Cover Letter - Cingal 17-02 Protocol Version 2.0

Extension Study to Cingal 16-02: Trial Extension to 39 week Follow Up in the Randomized, Double-Blind, Active Comparator 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

NCT # 03390036

Date of Protocol: 03 January 2018

ANIKA THERAPEUTICS, INC.
32 Wiggins Avenue
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Extension Study to Cingal 16-02: Trial Extension to 39 week Follow Up in the Randomized, Double-Blind, Active Comparator 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

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Original Protocol (version 4.0) Cingal 16-02 Date 05 December 2017

EudraCT Number: 2017-003205-18

Signatures for the Sponsor that have reviewed and approved the protocol

Author: Director of Clinical Affairs or Designee: Adrian Orr	Signature	05 JAN 2018 Date
Vice President of Regulatory/Clinical Affairs or Designee: Steve J Cunliffe	Signature	05 JAN 2018 Date
Anika's CEO or Designee: Charles Sherwood, Ph.D.	Signature	05 JAN 2018 Date

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PROTOCOL SIGNATURE PAGE

Title:
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Sponsor: Anika Therapeutics, Inc.

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 Conference on Harmonization (ICH) Guidelines on Good Clinical Practice, Directive 2001/20/EC and Commission Directive 2005/28/EC, International Organization for Standardization (ISO) 14155, 21 CFR part 11, 50, 56, 312 and local ethical and legal requirements.

Principal Investigator:

_____ _____

Print Name Date

_____

Signature

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
BMI	Body Mass Index
CFR	Code of Federal Regulations
cm	Centimeters
CRO	Contract Research Organization
CTM	Clinical Trial Material
CV	Curriculum Vitae
D/C	Discontinued
DMP	Data Management Plan
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D	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
HIPAA	Health Insurance Portability and Accountability Act
IA	Intraarticular
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFU	Instructions for Use
IND	Investigational New Drug
ISO	International Organization for Standardization
ITT	Intent-to-Treat
K-L	Kellgren-Lawrence classification
MedDRA	Medical Dictionary for Regulatory Activities
mL, mm, m	milliliter, millimeter, meter
NSAIDs	Non-steroidal anti-inflammatory drug
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
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 PI to perform the assessments outlined in the protocol. The Blinded Evaluator will complete the 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.

Ethics Committee (EC): EC 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 Ethics Committees.

Rescue Medication: Acetaminophen/paracetamol 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 Principal Investigator (PI). He/she will administer the Cingal®, Monovisc® or steroid 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 39 week visit.

3 STUDY SYNOPSIS

Title	Extension Study to Cingal 16-02: Trial Extension to 39 Week Follow Up in the Randomized, Double-Blind, Active Comparator 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 evaluate the efficacy and safety of a single injection of Cingal for relief of joint pain at 39 week follow up in subjects with Osteoarthritis (OA) of the knee who have not responded to conservative treatment.
Investigational Product	Subjects enrolled in Cingal 17-02 will not receive an injection. For reference only, the investigational product utilized in Cingal 16-02 was: **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 Product	Subjects enrolled in Cingal 17-02 will not receive an injection. For reference only, the comparator products utilized in Cingal 16-02 were: **Triamcinolone Hexacetonide (TH)**: 20 mg/ml supplied as 1 mL unit dose in a glass ampoule. **Monovisc®:** A chemically cross-linked sodium hyaluronate supplied as a 4-mL unit dose in a 5-mL glass syringe.
Mode of Delivery	For reference only, the mode of delivery in Cingal 16-02 was: Cingal, Triamcinolone Hexacetonide, or Monovisc will be injected into the intraarticular (IA) space of the index knee using an 18-21 gauge needle.
Study Design	Multi-center, randomized, double-blind, parallel group, 3-arm, active comparator controlled study
Phase	Phase III
Sample Size	A total of 576 subjects will be enrolled. This equates to 256 subjects injected with Cingal, 256 subjects injected with Monovisc and 64 subjects injected with TH. All subjects who meet enrollment criteria and completed the 26 week follow up in Cingal 16-02 will have the option to participate in the sub-study.
Study Duration	The entire sub-study duration will be an additional 13 weeks. The follow up visit will be scheduled at 39 weeks post treatment.
Inclusion Criteria	1. Only subjects that were enrolled and met the inclusion criteria for the Cingal 16-02 trial and signed the informed consent are eligible for Cingal 17-02 trial. 2. Subject is able to understand and comply with the requirements of Cingal 17-02 and voluntarily provides consent. Patients will not be rescreened at enrollment to Cingal 17-02 as these patients were enrolled and met the inclusion / exclusion criteria for the Cingal 16-02 clinical trial. For reference only, the inclusion criteria used in Cingal 16-02 were: 1. Subject is 40-75 years old, with a Body Mass Index (BMI) ≤ 40 kg/m^2. 2. Subject has Kellgren-Lawrence (K-L) severity grade I, II or III in the index knee as determined by X-ray. Contralateral knee: K-L severity grade 0, I or II. 3. 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

	○ Symptoms: persistent knee pain, limited morning stiffness and reduced function 4. Subject must be willing to abstain from other IA treatments of the knee for the duration of the study. 5. Subject is willing to discontinue all analgesics including NSAIDs, except acetaminophen/paracetamol, at least seven days before the treatment injection and through the completion of the study. 6. Subject is willing to use only acetaminophen/paracetamol (up to a maximum of 4.0 grams per day per the package insert) 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/paracetamol. 7. 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). 8. Subject is able to understand and comply with the requirements of the study and voluntarily provides consent.
Exclusion Criteria	Patients will not be rescreened at enrollment to Cingal 17-02 as these patients were enrolled and met the inclusion / exclusion criteria for the Cingal 16-02 clinical trial. Only patients enrolled in the Cingal 16-02 trial will be eligible to participate in Cingal 17-02. For reference only, the exclusion criteria used in Cingal 16-02 were: 1. Subject received an IA injection of Hyaluronic Acid (HA) and/or steroid in either knee within 6 months of signing the informed consent form (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 10 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 HbA1c of >7%. 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/paracetamol. 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. Baseline Inclusion Criteria 1. Subject has a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain-sub-score ≥ 40 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 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 > 20 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.

Criteria for Evaluation	**Efficacy:** **Primary Endpoint:** • The responder rate as identified by the Outcomes Measures for Rheumatic Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) responder index at 39 weeks post treatment comparing the Cingal group to the TH group. **Secondary Endpoints:** • The change from baseline in knee pain as measured by the WOMAC Pain Score (100 mm VAS) at 39 weeks post treatment comparing the Cingal group to the TH group. • The change from baseline in WOMAC Physical Function score at 39 weeks post treatment comparing the Cingal group to the TH group. • The change from baseline in WOMAC Stiffness score at 39 weeks post treatment comparing the Cingal group to the TH group. • The change from baseline in Total WOMAC score at 39 weeks post treatment comparing the Cingal group to the TH group. • The change from baseline in the Patient Global Assessment 39 weeks post treatment in the Cingal group compared to the TH group. • The change from baseline in the Evaluator Global Assessment at 39 weeks post treatment in the Cingal group compared to the TH group. • The usage of rescue medication through 39 weeks post treatment in the Cingal group compared to the TH group. **Exploratory Endpoints:** Any comparisons between groups (Cingal, Monovisc, TH), within groups and / or time points (from baseline through to 39 weeks) not described in the primary or secondary endpoints may be presented in the exploratory endpoints including: o EuroQol (EQ-5D) o WOMAC Pain Score (100mm VAS) o OMERACT-OARSI o Total WOMAC o WOMAC Stiffness Score o WOMAC Physical Function o Patient Global Assessment o Evaluator Global Assessment o Range of Motion o Rescue Medication Usage o Number of Treatment Failures due to Additional Procedure or Use of Disallowed Medication **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. 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 39 weeks, this is all subjects who complete the 39 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 group.

Sites	Up to 40 clinical sites within Europe may participate.
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4 INTRODUCTION

Osteoarthritis (OA) is the most prevalent joint disorder worldwide and is associated with significant pain and disability [1]. It is a progressive disease that can affect any joint, but most often involves the weight bearing joints such as the knee. The European Project on Osteoarthritis reported on prevalence rates for knee OA in Europe and the United Kingdom (UK). For subjects aged 65-74 years, the rate of knee OA based on clinical judgment was 36.7% in Italy and 18.6 % in the UK. For subjects aged 75 years or older the rate, based on clinical judgment was 50.8% in Italy. In the Netherlands, the self-reported rate of knee OA in subjects 65-74 years was 23.6% and for subjects 75 years or older was 31.4% [2]. Because of the high prevalence of knee OA, this disease ranked as either the top or second leading cause of disability [3]. 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 [3].

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” [4]. OA is characterized by a decreased concentration of HA in synovial fluid and a slow degradation of cartilage over years [5, 6]. 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 [6]. Accordingly, the average molecular weight is diminished resulting in a loss of the viscoelastic properties of the synovial fluid for which HA is responsible [5].

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.[7] 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.[7]

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 [6]. HA in synovial fluid binds to chondrocytes, supporting a role for HA in healthy cartilage [5]. 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 [6].

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 [8].

Because data show a delayed treatment effect of HA, Anika Therapeutics wanted to create a product (Cingal) that could provide quicker pain relief for subjects suffering from osteoarthritis while still providing the established pain relief of an HA product.

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 indicated in the treatment on pain in osteoarthritis (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. This clinical trial will evaluate the efficacy and safety of a single injection of Cingal for relief of joint pain in subjects with OA of the knee who have not responded to conservative treatment.

Anika Therapeutics, Inc are currently conducting the Cingal 16-02 study, which is a randomized, double-blind, active- controlled, multi-center study of a single injection of cross-linked sodium hyaluronate combined with triamcinolone hexacetonide (Cingal®) to provide symptomatic relief of osteoarthritis of the knee. Enrollment of 576 patients at up to 30 sites is being completed in a randomization of 4:4:1 (Cingal, Monovisc: triamcinolone hexacetonide). Subjects are currently in the enrollment or follow up stage of the Cingal 16-02 trial. The purpose of the Cingal 17-02 sub-study will be to evaluate the efficacy and safety of the treatment at 39 weeks post treatment.

5 PRINCIPAL INVESTIGATOR

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6 STUDY OBJECTIVES

The objective of this sub-study is to evaluate the efficacy and safety at 39 week follow up of a single injection of Cingal for relief of joint pain in subjects with OA of the knee who have not responded to conservative treatment (weight reduction, physical therapy, pain medications, etc.).

7 ENDPOINTS

7.1 Primary Efficacy Endpoint

- The responder rate as identified by the Outcomes Measures for Rheumatic Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) responder index at 39 weeks post treatment comparing the Cingal group to the TH group.

7.2 Secondary Efficacy Endpoints

- The change from baseline in knee pain as measured by the WOMAC Pain Score (100 mm VAS) at 39 weeks post treatment comparing the Cingal group to the TH group.
- The change from baseline in WOMAC Physical Function score at 39 weeks post treatment comparing the Cingal group to the TH group.
- The change from baseline in WOMAC Stiffness score at 39 weeks post treatment comparing the Cingal group to the TH group.
- The change from baseline in Total WOMAC score at 39 weeks post treatment comparing the Cingal group to the TH group.
- The change from baseline in the Patient Global Assessment 39 weeks post treatment in the Cingal group compared to the TH group.
- The change from baseline in the Evaluator Global Assessment at 39 weeks post treatment in the Cingal group compared to the TH group.
- The usage of rescue medication through 39 weeks post treatment in the Cingal group compared to the TH group.

7.3 Exploratory Endpoints

Any comparisons between groups (Cingal, Monovisc, TH), within groups and / or time points (from baseline through to 39 weeks) not described in the primary or secondary endpoints may be presented in the exploratory endpoints including:

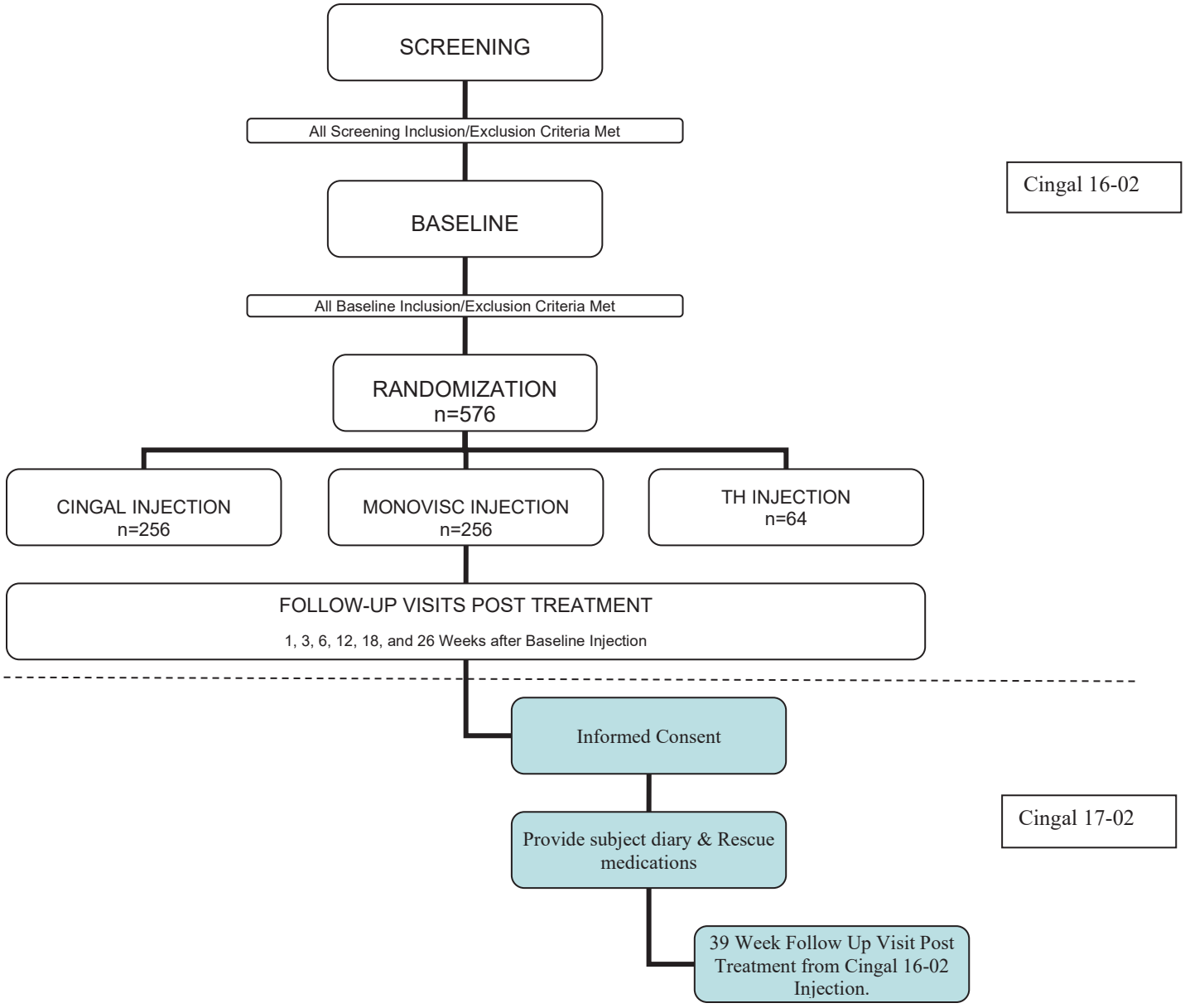
- EuroQol (EQ-5D)
- WOMAC Pain Score (100mm VAS)
- OMERACT-OARSI
- Total WOMAC
- WOMAC Stiffness Score
- WOMAC Physical Function
- Patient Global Assessment
- Evaluator Global Assessment
- Range of Motion
- Rescue Medication Usage
- Number of Treatment Failures due to Additional Procedure or Use of Disallowed Medication

7.4 Safety Endpoint:

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.

8 STUDY DESIGN

8.1 Diagram



8.2 Trial Design

This sub-study is an extension of the ongoing Cingal 16-02 trial which is a multi-center, randomized, double-blind, parallel group, active comparator controlled trial to evaluate the efficacy and safety of a single injection of Cingal for the relief of joint pain in subjects with OA of the knee.

Subjects with OA defined as Kellgren-Lawrence (K-L) I-III in the index knee were eligible for this study [9, 10]. Felson et al 2004, encouraged the use of both OA symptoms and radiographic changes in the assessment of OA [11]. Cingal 16-02 study employed both methods to screen subjects. Structural severity was 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 4) [9, 10].

For the evaluation of symptomatic severity, two main domains are important [12]. 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 were captured as part of the Cingal 16-02 study [12].

Baseline and post-treatment pain, physical function and stiffness is measured using the WOMAC questionnaire in the Cingal 16-02 up to 26 weeks and then to 39 weeks within the Cingal 17-02 trial. Range of Motion, Patient and Evaluator Global Assessment and the EuroQol are used to assess symptomatic severity throughout both studies. In addition, the number of acetaminophen/paracetamol pills taken is captured as an indirect measure of pain and will be done at each visit.

Subjects meeting the inclusion/exclusion criteria for Cingal 16-02 will have been randomized to receive a single injection of Cingal, Monovisc or triamcinolone hexacetonide (TH) in the index knee. Since there is a difference in volume between Cingal, Monovisc and TH, the treating physician is not considered blinded. To maintain the double-blind design of the study, there is 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 have been prepared separate from the patient and the injection will be masked from the subject. The blinding of the patient and the blinded evaluator will be maintained in both the Cingal 16-02 and Cingal 17-02 trials.

The subject will have been trained on how to complete the WOMAC, Patient Global Assessment and

EuroQol within the Cingal 16-02 trial. The subject should complete these questionnaires prior to any physical evaluation that must be done at the 39 week follow-up visit.

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, 10.1 Schedule of Events).

Up to 40 sites in Europe are participating in the study to enroll 576 subjects. Subject participation in this extension study will last approximately 13 additional weeks beyond the Cingal 16-02 trial with follow-up the visit scheduled at weeks 39 after the treatment injection in Cingal 16-02.

9 ELIGIBILITY

9.1 Enrollment Criteria

9.1.1 Inclusion Criteria

1. Only subjects that were enrolled and met the inclusion criteria for the Cingal 16-02 trial and signed the informed consent are eligible for Cingal 17-02.
2. Subject is able to understand and comply with the requirements of Cingal 17-02 and voluntarily provides consent.

Patients will not be rescreened at enrollment to Cingal 17-02 as these patients were enrolled and met the inclusion / exclusion criteria for the Cingal 16-02 clinical trial. All patients enrolled in the Cingal 16-02 trial will be eligible to participate in Cingal 17-02.

For reference only, the inclusion criteria used in Cingal 16-02 were:

1. Subject is 40-75 years old, with a Body Mass Index (BMI) ≤ 40 kg/m^2.
2. Subject has Kellgren-Lawrence (K-L) severity grade I, II or III in the index knee as determined by X-ray. Contralateral knee: K-L severity grade 0, I or II.
3. 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:
    a. Signs: crepitus, restricted movement and bony enlargement
    b. Symptoms: persistent knee pain, limited morning stiffness and reduced function

4. Subject must be willing to abstain from other intraarticular (IA) treatments of the knee for the duration of the study.
5. Subject is willing to discontinue all analgesics including NSAIDs, except acetaminophen/paracetamol, at least seven days before the treatment injection and through the completion of the study.
6. Subject is willing to use only acetaminophen/paracetamol (up to a maximum of 4.0 grams per day per the package insert) 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/paracetamol.
7. 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).
8. Subject is able to understand and comply with the requirements of the study and voluntarily provides consent.

9.1.2 Exclusion Criteria

Patients will not be rescreened at enrollment to Cingal 17-02 as these patients were enrolled and met the inclusion / exclusion criteria for the Cingal 16-02 clinical trial.

Only patients enrolled in the Cingal 16-02 trial will be eligible to participate in Cingal 17-02.

For reference only, the exclusion criteria used in Cingal 16-02 were:

9.1.3 Screening Exclusion Criteria in Cingal 16-02

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 the 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 10 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 HbA1c of >7%.
14. Subject is taking medications at the time of signing 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/paracetamol.
19. Subject has any contraindication to the receipt of corticosteroids.
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.

9.1.4 Baseline Inclusion Criteria in Cingal 16-02

1. Subject has a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain-sub-score ≥ 40 mm and ≤ 90 mm in the affected knee and ≤ 30 mm in the contralateral knee on a 100 mm Visual Analog Scale (VAS) scale.

9.1.5 Baseline Exclusion Criteria in Cingal 16-02

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 > 20 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 ROM of less than 100° flexion in either knee.

10 STUDY PROCEDURES

10.1 Schedule of Events

	Pre-Treatment	Treatment		Post-Treatment Follow-Up Visits						17-02 Follow-Up Visits	
Assessments	-7 to -14 Days	Day 0 (7-14 days after screening visit)		1 week	3 weeks	6 weeks	12 weeks	18 weeks	26 weeks	Consent	39 Weeks
	Screening	Baseline	Treatment	±3 days				± 1 week			± 1 week
Informed Consent	X									X	
Demographics Medical History	X										
Physical Exam, Vitals, BMI	X										
Urine / Blood Pregnancy Test	X										
Chemistry/Hematology/Urinalysis	X										
Bilateral Knee X-rays and assessment of K-L	X										
Review of X-rays by Independent Radiologist	X										
Physical Evaluation (Both Knees)	X	X		X	X	X	X	X	X		X
ROM (Index Knee)	X	X		X	X	X	X	X	X		X
ROM (Contralateral Knee)	X	X					X		X		X
WOMAC (Both Knees)	X	X		X	X	X	X	X	X		X
Evaluation of Enrollment Criteria	X	X	X							X	
Stop Analgesics/NSAIDs except Paracetamol	X										
Assess D/C Paracetamol ≥ 48 hours before Visit		X		X	X	X	X	X	X	X	X
Paracetamol Dispense/Pill Count	X	X		X	X	X	X	X	X	X	X
Distribute Subject Diary	X									X	
Randomization			X								
Aspiration/ Evaluation of Synovial Fluid			X								
IA Injection			X								
Evaluate Diary		X		X	X	X	X	X	X		X
EuroQol		X		X	X	X	X	X	X		X
Patient Global Assessment		X		X	X	X	X	X	X		X
Evaluator Global Assessment		X		X	X	X	X	X	X		X
Concomitant Medication Assessment	Throughout the study										
Adverse Event Assessment	Throughout the study										

† -Cells in grey indicate assessments conducted only during Cingal 16-02 trial.

10.2 Procedure Description

10.2.1 Informed Consent Form (ICF)

The subject will be asked to sign the ICF prior to attending the 39 week follow up visit.

All data collected in the clinical trial Cingal 16-02 will be utilized in Cingal 17-02. The demographics and assessments conducted at screening and baseline for Cingal 16-02 will be utilized as the demographic and baseline data for Cingal 17-02.

10.2.2 Demographics

The following demographic information will have been collected at the Screening Visit of Cingal 16-02 trial: Age, Gender, Race and Ethnicity. The demographic data for Cingal 16-02 will be used for Cingal 17-02.

10.2.3 Physical Exam (PE)

The Physical Exam performed at the screening of Cingal 16-02 will be utilized for Cingal 17-02. 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.

10.2.4 Vital Signs

Vital signs (blood pressure, pulse, temperature) at the screening of Cingal 16-02 will be utilized for Cingal 17-02.

10.2.5 Pregnancy Test

For females of childbearing potential, a urine or blood pregnancy test at the screening of Cingal 16-02 will be utilized for Cingal 17-02. Women who can confirm that they are surgically sterile or have been postmenopausal for at least 1 year prior to signing the ICF did need not undergo a pregnancy test in Cingal 16-02.

10.2.6 Chemistry/Hematology/Urinalysis

For all subjects, the blood tests at the screening of Cingal 16-02 will be utilized for Cingal 17-02. A routine and microscopic analysis of the urine at the screening of Cingal 16-02 will be utilized for Cingal 17-02.

Table 1 Laboratory Analytes		
Hematology	**Clinical Chemistry**	
Hematocrit	Sodium	AST/SGOT
Hemoglobin	Potassium	ALT/SGPT
RBC count	Chloride	Alkaline Phosphatase
WBC count	Glucose	Total protein
Differential WBC count	Urea nitrogen	Albumin
Platelet count	Creatinine	
HbA1c (for diabetics only)	Total bilirubin	
	Triglycerides	
	Calcium	

10.2.7 Knee X-rays/Assessment of Kellgren-Lawrence Score

Subjects will have completed screening within the Cingal 16-02 trial to have the following X-rays of both knees collected at the Screening Visit. The results of the X-rays of both knees in Cingal 16-02 will be utilized for Cingal 17-02:

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

These screening images will have been 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 have evaluated the Screening plain films of both knees for osteoarthritic changes using the K-L scoring system (Appendix 4) and excluded subjects with K-L severity grade of IV in the index knee or K-L severity grade III or IV in the contralateral knee. Additionally, varus/ valgus alignment will have been assessed in both knees and subjects with greater than 10 degrees of malalignment in either knee will have been excluded.

Furthermore, the independent radiologist will have evaluated 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 have confirmed the eligibility of screened subjects based on the imaging enrollment criteria. In the event the independent radiologist determined that a subject is ineligible based on an imaging finding, the decision of the independent radiologist would have prevailed.

All the Screening X-rays were paid for by the Cingal 16-02 study and were free of charge to the subject. The images acquired for the Cingal 16-02 trial will have been transferred from the imaging site to the Central Imaging Core lab electronically and are available for use within Cingal 17-02. The X-rays will have been identified by the subject's study identification (ID) number. No personal identifiable information would have been included on the image.

10.2.8 Medical History

A complete medical history will have been obtained at the Screening Visit for Cingal 16-02 and will be utilized for Cingal 17-02. The medical history will have included 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

10.2.9 Physical Evaluation of Knee

The Blinded Evaluator will perform the physical evaluation of the knee at the 39-week time point included in Section 10.1, 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 cm will also be measured in the index knee.

10.2.10 Range of Motion

The ROM will assess the maximum flexion and extension in degrees using a goniometer at the 39-week time point included in Section 10.1, Schedule of Events. The ROM will be documented as a hyphenated number. For instance, normal ROM in the knee is about 0-140 degrees.

10.2.11 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) [14]. This trial will utilize the VAS version of the WOMAC index. The subject will be trained on how to complete the WOMAC which will be collected at the 39-week time points indicated in Section 10.1.

10.2.12 Medications

Medications that the subject may have been taking prior to enrollment in Cingal 16-02 for conditions unrelated to the treatment of knee osteoarthritis, other than analgesics including NSAIDs, may be continued through to Cingal 17-02 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 osteoarthritis prior to signing the informed consent form for Cingal 16-02, the products may be continued through to Cingal 17-02, but the subject must maintain a stable regimen for the duration of the Cingal 16-02 and the Cingal 17-02 studies.

10.2.12.1 Restricted Medications

All analgesics other than acetaminophen/paracetamol 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 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.

10.2.12.2 Rescue Medications

Acetaminophen/paracetamol (up to a maximum of 4.0 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 Cingal 17-02. At least forty eight hours prior to the 39 week follow-up visit the subject should discontinue use of the rescue medication.

At the Screening Visit for Cingal 17-02, the rescue acetaminophen/paracetamol specifically labelled for use within Cingal 17-02 will be dispensed. The rescue medications provided to the subject for Cingal 16-02 should be returned to the investigational site at the Cingal 16-02 26 week follow up visit.

The subject should be instructed to bring the rescue medication with them to 39-week follow-up visit for a pill count. Additional rescue acetaminophen/paracetamol will be dispensed as needed only if there is an unscheduled the follow-up visit before the 39 week follow up visit.

10.2.12.3 Concomitant Medications

A medication is considered concomitant if taken after signing the ICF and up to and including the 39 week 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.

10.2.13 Subject Diary

The subject diary will be dispensed at the Screening Visit and the subject will receive training on when and how to complete the diary. The subject diary will be used to collect information on medication usage including rescue medications, concomitant therapies (e.g. physical therapy) and AEs. The subject 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.

10.2.14 EuroQoL EQ-5D

Outcomes information from the subject-completed EuroQol EQ-5D will be obtained at the 39-week follow up specified in Section 10.1, Schedule of Events. 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 [15].

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 [15]. 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' as shown in Appendix 3. This information is used as a quantitative measure of health outcome as judged by the individual respondents [15].

10.2.15 Patient Global Assessment

The Patient Global Assessment (Appendix 2) is a VAS that will be completed by the subject at the 39 week follow up visit as specified in Section 10.1, Schedule of Events, to determine the Patient Global Assessment of response to therapy score. "Considering all the ways the osteoarthritis in your study index knee affects you, what is your assessment of how much your study knee is bothering you today?"

10.2.16 Evaluator Global Assessment

The Evaluator Global Assessment (Appendix 2) will be completed by the Blinded Evaluator at the 39 week follow up visit as specified in Section 10.1, 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?"

10.2.17 Blinding

During the Cingal 16-02 trial the Treating Physician will have been aware of the differences between the Clinical Trial Materials and will have been unblinded, therefore; there were two clearly defined roles of a **Treating Physician** (unblinded) and a **Blinded Evaluator** (blinded) at each site. The site personnel fulfilling these roles will remain the same in Cingal 16-02 and Cingal 17-02.

- **Treating Physician:** The Treating Physician is most often the PI. He/she will have administered

the Cingal, Monovisc or Triamcinolone Hexacetonide (TH) injection but will not participated in the efficacy evaluations in either Cingal 16-02 or Cingal 17-02.

- **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 Cingal 16-02 and Cingal 17-02 protocols. The Blinded Evaluator will have completed the physical evaluation of both knees, ROM assessments of both knees, and the Evaluator Global Assessment for both Cingal 16-02 and Cingal 17-02 trials.

The identity of the syringes would not have been revealed during the Cingal 16-02 trial to the patients or the blinded evaluator. This blinding of the treatments given to the patients in the Cingal 16-02 trial will be maintained for the patients and the blinded evaluators in the Cingal 17-02 trial.

10.3 Screening

Each subject will indicate his or her willingness to participate in the study by signing the ICF. Subjects will maintain the unique subject ID (e.g., 01-001) allocated during the Cingal 16-02 trial where the first two 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 same unique subject ID for the duration of their participation in both the Cingal 16-02 and the Cingal 17-02 trials.

All data collected in the clinical trial Cingal 16-02 will be utilized in Cingal 17-02. The demographics and assessments conducted at screening and baseline for Cingal 16-02 will be utilized as the demographic and baseline data for Cingal 17-02.

The following screening and eligibility data will be collected at the Screening Visit for Cingal 17-02:

- Informed Consent
- Eligibility Data collected in Cingal 16-02 will be utilized for Cingal 17-02
- Distribute Subject Diary
- Assess AEs
- Assess Concomitant Medications
- Dispense Rescue Medication labelled for Cingal 17-02

During the Screening Visit inform the subject about discontinuation of all analgesics including NSAIDs except acetaminophen/paracetamol. Acetaminophen/paracetamol will be used as a rescue pain medication through the completion of the study, however; acetaminophen/paracetamol 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.

10.4 Post-Treatment Follow-Up

All study subjects will have follow-up assessments at 39 weeks after injection day in Cingal 16-02 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.

More than 48 hours prior to the visit, the subject will be reminded of the visit date and time, the need to abstain from acetaminophen/paracetamol for at least 48 hours prior to each follow-up visit and the requirement to bring their subject diary and the acetaminophen/paracetamol for a pill count with them to the appointment.

If the subject arrives for a study visit without discontinuing acetaminophen/paracetamol for at least 48 hours prior to the visit, the visit should be rescheduled within the allowed window of time. 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.

39 Weeks ± 7 Days

- Confirm Rescue Medication Washout
- Evaluate Subject Diary
- Count Rescue Medication Pills (if needed)
- Physical Evaluation (both knees)
- ROM (both knees)
- WOMAC (both knees)
- Patient Global Assessment
- Evaluator Global Assessment
- EuroQol
- Assess Concomitant Medications

- Assess AEs

11 ADVERSE EVENTS / ADVERSE REACTIONS

11.1 Definitions – Device Adverse Events

Adverse Event (AE): An AE is any untoward medical occurrence in a subject administered the CTM, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, (including an abnormal laboratory finding) symptom or disease temporally associated with the use of the CTM, whether or not related to the CTM.

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

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

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

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death;
- Is life-threatening ("Life-threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Required intervention to prevent permanent impairment or damage.

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

Unanticipated Serious Adverse Device Event: An SAE effect which by its nature, incidence, severity or outcome has not been identified in the current version of the Investigator's Brochure.

11.2 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 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.

11.3 Relationship

The Relationship between an AE and the CTM 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; the AE follows a known or expected response pattern to the CTM.

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

Unlikely Related: The AE which etiology is unlikely related to the CTM even if event may follow a known or expected response pattern to the CTM, 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. One or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence following administration of the CTM;
- 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 athrocentesis and study injection will be captured.

11.4 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.

11.5 Reporting

11.5.1 Adverse Events

All AEs that occur after signing the ICF 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 ECs and investigators within timelines required by the regulatory agencies.

11.5.2 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 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, 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.

11.5.3 Expedited Reporting

Any unexpected fatal or life-threatening AEs will be reported by the Sponsor or designee to the appropriate regulatory authorities 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.

11.5.4 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will review the data to assess if the trial should be revised or closed. This IDMC will be made up of individuals who have expertise in the field, experience in the conduct of clinical trials, and/or statistical knowledge without conflicts of interest which may affect objectivity. The IDMC will operate in accordance to the IDMC Charter. A Sponsor signed and dated original of this document will be kept in the Sponsor's study files.

11.5.5 Study Discontinuation

Enrollment will 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 stopped if in the opinion of the PI, medical monitor, and Sponsor that the safety of subjects is uncertain. The decision to resume enrollment, permanently discontinue the trial, or otherwise modify the study will be made by the Medical Monitor in consultation with the IDMC. Additionally, the triggering of the stopping rules will prompt notification to the appropriate regulatory agencies including the Competent Authorities and the ECs.

12 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.

12.1 Sample Size

The sample size for Cingal 16-02 was based on the primary comparison in the study between Cingal and triamcinolone hexacetonide with respect to the difference in the change in the WOMAC pain score from baseline at 26 weeks after study injection. The first secondary comparison is between Cingal and Monovisc with respect to the difference in the change in the WOMAC pain score from baseline at 3 weeks after study injection. All comparisons are made using a 5% significance level. The primary comparison is powered at 90% power and in a 2:1 randomization requires 128 patients in the Cingal group and 64 in the triamcinolone hexacetonide group. It is assumed that the difference in the mean responses for Cingal and triamcinolone hexacetonide at 26 weeks would be 10 mm based on previous clinical trials of similar viscosupplementation products [20, 21] and the Cingal 13-01 trial with a standard deviation of 20. The sample size calculation is based upon a t-test. The sample size that is necessary to detect that specified difference at a power of 90% with a significance level of 5% in a 2:1 enrollment ratio is 128 in the Cingal group and 64 in the triamcinolone hexacetonide group.

It is further assumed that the difference between Cingal and Monovisc at 3 weeks will be 5 mm and a standard deviation of 20 mm, thus it will require a minimum of 253 patients in each group to detect that difference at 80% power. With the triamcinolone hexacetonide group set at 64 patients, the number of patients in the Cingal and Monovisc groups will be increased to provide a 4: 1 randomization ratio. This will yield 256 in the Cingal group, 256 in the Monovisc group and 64 in the triamcinolone hexacetonide group. This provides a total sample size of 576 patients.

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 drop out rate will be assumed for this study. Thus the total sample size for Cingal 16-02 was set at 576 patients.

12.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the responder rate as identified by the OMERACT-OARSI responder index at 39 weeks post treatment comparing the Cingal group to the triamcinolone hexacetonide group

The response rate for the Cingal group and Triamcinolone Hexacetonide (TH) group will be calculated and tested using Fisher's exact test. Formally, the hypothesis to be tested is:

H0: $\pi_C = \pi_T$ versus HA: $\pi_C \neq \pi_T$

Where π_C is the responder rate for the Cingal group and π_T is the responder rate for the triamcinolone hexacetonide group.

12.1.2 Secondary Efficacy Endpoints

There are multiple secondary endpoints. In order to preserve the integrity of the Type I error, these will be tested in a hierarchical manner. The order of the testing is as the order presented here.

The change from baseline in knee pain as measured by the WOMAC Pain Score (100 mm VAS) at 39 weeks post treatment comparing the Cingal group to the TH group.

This secondary efficacy endpoint is the change from baseline in knee pain as measured by the WOMAC Pain Score (100 mm VAS) at 39 weeks post treatment comparing the Cingal group to the TH group.

Data will be analyzed via an analysis of variance (ANOVA) with a term for treatment and baseline pain score as a covariate. The primary hypothesis will be tested by a predefined contrast for comparing the Cingal group to the TH group. Formally, the hypothesis to be tested is:

H0: $\mu_{DC} = \mu_{DT}$ versus HA: $\mu_{DC} \neq \mu_{DT}$.

Where μ_{DC} is the mean change from baseline in the WOMAC Pain Score for the Cingal group at 39 weeks and μ_{DT} is the mean change from baseline in the WOMAC Pain Score for the TH group at 39 weeks. Since there are three treatment groups in this study, this hypothesis will be tested using a one way ANOVA and constructing a contrast for this hypothesis. This process is the same as using a baseline pain adjusted two-sample t-test with the common variance estimate from the ANOVA.

The change from baseline in WOMAC Physical Function score at 39 weeks post treatment comparing the Cingal group to the triamcinolone hexacetonide group.

This secondary efficacy endpoint is the change from baseline in WOMAC Physical Function Score at 39 weeks post treatment comparing the Cingal group to the TH group.

Data will be analyzed via an analysis of variance (ANOVA) with a term for treatment and baseline Physical Function score as a covariate. The hypothesis will be tested by a predefined contrast for comparing the Cingal group to the TH group. Formally, the hypothesis to be tested is:

H0: $\mu_{DC} = \mu_{DT}$ versus HA: $\mu_{DC} \neq \mu_{DT}$.

Where μ_{DC} is the mean change from baseline in the WOMAC Physical Function Score for the Cingal group at 39 weeks and μ_{DT} is the mean change from baseline in the WOMAC Physical Function Score for the TH group at 39 weeks.

The change from baseline in WOMAC Stiffness score at 39 weeks post treatment comparing the Cingal group to the triamcinolone hexacetonide group.

This secondary efficacy endpoint is the change from baseline in WOMAC Stiffness Score at 39 weeks post treatment comparing the Cingal group to the TH group.

Data will be analyzed via an analysis of variance (ANOVA) with a term for treatment and baseline Stiffness score as a covariate. The hypothesis will be tested by a predefined contrast for comparing the Cingal group to the TH group. Formally, the hypothesis to be tested is:

H0: $\mu_{DC} = \mu_{DT}$ versus HA: $\mu_{DC} \neq \mu_{DT}$.

Where μ_{DC} is the mean change from baseline in the WOMAC Stiffness Score for the Cingal group at 39 weeks and μ_{DT} is the mean change from baseline in the WOMAC Stiffness Score for the TH group at 39 weeks.

The change from baseline in Total WOMAC score at 39 weeks post treatment comparing the Cingal group to the triamcinolone hexacetonide group.

This secondary efficacy endpoint is the change from baseline in Total WOMAC Score at 39 weeks post treatment comparing the Cingal group to the TH group.

Data will be analyzed via an analysis of variance (ANOVA) with a term for treatment and baseline Total WOMAC score as a covariate. The hypothesis will be tested by a predefined contrast for comparing the Cingal group to the TH group. Formally, the hypothesis to be tested is:

H0: $\mu_{DC} = \mu_{DT}$ versus HA: $\mu_{DC} \neq \mu_{DT}$.

Where μ_{DC} is the mean change from baseline in the Total WOMAC Score for the Cingal group at 39 weeks and μ_{DT} is the mean change from baseline in the Total WOMAC Score for the TH group at 39 weeks.

The change from baseline in the Patient Global Assessment at 39 weeks post treatment comparing the Cingal group to the triamcinolone hexacetonide group.

Since this is a secondary endpoint the data will be analyzed for each time point individually with no adjustment for multiplicity. Data will be analyzed via an analysis of variance with a term for treatment and baseline pain score as a covariate. The primary hypothesis will be tested by a predefined contrast for comparing the Cingal group to the Triamcinolone Hexacetonide group. Formally, the hypothesis to be tested is:

H0: $\mu_{DC} = \mu_{DT}$ versus HA: $\mu_{DC} \neq \mu_{DT}$.

Where μ_{DC} is the mean change from baseline in the Patient Global Assessment Score for the Cingal group at 39 weeks and μ_{DT} is the mean change from baseline in the Patient Global Assessment Score for the triamcinolone hexacetonide group. At 39 weeks. Since there are three treatment groups in this study, this hypothesis will be tested using a one way ANOVA and constructing a contrast for this hypothesis. This process is the same as using a two-sample t-test with the common variance estimate

from the ANOVA.

The change from baseline in the Evaluator Global Assessment through 39 weeks post treatment comparing the Cingal group to the triamcinolone hexacetonide group.

Since this is a secondary endpoint the data will be analyzed for each time point individually with no adjustments for multiplicity. Data will be analyzed via an analysis of variance with a term for treatment and baseline pain score as a covariate. The primary hypothesis will be tested by a predefined contrast for comparing the Cingal group to the triamcinolone hexacetonide group. Formally, the hypothesis to be tested is:

H0: $\mu_{DC} = \mu_{DT}$ versus HA: $\mu_{DC} \neq \mu_{DT}$

Where μ_{DC} is the mean change from baseline in the Evaluator Global Assessment for the Cingal group at 39 weeks and μ_{DT} is the mean change from baseline in the Evaluator Global Assessment for the triamcinolone hexacetonide group at 39 weeks. Since there are three treatment groups in this study, this hypothesis will be tested using a one way ANOVA and constructing a contrast for this hypothesis. This process of constructing a contrast is the same as using a two-sample t-test with the common variance estimate from the ANOVA.

The usage of rescue medication through 39 weeks post treatment comparing the Cingal group to the triamcinolone hexacetonide group.

This secondary efficacy endpoint is the usage of rescue medications through 39 weeks post treatment comparing the Cingal group to the TH group.

The hypothesis will be tested by a predefined contrast for comparing the Cingal group to the TH group. Formally, the hypothesis to be tested is:

H0: $\mu_{DC} = \mu_{DT}$ versus HA: $\mu_{DC} \neq \mu_{DT}$.

Where μ_{DC} is the total usage of rescue medications for the Cingal group at 39 weeks and μ_{DT} is the mean change from baseline in the WOMAC Pain Score for the TH group at 39 weeks.

12.1.3 Exploratory Endpoints

Any comparisons between groups (Cingal, Monovisc, TH), within groups and / or time points (from baseline through to 39 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)
- OMERACT-OARSI
- Total WOMAC
- WOMAC Stiffness Score
- WOMAC Physical Function Score
- Patient Global Assessment
- Evaluator Global Assessment
- Range of Motion
- Rescue Medication Usage: Difference in analgesic use measured by number of pills taken between visits will be compared between treatment groups 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 39 week visit.

For the exploratory analyses, the continuous variables will be analyzed via an analysis of variance and contrasts used to assess the prescribed comparisons. For the discrete variables, a Fisher's exact test will be used to assess the desired comparisons.

12.2 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 testing and confidence intervals will use a significance level of 5%.

12.3 Demographic and Baseline Characteristics

All demographic and baseline characteristics will be tabulated by treatment group and a test of homogeneity between the treatment groups 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 examinations and concomitant medications will be tabulated by treatment group.

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.

12.4 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. TEAEs will be summarized with frequencies and percentages by system organ class and preferred term, severity, and relationship to study CTM for each treatment group. In summaries of TEAEs by severity and relationship to CTM 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.

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

12.5 Subject Populations

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

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.[25]

Missing Data Because of Attrition in the Course of the Study The longer the planned length of a clinical trial, the greater the chance that participants will drop out of the trial due to their moving out of the area or otherwise experiencing changes in their lives that preclude or complicate further participation. If dropping out due to these situations is known to be unrelated to changes in health status, an MAR assumption for the missing values seems justified;

Since none of these patients are likely to be in a life threatening disease situation and many have had knee pain for a period of time, the missing data will unlikely be due to any treatment effect or lack thereof. Previous studies have demonstrated a missing data rate of less than 1%. Thus, any missing data in this study follows that paradigm and thus should be considered MAR. Under this MAR assumption, it is well known that the mixed effects repeated measures analysis yields unbiased estimates of the treatment effects and thus will be utilized in the analysis. However, since the primary and secondary analyses are being performed at a single time point using an ANCOVA model and not a repeated measures model, missing data will be imputed using a multiple imputation EM algorithm. The missing data for the WOMAC pain, WOMAC function, and PGA will be imputed in this algorithm.

A secondary analysis will be conducted on the Per Protocol (PP) population. Since the primary endpoint is at 39 weeks, this is all subjects who complete the 39 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. Also, to complete this sensitivity analysis, a mixed models analysis of variance will be performed without imputing data for missing values.

12.6 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.

13 DATA MANAGEMENT CONSIDERATIONS

13.1 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. The same database utilized to collect the data in Cingal 16-02 will be

extended to collect the data for Cingal 17-02.

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 user name and password, after training has been completed in order to access the EDC System.

13.2 Data Collection

One eCRF will be completed for each study subject based on the source documents. Once a subject 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.

13.3 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.

13.4 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 5 years after study completion or longer depending on the 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 5 years after study completion or longer depending on the applicable regulatory requirements

14 CLINICAL SUPPLIES IN CINGAL 16-02

14.1 Packaging and Labeling

Clinical Trial Materials (CTM) were provided as part of Cingal 16-02. These were enclosed in a carton containing required labeling and caution statements and a unique identifying kit number. An independent third party maintained the master randomization scheme. The third party shipped the CTM to the sites as needed.

Details on the instructions for use, contraindications and precautions remain the same as detailed in the Cingal 16-02 protocol and are provided for reference here.

14.2 Instructions for Use

Instructions for Use (IFU) for CTM have been supplied to each site and are contained in the Cingal 16-02 files. The IFU document contains the following risk information:

14.2.1 Contraindications

Cingal:

CINGAL is composed of cross-linked hyaluronic acid and an ancillary corticosteroid triamcinolone hexacetonide (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, triamcinolone hexacetonide, is contraindicated in the case of:

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

Monovisc:

Monovisc® is a sterile, non-pyrogenic, viscoelastic solution of hyaluronan contained in a single-use syringe. Monovisc® consists of high molecular weight, ultra-pure, natural hyaluronan, a complex sugar of the glycosaminoglycan family. The hyaluronan in Monovisc® is derived from bacterial cells and is cross-linked with a proprietary cross-linker.

The following pre-existing conditions may constitute relative or absolute contraindications to the use of Monovisc:

- Hypersensitivity (allergy) to hyaluronate preparations
- Hypersensitivity (allergy) to gram positive bacterial proteins
- Infections or skin diseases in the area of the infection site or joint
- Systemic bleeding disorders

Triamcinolone hexacetonide:

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 triamcinolone hexacetonide.

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

- Known hypersensitivity to triamcinolone hexacetonide 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)

14.2.2 Anticipated Adverse Reactions

Reported adverse reactions associated with the IA use of hyaluronic acid:

Intra-articular injection of sodium hyaluronate preparations has occasionally been associated with allergic/anaphylactic reactions and transient hypotension, which have generally resolved spontaneously or after conservative treatment.

The most common reported adverse events associated with Monovisc are the following: arthralgia, joint swelling 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.

A study conducted by Anika Therapeutics, Inc. on Monovisc recorded information on AEs that were possibly, probably and definitely related to the study injection. Patients who received Monovisc had 7.1% of AEs related to the study injection and 5.4% of patients who received saline had an AE related to the study injection. Most of the AEs were minor complications that required little or no treatment. These included injection site events, joint swelling, joint pain, and limb pain. The rate of joint pain and limb pain not related to the study injection was higher than the rate related to the study injection [26].

Reported adverse reactions associated with the IA use of corticosteroids:

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.

14.3 CTM Accountability

Clinical Trial Material (CTM) accountability was completed within the Cingal 16-02 trial.

A batch of acetaminophen / paracetamol rescue medication will be provided for the Cingal 17-02 trial and will be labelled accordingly. These rescue medications are not investigational and are considered as clinical supplies. However, the use of rescue medications will be recorded as previously described.

14.4 Emergency Unblinding

Unblinding should only occur when a SAE requires the allocation code in order to enable clinical treatments to be planned. The PI, in consultation with 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.

15 DATA QUALITY ASSURANCE

Anika Therapeutics, Inc. performs quality assurance checks on all clinical trials that it sponsors. Investigational sites have been qualified and initiated within the Cingal 16-02 trial. Before enrollment of a subject in this extension 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 which will be an extension of the Cingal 16-02 Monitoring Plan.

16 REGULATORY OBLIGATIONS

The Principal Investigator agrees that the study will be conducted according to the principles of the ICH E6 (R1) Guideline for Good Clinical Practice (GCP) Step 6, ISO 14155:2011, Directive 2001/20/EC and Commission Directive 2005/28/EC, 21 CFR part 11, 50, 56, 312 and the ethical principles that have their origins in the World Medical Association Declaration of Helsinki, and local ethical 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.

16.1 Clinical Trial Information

The Investigator's Brochure for Cingal 16-02 will apply for Cingal 17-02 as this extension study does not relate any new information on the investigational product. 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 EC and other applicable oversight committees with the agreement that these committees are required to keep the information confidential.

16.2 Regulatory Approval

The study outlined in this protocol will only be conducted following written approval by the appropriate regulatory authorities for sites located in the European Union (EU).

16.3 Ethics Committee (EC) Approval

The protocol and the ICF must have the approval of a properly constituted EC responsible for approving clinical trials for each investigational site. Any additional requirements imposed by the EC shall be addressed in the protocol amendments. The signed EC approval letter must identify that the documents approved, 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 EC. Anika Therapeutics, Inc. or designee will not ship any CTM to a site until an approval letter has been received from the EC and a Clinical Trial Agreement has been fully executed.

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

16.4 Amendments to the Protocol

Any amendment to the study protocol must be agreed upon between the Investigator(s) and Anika Therapeutics, Inc. Once a protocol amendment has received approval from Anika Therapeutics Inc., the Investigators will submit it to the EC and regulatory agencies (as required) for written approval. The approval letter, signed by the EC, should refer specifically to the Investigator, Anika Therapeutics, Inc., protocol title, the protocol amendment number, and the date of the protocol amendment. Anika Therapeutics, Inc. will submit a copy of the protocol amendment to the appropriate regulatory agencies. The protocol amendment may be implemented after it has been approved by the EC and the

appropriate regulatory agencies, unless immediate implementation of the change is necessary for subject safety in which case a protocol change must be documented in an amendment and reported to the EC and regulatory agencies, as required within the required timeframe.

16.5 Pre-Study Documentation

The Investigators in Cingal 16-02 will have enrolled subjects into that study having provided the following documents prior to the enrollment of any subjects as appropriate to local country regulation:

- Completed and signed Investigator Agreement/Form FDA 1572 signed by Principal Investigator.
- Signed and dated protocol signature page by the Principal Investigator (Investigator) and all Sub-Investigators (including Blinded Evaluator).
- Signed and dated protocol amendment(s) signature page by the Investigator and all Sub-Investigators (including Blinded Evaluator), when applicable.
- 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 EC approval letter for the protocol and any other pertinent documents.
- List of EC committee members.
- Copy of the EC-approved ICF to be used.
- Fully executed Clinical Trial Agreement.
- Delegation of Authority form.
- Certified translations of EC approval letters, and approved ICF document (when applicable).
- Insurance certificate as required.

16.6 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 in Cingal 16-02 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 Cingal 16-02 protocol and in the Cingal 16-02 Investigator's Brochure.
- 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 authorities. 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 EC 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 EC.
- The Investigator will continue to utilize the alert card given to each subject participating in the Cingal 16-02 trial, which has been previously agreed by the Sponsor and approved by the EC, containing at minimum the name of the subject, the investigator contact number and blinded information regarding the medical treatment.
- The Investigator must be aware of the AE and adverse reaction reporting process, including reactions related to application of the CTM used in Cingal 16-02.

- 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 utilized in Cingal 16-02, 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.
- 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 used in Cingal 16-02. 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 (alert card) 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 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 sign the Clinical Investigation Report at the close-out of the clinical study.

16.7 Sponsor's Responsibilities

- Anika Therapeutics, Inc. may delegate some of the responsibilities to a CRO but will maintain oversight of the clinical study. Anika 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 ISO 14155:2011 and ICH E6, 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 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:
    - 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; and any other applicable regulatory procedures.
- Anika Therapeutics, Inc. will receive disclosures of conflicts of interest from PIs and Investigators.
- Anika Therapeutics, Inc. will assure the accuracy of any translations, as applicable.
- Anika Therapeutics, Inc. will establish an IDMC to assess the progress of a clinical study, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the Sponsor whether to continue, modify, or stop a trial.
- 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(ies) 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 EC:
  - The name and address of the EC.
  - A statement obtained from the EC that it is organized and operates according to GCP and the applicable laws and regulations.
  - Documented EC 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 verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, EC 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(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the EC approval/favorable opinion to continue the trial.

- Anika Therapeutics, Inc. will submit any required application(s) to the appropriate authority(ies) 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 EC, or other regulatory approvals are obtained and documented; and that appropriate provisions are made to meet any specific conditions imposed by the EC. Anika will ensure that any modification(s) required by the EC or other regulatory authority are made and documented by the PI and have gained the approval of the EC or other regulatory authority.
- Anika Therapeutics, Inc. will expedite the reporting to all concerned Investigator(s)/institutions(s), to the EC, where required, and to the regulatory authority(ies) of all ADEs that are both serious and unexpected.
- Anika Therapeutics, Inc. will submit to the regulatory authority(ies) 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:
    - Documenting correspondence with all parties involved in the clinical study, including the EC and regulatory authorities;
    - 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 EC's and the regulatory authorities.

16.8 Informed Consent

All subjects in this study are to be completely informed, in accordance with local EC 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 ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (ICH Topic E 6 (R1) 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 have been 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, EC, or the appropriate regulatory authorities, 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 competent authorities 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 EC 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 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. An ICF will be required for all subjects. The Investigator is responsible for maintaining each subject's ICF in the study file and providing each subject with a copy of the ICF.

16.9 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. 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, EC and regulatory authorities, 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.

16.10 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 EC and other regulatory authorities (as applicable) of any reportable events and adhering to local EC 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.

16.11 Permission to Review Subject's Source Records

The Investigator agrees that Anika Therapeutics, Inc., its employees or agents, and the respective Competent Authorities 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 participating Competent Authority. Subjects will not be identified by name, and confidentiality of information in medical records will be preserved.

16.12 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.

16.13 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 until at least 5 years after study completion or longer depending on the 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.

16.14 Study Monitoring

An appropriate representative of Anika Therapeutics, Inc. or designee (Study Monitor) will maintain contact with the Investigator and will contact 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 have been made by the Study Monitor to discuss the Cingal 16-02 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)
- 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 EC, 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.

16.15 Case Report Form

Electronic Case Report Forms must be completed for each subject in accordance with the DMP 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.

16.16 Auditing

The Investigator will make all pertinent records available including source documentation for inspection by regulatory authorities 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.

16.17 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 EC 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 authorities 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.

16.18 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), European Union Data Protection Directive 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 health authorities. Subjects will be advised that all data may be transferred to other countries.

16.19 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 authorities,

• 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(ies) of the termination or suspension and the reason(s) for the termination or suspension. The Investigator should notify the EC promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution.

16.20 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

• Termination of the site's study participation by Anika Therapeutics, Inc., the institution, EC or other 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.

17 GENERAL INFORMATION

17.1 Study Contact Information

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

Medical Monitor EU:
During Office Hours:
Dr. Josep-Maria Badenas
Address: SynteractHCR Iberica, SL
Príncep Jordi, 21-23, Esc. B, Entlo. 1-B
08014 Barcelona, Spain
Tel: + 34 674 746 106

Contract Research Organization (CRO):
SynteractHCR
5909 Sea Otter Place
Carlsbad, CA 92010
Phone: +1 760 268 8200
Fax: +1 760 929 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

17.2 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 Manager
Josep-Maria Badenas M.D.	SynteractHCR Iberica, SL Príncep Jordi, 21-23, Esc. B, Entlo. 1-B 08014 Barcelona, Spain Phone: + 34 674 746 106	Medical Monitor EU
SynteractHCR, Inc.	CRO 5909 Sea Otter Place Carlsbad, CA 92010 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 Phone: 585.301.4300	Imaging
Axiom Real-Time Metrics Inc.	EDC Vendor 50 Ronson Drive, Suite 190 Toronto, ON M9W 1B3 Phone: 416.804.1110	EDC and Data Management

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

18 REFERENCES

1. Bellamy, N., et al., *Intraarticular corticosteroid for treatment of osteoarthritis of the knee.* Cochrane Database of Systematic Reviews, 2006(2).
2. Schaap, L.A., et al., *European Project on OSteoArthritis (EPOSA): methodological challenges in harmonization of existing data from five European population-based cohorts on aging.* BMC musculoskeletal disorders, 2011. **12**: p. 272.
3. Guccione, A.A., et al., *The effects of specific medical conditions on the functional limitations of elders in the Framingham Study.* American journal of public health, 1994. **84**(3): p. 351-8.
4. Altman, R., et al., *Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association.* Arthritis and rheumatism, 1986. **29**(8): p. 1039-49.
5. Moreland, L.W., *Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action.* Arthritis research & therapy, 2003. **5**(2): p. 54-67.
6. Stitik, T.P. and J.A. Levy, *Viscosupplementation (biosupplementation) for osteoarthritis.* American journal of physical medicine & rehabilitation / Association of Academic Physiatrists, 2006. **85**(11 Suppl): p. S32-50.
7. Neustadt, D.H., *Intra-articular injections for osteoarthritis of the knee.* Cleve Clin J Med, 2006. **73**(10): p. 897-8, 901-4, 906-11.
8. Bellamy, N., et al., *Viscosupplementation for the treatment of osteoarthritis of the knee.* Cochrane Database of Systematic Reviews 2006(2).
9. Kellgren, J.H. and J.S. Lawrence, *Radiological assessment of osteo-arthrosis.* Annals of the rheumatic diseases, 1957. **16**(4): p. 494-502.
10. Kellgren, J. and J. Lawrence, *Atlas of standard radiographs: The epidemiology of chronic rheumatism.* , in *Blackwell Scientific Publications*. 1963, Oxford.
11. Felson, D.T. and M.C. Nevitt, *Epidemiologic studies for osteoarthritis: new versus conventional study design approaches.* Rheumatic diseases clinics of North America, 2004. **30**(4): p. 783-97, vii.
12. Bellamy, N., et al., *Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III.* The Journal of rheumatology, 1997. **24**(4): p. 799-802.
13. Zhang, W., et al., *EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis.* Ann Rheum Dis, 2010. **69**(3): p. 483-9.
14. *WOMAC*. [cited 2012 December 12]; Available from: http://www.womac.org/womac/index.htm.
15. Cheung, K., et al. *EQ-5D User Guide-Basic Information on how to use the EQ-5D, 2009*. 2009; Available from: www.euroqol.org.
16. Brooks, R., *EuroQol: the current state of play.* Health Policy, 1996. **37**(1): p. 53-72.
17. Knoop, J., et al., *Proprioception in knee osteoarthritis: a narrative review.* Osteoarthritis Cartilage, 2011. **19**(4): p. 381-8.
18. Jackson, D.W., N.A. Evans, and B.M. Thomas, *Accuracy of needle placement into the intra-articular space of the knee.* J Bone Joint Surg Am, 2002. **84-A**(9): p. 1522-7.
19. Toda, Y. and N. Tsukimura, *A comparison of intra-articular hyaluronan injection accuracy rates between three approaches based on radiographic severity of knee osteoarthritis.* Osteoarthritis Cartilage, 2008. **16**(9): p. 980-5.
20. Strand, V., et al., *A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee.* Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society, 2012. **20**(5): p. 350-6.
21. Day, R., et al., *A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee.* The Journal of rheumatology, 2004. **31**(4): p. 775-82.
22. Pham, T., et al., *OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited.* Osteoarthritis Cartilage, 2004. **12**(5): p. 389-99.
23. Pham, T., et al., *Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria.* J Rheumatol, 2003. **30**(7): p. 1648-54.
24. Pham, T., et al., *Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria.* The Journal of rheumatology, 2003. **30**(7): p. 1648-54.
25. *The Preventions and Treatment of Missing Data in Clinical Trials*. 2010, Washington, DC: The National Academies Press.
26. *Monovisc Study Data: "A Randomized, Double-Blind, Placebo Controlled, Multi-Center Study of a Single Injection Cross-linked Sodium Hyaluronate to Provide Symptomatic Relief of Osteoarthritis of the Knee"*. 2009.

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 **WOM**C2-3

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 Global Assessment of Disease Activity

A VAS is to be completed by the subject and the evaluating physician at time points specified in Section 7.1 for determining the Patient's and the Evaluator's Global Assessment of response to therapy score.

EVALUATOR GLOBAL ASSESSMENT (VAS SCALE)

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)

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 index knee affects you, what is your assessment of how much your STUDY knee is bothering you today?"

No pain _____ Extreme pain

Appendix 3 EQ-5D

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

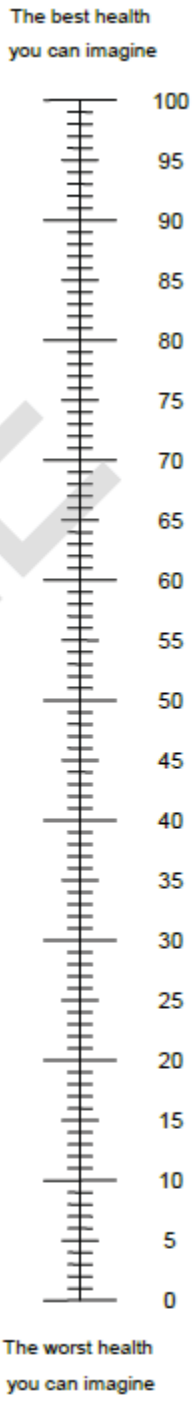
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 4 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
Title Page & Throughout	Protocol version 1.0 Date 08 August 2017 Original Protocol version 3.0 Cingal 16-02 Date 05 May 2017	Protocol version 2.0 Date 28 December 2017 Original Protocol version 4.0 Cingal 16-02 Date 05 December 2017	Protocol revision. Cingal 16-02 amended to version 4.0
Study Synopsis	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.	Investigational Product Subjects enrolled in Cingal 17-02 will not receive an injection. For reference only, the investigational product utilized in Cingal 16-02 was: 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.	Clarification that no injection performed in Cingal 17-02 trial.
Study Synopsis	Comparator Product Triamcinolone Hexacetonide (TH): 20 mg/ml supplied as 1 mL unit dose in a glass ampoule. Monovisc®: A chemically cross-linked sodium hyaluronate supplied as a 4-mL unit dose in a 5-mL glass syringe.	Comparator Product Subjects enrolled in Cingal 17-02 will not receive an injection. For reference only, the comparator products utilized in Cingal 16-02 were: Triamcinolone Hexacetonide (TH): 20 mg/ml supplied as 1 mL unit dose in a glass ampoule. Monovisc®: A chemically cross-linked sodium hyaluronate supplied as a 4-mL unit dose in a 5-mL glass syringe.	Clarification that no injection performed in Cingal 17-02 trial.
Study Synopsis	Mode of Delivery Cingal, Triamcinolone Hexacetonide, or Monovisc will be injected into the intraarticular (IA) space of the index knee using an 18-21 gauge needle.	Mode of Delivery For reference only, the mode of delivery in Cingal 16-02 was: Cingal, Triamcinolone Hexacetonide, or Monovisc will be injected into the intraarticular (IA) space of the index knee using an 18-21 gauge needle.	Clarification that no injection performed in Cingal 17-02 trial.
Study Synopsis Section 9.1	Inclusion Criteria 1. Subjects meet the inclusion criteria for Cingal 16-02 and signed the informed consent.	Inclusion Criteria 1 Only subjects that met the inclusion criteria for the Cingal 16-02 trial and signed the informed consent are eligible for Cingal 17-02 trial.	Clarification that only Cingal 16-02 subjects will be enrolled in Cingal 17-02 trial.
Study Synopsis Section 9.1	Exclusion Criteria Patients will not be rescreened at enrollment to Cingal 17-02 as these patients met the inclusion / exclusion criteria for the Cingal 16-02 clinical trial. All patients enrolled in the Cingal 16-02 trial will be eligible to participate in Cingal 17-02.	Exclusion Criteria Patients will not be rescreened at enrollment to Cingal 17-02 as these patients were enrolled and met the inclusion / exclusion criteria for the Cingal 16-02 clinical trial. Only patients enrolled in the Cingal 16-02 trial will be eligible to participate in Cingal 17-02.	Clarification that only Cingal 16-02 subjects will be enrolled in Cingal 17-02 trial.

Study Synopsis Section 7.2, 12.1.2 & 12.1.3	Secondary Endpoints •The change from baseline in knee pain as measured by the WOMAC Pain Score (100 mm VAS) at 39 weeks post treatment comparing the Cingal group to the TH group. •The change from baseline in the Patient Global Assessment 39 weeks post treatment in the Cingal group compared to the TH group. •The change from baseline in the Evaluator Global Assessment at 39 weeks post treatment in the Cingal group compared to the TH group Exploratory Endpoints: • EuroQol (EQ-5D) • Total WOMAC • WOMAC Stiffness Score • WOMAC Physical Function • Range of Motion • Rescue Medication Usage • Number of Treatment Failures due to Additional Procedure or Use of Disallowed Medication	Secondary Endpoints •The change from baseline in knee pain as measured by the WOMAC Pain Score (100 mm VAS) at 39 weeks post treatment comparing the Cingal group to the TH group. •The change from baseline in WOMAC Physical Function score at 39 weeks post treatment comparing the Cingal group to the TH group. •The change from baseline in WOMAC Stiffness score at 39 weeks post treatment comparing the Cingal group to the TH group. •The change from baseline in Total WOMAC score at 39 weeks post treatment comparing the Cingal group to the TH group. •The change from baseline in the Patient Global Assessment 39 weeks post treatment in the Cingal group compared to the TH group. •The change from baseline in the Evaluator Global Assessment at 39 weeks post treatment in the Cingal group compared to the TH group. •The usage of rescue medication through 39 weeks post treatment in the Cingal group compared to the TH group. Exploratory Endpoints: Any comparisons between groups (Cingal, Monovisc, TH), within groups and / or time points (from baseline through to 39 weeks) not described in the primary or secondary endpoints may be presented in the exploratory endpoints including: o EuroQol (EQ-5D) o WOMAC Pain Score (100mm VAS) •o OMERACT-OARSI o Total WOMAC o WOMAC Stiffness Score o WOMAC Physical Function o Patient Global Assessment •o Evaluator Global Assessment o Range of Motion o Rescue Medication Usage o Number of Treatment Failures due to Additional Procedure or Use of Disallowed Medication	Aligned secondary and exploratory endpoints with latest version of Cingal 16-02 protocol.
Section 10.1	Post-Treatment Follow-Up Visits: Reconsent	Post-Treatment Follow-Up Visits: Consent	Clarified the Cingal 17-02 Visit as a consent and not re-consent visit.
Section 10.1	Post-Treatment Follow-Up Visits	Addition of header: Post-Treatment Follow-Up Visits 17-02 Follow-Up Visits	Clarification of 17-02 assessments

Section 17.1 & 17.2	Study Contact Information: Contract Research Organization (CRO): SynteractHCR 5759 Fleet Street, Suite 100 Carlsbad, CA 92008 USA	Study Contact Information: Contract Research Organization (CRO): SynteractHCR 5909 Sea Otter Place Carlsbad, CA 92010	Change of address for CRO