Delivering Hope for Life

PROTOCOL AMENDMENT

NCT number: NCT04123561

PRODUCT NAME/NUMBER:	TLC599 (Lipid-based Dexamethasone Sodium Phosphate Sustained Release Formulation)
PROTOCOL NUMBER:	TLC599A3005
IND NUMBER:	[redacted]
DEVELOPMENT PHASE:	Phase 3
PROTOCOL TITLE:	A Phase 3, Randomized, Double-blind, Placebo- and Active-controlled Study to Evaluate the Efficacy and Safety of TLC599 in Patients with Osteoarthritis of the Knee
PROTOCOL DATE:	[redacted]
AMENDMENT 4 DATE	Final Version 5.0, 09-Mar-2022
SPONSORED BY:	Taiwan Liposome Company, Ltd. 11F-1, 3 Yuanqu Street, Nangang District, Taipei 11503 Taiwan +886-2-2655-7377
CONTRACT RESEARCH ORGANIZATION:	[redacted]

APPROVAL SIGNATURES

PROTOCOL NUMBER:	TLC599A3005
PROTOCOL TITLE:	A Phase 3, Randomized, Double-blind, Placebo- and Active-controlled Study to Evaluate the Efficacy and Safety of TLC599 in Patients with Osteoarthritis of the Knee
PROTOCOL VERSION:	Amendment 4, Version 5.0 (09-Mar-2022)

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

SIGNATURE **DATE:**

[redacted]

[redacted]

Taiwan Liposome Company, Ltd.

[redacted]

[redacted]

Taiwan Liposome Company, Ltd.

[redacted]

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1. PROTOCOL SUMMARY

PRODUCT NAME/NUMBER: TLC599 (Lipid-based Dexamethasone Sodium Phosphate Sustained Release Formulation)

PROTOCOL NUMBER: TLC599A3005

DEVELOPMENT PHASE: Phase 3

PROTOCOL TITLE: A Phase 3, Randomized, Double-blind, Placebo- and Active-controlled Study to Evaluate the Efficacy and Safety of TLC599 in Patients with Osteoarthritis of the Knee

INDICATION: Osteoarthritis of the knee

PLANNED STUDY SITES: Approximately 45 to 50 study sites in the United States and Australia

OBJECTIVES

Primary Objective:

- To evaluate the efficacy of a single intra-articular (IA) dose of TLC599 in patients with osteoarthritis (OA) of the knee

Secondary Objectives:

- To evaluate the efficacy of repeat doses of TLC599 in patients with OA of the knee
- To evaluate the safety of single and repeat IA doses of TLC599 in patients with OA of the knee

RATIONALE

Osteoarthritis is a common degenerative joint disorder of the articular cartilage associated with hypertrophic bone changes. Treatment for OA primarily involves a non-pharmacological combination of exercise and lifestyle modification, pharmacological treatment, supplementation with glucosamine or chondroitin sulphate, and surgical joint replacement. Among pharmacological treatments, corticosteroids have both anti-inflammatory and anti-angiogenic properties, and they are routinely given via inject IA injection for the treatment of chronic knee joint diseases to relieve pain, reduce inflammation, and improve mobility.

IA corticosteroid injection is a commonly used treatment with an excellent safety profile. A limitation of IA injection with corticosteroids is the modest duration of treatment effect, which often lasts for only 2 to 4 weeks. Repeat injections are possible in the same joint, but there are limited data on the safety and duration of the effectiveness of this procedure. Thus, there is a pressing need for a more sustained duration of an IA corticosteroid injection.

Taiwan Liposome Company (TLC) is developing TLC599, a sustained release liposomal formulation of dexamethasone sodium phosphate (DSP) for the treatment of OA. DSP, an injectable form of dexamethasone, is formulated with lipid excipients to allow a sustained release of DSP to maintain therapeutic concentrations of dexamethasone in the joint space for an extended period of time. The formulation of TLC599 is specifically designed to provide both immediate-release DSP and long-acting liposomal form of DSP, providing both short-term and sustained pain and symptom relief for up to 6 months in patients with knee OA pain. To date, TLC has completed 2 studies to evaluate the safety and efficacy of a single-dose IA injection of TLC599 in patients with knee OA. Based on data from both trials, TLC599 with 12 mg DSP demonstrated a rapid onset of OA pain and symptom relief, with sustained therapeutic benefit up to 6 months with a single IA injection.

METHODOLOGY

Study Design:

- This is a Phase 3 randomized, double-blind, placebo- and active comparator-controlled pivotal study.
- Efficacy and safety of 2 doses of TLC599 will be evaluated in comparison with Placebo and DSP through Week 52.
- Approximately 500 adult patients with moderate to severe pain due to OA of the knee will be randomized in a 2:1:1 ratio to receive TLC599 12 mg (Group A), DSP 4 mg (Group B), or Placebo (normal saline) (Group C) via IA injection into the designated index knee at Baseline (Injection 1).
- At Week 24, patients will receive blinded Injection 2 per their randomly assigned dosing regimen (Group A, B, or C) via IA injection into the index knee. Patients who received TLC599 12 mg (Group A) or DSP (Group B) for Injection 1 will receive blinded TLC599 12 mg for Injection 2 and those who received Placebo for Injection 1 (Group C) will receive Placebo for Injection 2.

- All patients will be followed for a total of 52 weeks, regardless of whether or not they receive Injection 2. Patients who do not receive Injection 2 at the Week 24 Visit will be encouraged to continue in the study through the entire 52 weeks of follow-up.
- The study design and visit schedule are illustrated in the following figure:

Abbreviations: BL = Baseline (Day 1); DSP = dexamethasone sodium phosphate; Rand = Randomization; SCR = Screening; W = Week.

Study Procedures:

- Patients will be screened for eligibility at Visit 1 (Screening); procedures will include, but is not limited to, medical history and concomitant medication review, knee pain assessments, knee radiographs, physical examination, and clinical laboratory assessments. Initial eligibility for pain in each knee will be assessed using a patient-reported numeric rating scale (NRS) (rating of average pain over the previous 24 hours).
- Patients will be trained on the use of diaries, accurate pain reporting, and appropriate expectations for a clinical trial.
- During the screening period, patients will complete daily diaries including assessments of pain in each knee by NRS as well as rescue medication use. Every evening, patients must score their average pain in each knee by NRS over the previous 24 hours. The diary must be completed for at least 5 of the last 7 days of the screening period before returning to the study site for Visit 2 (Baseline/Day 1).
- At Visit 2 (Baseline/Day 1), after baseline assessments, eligibility will be confirmed and the index knee will be determined, and eligible patients will be randomized in a 2:1:1 ratio to receive TLC599 12 mg (Group A), DSP 4 mg (Group B), or Placebo (Group C) via IA injection into the index knee (Injection 1).
- Patients will return to the study site at Week 1, Week 2, Week 4, and every 4 weeks through Week 24 to complete efficacy and safety assessments as applicable.
- At Week 24, patients (see Criteria for Injection 2 [Week 24]) will receive blinded Injection 2 via IA injection into the index knee according to their randomly assigned dosing regimen: TLC599 12 mg (Groups A and B) or Placebo (Group C).
- Patients will continue to return to the study site every 4 weeks through Week 52 to complete efficacy and safety assessments as applicable.
- Patients who receive Injection 2 at Week 24 will also return to the study site at 1 week (Week 25) and 2 weeks (Week 26) after Injection 2.
- Patients who do not receive Injection 2 will continue to be followed through Week 52. Patients who do not complete the study through Week 52 will complete early termination procedures.

VISIT STRUCTURE: There will be up to 19 study visits, including Screening (Visit 1), Baseline (Day 1/Visit 2), Week 1 (Visit 3), Week 2 (Visit 4), and 6 visits occurring every 4 weeks from Week 4 (Visit 5) through Week 24 (Visit 10), Week 25 (Visit 11), Week 26 (Visit 12), and every 4 weeks from Week 28 (Visit 13) through Week 52 (Visit 19). Week 25 (Visit 11) and Week 26 (Visit 12) will only be required for patients who receive Injection 2 at Week 24 (Visit 10).

STUDY DURATION: Duration of patient participation will be up to 56 weeks, including a Screening period of up to 4 weeks before randomization, Injection 1 Period of 24 weeks and Injection 2 Period of 28 weeks.

STUDY POPULATION

This study will randomize approximately 500 patients, according to the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Male or female ≥40 years of age, inclusive.
2. Body mass index ≤40 kg/m^2.
3. Has symptoms associated with OA of the index knee for at least 6 months before Screening.
4. Documented diagnosis of OA in the index knee based on American College of Rheumatology Criteria for Classification of Idiopathic OA of the knee (clinical and radiological including standing fixed-flexion posterior-anterior X-ray of the knee).
5. OA with Kellgren-Lawrence Grade 2 to 3 severity in the index knee based on the grade per X-ray assessed by a central radiologist reader at Screening.
6. Initial patient-reported pain with NRS score ≥4 (on a 0-10 scale) in at least 1 knee (index knee) at Screening (rating of average pain over the previous 24 hours).
7. Patient-reported pain with average daily NRS score of 5.0 to 9.0 (inclusive) in the index knee, AND with non-index knee pain score of ≤4.0, based on diaries completed daily for at least 5 of the last 7 days of the screening period before randomization.
8. Patient-reported WOMAC Pain sub-scale (hereafter referred to as WOMAC Pain) score ≥6 (combined score on a 0-20 scale) in the index knee before dosing at Baseline.
9. a. IF FEMALE, must meet all of the following:
   - Not breast feeding;
   - Not planning to become pregnant during the study;
   - If of childbearing potential (defined as non-post-hysterectomy or non-post-menopausal [amenorrheic for at least 2 years]), must have a negative pregnancy test result (human chorionic gonadotropin, beta subunit [β-hCG]) at Screening and Baseline, and must commit to the use of an acceptable and effective form of birth control for the duration of the study and until at least 6 months after the last dose of study drug.

   b. IF MALE, must be surgically sterile (biologically or surgically) or commit to the use of a reliable method of birth control (must agree to use double-barrier contraception in the event of sexual activity), or be practicing abstinence for the duration of the study and until at least 6 months after the last dose of study drug.
10. Is able to read, understand, and sign the informed consent form (ICF), communicate with the investigator, and understand and comply with protocol requirements.

Exclusion Criteria:

1. Use of any of the following medications within the specified period:
   a. IA corticosteroid in any joint within 3 months before Screening, or triamcinolone acetate extended-release injectable suspension (Zilretta®) within 6 months before Screening
   b. IA hyaluronic acid in any knee joint within 6 months before Screening
   c. Systemic corticosteroids within 4 months before Screening or chronic use within 1 year before Screening
   d. NSAIDs (except topical use on regions other than the index knee) within 14 days before the Baseline visit
   e. Platelet-rich plasma or other prolotherapy within 6 months before Screening
   f. Chronic opioid use (use exceeding 4 days per week) within the last 30 days before Screening.
   g. Any chemotherapeutic or systemic immunosuppressant agents for inflammatory diseases within 6 months before Screening
   h. Anti-coagulants, including warfarin, heparin, low molecular weight heparin, or dabigatran within 1 week of Screening and the Baseline visit. Low-dose acetylsalicylic acid or other anti-platelet medications are allowed
   i. Live attenuated vaccine within 3 months before Screening
   j. Any investigational therapy within 4 weeks or within 5 half-lives before Screening, whichever is longer
2. Patient who is not ambulatory.
3. Any surgery or arthroscopy in the index knee within 12 months before Screening.

4. Unstable index knee joint as determined by the investigator based on physical examination (with or without buckling or giving way) because of an acute injury (defined as injury within 6 months of Screening, e.g., anterior cruciate ligament injury or tear).
5. History of infective arthritis in the index knee.
6. Suspected/concurrent infection in either knee at Screening or Baseline before study drug administration.
7. Any skin lesion/breakdown at the anticipated injection site or any condition that impairs penetration of the index knee joint space.
8. Documented gout attack in index knee within 6 months before Screening or presence of tophus in index knee.
9. Patient with any amputation in any lower limb.
10. Documented history and confirmed autoimmune disease including but not limited to, reactive arthritis, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, inflammatory myositis, mixed connective tissue disease, palindromic rheumatism, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Behcet's disease, arthritis associated with inflammatory bowel disease, sarcoidosis, vasculitis, cryoglobulinemia, or amyloidosis.
11. Any condition that could possibly confound the patient's assessment of index knee pain per the investigator's judgment (i.e., ipsilateral hip OA, radicular low back pain, and hip pain referred to the index knee).
12. Substance abuse disorder, or positive urine drug test for illegal drug substances or non-prescribed controlled substances including amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol; or positive alcohol breath test.
13. History of primary or secondary adrenal insufficiency.

16. History of bleeding disorders.
17. History of acquired or congenital immunodeficiency diseases, or positive test results for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) current infection at Screening.
18. Any active infection requiring treatment with antibiotics.
19. History of treated malignancy which is disease free for ≤5 years before Screening, except basal cell carcinoma of skin or carcinoma in situ of the uterine cervix.
20. Stroke or myocardial infarction within 12 months before Screening.
21. Uncontrolled and unstable concurrent medical or psychiatric illness, including but not limited to, poorly controlled diabetes, poorly controlled hypertension, dementia, schizophrenia, or bipolar disorder that will jeopardize the safety of the patient, interfere with the objectives of the protocol, or affect the patient compliance with study requirements, as determined by the investigator.
22. Abnormalities of the following laboratory parameters at Screening:
    a. HbA1c >9.0%
    b. platelet count <80,000/μL
    c. hemoglobin <8.0 g/dL
    d. total white blood cell count <4000/μL
    e. serum bilirubin/alanine aminotransferase/ aspartate aminotransferase >2 times upper limit of normal (ULN) for the laboratory reference ranges
    f. serum creatinine level >1.5X ULN
    g. prothrombin time/International Normalized Ratio > ULN for the laboratory reference range
23. Known allergy or hypersensitivity to the study drugs or their components.
24. Is an immediate family member (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the clinical study site.
25. Employed by sponsor (i.e., is an employee, temporary contract worker, or designee responsible for the conduct of the study).

Criteria for Injection 2 (Week 24):
Patients will not continue with Injection 2 if any of the following criteria are met:

[redacted]

2. Occurrence of adrenal insufficiency through Week 24.
3. If female and of childbearing potential, have a positive urine pregnancy test result at Week 24.
4. Positive urine drug or alcohol test result at Week 24. (Drug use allowed with prescription.)

[redacted]

STUDY DRUGS
Study drug will be administered in a blinded manner via IA injection into the index knee.

- **Study Drug (TLC599):**
  - Dexamethasone sodium phosphate (DSP) 12 mg with 100 mM phospholipid (PL) (1 mL)
- **Reference Drug (DSP):**
  - DSP 4 mg (1 mL)
- **Placebo:**
  - Normal saline (1 mL)

Patients will be randomly assigned to one of the following treatment groups in a 2:1:1 ratio.

Group	Injection 1 (Day 1)	Injection 2 (Week 24)
A	TLC599	TLC599
B	DSP	TLC599
C	Placebo	Placebo

Rescue Medication:

- Total acetaminophen use up to 3 g/day (not allowed within 24 hours before study visits)

ASSESSMENTS

Efficacy Assessments:

- Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC, Version 3.1)
  - WOMAC comprises 24 questions, each on a 0-4 Likert scale (total score on a 0-96 scale) with assessment based on the previous 24 hours
  - Sub-scale scores of Pain (5 items, total sub-scale score on a 0-20 scale), Stiffness (2 items, total sub-scale score on a 0-8 scale), and Physical Function (17 items, total sub-scale score on a 0-68 scale) are added together to determine the WOMAC Composite score
  - Composite and sub-scale scores of WOMAC will be normalized to a scale of 0-4 for analysis.
- Patient Global Impression of Change (PGIC)
  - PGIC is a single-item question that measures change in patients' overall improvement rated on a 7-point scale including "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse"
- [redacted]
- Numeric rating scale (NRS) for average pain, as recorded on a daily patient diary
  - 0-10 scale, with 0 representing "no pain" and 10 as "the worst possible pain"
  - Every evening patients will assess their average pain intensity for the previous 24 hours
- Use of rescue medication for index knee pain: acetaminophen as recorded in a daily patient diary

Safety Assessments:

- Patient safety will be evaluated by physical examination, vital signs assessments (heart rate, respiratory rate, sitting blood pressure, and temperature), clinical laboratory assessments (hematology, chemistry, urinalysis), HbA1c, morning serum cortisol, [redacted] 12-lead electrocardiogram (ECG), knee radiographs, concomitant medications/therapies, adverse events (AEs), and signs and symptoms of adrenal insufficiency.

ENDPOINTS

The primary efficacy endpoint is:

1. Change from Baseline in WOMAC Pain at Week 12 (Group A vs. Group C)

The secondary efficacy endpoints are:

1. Change from Baseline in WOMAC Pain at Week 16 (Group A vs. Group C)
2. Change from Baseline in WOMAC Pain at Week 20 (Group A vs. Group C)
3. Change from Baseline in WOMAC Pain at Week 24 (Group A vs. Group C)
4. Change from Baseline in WOMAC Pain at Week 36 (Group A vs. Group C)
5. Change from Baseline in WOMAC Function at Week 12 (Group A vs. Group C)
6. Patient Global Impression of Change (PGIC) at Week 12 (Group A vs. Group C)
7. Total rescue acetaminophen consumption through Week 12 (Group A vs. Group C)
8. Durable responder with ≥30% decrease in WOMAC Pain from Baseline for Weeks 4 through 12 (Group A vs. Group C)
9. Change from Baseline in WOMAC Function at Week 36 (Group A vs. Group C)
10. PGIC at Week 36 (Group A vs. Group C)
11. Change from Baseline in WOMAC Pain at Week 12 (Group A vs. Group B)
12. Change from Baseline in WOMAC Pain at Week 52 (Group A vs. Group C)

STATISTICAL METHODS

General Statistical Considerations:

All efficacy and safety data will be listed and descriptively summarized by injection (Injection 1 or Injection 2) and treatment group (Group A, B, or C). Continuous variable summaries will include the number of patients, mean, standard deviation (SD), first quartile, median, third quartile, minimum, and maximum. Categorical variables will include the frequency and percentage of patients in each category. All statistical assessments will be 2-sided 0.05 significance level.

Database lock and unblinding will occur after the last patient in the study has completed the study.

Analysis Populations:

- **Safety Population (SAF)**: The Safety Population includes all patients who receive any dose of study drug; the population will be determined for each study period. The SAF population will be the primary population for safety evaluation.
- **Full Analysis Set (FAS)**: The FAS includes all randomized patients who receive Injection 1. The FAS population will be the primary population for efficacy analysis, as well as for descriptive summaries other than safety (demographic and baseline, disposition, protocol deviations, medical history, etc.).
- **Per Protocol Population (PP)**: The PP Population includes all patients who receive 2 doses of study drug, have primary efficacy evaluation at Weeks 12, 24, and 36, and do not have important protocol deviations affecting primary efficacy evaluation.
- **Modified Per Protocol (mPP)**: The mPP Population includes all patients who receive the first dose of study drug, have primary efficacy evaluation at Weeks 12 and 24, and do not have important protocol deviations affecting primary efficacy evaluation.

Efficacy Analysis:

Analysis of Primary and Key Secondary Endpoints:

Efficacy variables will be descriptively summarized by treatment group and by injection period within each group, based on the FAS population, unless otherwise specified. For all the continuous variables, the normalized numbers will be used for analysis, where applicable, unless otherwise specified.

The overall type I error rate will be controlled for primary and key secondary endpoints using hierarchical testing based on a fixed-sequence procedure. If statistical significance is declared for the primary analysis, formal statistical inference will continue at the 0.05 level for the secondary endpoints in the defined sequence until a non-significant result is reached. All other P values from key secondary endpoints, after a non-significant P value is reached, as well as other additional endpoints, will be considered exploratory.

An analysis of covariance (ANCOVA) model with treatment group as fixed effect and baseline value of the endpoint (when applicable) as covariates will be performed for the primary and key secondary continuous endpoints.

Sensitivity analyses will be conducted to estimate sensitivity estimators and to assess the robustness of efficacy results.

Additional Endpoints:

Additional endpoints and subgroup analyses will also be tested at a 2-sided 0.05 significance level.

The analysis of all continuous and categorical additional endpoints will be performed using an ANCOVA model

Safety Analysis:
Safety variables include physical examination, vital signs assessments (heart rate, respiratory rate, sitting blood pressure, and temperature), clinical laboratory assessments (hematology, chemistry, urinalysis), HbA1c, morning serum cortisol, [redacted] 12-lead electrocardiogram (ECG), knee radiographs, concomitant medications/therapies, AEs, and signs and symptoms of adrenal insufficiency. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medication will be coded using the World Health Organization Drug (WHODrug) Global Dictionary. Continuous safety data will be summarized by visit and include changes from baseline. Continuous data will also be converted to categorical values where possible (i.e., below, within, and above normal ranges) and summarized in shift from baseline tables. Categorical safety data collected by visit will be summarized showing the counts and percentages in each category at each visit, as well as shifts from baseline as appropriate.

Interim Analysis:
An interim analysis will not be performed.

SAMPLE SIZE DETERMINATION
This is a 3-arm parallel-group randomized controlled study. Approximately 500 patients will be randomized in

[redacted]

According to these assumptions, 500 patients will be randomly assigned in a 2:1:1 ratio to ensure that the study is well powered for primary and key secondary endpoints to be tested via the fixed-sequence testing method.

1.1. Schedule of Events

Period	SCR[a]	Injection 1 Period								Injection 2 Period									
Visit	1	2 / BL	3	4	5	6	7	8	9	10 / BL	11	12	13	14	15	16	17	18	19 EOS/ ET
Day (D)/Week (W)	N/A	D1	W1	W2	W4	W8	W12	W16	W20	W24[b]	W25[c]	W26[c]	W28	W32	W36	W40	W44	W48	W52
Window (days)[d]	≤ -28	N/A	±3	±3	±7	±7	±7	±7	±7	±7	±3	±3	±7	±7	±7	±7	±7	±7	±7
Informed consent	X																		
Inclusion/ exclusion criteria	X	X																	
Demographics and medical history	X	X																	
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight	X																		
Physical examination	X									X									X
Knee radiograph[f]	X									X									X
12-lead ECG[g]	X									X								X	X
Clinical chemistry/ hematology and HbA1c (fasted state)	X[h]	X[i]					X			X					X			X	X
Coagulation Panel	X[h]																		
Serology (HIV/HBV/HCV)	X[h]																		
Urinalysis	X									X								X	
Pregnancy test[j]	X	X								X									X
Drug screen and alcohol breath tests (onsite)	X	X								X									X
Morning serum cortisol[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Training[m]	X	X					X			X					X				
Daily knee pain diary (NRS)[n]	← **Record throughout the study** →																		
WOMAC		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIC			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X																	
Synovial fluid aspiration/ Study drug administration		X								X[o]									
Rescue medication[p]	← **Review throughout the study** →																		
Concomitant medications	← **Record throughout the study** →																		
Adverse events	← **Record throughout the study** →																		

Abbreviations: BL = Baseline; D = Day; ECG = electrocardiogram; EOS = End of Study Visit; ET = Early Termination Visit; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NRS = numeric rating scale; PGIC = Patient Global Impression of Change; W = Week; WOMAC = Western Ontario & McMaster Universities Osteoarthritis Index.

a Screening procedures may occur at any time during the Screening period unless otherwise specified. Patients who fail screening because of a mild infectious illness present at the Baseline or Screening, may be rescreened after the infection has resolved with approval of the medical monitor. Documented diagnosis of OA in the index knee can be completed as part of study screening.

b Patients who cannot attend the Week 24 visit within the visit window because of restrictions resulting from COVID-19, will be encouraged to return to the site before Week 28 to complete the Week 24 visit assessments, if feasible. However, Injection 2 may only be administered within the allowed visit window.

c These procedures and visits (Week 25 and Week 26) are only required for patients who receive Injection 2 and will take place at **1 and 2 weeks after Injection 2**, respectively.

d Visit 3 (Week 1) to Visit 19 (Week 52) should occur at the specified time point relative to Visit 2 (Day 1/Baseline), except **Visit 11 (Week 25)** and **Visit 12 (Week 26)**.

e Heart rate, respiratory rate, sitting blood pressure, and temperature will be measured after the patient has been in a sitting position for 5 minutes.

f A posterior-anterior X-ray radiograph will be performed for both knees in standing fixed-flexion (approximately 20 degrees), as applicable. For the Week 24 and Week 52 visits, the posterior-anterior X-ray radiograph may be performed within 14 days before the visit.

g The 12-lead ECG will be performed after the patient has been supine for at least 5 minutes.

h If the patient is potentially eligible based on currently available data except laboratory abnormalities, the assessments may be repeated once only to reassess eligibility.

i Only glucose (fasted state) will be tested in the Visit 2 (Baseline) visit before 9 AM and before study drug administration (Injection 1).

j Pregnancy tests performed only for women of childbearing potential. Serum pregnancy tests will be performed at Screening; urine pregnancy tests will be performed before dosing at Visit 2 (Baseline/Day 1) and Visit 10 (Week 24, only required for patients receiving Injection 2); and performed at EOS (Week 52) or ET.

k Serum samples for measurement of cortisol should be collected before 9 AM (and before study drug administration for Injection 1 and Injection 2 at Visit 2 [Day 1] and Visit 10 [Week 24], respectively). A serum cortisol value <5 µg/dL at Screening cannot be retested.

m Training and assessment of knowledge on pain ratings, allowable rescue medication, and entering data into the diary will be conducted at Screening, Baseline, Week 12, Week 24, and Week 36; and as needed throughout the study.

n A diary will be used daily to collect responses from patients on index knee pain over the previous 24 hours. Training regarding entering data into the diary will be given. Patients will first be asked to score their average pain in each knee by NRS over the previous 24 hours at the initial Screening visit. After the first Screening visit (Visit 1), the diary must be completed for each knee in the evening daily for at least 5 of the last 7 days of the screening period before returning to the study site for Visit 2 (Day 1/Baseline). After randomization, the patient will record their response on index knee pain in the diary every evening throughout the study until the last day prior to the EOS/ET visit. Sites should monitor patient compliance of diary entries regularly throughout the 52 weeks. If a patient is not compliant, the site should contact the patient as soon as non-compliance is observed.

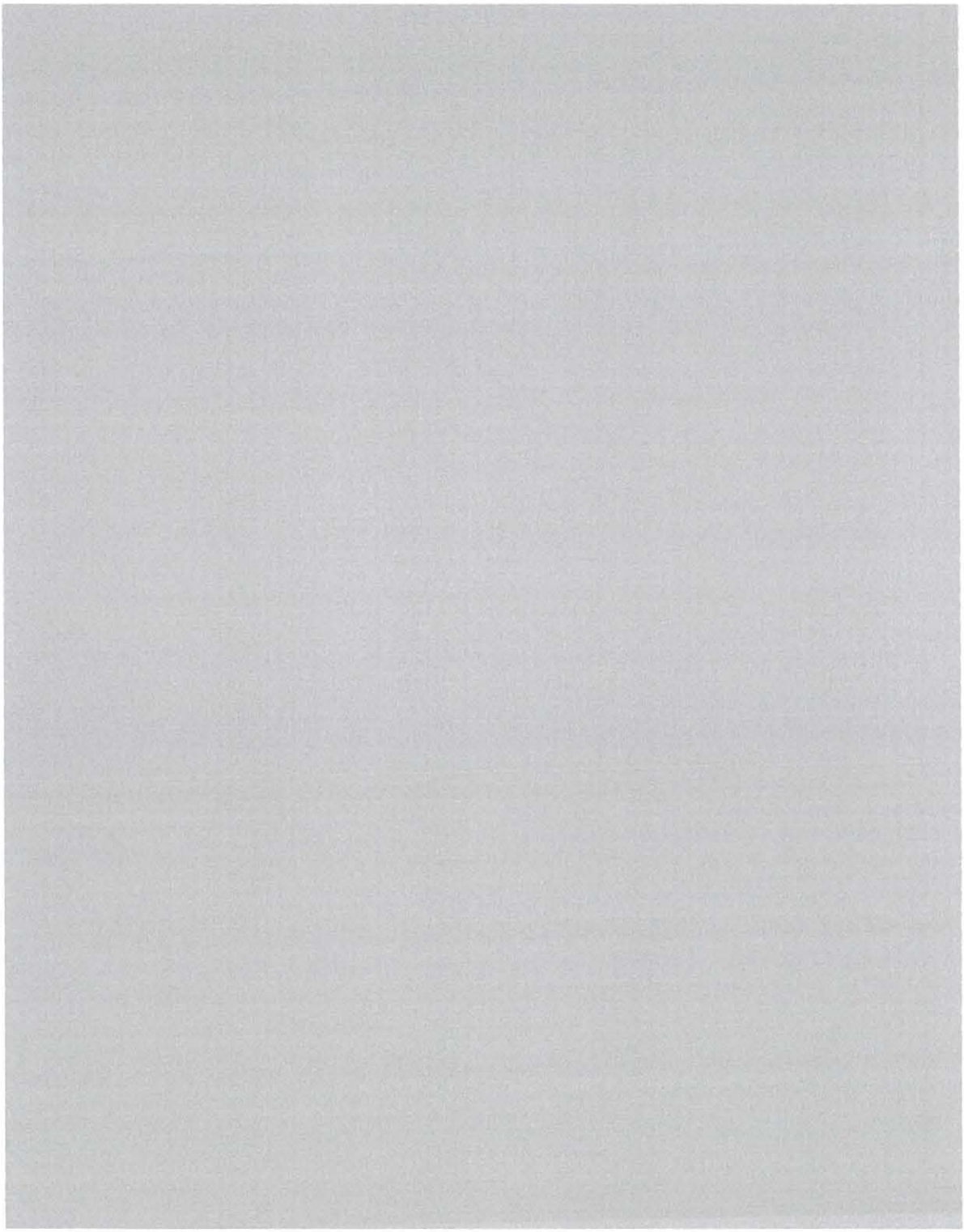
o Procedures for those receiving Injection 2. The patient should be checked for the criteria listed in Section 6.6.3 before study drug administration.

p Initial rescue medication bottle will be dispensed at Screening and as needed. Between Screening and EOS/ET, patients will record the previous 24-hour use of acetaminophen rescue medication daily into the diary. Rescue medication will be reviewed at every study visit.

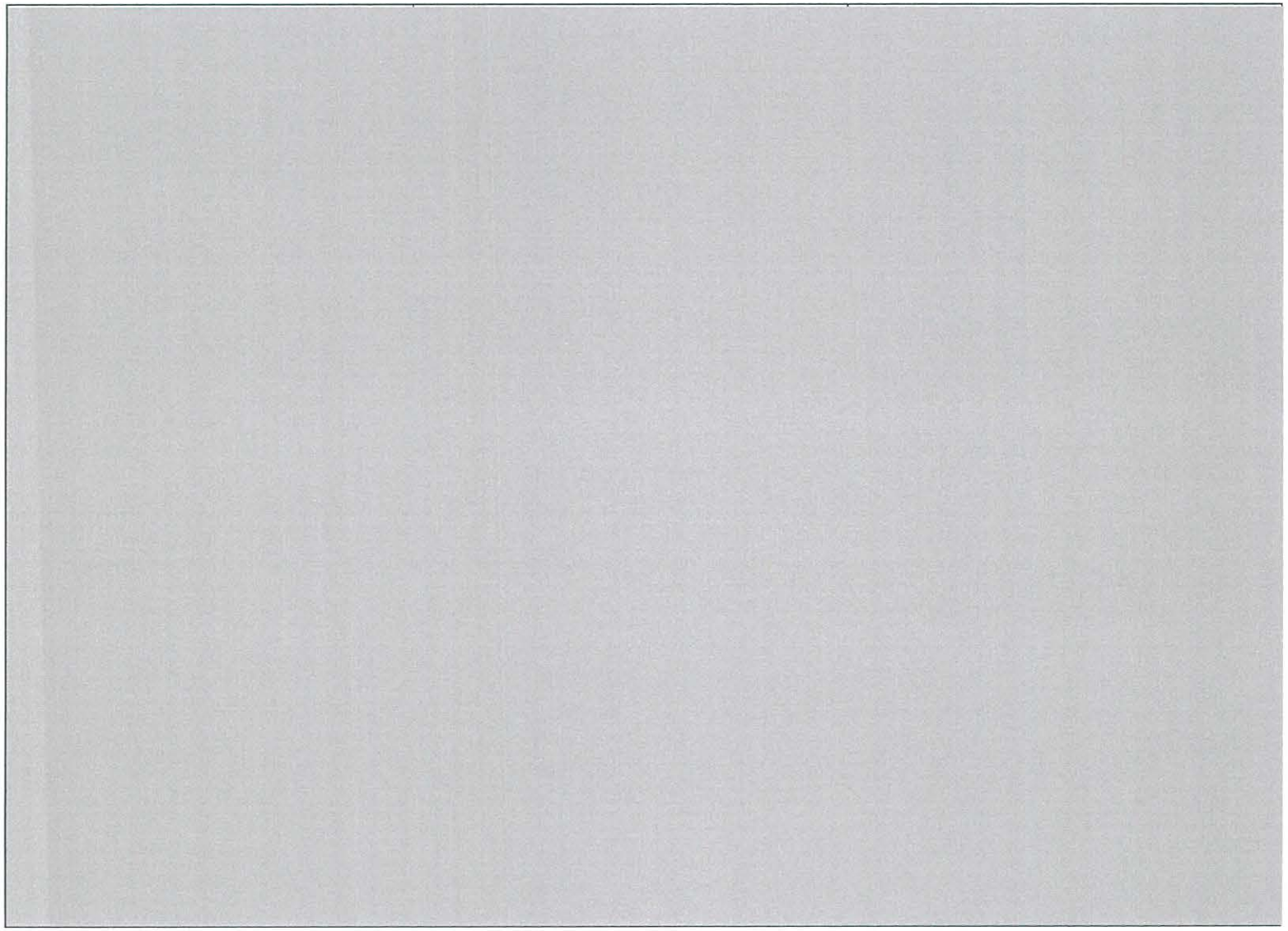
2. TABLE OF CONTENTS

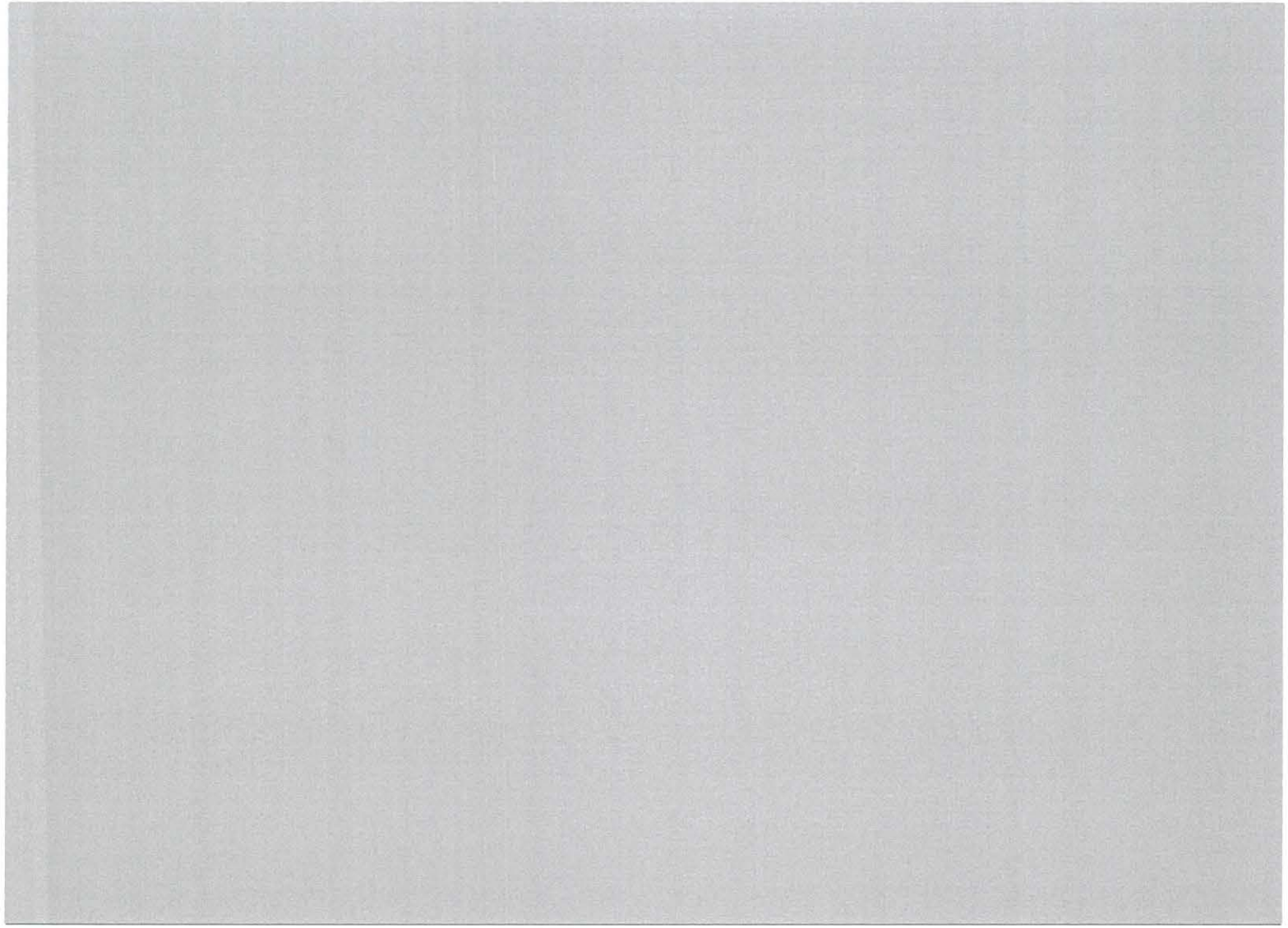
2.1. List of In-text Figures

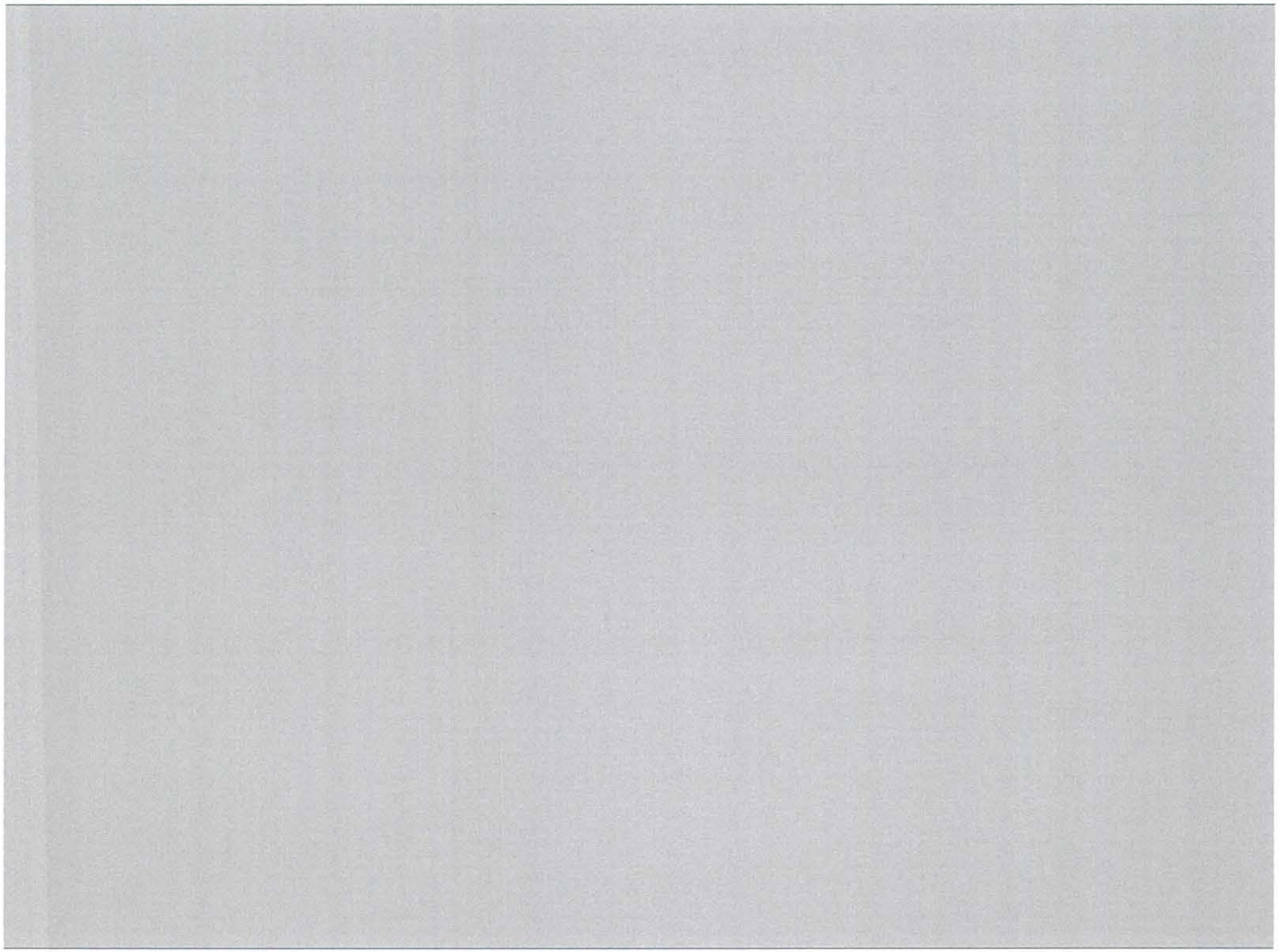
AMENDMENT 04 – SUMMARY OF CHANGES AND RATIONALE



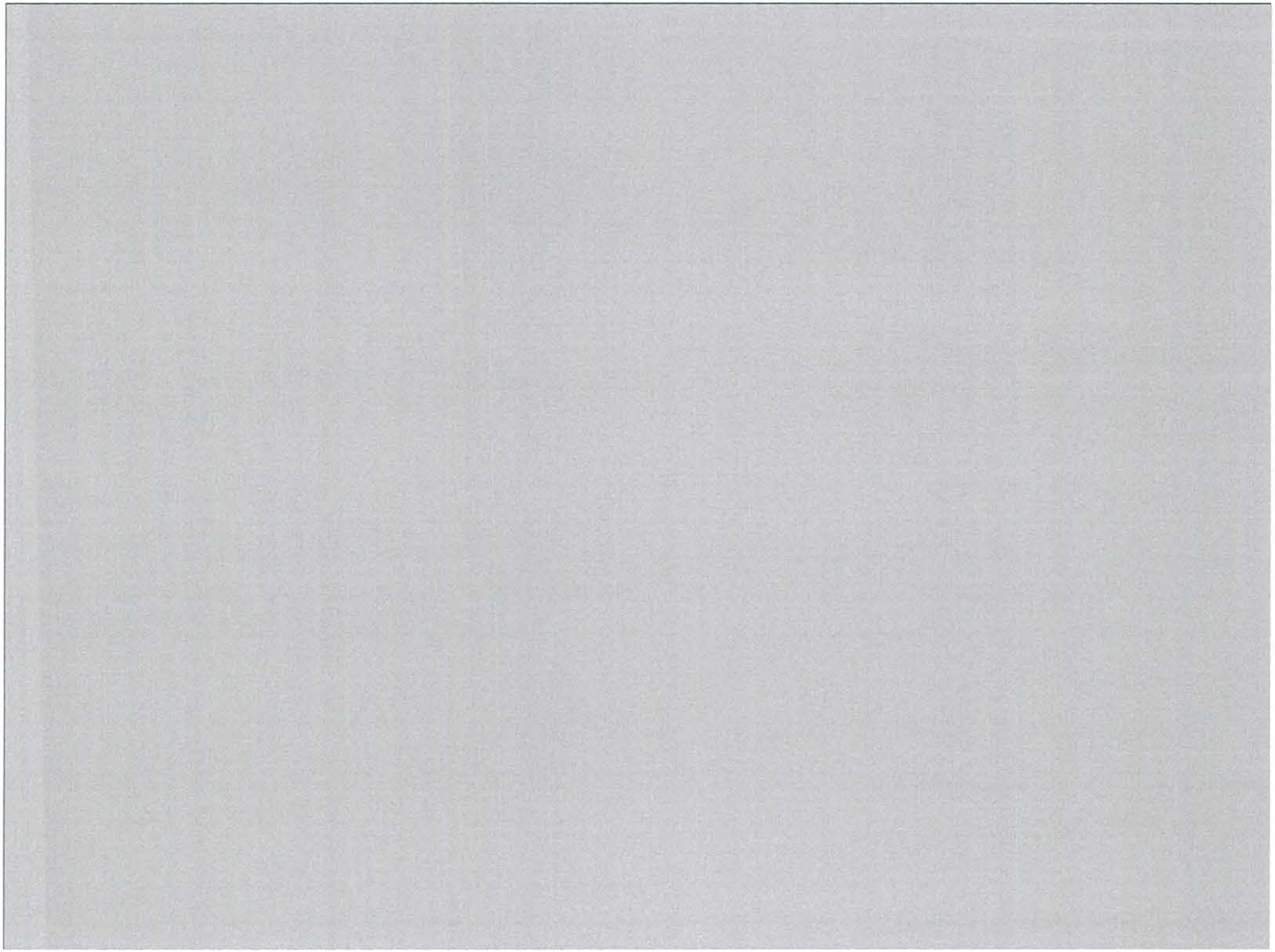
SUMMARY OF AMENDED SECTIONS

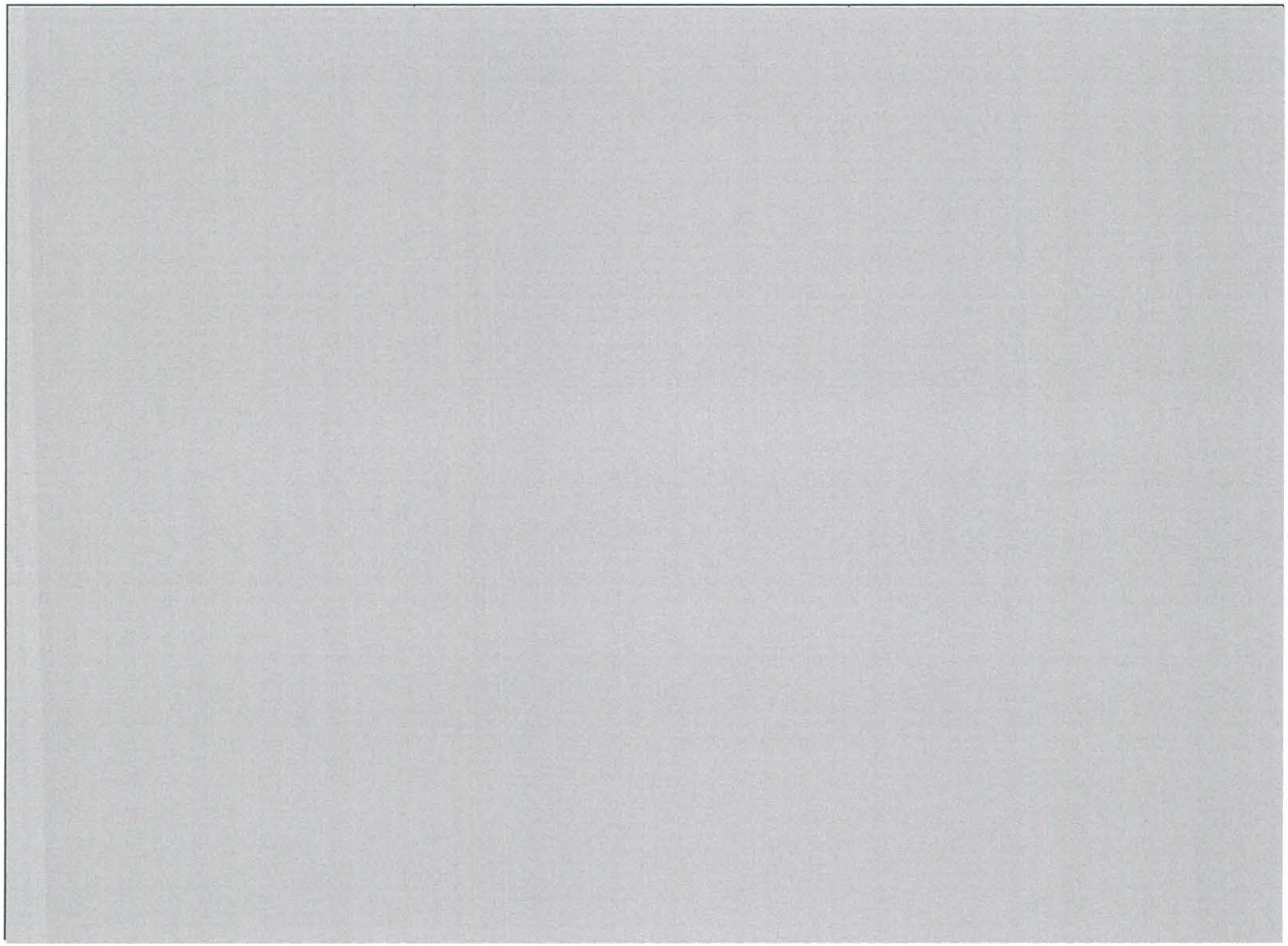


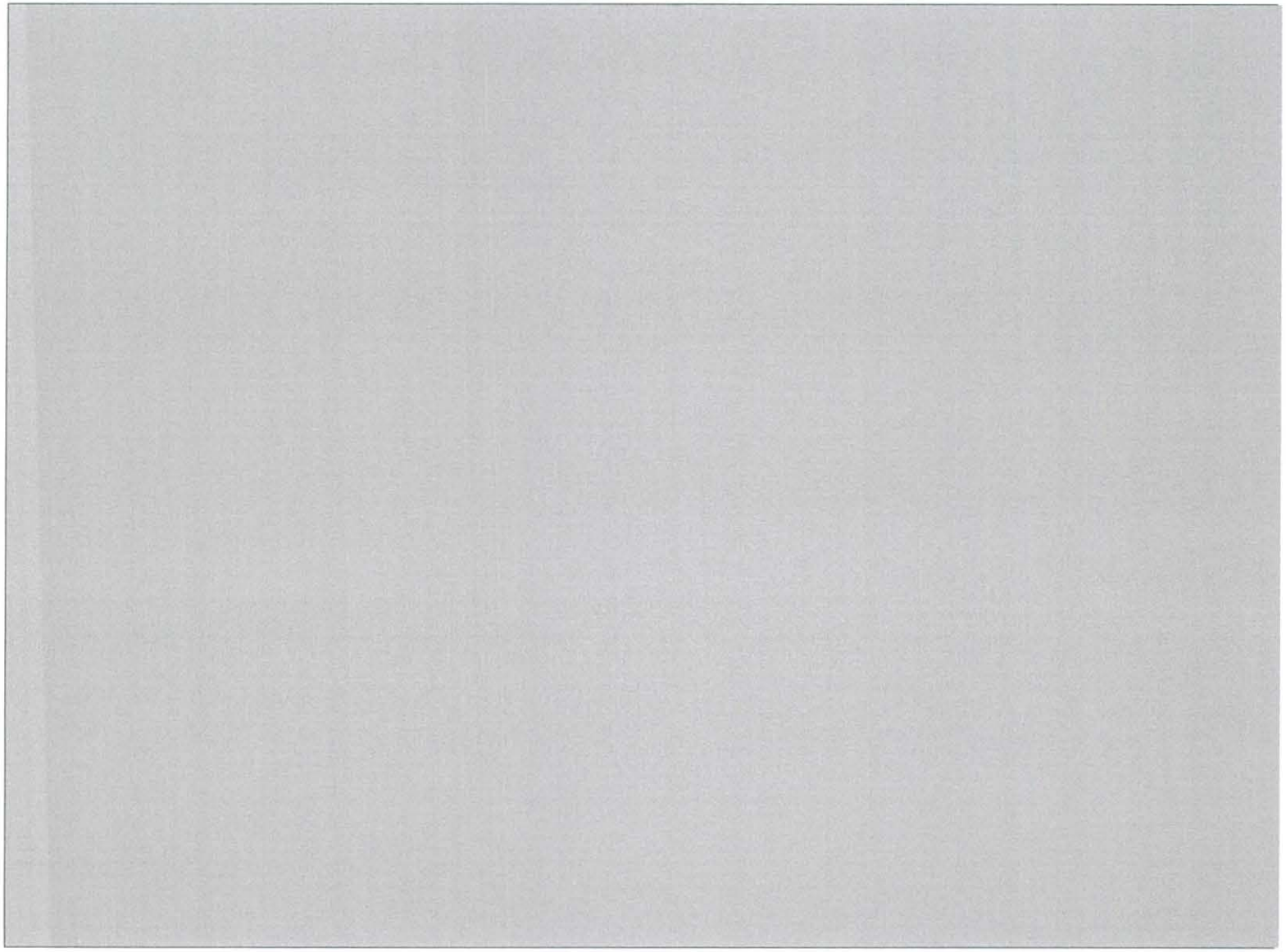


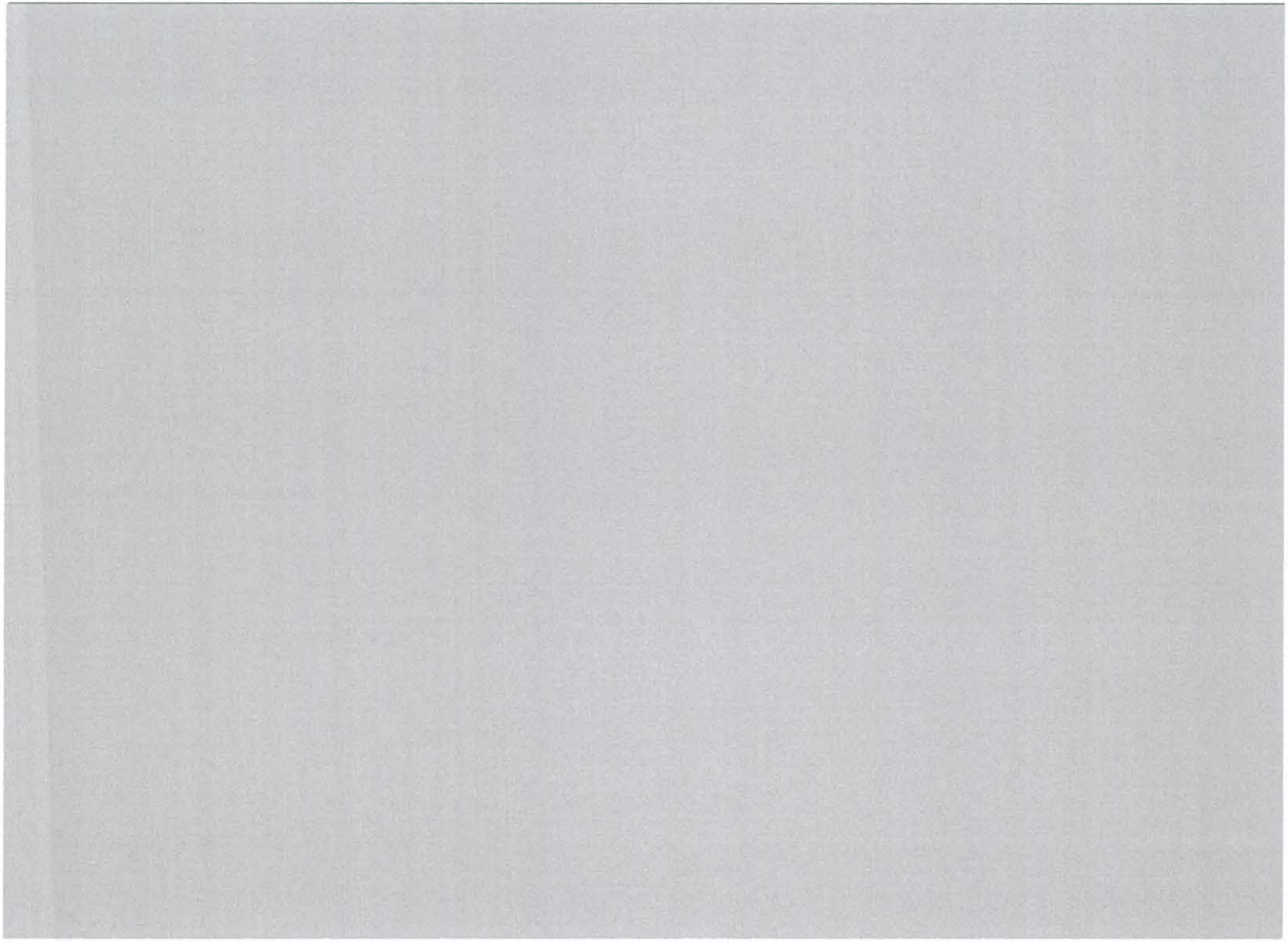


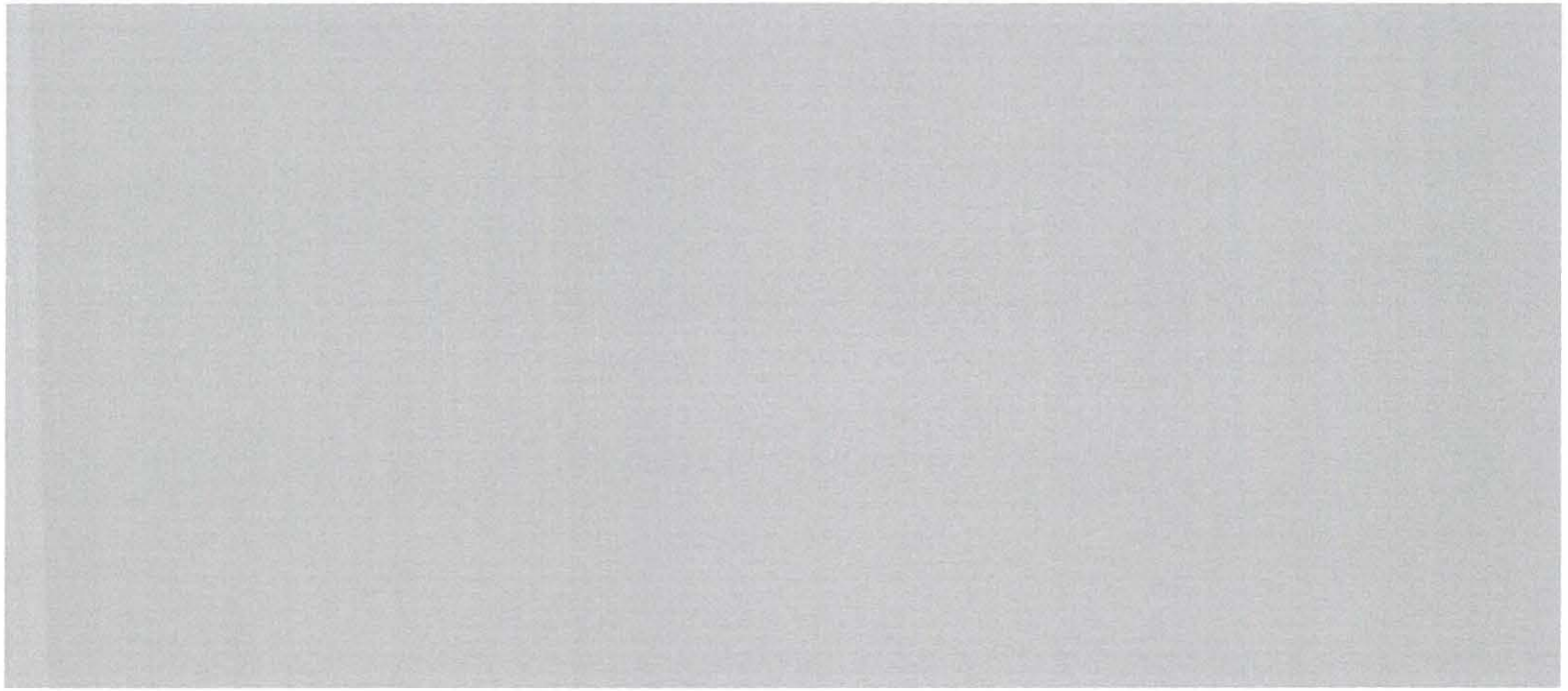
Section	Protocol Amendment 3 (v4)	Protocol Amendment 4 (v5)
11.2 Analysis Populations		
11.3.1.2. Protocol Deviations		











AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified above.

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ACR	American College of Rheumatology
ADL	Activities of Daily Living
AE	adverse event
AEAI	AE which is a potential symptom or sign of adrenal insufficiency
AESI	AE of special interest
ANCOVA	analysis of covariance
AUC	area under the time-concentration curve
β-hCG	human chorionic gonadotropin, beta subunit
BOCF	baseline-observation-carried-forward
CFR	Code of Federal Regulations
CIA	collagen-induced arthritis
CRA	clinical research associate
CSR	clinical study report
DSP	dexamethasone sodium phosphate
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study
ET	Early Termination
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA	intra-articular
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IND	investigational new drug

ABBREVIATION	EXPLANATION
IRB	institutional review board
IWRS	interactive web response system
JSN	Joint space narrowing
[redacted]	
LOCF	last-observation-carried-forward
MAR	missing at random
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	missing not at random
mPP	Modified Per Protocol
NSAID	Non-steroidal anti-inflammatory drug
NRS	numeric rating scale
OA	osteoarthritis
PGIC	Patient Global Impression of Change
PL	phospholipid
PP	Per Protocol
PT	preferred term
QOL	Quality of life
QTc	QT interval corrected for heart rate
RBC	red blood cell count
SAE	serious adverse event
SAF	Safety population
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TLC	Taiwan Liposome Company, Ltd.
ULN	upper limit of normal
US	United States
WOMAC	Western Ontario & McMaster Universities Osteoarthritis Index

4. INTRODUCTION

4.1. Background and Rationale

Osteoarthritis (OA) is a common degenerative joint disorder of the articular cartilage associated with hypertrophic bone changes. Treatment for OA primarily involves a non-pharmacological combination of exercise and lifestyle modification, pharmacological treatment, supplementation with glucosamine or chondroitin sulphate, and surgical joint replacement. Among pharmacological treatments, corticosteroids have both anti-inflammatory and anti-angiogenic properties, and they are routinely given via inject intra-articular (IA) injection for the treatment of chronic knee joint diseases to relieve pain, reduce inflammation, and improve mobility. There are several Food and Drug Administration (FDA)-approved corticosteroids for IA use, including dexamethasone, methylprednisolone, betamethasone, and triamcinolone. However, when effective, the mean duration of benefit may be relatively short, often lasting for only 2 to 4 weeks.[1] Furthermore, repeated injections of corticosteroids may increase the risk of local and systemic side effects, including pericapsular calcification, tendon rupture, skin atrophy/depigmentation, steroid arthropathy, joint infection, facial flushing, hypersensitivity, and hyperglycemia. Common practice is to use IA corticosteroids no more than once every 3 months.

Dexamethasone is a highly potent glucocorticoid whose action is mediated by the binding of the corticosteroid molecule to receptors located within sensitive cells. The physiological function of glucocorticoid is complex and may include a number of mechanisms such as modification of movement and function of leukocytes, reduction of vascular permeability, and reduced prostaglandin synthesis.[2] TLC599 is a drug product designed to improve the stability of dexamethasone sodium phosphate (DSP) through formulation with the BioSeizer platform technology. DSP is the pro-drug of dexamethasone and has been approved for indications of endocrine disorders, rheumatic diseases, and dermatologic, allergic, or ophthalmic diseases through intravenous or intramuscular administration route. Also, DSP is used to treat the synovitis of osteoarthritis, rheumatoid arthritis or gouty arthritis through IA or soft tissue administration route and keloid, localized inflammation of lichen planus, psoriatic plaques, granuloma annulare or discoid lupus erythematosus may be treated through intralesional administration route. BioSeizer is a proprietary, lipid-based drug delivery system developed by Taiwan Liposome Company (TLC), which can entrap both small molecules and large molecules and then slowly release these therapeutic agents. The release profile of compounds or proteins can be adjusted by modulating the concentration of phospholipids (PLs). By prolonging the local residence time of therapeutic agents, TLC599 in turn reduces treatment frequency and risk to maximize the clinical benefit. Therefore, TLC599 provides an ideal, safe, and long-acting DSP delivery for the treatment in OA.

4.2. Clinical Experience

Two clinical studies for treating knee osteoarthritis with TLC599 via IA route at different dose levels (Study TLC599A1001 in Taiwan and Study TLCA599A2003 in Taiwan/Australia) were completed. TLC599A1001 was completed and TLCA599A2003 was completed, and the clinical study report was prepared for submission. Another pharmacokinetic study of TLC599 (TLC599A2004) filed under the US Investigational New Drug (IND) is currently in the patient recruitment phase.

Study TLC599A1001 (Clinicaltrials.gov No: NCT02803307) was the first study to administer TLC599 by IA injection in patients with OA of the knee and there were no significant safety signals detected. It was a randomized, open-label study to evaluate the preliminary efficacy and safety of TLC599 dose levels of 6 mg and 12 mg DSP, with 20 patients per dose group.

TLC599A2003 (ClinicalTrials.gov Identifier: NCT03005873) was a randomized Phase 2a study with single IA injection of either TLC599 at 2 dose levels or Placebo (normal saline) on Day 0, with a follow-up period of 24 weeks. A total of 75 patients were administered with 1 of the 3 study treatments.

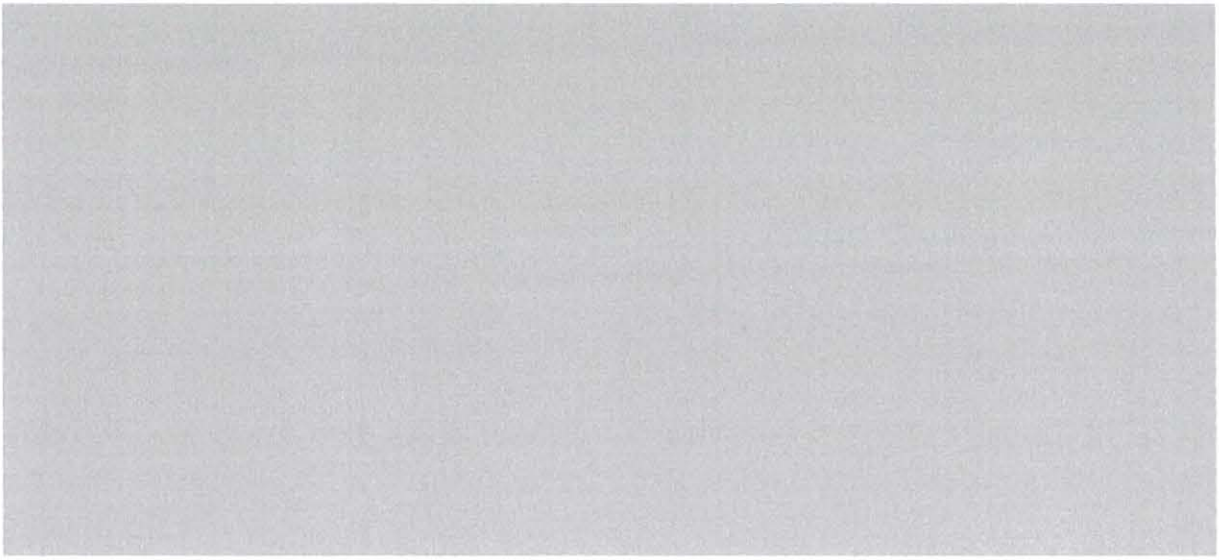
4.3. Non-clinical Experience

Local treatment of TLC599 by IA administration showed markedly sustained inhibitory activity in animal models of inflammatory diseases. The TLC599-induced amelioration of collagen-induced arthritis (CIA) was evaluated in 2 rat studies. Following a single intra-plantar dose administration of DSP solution of TLC599 in rats with CIA, the hind-paw swelling decreased in animals treated with either unformulated DSP treatment or TLC599. However, swelling recurred earlier for unformulated DSP treatment (Day 22) compared to TLC599 (Day 26). A similar outcome was obtained following repeat-dose administration, though the duration of anti-arthritic effects associated with TLC599 persisted for a longer period following repeat vs. single doses.

Also, TLC599 did not cause significant toxic effect locally and systemically after IA administration in single- and repeat-dose studies in rabbits and dogs. The toxic findings of TLC599 after IV administration to rats are comparable to those of DSP without significant additional toxic findings and delayed toxicities.

4.4. Summary of Potential Risks and Benefits

The potential benefits of study participation are that patients with OA of the knee may experience sustained pain relief as a result of treatment with TLC599.



5. OBJECTIVES

5.1. Primary Objective

The primary objective is to evaluate the efficacy of a single IA dose of TLC599 in patients with OA of the knee.

5.2. Secondary Objectives

Secondary objectives include the following:

- To evaluate the efficacy of repeat doses of TLC599 in patients with OA of the knee
- To evaluate the safety of single and repeat IA doses of TLC599 in patients with OA of the knee

6. STUDY DESIGN

6.1. Overall Study Design and Plan

This is a Phase 3 randomized, double-blind, placebo- and active comparator-controlled pivotal study. Approximately 500 adult patients with moderate to severe pain due to OA of the knee who meet all entry criteria will be enrolled and randomized into in a 2:1:1 ratio to receive TLC599 12 mg (Group A), DSP 4 mg (Group B), or Placebo (normal saline) (Group C) via IA injection into the designated index knee at Baseline (Injection 1). At Week 24, patients will receive Injection 2 per their randomly assigned dosing regimen (Group A, B, or C) via IA injection into the index knee (see Section 6.6.3 for Criteria for Injection 2). Patients who received TLC599 12 mg (Group A) or DSP (Group B) for Injection 1 will receive blinded TLC599 12 mg for Injection 2 and those who received Placebo for Injection 1 (Group C) will receive Placebo for Injection 2.

All patients will be followed for a total of 52 weeks, regardless of whether or not they receive Injection 2. Patients who do not receive Injection 2 will be encouraged to continue in the study through 52 weeks of follow-up. Efficacy and safety of 2 doses of TLC599 will be evaluated in comparison with Placebo and DSP through Week 52.

To enter the study, patients must be at least 40 years of age and have documented diagnosis of OA in the index knee based on American College of Rheumatology (ACR) Criteria for Classification of Idiopathic OA of the knee (the ACR diagnostic criteria is provided in Appendix A). Patients will not be eligible if they have unstable index knee joint as determined by the investigator based on physical examination (with or without buckling or giving way) because of an acute injury (defined as injury within 6 months, e.g., anterior cruciate ligament injury or tear).

The study duration is expected to be up to 56 weeks for each patient, including a Screening period of up to 4 weeks before randomization, Injection 1 Period of 24 weeks and Injection 2 Period of 28 weeks.

Patients will return to the study site at Week 1, Week 2, and every 4 weeks through Week 52 post-dose to complete efficacy and safety assessments as applicable. Patients who receive Injection 2 will return to the clinic for 2 additional follow-up visits (Week 25 and Week 26).

Efficacy will be assessed by WOMAC, numeric rating scale (NRS), and Patient Global Impression of Change (PGIC) at the time points indicated in the schedule of events (Section 1.1).

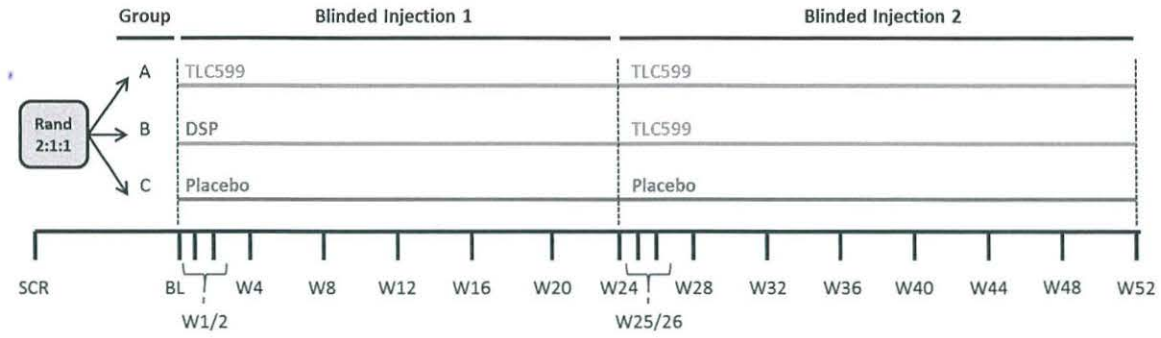
Safety will be assessed by physical examination, vital signs measurements (heart rate, respiratory rate, sitting blood pressure and temperature), clinical laboratory assessments (hematology, chemistry, urinalysis), HbA1c, morning serum cortisol, 12-lead electrocardiogram (ECG), knee radiographs, concomitant medications/therapies, adverse events (AEs), and signs and symptoms of adrenal insufficiency.

All AEs observed by the study personnel or reported by the patient during the study (after the patient has signed the informed consent form [ICF] through the End of Study [EOS]/Early Termination [ET] visit) will be documented.

Patients who do not complete the study through Week 52 will make every effort to complete ET procedures.

The diagram of the study design is provided in Figure 1.

Figure 1: Study Design



Abbreviations: BL = Baseline (Day 1); DSP = dexamethasone sodium phosphate; Rand = Randomization; SCR = Screening; W = Week.

6.2. Rationale and Discussion of Study Design

IA corticosteroid injection is a commonly used treatment with an excellent safety profile. A limitation of IA injection with corticosteroids is the modest duration of treatment effect, which often lasts for only 2 to 4 weeks. Repeat injections are possible in the same joint, but there are limited data on the safety and duration of the effectiveness of this procedure. Thus, there is a pressing need for a more sustained duration of an IA corticosteroid injection.

This is a Phase 3, randomized, double-blind, placebo- and active-controlled study to evaluate the efficacy and safety of TLC599 in patients with OA of the knee. The duration of follow-up after an IA injection for this study (up to 52 weeks) is somewhat longer than typical OA studies (12 to 16 weeks) as the duration of effect from the study drug is expected to be longer. Additionally, a second injection in the same index knee will be administered where appropriate at Week 24 to assess the safety and effectiveness of repeat dosing. The planned efficacy, safety, and tolerability endpoints for single and repeated dosing of TLC599 are appropriate for evaluating its sustained pain relief through an extended period of up to 52 weeks follow-up monitoring.

6.4. Study Sites

The study will take place at approximately 45 to 50 sites in the US and Australia.

6.5. Study Completion Definition

The clinical trial is considered completed when the last participant's last study visit has occurred.

6.6. Study Population

Approximately 500 patients are planned for randomization.

6.6.1. Inclusion Criteria

A patient will be eligible for study participation if he or she meets all of the following criteria:

1. Male or female ≥40 years of age, inclusive.
2. Body mass index ≤40 kg/m^2.
3. Has symptoms associated with OA of the index knee for at least 6 months before Screening.
4. Documented diagnosis of OA in the index knee based on ACR Criteria for Classification of Idiopathic OA of the knee (clinical and radiological including standing fixed-flexion posterior-anterior X-ray of the knee).
5. OA with Kellgren-Lawrence Grade 2 to 3 severity in the index knee based on the grade per X-ray assessed by a central radiologist reader at Screening.
6. Initial patient-reported pain with NRS score ≥4 (on a 0-10 scale) in at least 1 knee (index knee) at Screening (rating of average pain over previous 24 hours).
7. Patient-reported pain with average daily NRS score of 5.0 to 9.0 (inclusive) in the index knee, AND with non-index knee pain score of ≤4.0, based on diaries completed daily for at least 5 of the last 7 days of the screening period before randomization.
8. Patient-reported WOMAC Pain sub-scale (hereafter referred to as WOMAC Pain) score ≥6 (combined score on a 0-20 scale) in the index knee before dosing at Baseline.
9. a. IF FEMALE, must meet all of the following:
   - Not breast feeding;
   - Not planning to become pregnant during the study;
   - If of childbearing potential (defined as non-post-hysterectomy or non-post-menopausal [amenorrheic for at least 2 years]), must have a negative pregnancy test result (human chorionic gonadotropin, beta subunit [β-hCG]) at Screening and Baseline, and must commit to the use of an acceptable and effective form of birth control for the duration of the study and until at least 6 months after the last dose of study drug.

   b. IF MALE, must be surgically sterile (biologically or surgically) or commit to the use of a reliable method of birth control (must agree to use double-barrier contraception in the event of sexual activity), or be practicing abstinence for the duration of the study and until at least 6 months after the last dose of study drug.
10. Is able to read, understand, and sign the ICF, communicate with the investigator, and understand and comply with protocol requirements.

6.6.2. Exclusion Criteria

A patient will be excluded from the study if he or she meets any of the following criteria:

1. Use of any of the following medications within the specified period:
   a. IA corticosteroid in any joint within 3 months before Screening, or triamcinolone acetate extended-release injectable suspension (Zilretta®) within 6 months before Screening
   b. IA hyaluronic acid in any knee joint within 6 months before Screening
   c. Systemic corticosteroids within 4 months before Screening or chronic use within 1 year before Screening
   d. NSAIDs (except topical use on regions other than the index knee) within 14 days before the Baseline visit
   e. Platelet-rich plasma or other prolotherapy within 6 months before Screening
   f. Chronic opioid use (use exceeding 4 days per week) within the last 30 days before Screening
   g. Any chemotherapeutic or systemic immunosuppressant agents for inflammatory diseases within 6 months before Screening
   h. Anti-coagulants, including warfarin, heparin, low molecular weight heparin, or dabigatran within 1 week of Screening and the Baseline visit. Low-dose acetylsalicylic acid or other anti-platelet medications are allowed
   i. Live attenuated vaccine within 3 months before Screening
   j. Any investigational therapy within 4 weeks or within 5 half-lives before Screening, whichever is longer
2. Patient who is not ambulatory.
3. Any surgery or arthroscopy in the index knee within 12 months before Screening.
4. Unstable index knee joint as determined by the investigator based on physical examination (with or without buckling or giving way) because of an acute injury (defined as injury within 6 months of Screening, e.g., anterior cruciate ligament injury or tear).
5. History of infective arthritis in the index knee.
6. Suspected/concurrent infection in either knee at Screening or Baseline before study drug administration.
7. Any skin lesion/breakdown at the anticipated injection site or any condition that impairs penetration of the index knee joint space.
8. Documented gout attack in index knee within 6 months before Screening or presence of tophus in index knee.
9. Patient with any amputation in any lower limb.
10. Documented history and confirmed autoimmune disease including but not limited, reactive arthritis, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, inflammatory myositis, mixed connective tissue disease, palindromic rheumatism, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Behcet's disease, arthritis associated with inflammatory bowel disease, sarcoidosis, vasculitis, cryoglobulinemia, or amyloidosis.

11. Any condition that could possibly confound the patient's assessment of index knee pain per the investigator's judgment (i.e., ipsilateral hip OA, radicular low back pain, and hip pain referred to the index knee).
12. Substance abuse disorder, or positive urine drug test for illegal drug substances or non-prescribed controlled substances including amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol; or positive alcohol breath test.
13. History of primary or secondary adrenal insufficiency.

16. History of bleeding disorders.
17. History of acquired or congenital immunodeficiency diseases, or positive test results for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) current infection at Screening.
18. Any active infection requiring treatment with antibiotics.
19. History of treated malignancy which is disease free for ≤5 years before Screening, except basal cell carcinoma of skin or carcinoma in situ of the uterine cervix.
20. Stroke or myocardial infarction within 12 months before Screening.
21. Uncontrolled and unstable concurrent medical or psychiatric illness, including but not limited to, poorly controlled diabetes, poorly controlled hypertension, dementia, schizophrenia, or bipolar disorder that will jeopardize the safety of the patient, interfere with the objectives of the protocol, or affect the patient compliance with study requirements, as determined by the investigator.
22. Abnormalities of the following laboratory parameters at Screening:
    a. hemoglobin A1c (HbA1c) >9.0%
    b. platelet count <80,000/μL
    c. hemoglobin <8.0 g/dL
    d. total white blood cell count <4000/μL
    e. serum bilirubin/alanine aminotransferase/ aspartate aminotransferase >2 times upper limit of normal (ULN) for the laboratory reference ranges
    f. serum creatinine level >1.5X ULN
    g. prothrombin time/International Normalized Ratio > ULN for the laboratory reference range
23. Known allergy or hypersensitivity to the study drugs or their components.
24. Is an immediate family member (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the clinical study site.
25. Employed by sponsor (i.e., is an employee, temporary contract worker, or designee responsible for the conduct of the study).

6.6.3. Criteria for Injection 2 (Week 24)

Patients will not continue with Injection 2 if any of the following criteria are met:

2. Occurrence of adrenal insufficiency through Week 24.
3. If female and of childbearing potential, have a positive urine pregnancy test result at Week 24.
4. Positive urine drug or alcohol test result at Week 24. (Drug use allowed with prescription.)

6.7. Patient Withdrawal from the Study

All patients will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep patients in the study; however, patients must be withdrawn from the study if they withdraw consent to participate. Patients who do not receive Injection 2 do not need to be withdrawn and will be encouraged to continue in the study through 52 weeks of follow-up. If a patient does not receive Injection 2, it will not be considered a protocol deviation. Investigators must attempt to contact patients who fail to attend scheduled visits by telephone or other means to assess the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 9.2.

A participant should be withdrawn from the study if any of the following occurs:

- Pregnancy
- Significant study non-compliance
- Lost to follow-up
- A surgical procedure or IA drug administration in the index knee
- Lack of therapeutic effect that is intolerable or otherwise unacceptable to the patient
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The investigator or the Sponsor stops the study for any reason

If important restricted medication deviations occur, they should be discussed with the medical monitor before withdrawing the patient from the study.

The investigator should contact the medical monitor to discuss any non-compliance or safety concerns before withdrawing a patient from the study.

The reason for participant withdrawal from the study will be recorded on the eCRF. Patients who sign the ICF, are randomized, and receive study drug, and subsequently withdraw, or are withdrawn from the study, will not be replaced.

6.8. Patient Replacement Criteria

Withdrawn patients will not be replaced. Randomized and treated patients withdrawn from the study may not re-enter. The patient number for a withdrawn patient will not be reassigned to another patient.

7. TREATMENTS

7.1. Identification of Study Drugs

[redacted]

Packaging, labeling, and dispensing information for TLC599 are provided in the pharmacy manual, available as a separate document.

The active comparator, DSP, will be supplied to study centers. The vial of DSP for injection contains DSP solution at the concentration of 4.0 mg/mL. DSP should be stored at 20°C to 25°C (68°F to 77°F) (see USP Controlled Room Temperature) in accordance with the package insert. Protect from freezing, sensitive to head. Do not autoclave.

Placebo will be supplied to study centers. The vial of Placebo contains 0.9% normal saline. Normal saline should be stored below 25°C (77°F) or in accordance with the package insert.

7.2. Treatment Administration

Study drug will be administered in a blinded manner via IA injection into the index knee:

Study Drug (TLC599):

- Dexamethasone sodium phosphate (DSP) 12 mg with 100 mM phospholipid (PL) (1 mL)

Reference Drug (DSP):

- DSP 4 mg (1 mL)

Placebo:

- Normal saline (1 mL)

Patients will be randomly assigned in a 2:1:1 ratio to one of the following treatment groups (Group A, B, or C).

Treatment Assignment for Injection 1 and Injection 2

Group	Injection 1 (Day 1)	Injection 2 (Week 24)
A	TLC599	TLC599
B	DSP	TLC599
C	Placebo	Placebo

Guidance and recommendations for the study drug injection procedure are provided in the pharmacy manual.

The index knee for study drug administration will be determined before randomization at Visit 2 (Baseline). The index knee is selected primarily based on the documented diagnosis of OA, Kellgren-Lawrence grade, NRS score at the initial Screening visit, and average daily NRS score before randomization. Therefore, the index knee can only be identified at the Baseline visit. The study drug injection may be administered using ultrasound-guided needle placement, depending on the facility available at each study site. If imaging-guided injection is not used, then confirmation of location of the needle within the index knee joint may be verified by aspirating

joint fluid. If there is a substantial effusion within the knee joint, the effusion should be aspirated, when possible, such that the estimated remaining joint fluid in the knee is approximately 5 to 10 mL. The amount of joint fluid aspirated should be recorded. If it is part of the site's standard practice, pre-injection analgesics may be administered. However, nothing other than the study drug may be administered into the IA space. All medications used should be recorded in the concomitant medication record.

Post-procedure observation for patient safety can be per the investigator's discretion. Patients should not take a hot bath or shower, or expose the injected knee to external heat, within 12 hours after the injection.

7.3. Selection of Timing of Dose for Each Patient

The study drug injection will only be given on Day 1 (Injection 1) and Week 24 (Injection 2) if the patient meets the eligibility criteria (Sections 6.6.1 through 6.6.3).

7.4. Dose Adjustment Criteria

Not applicable.

7.5. Treatment Compliance

All injections at the study site should be under the surveillance of appropriate study personnel. Injection procedure details will be recorded in the patient's eCRF.

7.6. Method of Assigning Patients to Treatment Groups

In this parallel-group randomized study, patients who meet study eligibility criteria will be randomly assigned in a 2:1:1 ratio to 12 mg TLC599, 4 mg DSP, or Placebo (normal saline). The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate study drug to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as patients meet the eligibility criteria. Study center will not be a blocking factor in the randomization schedule.

The randomization schedule will be prepared by [redacted] before the start of the study. No one involved in the study performance will have access to the randomization schedule before official unblinding of treatment assignment. No patient will be randomized into this study more than once.

7.7. Blinding and Unblinding Treatment Assignment

All patients, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment, with the exception of a specified unblinded statistician and programmer from [redacted] who will have access to the randomization code, the unblinded medical monitor, and the unblinded pharmacist or designee and unblinded injector at each study site. The unblinded study personnel will not participate in study procedures or data analysis before unblinding of the study data to all study-related personnel. The patient treatment assignment for Injection 1 will remain blinded until the last patient has completed the study. The procedure for treatment blinding is presented in the pharmacy manual.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency.

Unblinding will be permitted in a medical emergency that requires immediate knowledge of the patient's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study personnel will use the IWRS to obtain unblinding information. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the patient's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate eCRF for that patient. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor before unblinding the patient's treatment assignment.

If treatment assignment is unblinded for an individual patient, study personnel will be notified of that patient's treatment assignment without unblinding the treatment assignments for the remaining patients in the study. The overall study blind will not be compromised. If a patient's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor and the sponsor.

Overall unblinding will take place only after database lock has been achieved.

7.8. Rescue Medication

Acetaminophen rescue medication may be used and will be provided to and managed by the study sites. The daily allowed acetaminophen dosage is up to 3 g/day. No acetaminophen is allowed within 24 hours before study visits.

[redacted] will provide the appropriate package insert for the acetaminophen rescue medication to be used during the study to each investigator.

The name and dosage regimen of the rescue medication must be recorded daily in the diary with the indication recorded as "rescue medication."

7.9. Concomitant Medications

Patients may continue to receive any ongoing prescription medications, dietary supplement, or exercise program of the knee that they were receiving at the time of Screening, unless otherwise prohibited (See Prohibited Therapies, Section 7.10), and which are recorded in the source document and appropriate eCRF. These medications, or their doses, should not be changed during the course of the study unless under the direction of the prescribing physician.

7.10. Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

The following therapies are prohibited after the informed consent is signed, and throughout the study, unless otherwise specified:

- IA corticosteroid in any joint
- IA hyaluronic acid in any knee joint
- Systemic corticosteroids (topical use allowed except on the index knee)
- Acetaminophen within 24 hours prior to Baseline and subsequent study visits

- Non-steroidal anti-inflammatory drugs within 14 days before the Baseline visit and throughout the study (topical use allowed except on the index knee)
- New initiation of duloxetine, pregabalin and gabapentin (a patient may continue the prior use of these drugs during the study)
- Platelet-rich plasma or other prolotherapy
- Opioid use is not permitted, with the exception of hydrocodone, oxycodone, or tramadol, which may be used with the following limitations:
  - Any combination analgesic containing an opioid is prohibited
  - However, episodic use (<4 days per week) of hydrocodone, oxycodone, or tramadol is permitted
  - The use of any opioid (including hydrocodone, oxycodone, or tramadol) within 24 hours before the Baseline visit and subsequent study visits is prohibited
- Any chemotherapeutic or systemic immunosuppressant agents for inflammatory diseases
- Anti-coagulants, including warfarin, heparin, low molecular weight heparin, or dabigatran (low-dose acetylsalicylic acid and other anti-platelet medications allowed)
- Live attenuated vaccine
- Any investigational therapy
- Physical and occupational therapy or new rehabilitation program in index knee
- Acupuncture or any surgical or invasive procedure on either knee (including study knee joint synovial fluid aspiration except prior to study drug administration)
- Oral cannabidiol (CBD) in any form; inhalation is allowed and topical use is allowed except on the index knee

Patients receiving excluded therapies during the screening period will be treated as screen failures and ineligible for randomization. If a patient uses any prohibited medication or treatments mentioned as above after study drug administration during the study period, it will be defined as a protocol deviation. Whether such protocol deviation is considered as significant study non-compliance leading to withdrawal will be based on the investigator's judgment after consulting the sponsor and the blinded medical monitor.

7.11. Dispensing and Storage

Details regarding dispensing and storage of study drug are provided in the pharmacy manual.

7.12. Drug Accountability

The investigator or designee must maintain adequate records showing the receipt, dispensing, return, or other disposition of the study drugs, including the date, quantity, batch or code number, and identification of patients (patient number) who received the study drugs. The investigator will not supply the study drug to any person except those named as sub-investigators on the Form FDA 1572, designated study personnel, and patients in this study. The accountability will be performed by separate unblinded monitors during the time that blinding is required.

Upon completion of the study, the study drugs (partly used, unused, and empty packaging) must be left in the original packaging and returned to the sponsor or designee for destruction, unless the sponsor makes other arrangements for local destruction.

8. STUDY PROCEDURES AND ASSESSMENTS

Patients must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Section 1.1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each patient. If a patient misses a study visit for any reason, the visit should be rescheduled as soon as possible.

8.1. Study Visits

Study assessments throughout the study should occur in-person at the study site. If a patient cannot attend a study site visit because of restrictions resulting from the novel coronavirus (COVID-19), phone visits may replace in-person site visits and should occur per protocol schedule and within the regular visit window when possible (see Section 8.1.1). Patients who cannot attend the Week 24 visit within the visit window because of restrictions resulting from COVID-19, will be encouraged to return to the site before Week 28 to complete the Week 24 visit assessments, if feasible. However, Injection 2 may only be administered within the allowed visit window.

8.1.1. Phone Visits

On the scheduled day of the phone visit, site staff shall contact the patient by phone and conduct all study procedures that do not require direct physical contact (e.g., laboratory tests, physical examinations, radiographs, etc.). Adverse event and concomitant medication review should occur as per usual procedure.

Patients with symptoms of potential adrenal insufficiency should be encouraged to visit the study site for a laboratory test. If the study site is closed for patient's visiting, the patient should be referred to a local laboratory, urgent care, primary care physician, or emergency room for testing and/or follow-up as appropriate.

Prior to the phone call, the site staff will activate visit date in the electronic data capture (EDC) system. Site staff should enable the Patient Diary Activation for the site visit in interactive response technology. Site staff will confirm with the patient that assessments have populated. If the daily diary is not functioning during the call, the site will need to manually document the patient's responses on paper assessments. Then contact their assigned CRA for instructions on how to enter responses into the EDC manually.

If the study site is closed, site staff will work from home calling patients and use the EDC website provided - https://login.imedidata.com/login. There is no change in username/password. The process for entering the date of visit is the same whether or not the user is working from the office. Site staff should remain in contact with the Principal Investigator and keep them aware of the patients' condition to ensure patient safety. The authorized investigator should be responsible for any medical judgment (when needed) and/or monitoring of potential symptom of adrenal insufficiency (local laboratory test for cortisol can be taken if it is medically urgent).

8.2. Study Duration

The planned sequence and maximum duration of the study periods for each patient will be as follows:

1. Screening period: up to 4 weeks
2. Injection 1 period: up to 24 weeks following the administration of Injection 1
3. Injection 2 period: up to 28 weeks following the administration of Injection 2

   Patients who do not receive Injection 2 will be followed for up to 52 weeks following the administration of Injection 1.

The maximum study duration for each patient is approximately up to 56 weeks.

8.3. Study Periods and Visits

8.3.1. Screening (Visit 1)

The patient must be screened within 28 days before enrollment in the study. The following procedures will be performed at Screening:

1. Obtain written informed consent.
2. Assess inclusion/exclusion criteria. Documented diagnosis of OA in the index knee can be completed as part of study screening.
3. Training and assessment of knowledge on pain ratings, allowable rescue medication, and entering data into the diary.
4. Ask patients to score their average pain in each knee over the previous 24 hours by NRS (diary) onsite.
5. Collect demographic information and medical history.
6. Measure vital signs (heart rate, respiratory rate, sitting blood pressure, and temperature) after the patient has been in a sitting position for 5 minutes.
7. Measure height and weight.
8. Perform a physical examination.
9. Perform a posterior-anterior X-ray radiograph for both knees in standing fixed-flexion (approximately 20 degrees), if applicable.
10. Perform 12-lead ECG after the patient has been supine for at least 5 minutes.
11. Collect blood samples (fasted state) for clinical chemistry, hematology, HbA1c, serology, and coagulation tests. If the patient is potentially eligible based on currently available data, except laboratory abnormalities, the assessments may be repeated once only to reassess eligibility.

13. Collect urine sample for urinalysis.

14. For women of childbearing potential, perform serum pregnancy test (β-hCG).
15. Perform drug screen and alcohol breath tests (onsite).
16. Dispense initial rescue medication. Rescue medication will be dispensed as needed at the subsequent visits.
17. Ask patients to score their average pain in each knee over the previous 24 hours by NRS every evening (diary) for at least 5 of the last 7 days of the screening period before returning to the study site for Visit 2 (Baseline, Day 1).
18. Ask patients to record their rescue medication use daily in the diary.
19. Record concomitant medications use.

8.3.2. Visit 2 (Baseline, Day 1, and Injection 1)

The following procedures will be performed at Visit 2 (Baseline Day 1):

1. Confirm inclusion/exclusion criteria,
2. Review demographics and medical history.
3. Measure vital signs (heart rate, respiratory rate, sitting blood pressure, and temperature) after the patient has been in a sitting position for 5 minutes.
4. For women of childbearing potential, perform urine pregnancy test before dosing.
5. Perform drug screen and alcohol breath tests (onsite).
6. Collect serum samples for measurement of cortisol and fasting glucose, before 9 AM and before study drug administration (Injection 1).
7. Review rescue medication use and the diary records. Rescue medication will be dispensed as needed.
8. Record concomitant medications use.
9. Record AEs.
10. Review training and assessment of knowledge on pain ratings, allowable rescue medication, and entering data into the diary.
11. Complete WOMAC.
13. After Steps 1 through 11 are completed, perform randomization for eligible patients.
14. Perform synovial fluid aspiration and administer study drug (Injection 1).
15. Investigator to assess patient for AEs after the injection.
16. Ask patients to score their average pain in the index knee for the previous 24 hours by NRS every evening.
17. Ask patients to record rescue medication use daily in the diary.

8.3.3. Follow-up Assessments

8.3.3.1. Visit 3 (Week 1) and Visit 4 (Week 2)

Patients will return to the study site at Week 1 (±3 days) and Week 2 (±3 days) after Injection 1 and have the following procedures performed.

1. Measure vital signs (heart rate, respiratory rate, sitting blood pressure, and temperature) after the patient has been in a sitting position for 5 minutes.
2. Collect serum sample for measurement of cortisol before 9 AM.
3. Review rescue medication use and the diary records. Rescue medication will be dispensed as needed.
4. Complete WOMAC.
5. Complete PGIC.
6. Record concomitant medications use.
7. Record AEs.
8. Ask patients to score their average pain in the index knee for the previous 24 hours by NRS every evening.
9. Ask patients to record their rescue medication use daily in the diary.

8.3.3.2. Visits 5 Through 9 (Every 4 Weeks from Week 4 Through Week 20)

Patients will return to the study site at Week 4 (±7 days) and every 4 weeks (±7 days) through Week 20 to have the following procedures performed:

1. Measure vital signs (heart rate, respiratory rate, sitting blood pressure, and temperature) after the patient has been in a sitting position for 5 minutes.
2. Collect blood samples for clinical chemistry, hematology, and HbA1c in a fasted state (Visit 7 only).
3. Collect serum sample for measurement of cortisol before 9 AM.
4. Review training and assessment of knowledge on pain ratings, allowable rescue medication, and entering data into the diary (Visit 7 or as needed).
5. Complete WOMAC.
6.
7. Complete PGIC.
8. Record concomitant medication use.
9. Record AEs.
10. Review rescue medication use and the diary records. Rescue medication will be dispensed as needed.

11. Ask patients to score their average pain in the index knee for the previous 24 hours by NRS every evening.
12. Ask patients to record their rescue medication use daily in the diary.

[redacted]

8.3.3.3. Visit 10 (Week 24 and Injection 2)

Patients who have completed through Week 24 and meet the Injection 2 criteria (Section 6.6.3) will receive a second injection of blinded study drug (see Section 7.2) at Week 24 (± 7 days). Patients who do not receive Injection 2 may remain in the study unless they choose to withdraw or are withdrawn from the study for other reasons.

The following procedures will be performed (Steps 1 through 17 should be completed before study drug administration):

1. Measure vital signs (heart rate, respiratory rate, sitting blood pressure, and temperature) after the patient has been in a sitting position for 5 minutes.
2. Perform physical examination.
3. Collect serum sample for measurement of cortisol before 9 AM.
4. Collect blood samples for clinical chemistry, hematology, and HbA1c in a fasted state.
5. Perform a posterior-anterior X-ray radiograph for both knees in standing fixed-flexion (approximately 20 degrees), as applicable. This may be performed within 14 days before this visit.
6. Perform 12-lead ECG after the patient has been supine for at least 5 minutes.
7. Collect urine sample for urinalysis.
8. For women of childbearing potential, perform urine pregnancy test (β-hCG) before dosing.
9. Perform drug screen and alcohol breath tests (onsite).
10. Review training and assessment knowledge on pain ratings, allowable rescue medication, and entering data into the diary.
11. Review rescue medication use and the diary records. Rescue medication will be dispensed as needed.
12. Record concomitant medications.
13. Record AEs.
14. Complete WOMAC.
15. [redacted]
16. Complete PGIC.
17. Confirm if the patient is disqualified from receiving Injection 2 (see Section 6.6.3).
18. Perform synovial fluid aspiration and administer study drug (Injection 2).

19. Investigator to assess patient for AEs after the injection.
20. Ask patients to score their average pain in the index knee for the previous 24 hours by NRS.
21. Ask patients to record their rescue medication use daily in the diary.

8.3.3.4. Visits 11 and 12 (Weeks 25 and 26) – Injection 2 Follow-up Assessments

Patients who receive Injection 2 will return to the clinic for Injection 2 follow-up assessments 1 week (±3 days) and 2 weeks (±3 days) after Injection 2. Patients who do not receive Injection 2 will continue with their follow-up assessments as described in Section 8.3.3.5.

1. Measure vital signs (heart rate, respiratory rate, sitting blood pressure, and temperature) after the patient has been in a sitting position for 5 minutes.
2. Collect serum sample for measurement of cortisol before 9 AM.
3. Review rescue medication use and the diary records. Rescue medication will be dispensed as needed.
4. Complete WOMAC.
5. Complete PGIC.
6. Record concomitant medications use.
7. Record AEs.
8. Ask patients to score their average pain in the index knee for the previous 24 hours by NRS every evening.
9. Ask patients to record their rescue medication use daily in the diary.

8.3.3.5. Visits 13 Through 18 (Every 4 Weeks from Week 28 Through Week 48)

Patients will return to the study site at Week 28 (±7 days) and every 4 weeks (±7 days) through Week 48 to have the following procedures performed:

1. Measure vital signs (heart rate, respiratory rate, sitting blood pressure, and temperature) after the patient has been in a sitting position for 5 minutes.
2. Perform 12-lead ECG after the patient has been supine for at least 5 minutes (Visit 18 only).
3. Collect serum sample for measurement of cortisol before 9 AM.
4. Collect blood samples for clinical chemistry, hematology, and HbA1c (Visits 15 and 18 only) in a fasted state.
5. Perform urinalysis (Visit 18 only).
6. Review rescue medication use and the diary records. Rescue medication will be dispensed as needed.
7. Review training and assessment of knowledge on pain ratings, allowable rescue medication, and entering data into the diary (Visit 15 or as needed).
8. Complete WOMAC.

9. [redacted]
10. Complete PGIC.
11. Record concomitant medications use.
12. Record AEs.
13. Ask patients to score their average pain in the index knee for the previous 24 hours by NRS every evening.
14. Ask patients to record their rescue medication use daily in the diary.

8.3.4. End of Study (Week 52) or Early Termination Visit

At Week 52 (EOS) or upon early termination of the study, the following procedures will be performed for all patients, if applicable:

1. Measure vital signs (heart rate, respiratory rate, sitting blood pressure, and temperature) after the patient has been in a sitting position for 5 minutes.
2. Perform physical examination.
3. Perform a posterior-anterior X-ray radiograph for both knees in standing fixed-flexion (approximately 20 degrees), as applicable. This may be performed within 14 days before this visit.
4. Perform 12-lead ECG after the patient has been supine for at least 5 minutes.
5. Collect blood samples for clinical chemistry, hematology, and HbA1c in fasted state.
6. For women of childbearing potential, perform urine pregnancy test (β-hCG).
7. Perform drug screen and alcohol breath tests (onsite).
8. Collect serum sample for measurement of cortisol before 9 AM.
9. Complete WOMAC.
10. [redacted]
11. Complete PGIC.
12. Review rescue medication use and the diary records.
13. Record concomitant medications.
14. Record AEs.

8.4. Assessments

8.4.1. Efficacy

8.4.1.1. Western Ontario & McMaster Universities Osteoarthritis Index (V3.1)

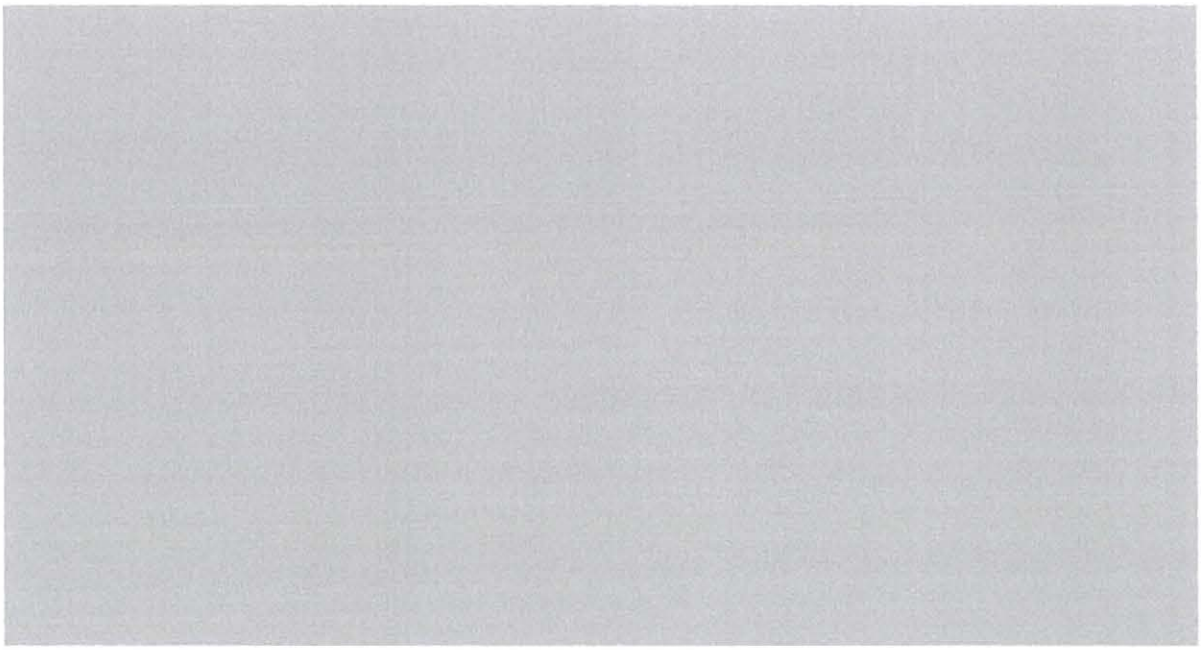
The WOMAC is a widely used, self-administered assessment used to measure pain, stiffness, and physical function in patients with OA. It is considered to be a reliable and valid instrument.[3,4,5] It comprises 24 questions, each on a 0-4 Likert scale (total score on a 0-96 scale) with assessment based on the previous 24 hours. The 3 sub-scale scores of Pain (5 items, total sub-scale score on a 0-20 scale), Stiffness (2 items, total sub-scale score on a 0-8 scale), and Difficulty Performing Daily Activities (Physical Function) (17 items, total sub-scale score on a 0-68 scale) are added together to determine the WOMAC Composite score. Composite and sub-scale scores of WOMAC will be normalized to a scale of 0-4 for analysis. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

The WOMAC is provided in Appendix C.

8.4.1.2. Patient Global Impression of Change

The PGIC is a self-administered instrument that measures patients' rating of overall improvement with treatment on a 7-point scale including "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

The PGIC assessment is provided in Appendix D.



8.4.1.4. Numeric Rating Scale

The NRS is an 11-point scale from 0 to 10. On this scale, 0 = no pain and 10 = the worst possible pain. The NRS will be assessed as the average pain over the last 24 hours.

Every evening, the patient will rate his or her knee pain intensity using the following question on a daily patient diary for the previous 24 hours: "On a scale from 0 to 10, where "zero" represents "no pain" and "10" represents "the worst possible pain," how would you rate the average pain that you have been feeling in your knee over the last 24 hours?"

8.4.1.5. Rescue Medication Use

Patients may take the rescue medication provided by the study site for pain of the index knee as needed, except within 24 hours before a planned study visit. Acetaminophen is provided as the only allowed rescue medication. The name and dosage regimen must be recorded in the patient diary with the indication of "rescue use" specified. The daily allowed acetaminophen dosage is up to 3 g/day.

8.4.2. Safety

Patient safety will be evaluated by physical examination, vital signs assessments (heart rate, respiratory rate, sitting blood pressure, and temperature), clinical laboratory assessments (hematology, chemistry, urinalysis), HbA1c, morning serum cortisol, 12-lead ECG, knee radiographs, concomitant medications/therapies, AEs, and signs and symptoms of adrenal insufficiency.

8.4.2.1. Clinical Laboratory Safety Assessments

8.4.2.1.1. Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (Section 1.1). Hematology, clinical chemistry, and HbA1c will be collected in a fasted state.

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count (or estimate), white blood cell count including differential
Clinical Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid
Coagulation Panel	prothrombin time (PT), international normalized ratio (INR)
Serum Cortisol	morning cortisol should be before 9 AM
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones, nitrite, leukocyte esterase

Serology:	human immunodeficiency virus (HIV) anti-body, hepatitis B surface antigen, HCV anti-body
Urine Drug Screen:	amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol. The panel also includes methadone, oxycodone, methamphetamine, and ecstasy per the standard kit
Pregnancy Test Urine/serum (β-hCG)	for women of childbearing potential only
HbA1c	hemoglobin A1c
Alcohol breath test	Estimated measurement of blood alcohol content

Blood and urine samples for hematology, clinical chemistry, urinalysis, and serum pregnancy tests (β-hCG), serum cortisol, and coagulation panel will be sent to a central laboratory for analysis. Urine pregnancy test, urine drug screen, and breath test will be performed at the study site. Serology will also include a confirmation test for all positive HIV, HBV, and HCV test results.

Central laboratory morning serum cortisol results will be blinded to the patient, site staff, and blinded study team members (except Screening, Day 1 [pre-dose], and Week 20); results will be available to a separate unblinded medical monitor. Monitoring of cortisol values and management of potential signs and symptoms of adrenal insufficiency are discussed in greater detail in Section 9.3.1.1.

8.4.2.1.2. Specimen Handling Requirements

Standard operating procedures at the study sites will be followed for sample handling.

8.4.2.1.3. Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to TLC before the beginning of the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically significant. The investigator must evaluate the out-of-range values.

All clinical laboratory values that in the investigator's opinion show clinically significant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 9.2.

All measurements described in this section are recognized standard methods.

8.4.2.2. Clinical Examinations

8.4.2.2.1. Vital Signs

Vital signs (heart rate, respiratory rate, sitting blood pressure, and temperature) will be measured after the patient has been in a sitting position for 5 minutes.

Height and weight will be measured at Screening only.

8.4.2.2.2. Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the patient has been supine for at least 5 minutes. All ECG recordings will be identified with the patient number, date, and time of the recording and recorded in the patient's eCRF.

8.4.2.2.3. Physical Examination

The following physical examination will be performed at the time points indicated in the schedule of events (Section 1.1):

- General Appearance
- Head/Face
- Eyes/Fundoscopy
- Ears/Hearing
- Nose
- Mouth, Teeth, and Throat
- Neck and Thyroid
- Chest/Lungs
- Abdomen
- Skin, Hair, and Nails
- Musculoskeletal: Extremities, Spine
- Vascular/Circulatory
- Lymphatic
- Psychiatric/Behavior
- Brief neurologic

8.4.2.2.4. Knee Radiographs

A posterior-anterior X-ray radiograph will be performed for both knees (as applicable) in standing fixed-flexion (approximately 20 degrees) at the time points indicated in the schedule of events (Section 1.1). Minimum joint space width (in unit of millimeter) in the standing fixed-flexion anteroposterior view will be measured and recorded for analysis. Presence or absence of subchondral bone changes, osteonecrosis, and insufficiency fracture will be assessed.

9. ADVERSE EVENTS

9.1. Definitions

9.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

9.1.2. Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  An elective hospital admission to treat a condition present before exposure to the study drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE. However, a newly diagnosed pregnancy in a patient that has received a study drug is not considered an SAE unless it is suspected that the study drug(s) interacted with a contraceptive method and led to the pregnancy.
- Is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse.

9.1.3. Treatment-emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening at the time of or following the start of treatment with study drug through the Follow-up Visit or ET, whichever occurs first.

9.2. Event Assessment and Follow-up of Adverse Events

Any AE will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by a known cause (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the patient's medical record and recorded on the eCRF page.

9.2.1. Collection

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the patient will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as the following:

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations (including laboratory abnormalities) made during the visit will also be considered AEs. All AEs observed by the study personnel or reported by the patient during the study (after the patient has signed the ICF through the EOS/ET visit) will be documented.

9.2.2. Evaluation

9.2.2.1. Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria.

9.2.2.2. Seriousness

The investigator is to evaluate whether the AE meets serious criteria.

9.2.2.3. Action(s) Taken

Action taken may consist of the following:

Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.
Other action taken	Specify other action taken.

9.2.2.4. Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than 1 AE is judged to be possibly related to the patient's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

9.2.2.5. Adverse Event Relationship to Study Drug

The investigator must make an assessment of each AE's relationship to the study drug. The categories for classifying the investigator's opinion of the relationship are as follows:

Not related	An AE with sufficient evidence to accept that there is no causal relationship to study drug administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.)
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable, and in which other drugs, events, or underlying disease provide plausible explanations.
Possibly related	An AE with a reasonable time sequence to administration of the study drug, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.

Probably related	An AE with evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
Definitely related	An AE occurring in a plausible time relationship to study drug administration and that cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (de-challenge) is clinically reasonable.

9.2.3. Documentation

All AEs that occur within the period of AE follow-up for the study must be documented in the eCRF with the following information, where appropriate. (The AE follow-up period for the study is described in Section 9.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the study drug(s)
- Whether it is an AE of special interest (AESI) and whether it is an AE which is a potential symptom or sign of adrenal insufficiency (AEAI) (see Section 9.3.1)

9.2.4. Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. The decision about whether the patient may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a patient that are not tolerable, the investigator must decide whether to stop the patient's involvement in the study and/or treat the patient. Special procedures may be recommended for the specific study drug, such as the collection of a serum sample for determining blood concentrations of study drug, specific tapering procedures, or treatment regimens, as appropriate.

For double- or triple-blinded studies, it is not necessary to unblind a patient's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 7.7 for a description of the unblinding procedures.

9.2.5. Reporting

9.2.5.1. Serious Adverse Events

Any SAE must be reported by the investigator if it occurs during the clinical study or within 30 days of receiving the study drug, whether or not the SAE is considered to be related to the investigational product. A copy of SAE forms and supporting documents must be emailed within 24 hours to the attention of the safety officer at:

[redacted]

At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Patient's study number
- Patient's year of birth
- Patient's gender
- Date of first dose of study drug(s)
- Date of last dose of study drug(s), if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to study drug(s) ("Is there a reasonable possibility that the study drug caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the patient's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, AE, date of occurrence, patient identification, study identification, study drug, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by [redacted] using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidance) regarding the notification of his or her health authorities, institutional review board (IRB)/independent ethics committee (IEC), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his or her country. The study monitor may be able to assist with this.

9.3. Special Considerations

9.3.1. Adverse Events of Special Interest

and patients should be closely monitored should these AEs occur.

These events will be followed closely during the study and considered AESIs.

9.3.1.1. Potential for Adrenal Suppression

Transient cortisol reduction is a well described physiologic response in patients who receive IA cortisol injections and should not necessarily be considered an AE. Laboratory evidence of adrenal insufficiency should be assessed in conjunction with clinical signs and symptoms.

Patients and investigators will be educated about symptoms of adrenal insufficiency, and an assessment of clinical signs and symptoms indicating potential adrenal insufficiency will be performed as part of AE evaluation at every visit or contact.

Patients will be provided a wallet card identifying the potential risk for adrenal insufficiency and asked to carry it at all times. This card should include the patient's identifying information, contact information for the investigator, and should note the potential need for emergency glucocorticoid therapy in the setting of shock, surgery, etc.

Morning serum cortisol as measured by the central laboratory will be blinded to the patient, site staff, and blinded study team members (except Screening, Day 1 [pre-dose], and Week 20); results will be reviewed by a separate unblinded medical monitor.

If there is clinical evidence of adrenal insufficiency that may compromise the patient's safety, the investigator should use a local laboratory to obtain a cortisol level or and/or refer the patient to his or her primary care physician or to an endocrinologist. The investigator may also contact the blinded medical monitor to discuss the patient's case and request review of prior cortisol values.

The unblinded medical monitor will monitor all serum cortisol values. If sustained cortisol suppression is observed beyond 4 weeks following an injection, or any other cortisol values are seen that might appear to compromise patient safety, the unblinded medical monitor may contact

the investigator to review the patient's condition including any potential signs or symptoms of adrenal insufficiency and discuss potential follow-up laboratory testing.

9.3.2. Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation.

Women of childbearing potential must use a highly effective method of birth control until at least 6 months after the last dose of study drug. Acceptable and effective methods of birth control for this study include:

- Absolute sexual abstinence (no sexual intercourse or genital contact with a male partner)
- Monogamous partner who is vasectomized
- Use of double-barrier contraception
- Use of an approved insertable, injectable, transdermal, or combination oral contraceptive for greater than 2 months prior to Screening.

Pregnancy testing will be conducted before administration of the study drug on every woman of childbearing potential. A woman who is found to be pregnant at Screening will be excluded from the study and considered to be a screening failure.

After participation in the study, women should be asked to contact the investigator or study staff immediately if pregnancy occurs or is suspected. The investigator is responsible for following the pregnancy until delivery or termination.

10. DATA SAFETY MONITORING BOARD

A data safety monitoring board will not be used in this study.

11. STATISTICS

11.1. Study Endpoints

11.1.1. Efficacy Endpoints

11.1.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is:

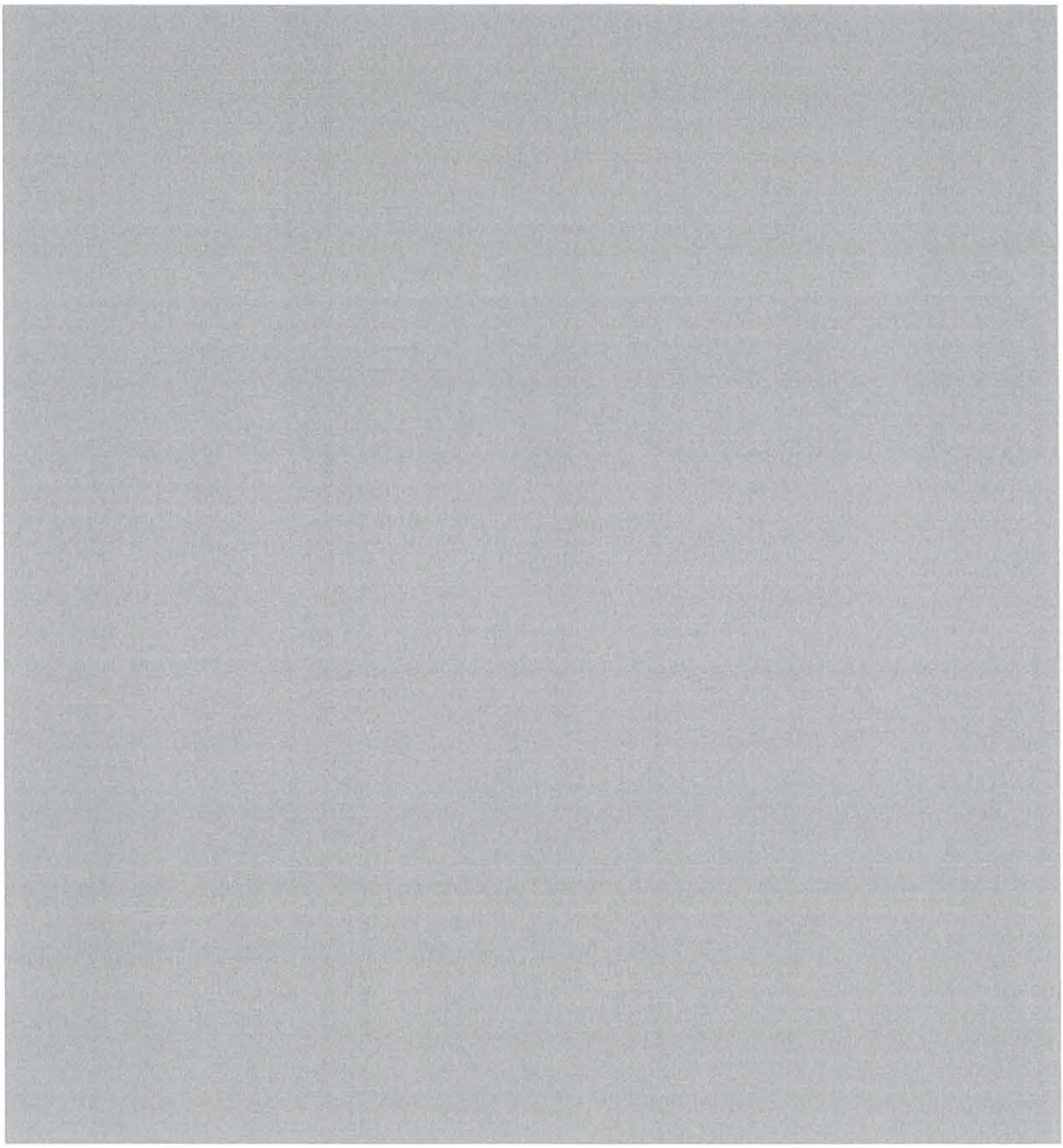
- Change from Baseline in WOMAC Pain at Week 12 (Group A vs. Group C)

11.1.1.2. Secondary Efficacy Endpoints

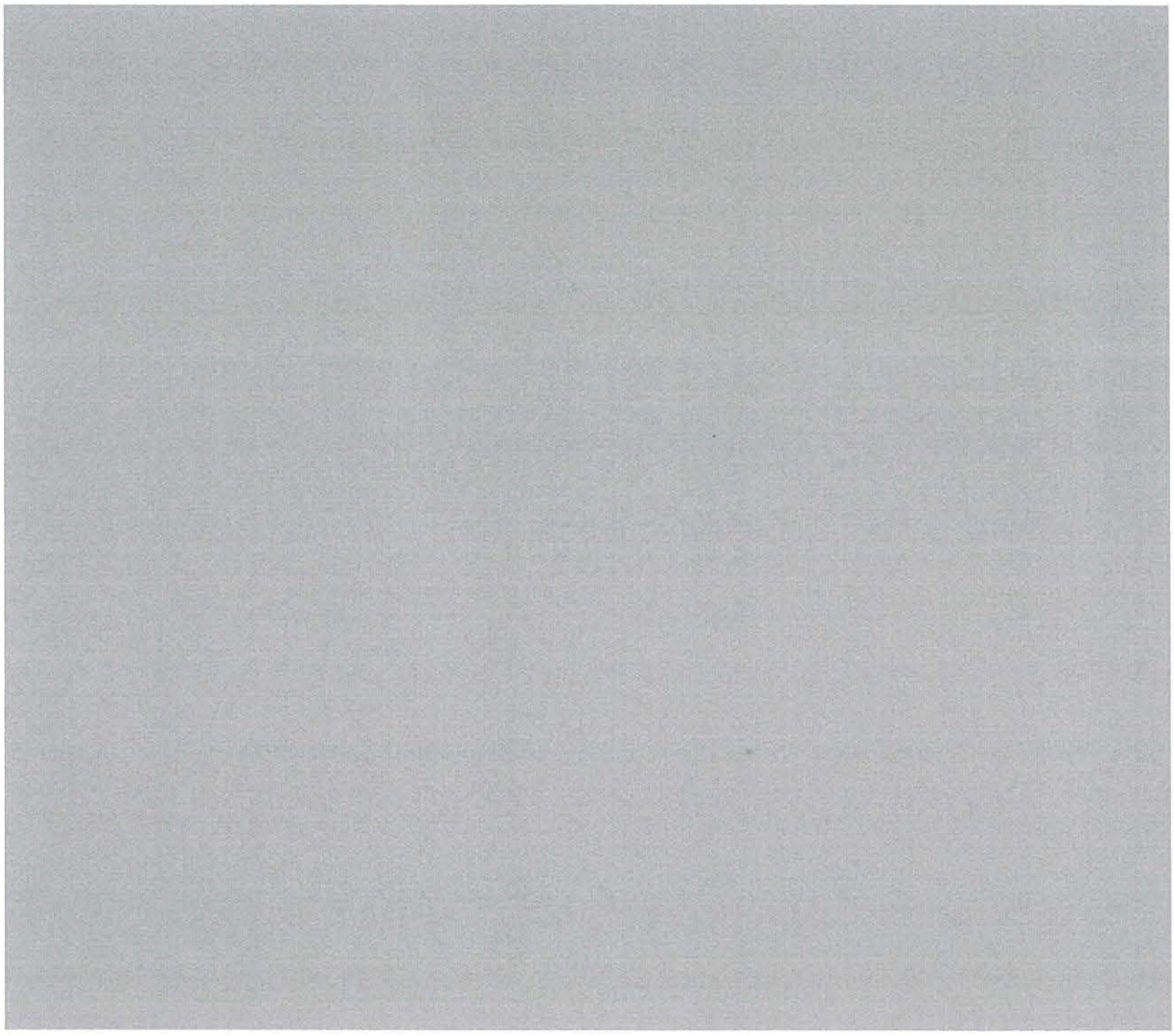
The following key secondary efficacy endpoints will be evaluated in a hierarchical sequence:

1. Change from Baseline in WOMAC Pain at Week 16 (Group A vs. Group C)
2. Change from Baseline in WOMAC Pain at Week 20 (Group A vs. Group C)
3. Change from Baseline in WOMAC Pain at Week 24 (Group A vs. Group C)
4. Change from Baseline in WOMAC Pain at Week 36 (Group A vs. Group C)
5. Change from Baseline in WOMAC Function at Week 12 (Group A vs. Group C)
6. PGIC at Week 12 (Group A vs. Group C)
7. Total rescue acetaminophen consumption through Week 12 (Group A vs. Group C)
8. Durable responder with ≥30% decrease in WOMAC Pain from Baseline for Weeks 4 through 12 (Group A vs. Group C)
9. Change from Baseline in WOMAC Function at Week 36 (Group A vs. Group C)
10. PGIC at Week 36 (Group A vs. Group C)
11. Change from Baseline in WOMAC Pain at Week 12 (Group A vs. Group B)
12. Change from Baseline in WOMAC Pain at Week 52 (Group A vs. Group C)

11.1.2. Additional Endpoints



- Absolute value, change, and percent change from Injection 1 Baseline at each week in average daily pain in the index knee
- Total and average daily consumption of rescue acetaminophen by week



11.2. Analysis Populations

The following analysis populations are planned for this study:

Safety Population (SAF): The Safety Population includes all patients who receive any dose of study drug; the population will be determined for each study period. Injection 1 Period reporting will require that Injection 1 has been received; Injection 2 Period reporting will require that Injection 2 has been received. The SAF population will be the primary population for safety evaluation.

Full Analysis Set (FAS): The FAS includes all randomized patients who receive Injection 1. The FAS population will be the primary population for efficacy analysis, as well as for descriptive summaries other than safety (demographic and baseline, disposition, protocol deviation, medical history, etc.).

Per Protocol Population (PP): The PP Population includes all patients who receive 2 doses of study drug, have primary efficacy evaluation at Weeks 12, 24, and 36, and do not have important protocol deviations affecting primary efficacy evaluation.

Modified Per Protocol (mPP): The mPP Population includes all patients who receive the first dose of study drug, have primary efficacy evaluation at Weeks 12 and 24, and do not have important protocol deviations affecting primary efficacy evaluation.

The **PP** and **mPP** populations will be used for supportive analysis of selected efficacy endpoints. For the PP population, patients must have a valid WOMAC Pain assessment at Baseline, Week 12, Week 24, and Week 36; for the mPP population, patients must have a valid WOMAC Pain assessment at Baseline, Week 12, and Week 24. (A valid assessment is within the analysis visit window and not excluded due to an intercurrent event as described in Section 11.3.3.1).

Important protocol deviations are determined in accordance with the protocol deviation guidance plan. Membership in the PP and mPP analysis populations will be determined after blinded data review of important protocol deviations affecting primary efficacy evaluation before database lock and study unblinding.

If a patient is randomized incorrectly or is administered the incorrect study drug, analyses of the FAS population will be based on the assigned treatment, whereas analyses of all other populations will be based on the actual treatment received.

11.3. Statistical Analyses

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written before database lock.

Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a P value of ≤ 0.05 will be considered statistically significant. All other P values from key secondary endpoints, after a non-significant P value is reached as well as other additional endpoints, will be considered exploratory.

Summary statistics will be provided for the variables described in the following subsections. Continuous variable summaries will include the number of patients, mean, standard deviation (SD), first quartile, median, third quartile, minimum, and maximum. Categorical variables will include the frequency and percentage of patients in each category.

11.3.1. Study Patients and Demographics

11.3.1.1. Disposition and Withdrawals

The numbers of patients screened, failed screening, randomized, receiving Injection 1 or 2, completing, and withdrawing, along with reasons for withdrawal and timing of withdrawal, will be tabulated overall and by treatment group. Reasons for not receiving Injection 2 will also be tabulated. The number of patients in each analysis population will be reported.

11.3.1.2. Protocol Deviations

Protocol deviations will be identified and important deviations will be classified before unblinding and will be summarized or listed as appropriate. Important protocol deviations affecting primary efficacy evaluation will be used to assess patient inclusion into PP and mPP populations.

11.3.1.3. Demographics and Other Baseline Characteristics

These analyses will be conducted for all analysis populations.

Demographic variables will include age, sex, race, weight, BMI, and region. Baseline patient characteristics will include medical history, including confirmation of OA diagnosis and time since diagnosis, Kellgren-Lawrence Grade, normalized WOMAC scores, and average daily pain.

11.3.2. Exposure and Compliance

All patients will receive up to 2 study drug injections at the study site under the surveillance of appropriate study personnel and, therefore, no compliance will be calculated. Injection procedure details and study drug batch or lot number(s) will be recorded in the patient's EDC system and summarized or listed as appropriate.

11.3.3. Efficacy Analysis

Efficacy variables will be summarized by treatment group and by injection period within each group using the FAS population, unless otherwise specified. For all the continuous variables, the normalized numbers will be used for analysis, where applicable, unless otherwise specified.

The overall type I error rate will be controlled for primary and key secondary endpoints using hierarchical testing, based on a fixed-sequence procedure.

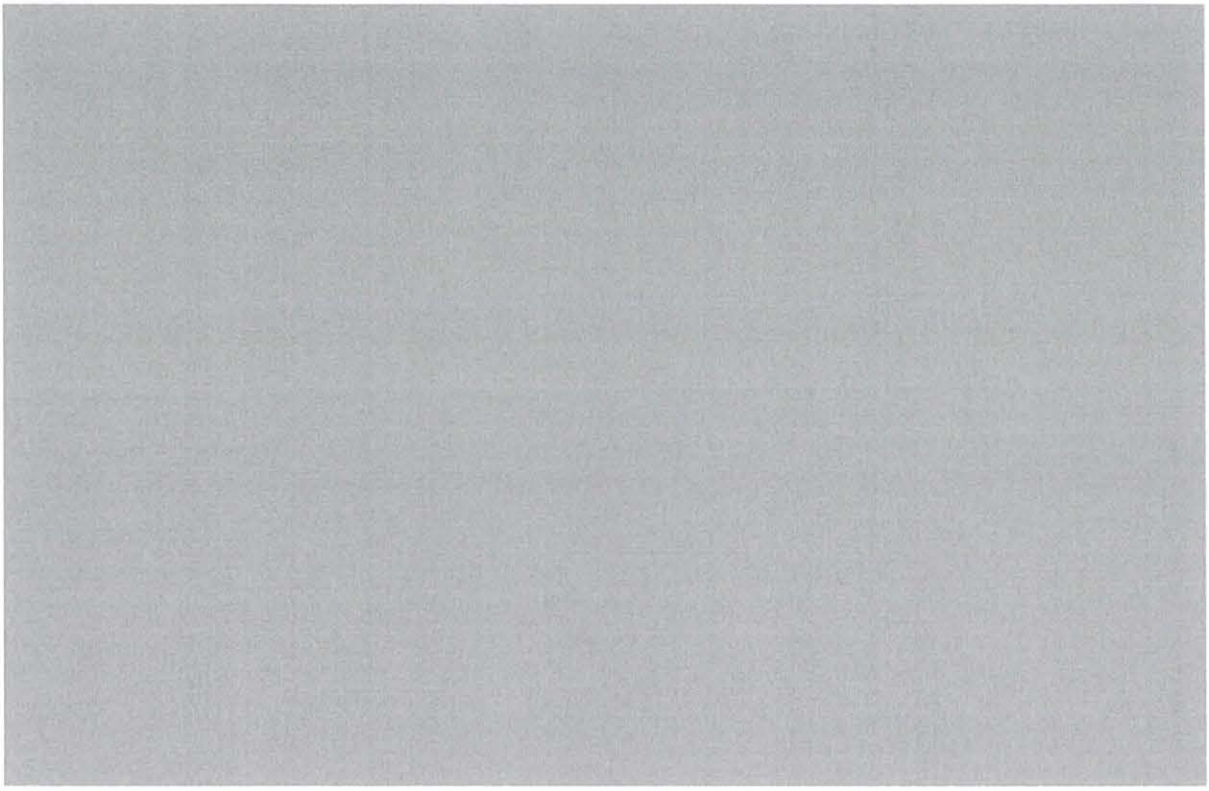
If statistical significance is declared for the primary analysis, formal statistical inference will continue at the 0.05 level for the secondary endpoints in the defined sequence until a non-significant result is reached. All other P values from key secondary endpoints, after a non-significant P value is reached, as well as other additional endpoints, will be considered exploratory.

11.3.3.1. Primary Analysis

The primary efficacy analysis and estimation of the primary estimand will be based on the FAS population, the mPP population, and the PP population.

The primary estimand is the difference in mean change from Baseline in WOMAC Pain score at Week 12 between TLC599 vs. Placebo (as defined in the Treatment Assignment Table in Section 7.2). The endpoint and intercurrent events for the primary estimand are defined as follows:

- Endpoint: Change from Baseline in WOMAC Pain score at Week 12
- Intercurrent Events:



An ANCOVA will be performed with treatment group as a fixed effect and Baseline WOMAC Pain score as a covariate. Multiple imputation will be used to impute missing intermittent and post-withdrawal WOMAC Pain scores considered to be missing at random. Post-withdrawal missing data due to lack of efficacy, AE, or surgical procedure/IA drug administration in the index knee will be assumed to be MNAR; all other missing and post-withdrawal data will be assumed to be MAR.

The ANCOVA model will be conducted on each imputation and the results will be combined using Rubin's rules in SAS PROC MIANALYZE.

The least-squares mean comparing TLC599 to Placebo along with the corresponding 95% confidence interval, will be used to estimate the treatment difference.

Sensitivity analyses will be conducted to estimate sensitivity estimators and to assess the robustness of efficacy results, including:

- A sensitivity analysis using a tipping point procedure to assess the robustness of the multiple imputation results.
- A mixed-effects model repeated measures (MMRM) approach will be used as a sensitivity analysis for the primary endpoint. Treatment group, study visit (as a categorical variable) and

site will be modeled as fixed effects, with a treatment-by-visit interaction and baseline WOMAC Pain score as a covariate. Patient will be included as a random effect. Prior to implementing the model, MNAR data due to intercurrent events will be imputed using BOCF and non-missing data affected by the use of intercurrent medications and procedures will be replaced using BOCF, as described for the primary analysis method. The MMRM will include both observed and BOCF imputed data.

If further sensitivity analysis on the primary endpoint is performed, it will be described in the SAP. Descriptive summaries (such as mean, standard error, first quartile, median, third quartile, minimum, and maximum) will also be provided for the primary endpoint.

11.3.3.2. Secondary Analyses

Continuous secondary endpoints will be analyzed using the same methodology as for the primary endpoint, unless otherwise indicated.

For analysis of categorical secondary endpoints, the difference in the predictive marginal proportions will be the basis of comparison between treatment groups. The corresponding 95% CI and P value will also be presented.

11.3.3.3. Exploratory Analyses

For additional endpoints derived using the baseline prior to Injection 1, descriptive statistics for each variable will be presented for each visit until the end of study and summarized by treatment group and by injection period within each group. For additional endpoints derived using the baseline prior to Injection 2, descriptive statistics for each variable will be presented by treatment group. Efficacy endpoints relative to Injection 2 baseline will only be analyzed for patients who receive Injection 2.

The analysis of all continuous additional endpoints will be performed using an ANCOVA model as described for the single-dose primary endpoint.

Categorical exploratory endpoints will be analyzed using the same methodology as the categorical secondary endpoints.

P values from additional endpoints will be considered nominal and no adjustments for multiplicity will be made.

Subgroup analyses of the primary and secondary endpoints will be performed by age (<65 or ≥65 years), sex, race (Caucasian or non-Caucasian), and Kellgren-Lawrence grade (2 or 3). Further details will be provided in the SAP.

Mean value, mean change, and percent change from baseline in WOMAC Pain and weekly average daily pain will be plotted over time.

A cumulative distribution plot of percent change in WOMAC Pain by treatment group will be produced for each time point from Injection 1 Baseline through Week 52 Patients who discontinue treatment are defined as non-responders with 0% improvement (no change from Baseline).

11.3.4. Safety and Tolerability Analyses

Safety analyses will be conducted using data from the SAF population (as defined in Section 11.2). Safety variables include physical examination, vital signs assessments (heart rate, respiratory rate, sitting blood pressure, and temperature), clinical laboratory assessments (hematology, chemistry, urinalysis), HbA1c, morning serum cortisol, [redacted] 12-lead electrocardiogram (ECG), knee radiographs, concomitant medications/therapies, AEs, and signs and symptoms of adrenal insufficiency. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medication will be coded using the World Health Organization Drug (WHODrug) Global Dictionary.

The safety data will be descriptively summarized by treatment group within each injection period.

The safety profile following the first and second injections will be evaluated through the examination of the following comparisons:

1. Group A versus Group B for safety data collected following Injection 2.
2. Safety data in Group A, collected following Injection 1 versus Injection 2.

Continuous safety data will be summarized by visit and include changes from baseline (Injection 1 and/or Injection 2 Baseline). Continuous data will also be converted to categorical values where possible (i.e., below, within, and above normal ranges) and summarized in shift from baseline tables. Categorical safety data collected by visit will be summarized showing the counts and percentages in each category at each visit, as well as shifts from baseline as appropriate.

11.3.4.1. Adverse Events

The Medical Dictionary for Regulatory Activities terminology will be used to classify all AEs with respect to system organ class (SOC) and PT.

Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with study drug through EOS or ET, whichever occurs first.

The number and percentage of patients with AEs will be displayed for each treatment group by SOC and PT. Summaries of AEs by severity and relationship to study drug will also be provided. Serious AEs and AEs resulting in discontinuation of study drug will be summarized separately in a similar manner. Patient listings of AEs, SAEs and AEs causing discontinuation of study drug will be produced.

11.3.4.2. Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, first quartile, median, third quartile, minimum, and maximum) of actual (absolute) values and changes from Baseline values and GeoMean percentage change (if appropriate) will be presented for clinical laboratory values by treatment group and time point.

The number of patients with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from Baseline (shift tables) for each clinical laboratory analyte by treatment group and by time point. Pre- and post-treatment values will also be presented with analysis summary of mean changes from Baseline.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with the corresponding normal ranges.

11.3.4.3. Vital Signs

Vital sign parameters will be summarized using descriptive statistics at Baseline and at each post-Baseline time point. Vital signs will be tabulated showing change from Baseline (shift tables) for each parameter by treatment group and by time point. Pre- and post-treatment values may also be presented with a summary of mean changes from Baseline.

11.3.4.4. Twelve-lead Electrocardiograms

The number and percentage of patients with normal and abnormal ECG findings will be summarized by treatment group and time point. Summary statistics will be displayed by treatment group for QT and QT interval corrected for heart rate (QTc) calculated using Bazett's and Fridericia's QT correction methods.

Descriptive summaries (mean, SD, first quartile, median, third quartile, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTc interval (both correction methods), and heart rate by treatment group and time point.

11.3.4.5. Physical Examination Findings

The number and percentage of patients with normal and abnormal findings in the complete physical examination will be displayed by each treatment group.

11.3.4.6. Knee Radiographs

The change in joint space width from baseline will be summarized descriptively. The number of patients with presence of subchondral bone changes or osteonecrosis/insufficiency fracture will be summarized.

11.3.4.7. Concomitant Medications

The number and percentage of patients with incidence of concomitant medications (other than acetaminophen) used as a rescue medication as determined by an indication for index knee pain will be summarized by treatment group.

11.3.5. Interim Analysis

An interim analysis will not be performed.

11.4. Sample Size Determination

This is a 3-arm parallel-group randomized controlled study. Approximately 500 patients will be

According to these assumptions, 500 patients will be randomly assigned in a 2:1:1 ratio to ensure that the study is well powered for primary and key secondary endpoints to be tested via the fixed-sequence testing method.

12. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

12.1. Sponsor and Investigator Responsibilities

12.1.1. Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 14).

Taiwan Liposome Company, Ltd. agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

12.1.2. Investigator Responsibilities

By signing the Investigator's Agreement (Section 16.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The trial will be conducted in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable US Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the IND sponsor, and funding agency; and documented approval from the IRB/IEC, except where necessary to eliminate an immediate hazard(s) to trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the study drug(s), and their specific duties within the context of the study. Investigators are responsible for providing TLC with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

12.1.3. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples, in addition to clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/IEC, regulatory agencies, or pharmaceutical company supplying study drug may inspect all documents

and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be stored securely at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored a . This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by staff will be secured and password-protected. At the end of the study, all study databases will be de-identified and archived at

12.2. Site Initiation

Study personnel may not screen or enroll patients into the study until receiving notification from the sponsor or designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory/GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting or received proper training for the study.

12.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention.

Patients who fail inclusion and/or exclusion criteria may be rescreened for the study with approval of the medical monitor. Also, patients may only be rescreened once. Individuals who do not meet the criteria for participation in this study (screen failure) because of a laboratory test finding or insufficient washout of previously administered prohibited medications or mild infectious illness present at Screening or Baseline may be rescreened following confirmation with the medical monitor.

Patients who initially do not meet any of the following inclusion/exclusion criteria may not be rescreened:

- Patients who fail to meet screening morning serum cortisol (cortisol value <5 µg/dL)
-
- Patients who do not meet X-ray Kellgren-Lawrence grade criteria
- Patients who do not meet criteria related to knee pain

For rescreening, a repeat X-ray is not needed if one was completed within 6 months of the rescreen date through the Central Imaging Vendor for this study, and as long as the X-ray met eligibility requirements and site has received approval from the medical monitor to rescreen. Documented diagnosis of OA in the index knee can be completed as part of the initial study screening and does not need to be repeated.

If a patient is eligible to enter the study after having previously failed Screening, the patient will be assigned a new patient identification number.

12.4. Study Documents

All documentation and material provided by TLC for this study are to be retained in a secure location and treated as confidential material.

12.4.1. Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant. Written documentation of informed consent is required before starting intervention/administering study intervention.

Consent forms will be IRB/IEC-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions before signing. The participant will sign the informed consent document before any procedures being done specifically for the study.

12.4.2. Case Report Forms

By signing the Investigator's Agreement (Section 16.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all patients who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual patient visits should be completed as soon as possible after the visit. All requested information must be entered in the eCRF/EDC system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a sub-investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

12.4.3. Source Documents

Information recorded in the eCRF/EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be transferred electronically from the central laboratory to the sponsor or designee. A paper copy of laboratory results will be provided to the study site and should be retained with each patient's source data.

12.5. Data Quality Control

TLC and its designees will perform quality control checks on this clinical study.

12.5.1. Monitoring Procedures

TLC and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized TLC personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review the following:

- Regulatory documents, directly comparing entries in the eCRF/EDC system with the source documents
- Consenting procedures
- AE procedures
- Storage and unblinded monitoring for accountability of study drug and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 16.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow TLC or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

12.5.2. Data Management

TLC or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and [redacted] standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated eCRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

12.5.3. Quality Assurance/Audit

This study will be subject to audit by TLC or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- Site audits
- Trial Master File audits
- Database audits
- Document audits (e.g., protocol and/or clinical study report [CSR])

TLC or its designee may conduct additional audits on a selection of study sites, requiring access to patient notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify TLC immediately.

12.6. Study Termination

The study may be terminated at the discretion of TLC at any time and for any reason.

The end of this study is defined as the date of the last visit of the last patient (last patient out or last patient last visit) participating in the study. Within 90 days of the end of the clinical study, TLC or designee will notify the IRBs/IECs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

12.6.1. Premature Study Termination

The study may be suspended temporarily or terminated prematurely is there is sufficient reasonable cause at any time by TLC, IRBs/IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, TLC or its designee will notify the IRBs/IECs and regulatory authorities about the premature termination as required according to national laws and regulations. TLC or its designee must clearly explain the reasons for premature termination.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

- Determination of futility

If the study is terminated prematurely, all investigators must inform their patients and take appropriate follow-up measures to ensure protection of the patients' interests. Study sites may be asked to have all patients currently participating in the study complete all of the assessments for the ET visit.

12.7. Study Site Closure

At the end of the study, all study sites will be closed. TLC may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Non-compliance with the protocol and/or applicable regulations and guidelines
- Inadequate patient enrollment

12.7.1. Record Retention

After completing the study, TLC will receive the original eCRFs or at least a legible copy and retain the documents for at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the patient identification codes, patient files and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

12.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of TLC. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

12.9. Use of Information and Publication

All information concerning TLC599, TLC's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by TLC or designee to the investigator, and not previously published, is considered confidential and remains the sole property of TLC. Case report forms also remain the property of TLC. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by TLC in connection with the continued development of TLC599 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of TLC. Publication or other public presentation of TLC599 data resulting from this study requires prior review and written approval of TLC. Abstracts, manuscripts, and presentation materials should be provided to TLC for review and approval at least 30 days before the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until TLC has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

13. FINAL CLINICAL STUDY REPORT

TLC will retain ownership of the data.

The final CSR may be submitted to the regulatory authorities.

14. ETHICAL AND LEGAL CONSIDERATIONS

14.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the countries in which the study is conducted, and with the Commission Directives 2001/20/Ethics Committee (EC) and 2005/28/EC.

14.2. Patient Information and Informed Consent and/or Assent

A properly constituted, valid IRB/IEC must review and approve the protocol, the investigator's ICF, and related patient information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

14.3. Approval by Institutional Review Board and Independent Ethics Committee

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's monitor before shipment of study drug supplies and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed IRB/IEC approval form containing the same information.

Until the investigator has received written approval by the IRB/IEC, no patient may undergo any procedure not part of routine care for the patient's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by TLC before implementation. This written approval will consist of a completed IRB/IEC approval form containing the same information.

14.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

15. REFERENCES

1. Jüni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev. 2015 Oct 22;(10):CD005328.
2. Pekarek B, Osher L, Buck S, Bowen M. Intra-articular corticosteroid injections: a critical literature review with up-to-date findings. Foot (Edinb). 2011 Jun;21 (2):66-70.
3. Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. Semin Arthritis Rheum. 1989;18:14 17.
4. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation. 2006;113(12):1578 1587.
5. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15:1833 1840.

16. ATTACHMENTS

16.1. Investigator's Agreement

PROTOCOL NUMBER: TLC599A3005

PROTOCOL TITLE: A Phase 3, Randomized, Double-blind, Placebo- and Active-controlled Study to Evaluate the Efficacy and Safety of TLC599 in Patients with Osteoarthritis of the Knee

PROTOCOL VERSION: Amendment 4, Version 5.0 (09-Mar-2022)

The undersigned acknowledges possession of and has read the investigator's brochure on the study drug and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the study drug to selected patients in his or her care, according to the study protocol.

He or she agrees to use the study material, including the study drug, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Taiwan Liposome Company, Ltd.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to Taiwan Liposome Company, Ltd. within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of the study drug.

He or she agrees to comply with Taiwan Liposome Company, Ltd. and regulatory requirements for the monitoring and auditing of this study.

In addition, he or she agrees that the study will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name:

_____

Signature:

_____

Date:

_____

Investigator's name and address (stamp)

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APPENDICES

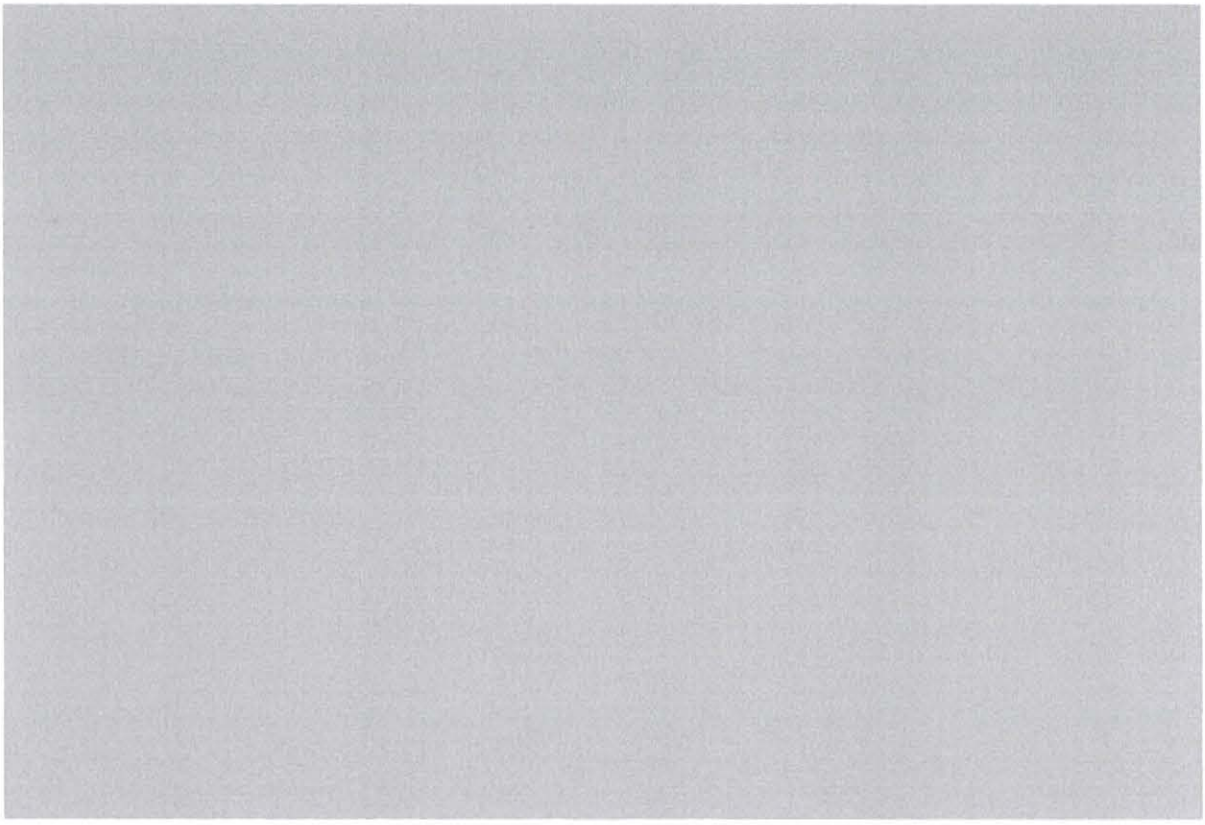
A. American College of Rheumatology (ACR) Classification Criteria for Osteoarthritis of the Knee

B. Kellgren and Lawrence System for Classification of Osteoarthritis of Knee

C. WOMAC Osteoarthritis Index Version VA3.1

D. Patient Global Impression of Change (PGIC) Assessment

A. American College of Rheumatology Classification Criteria for Osteoarthritis of the Knee



Adapted from R. Altman, E. Asch, D. Bloch, G. Bole, D. Borenstein, K. Brandt, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039-1049.

B. Kellgren and Lawrence System for Classification of Osteoarthritis of the Knee

The Kellgren and Lawrence system is a method of classifying the severity of knee osteoarthritis (OA) using 5 grades:

Grade 0: No radiographic features of OA are present

Grade 1: Doubtful joint space narrowing (JSN) and possible osteophytic lipping

Grade 2: Definite osteophytes and possible JSN on posteroanterior weight-bearing radiograph

Grade 3: Multiple osteophytes, definite JSN, sclerosis, possible bony deformity

Grade 4: Large osteophytes, marked JSN, severe sclerosis and definite bony deformity

C. WOMAC Osteoarthritis Index Version V3.1

INSTRUCTIONS TO PATIENTS

In Sections A, B, and C questions are asked in the following format. Please mark your answers by putting an " ✗ " in one of the boxes.

EXAMPLES:

1. If you put your " ✗ " in the box on the far left as shown below,

none	mild	moderate	severe	extreme
☒	☐	☐	☐	☐

then you are indicating that you feel **no** pain.

2. If you put your " ✗ " in the box on the far right as shown below,

none	mild	moderate	severe	extreme
☐	☐	☐	☐	☒

then you are indicating that you feel **extreme** pain.

3. Please note:
   a) that the further to the right you place your " ✗ ", the **more** pain you feel.
   b) that the further to the left you place your " ✗ ", the **less** pain you feel.
   c) **please do not** place your " ✗ " **outside any of the boxes**.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 24 hours.

Think about your _____ (study joint) when answering the questions. Indicate the severity of your pain and stiffness and the difficulty you have in doing daily activities that you feel are caused by the arthritis in your _____ (study joint).

Your study joint has been identified for you by your health care professional. If you are unsure which joint is your study joint, please ask before completing the questionnaire.

Section A

PAIN

Think about the pain you felt in your _____ (study joint) caused by your arthritis during the last 24 hours.

(Please mark your answers with an "✗".)

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

Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your_____ (study joint) caused by the arthritis during the last 24 hours.

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

(Please mark your answers with an " ✗ ".)

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

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 24 hours. By this we mean **your ability to move around and take care of yourself.** (Please mark your answers with an " ✗ ".)

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

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 24 hours. By this we mean **your ability to move around and take care of yourself.** (Please mark your answers with an "✗".)

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

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 24 hours. By this we mean **your ability to move around and take care of yourself**. (Please mark your answers with an " ✗ ".)

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

D. Patient Global Impression of Change (PGIC) Assessment

Compared to before study treatment, the overall pain from my knee osteoarthritis is:
(Tick only one response)

- ☐ 1. very much improved
- ☐ 2. much improved
- ☐ 3. minimally improved
- ☐ 4. no change
- ☐ 5. minimally worse
- ☐ 6. much worse
- ☐ 7. very much worse