A Randomized, Double-Blind, Placebo Controlled, Multi-Center Study of a Single Injection Cross-Linked Sodium Hyaluronate Combined with Triamcinolone Hexacetonide (Cingal®) to Provide Symptomatic Relief of Osteoarthritis of the Knee

Protocol Number: Cingal 19-01

Protocol Version 1.0

Date: 11-December 2019

Signatures for the Sponsor that have reviewed and approved the protocol

Author: Director of Clinical Affairs or Designee: Adrian Orr	Signature	13 DEC 2019 Date
Vice President of Clinical Affairs or Designee: Carol Pekar	Signature	13 DEC 2019 Date
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PROTOCOL SIGNATURE PAGE

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My signature below confirms that I have read and understand the clinical protocol contained herein and agree to conduct the study according to this protocol and in accordance with the ethical principles of the Declaration of Helsinki, International Council for Harmonization (ICH) Guidelines on Good Clinical Practice (GCP), International Standards Organization (ISO) 14155, 21 CFR part 11, 50, 56, 312 and local ethical and legal requirements.

Principal Investigator:

_____ _____

Print Name Date

_____

Signature

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1 LIST OF ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ADE	Adverse Device Effect
AE	Adverse Event
ALT/SGPT	Alamine Transaminase/Serum Glutamic Pyruvic Transaminase
ANOVA	Analysis of Variance
AP	Anterior Posterior
AR	Adverse Reaction
AST/SGOT	Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase
AUC	Area Under the Curve
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CTM	Clinical Trial Material
CV	Curriculum Vitae
DMP	Data Management Plan
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcomes
EQ-5D-5L	EuroQoL 5 Dimension
EQ VAS	EuroQoL Visual Analog Scale
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
g, mg, kg	gram, milligram, kilogram
GCP	Good Clinical Practices
GEE	Generalized Estimating Equations
h	hour(s)
HA	Hyaluronan / Sodium Hyaluronate / Hyaluronic Acid
HbA1C	Hemoglobin A1C
HIPAA	Health Insurance Portability and Accountability Act
IA	Intra-articular
ICF	Informed Consent Form
ICH	International Council for Harmonization
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
K-L	Kellgren-Lawrence classification
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mL, mm, m	milliliter, millimeter, meter
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NRS	Numerical Rating Scale
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcomes Measures for Rheumatic Arthritis Clinical Trials
PA	Posterior Anterior
PE	Physical Exam

PI	Principal Investigator
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
ROM	Range of Motion
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TH	Triamcinolone Hexacetonide
UADE	Unanticipated Adverse Device Effect
UK	United Kingdom
US	United States
VAS	Visual Analog Scale
WBC	White Blood Cell
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

2 DEFINITIONS

Baseline: The assessments performed prior to the study injection after the Screening Visit.

Blinded Evaluator: The Blinded Evaluator will be a physician, research nurse, registered physiotherapist or physician assistant trained by the Principal Investigator (PI) to perform the assessments outlined in the protocol. The Blinded Evaluator will complete the Physical Exam, Physical Evaluation of both knees, Range of Motion (ROM) assessment of both knees, and the Evaluator Global Assessment.

End of Study: End of study is defined as the last subject's last visit.

Enrolled: A Subject who has signed the informed consent form (ICF) is enrolled.

Index Knee: The knee that meets the eligibility criteria for treatment. The Index knee may also be termed the "study knee". In subjects with bilateral knee Osteoarthritis (OA), where both knees meet eligibility criteria, the more symptomatic knee is the Index knee.

Institutional Review Board (IRB) refers to an independent body (e.g. Research Ethics Boards, Independent Ethics Committees) whose responsibility is to ensure the protection of rights, safety and well-being of human subjects involved in a trial. Committees with these responsibilities will be referred to in this document as IRB.

Rescue Medication: Acetaminophen will be distributed as the rescue medication. It is the only medication that should be taken for knee pain during the entire study. Rescue medication will be discontinued at least 48 hours prior to Baseline and all follow-up visits.

Treating Physician: The Treating Physician will most often be the PI. He/she will administer the Cingal®, Triamcinolone Hexacetonide (TH), or Placebo injection but will not participate in the efficacy evaluation.

Treatment Failure: A Subject who undergoes a procedure or uses a medication (other than the rescue medication) for the treatment of OA in the Index knee at any time after the study injection through the 26-week visit.

3 STUDY SYNOPSIS

Title	A Randomized, Double-Blind, Placebo Controlled, Multi-Center Study of a Single Injection Cross-Linked Sodium Hyaluronate Combined with Triamcinolone Hexacetonide (Cingal®) to Provide Symptomatic Relief of Osteoarthritis of the Knee
Study Objective	To determine the contribution of Triamcinolone Hexacetonide (TH) to pain relief, both in terms of magnitude and duration, when used within a single injection of Cingal® compared to a single injection of TH in subjects with OA of the knee. A saline placebo is included within the trial to set the expectation of a return to Baseline pain for the Subjects.
Investigational Product	**Cingal®:** A chemically cross-linked sodium hyaluronate supplied as a 4-mL unit dose with a nominal 18 mg of Triamcinolone Hexacetonide (TH) in a 5-mL glass syringe.
Comparator Products	**Triamcinolone Hexacetonide (TH)**: 20 mg/ml supplied as 1 mL unit dose in a glass ampoule. **Placebo:** 0.9% saline supplied as a 4-mL unit dose in a 5-mL glass syringe.
Mode of Delivery	Cingal®, Triamcinolone Hexacetonide, or Placebo will be injected into the intra-articular (IA) space of the Index knee using an 18-21 gauge needle.
Study Design	Multi-center, randomized, double-blind, parallel group, 3-arm, placebo controlled study
Phase	Pilot Study
Sample Size	A total of 231 subjects will be enrolled and treated.
Study Duration	The entire study duration from first Subject in to last Subject out will be 12-16 months. The enrollment phase will be approximately 7-9 months with a follow-up phase of 6 months. Visits will be scheduled at Screening, Baseline, 1 week, 3 weeks, 6 weeks, 12 weeks,18 weeks and 26 weeks post treatment.
Inclusion Criteria	Screening Inclusion Criteria 1. Subject is 40-75 years old. 2. Body Mass Index (BMI) ≤ 40 kg/m^2. 3. Subject has Kellgren-Lawrence (K-L) severity grade II or III in the Index knee as determined by X-Ray. Contralateral knee: K-L severity grade 0, I or II. 4. Subject has had at least two signs and at least two symptoms of OA disease (based on the European League Against Rheumatism (EULAR) recommendations for diagnosing knee OA) in the Index knee for at least 6 months despite conservative treatment (weight reduction, physical therapy, pain medications, etc.). The EULAR signs and symptoms are as follows: o Signs: crepitus, restricted movement and bony enlargement o Symptoms: persistent knee pain, limited morning stiffness and reduced function 5. Subject must be willing to abstain from other IA treatments of the knee for the duration of the study. 6. Subject is willing to discontinue all analgesics including nonsteroidal anti-inflammatory drugs (NSAIDs), except acetaminophen before the treatment injection and through the completion of the study. NSAIDs should be discontinued through the Screening period. 7. Subject is willing to use only acetaminophen (up to a maximum of 3.0 grams per day) for the treatment of joint pain for the duration of the study. At least forty-eight hours prior to the Baseline Visit and each follow-up visit, the Subject is willing to discontinue use of acetaminophen 8. Subject is willing to maintain a stable dose of oral glucosamine and/or chondroitin sulfate products throughout the study, if taken prior to signing ICF. 9. Subject is able to understand and comply with the requirements of the study and voluntarily provides consent.
Exclusion Criteria	Screening Exclusion Criteria 1. Subject received an IA injection of Hyaluronic Acid (HA) and/or steroid in either knee within 6 months of signing the ICF. A Subject will be excluded if they are planning to receive an HA or steroid injection (other than the study injection) in either knee during the course of this study. 2. Subject had an arthroscopy of either knee within 3 months of signing the ICF.

	3. Subject had an open surgical procedure of either knee or hip or any surgery of the spine within 12 months of signing ICF. Subject plans to have knee, hip or spine surgery within the study period. 4. Subject has intra-articular trauma to the Index knee. Subject has concurrent multi-system or multi-limb trauma. 5. Subject has evidence or medical history of the following diseases in the Index knee: septic arthritis; inflammatory joint disease; history of Reiter's syndrome; gout; chondrocalcinosis associated with recurrent episodes of acute synovitis of the knee consistent with pseudogout; osteochondritis dissecans, Paget disease of the bone; ochronosis; acromegaly; hemochromatosis; primary osteochondromatosis; known history of Wilson disease; heritable disorders or collagen gene mutations. 6. Subject has a history of cartilage repair surgery in the Index knee within 3 years of signing the ICF. 7. Subject has a history of Anterior cruciate ligament (ACL) repair, reconstruction or injury in the Index knee within 3 years of signing the ICF. 8. Subject has X-Ray findings of acute fractures, severe bone loss, avascular necrosis, severe bone or joint deformity in the Index knee. 9. Subject has significant varus or valgus deformity greater than 8 degrees in either knee. 10. Subject has a clinically apparent tense effusion of the Index knee. 11. Subject has knee instability in either knee per the Investigator's assessment. 12. Subject requires consistent use of an assistive device (e.g. wheelchair, walker, etc.) Occasional use of a cane is acceptable. 13. Subject has medical condition(s) which could affect study assessments or may adversely affect the safety and/or success of the study treatment. This includes but is not limited to the following: a. Peripheral neuropathy severe enough to interfere with evaluation of the subject, b. Vascular insufficiency severe enough to interfere with evaluation of the subject, c. Active fibromyalgia, d. Hemiparesis involving either lower extremity, e. Immunocompromised or immunosuppressive disorder or receiving medications to treat immunosuppressive disorders, f. Systemic bleeding disorder(s), g. Current malignancy or treatment within the last 5 years, except for non-melanoma skin cancer, h. Significant psychiatric disorder, i. Active drug and/or alcohol abuse within the past year, j. Uncontrolled diabetes with a Screening Hemoglobin A1C (HbA1c) of >7% k. contraindication to Triamcinolone Hexacetonide (TH) including active tuberculosis, herpes simplex keratitis, acute psychoses and systemic mycoses and paracitoses. 14. Subject is taking medications at the time the subjects signs the ICF which could interfere with the treatment procedure, healing and/or assessments. This includes but is not limited to oral or injectable anticoagulant treatments, anti-aggregant platelet treatment, chronic opioid analgesics. Low dose aspirin used for cardiovascular protection is allowed if a stable regimen is maintained for the duration of the study. 15. Subject is receiving treatment using electromagnetic stimulation and/or low intensity ultrasound in the Index knee at the time of signing the ICF, within 3 months of signing the ICF or plans to receive treatment any time during the study period. 16. Subjects who had an oral, intramuscular, intravenous, rectal suppository or topical (excluded in Index knee only) corticosteroid within 30 days of signing the ICF are excluded. Topical corticosteroid use at any site other than the Index knee is allowed. 17. Subject has a pre-treatment contraindication to IA injections or aspiration of the Index knee, including cutaneous infection in the injection site area, active IA infection (as suggested by moderate or marked effusion), knee deformity or condition which, in the opinion of the Investigator could jeopardize the sterility or delivery of the IA injection. 18. Subjects with a history of hypersensitivity to any of the ingredients in the

	hyaluronan or previous hypersensitivity to the administration of corticosteroids or an inability to tolerate acetaminophen. 19. Subject has any contraindication to the receipt of a corticosteroid. 20. Subject is receiving or in litigation for worker's compensation. 21. Subject is a woman who is pregnant or breastfeeding at the Screening Visit or a woman of child bearing potential who refuses to use effective contraception during the course of the study. 22. Subject was involved in any other research study involving an investigational product, or a new application of an approved product, within 60 days of signing the ICF. 23. Subject previously treated with Cingal for knee osteoarthritis. Baseline Inclusion Criteria 24. Subject has a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain-sub-score ≥ 50 mm and ≤ 90 mm in the affected knee and ≤ 30 mm in the contralateral knee on a 100 mm Visual Analog Scale (VAS) scale. Baseline Exclusion Criteria 25. Subject has a decrease of ≥ 20 mm in the WOMAC pain-sub-score (average of 5 pain scales) from Screening to Baseline in the Index knee on a 100 mm Visual Analog Scale (VAS) scale. 26. Subject has a synovial fluid aspirate volume > 10 mL in the Index knee. 27. Subject has a contraindication to continue with the study treatment injection based on the visual appearance of the synovial fluid aspirate unless the fluid is examined microscopically prior to injection with no clinically significant findings (e.g. bacteria, crystals or blood). 28. Subject has range of motion of less than 100° flexion in either knee.
Criteria for Evaluation	**Efficacy:** **Primary Endpoint:** • The change from Baseline in knee pain as measured by the WOMAC Pain Score (100 mm VAS) at 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. **Secondary Endpoints:** • The responder rate as identified by the Outcomes Measures for Rheumatic Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) responder index at 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. • The change from Baseline in knee pain as measured by daily VAS Pain Score and average weekly VAS Pain Score (100 mm VAS) through 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. • The change from Baseline in knee pain as measured by daily NRS Pain Score and average weekly NRS Pain Score (0-10 NRS) through 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. • The change from Baseline in WOMAC Physical Function score at 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. • The change from Baseline in WOMAC Stiffness score at 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. • The change from Baseline in Total WOMAC score at 26 weeks post

	treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. • The change from Baseline in the Patient Global Assessment at 26 weeks post treatment in the Cingal® arm compared to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. • The change from Baseline in the Evaluator Global Assessment at 26 weeks post treatment in the Cingal® arm compared to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. • The usage of Rescue Medication through 26 weeks post treatment in the Cingal® arm compared to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. **Exploratory Endpoints:** Any comparisons between arms (Cingal®, TH, Placebo), within arms and / or time points (from Baseline through to 26 weeks) not described in the primary or secondary endpoints may be presented in the exploratory endpoints including: • EuroQoL (EQ-5D-5L) • WOMAC Pain Score (100mm VAS) • Daily & weekly VAS pain scores • Daily & weekly Numerical Rating Scale (NRS) pain scores • OMERACT-OARSI • Total WOMAC • WOMAC Stiffness Score • WOMAC Physical Function Score • Patient Global Assessment • Evaluator Global Assessment • Range of Motion • Rescue Medication Use • Number of Treatment Failures **Safety:** The incidence, timing, severity, and relationship to treatment of all Adverse Events (AE) will be collected and coded using Medical Dictionary for Regulatory Activities (MedDRA). Local injection site and non-local events will be recorded separately.
Statistical Analysis	The primary analysis on the endpoints will be performed on the ITT (Intent to Treat) populations using the Multiple Imputation Methodology. The Multiple Imputation Methodology will use a mixed effects repeated measures model to predict the missing values. All Primary and Secondary endpoints will be analyzed using the ITT population. A secondary analysis will be conducted on the Per Protocol (PP) population. Since the primary endpoint is at 26 weeks, this is all subjects who complete the 26 week visit and who are not major violators of the protocol. For all other visits, this is defined as the subjects who complete those visits according to the protocol. All safety analyses will be conducted on all subjects who undergo treatment in any arm.
Sites	Up to 40 clinical sites in US only
Sponsor	Anika Therapeutics, Inc. 32 Wiggins Avenue Bedford, MA 01730, United States of America Phone: + 1 781-457-9000 Fax: + 1 781-305-9720

4 INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder globally [1] affecting over 27 million people in the U.S.[2] and 40 million people in Europe [3]. OA is characterized by a decreased concentration of HA in synovial fluid [4] and a slow degradation of cartilage [5]. OA causes joint pain and significant functional limitations; an estimated 11 million Americans with arthritis cannot walk ¼ mile [6]. The economic burden of OA is high, with health care expenditures of over $185 billion annually in the U.S. due to OA [2].

Given an aging population and an increase in obesity, the incidence of OA is projected to rise. Nearly 1 in 2 people are projected to develop symptomatic knee OA by age 85 [7]. Over half of adults in the U.S. diagnosed with knee osteoarthritis will eventually undergo a total knee replacement [8] leading to over 3.5 million knee replacement surgeries by 2030 [9]. Because of the high prevalence of knee OA, this disease ranked as either the top or second leading cause of disability [10]. In particular, this disease accounted for more dependence on others in climbing stairs, housekeeping and walking a mile than any other disease after adjustment for age, sex and comorbidity [10].

Osteoarthritis is defined as a "heterogenous group of conditions that leads to joint symptoms and signs which are associated with defective integrity of articular cartilage in addition to related changes in the underlying bone and at the joint margins" [11]. OA is characterized by a decreased concentration of HA in synovial fluid and a slow degradation of cartilage over years [4, 5]. The decreased concentration of HA in the synovial fluid of an osteoarthritic joint is probably caused by dilution from exudation, a decreased production of hyaluronans, and increased degradation [5]. Accordingly, the average molecular weight is diminished resulting in a loss of the viscoelastic properties of the synovial fluid for which HA is responsible [4].

Corticosteroids have long been used to alleviate pain and inflammation by injecting into the intra-articular space. Commonly used corticosteroids have been Triamcinolone Acetonide (TA) and Triamcinolone Hexacetonide (TH) which have been reviewed in the literature and found to be safe and effective for short term relief of the symptoms of osteoarthritis [12]. Standard dosing for intra-articular injections to the knee for Triamcinolone Hexacetonide (TH) have been reported as a 1 ml injection at a concentration of 20 mg/ml which will be the proposed dose for the active control in this trial [12].

Viscosupplements are believed to restore the concentration of hyaluronans in synovial fluid, elevate the viscosity and improve the lubricating and cushioning properties of the synovial fluid to a healthier state to alleviate pain in OA [5]. HA in synovial fluid binds to chondrocytes, supporting a role for HA in healthy cartilage [4]. HA has been studied as a substance capable of restoring the normal properties of synovial fluid and cartilage, thereby reducing pain and stiffness in the osteoarthritic joints. Exogenously administered HA immediately restores the synovial fluid's viscoelastic (or rheologic) properties [5].

Bellamy et al (2006) conducted a systematic analysis of 76 single and double-blinded studies and

concluded that viscosupplements are an effective treatment for OA of the knee with beneficial effects on pain, function and Patient Global Assessment from a 5 to 13 week post injection period showing a percent improvement from Baseline of 28% to 54% for pain and 9% to 32% for function [13].

Because data show a delayed treatment effect of HA, Anika Therapeutics, Inc. wanted to create a product, Cingal®, that could provide quicker pain relief for subjects suffering from OA while still providing the established pain relief of an HA product. Anika Therapeutics, Inc. chose to add a corticosteroid, Triamcinolone Hexacetonide (TH), that was approved in the U.S. and Europe for intra-articular use in osteoarthritis and was labeled for frequency of injection every 3-4 weeks, to a cross-linked HA product which provides pain relief of up to 26 weeks after a single injection.

Cingal® is a sterile, biocompatible, non-pyrogenic, viscoelastic, uniform white/off white opaque solution composed of molecules of HA and Triamcinolone Hexacetonide (TH). Cingal® is intended to treat the pain of OA of the knee in patients who have failed to respond to conservative non-pharmacological therapy and to simple analgesics, e.g., acetaminophen. Cingal® functions as a viscoelastic supplement or a replacement for synovial fluid in human joints with short term pain relief is provided by Triamcinolone Hexacetonide.

Cingal® has been studied in two Phase III trials, Cingal 13-01 and Cingal 16-02, and several follow-on studies, Cingal 13-02 and Cingal 17-02 [14-17]. Cingal® studies generated a safety data base of 642 subjects treated intra-articularly with a Cingal® injection, including 94 subjects retreated with a second injection.

The data supports the safety of Cingal®. There were no deaths in any of the trials, and all SAEs were found not related to the study injection. The types of adverse events considered related to the study injection were typical side effects of any intra-articular injection: arthralgia, injection site pain, joint swelling, injection site reaction, joint warmth and decreased ROM. All AEs considered related to the study injection across all studies were transitory and resolved without sequelae.

The integrated analysis of the two Phase III trials showed Cingal reduced WOMAC Pain from Baseline an average of 73% at 26 weeks post-injection.

This clinical trial will determine the contribution of TH to pain relief, both in terms of magnitude and duration, when used within a single injection of Cingal® compared to a single injection of TH in subjects with OA of the knee. A saline placebo is included within the trial to prevent expectation bias by study subjects that could occur in an all-active comparator study.

5 STUDY OBJECTIVES

To determine the contribution of Triamcinolone Hexacetonide (TH) to pain relief, both in terms of magnitude and duration, when used within a single injection of Cingal® compared to a single injection of TH in subjects with OA of the knee. A saline placebo is included within the trial to set the expectation

of a return to pain in Subjects.

6 ENDPOINTS

6.1 Primary Efficacy Endpoint

- The change from Baseline in knee pain as measured by the WOMAC Pain Score (100 mm VAS) at 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.

6.2 Secondary Efficacy Endpoints

- The responder rate as identified by the Outcomes Measures for Rheumatic Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) responder index at 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.
- The change from Baseline in knee pain as measured by daily VAS Pain Score and average weekly VAS Pain Score (100 mm VAS) through 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.
- The change from Baseline in knee pain as measured by daily NRS Pain Score and average weekly NRS Pain Score (0-10 NRS) through 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.
- The change from Baseline in WOMAC Physical Function score at 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.
- The change from Baseline in WOMAC Stiffness score at 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.
- The change from Baseline in Total WOMAC score at 26 weeks post treatment comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.
- The change from Baseline in the Patient Global Assessment at 26 weeks post treatment in the Cingal® arm compared to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.
- The change from Baseline in the Evaluator Global Assessment at 26 weeks post treatment in the Cingal® arm compared to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.
- The usage of Rescue Medication through 26 weeks post treatment in the Cingal® arm compared to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.

6.3 Exploratory Endpoints

Any comparisons between arms (Cingal®, TH, Placebo), within arms and / or time points (from Baseline through to 26 weeks) not described in the primary or secondary endpoints may be presented in the exploratory endpoints including:

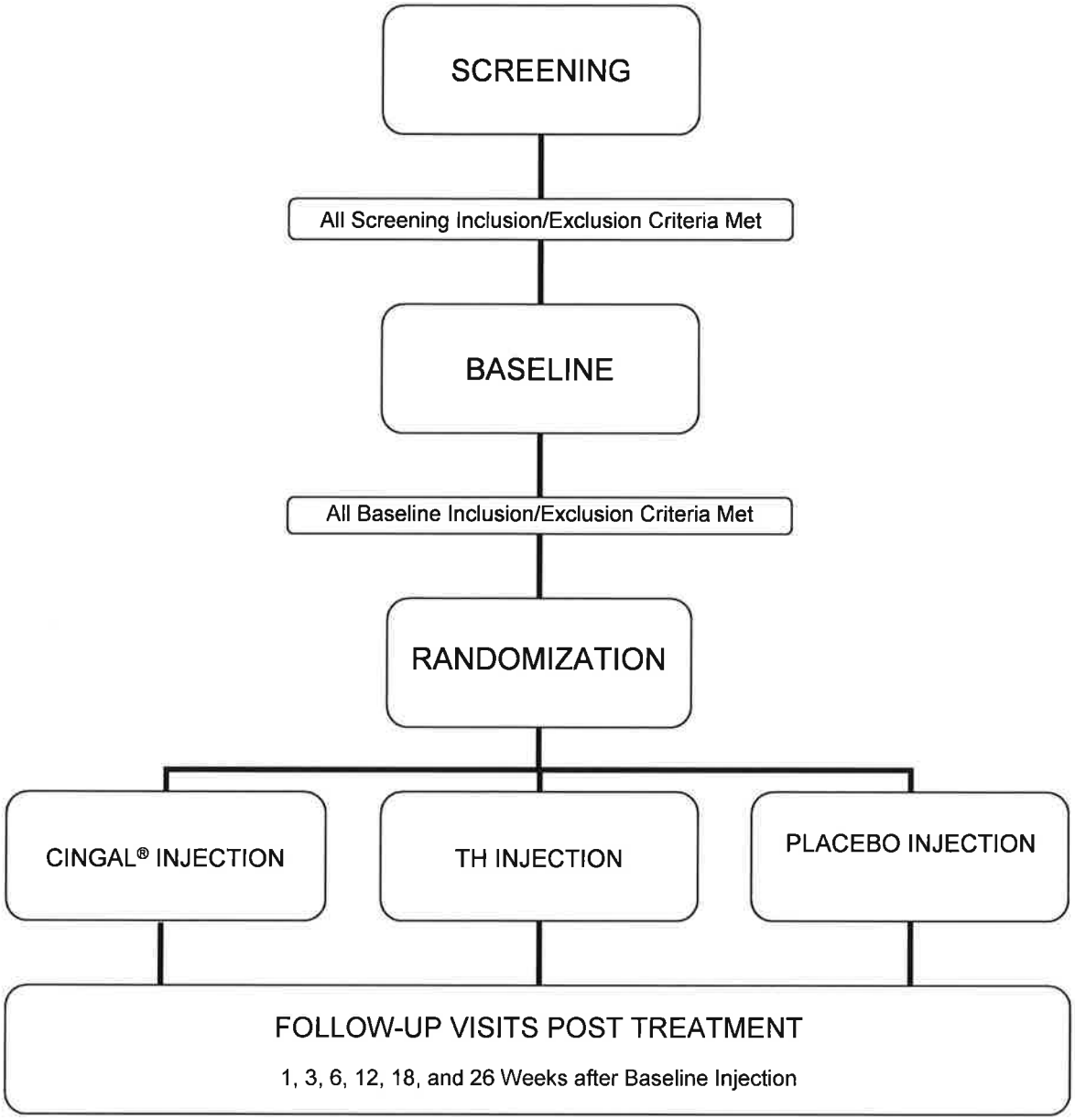
- EuroQoL (EQ-5D-5L)
- WOMAC Pain Score (100mm VAS)
- Daily VAS pain scores & weekly average VAS pain scores
- Daily NRS pain scores & weekly average NRS pain scores
- OMERACT-OARSI
- Total WOMAC
- WOMAC Stiffness Score
- WOMAC Physical Function
- Patient Global Assessment
- Evaluator Global Assessment
- Range of Motion
- Rescue Medication Use
- Number of Treatment Failures

6.4 Safety Endpoint

The incidence, timing, severity, and relationship to treatment of all AEs will be collected and coded using MedDRA. Local injection site and non-local events will be recorded separately.

7 STUDY DESIGN

7.1 Diagram



7.2 Trial Design

This is a multi-center, randomized, double-blind, parallel arm, placebo-controlled trial to determine the contribution of Triamcinolone Hexacetonide (TH) to pain relief, both in terms of magnitude and duration, when used within a single injection of Cingal® compared to a single injection of TH in subjects with Osteoarthritis (OA) of the knee.

Subjects with OA defined as Kellgren-Lawrence (K-L) II or III in the Index knee will be eligible for this study [18, 19]. Felson et al 2004, encouraged the use of both OA symptoms and radiographic changes in the assessment of OA [20]. This study will employ both methods to screen subjects. Structural severity will be evaluated with the K-L classification score, a composite index of the presence and severity of joint space narrowing, osteophytes, sclerosis, deformity and cysts (see Appendix 6) [18, 19].

For the evaluation of symptomatic severity, two main domains are important [21]. The first is pain and the second is functional impairment. Other domains often used include subject's overall assessment, ROM and performance. Domains identified by OMERACT as core variables to be used in clinical trials involving OA are pain, function and the Patient Global Assessment which will be captured as part of this study [21].

Baseline and post-treatment pain, physical function and stiffness will be measured using the WOMAC questionnaire. VAS and NRS pain, ROM, Patient and Evaluator Global Assessment and the EuroQoL-5D-5L will be used to assess symptomatic severity throughout the study. In addition, the number of acetaminophen pills taken will be captured as an indirect measure of pain and will be done at follow up visits.

Subjects meeting the inclusion/exclusion criteria will be randomized to receive a single injection of Cingal®, Triamcinolone Hexacetonide (TH) or placebo in the Index knee. Since there is a difference in volume between Cingal®, TH and placebo, the treating physician will not be considered blinded. To maintain the double-blind design of the study, there will be a person assigned to the role of Treating Physician and one person assigned to the role of Blinded Evaluator. The Treating Physician, most often the PI, will administer the injection but will not participate in the evaluation of study treatment effectiveness. A second individual, designated as the Blinded Evaluator, is blinded to treatment and will complete the pre- and post-treatment Evaluator Global Assessment, knee exams and ROM measurements. To maintain the Subject blinding, the injection syringe will be prepared separate from the patient and the injection will be masked from the subject.

The Subject will be trained on how to complete the WOMAC, VAS Pain, NRS Pain, Patient Global Assessment and EuroQoL.

The Blinded Evaluator will collect and record AEs from the subjects and consult the Treating Physician only as needed in the management of AEs. The Blinded Evaluator will be a physician,

research nurse, registered physiotherapist or physician assistant trained to perform the assessments outlined in the protocol (Section, 9.1 Schedule of Events).

Up to 40 sites in US may participate in the study to enroll and treat 231 subjects. Subject participation will last approximately 7 months with follow-up visits scheduled at weeks 1, 3, 6, 12, 18, and 26 after the treatment injection.

8 ELIGIBILITY

8.1 Screening Enrollment Criteria

8.1.1 Screening Inclusion Criteria

1. Subject is 40-75 years old.
2. Body Mass Index (BMI) ≤ 40 kg/m^2.
3. Subject has Kellgren-Lawrence (K-L) severity grade II or III in the Index knee as determined by X-Ray. Contralateral knee: K-L severity grade 0, I or II.
4. Subject has had at least two signs and at least two symptoms of OA disease (based on the European League Against Rheumatism (EULAR) recommendations for diagnosing knee OA) in the Index knee for at least 6 months despite conservative treatment (weight reduction, physical therapy, pain medications, etc.). The EULAR signs and symptoms are as follows [22]:
    - Signs: crepitus, restricted movement and bony enlargement
    - Symptoms: persistent knee pain, limited morning stiffness and reduced function
5. Subject must be willing to abstain from other IA treatments of the knee for the duration of the study.
6. Subject is willing to discontinue all analgesics including nonsteroidal anti-inflammatory drugs (NSAIDs), except acetaminophen before the treatment injection and through the completion of the study. NSAIDs should be discontinued through the Screening period.
7. Subject is willing to use only acetaminophen (up to a maximum of 3.0 grams per day) for the treatment of joint pain for the duration of the study. At least forty-eight hours prior to the Baseline Visit and each follow-up visit, the Subject is willing to discontinue use of acetaminophen.
8. Subject is willing to maintain a stable dose of oral glucosamine and/or chondroitin sulfate products throughout the study, if taken prior to signing the informed consent form (ICF).
9. Subject is able to understand and comply with the requirements of the study and voluntarily provides consent.

8.1.2 Screening Exclusion Criteria

1. Subject received an IA injection of HA and/or steroid in either knee within 6 months of signing the ICF. A Subject will be excluded if they are planning to receive an HA or steroid injection

(other than the study injection) in either knee during the course of this study.

2. Subject had an arthroscopy of either knee within 3 months of signing the ICF.

3. Subject had an open surgical procedure of either knee or hip or any surgery of the spine within 12 months of signing ICF. Subject plans to have knee, hip or spine surgery within the study period.

4. Subject has intra-articular trauma to the Index knee. Subject has concurrent multi-system or multi-limb trauma.

5. Subject has evidence or medical history of the following diseases in the Index knee: septic arthritis; inflammatory joint disease; history of Reiter's syndrome; gout; chondrocalcinosis associated with recurrent episodes of acute synovitis of the knee consistent with pseudogout; osteochondritis dissecans, Paget disease of the bone; ochronosis; acromegaly; hemochromatosis; primary osteochondromatosis; known history of Wilson disease; heritable disorders or collagen gene mutations.

6. Subject has a history of cartilage repair surgery in the Index knee within 3 years of signing the ICF.

7. Subject has a history of ACL repair, reconstruction or injury in the Index knee within 3 years of signing the ICF.

8. Subject has X-Ray findings of acute fractures, severe bone loss, avascular necrosis, severe bone or joint deformity in the Index knee.

9. Subject has significant varus or valgus deformity greater than 8 degrees in either knee.

10. Subject has a clinically apparent tense effusion of the Index knee.

11. Subject has knee instability in either knee per the Investigator's assessment.

12. Subject requires consistent use of an assistive device (e.g. wheelchair, walker). Occasional use of a cane is acceptable.

13. Subject has medical condition(s) which could affect study assessments or may adversely affect the safety and/or success of the study treatment. This includes but is not limited to the following: a. Peripheral neuropathy severe enough to interfere with evaluation of the subject, b. Vascular insufficiency severe enough to interfere with evaluation of the subject, c. Active fibromyalgia, d. Hemiparesis involving either lower extremity, e. Immunocompromised or immunosuppressive disorder or receiving medications to treat immunosuppressive disorders, f. Systemic bleeding disorder(s), g. Current malignancy or treatment within the last 5 years, except for non-melanoma skin cancer, h. Significant psychiatric disorder, i. Active drug and/or alcohol abuse within the past year, j. Uncontrolled diabetes with a Screening HbA1c of >7%, k. contraindication to Triamcinolone Hexacetonide (TH) including active tuberculosis, herpes simplex keratitis, acute psychoses and systemic mycoses and paracitoses.

14. Subject is taking medications at the time the subjects signs the ICF which could interfere with the treatment procedure, healing and/or assessments. This includes but is not limited to oral or injectable anticoagulant treatments, anti-aggregant platelet treatment, chronic opioid analgesics. Low dose aspirin used for cardiovascular protection is allowed if a stable regimen is maintained for the duration of the study.

15. Subject is receiving treatment using electromagnetic stimulation and/or low intensity ultrasound in the Index knee at the time of signing the ICF, within 3 months of signing the ICF or plans to receive treatment any time during the study period.

16. Subjects who had an oral, intramuscular, intravenous, rectal suppository or topical (excluded in Index knee only) corticosteroid within 30 days of signing the ICF are excluded. Topical corticosteroid use at any site other than the Index knee is allowed.

17. Subject has a pre-treatment contraindication to IA injections or aspiration of the Index knee, including cutaneous infection in the injection site area, active IA infection (as suggested by moderate or marked effusion), knee deformity or condition which, in the opinion of the Investigator could jeopardize the sterility or delivery of the IA injection.

18. Subjects with a history of hypersensitivity to any of the ingredients in the hyaluronan or previous hypersensitivity to the administration of corticosteroids or an inability to tolerate acetaminophen.

19. Subject has any contraindication to the receipt of a corticosteroid.

20. Subject is receiving or in litigation for worker's compensation.

21. Subject is a woman who is pregnant or breastfeeding at the Screening Visit or a woman of child bearing potential who refuses to use effective contraception during the course of the study.

22. Subject was involved in any other research study involving an investigational product, or a new application of an approved product, within 60 days of signing the ICF.

23. Subject previously treated with Cingal for knee osteoarthritis.

8.2 Baseline Enrollment Criteria

8.2.1 Baseline Inclusion Criteria

1. Subject has a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain-sub-score ≥ 50 mm and ≤ 90 mm in the affected knee and ≤ 30 mm in the contralateral knee on a 100 mm Visual Analog Scale (VAS) scale.

8.2.2 Baseline Exclusion Criteria

1. Subject has a decrease of ≥ 20 mm in the WOMAC pain-sub-score (average of 5 pain scales) from Screening to Baseline in the Index knee on a 100 mm Visual Analog Scale (VAS) scale.

2. Subject has a synovial fluid aspirate volume > 10 mL in the Index knee.

3. Subject has a contraindication to continue with the study treatment injection based on the visual appearance of the synovial fluid aspirate unless the fluid is examined microscopically prior to injection with no clinically significant findings (e.g. bacteria, crystals or blood).

4. Subject has range of motion of less than 100° flexion in either knee.

9 STUDY PROCEDURES

9.1 Schedule of Events

	Pre-Treatment	Treatment		Post-Treatment Follow-Up Visits						
Assessments	-14 ±3 Days	Day 0 (14 ±3 days after Screening visit)		1 week	3 weeks	6 weeks	12 weeks	18 weeks	26 weeks	Early Term
	Screening	Baseline	Treatment	±3 days				± 7 Days		
Informed Consent	X									
Demographics	X									
Medical History	X									
Concomitant Medication	X	X		X	X	X	X	X	X	X
Adverse Event Assessment		X		X	X	X	X	X	X	X
Confirm Acetaminophen discontinued ≥48hrs before visit		X		X	X	X	X	X	X	X
Confirm all other pain medications discontinued since Screening		X		X	X	X	X	X	X	X
Acetaminophen Pill Count / ePRO Rescue Medication		X		X	X	X	X	X	X	X
Dispense Rescue Medications (as required)	X	X		X	X	X	X	X		
Review Daily ePRO Pain Scores (VAS & NRS Index knee)		X		X	X	X	X	X	X	X
Physical Exam, Vitals, BMI	X									
Physical Evaluation (Both Knees) *(conducted by Blinded Evaluator)*	X	X		X	X	X	X	X	X	X
ROM (Index Knee) *(conducted by Blinded Evaluator)*	X	X		X	X	X	X	X	X	X
ROM (Contralateral Knee) *(conducted by Blinded Evaluator)*	X	X					X		X	X
Evaluator Global Assessment *(conducted by Blinded Evaluator)*	X	X		X	X	X	X	X	X	X
Urine / Blood Pregnancy Test	X									
Chemistry/Hematology/Urinalysis	X									
Rater Training: Accurate Pain Report Training Placebo Response Reduction Training	X									
WOMAC (Both Knees)	X	X		X	X	X	X	X	X	X
VAS Pain Scale (Both Knees)	X	X		X	X	X	X	X	X	X
NRS Pain Scale (Both Knees)	X	X		X	X	X	X	X	X	X
EuroQoL 5D-5L	X	X		X	X	X	X	X	X	X
Patient Global Assessment	X	X		X	X	X	X	X	X	X

	Pre-Treatment	Treatment		Post-Treatment Follow-Up Visits						
Assessments	-14 ±3 Days	Day 0 (14 ±3 days after Screening visit)		1 week	3 weeks	6 weeks	12 weeks	18 weeks	26 weeks	Early Term
	Screening	Baseline	Treatment	±3 days				± 7 Days		
Distribute Subject Electronic Diary	X									
Daily ePRO VAS & NRS Scales (between & during visits)	X	X		X	X	X	X	X	X	X
Aspirate Synovial Fluid			X							
Evaluate Baseline Enrollment Criteria			X							
IA Injection *(conducted by Treating Physician)*			X							
Bilateral Knee X-Rays	X									
Independent Radiologist X-Ray Review	X									
Evaluate Screening Enrollment Criteria	X									
Randomization		X								

9.2 Procedure Description

9.2.1 Informed Consent Form (ICF)

The Subject will be asked to sign the ICF prior to undergoing any study related procedures.

9.2.2 Demographics

The following demographic information will be collected at the Screening Visit: Age, Gender, Race and Ethnicity.

9.2.3 Medical History

A complete Medical History will be obtained at the Screening Visit. The Medical History will include an inquiry of past medical conditions in the following body systems: neurological, psychological, cardiovascular, hematological, respiratory, endocrine/metabolic, musculoskeletal, and immunologic (including allergies). The Medical History will also include an assessment of the subject's history of the following:

- History/duration of knee OA
- History of operative arthroscopies
- History of open surgical procedures of either knee
- History of open surgical procedures of either hip
- History of IA injections including HA and steroid
- History of electromagnetic stimulation therapy
- History of other OA surgeries

- History of other OA procedures
- History of other OA abnormalities

9.2.4 Concomitant Medication

Medications that the Subject may have been taking prior to study enrollment for conditions unrelated to the treatment of knee osteoarthritis, other than analgesics including NSAIDs, may be continued as long as they will not interfere with study assessments. If the Subject was taking oral glucosamine and/or chondroitin sulfate products for the treatment of knee OA prior to signing the ICF, the products may be continued, but the Subject must maintain a stable regimen for the duration of the study.

9.2.5 Restricted Medications

All analgesics other than acetaminophen are prohibited during the study. This includes, but is not restricted to, NSAIDs, opioids and topical agents for treatment of OA in the Index knee. Topical corticosteroids are allowed at any other site other than the Index knee. The analgesic medication use will be monitored at each Subject visit through review of the Subject Electronic Diary.

The use of IA injection of steroids in any joint and the use of IA injection of viscosupplements in the knee joint is prohibited throughout the study. The use of immunosuppressive agents such as cyclosporine, methotrexate are prohibited throughout the study.

9.2.6 Rescue Medications

Acetaminophen (up to a maximum of 3.0 grams per day per the package insert or as per regional limitations) will be allowed as the rescue medication for the treatment of joint pain for the duration of the study. At least forty-eight hours prior to the Baseline Visit and each follow-up visit the Subject should discontinue use of the Rescue Medication.

At the Screening Visit, the Rescue Medication (i.e. acetaminophen) will be dispensed. The Subject should be instructed to bring the Rescue Medication with them to each follow-up visit for a pill count. Additional Rescue Medication (i.e. acetaminophen) will be dispensed as needed at the follow-up visits.

A medication is considered concomitant if taken after signing the ICF and up to and including the last follow-up visit. Data on medications will include: medication name, dose, unit, route, frequency, start date, stop date, indication and whether the medication was taken for an AE.

At each study visit, the Subject will be asked about any new medications that were started since the last visit. Indications for any new medications during the study period will be recorded as AEs, unless the medications are administered for a pre-existing condition.

9.2.7 Physical Exam (PE)

The PE will be performed at the time points included in Section 9.1 Schedule of Events. The PE will include an assessment of general appearance, chest and lungs, heart, abdomen, skin, musculoskeletal system, neurologic systems and other (as applicable). This PE will include an assessment of height and weight for calculation of a BMI.

9.2.8 Vital Signs

Vital signs (blood pressure, pulse, temperature) will be collected at the time points included in Section 9.1 Schedule of Events.

9.2.9 Physical Evaluation of Knees

The Blinded Evaluator will perform the Physical Evaluation of the knees at the time points included in Section 9.1, Schedule of Events. This will include assessment of effusion grade of both knees (none, mild, moderate or marked), symptoms (e.g. persistent knee pain, limited morning stiffness and reduced function) and signs (crepitus, restricted movement and bony enlargement). Knee circumference in centimeter will also be measured in both knees.

9.2.10 Range of Motion (ROM)

The Blinded Evaluator will assess the maximum ROM flexion and extension in degrees using a goniometer at the time points included in Section 9.1, Schedule of Events. The ROM will be documented as a hyphenated number. For instance, normal ROM in the knee is about 0-140 degrees.

9.2.11 Pregnancy Test

For females of childbearing potential, a urine or blood pregnancy test will be performed at the Screening Visit. Women who can confirm that they are surgically sterile or have been postmenopausal for at least 1 year prior to signing the ICF need not undergo a pregnancy test.

9.2.12 Chemistry/Hematology/Urinalysis

For all subjects, the blood / urine tests in Table 1 will be performed to assist in assessing Subject eligibility at the Screening Visit. A routine and microscopic analysis of the urine will be conducted at the Screening Visit.

Subjects will be eligible to repeat screening after a minimum of 14 days at the discretion of the Investigator and with approval of the Sponsor.

Table 1 Laboratory Analytes					
Hematology		**Clinical Chemistry**		**Urinalysis**	
Hematocrit	MCV	Sodium	Triglycerides	pH	Blood
Hemoglobin	MCH	Potassium	Calcium	Specific Gravity	Leukocytes
Red Blood Cell (RBC) count	MCHC	Chloride	AST/SGOT	Osmolality	Bilirubin
White Blood Cell (WBC) count		Glucose	ALT/SGPT	Clarity	Ketones
Differential WBC count		Urea nitrogen	Alkaline Phosphatase	Color	Urobilinogen
Platelet count		Creatinine	Total protein	Protein	Nitrites
HbA1c (for diabetics only)		Total bilirubin	Albumin	Glucose	

The clinical laboratory will clearly mark all laboratory test values that are outside the normal range and the Investigator will indicate which of these deviations are clinically significant. Any clinically significant observations in results of clinical laboratory are to be recorded as part of the patient's medical history if observed as part of the screening laboratory results.

9.2.13 Rater Training

Prior to completing any of the patient reported assessments, Subjects will complete rater training in two parts:

9.2.13.1 Accurate Pain Reporting (APR)

The Accurate Pain Reporting training instructs subjects how to accurately and reliably report pain scores, and on the proper use of pain scales, with the aim of increasing subjects' pain reporting accuracy. Subjects receive training as indicated in the Schedule of Events.

9.2.13.2 Placebo Response Reduction (PRR)

The Placebo Response Reduction training teaches appropriate expectations of personal benefit while participating in a clinical trial. The purpose is to provide subjects truthful information that will neutralize the typically excessive expectations that drive high placebo responses in clinical studies. Subjects receive training as indicated in the Schedule of Events.

9.2.14 WOMAC

The WOMAC index is self-administered and assesses the three dimensions of pain, disability and joint stiffness in knee and hip osteoarthritis using a battery of 24 questions (5 pain, 2 stiffness,17 physical

function) [23] (see Appendix 1). This trial will utilize the VAS version of the WOMAC index on the Electronic Patient Reported Outcomes (ePRO) system provided to the investigational sites. The Subject will be trained on how to complete the WOMAC which will be collected at the time points indicated in Section 9.1.

9.2.15 Visual Analog Scale (VAS) Pain Score

During the site visits, the Subject will report pain related to the index and contralateral knee measured with a 0-100 mm Visual Analog Scale (VAS) Scale (see Appendix 2).

9.2.16 Numerical Rating Scale (NRS) Pain Score

During the site visits, the Subject will report pain related to the index and contralateral knee measured with a 0-10 Numerical Rating Scale (see Appendix 3).

9.2.17 EuroQoL EQ-5D

Outcomes information from the subject-completed EuroQoL EQ-5D will be obtained at all evaluation points specified in Section 9.1, Schedule of Events [24, 25] (see Appendix 5). The EQ-5D is a standardized measure of health status developed by the EuroQoL Group which is applicable to a wide range of health conditions and treatments. The EQ-5D provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys [24].

The EQ-5D is designed for self-completion by respondents and consists of 2 pages - the EQ-5D descriptive system and the EQ Visual Analog Scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [24]. The Subject is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the subject's self-rated health on a vertical VAS where the endpoints are labeled 'Best health you can imagine' and 'Worst health you can imagine'. This information is used as a quantitative measure of health outcome as judged by the individual respondents [24].

This trial will utilize the EQ-5D on the ePRO system provided to the investigational sites.

9.2.18 Patient Global Assessment

The Patient Global Assessment (see Appendix 4) is a VAS that will be completed by the Subject at time points specified in Section 9.1, Schedule of Events, to determine the Patient Global Assessment of response to therapy score. "Considering all the ways the osteoarthritis in your study knee affects you, what is your assessment of how much your study knee is bothering you today?"

This trial will utilize the Patient Global Assessment on the ePRO system provided to the investigational sites.

9.2.19 Evaluator Global Assessment

The Evaluator Global Assessment (see Appendix 4) will be completed by the Blinded Evaluator at the time points delineated in Section 9.1, Schedule of Events. To reduce the potential for bias, it is important for the Blinded Evaluator to complete the Evaluator Global Assessment prior to collecting the Patient Global Assessment.

The Blinded Evaluator will be asked "Considering all the ways the osteoarthritis in the patient's Index knee affect him/her, what is your assessment of how much the patient's knee is bothering him/her today?"

This trial will utilize the Evaluator Global Assessment on the ePRO system provided to the investigational sites.

9.2.20 Subject Electronic Diary / Patient Reported Outcome ePRO

The Subject will be provided with an electronic application "app" or an electronic device to utilize as a Subject Electronic Diary. This will be provided at the Screening Visit and the Subject will receive training on when and how to complete the Subject Electronic Diary. The Subject Electronic Diary will be used to collect information on daily pain scores using VAS and NRS scales; medication usage including rescue medications; concomitant therapies (e.g. physical therapy) and AEs. The Subject Electronic Diary will be reviewed by site staff to determine if there are AEs that need to be captured within the Electronic Data Capture (EDC) system and to assess rescue medication usage and compliance with the protocol.

9.2.21 Knee X-Rays/Assessment of Kellgren-Lawrence Score

Subjects will be asked to have the following X-Rays of both knees collected at the Screening Visit:

- Long Limb Standing Anterior Posterior (AP) view
- Fixed Flexion Posterior Anterior (PA) view

These screening images will be transferred to, as well as handled by, the Central Imaging Core lab according to their Standard Operating Procedures (SOPs). An Independent Radiologist from the Central Imaging Core lab will evaluate the Screening plain films of both knees for osteoarthritic changes using the K-L scoring system (see Appendix 6) and exclude subjects with K-L severity grade of 0, I or IV in the Index knee or K-L severity grade III or IV in the contralateral knee. Additionally, varus / valgus alignment will be assessed in both knees and subjects with greater than 8 degrees of malalignment in either knee will be excluded.

The Independent Radiologist will furthermore evaluate the screening X-Rays to determine the following exclusion criteria for the Index knee:

- Presence of osteochondromatosis

- History of ACL repair, reconstruction or injury
- History of cartilage repair surgery
- X-Ray findings of acute fracture(s)
- Severe loss of bone density
- Avascular necrosis
- Severe bone or joint deformity in the Index knee
- Advanced cases of gout
- Advanced cases of Paget
- Acromegaly
- Osteochondritis dissecans

The Independent Radiologist will confirm the eligibility of screened subjects based on the imaging enrollment criteria. In the event the Independent Radiologist determines that a Subject is ineligible based on an imaging finding, the decision of the Independent Radiologist will prevail.

All the Screening X-Rays are paid for by this research study and are free of charge to the subject.

The images acquired for this trial will be transferred from the imaging site to the Central Imaging Core lab electronically and uploaded to EDC. The X-Rays will be identified by the subject's study identification (ID) number. No personal identifiable information will be included on the image.

9.2.22 Blinding

Although the identity of the syringes will not be revealed, it is recognized that there is a visible difference in the Clinical Trial Material (CTM) in the syringes as well as a difference in the extrusion force among Cingal®, Triamcinolone Hexacetonide (TH), and Placebo and also a difference in volume. To maintain the double-blind design (Blinded Evaluator, Subject) of the study, the following measures will be taken. To maintain the blind of the subject, a drape will be used to shield the view of the subject, or the patient will be positioned in such a manner, that they cannot observe the syringe or injection. Furthermore, due to the lack of proprioceptive receptors in the cartilage of the knee [26], the Subject should not be able to detect the viscosity or volume of the CTM being injected.

The Treating Physician will be aware of the differences and will be unblinded, therefore; there will be a **Treating Physician** (unblinded) and a **Blinded Evaluator** (blinded) at each site with clearly defined roles.

- **Treating Physician:** The Treating Physician is most often the PI. He/she will administer the Cingal, TH, or Placebo injection but will not participate in the efficacy evaluation.

- **Blinded Evaluator:** The Blinded Evaluator will be a physician, research nurse, registered physiotherapist or physician assistant trained by the PI to perform the assessments outlined in the protocol. The Blinded Evaluator will complete the Physical Exam, Physical Evaluation of both knees, Range of Motion (ROM) assessment of both knees, and the Evaluator Global

Assessment.

9.3 Screening

Each Subject will indicate his or her willingness to participate in the study by signing the ICF. Subjects will receive a unique Subject ID (e.g., 100-001) where the first three digits represent the number assigned to the investigative site and the last three digits represent the Subject number. The number will be recorded on the Enrollment Log and in the subject's electronic Case Report Forms (eCRFs). Subjects will be identified by the unique Subject ID for the duration of their participation in the study.

The following screening and eligibility data will be collected 14 ±3 days prior to the Baseline/Treatment Visit:

- Informed Consent
- Demographics (age, gender, race, and ethnicity)
- Medical History
- Assess Concomitant Medications
- Physical Examination including BMI and Vitals
- Physical Evaluation of Both Knees to be performed by Blinded Evaluator
- Range of Motion Evaluation of Both Knees to be performed by Blinded Evaluator
- Evaluator Global Assessment to be performed by Blinded Evaluator
- Pregnancy Test (women of childbearing potential)
- Screening Laboratory Testing
    - Chemistry
    - Hematology
    - Urinalysis
- Rater Training
- WOMAC Pain Scale (Both Knees)
- VAS Pain Scale (Both Knees) taken at Screening and daily until the Baseline visit using Subject Electronic Diary

  NRS Pain Scale (Both Knees) taken at Screening and daily until the Baseline visit using Subject Electronic Diary
- EuroQoL 5D-5L
- Patient Global Assessment
- Bilateral Knee X-Ray and Assessment of K-L Severity Grade
- Review of X-Rays by Independent Radiologist
- Distribute Subject Electronic Diary
- Dispense Rescue Medication
- Rescue Medication will be recorded between Screening and Baseline visit using Subject Electronic Diary
- Assessment of Screening Enrollment Criteria

During the Screening Visit inform the Subject about discontinuation of all analgesics including NSAIDs except acetaminophen. Acetaminophen will be used as a Rescue Medication (Pain Control) through the completion of the study, however; acetaminophen should be discontinued at least 48 hours before each follow-up study visit. Subjects who are taking oral glucosamine and chondroitin sulfate products should be informed that a stable dose of these supplements must be maintained for the duration of the study.

Subjects who fail to meet screening eligibility criteria may, at the discretion of the Investigator and with Sponsor approval, be rescreened after a minimum of 14 days post- screening. A new Subject number will be assigned.

9.4 Baseline

The Baseline Visit will occur 14±3 days after the Screening Visit. The following assessments will take place during this visit:

- Concomitant Medications
- Confirm Rescue and Prohibited Medication Washout
- Count/Dispense Rescue Medication Pills
- Evaluate Subject Electronic Diary including daily pain scores
- Physical Evaluation (Both Knees) to be performed by Blinded Evaluator
- Range of Motion (Both Knees) to be performed by Blinded Evaluator
- Evaluator Global Assessment to be performed by Blinded Evaluator
- WOMAC (Both Knees)
- VAS Pain Scale (Both Knees)
- NRS Pain Scale (Both Knees)
- EuroQoL-5D-5L
- Patient Global Assessment
- Randomization – if Subject meets all Screening and Baseline assessments (except IA aspiration)
- Aspirate Synovial Fluid
- Evaluation of Baseline Enrollment Criteria
- Intra-articular Injection to be performed by Treating Physician
- Assess Treatment-Emergent Adverse Events

9.5 Pre-Treatment Screening

Evaluate the Subject for the Baseline enrollment criteria regarding the WOMAC and ROM. Section 9.2

9.6 Randomization

If the Subject has met the Screening and Baseline enrollment criteria (except assessment of IA fluid), he/she will be randomized using the EDC system. The EDC system will indicate which blinded carton should be used for that injection using a kit number (__ __ __ __ __).

9.7 Treatment

The Treating Physician will prep and drape the subject's Index knee. The Treating Physician will always perform the Index knee injection for each Subject and will not participate in the efficacy evaluation.

Using a sterile syringe and an 18-21 gauge needle, the Treating Physician should penetrate the joint space, aspirate to dryness and retain any synovial fluid for measurement of volume and laboratory analysis (if needed). Aspiration should be attempted on all subjects, regardless of whether there is clinical appearance of effusion.

Evaluate the Subject for the Baseline Enrollment Criteria regarding the volume and appearance of the synovial fluid aspirate. If needed, the aspirate should be sent for microscopic examination and results evaluated prior to the injection. The injection should be postponed until the results of the microscopic examination are received and the Treating Physician determines it is safe to proceed with the study injection. Any Subject found to not meet the inclusion/exclusion criteria will be excluded from the study. If this possibility is anticipated, an alternate plan for treatment should be pre-arranged.

For the TH arm, an ampoule of Triamcinolone Hexacetonide will be provided by the Sponsor as CTM. The Treating Physician will draw the TH into an empty syringe as standard practice for an IA injection.

Once the synovial fluid characteristics and volume are confirmed to be acceptable, the Treating Physician should inject the entire contents of the syringe into the joint space unless this volume is felt to be too much. The Treating Physician should advise each Subject to avoid heavy physical activities (including jogging, tennis, heavy lifting, prolonged standing) for 24 hours after the study injection.

The Blinded Evaluator must not be present for the injection.

9.8 Injection Technique

It is recommended that a lateral midpatellar injection be performed in accordance with the findings of Jackson et al. (2002) who demonstrated a greater rate of injection accuracy when compared to anterolateral and anteromedial injections [27]. Because this study is enrolling subjects with K-L II and III in the Index knee, it should be noted that in a study by Toda et al (2008), it was found that the best injection approach may be determined by the severity of knee OA [28]. However, each treating physician may utilize the preferred method of injection based on their clinical practice.

To perform a lateral midpatellar injection, the lower limb is extended on the examination table. The patella will be manually everted and moved laterally by the physician's free hand. The needle will be

advanced transversely between the articular surfaces of the patellofemoral joint at the midpoint of the patella [27].

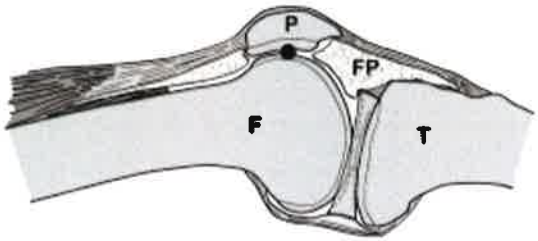


Diagram showing the lateral midpatellar portal [27]
P = patella,F = femur, T = tibia, and FP = fat pad.

Post-Treatment Assessments and Instructions

Prior to leaving the clinic, the Subject should be evaluated for local and non-local AEs and the Index knee assessed for local AEs. All post-treatment signs and symptoms that are unexpected should be recorded as AEs. The expected appearance of the Index knee should be discussed with the Subject with a request that all unexpected symptoms be reported to a member of the study team.

Subjects who exhibit significant complications, (e.g., significant inflammation or significant swelling of the joint) may warrant diagnostic or therapeutic procedures as determined by the Treating Physician in conjunction with the Blinded Evaluator. All subjects will be evaluated for safety for the duration of their participation in the study. Inclusion of the Subject in the efficacy evaluation will be decided on a case by case basis.

9.9 Post-Treatment Follow-Up

All study subjects will have follow-up assessments at 1, 3, 6, 12, 18, and 26 weeks after injection day to evaluate effectiveness of the treatment and to assess AEs and protocol compliance. The Blinded Evaluator will evaluate the clinical status of the Subject at each visit.

At least 48 hours prior to the visit, the Subject will be reminded of the visit date and time, the need to abstain from acetaminophen for at least 48 hours prior to each follow-up visit and the requirement to bring their Subject Electronic Diary and the acetaminophen for a pill count with them to the appointment.

If the Subject arrives for a study visit without discontinuing acetaminophen for at least 48 hours prior to the visit, the visit should be rescheduled within the allowed study window. Study assessments should be performed as soon as possible and the protocol deviation, if applicable, recorded in the source and eCRF. The Subject must be re-educated about the importance of protocol compliance.

If the Subject does not come in at the expected time, at least three attempts will be made to contact the Subject in order to accomplish maximum Subject compliance with the follow-up schedule.

The following post-treatment visits will be performed. The Subject will be asked whether any concomitant medications have been taken. All assessments will be done by the Blinded Evaluator.

9.9.1 1 Week ± 3 Days

- Concomitant Medications
- Assess Adverse Events
- Confirm Rescue Medication Washout
- Count/Dispense Rescue Medication Pills (if needed)
- Evaluate Subject Electronic Diary
- Physical Evaluation (Both Knees) to be performed by Blinded Evaluator
- ROM (Index Knee) to be performed by Blinded Evaluator
- Evaluator Global Assessment to be performed by Blinded Evaluator
- WOMAC (Both Knees)
- VAS Pain Scale (Both Knees)
- NRS Pain Scale (Both Knees)
- EuroQoL-5D-5L
- Patient Global Assessment

9.9.2 3 Weeks ± 3 Days

- Concomitant Medications
- Assess Adverse Events

- Confirm Rescue Medication Washout
- Count/Dispense Rescue Medication Pills (if needed)
- Evaluate Subject Electronic Diary
- Physical Evaluation (Both Knees) to be performed by Blinded Evaluator
- Evaluator Global Assessment to be performed by Blinded Evaluator
- ROM (Index Knee) to be performed by Blinded Evaluator
- WOMAC (Both Knees)
- VAS Pain Scale (Both Knees)
- NRS Pain Scale (Both Knees)
- EuroQoL-5D-5L
- Patient Global Assessment

9.9.3 6 Weeks ± 3 Days

- Concomitant Medications
- Assess Adverse Events
- Confirm Rescue Medication Washout
- Count/Dispense Rescue Medication Pills (if needed)
- Evaluate Subject Electronic Diary
- Physical Evaluation (Both Knees) to be performed by Blinded Evaluator
- Evaluator Global Assessment to be performed by Blinded Evaluator
- ROM (Index Knee) to be performed by Blinded Evaluator
- WOMAC (Both Knees)
- VAS Pain Scale (Both Knees)
- NRS Pain Scale (Both Knees)
- EuroQoL-5D-5L
- Patient Global Assessment

9.9.4 12 Weeks ± 3 Days

- Concomitant Medications
- Assess Adverse Events
- Confirm Rescue Medication Washout
- Count/Dispense Rescue Medication Pills (if needed)
- Evaluate Subject Electronic Diary
- Physical Evaluation (Both Knees) to be performed by Blinded Evaluator
- ROM (Both Knees) to be performed by Blinded Evaluator
- Evaluator Global Assessment to be performed by Blinded Evaluator
- WOMAC (Both Knees)
- VAS Pain Scale (Both Knees)
- NRS Pain Scale (Both Knees)

- EuroQoL-5D-5L
- Patient Global Assessment

9.9.5 18 Weeks ± 7 Days

- Concomitant Medications
- Assess Adverse Events
- Confirm Rescue Medication Washout
- Count/Dispense Rescue Medication Pills (if needed)
- Evaluate Subject Electronic Diary
- Physical Evaluation (Both Knees)
- ROM (Index Knee) to be performed by Blinded Evaluator
- Evaluator Global Assessment to be performed by Blinded Evaluator
- WOMAC (Both Knees)
- VAS Pain Scale (Both Knees)
- NRS Pain Scale (Both Knees)
- EuroQoL-5D-5L
- Patient Global Assessment

9.9.6 26 Weeks ± 7 Days

- Concomitant Medications
- Assess Adverse Events
- Confirm Rescue Medication Washout
- Count Rescue Medication Pills
- Evaluate Subject Electronic Diary
- Physical Evaluation (Both Knees)
- ROM (Both Knees) to be performed by Blinded Evaluator
- Evaluator Global Assessment to be performed by Blinded Evaluator
- WOMAC (Both Knees)
- VAS Pain Scale (Both Knees)
- NRS Pain Scale (Both Knees)
- EuroQoL-5D-5L
- Patient Global Assessment

9.9.7 Early Termination due to lack of efficacy in the Index knee

If a subject wants to obtain additional treatments such as HA and steroid injection in Index knee, the subject should undergo below assessment before receiving the additional treatment:

- Concomitant Medications
- Assess Adverse Events

- Confirm Rescue Medication Washout
- Count Rescue Medication Pills
- Evaluate Subject Electronic Diary
- Physical Evaluation (Both Knees)
- ROM (Both Knees) to be performed by Blinded Evaluator
- Evaluator Global Assessment to be performed by Blinded Evaluator
- WOMAC (Both Knees)
- VAS Pain Scale (Both Knees)
- NRS Pain Scale (Both Knees)
- EuroQoL-5D-5L
- Patient Global Assessment

After completing the assessment, the subject should be terminated from the study. These subjects will be considered as Treatment Failure.

10 ADVERSE EVENTS / ADVERSE REACTIONS

10.1 Definitions – Device Adverse Events

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

NOTE 1 This definition includes events related to the investigational medical device or the comparator.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices"

Adverse Device Effect (ADE): An AE related to the use of the investigational medical device

NOTE 1: This definition includes Adverse Events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the CTM.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the CTM.

Anticipated Serious Adverse Device Effect: An effect which by its nature, incidence, severity or outcome has been identified in the Investigator's Brochure.

Serious Adverse Event (SAE): Adverse Event that:

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to foetal distress, foetal death or a congenital abnormality or birth defect

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Event (USADE): Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

10.2 Definitions – Drug Adverse Events

Adverse Event (AE): An adverse event (sometimes referred to as an adverse experience) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction (SAR): A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the event.

Adverse Reaction (AR): An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected AE/SAR/AR: An adverse event, suspected adverse reaction or adverse reaction is considered "unexpected" if it not listed in the Investigator's Brochure.

Serious AE/SAR/AR: An adverse event, suspected adverse reaction or adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. If either the Investigator or Sponsor believes that an event is serious, the event will be considered serious and evaluated by the Sponsor for expedited reporting.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse event, suspected adverse reaction or adverse reaction is considered a SUSAR if it meets the criteria of both "Unexpected" and "Serious" as defined in this section. Any event believed to be a SUSAR by the Investigator and/or the Sponsor will be evaluated by the Sponsor for expedited reporting.

10.3 Relationship

The Relationship between an AE and the CTM and / or the study procedure will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

Definitely Related: The AE follows a reasonable temporal sequence from administration of the CTM/study procedure; the AE follows a known or expected response pattern to the CTM/study procedure.

Probably Related: The AE follows a reasonable temporal sequence from administration of the CTM/study procedure; the AE follows a known or expected response pattern to the CTM/study procedure; and the AE could not be reasonably explained by the known characteristics of the

subject's clinical state.

Possibly Related: The AE follows a reasonable temporal sequence from administration of the CTM/study procedure; the AE follows a known or expected response pattern to the CTM/study procedure but could readily have been produced by a number of other factors.

Unlikely Related: The AE which etiology is unlikely related to the CTM/study procedure even if event may follow a known or expected response pattern to the CTM/study procedure, and likely to be produced by a number of other factors. Sufficient information is not available at the time of the AE to determine its causality.

Not Related: An AE for which sufficient information exists to indicate that the etiology is unrelated to the CTM/study procedure. One or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence following administration of the CTM/study procedure;
- The AE is readily explained by the subject's clinical state or other therapies.

For events that are determined to be definitely, probably or possibly related, additional information on the relationship and timing of the event in relation to the arthrocentesis and study injection will be captured.

10.4 Severity

The severity of AEs will be assessed according to the following definitions:

Mild: The Adverse Event is noticeable to the subject but does not interfere with routine activity.

Moderate: The Adverse Event interferes with routine activity but responds to symptomatic therapy or rest.

Severe: The Adverse Event significantly limits the subject's ability to perform routine activities despite symptomatic therapy.

10.5 Reporting

10.5.1 Adverse Events

Only AEs that occur during and after treatment (treatment emergent AEs) will be recorded. At each visit during the trial, AEs that have occurred since the previous visit must be recorded. All subjects will be questioned and evaluated for AEs or complications associated with the procedure. Complications of the injection include, but are not necessarily limited to: pain, swelling and/or inflammation at the injection site. The Investigator will determine the severity and relationship of each event, as defined above.

AEs observed during the course of this study, regardless of severity or relationship to the injection will

be recorded on the appropriate eCRF. Each reported complication/AE will also include the duration, action taken to address the AE, and the resolution status (e.g. ongoing, resolved). These subjects will continue to be evaluated for safety and efficacy at all scheduled follow-up points.

The Sponsor must report the results of an evaluation of an Unanticipated Adverse Device Effect (UADE) to relevant regulatory agencies and all reviewing IRBs and Investigators within timelines required by the regulatory agencies.

10.5.2 Serious Adverse Events/Serious Adverse Device Effects/Serious Adverse Reactions

All SAE/SADE/SAR/ SUSAR must be reported to the Sponsor or designee within 24 hours of the investigative site becoming aware of its occurrence. This requirement is irrespective of whether the SADE/SAE is thought to be possibly related to the CTM/study procedure or not.

SAE/SADE/SAR/ SUSAR Reporting Procedures

Information such as the Investigator name, study name/protocol number, Subject ID number, the name of the SAE/SADE/SAR, the Investigator's assessment as to the relationship to the CTM/study procedure, and the reporting source should be included in the initial report. Any additional supporting documentation (e.g., autopsy report, hospital records, etc.) must be submitted to the Sponsor or designee. This also includes forwarding pertinent follow-up information (e.g., hospital discharge summary) as it becomes available. A completed SAE/SADE/SAR/ SUSAR form needs to be submitted with each follow-up. The Subject must be monitored carefully until the condition disappears, or the etiology is identified.

All SAE/SADE/SAR/ SUSAR will be entered into the EDC system. The EDC system will automatically notify the Medical Monitor and the Sponsor or designee.

10.5.3 Expedited Reporting

Any unexpected fatal or life-threatening AEs will be reported by the Sponsor or designee to the appropriate Regulatory Authority in accordance with applicable expedited reporting guidelines. Any event considered serious by either the Investigator or Sponsor will be evaluated by the Sponsor for expedited reporting.

10.5.4 Study Discontinuation

Enrollment and treatment may be suspended if a Subject experiences a serious and/or life-threatening AE that is probably or definitely related to the study injection. The study will be suspended if in the opinion of the medical monitor and Sponsor that the safety of subjects is uncertain. The decision to resume enrollment and treatment, permanently discontinue the trial, or otherwise modify the study will be made by the Medical Monitor in consultation with the Sponsor. Additionally, the triggering of the stopping rules will prompt notification to the appropriate regulatory agencies including the Food and Drug Administration (FDA) and the IRBs.

11 STATISTICAL CONSIDERATIONS

The statistical analysis of the study is described in detail in a separate version-controlled prospective Statistical Analysis Plan (SAP). However, the statistical methodology described in this section of the protocol will be the basis for the detailed SAP. It should be noted that this is a pilot study designed to assess the differences between Cingal and TH for change in pain and function scores between Baseline and 26 weeks post treatment. This change in scores will be conducted on multiple assessments and therefore, no formal hypothesis testing will be performed.

11.1 Sample Size

This is a pilot study designed to estimate as the primary assessment, the differences between Cingal and TH with respect to the difference in the change in WOMAC pain score from Baseline to 26 weeks post treatment. For convenience the sample size will be assessed in a 3:3:1 ratio (Cingal: TH: Placebo) with the sample sizes being 99:99:33, for a total sample size of 231 patients treated. It should be noted that if the standard deviation for the difference in change from Baseline in the WOMAC Pain Score between Cingal and TH is approximately 20 points and a difference of 8 points would yield 80% power of detecting that difference. If the difference is 10 points, this sample size yields over 90% power of detecting that difference.

Since the primary analysis in this study is an intent to treat analysis and the missing data for a patient will be imputed using mixed effects models, no dropout rate will be assumed for this study. Thus, the total sample size will be 231 patients treated.

11.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline in knee pain as measured by the WOMAC Pain Score (100 mm VAS).

The time point of main interest is 26 weeks, but in order to study the time course profile, the data will be analyzed at each time point. Data will be analyzed via an Analysis of Variance (ANOVA) with a term for treatment and Baseline pain score as a covariate. The primary analysis will be conducted by constructing 95% confidence intervals using the predefined contrasts for comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm. These confidence intervals will be constructed as:

$$(\overline{X}_i - \overline{X}_j) \pm z_{\alpha/2} s_D$$

Where $\overline{X}_i$ and $\overline{X}_j$ are the Least Squares Means for the two treatments being utilized and s_D is the standard deviation of that difference.

11.3 Secondary Efficacy Endpoints

There are many secondary endpoints to be investigated in this study. Again, these endpoints will be evaluated utilizing pairwise confidence intervals. For continuous variables the confidence intervals will be constructed as in section 11.2. For the dichotomous variables, the confidence intervals for the responder rates will be constructed utilizing the normal approximation to the binomial.

11.3.1 OMERACT-OARSI responder

The OMERACT-OARSI response rates for the Cingal® arm, TH arm, and the Placebo arm will be calculated for each time point and all pairwise difference confidence intervals will be constructed utilizing the normal approximation to the binomial distribution [29, 30].

11.3.2 VAS Knee Pain (0-100mm VAS)

The time point of main interest is 26 weeks, but in order to study the time course profile, the data will be analyzed at each time point. The average weekly pain score and the Area Under the weekly pain Curve (AUC) will be analyzed via an ANOVA and a mixed effects repeated measures ANOVA with a term for treatment and Baseline pain score as a covariate. The analysis will be conducted by constructing 95% confidence intervals using the predefined contrasts for comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.

11.3.3 NRS Knee Pain (0-10 NRS)

The time point of main interest is 26 weeks, but in order to study the time course profile, the data will be analyzed at each time point. The average weekly pain score and the Area Under the weekly pain Curve (AUC) will be analyzed via an ANOVA and a mixed effects repeated measures ANOVA with a term for treatment and Baseline pain score as a covariate. The analysis will be conducted by constructing 95% confidence intervals using the predefined contrasts for comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.

11.3.4 WOMAC Physical Function change from Baseline

The time point of main interest is 26 weeks, but in order to study the time course profile, the data will be analyzed at each time point. Data will be analyzed via an ANOVA with a term for treatment and Baseline score as a covariate. The analysis will be conducted by constructing 95% confidence intervals using the predefined contrasts for comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.

11.3.5 WOMAC Stiffness score change from Baseline

The time point of main interest is 26 weeks, but in order to study the time course profile, the data will be analyzed at each time point. Data will be analyzed via an ANOVA with a term for treatment and

Baseline score as a covariate. The analysis will be conducted by constructing 95% confidence intervals using the predefined contrasts for comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.

11.3.6 Total WOMAC score change from Baseline

The time point of main interest is 26 weeks, but in order to study the time course profile, the data will be analyzed at each time point. Data will be analyzed via an ANOVA with a term for treatment and Baseline score as a covariate. The analysis will be conducted by constructing 95% confidence intervals using the predefined contrasts for comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.

11.3.7 Patient Global Assessment change from Baseline

The time point of main interest is 26 weeks, but in order to study the time course profile, the data will be analyzed at each time point. Data will be analyzed via an ANOVA with a term for treatment and Baseline score as a covariate. The analysis will be conducted by constructing 95% confidence intervals using the predefined contrasts for comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.

11.3.8 Evaluator Global Assessment change from Baseline

The time point of main interest is 26 weeks, but in order to study the time course profile, the data will be analyzed at each time point. Data will be analyzed via an ANOVA with a term for treatment and Baseline score as a covariate. The primary analysis will be conducted by constructing 95% confidence intervals using the predefined contrasts for comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.

11.3.9 Rescue Medication Usage

The time point of main interest is 26 weeks, but in order to study the time course profile, the data will be analyzed at each time point. Data will be analyzed via an ANOVA with a term for treatment and Baseline score as a covariate. The primary analysis will be conducted by constructing 95% confidence intervals using the predefined contrasts for comparing the Cingal® arm to the TH arm, the Cingal arm to the Placebo arm, and the TH arm to the Placebo arm.

11.4 Exploratory Endpoints

Any comparisons between arms (Cingal®, TH, Placebo) utilizing a weekly ANOVA model with contrasts for pairwise differences, within arms and / or time points (from Baseline through to 26 weeks) not described in the primary or secondary endpoints may be presented in the exploratory endpoints including:

- EuroQoL (EQ-5D)

- WOMAC Pain Score (100mm VAS)
- Daily & weekly VAS pain scores
- Daily & weekly NRS pain scores
- OMERACT-OARSI
- Total WOMAC
- WOMAC Stiffness Score
- WOMAC Physical Function Score
- Patient Global Assessment
- Evaluator Global Assessment
- Range of Motion
- Rescue Medication Use: Difference in analgesic use measured by number of pills taken between visits will be compared between treatment arms descriptively.
- Number of Subjects Considered Treatment Failures: Treatment Failure: A subject who undergoes a procedure or uses a medication (other than the Rescue Medication) for the treatment of OA in the Index knee at any time after the study injection through the 26-week visit.

11.5 Statistical Methods

Tabulation of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software 9.1.3 or higher version. Where not otherwise specified, the last pre-treatment observation will be used as Baseline for calculating post-treatment changes from Baseline. The primary presentations and analyses will be based on data pooled across study centers. Relevant summaries for individual centers, or combinations of centers, may be presented for primary data. All confidence intervals will use a significance level of 5%.

11.6 Demographic and Baseline Characteristics

All demographic and Baseline characteristics will be tabulated by treatment arm and a test of homogeneity between the treatment arms will be conducted. For continuous variables (e.g. age, height, weight) a one-way ANOVA will be used. For categorical variables (e.g. gender, race), a Fisher's exact test or chi-squared test will be used. Medical History findings, Physical Exam and Concomitant Medications will be tabulated by treatment arm.

The Baseline Chemistry, Hematology, Urinalysis, Vital Signs, and BMI data will be summarized via descriptive statistics and tested for homogeneity using a one-way ANOVA.

11.7 Adverse Events

All AEs will be coded according to MedDRA. Safety assessments will include Treatment-Emergent Adverse Events (TEAEs) which are defined as AEs with an Investigator assessment of definitely,

probably, or possibly related to CTM/study procedure. TEAEs will be summarized with frequencies and percentages by system organ class and preferred term, severity, and relationship to study CTM/study procedure for each treatment arm. In summaries of TEAEs by severity and relationship to CTM/study procedure for subjects reporting multiple episodes, all reported events will be included, not only the worst reported case. Serious Adverse Events will also be presented by relationship to the CTM/study procedure.

The number of subjects with at least one AE will be tabulated for each treatment arm. Differences between the treatment arms will be tested using Fisher's exact test. Then the number of AEs for each treatment arm will also be tabulated.

The number of subjects and the number of AEs will be tabulated by severity, relationship, and local injection site specific events versus non local events.

11.8 Subject Populations

All safety analyses will be conducted on all subjects who undergo treatment in any arm.

The primary analysis on the primary endpoint will be performed on the ITT populations using the Multiple Imputation Methodology. The Multiple Imputation Methodology will use a mixed effects repeated measures model to predict the missing values. All Primary and Secondary endpoints will be analyzed using the ITT population.

It has been determined that any missing data in this study will follow the Missing at Random (MAR) assumption and is justified by the following section from the guide on missing data [31].

11.9 Additional Analyses

All of the analyses are performed on the data without covariates or other factors assumed in the model. If it is determined that certain factors may influence the outcomes of the endpoints, then additional analyses will be performed. For the continuous variables, the factors will be added to the ANOVA model and evaluated in a stepwise fashion for significance. For the discrete variables, the data will be analyzed via a GEE model with the factors added to the model.

12 DATA MANAGEMENT CONSIDERATIONS

12.1 Electronic Data Capture (EDC) System

The EDC system to be used in this study will be 21CFR part 11 compliant and have appropriate Quality Management Systems in place.

All sites will receive appropriate training on using the EDC System including completing the eCRF and responding to queries. Each designated site participant will receive a unique electronic signature: consisting of a username and password, after training has been completed in order to access the EDC System.

12.2 Data Collection

One eCRF will be completed for each study Subject based on the source documents. Once a Subject's eCRF has been completed by the site, the data management group will begin the data cleaning process. The details of completing the eCRF by the site can be found in the eCRF Completion Guidelines.

12.3 Data Management

Once the eCRF is ready for review, the data management group will complete automated and manual validation checks according to the Data Management Plan (DMP) to ensure the quality, consistency, and completeness of all data entered. Instances of incomplete, uninterpretable or inconsistent data will be resolved with the site through issuing a query or other means of communication as necessary. The site is responsible to respond and / or correct the data for all queries issued in a timely manner. All queries and changes to the data will be tracked.

12.4 Data Retention

At the end of the study, an electronic transfer of all data will be provided to the Sponsor. The Contract Research Organization (CRO) and Sponsor will be responsible for retaining all data and documents pertaining to this study for a period of at least 2 years after the Cingal FDA marketing application is approved; or, if an application is not approved for Cingal, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified; or as required by local applicable regulatory requirements.

The Sponsor will be responsible for retaining the final data set and documents pertaining to this study for a period of at least 2 years after the Cingal FDA marketing application is approved; or, if an application is not approved for Cingal, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified; or as required by local applicable regulatory requirements.

13 CLINICAL SUPPLIES

13.1 Packaging and Labeling

CTM will be provided enclosed in a carton containing required labeling and caution statements and a unique identifying kit number. An independent third party will maintain the master randomization scheme. The Cingal, TH and Placebo will be supplied by the Sponsor to the Investigational Sites for use in the trial. The third party will ship the CTM to the sites as needed. Specific instructions for ordering CTM will be provided to the sites.

13.2 Storage Requirements

The storage requirements for CTM are to be maintained in a secure controlled environment at room temperature below 77° F / 25° C. DO NOT FREEZE.

13.3 Instructions for Use

Instructions for Use will be provided in the Investigator's Brochure. The Investigator's Brochure document contains the following risk information:

13.3.1 Contraindications

Cingal®:

CINGAL® is composed of cross-linked hyaluronic acid and an ancillary corticosteroid TH. The following pre-existing conditions may constitute relative or absolute contraindications to the use of CINGAL®:

- Hypersensitivity to the active substance or to any of the excipients contained in CINGAL
- Pre-existing infections of the skin region of the intended injection site
- Infection of the index joint
- Systemic bleeding disorders

The ancillary medicinal substance, TH, is contraindicated in the case of:

- Hypersensitivity to TH
- Active tuberculosis
- Herpes simplex keratitis
- Acute psychoses
- Systemic mycoses and parasitoses (strongyloid infections)

TH:

Lederlon® 20 mg is a glucocorticoid (adrenal cortex hormone) that acts on the metabolism, the salt (electrolyte) balance and tissue functions. Glucocorticoids have anti-inflammatory and other therapeutic properties. The glucocorticoid in Lederlon® 20 mg is called TH.

Lederlon® 20 mg may NOT be used in the event of:

- Known hypersensitivity to TH or one of the following other ingredients in this medication: benzyl alcohol (9 mg per 1 ml), polysorbate 80, sorbitol (Ph. Eur.)
- Infections within or in direct proximity of the joint to be treated
- Joint inflammation due to bacterial infections (bacterial arthritis)
- Instability of the joint to be treated
- Tendency toward bleeding, either spontaneously or due to taking medications to inhibit coagulation (anticoagulants)
- Calcium deposits around joints
- Bone necrosis due to sporadic or persistent perfusion disorders (non-vascularized bone necrosis)
- Ruptured tendon
- Joint disease due to decreased pain perception in the joint (neuropathic arthropathy)

13.3.2 Anticipated Adverse Reactions

Reported adverse reactions associated with the IA use of combined Hyaluronic Acid and Triamcinolone Hexacetonide:

Single intra-articular injections of sodium hyaluronate combined with Triamcinolone Hexacetonide has been studied by Anika Therapeutics, Inc. in two Phase III clinical trials: Cingal 13-01, 16-02 and additionally the 39-week extension trial: Cingal 17-02

The most common reported adverse events associated are the following: arthralgia, joint swelling, warmth, range of motion decrease and injection site pain.

Incidences of rash, headache, dizziness, chills, hives, itching, nausea, muscle cramps, peripheral edema, and malaise have also been reported in association with intra-articular injections.

In Cingal 13-01, 16-02, and 17-02 the AEs that were possibly, probably and definitely related to the study injection for patients receiving Cingal were 2.0%, 7.6% and 0 % respectively [14-16]. These AEs were minor or moderate complications that required little or no treatment. These included injection site events, joint swelling, joint pain, and limb pain.

Reported adverse reactions associated with the IA use of corticosteroids:

Single intra-articular injections of Triamcinolone Hexacetonide have been associated with the following adverse reactions:

- Dermatologic: Whitening of the skin at the injection site, local fat atrophy.
- Musculoskeletal: Joint infection, joint swelling and pain several hours after injection, tendon rupture, pain, swelling, ligament damage.
- Neurological: Nerve damage.

- General: Infection, local bleeding, allergic reactions.

Anika Therapeutics, Inc. has conducted one Phase III trial utilizing Triamcinolone Hexacetonide (Lederlon) in Cingal 16-02 and additionally the 39-week extension trial: Cingal 17-02 [14, 15]. The AEs that were possibly, probably and definitely related to the study injection for patients receiving Triamcinolone Hexacetonide were 4.1% and 0 % respectively. These AEs were minor or moderate complications that required little or no treatment. These involved injection site pain and joint pain.

13.4 CTM Accountability

It is important to account for the disposition of all CTM received by a clinical site. Required information includes the date received, date injected, batch number, quantity injected, expiry date and the Subject who received the CTM.

The site will use a form to document CTM disposition which will be reviewed by the study monitor during routine monitoring visits. Each time CTM is dispensed, the following information should be recorded: the subject's initials, Subject ID, the Subject randomization number, date, the number of the CTM dispensed, and the initials of the person dispensing the CTM. At the termination of the study, Anika Therapeutics, Inc. will instruct sites on the disposition of unused CTM.

13.5 Emergency Unblinding

Unblinding should only occur when a SAE requires the allocation code in order to enable clinical treatments to be planned. The clinical team and Medical Monitor should assess the need for unblinding as time permits. The allocation details can then be provided. Upon unblinding, the site personnel should record withdrawal of the Subject and the allocation in the clinical trial notes.

14 DATA QUALITY ASSURANCE

Anika Therapeutics, Inc. performs quality assurance checks on all clinical trials that it sponsors. Before enrollment of a Subject in this study, a monitor (from Anika or designee) and the site staff will review the protocol, the eCRFs and instructions for completing them, the procedure for obtaining informed consent, the procedure for reporting AEs and all other relevant study procedures and forms. Site monitoring visits will be performed on a regular basis according to the Monitoring Plan.

15 REGULATORY OBLIGATIONS

The PI agrees that the study will be conducted according to the FDA Regulations in 21 CFR Part 312 and the principles of the ICH E6 (R2) GCP, ISO 14155:2011, 21 CFR part 11, 50, 56 and the ethical principles that have their origins in the World Medical Association Declaration of Helsinki, and local Institutional Review Board and legal requirements. To ensure compliance the Investigator agrees, by written consent to this protocol, to fully cooperate with compliance checks by allowing access to all documentation by authorized individuals. The Investigator must conduct the trial as outlined in the protocol and in accordance with Declaration of Helsinki, as well as all applicable government

regulations.

15.1 Clinical Trial Information

Before the beginning of the study the Investigator will be given the latest Investigator's Brochure. If the Investigator's Brochure is revised during the study, the Investigator will receive a copy of the revised version. The Investigator's Brochure and the protocol are confidential communications of Anika Therapeutics, Inc. Acceptance constitutes the agreement by the recipient that no unpublished information therein contained will be published or disclosed without Anika Therapeutics, Inc.'s prior written approval except that these documents must be submitted in accordance with the SOPs of the IRB and other applicable oversight committees with the agreement that these committees are required to keep the information confidential.

15.2 Regulatory Approval

The study outlined in this protocol will only be conducted following written approval by the appropriate Regulatory Authority for sites located in the United States. The protocol will be conducted under an approved Investigational New Drug (IND) amendment. The Sponsor has the responsibility to obtain FDA approval of the IND prior to the study initiation.

15.3 Independent Review Board (IRB) Approval

The protocol and the ICF must have the approval of a properly constituted IRB responsible for approving clinical trials for each investigational site. Any additional requirements imposed by the FDA shall be addressed in the protocol amendments. The signed IRB approval letter must list the Investigator's name, the Anika Therapeutics, Inc. protocol title, and the date of approval of the protocol and the ICF. Any advertisements used to recruit subjects or any Subject handouts should also be reviewed and approved by the IRB. Anika Therapeutics, Inc. or designee will not ship any CTM to a site until an approval letter has been received from the IRB and a Clinical Trial Agreement has been fully executed.

The Investigator is committed in accordance with regulatory requirements to inform the Sponsor and the IRB of any emergent problem, SADEs/SAEs, and/or protocol amendments.

15.4 Amendments to the Protocol

Any amendment to the study protocol must be agreed upon between the Investigator(s) and Anika Therapeutics, Inc. A protocol amendment must be approved by Anika Therapeutics, Inc., who will be responsible for obtaining approval from the FDA via an IND amendment. Protocol amendments must be approved by the FDA and IRB before being implemented at the site.

15.5 Pre-Study Documentation

The Investigator must provide the following documents prior to the enrollment of any subjects as appropriate to U.S. FDA regulation:

- Completed and signed Investigator Agreement/Form FDA 1572 signed by Principal Investigator.
- Signed and dated protocol signature page by the Principal Investigator.
- Signed and dated protocol amendment(s) signature page by the Principal Investigator.
- Current curriculum vitae (CV) for the Investigator and all Sub-Investigators (including Blinded Evaluator).
- Current medical license for the Principal Investigator and all Sub-Investigators (if applicable).
- Financial disclosure statements signed and dated by the Investigator and all Sub-Investigator (including Blinded Evaluator).
- Copy of the IRB approval letter for the protocol and any other pertinent documents.
- List of IRB committee members and/or multiple assurance number.
- Copy of the IRB-approved ICF to be used.
- Fully executed Clinical Trial Agreement.
- Delegation of Authority form.
- Certified translations approved ICF document (when applicable).
- Insurance certificate as required.

15.6 Investigator Responsibilities

- The Investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical study.
- The Investigator must have knowledge on the use, application, implementation or administration of the CTM and the requirements for clinical, efficacy and safety follow-up.
- The Investigator should be familiar with and trained on the appropriate use of CTM as described in the protocol and in the current Investigator's Brochure.
- The Investigator is responsible to ensure that the CTM is administered only by trained personnel in accordance with the protocol and instructions for use.
- The Investigator should disclose any potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of the results.
- The Investigator should be trained on and comply with GCP regulations and the applicable regulatory requirements.
- The Investigator should demonstrate that the proposed Clinical Trial Site has the following:
    - One or more qualified Investigators;
    - Qualified site staff;
    - Adequate facilities for the foreseen duration of the clinical study;
    - Required number of eligible subjects needed within the agreed recruitment period.

- The Investigator must create and maintain source documentation throughout the clinical study and make it available as requested during monitoring visits and audits.
- The Investigator should permit monitoring and auditing by the Sponsor or Sponsor's designee and inspection by the appropriate Regulatory Authority. Investigator should be accessible (when possible) to the monitor to respond to questions.
- The Investigator should have sufficient time to conduct and oversee the trial.
- The Investigator should ensure the IRB has the most up to date study related documentation (e.g. Investigator's Brochure, Protocol).
- The Investigator should inform the subject's primary physician about the subject's participation in the trial if permitted to do so by the subject.
- The Investigator will provide the Sponsor with copies of any clinical-investigation-related communications between the Investigator and the IRB.
- The Investigator must be aware of the AE and adverse reaction reporting process, including reactions related to application of the CTM/study procedure.
- The Investigator shall ensure accuracy, completeness legibility and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.
- The Investigator must have knowledge of the risk analysis of the CTM, knowledge of the requirements for storage, handling, administration, and destruction or disposal of the CTM including any hazard to those handling the product and close contacts and the risk to the environment. Investigator will also maintain CTM accountability records.
- The Investigator must ensure that the particular requirements for the application of the CTM, such as standardization of injection procedures if possible and training of the healthcare professionals involved, are communicated to the site staff including the surgeons or other specialists involved.
- The Investigator shall ensure maintenance and calibration of the equipment relevant for the assessment of the clinical study is appropriately performed and documented, when applicable.
- The Investigator must be knowledgeable with the method of obtaining informed consent.
- The Investigator shall ensure and document appropriate training if any authorized designee is appointed to conduct the informed consent process.
- The Investigator must inform the trial Subject of the particular issues that arise for the CTM. In particular, both the ICF and any other written information to be provided to the subjects should include an explanation of the following:
    - Provisions for Subject data protection and confidentiality;
    - The arrangements for follow-up before and after the end of the trial, including after subjects withdraw from the study and including the information to be provided to the Subject for use in the event of problems arising after the end of the trial;
    - The length of follow-up;
    - The definition of the end of the trial and its relationship to the follow-up after the end of the trial;

  - The need to keep an accurate Subject's Electronic Diary;
  - The irreversible nature of the CTM;
  - The need, where applicable, for the presence of a representative of the Sponsor for assistance during the administration of the CTM and the rationale for this.
- The Investigator shall provide adequate medical care to a Subject during and after subject's participation in a clinical study in the case of AEs.
- The Investigator shall ensure that clinical records are clearly marked to indicate that the Subject is enrolled in a particular clinical study.
- The Investigator must provide the Subject with the following:
  - Any necessary instructions on the proper use, handling, storage, and return of the rescue medications. Investigator shall retain all clinical-investigation-related records;
  - Information on any new significant findings occurring during the clinical study, including the need for additional medical care that may be required;
  - Well-defined procedures for possible emergency situations to the clinical study and make arrangements for emergency treatment, including decoding procedures for blinded/masked clinical studies;
  - Some means of showing the subjects participation in the clinical study, together with identification and compliance information for the concomitant treatment measures (If appropriate).
- The Investigator shall review the Clinical Study Report at the close-out of the clinical study.

15.7 Sponsor's Responsibilities

- Anika Therapeutics, Inc. may delegate some of the responsibilities to a CRO but will maintain oversight of the clinical study. Anika Therapeutics, Inc. shall define, establish and allocate all the roles and responsibilities related to the clinical study in one or more written agreements.
- Anika Therapeutics, Inc. shall implement and maintain written clinical quality procedures to ensure that the clinical study is designed, conducted and monitored, and that data are generated, documented, recorded and reported in compliance with FDA 21 CFR Part 11, 50, 56, 312, ISO 14155:2011 and ICH E6 (R2), this protocol, any subsequent amendments, and any other applicable standards and regulatory requirements.
- Anika Therapeutics, Inc. will ensure that there is written agreement with the Investigator/institution and any other parties involved with the clinical study.
- Anika Therapeutics, Inc. will designate appropriately qualified medical personnel to advise on medical questions or problems.
- Anika Therapeutics, Inc. will utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.
- Anika Therapeutics, Inc. will select Investigators/institutions that are qualified by training and experience with adequate resources to properly conduct this trial for which the Investigator is

selected. Anika will also select a coordinating Investigator, if appropriate. Anika Therapeutics, Inc. will ensure members of the site staff and their designated authorization(s) are identified in a log with details.

- Anika Therapeutics, Inc. will ensure that all Investigators and all other parties involved are given instructions on uniformly assessing and documenting clinical and laboratory findings.
- Anika Therapeutics, Inc. will establish the particular requirements for the application of the CTM, and train the Investigator in the requirements for storage, handling, administration, and destruction or disposal of the CTM including hazards to those handling the product and close contacts and the risk to the environment.
- Anika Therapeutics, Inc. will designate or appoint one or more monitors, or otherwise assume the responsibilities of the monitor(s) and ensure documentation of training, experience and scientific or clinical knowledge for all the relevant parties involved in order to adequately conduct the clinical study. This includes training on the following:
  - Use of the CTM
  - Accountability procedures
  - Investigator's Brochure
  - Protocol
  - eCRFs and instructions for completion
  - The written ICF and informed consent process as well as other written information provided to subjects
  - Sponsors written procedures; ISO 14155:2011; 21 CFR part 11, 50, 56, 312, ICH E6 (R2) and any other applicable regulatory procedures.
- Anika Therapeutics, Inc. will receive disclosures of conflicts of interest from PIs and Sub - Investigators.
- Anika Therapeutics, Inc. will assure the accuracy of any translations, as applicable.
- Anika Therapeutics, Inc. will ensure that any electronic trial data handling and/or remote electronic trial data systems, are validated with the following characteristics:
  - Data changes are allowed with an audit trail;
  - System is secure and does not allow for unauthorized access to the data;
  - A list of the individuals who are authorized to make data changes is maintained;
  - Adequate backup of the data is maintained;
  - An unambiguous Subject ID is used to allow identification of all the data reported for each subject.
- Anika Therapeutics, Inc. will ensure maintenance of Sponsor-specific essential documents pertaining to the trial in conformance with the applicable regulatory requirement(s) of the country where the product is approved, and/or where the Sponsor intends to apply for approval(s).
- Anika Therapeutics, Inc. will inform the Investigator/institution in writing of the need for record retention and will notify the Investigator/institution in writing when the trial related records are no longer needed.

- Anika Therapeutics, Inc. will provide insurance or indemnify the Investigator/institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.
- Anika Therapeutics, Inc. will obtain the following information documentation from each participating IRB:
  - The name and address of the IRB.
  - A statement obtained from the IRB that it is organized and operates according to GCP and the applicable laws and regulations.
  - Documented IRB approval/favorable opinion for the protocol and any subsequent amendments (as applicable) and re-approvals.
- Anika Therapeutics, Inc. will update the Investigator's Brochure as significant new information becomes available.
- Anika Therapeutics, Inc. will ensure the CTM is transported at the acceptable storage temperatures and transport conditions.
- Anika Therapeutics, Inc. will not supply an Investigator/institution with the CTM until it obtains all required documentation ensuring the site has a signed contract with the Sponsor, and IRB, or other regulatory approvals as required.
- Anika Therapeutics, Inc. will verify that each Subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB review, and regulatory inspection.
- Anika Therapeutics, Inc. is responsible for the ongoing safety evaluation of the CTM.
- Anika Therapeutics, Inc. will notify all concerned Investigators/institutions and the Regulatory Authority of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB approval/favorable opinion to continue the trial.
- Anika Therapeutics, Inc. will submit any required application(s) to the appropriate Regulatory Authority for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s).
- Anika Therapeutics, Inc. will ensure that all required IRB, or other regulatory approvals are obtained and documented; and that appropriate provisions are made to meet any specific conditions imposed by the FDA or IRB. Anika will ensure that any modification(s) required by the IRB or other Regulatory Authority are made and documented by the Investigator and have gained the approval of the IRB or the Regulatory Authority.
- Anika Therapeutics, Inc. will expedite the reporting to all concerned Investigator(s)/institutions(s), to the IRB, where required, and to the Regulatory Authority of all AEs/ADEs that are both serious and unexpected.
- Anika Therapeutics, Inc. will submit to the Regulatory Authority all safety updates and periodic reports, as required by applicable regulatory requirement(s).
- Anika Therapeutics, Inc. will ensure that an ongoing risk analysis, based on existing knowledge of the type of product and its intended use, is performed and provided to the Investigator involved in a clinical study with the CTM, through the Investigator's Brochure or

updates to it and to the Subject through the ICF or updates to it.

- Anika Therapeutics, Inc. will also incorporate the risk analysis and risk management plan of the CTM and share this with the Investigators;
- Anika Therapeutics, Inc. shall be responsible for:
  - Accountability of the CTM throughout clinical study;
  - Documenting correspondence with all parties involved in the clinical study, including the IRB and FDA;
  - Ensuring that the clinical study is appropriately monitored by determining the extent and nature of the monitoring;
  - Reviewing the monitoring reports and follow-up on actions required in the monitoring report;
  - Taking prompt action to secure compliance with all clinical study requirements;
  - Submitting progress reports, including safety summary deviations, when requested, to all reviewing IRB's and FDA.

15.8 Informed Consent

All subjects in this study are to be completely informed, in accordance with local IRB or other regulatory authority requirements, concerning the pertinent details and purpose of the study. Informed consent for each Subject will be obtained in accordance with FDA regulations in 21 CFR Part 50 and ICH Guidance for Industry E6 GCP: Consolidated Guidance (ICH Topic E 6 (R2) Guideline for Good Clinical Practice). One copy of the signed ICF document must be given to each Subject in his/her native language and one signed copy must be retained in the subject's file.
All subjects must sign and personally date an approved ICF after receiving detailed written and verbal information about the reason, the nature and the possible risks associated with the administration of the CTM. An ICF will be required for all subjects.

All foreseeable risks and potential benefits which might occur with the use of the CTM will be discussed with the subject. The Subject will be informed that, should an unanticipated adverse product-related event occur, which presents an unreasonable risk to participating subjects, he/she will be notified. The Subject will be informed that his/her medical records are Subject to review by representatives of the Sponsor, IRB, or the appropriate Regulatory Authority, as necessary. The Subject will be informed that the information obtained during the study will be used to evaluate the safety and efficacy of the CTM. However, his/her confidentiality will be maintained at all times. The Subject will be told that he/she is free to refuse study participation or to withdraw from the study at any time without compromising future medical care.

The Subject must be made aware and agree that personal information may be scrutinized during an audit by the Regulatory Authority and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available.

A sample ICF template with standard wording suggested for this study will be provided to each Investigator. Prior to IRB submission, the Investigator must send a copy of the ICF to be used at their institution to Anika Therapeutics, Inc. or designee for review to assure compliance with the FDA and ICH requirements. The approved written consent form is to be supplied by the Investigator and will be understood and signed by each Subject prior to enrolling in the study. The Investigator is responsible for maintaining each subject's ICF in the study file and providing each Subject with a copy of the ICF.

15.9 Protocol Adherence

The Investigator agrees to conduct the study according to the protocol and agrees that all persons delegated to perform study procedures will do so as well. The Investigator must read the protocol thoroughly and must follow the instructions exactly. Investigators shall propose to Anika Therapeutics, Inc. any appropriate modifications to the Protocol or of the use of the CTM. Any change should be agreed to by prior discussion between Anika Therapeutics, Inc. and the Investigator, with written protocol amendments made prior to affecting the changes agreed upon. The Investigator is not to conduct any protocol modifications without prior written permission from Anika Therapeutics, Inc. Investigator will refrain from implementing any modifications to the protocol without agreement from the Sponsor, IRB and FDA, if applicable. Each Investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria.
Deviations from the protocol include, but are not limited to, the use of prohibited medications or therapies, out of window visits, etc. All protocol deviations should be documented and explained. Major protocol violations are defined as those that could impact the efficacy evaluation such as a Subject is ineligible, missing key data, received an unauthorized treatment, etc. All subjects with protocol deviations will continue to be followed for safety and efficacy assessments. Analysis of study data will be done on both the ITT and PP populations.

15.10 Adverse Event Reporting

The Investigator agrees to document and report all AEs / ARs to Anika Therapeutics, Inc. or its designee. The Investigator is further responsible for ensuring that any Sub-Investigator promptly brings AEs / ARs to the attention of the Investigator. The Investigator is also responsible for informing the participating IRB and other Regulatory Authority (as applicable) of any reportable events and adhering to local IRB requirements. The Investigator agrees to supply Anika Therapeutics, Inc., upon request, any additional information related to the safety reporting of a particular event. The Investigator shall inform the Subject of the nature and possible cause of any AEs/ ARs experienced.

15.11 Permission to Review Subject's Source Records

The Investigator agrees that Anika Therapeutics, Inc., its employees or agents, and the FDA will have the right from time to time, both during and after this trial, to audit and review pertinent medical records related to the clinical study. A signed statement will be obtained from each Subject who participates in the trial that permits the release of his or her medical records as necessary for inspection by authorized personnel from Anika Therapeutics, Inc., its designee or the FDA. Subjects will not be identified by name, and confidentiality of information in medical records will be preserved.

15.12 Change in Investigator

If any Investigator retires, relocates, or withdraws from an investigation, the responsibility for conducting the study and maintaining records may be transferred to another person who will accept the responsibility at the same institution. Anika Therapeutics, Inc. must be notified of and agree to the change.

15.13 Records Retention

All documents related to this clinical study should be kept in appropriate study files. Copies of the protocol, Subject ID, eCRF, source data, ICF and other documents pertaining to the study conduction must be retained for a period of at least 2 years after the Cingal FDA marketing application is approved; or, if an application is not approved for Cingal, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified; or as required by local applicable regulatory requirements. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. No study document will be destroyed without prior written agreement between Anika Therapeutics, Inc. and the Investigator.

15.14 Study Monitoring

An appropriate representative of Anika Therapeutics, Inc. or designee (Study Monitor) will maintain contact with the Investigator and will visit the Clinical Trial Site for the purpose of overseeing the progress of the study, and ensuring it is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and applicable regulatory requirements.

An initiation visit will be made by the Study Monitor to discuss the protocol and the obligations of both the Sponsor and the Investigator. The Investigator must allow the Study Monitor to perform periodic, interim monitoring visits. The purposes of these visits are:

- Verify that written informed consent was obtained prior to each subject's participation in the trial
- Ensure the conduct of the trial is in compliance with the currently approved

protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s)
- Ensure the rights and well-being of human subjects are protected
- Ensure the reported trial data are accurate, complete, and verifiable from source documents.
- Assess the progress of the study
- Review the compliance with the study protocol
- Determine whether the Investigator is maintaining the essential documents
- Discuss any emergent problem(s)
- Assess adequate documentation of CTM accountability
- Act as the main line of communication between the Sponsor and the Investigator
- Ensure that the Investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s)
- Ensure that the Investigator and the Investigator's site staff are adequately informed about the trial
- Verify that the Investigator and the Investigator's site staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the Sponsor and the Investigator/institution, and have not delegated these functions to unauthorized individuals
- Verify that the Investigator is enrolling only eligible subjects
- Inform the Investigator of any eCRF entry error, omission, or illegibility
- Determine whether all AEs are appropriately reported within the time periods required by GCP, the protocol, the IRB, the Sponsor, and the applicable regulatory requirement(s)
- Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the Investigator and ensuring that the site staff takes appropriate action designed to prevent recurrence of the detected deviations

All data required by the protocol must be reported accurately on the eCRFs and must be consistent with the source documents. Source documents are original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays or other diagnostic images, subject's files, pharmacy records and laboratory records). The Investigator will make available the source documents for inspection. This information will be considered as confidential.

The Study Monitor will perform a closeout visit at the conclusion of the Investigator's involvement in the study.

15.15 Case Report Form

Electronic Case Report Forms must be completed for each Subject in accordance with the Data Management Plan and any eCRF Completion Guidelines. The Investigator must ensure data are reported into the eCRF in a timely fashion and that data recorded in the eCRF is consistent with the source documents or the discrepancies should be explained. Any change or correction should have an audit trail and explanation of the change.

15.16 Auditing

The Investigator will make all pertinent records available including source documentation for inspection by the Regulatory Authority and for auditing by the Sponsor. This information will be considered as confidential. The Sponsor's audit will be independent of and separate from routine monitoring or quality control function and will serve to evaluate the trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

15.17 Use and Publication of Study Results

All unpublished documentation (including the protocol, eCRF and Investigator's Brochure) given to the Investigator is strictly confidential. All recipients must agree not to disclose the information herein contained to any person without the prior written authorization of Anika Therapeutics, Inc. The submission of these documents to the IRB is expressly permitted. The Investigator agrees that Anika Therapeutics, Inc. maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and Regulatory Authority of any country.

The results of the study may be presented during scientific symposia or published in a scientific journal only after review by Anika Therapeutics, Inc. in accordance with the guidelines set forth in the applicable publication or the Investigator agreement.

15.18 Confidentiality

All information that is provided to the Investigator dealing with the CTM is regarded as confidential. Subjects will be told that data will be handled in compliance with Health Insurance Portability and Accountability Act (HIPAA), and other national laws on the protection of personal data. Subjects will be informed that the Anika Therapeutics, Inc. or designee will have access to their medical records. Subject's participation in the study will be treated as confidential and subject's will not be referred to by name in any report of the study. The identity of the subjects will not be disclosed in any study records and subjects' data will be described with a unique Subject identifier. Subject data will be processed electronically to determine the outcome of this study, and to provide to the Regulatory Authority. Subjects will be advised that all data may be transferred to other countries.

15.19 Early Study Discontinuation

If the Sponsor, Investigator, or Study Medical Monitor discover conditions during the study that indicate that the study or Clinical Trial Site should be terminated, this action may be taken after appropriate consultation between the Sponsor, Investigator, and Study Medical Monitor.

Conditions that may warrant termination of the Clinical Trial Site include, but are not limited to:

- The discovery of any unexpected, serious, or unacceptable risk to subjects enrolled in the study,
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the CTM.
- Failure of the Investigator to comply with GCP guidelines,
- Submission of knowingly false information from the research facility to the Sponsor,
- Clinical Monitor, or Regulatory Authority,
- Insufficient adherence to protocol requirements.

If Anika Therapeutics, Inc. and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. Anika Therapeutics, Inc. also reserves the right to discontinue this study for administrative reasons at any time.

If a trial is suspended, Anika Therapeutics, Inc. will promptly inform the Investigators/institutions, and the Regulatory Authority of the termination or suspension and the reason(s) for the termination or suspension. The Investigator should notify the IRB promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution.

15.20 Subject Withdrawal

Each Subject is free to discontinue from the study at any time, for any reason. If a Subject discontinues the study, the Investigator will record the reason for withdrawal on the eCRF. Examples of reasons for premature withdrawal of a Subject from the study include:

- Inter-current illness that would, in the judgment of the Investigator, affect study assessment to a significant degree
- Subject noncompliance with follow-up assessments
- Subject request to withdraw
- Subject lost to follow-up
- Treatment failure
- Termination of the site's study participation by Anika Therapeutics, Inc., the institution, IRB or the Regulatory Authority
- Other (reason to be documented in the eCRF)

Every effort shall be made to have withdrawn subjects return for the required safety evaluations as detailed in the protocol.

15.21 Pregnancy

Pregnancies occurring while the patient is in the study need to be reported. In the event of a pregnancy, the patient should be referred to an obstetrician/gynecologist for further evaluation and counseling.

The Investigator will follow the patient until completion of the pregnancy and must notify the Medical Monitor of the outcome within 5 days. The Investigator will provide this information as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such. Furthermore, all neonatal deaths that occur within 30 days of birth are to be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in-utero exposure to the study drug should also be reported.

16 GENERAL INFORMATION

16.1 Study Contact Information

Sponsor:
Anika Therapeutics, Inc.
32 Wiggins Avenue
Bedford, MA 01730
Phone: 781-457-9000
Fax: 781-305-9720

Medical Monitor:
During Office Hours:
Rich Paul, MD
Synteract
5909 Sea Otter Place
Carlsbad, CA 92010
Email: richard.paul@synteract.com
Phone: 760-268-8013

Contract Research Organization (CRO):
Synteract
5909 Sea Otter Place
Carlsbad, CA 92010
Phone: 760-268-8200
Fax: 760-929-1419

Central Core Imaging Laboratory:
Qmetrics Technologies
1250 Pittsford-Victor Road
Suite 110, Building 200
Pittsford, NY 14534
Phone: 585-301-4300
Fax: 585-301-4300 X250

16.2 Study Administrative Structure

Name/Affiliation	Address/Phone Number	Responsibility
Adrian Orr	Director of Clinical Affairs Anika Therapeutics, Inc. 32 Wiggins Avenue Bedford, MA 01730 USA Tel: 781-457-9226 Fax: 781-305-9720 Email: aorr@anikatherapeutics.com	Sponsor Project Director
Rich Paul, MD	Synteract 5909 Sea Otter Place Carlsbad, CA 92010 USA Email: richard.paul@synteract.com Phone: 760-268-8013	Medical Monitor
Synteract Inc.	CRO 5909 Sea Otter Place Carlsbad, CA 92010 USA Phone: 760-268-8200	Safety, Site Management and Monitoring
Qmetrics Clinical Services	Core Imaging Laboratory 1250 Pittsford-Victor Road, Bldg 2, Suite 110 Pittsford, NY 14534 USA Phone: 585-301-4300	Imaging
Axiom Real-Time Metrics Inc.	EDC and Data Management Vendor 1 City View Dr Etobicoke, ON M9W 1J1, Canada	EDC and Data Management

In case of emergency, refer to the study manual of operations for alternate contact information.

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Appendix 1 WOMAC

WOMAC OSTEOARTHRITIS INDEX VERSION VA3.1

INSTRUCTIONS TO PATIENTS

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

EXAMPLES:

1. If you put your " ✗ " at the left-hand end of the line as shown below, then you are indicating that you feel **no** pain.

2. If you put your " ✗ " at the right-hand end of the line as shown below, 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 " ✗ " **past either end of the line**.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 48 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.

English for USA - V2

WOMAC VA3.1 QUESTIONNAIRE **WOMA**

Section A

PAIN

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

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

QUESTION: **How much pain have you had . . .**	Study Coordinator Use Only
1. when walking on a flat surface? No Pain — Extreme Pain	PAIN1 ____
2. when going up or down stairs? No Pain — Extreme Pain	PAIN2 ____
3. at night while in bed? (that is - pain that disturbs your sleep) No Pain — Extreme Pain	PAIN3 ____
4. while sitting or lying down? No Pain — Extreme Pain	PAIN4 ____
5. while standing? No Pain — Extreme Pain	PAIN5 ____

English for USA - V2

WOMAC VA3.1 QUESTIONNAIRE **WOMB**

Section B

STIFFNESS

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

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

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

	Study Coordinator Use Only
6. How **severe** has your stiffness been **after you first woke up** in the morning? No Stiffness ——— Extreme Stiffness	STIFF6 ____
7. How **severe** has your stiffness been after sitting or lying down or while resting **later in the day**? No Stiffness ——— Extreme Stiffness	STIFF7 ____

English for USA - V2

WOMAC VA3.1 QUESTIONNAIRE **WOM**C1-3

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

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

QUESTION: **How much difficulty have you had . . .**	Study Coordinator Use Only
8. when going down the stairs? No Difficulty — Extreme Difficulty	PFTN8 ____
9. when going up the stairs? No Difficulty — Extreme Difficulty	PFTN9 ____
10. when getting up from a sitting position? No Difficulty — Extreme Difficulty	PFTN10 ____
11. while standing? No Difficulty — Extreme Difficulty	PFTN11 ____
12. when bending to the floor? No Difficulty — Extreme Difficulty	PFTN12 ____
13. when walking on a flat surface? No Difficulty — Extreme Difficulty	PFTN13 ____

English for USA - V2

WOMAC VA3.1 QUESTIONNAIRE **WOMC2-3**

DIFFICULTY PERFORMING DAILY ACTIVITIES

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

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? No Difficulty — Extreme Difficulty	PFTN14 _____
15. while going shopping? No Difficulty — Extreme Difficulty	PFTN15 _____
16. when putting on your socks or panty hose or stockings? No Difficulty — Extreme Difficulty	PFTN16 _____
17. when getting out of bed? No Difficulty — Extreme Difficulty	PFTN17 _____
18. when taking off your socks or panty hose or stockings? No Difficulty — Extreme Difficulty	PFTN18 _____
19. while lying in bed? No Difficulty — Extreme Difficulty	PFTN19 _____

English for USA - V2

WOMAC VA3.1 QUESTIONNAIRE **WOMC3-3**

DIFFICULTY PERFORMING DAILY ACTIVITIES

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

QUESTION: **How much difficulty have you had . . .**	Study Coordinator Use Only
20. when getting in or out of the bathtub? No Difficulty — Extreme Difficulty	PFTN20 _____
21. while sitting? No Difficulty — Extreme Difficulty	PFTN21 _____
22. when getting on or off the toilet? No Difficulty — Extreme Difficulty	PFTN22 _____
23. while doing heavy household chores? No Difficulty — Extreme Difficulty	PFTN23 _____
24. while doing light household chores? No Difficulty — Extreme Difficulty	PFTN24 _____

English for USA - V2

Appendix 2 VAS Pain Scale

INSTRUCTIONS

Place an "X" on the line below that indicates the amount of pain felt in the knee joint in the last 24 hours.

Index Knee

No pain _____ Extreme pain

Contralateral Knee

No pain _____ Extreme pain

Appendix 3 NRS Pain Scale

INSTRUCTIONS

Place an "X" in the box below that indicates the amount of pain felt in knee joint in the last 24 hours.

Index Knee

0	1	2	3	4	5	6	7	8	9	10
No Pain										Extreme Pain

Contralateral Knee

0	1	2	3	4	5	6	7	8	9	10
No Pain										Extreme Pain

Appendix 4 Global Assessments

A VAS is to be completed by the Blinded Evaluator and the Subject at time points specified in Schedule of Events 9.1 for determining the Evaluator's and the Patient's Global Assessment of response to therapy score.

EVALUATOR GLOBAL ASSESSMENT (VAS SCALE)

Blinded Evaluator: Record your response with an "X":

"Considering all the ways the osteoarthritis in the patient's Index knee affect him/her, what is your assessment of how much the patient's knee is bothering him/her today?"

No pain _____ Extreme pain

PATIENT GLOBAL ASSESSMENT (VAS SCALE)

Subject: Record your response with an "X":

Think about the pain you felt in your STUDY knee caused by your osteoarthritis during the last 24 hours.

"Considering all the ways the osteoarthritis in your STUDY knee affects you, what is your assessment of how much your STUDY knee is bothering you today?"

No pain _____ Extreme pain

Appendix 5 EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

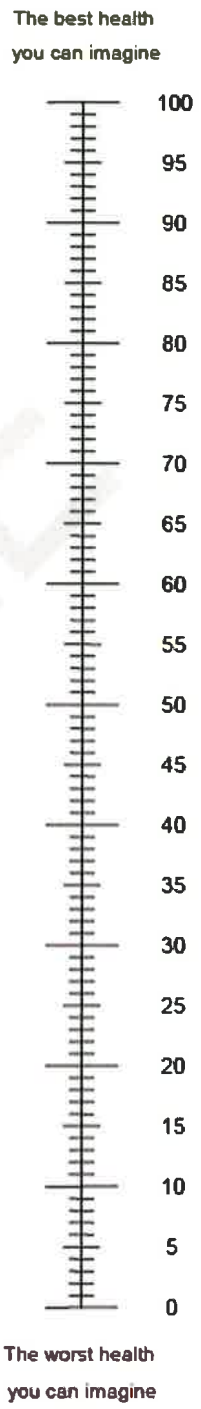
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6 Kellgren-Lawrence Grading Scale

Grade 1: doubtful narrowing of joint space and possible osteophytic lipping

Grade 2: definite osteophytes, definite narrowing of joint space

Grade 3: moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour

Grade 4: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour

Change History

Location of Change	Original Text	Changed Text	Reason