2. Randomization

Immediately prior to injection at Week 0, subjects who meet all eligibility criteria will be randomized to a treatment group using a 1:1 ratio of SI-613:placebo.

Subjects will be randomized using a dynamic procedure by a minimization protocol,[10] balancing treatment assignment on K-L score, baseline WOMAC VAS pain score, sex, and investigational site.

13.3. Analysis Populations

The analysis populations are defined as follows:

- The safety population is defined as all randomized subjects who received the study injection, analyzed according to the treatments subjects received.
- The intention-to-treat (ITT) population is defined as all randomized subjects who received the study injection, analyzed according to the assigned treatment.
- The per-protocol (PP) population is defined as all ITT subjects who had no major protocol deviations that would affect the primary efficacy assessment. The details of major protocol deviations will be defined in the statistical analysis plan.

The efficacy analyses will be performed on the ITT population. Efficacy analyses of the PP population will be supportive of the ITT analysis.

The safety analyses will be performed on the safety population.

13.4. Efficacy and Safety Analyses

13.4.1. Background and Demographic Characteristics

Baseline demographic and background variables will be summarized by treatment group and overall. For categorical variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics including sample size, mean, median, standard deviation, minimum, and maximum will be presented. A pretreatment score is the average of the scores at the Screening and Randomization visits.

13.4.2. Subjects Accountability

All enrolled subjects will be included in a summary of subject accountability for this study. The frequencies and percentages of enrolled subjects, subjects who received each study injection, subjects

who presented at each visit, subjects who discontinued before study completion (including reason for discontinuation), and subjects who completed the study will be presented.

13.4.3. Efficacy Analyses

13.4.3.1. Primary Efficacy Analysis

The primary efficacy analysis will be performed on the WOMAC VAS pain subscore using longitudinal analysis to incorporate information from pain scores assessed at Weeks 1, 2, 4, 6, 8, 10, and 12. A direct likelihood approach as implemented in the SAS MIXED procedure will be used to estimate model parameters designed to reflect group-specific mean values over time. The primary efficacy hypothesis concerns the over a 12-week evaluation period from Week 1 to Week 12, and the group comparison is defined as the average effect over assessments during these weeks. Supporting analyses involve comparisons reflecting group differences at the various study visits, including landmark analysis at Week 12 and early onset of efficacy at Week 1. In all cases, model parameters will be used to determine comparisons for which statistical significance against null zero hypotheses and corresponding 95% confidence intervals will be provided. The basic longitudinal model will be specified as a repeated-measures model that expresses the pain score as a linear function of treatment, time, treatment-by-time interaction, and clinically relevant covariates (pretreatment pain measurement, K-L score, and sex) and a fixed-site effect.

The model is designed to account for correlations among responses over time and to use these correlations to implicitly impute missing values from the non-missing values. The type=UN option in the SAS MIXED procedure will be used to model correlation patterns across time.

13.4.3.2. Secondary Efficacy Analyses

A longitudinal analysis model will be used as described in the primary efficacy analysis for the analysis of WOMAC VAS physical function subscore, WOMAC VAS stiffness subscore, WOMAC VAS total score, PGIC, CGIC, SF-36 scores, weekly average of daily pain scores, and PASE scores.

Continuous responder analysis with WOMAC VAS pain subscore will be performed, and differences between the SI-613 and placebo groups in the percentages of subjects experiencing a >30% or >50% improvement in WOMAC VAS pain subscore will be analyzed with Fisher's exact test. For the analysis of the percentages of OMERACT-OARSI responders,[11,12] differences between the SI-613 and placebo groups in the percentages of positive responders over 12 weeks will be analyzed with generalized estimating equations (GEE) model. For each post-treatment study visit, subjects will be defined as responders or nonresponders based on the OMERACT-OARSI set of criteria. These repeated binary outcomes (responders/nonresponders) will be modeled with GEE, with the relevant pretreatment covariate of pain (average WOMAC VAS pain score from Visits 1 and 2), clinically relevant covariates (K-L score and sex), and a fixed-site effect. A Wald test based on the estimated regression parameter for treatment group assignment will be used for hypothesis testing for this secondary efficacy objective. For the analysis of the percentages of positive responders, subjects who discontinue from the study prior to Week 12 because of either target knee-related AEs or lack of efficacy will be classified as not improved subjects or nonresponders in the efficacy analysis.

For the analysis of the amount of acetaminophen rescue medication consumed for the target knee, the percentages of subjects using rescue medication will be presented. The analysis of the overall use of acetaminophen rescue medication over 12 weeks will be conducted in the analysis of covariance

(ANCOVA) model of the change from baseline of acetaminophen usage. The baseline acetaminophen usage, K-L score and sex will be included as covariates in the ANCOVA model.

Efficacy analyses will be repeated by using entire period from Week 1 to Week 26.

13.4.3.3. OMERACT-OARSI Responder

A subject will be considered an OMERACT-OARSI responder if he or she meets criteria for improvement in WOMAC VAS pain subscore, WOMAC VAS physical function subscore and PGIC.

13.4.4. Safety Analyses

Treatment-emergent AEs (any AEs recorded during or following the study injection) will be summarized by treatment group and categorized by severity, time of occurrence, and relationship to the study procedures and to the investigational product. If a subject has more than 1 occurrence of the same AE, he/she will be counted only once within that preferred term in the summary tables. The most severe occurrence of an AE, as well as the most extreme relationship of the AE to the study procedures and investigational product, will be indicated in cases of multiple occurrences of the same AE. Serious adverse events and target knee AEs also will be summarized separately. All AEs will be presented in a listing. Additionally, listings of SAEs and AEs leading to discontinuation will be generated.

Target knee examination and synovial assessments will be summarized by treatment group. In addition, these relationships will be analyzed.

13.4.5. Concomitant Medications and Concomitant Therapies

Concomitant medications will be categorized using a standardized coding dictionary and listed. Concomitant therapies will be listed only.

13.5. Other Statistical Considerations

13.5.1. Significance Levels

The type I error rate will be set at the 5% significance level for the primary efficacy analysis.

All secondary and exploratory efficacy analyses will be performed at the 2-sided 5% significance level.

13.5.2. Missing Data

For the efficacy analysis based on repeated-measures models of continuous endpoints, missing data will be implicitly handled via a mixed-effect model, without explicit imputation. Inferences based on this approach are unbiased under the assumption of missing at random, which is a weaker and more generally true assumption than missing completely at random. Sensitivity analysis based on multiple imputation methods which changes imputation methods by missing pattern such as discontinuations due to AEs, lack of efficacy, and other will be performed for the ITT population.

For the efficacy analysis based on percentages of positive responders, subjects who discontinue the study because of target knee AEs or lack of efficacy and subsequently have missing efficacy data will be classified as nonresponders.

No replacement of any missing data will be made for the safety analyses.

13.5.3. Visit Windows

All data collected during study follow-up will be displayed and analyzed according to the actual visit data in the eCRF. Assessments taken outside of windows described in the protocol will be displayed according to the eCRF assessment recorded by the investigator.

13.5.4. Multiplicity

Multiplicity will not be considered for the efficacy analyses.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

According to ICH GCP guidelines, the sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. Seikagaku Corporation or its designee is responsible for assigning the study monitor(s) to this study. The study monitor's duties are to aid the investigator and SKK or its designee in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an investigational product as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs throughout the study to protect the rights of the subjects; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the study monitoring plan.

14.2. Source Documents

Seikagaku Corporation or its designee requires that the investigator prepare and maintain adequate and accurate records for each subject treated with the investigational product. Source documents such as any hospital, clinic, or office charts and the signed informed consent forms are to be included in the investigator's files with the subject's study records.

Data will be captured electronically. Study site personnel will enter eCRF data from source documents. Subjects will record selected study assessments directly into the eCRF. If any data are first recorded onto documents such as laboratory reports, these documents will be considered source.

14.3. Data Collection and Management

This study will be conducted in compliance with the ICH document "Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance," dated April 1996. This study will also be conducted in accordance with the Declaration of Helsinki as currently accepted by the FDA (1998).

This study will use electronic data collection (techniques to collect data directly from the investigational site using eCRFs). The data will be stored centrally in a fully validated clinical database. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform 100% source document verification to ensure there are no inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP.

Data from external sources (such as laboratory data and MRI assessments) will be processed outside the clinical database according to the study Data Management Plan.

At intervals throughout the study and upon completion, data will be exported from the database into SAS datasets.

Data management will be coordinated by the data managers in accordance with their SOPs for data management and a formal study data management plan. The data managers will provide a quality control statement following database lock.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using World Health Organization – Drug Reference List.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A quality assurance representative from SKK (or a qualified delegate), who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

16. ETHICS

16.1. Ethics Review

The investigator will not start this study, nor will investigational products be shipped to the investigator's site, before the investigator provides SKK or its designee with evidence of IRB approval. The investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects. The investigator will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the subjects. The investigator will provide progress reports to the IRB as required by the IRB. The investigator will provide a final report to the IRB after completion of participation in the study.

16.2. Ethical Conduct of the Study

The investigator should conduct the study in accordance with this protocol, the Declaration of Helsinki, and ICH GCP guidelines. The investigator and SKK will sign the protocol and study contract to confirm agreement. The investigator will not implement any amendment (deviation or changes of the protocol) without agreement by SKK and the IRB approval/information, except when necessary to eliminate immediate hazards to study subjects or when changes involve only logistical or administrative aspects of the study.

16.3. Written Informed Consent

16.3.1. Subject Information and Informed Consent

The informed consent document will be approved by the IRB that is appropriate for each study site. The investigator is responsible for ensuring that the subject fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible. No subject should be obliged to participate in the study. Subjects, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the subject's subsequent care. Subjects must be allowed sufficient time to decide whether they wish to participate.

The subject must be made aware of and give consent to direct access to his/her source medical records by study monitors, auditors, the IRB, and regulatory authorities. The subject should be informed that such access will not violate subject confidentiality or any applicable regulations. The subject should also be informed that he/she is authorizing such access by signing the informed consent form.

Each subject will be given a signed copy of the informed consent form to keep for his/her records.

16.3.2. Provision of New and Important Information Influencing Subject's Consent and Revision of the Written Information

When any new and important information that may be relevant to the subject's consent is obtained, the investigator and SKK or its designee will consult with each other on how to deal with the information. When SKK or its designee and a responsible investigator judge it necessary, the investigator must immediately provide the subjects with such information, revise the written information and other

explanatory documents based on the new information, and obtain approval from the IRB. In this instance, the investigator should also immediately inform subjects currently participating in the clinical study of such information, confirm their intention to continue participation, re-explain the study to them using the revised written information and other explanatory documents, and obtain written consent to continue participation based on their voluntary decision.

16.4. Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being. Each subject will be asked to complete a form allowing the investigator to notify the subject's primary health care provider of his/her participation in this study.

16.5. Publications of the Clinical Study

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 Code of Federal Regulations § 50.25(c). The results of and data from this study belong to SKK.

16.6. Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the investigator or SKK after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator and SKK. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and SKK. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB will be promptly notified.

No deviation from the protocol or investigational plan will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of SKK, and the FDA or IRB if applicable, is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to SKK or its designee and to the IRB, if applicable, according to regulations. Major protocol deviations are defined as those deviations that are likely to have an impact on the subject's rights, safety, and/or well-being, and/or on the validity of the data for primary analysis. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

17. DATA HANDLING AND RECORD KEEPING

17.1. Inspection of Records

Seikagaku Corporation and its designee(s), the IRB, or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow SKK and its designee(s), the IRB, or regulatory authorities to inspect the investigational product storage area, investigational product stocks, investigational product records, subject charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The principal investigator must retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

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19. APPENDICES

19.1. Patient Global Impression of Change (PGIC)

Patient Global Impression of Change (PGIC)

Since the start of the study, my overall status is:

1 ☐ Very Much Improved
2 ☐ Much Improved
3 ☐ Minimally Improved
4 ☐ No Change
5 ☐ Minimally Worse
6 ☐ Much Worse
7 ☐ Very Much Worse

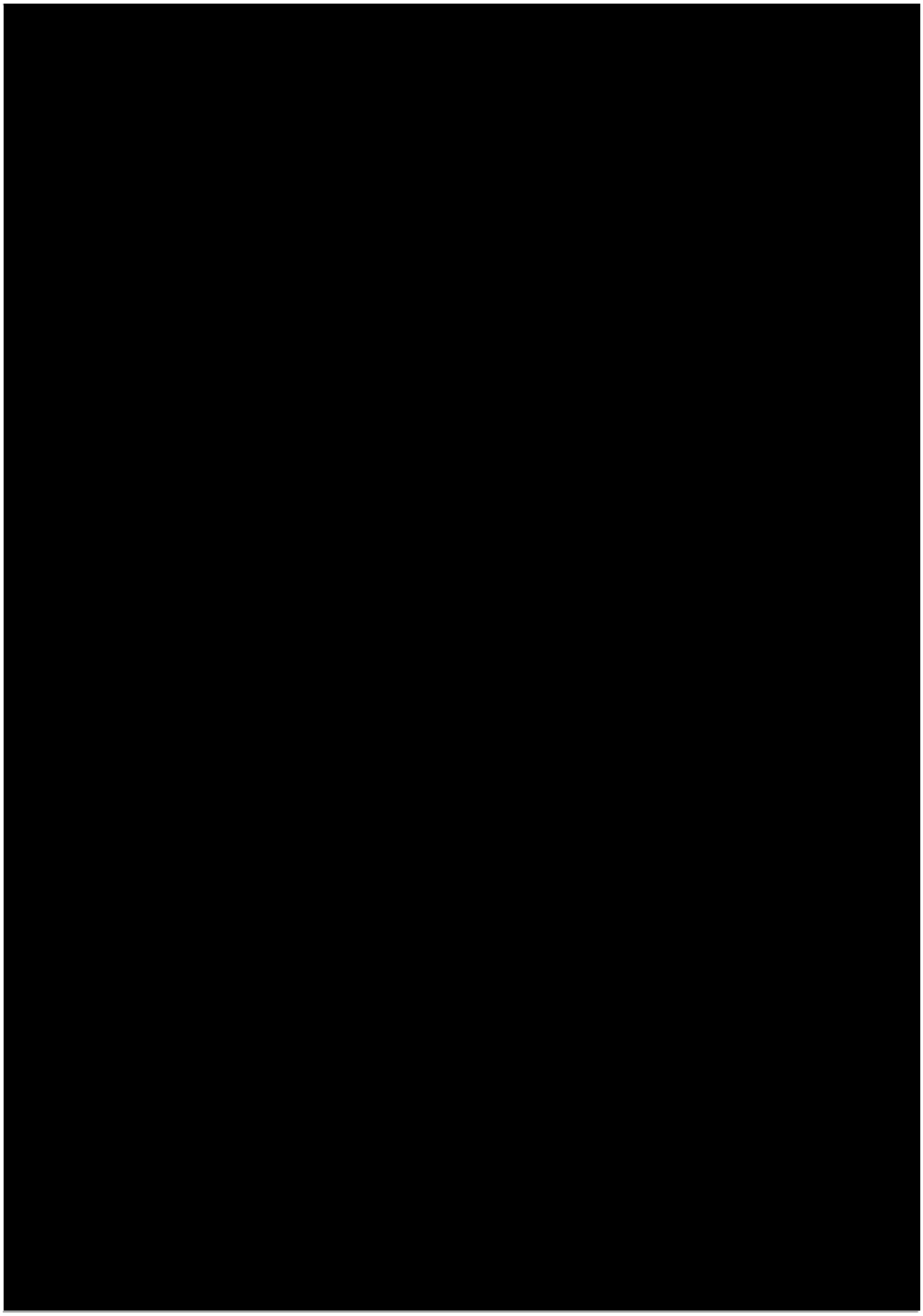
19.2. Clinical Global Impression of Change (CGIC)

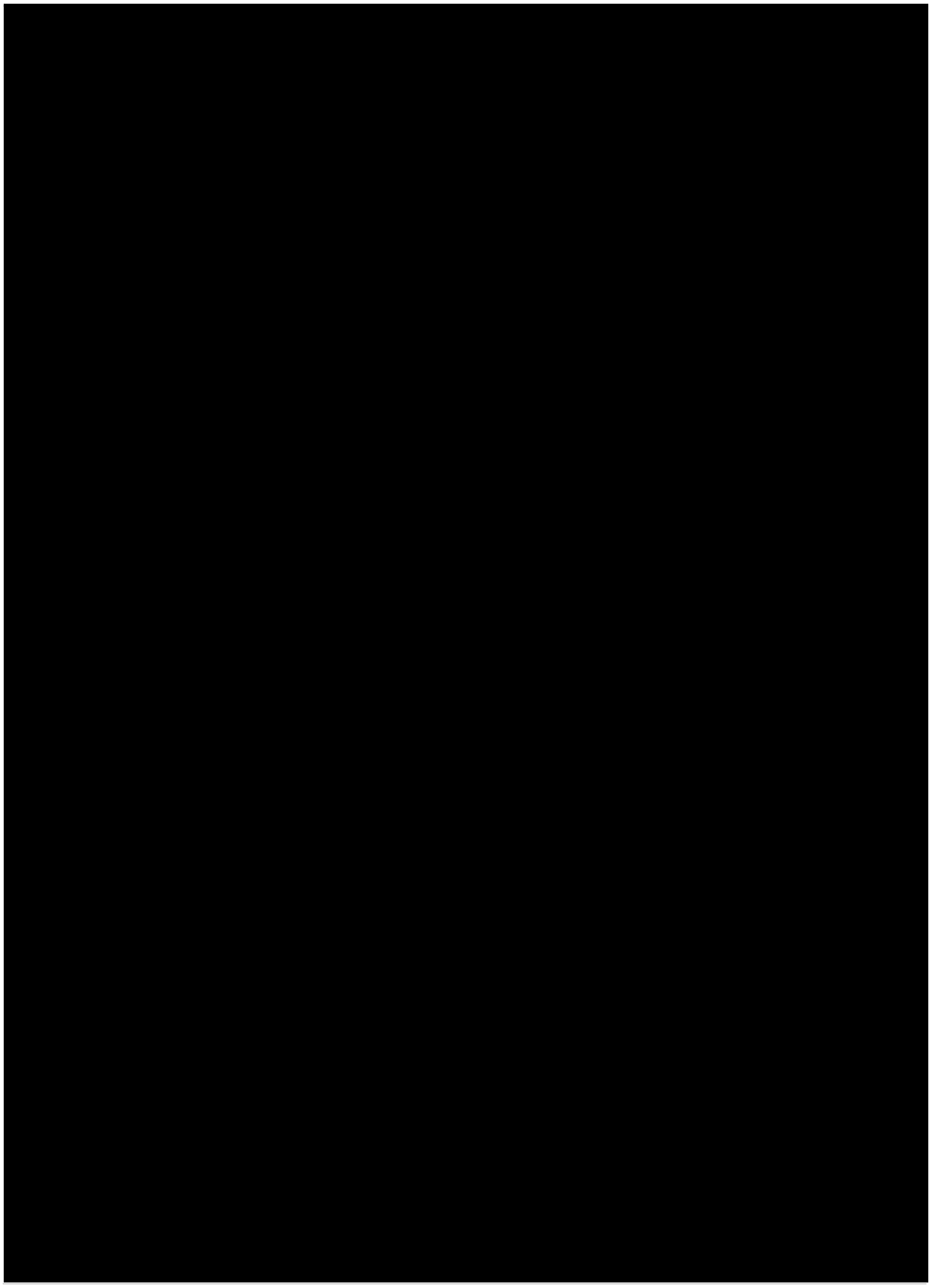
Clinical Global Impression of Change (CGIC)

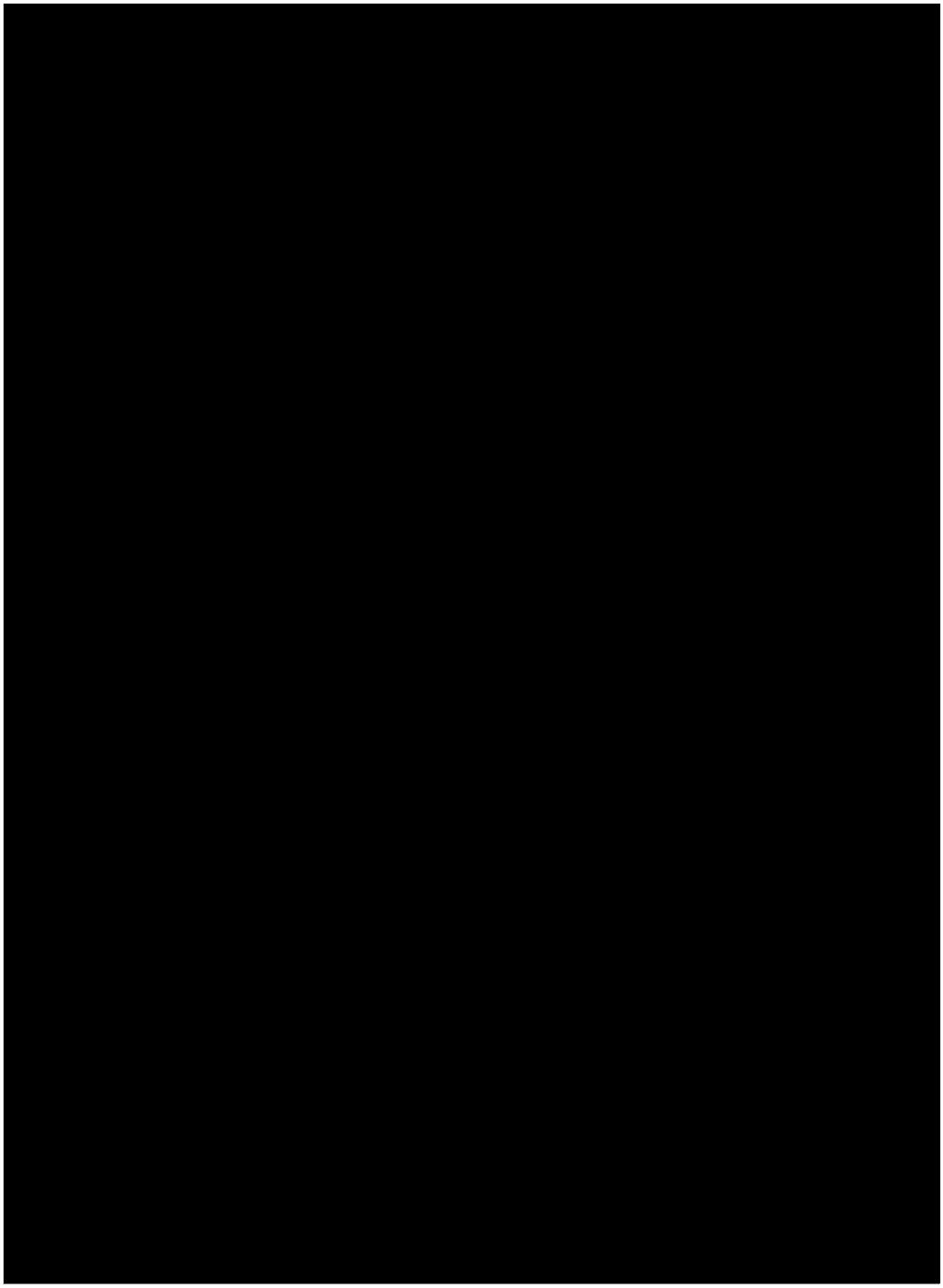
Since the start of the study, subject's overall status is:

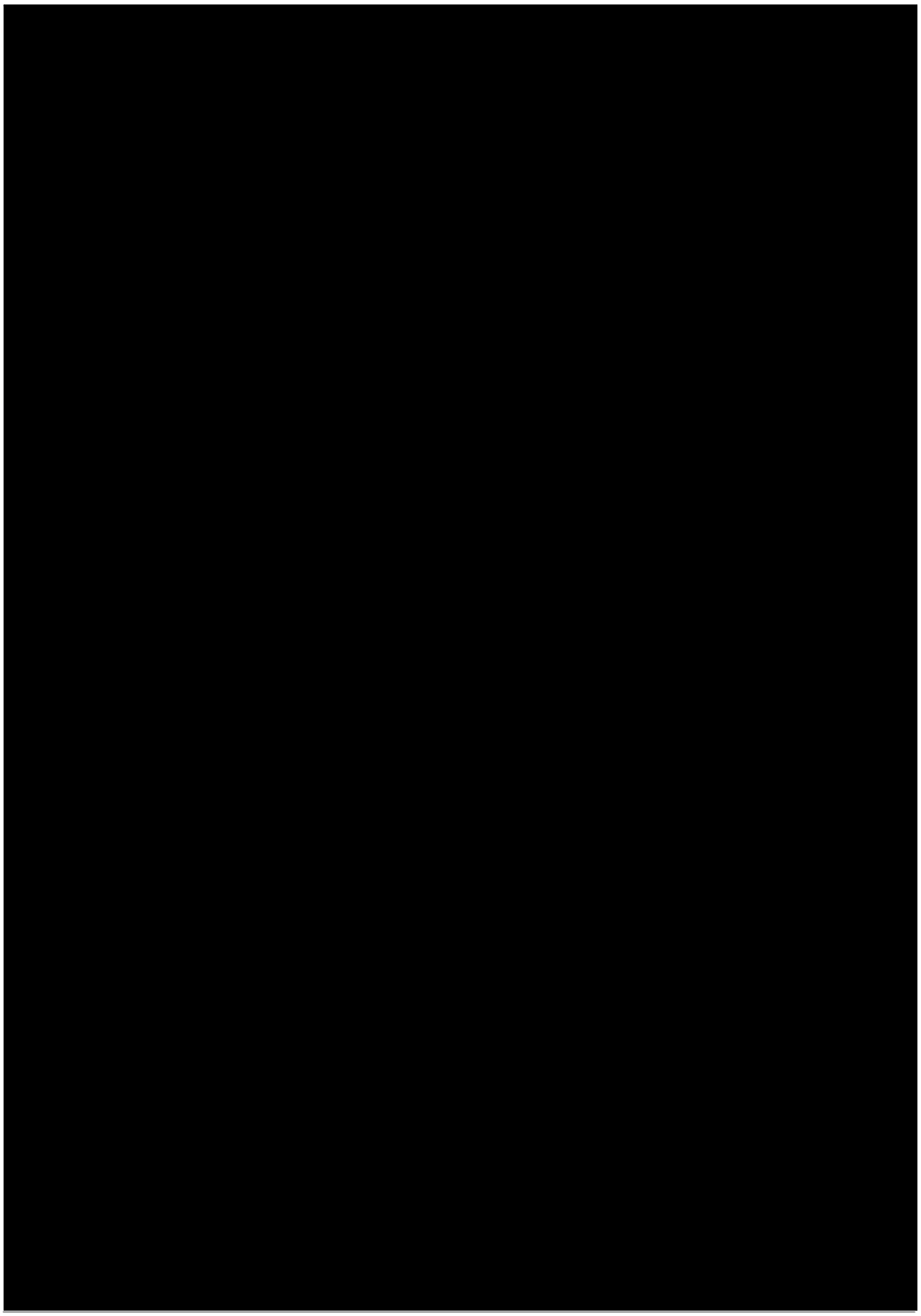
1 ☐ Very Much Improved
2 ☐ Much Improved
3 ☐ Minimally Improved
4 ☐ No Change
5 ☐ Minimally Worse
6 ☐ Much Worse
7 ☐ Very Much Worse

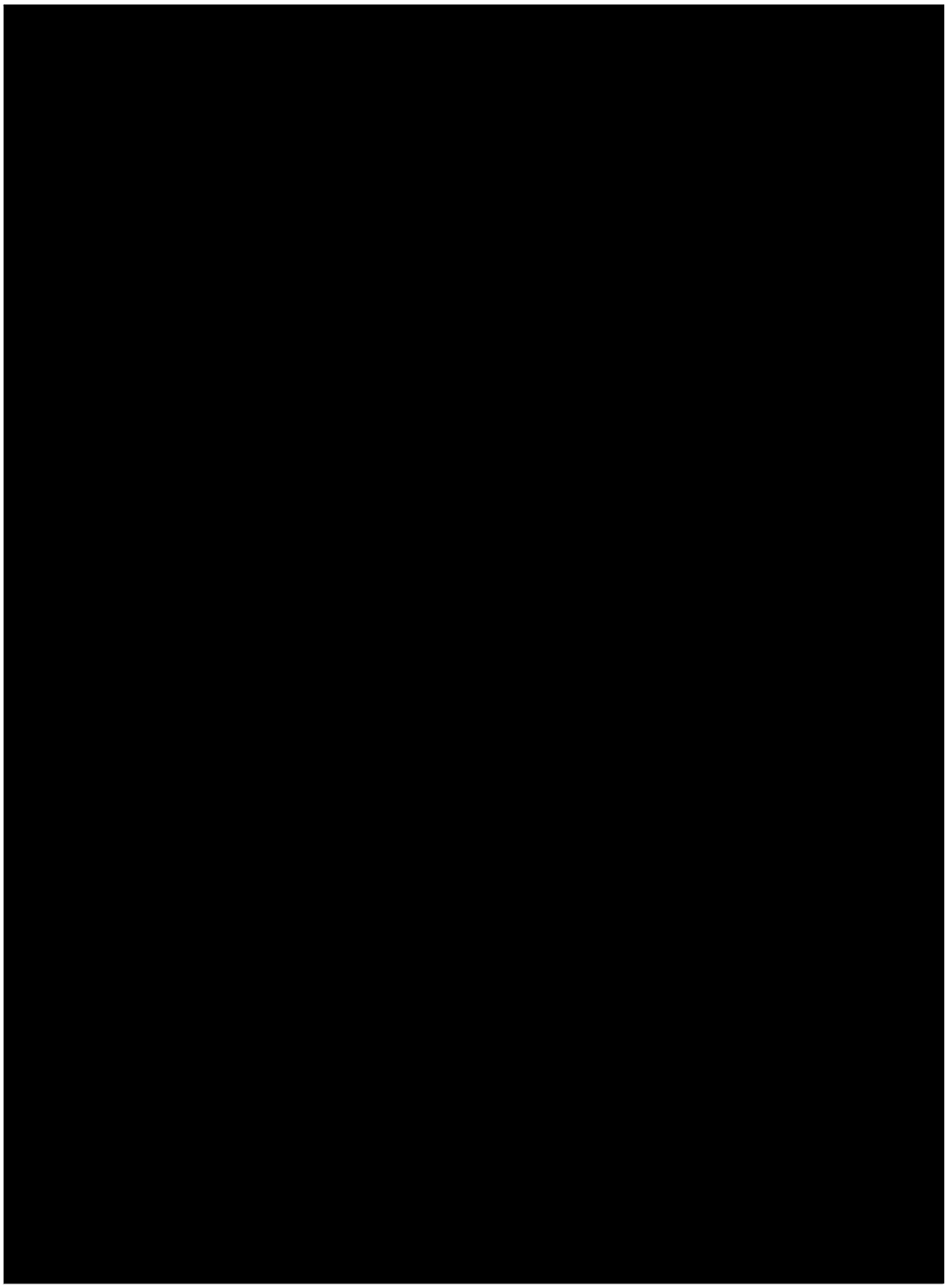
19.3. 36-Item Short Form Health Survey (SF-36)

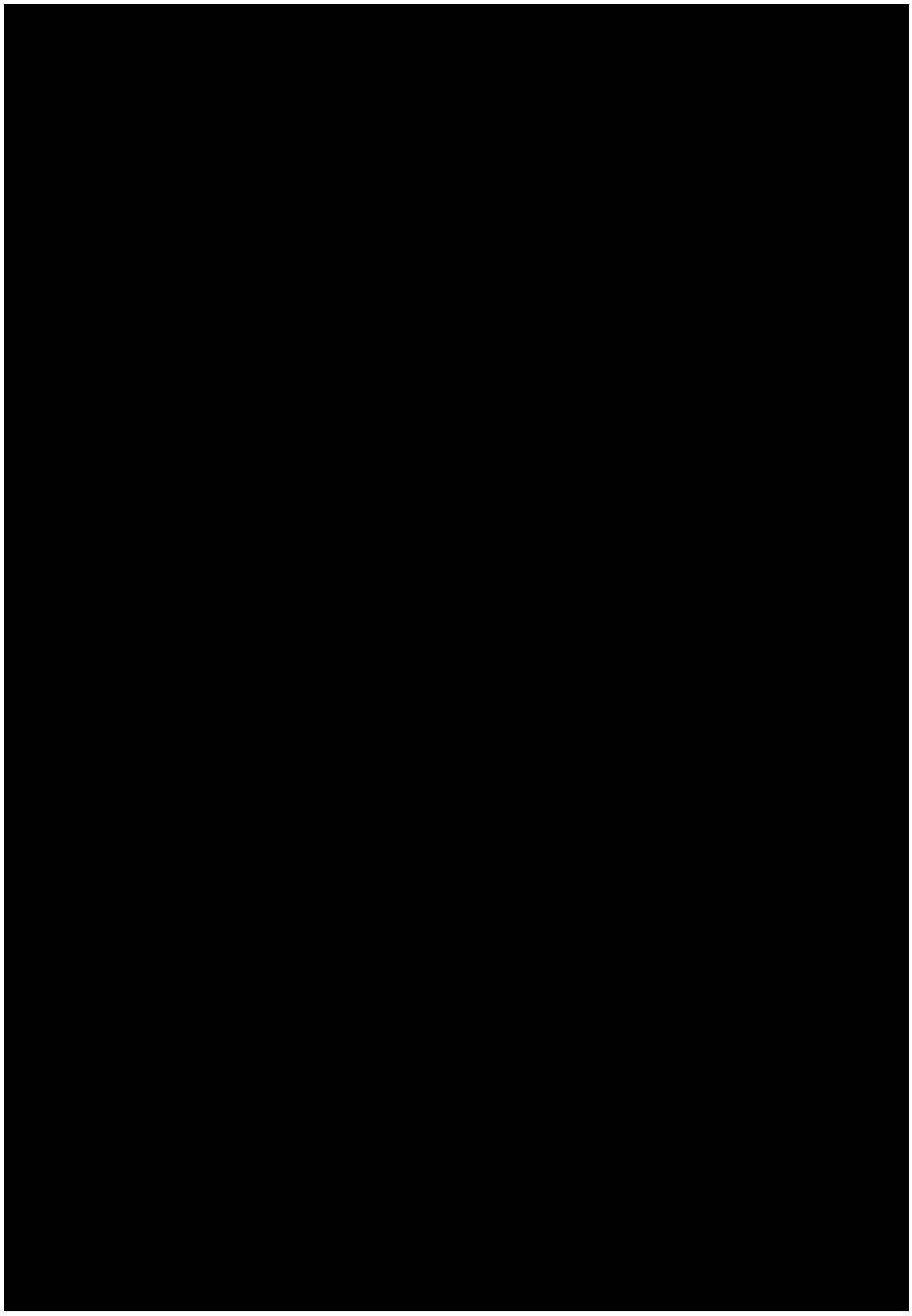












19.4. Physical Activity Scale for the Elderly (PASE)

INSTRUCTIONS:

Please complete this questionnaire by either circling the correct response or filling in the blank. Here is an example:

During the past 7 days, how often have you seen the sun?

[0.] NEVER	[1.] SELDOM (1-2 DAYS)	[2.] SOMETIMES (3-4 DAYS)	[3.] OFTEN (5-7 DAYS)

Answer all items as accurately as possible. All information is strictly confidential.

LEISURE TIME ACTIVITY

1. Over the past 7 days, how often did you participate in sitting activities such as reading, watching TV or doing handcrafts?

[0.] NEVER → GO TO Q.#2

[1.] SELDOM (1-2 DAYS) →

[2.] SOMETIMES (3-4 DAYS) →

[3.] OFTEN (5-7 DAYS) →

1a. What were these activities?

_____

1b. On average, how many hours per day did you engage in these sitting activities?

[1.] LESS THAN 1 HOUR [2.] 1 BUT LESS THAN 2 HOURS

[3.] 2-4 HOURS [4.] MORE THAN 4 HOURS

2. Over the past 7 days, how often did you take a walk outside your home or yard for any reason? For example, for fun or exercise, walking to work, walking the dog, etc.?

[0.] NEVER → GO TO Q.#3

[1.] SELDOM (1-2 DAYS) →

[2.] SOMETIMES (3-4 DAYS) →

[3.] OFTEN (5-7 DAYS) →

2a. On average, how many hours per day did you spend walking?

[1.] LESS THAN 1 HOUR [2.] 1 BUT LESS THAN 2 HOURS

[3.] 2-4 HOURS [4.] MORE THAN 4 HOURS

3. Over the past 7 days, how often did you engage in light sport or recreational activities such as bowling, golf with a cart, shuffleboard, fishing from a boat or pier or other similar activities?

[0.] NEVER	[1.] SELDOM (1-2 DAYS)	[2.] SOMETIMES (3-4 DAYS)	[3.] OFTEN (5-7 DAYS)
↓	↓	↓	↓
GO TO Q.#4			

3a. What were these activities?

_____

3b. On average, how many hours per day did you engage in these light sport or recreational activities?

[1.] LESS THAN 1 HOUR [2.] 1 BUT LESS THAN 2 HOURS

[3.] 2-4 HOURS [4.] MORE THAN 4 HOURS

4. Over the past 7 days, how often did you engage in moderate sport and recreational activities such as doubles tennis, ballroom dancing, hunting, ice skating, golf without a cart, softball or other similar activities?

[0.] NEVER	[1.] SELDOM (1-2 DAYS)	[2.] SOMETIMES (3-4 DAYS)	[3.] OFTEN (5-7 DAYS)
↓	↓	↓	↓
GO TO Q.#5			

4a. What were these activities?

_____

4b. On average, how many hours per day did you engage in these moderate sport and recreational activities?

[1.] LESS THAN 1 HOUR [2.] 1 BUT LESS THAN 2 HOURS

[3.] 2-4 HOURS [4.] MORE THAN 4 HOURS

5. Over the past 7 days, how often did you engage in strenuous sport and recreational activities such as jogging, swimming, cycling, singles tennis, aerobic dance, skiing (downhill or cross-country) or other similar activities?

[0.] NEVER → GO TO Q.#6

[1.] SELDOM (1-2 DAYS) →

[2.] SOMETIMES (3-4 DAYS) →

[3.] OFTEN (5-7 DAYS) →

5a. What were these activities?

_____

5b. On average, how many hours per day did you engage in these strenuous sport and recreational activities?

[1.] LESS THAN 1 HOUR [2.] 1 BUT LESS THAN 2 HOURS

[3.] 2-4 HOURS [4.] MORE THAN 4 HOURS

6. Over the past 7 days, how often did you do any exercises specifically to increase muscle strength and endurance, such as lifting weights or pushups, etc.?

[0.] NEVER → GO TO Q.#7

[1.] SELDOM (1-2 DAYS) →

[2.] SOMETIMES (3-4 DAYS) →

[3.] OFTEN (5-7 DAYS) →

6a. What were these activities?

_____

6b. On average, how many hours per day did you engage in exercises to increase muscle strength and endurance?

[1.] LESS THAN 1 HOUR [2.] 1 BUT LESS THAN 2 HOURS

[3.] 2-4 HOURS [4.] MORE THAN 4 HOURS

HOUSEHOLD ACTIVITY

7. During the past 7 days, have you done any light housework, such as dusting or washing dishes?

[1.] NO [2.] YES

8. During the past 7 days, have you done any heavy housework or chores, such as vacuuming, scrubbing floors, washing windows, or carrying wood?

[1.] NO [2.] YES

9. During the past 7 days, did you engage in any of the following activities?

Please answer YES or NO for each item.

		NO	YES
a.	Home repairs like painting, wallpapering, electrical work, etc.	1	2
b.	Lawn work or yard care, including snow or leaf removal, wood chopping, etc.	1	2
c.	Outdoor gardening	1	2
d.	Caring for an other person, such as children, dependent spouse, or an other adult	1	2

WORK-RELATED ACTIVITY

10. During the past 7 days, did you work for pay or as a volunteer?

[1.] NO [2.] YES

10a. How many hours per week did you work for pay and/or as a volunteer?

_____ HOURS

10b. Which of the following categories best describes the amount of physical activity required on your job and/or volunteer work?

[1] Mainly sitting with slight arm movements.
[Examples: office worker, watchmaker, seated assembly line worker, bus driver, etc.]

[2] Sitting or standing with some walking.
[Examples: cashier, general office worker, light tool and machinery worker.]

[3] Walking, with some handling of materials generally weighing less than 50 pounds.
[Examples: mailman, waiter/waitress, construction worker, heavy tool and machinery worker.]

[4] Walking and heavy manual work often requiring handling of materials weighing over 50 pounds.
[Examples: lumberjack, stone mason, farm or general laborer.]

THANK YOU FOR TAKING THE TIME AND EFFORT

TO COMPLETE THIS QUESTIONNAIRE!

19.5. Daily Pain Diary

Daily Diary

Please record your responses to the following items each day before you go to bed.

Date (DD/MM/YYYY) _ _/_ _/_ _ _ _

Target Knee Pain

Please record how bad you feel your osteoarthritis pain in the target knee was at its worst and on average in the last 24 hours.

Please rate your pain by circling the one number that best describes your pain at its *worst* in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Please rate your pain by circling the one number that best describes your pain on *average* in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

19.6. VAS Pain Scales for 50-foot Walk Test

Evaluation after 50-foot Walk Test
Pain in Target Knee

You have just completed a 50-foot walk. On the scale below, please record the severity of your pain in the target knee by placing a mark along the line indicating the point that best describes the pain in your knee.

No pain **Extreme pain**

Evaluation after 50-foot Walk Test
Pain in Contralateral Knee

You have just completed a 50-foot walk. On the scale below, please record the severity of you pain in the contralateral knee by placing a mark along the line indicating the point that best describes the pain in your knee.

No pain **Extreme pain**