Protocol Number: Cingal 20-01

Study Title: A Prospective Study of a Single Injection Cross-linked Sodium Hyaluronate combined with Triamcinolone Hexacetonide (CINGAL®) to Provide Symptomatic Relief of Osteoarthritis of Hip Joint

Short Title: CINGAL for Hip Joint Pain Relief

Signatures for the Sponsor that have reviewed and approved the protocol

Author Director, Clinical Affairs or designee Adrian Orr	Signature	07 DEC 2020 Date
Carol Pekar Vice President, Clinical Affairs Or designee	Signature	7 DEC 2020 Date
Mira Leiwant Vice President Regulatory, Quality & Clinical Affairs or designee	Signature	08 DEC 2020 Date

STUDY SPONSOR:

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PROTOCOL SIGNATURE PAGE

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Version: 3.0

Date: 07 December 2020

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My signature below confirms that I have read and understand the clinical protocol contained herein and agree to conduct the study according to the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), EN ISO 14155:2011, Council Directive 93/42/EEC and Commission Directive 2005/28/EC, and the ethical principles that have their origins in the World Medical Association Declaration of Helsinki, and local ethical and legal requirements.

Principal Investigator:

_____ _____

Print Name Date

_____

Signature

1. LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
CA	Competent Authority
DMP	Data Management Plan
EC	Ethics Committee
FDA	Food and Drug Administration
HA	Hyaluronan / Sodium Hyaluronate / Hyaluronic Acid
HIPAA	Health Insurance Portability and Accountability Act
IA	Intra-articular
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instructions for Use
ISO	International Organization for Standardization
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
OA	Osteoarthritis
PGA	Patient Global Assessment
PI	Principal Investigator
PP	Per Protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Event
USADE	Unanticipated Serious Adverse Device Effect

2. STUDY SYNOPSIS

Title	A Prospective Study of a Single Injection Cross-linked Sodium Hyaluronate combined with Triamcinolone Hexacetonide (CINGAL®) to Provide Symptomatic Relief of Osteoarthritis of Hip Joint
Study Objective	To obtain clinical data to support an expanded indication for a single injection of Cingal® used for the symptomatic relief of osteoarthritis in the hip joint.
Investigational Product	**CINGAL®**: A chemically cross-linked sodium hyaluronate combined with Triamcinolone Hexacetonide supplied as a 4-mL unit dose in a 5-mL glass syringe.
Mode of Delivery	Cingal will be injected into the intraarticular (IA) space of the index hip using an 18-21-gauge needle. Intra-articular injection of the index hip joint may be conducted under fluoroscopic or ultrasound guidance as required by standard of care treatment.
Study Design	Prospective, multi-center, open label expanded indication clinical trial.
Phase	Phase III
Sample Size	25 subjects will be enrolled and treated.
Study Duration	The entire study duration from first subject in to last subject out will be approximately one and half years. The enrollment phase will be approximately 12 months with a follow-up phase of 6 months. Visits will be scheduled at screening, baseline, 1 month, 3 months and 6 months post treatment. First patient in is expected Nov - Dec 2020.
Inclusion Criteria	Screening Inclusion Criteria 1. Age 18 years or older 2. Body Mass Index (BMI) ≤ 35 kg/m^2 3. Diagnosis of symptomatic osteoarthritic joint in the index hip (Kellgren-Lawrence grade I to III) to be treated with Cingal injection. 4. Failed conservative treatment for joint osteoarthritis. 5. NRS pain on walking ≥4 and ≤ 9 in index hip. 6. Subject must be willing to abstain from other treatments of the index hip for the duration of the study. 7. 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. 8. 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. 9. 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). 10. Able and willing to provide signed informed consent. Screening Exclusion Criteria 1. History of hypersensitivity to any of the ingredients in the hyaluronan or corticosteroids 2. Infection or skin disease in the area of the injection site or hip joint 3. NRS pain on walking > 3 in the contralateral hip 4. NRS pain on walking > 3 in the ipsilateral knee or ankle 5. Subject received an injection of Hyaluronic Acid (HA) and/or steroid in either joint 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 joint during the course of this study. 6. Known inflammatory or autoimmune disorders (including rheumatoid arthritis, gout), or other pre-existing medical conditions that, in the opinion of the investigator, could impact treatment of the hip joint or affect the ability of the subject to accurately complete the study questionnaires and comply with the study requirements. 7. 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. 8. Subjects who had an oral, intramuscular, intravenous, rectal suppository or topical (excluded in hip joint only) corticosteroid prior 30 days of signing the ICF are excluded. Topical corticosteroid use at any site other than the hip joint is allowed. 9. Significant trauma to the index hip within 26 weeks of screening 10. Chronic use of narcotics or cannabis. 11. Ligament instability or tear in hip joint. 12. Diagnosis of fibromyalgia 13. Diagnosis of osteonecrosis in hip joint 14. Subject has significant varus or valgus deformity greater than 10 degrees in either knee. 15. Subject requires consistent use of an assistive device (e.g. wheelchair, walker, etc.) Occasional use of a cane is acceptable. 16. Uncontrolled diabetes with HbA1c of >7%. 17. 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. 18. Subject is receiving or in litigation for worker's compensation. 19. Otherwise determined by the investigator to be medically unsuitable for participation in this study. Baseline Inclusion Criteria 1. NRS pain on walking ≥4 and ≤ 9 in index hip Baseline Exclusion Criteria 1. Subject has a decrease of ≥ 2 in the NRS pain on walking from Screening to Baseline in the index hip. 2. Subject has a contraindication to continue with the study treatment injection based on the visual appearance of the synovial fluid aspirate.
Criteria for Evaluation	**Primary Endpoint:** • Reduction of index hip Numerical Rating Scale (NRS) pain on walking from baseline to 6 Months post injection. **Secondary Endpoints:** • Improvement in Lequesne Hip index from baseline to 6 months post injection. • Improvement in Patient Global Assessment (PGA) from baseline to 6 months post injection. • OMERACT-OARSI responder rate in index hip at 6 months post injection. • Time to treatment failure • Reduction in Medication usage from baseline to 6 months post injection. **Exploratory Endpoints** Any comparisons across timepoints (baseline to 6 months) not described in the primary or secondary endpoints including but not limited to: • Demographics • Medical History

	• History of joint osteoarthritis • Rescue Medication Use • Treatment Failure • Injection procedure • Concomitant medications • Non-drug therapy **Safety Endpoint:** The incidence, severity, and relationship to treatment of all Adverse Events (AE) will be collected from the first treatment injection to the 6 month assessment.
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 6 months this is all subjects who complete the 6 month assessment and do not have a major deviation in the conduct 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 of Cingal in the hip joint.
Sites	Up to 10 clinical sites in EU
Sponsor	Anika Therapeutics, Inc. 32 Wiggins Avenue Bedford, MA 01730, United States of America Phone: + 1 781-457-9000 Fax: + 1 781-305-9720

3. 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 created 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. Anika chose to add a corticosteroid, triamcinolone hexacetonide (TH), that was approved in the U.S. and Europe for intra-articular use in osteoarthritis and was labeled for frequency of injection every 3-4 weeks, to a cross-linked HA product which provides pain relief of up to 26 weeks after a single injection.

Cingal® is a sterile, biocompatible, non-pyrogenic, viscoelastic, uniform white/off white opaque solution composed of molecules of HA and triamcinolone hexacetonide (TH). Cingal® is intended to treat the pain of 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.

Cingal® has been studied in two Phase III trials, Cingal 13-01 and Cingal 16-02, and several follow-on studies, Cingal 13-02 and Cingal 17-02 [26-29]. Cingal® studies generated a safety data base of 642 subjects treated intra-articularly with a Cingal® injection, including 94 subjects retreated with a second injection.

Hyaluronic Acid injections in non-knee synovial joints has been reported to show benefits in pain reduction and improvement in joint function. Patients with hip osteoarthritis had significantly improved Lequesne's function and reduced VAS pain at 3 and 6 months after injection (Migliore et al. *Arthritis Research & Therapy* 2009 Vol 11 No 6). A study on the use of intra-articular HA in the treatment of symptomatic osteoarthritis of the shoulder showed an improvement in VAS score of 24 points from baseline to 6-months (Silverstein et al. *Am J of Sports Medicine*, 2007, Vol 35, No. 6). The effect of a single injection of HA on patients with symptomatic ankle (talo-crural) osteoarthritis show an improvement in VAS score of 44.5 points from baseline to 3 months (Witteveen A.G.H. et al. / *Foot and Ankle Surgery* 2008 *Vol 14* p145-152).

The goal of this study is to demonstrate the clinical improvement and safety in patients treated with Cingal for hip osteoarthritis. Specifically, this study will provide confirmation to the safety and performance of Cingal at relieving hip joint pain to 6 months post-treatment.

4. BENEFITS / RISKS

4.1 Benefits

Intra-articular injections of Cingal and other hyaluronic acid viscosupplements have shown significant clinical benefits for knee osteoarthritis patients. It is anticipated that such benefits may result from the use of Cingal to treat hip OA pain.

4.2 Risks

Any intra-articular injection poses potential risks. However, subjects should incur no additional risks compared to injections of other frequently injected products, such as corticosteroids or diagnostic contrast agents.

Effects associated with Hyaluronic Acid

Hyaluronic acid is a naturally occurring component of the tissues of the body. Cingal is thoroughly tested to determine that each batch conforms to the product quality attributes. Mild to moderate episodes of transient swelling and discomfort have occasionally been observed following intra-articular injection of hyaluronic acid preparations. A risk of infection is possible with the procedure of injecting substances into joints.

Effects associated with Triamcinolone Hexacetonide

For assessment of adverse reactions (ADRs) following terms regarding frequency are used:

very common (≥1/10)

common (≥1/100 to <1/10)

uncommon (≥1/1,000 to <1/100)

rare (≥1/10,000 to 1</1,000)

very rare (<1/10,000)

not known (cannot be estimated from the available data)

Adverse effects depend on the dose and the duration of treatment. Systemic adverse effects are rare but may occur as a result of repeated periarticular injection. As with other intraarticular steroid treatments, transient adrenocortical suppression has been observed during the first week after injection. This effect is enhanced if corticotropin or oral steroids are used concomitantly.

Immune system disorders

Very rare: anaphylaxis-type reactions

Not known exacerbation or masking of infections

Endocrine disorders

Not known menstrual irregularities, amenorrhoea and postmenopausal vaginal bleeding; hirsutism; development of a cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly during periods of stress (e.g. trauma, surgery or illness); decreased carbohydrate tolerance; manifestation of latent diabetes mellitus

Psychiatric disorders

Not known insomnia; exacerbation of existing psychiatric symptoms; depression (sometimes severe); euphoria; mood swings; psychotic symptoms

Nervous system disorders

Rare: vertigo

Not known: increased intracranial pressure with papilloedema (pseudotumor cerebri) usually after treatment; headache

Eye disorders

Not known: posterior subcapsular cataracts; increased intraocular pressure; glaucoma

Cardiac disorders

Not known: cardiac failure; arrhythmias

Vascular disorders

Very rare: thromboembolism

Not known: hypertension

Gastrointestinal disorders

Not known peptic ulcers with possibility of subsequent perforation and haemorrhage; pancreatitis

Skin and subcutaneous tissue disorders

Very rare: hyperpigmentation or hypopigmentation

Not known: impaired wound healing; thin and fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; purpurea; striae; acneiform eruptions; hives; rash

Musculoskeletal and connective tissue disorders

Very rare: calcinosis; tendon rupture

Not known: loss of muscle mass; osteoporosis; aseptic necrosis of the heads of the humerus and femur; spontaneous fractures; Charcotlike arthropathy

Renal and urinary disorders

Not known: negative nitrogen balance owing to protein catabolism

General disorders and administration site conditions

Common: Local reactions include sterile abscesses, post-injection erythema, pain, swelling and necrosis at the injection site.

Rare: Excess dosage or too-frequent administration of injections into the same site may cause local subcutaneous atrophy, which, due to the properties of the drug will only return to normal after several months.

Adverse events associated with single intra-articular knee injections of Cingal can be found in the Cingal Investigator's Brochure. These events are expected to be similar for hip injections. In the clinical trial for Cingal in knee OA, adverse events that were related to the injection treatment were:

- injection site pain/swelling
- joint stiffness / swelling / effusion
- arthralgia,
- pain in extremity
- synovitis
- contusion
- subcutaneous nodule
- Baker's cyst

Adverse events not related to the knee for Cingal were:

- headache
- pain in extremity
- upper respiratory tract infection
- back pain

Other risks associated with intra-articular hip injections, regardless of treatment, include:

- temporary injection site pain, swelling or tenderness
- temporary stiffness of the hip
- malfunction of the syringe and/or needle

In rare instances, side effects could include:

- an allergic reaction to the fluoroscopic imaging contrast agent. Symptoms could include redness or inflammation at the injection site or inside the hip joint, hives or itching.
- an allergic reaction to the local anesthetic (lidocaine). Symptoms could include redness or inflammation at the injection site or inside the hip joint, hives or itching.
- injection site infection
- neurovascular, cartilage, or bone damage resulting from the injection itself

Finally, there is a low risk associated with radiation from the X-ray evaluation required for inclusion in the study. There is also a low risk from the radiation during fluoroscopy-guided injections

5. CONTRAINDICATIONS / WARNINGS AND PRECAUTIONS

5.1 Contraindications

Cingal has the following contraindications per its approved labeling (IFU AML 500-277):

5.1.1 CINGAL CONTRAINDICATIONS:

Cingal is composed of cross-linked hyaluronic acid, triamcinolone hexacetonide and inactive ingredients. 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
- Known infection of the index joint
- Known systemic bleeding disorders
- Weak populations including children and pregnant or lactating women

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

- active tuberculosis

- herpes simplex keratitis
- acute psychoses
- systemic mycoses and parasitoses (strongyloid infections)

5.1.2 CINGAL INVESTIGATIONAL USE CONTRAINDICATIONS:

The same contraindications in the approved Cingal labeling apply to investigational use in the hip, shoulder or ankle.

5.2 WARNINGS / PRECAUTIONS:

5.2.1 CINGAL WARNINGS

Cingal has the following Warnings and Precautions per its approved labeling:

PRECAUTIONS
General:

- Those precautions normally considered during injection of substances into joints are recommended.
- Appropriate examination of any joint fluid present is necessary to exclude a septic process
- Only medical professionals trained in accepted injection techniques for delivering agents to joint spaces should inject Cingal for this application.
- The synovial space should not be overfilled.
- If pain increases during the injection procedure, the injection should be stopped and the needle withdrawn.
- A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.
- Single Use only; reuse of the contents of the syringe may result in infection and increase occurrence of adverse events.

Triamcinolone hexacetonide

- This product contains a corticosteroid and so should be used with caution in patients suffering from the following conditions:
  - cardiac insufficiency, acute coronary artery disease,
  - hypertension,
  - thrombophlebitis, thromboembolism
  - myasthenia gravis,

- osteoporosis,
- gastric ulcer, diverticulitis, ulcerative colitis, recent intestinal anastomosis,
- exanthematous diseases,
- psychosis,
- Cushing's syndrome,
- diabetes mellitus,
- hypothyroidism,
- renal insufficiency, acute glomerulonephritis, chronic nephritis,
- cirrhosis,
- infections that cannot be treated with antibiotics,
- metastatic carcinoma.

- All corticosteroids may increase calcium excretion.
- The product must not be administered intravenously, intraocularly, epidurally or intrathecally.
- Intra-articular injection should not be carried out in the presence of active infection in or near joints.
- The load on strained joints in particular should be lightened immediately after the injection to avoid overloading.
- If, during treatment, the patient develops serious reactions or acute infections, the treatment must be stopped and appropriate treatment given.
- Caution should be used in the event of exposure to chickenpox, measles or other communicable diseases, since the course of specific viral diseases such as chickenpox and measles may be particularly severe in patients treated with glucocorticoids. At particular risk are individuals with no history of chickenpox or measles infection. If such individuals should come into contact with chickenpox or measles sufferers during treatment with Triamcinolone hexacetonide, prophylactic treatment should be considered as appropriate.
- Menstrual irregularities may occur and in postmenopausal women vaginal bleeding has been observed. This possibility should be mentioned to female patients but should not deter appropriate investigations as indicated.
- Triamcinolone hexacetonide contains sorbitol. Patients with very rare hereditary problems of fructose intolerance should not take this medicine.
- Glucocorticoids may induce growth suppression in children. The Safety of Cingal® in pediatric populations has not been established.

Interaction with other medicinal products

- Amphotericin B injection and potassium-depleting agents: Patients should be monitored for additive hypokalaemia.

- Anticholinesterases: The effect of anticholinesterase agent may be antagonised.
- Anticholinergics (e.g. atropine): Additional increase of intraocular pressure is possible.
- Anticoagulants, oral: Corticosteroids may potentiate or decrease anticoagulant effect. For this reason, patients receiving oral anticoagulants and corticosteroids should be closely monitored.
- Antidiabetics (e.g. sulfonylurea derivatives) and insulin: Corticosteroids may increase the levels of glucose in the blood. Diabetic patients should be monitored, especially on instigation and discontinuation of treatment of corticosteroids and if the dosage is changed.
- Antihypertensives, including diuretics: The reduction in arterial blood pressure may be diminished.
- Antituberculosis drugs: Isoniazid serum concentrations may be decreased.
- Cyclosporin: When used concomitantly, this substance may produce an increase in both cyclosporin and corticosteroid activity.
- Digitalis glycosides: Concomitant administration may increase the likelihood of digitalis toxicity.
- Hepatic Enzyme Inducers (e.g. barbiturates, phenytoin, carbamazepine, rifampicin, primidone, aminoglutethimide): There may be increased metabolic clearance of Triamcinolone hexacetonide. Patients should be carefully observed for possible reduced effect of Triamcinolone hexacetonide, and the dosage should be adjusted accordingly.
- Human growth hormone (somatropin): The growth-promoting effect may be inhibited during long-term therapy with Triamcinolone hexacetonide.
- Ketoconazole: Corticosteroid clearance may be decreased, resulting in increased effects.
- Non-depolarising muscle relaxants: Corticosteroids may decrease or enhance the neuromuscular blocking action.
- Non-steroidal anti-inflammatory agents (NSAIDs): Corticosteroids may increase the incidence and/or severity of gastrointestinal bleeding and ulceration associated with NSAIDs. Corticosteroids may also reduce serum salicylate levels and therefore decrease their efficacy. Conversely, discontinuing corticosteroids during high-dose salicylate therapy may result in salicylate toxicity. Caution must be exercised during concomitant use of acetylsalicylic acid and corticosteroids in patients with hypoprothrombinaemia.
- Oestrogens, including oral contraceptives: Corticosteroid half-life and concentration may be increased and clearance decreased.
- Thyroid drugs: Metabolic clearance of adrenocorticoids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustments to the dosage of adrenocorticoids.
- Vaccines: Neurological complications and a diminished antibody response may occur when patients taking corticosteroids are vaccinated. (see section 4.3)
- Medicines that prolong the QT interval or induce torsade de pointes:

- Concomitant treatment with triamcinolone hexacetonide and class Ia antiarrhythmic agents such as disopyramide, quinidine and procainamide, or other class II antiarrhythmic drugs such as amiodarone, bepridil and sotalol, is not recommended.
- Extreme caution is required in cases of concomitant administration with phenothiazines, tricyclic antidepressants, terfenadine and astemizole, vincamine, erythromycin i.v., halofantrine, pentamidine and sultopride.
- Combination with agents that cause electrolyte disturbances such as hypokalaemia (potassium-depleting diuretics, amphotericin B i.v. and certain laxatives), hypomagnesaemia and severe hypocalcaemia is not recommended.
- Interactions with laboratory tests - Corticosteroids may interfere with the nitroblue tetrazolium test for bacterial infection, producing false-negative results.
- Athletes should be informed that this medicinal product contains an ingredient (e.g.triamcinolone hexacetonide) that may produce a positive result in anti-doping tests.

Fertility, Pregnancy and Lactation

- The safety of Cingal in pregnant and lactating women has not been established.
- Fertility, pregnancy and lactation: Triamcinolone crosses the placenta. Corticosteroids are teratogenic in animal experiments. The significance of this fact for humans is not exactly known, but so far the use of corticosteroids has not been shown to increase the incidence of malformations. The product should be used during pregnancy only if the benefit to the mother is clearly greater than the risk to the fetus. Triamcinolone hexacetonide is excreted in human milk, but is not likely to have any effect on the child at therapeutic doses. Corticosteroid therapy may cause menstrual disorders and amenorrhea.

5.2.2 CINGAL INVESTIGATIONAL USE WARNINGS AND PRECAUTIONS:

The same warnings/precautions in the approved Cingal labeling apply to investigational use in the hip, shoulder or ankle.

5.3 Usage in Pregnancy

The safety of Cingal in pediatric populations, pregnant and lactating women has not been established.

6. ENDPOINTS

6.1 Primary Endpoint:

- Reduction of index hip Numerical Rating Scale (NRS) pain on walking from baseline to 6 Months post injection.

6.2 Secondary Endpoints:

- Improvement in Lequesne Hip index hip from baseline to 6 months post injection.
- Improvement in Patient Global Assessment (PGA) from baseline to 6 months post injection.
- OMERACT-OARSI responder rate in the index hip at 6 months post injection.
- Time to treatment failure
- Reduction in Medication usage from baseline to 6 months post injection.

6.3 Exploratory Endpoints

Any comparisons across timepoints (baseline to 6 months) not described in the primary or secondary endpoints, including but not limited to:

- Demographics
- Medical History
- History of joint osteoarthritis
- Rescue Medication Use
- Treatment Failure
- Injection procedure
- Concomitant medications
- Non-drug therapy

6.4 Safety Endpoint:

The incidence, severity, and relationship to treatment of all Adverse Events (AE) will be collected from the treatment injection to the 6 month assessment.

6.5 Trial Design

This is a prospective, expanded indications multi-center, open-label study to evaluate safety and performance of injections of Cingal for relief of pain in patients with a diagnosis of an osteoarthritic hip joint.

The subjects in this study will be patients with a diagnosis of osteoarthritic (OA) joint who the investigator determines are appropriate candidates for treatment with a viscoelastic injection of Cingal.

Up to 25 subjects will be enrolled and treated at up to 10 investigational sites in the EU. Subject participation will last approximately 6 Months, with visits scheduled at Screening, Baseline, 1 month,

3 month and 6 months.

6.6 Enrollment Criteria

At screening visit:

6.6.1 Screening Inclusion Criteria

1. Age 18 years or older
2. Body Mass Index (BMI) ≤ 35 kg/m^2
3. Diagnosis of symptomatic osteoarthritic joint in the index hip (Kellgren-Lawrence grade I to III) to be treated with CINGAL injection.
4. Failed conservative treatment for joint osteoarthritis.
5. NRS on walking ≥4 and ≤ 9 in index hip.
6. Subject must be willing to abstain from other treatments of the index hip for the duration of the study.
7. 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.
8. 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 assessment, the subject is willing to discontinue use of acetaminophen/paracetamol.
9. 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).
10. Able and willing to provide signed informed consent.

6.6.2 Screening Exclusion Criteria

1. History of hypersensitivity to any of the ingredients in the hyaluronan or corticosteroids
2. Infection or skin disease in the area of the injection site or hip joint
3. NRS pain on walking > 3 the contralateral hip.
4. NRS pain on walking > 3 in the ipsilateral knee or ankle joints.
5. Subject received an injection of Hyaluronic Acid (HA) and/or steroid in either joint 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 joint during the course of this study.
6. Known inflammatory or autoimmune disorders (including rheumatoid arthritis, gout), or other pre-existing medical conditions that, in the opinion of the investigator, could impact treatment of the hip joint or affect the ability of the subject to accurately complete the study questionnaires and comply with the study requirements.
7. 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.
8. Subjects who had an oral, intramuscular, intravenous, rectal suppository or topical (excluded in index hip only) corticosteroid within 30 days of signing the ICF are excluded. Topical corticosteroid use at any site other than the index hip is allowed.
9. Significant trauma to the index hip within 26 weeks of screening
10. Chronic use of narcotics or cannabis.

11. Ligament instability or tear in index hip.
12. Diagnosis of fibromyalgia
13. Diagnosis of osteonecrosis in index hip
14. Subject has significant varus or valgus deformity greater than 10 degrees in either knee.
15. Subject requires consistent use of an assistive device (e.g. wheelchair, walker, etc.) Occasional use of a cane is acceptable.
16. Uncontrolled diabetes with HbA1c of >7%.
17. 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.
18. Subject is receiving or in litigation for worker's compensation.
19. Otherwise determined by the investigator to be medically unsuitable for participation in this study.

At baseline visit:

6.6.3 Baseline Inclusion Criteria

1. NRS pain on walking ≥4 and ≤ 9 in index hip

6.6.4 Baseline Exclusion Criteria

2. Subject has a decrease of ≥ 2 in the NRS pain on walking from Screening to Baseline in the index hip.
3. Subject has a contraindication to continue with the study treatment injection based on the visual appearance of the synovial fluid aspirate.

7. STUDY PROCEDURES

7.1 Schedule of Events

Assessments	Screening Visit Day -14 to -7 ±2 days	Baseline Visit Day 0	Month 1 Visit ±3 days	Month 3 Visit ± 7 days	Month 6 Visit ± 7 days
Informed Consent	X				
Evaluation of Enrollment Criteria	X	X			
Demographics	X				
Vital Signs	X				
History Joint OA (Index & Contralateral for hip, knee and ankle)	X				
Medical History	X				
Concomitant Medication	X	X	X	X	X
Assess non-drug therapies	X	X	X	X	X
Adverse Event Assessment		X	X	X	X
Collect & Review Subject Diary		X	X	X	X
Rescue Medication usage / washout		X	X	X	X
Patient Global Assessment (PGA)	X	X	X	X	X
Lequesne index for index and contralateral hip	X	X	X	X	X
Index and Contralateral Joints Pain on Walking (0-10 Numeric Rating Scale) for Hip, Knee and Ankle joint	X	X	X	X	X
Physical Evaluation of Index and Contralateral for Hip, Knee and Ankle joints	X	X	X	X	X
Study Injection		X			
Dispense Subject Diary	X	X	X	X	

7.2 Procedure Description

7.3 Screening Visit (Day -14 to -2 days)

The following screening and eligibility data will be collected.

7.3.1 Informed Consent Form

The subject must sign the Informed Consent Form (ICF) prior to enrollment or undergoing study treatment.

7.3.2 Inclusion / Exclusion Criteria

Confirm subject eligibility against the inclusion and exclusion criteria.

7.3.3 Demographics

The following demographic information will be collected at the Screening Visit:

- Age
- Gender
- Race
- Height
- Weight
- Index hip – left / right
- Index / Contralateral Joint OA Grades for Hip, Knee and Ankle

7.3.4 Vital Signs

Patient will have vital signs assessed.

- Blood pressure
- Pulse
- Temperature

7.3.5 History of Joint Osteoarthritis

Subject's history of osteoarthritis including prior treatments for both index and contralateral hip, knee and ankle joints.

7.3.6 Medical History

The relevant medical history of the index and contralateral hip, knee and ankle joints will include, but is not limited to, an assessment of:

- History of trauma in the joints
- History of surgery in the joints
- History of injections to treat pain in the joints
- History of other treatments in the joints including failed prior treatments including but not limited to corticosteroid injection, HA injection, acupuncture, RICE (Rest, Ice, Compression, Elevation), NSAIDS.

7.3.7 Pain Assessment

Patient reported Pain on walking of the index and contralateral hip, knee and ankle joints will be measured with a Numerical Rating Scale (NRS).

7.3.8 Physical Evaluation of Index & Contralateral Joints

The Investigator will perform the physical evaluation of the index and contralateral hip, knee and ankle joints at the time points included in Schedule of Events, and will include the following assessments:

- Appearance of redness or swelling
- Assessment of pain upon palpation of the joints
- Assessment of comorbidities at the joints

7.3.9 Medications

Medications that the subject may have been taking prior to study enrollment for conditions unrelated to the treatment of osteoarthritis, other than analgesics including NSAIDs, may be continued as long as they will not interfere with study assessments. Low dose aspirin (81 mg) used for cardiovascular protection is allowed if a stable regimen is maintained for the duration of the study.

7.3.9.1 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 osteoarthritis of hip joint. Topical corticosteroids are allowed at any other site other than the hip joint. The analgesic medication use will be monitored at each subject assessment through review of the subject diary.

7.3.9.2 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 Osteoarthritis in the index hip for the duration of the study. At least forty-eight hours prior to the Baseline Visit, 1, 3 and 6 Month Assessments the subject should discontinue use of the rescue medication.

The subject should be instructed to track pill usage daily to convey accurate pill counts at follow-up assessments.

7.3.9.3 Concomitant Medications

A medication is considered concomitant if taken after signing the ICF and up to and including the last follow-up assessment. 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 assessment, the subject will be asked about any new medications that were started since the last assessment. Indications for any new medications started after the study treatment will be recorded as AEs, unless the medications are administered for a pre-existing condition.

7.3.9.4 Non-Drug Therapies

Non-drug therapies are any therapies used to treat the hip joint that are not a pharmaceutical treatments.

7.3.9.5 Joint Function Assessment

Subjects will receive assessment of the respective joints for functional use.

7.3.9.6 Subject Diary

Subjects will receive diary for to record rescue medications and concomitant medications.

7.4 Baseline Visit: Treatment Visit (Day 0)

The Baseline Visit (Day 0) will occur 7 to 14 days after the Screening Visit to allow for rescue medication washout. The injection will occur at this Baseline visit along with the following activities:

Before Treatment Injection

- Concomitant Medications
- Current non-drug therapies
- Confirm Medication Washout
    - If subject did not complete medications washout, reschedule the visit to allow washout to be completed.
- Patient Global Assessment (PGA)
- Lequesne Hip index
- Index & Contralateral Hip, Knee and Ankle Joint Pain on Walking (NRS Scale)
    - Confirm Baseline Inclusion & Exclusion Criteria for NRS pain on walking
- Physical Exam of Index and Contralateral Hip, Knee and Ankle Joints

Treatment Procedure

The Treating Physician may perform the Study Injection to the index hip as standard of care dictates or delegate the injection to qualified study staff.

Intra-articular injection of the index hip joint may be conducted under fluoroscopic or ultrasound guidance as required by standard of care treatment. Guidelines for the injection procedural steps are provided below. Modifications to this technique should be recorded in the CRFs.

- Patient is supine, index hip rotated internally 15-20 deg.
- Prep the skin at injection site with 1% betadine solution or equivalent.
- Peri- articular injection site anesthesia by injection of lidocaine or topical refrigerant anesthetic (e.g. ethyl chloride).
- Fluoroscopic or ultrasound guidance may be utilized if required to insert 18-21 gauge needle anteriorly towards the anterior-inferior joint capsule, approximately 8-10 cm below the inguinal ligament and just below the femoral head, taking care to avoid the femoral artery.
- If using fluoroscopic guidance, a small amount of fluoroscopic contrast agent (0.5 to 1.0 ml) should be injected through the needle to verify intra-articular placement.
- If using ultrasound guidance, a small volume of air (up to 0.5 ml) may be injected to verify IA positioning.
- If pooling of the contrast agent or air around the needle tip is observed, the needle should be repositioned.

- When contrast agent or air is successfully injected into the joint, intra-articular placement is confirmed.
- Following confirmation of intra-articular needle placement, the joint may be aspirated to remove synovial fluid.
    - Confirm the Baseline Exclusion for synovial aspirate.
- 4 ml of CINGAL is injected into the joint.
- Intra-articular anesthetic should NOT be administered as part of the injection procedure.
- Following the injection, the patient should be advised to maintain a low level of physical activity for the next 48 hours. Cold therapy and/or acetaminophen/ paracetamol may be prescribed to address short term injection site pain.

Post-Treatment Assessments and Instructions

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

7.5 Follow-Up Visits

All study subjects will have follow-up visits at 1, 3 and 6 Months after Baseline to evaluate the joint pain score and to assess adverse events.

The subject should be contacted at least 48 hours prior to their scheduled assessments to be reminded of the required assessment (and applicable wash out period) and to schedule the date and time of contact. At least three documented attempts will be made to contact the subject in order to accomplish maximum subject compliance with the follow-up schedule.

The following tests will be performed at the follow-up visits at 1, 3 and 6 months.

7.6 Follow-up Visits (± 7 days)

- Assess Concomitant Medications
- Assess Non- drug therapies
- Assessment of Adverse Events
- Confirm Rescue Medication Washout
    - If subject did not complete medications washout, reschedule the visit to allow washout to be completed.
- Assess Rescue Medication usage
- Collect and assess subject diary
- Patient Global Assessment (PGA)
- Lequesne Hip index and contralateral joints
- Index & Contralateral Hip, Knee and Ankle Joint Pain on Walking (NRS)

- Physical Exam of Index and Contralateral Hip, Knee and Ankle Joints

8. SAFETY PROCESSES

Safety of the subjects participating in this clinical investigation will be monitored throughout the clinical investigation using the Adverse Event (AE) reporting process in the EDC system, to identify real and potential safety issues.

Adverse events will be reported according to the ISO 14155:2011, while recognizing and following the requirements including reporting timelines specified in other specific laws, regulations, directives, standards and/or guidelines as appropriate and as required by the countries in which the study is conducted.

All AEs that occur during or after injection will be recorded. Worsening of a condition that existed prior to the study injection should be recorded as an AE. At each assessment during the trial, AEs that have occurred since the previous assessment 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, erythema, bleeding and/or infection 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 device and/or the procedure will be recorded on the CRF. 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 at all scheduled follow-up points.

8.1 Definition of Adverse Events

Adverse Device Effect (ADE)

Adverse event 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, operation, or any malfunction of the investigational medical device.

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

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

Note 1: This includes events related to the investigational medical device or the comparator.

Note 2: This includes events related to the procedures involved.

Note 3: For users or other persons this is restricted to events related to the investigational medical device.

Device Deficiencies (DD)

The inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

a) if either suitable action had not been taken,

b) if intervention had not been made, or

c) if circumstances had been less fortunate,

shall be reported under the same conditions as a serious adverse event.

Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan.

Serious Adverse Events (SAE)

An adverse event that:

a) led to a death,

b) led to a serious deterioration in the health of the subject user or other persons that either resulted in:

1) a life-threatening illness or injury, or

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

3) in-patient or prolonged hospitalization. or

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

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

Note: A planned hospitalization for pre-existing condition or a procedure required by the protocol without a serious deterioration in health is not considered to be a serious adverse event.

Serious Adverse Device Effects (SADE)

An Adverse Device Effect that has resulted in any of the consequences characteristic of a serious adverse event.

Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Unanticipated Serious Adverse Device Effects (USADE)

A Serious Adverse Device Effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

8.2 Safety Reporting Process – principal investigator responsibilities

The principal investigator shall report all adverse events and device deficiencies in the appropriate sections of the e-CRF and provide where requested by the sponsor, the necessary clinical or technical information that may contribute to clarifying the circumstances.

The principal investigator shall report all serious adverse events (SAEs) and device deficiencies (DDs) that might have led to a SAE: if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate, to the sponsor within 24 hours after knowledge of the event using the appropriate e-CRF.

When required by national or local regulations, the principal investigator shall also notify the EC/IRB and Regulatory Agencies of all reportable events according to national regulations within the by regulations required timelines and may also be requested by the EC/IRBs to provide annual reports. The principal investigator shall document all adverse events and device deficiencies in the e-CRF from the point of enrollment until the subject is exited from the study.

8.3 Information provided by the clinical investigation site

The principal investigator will provide the following information, at a minimum, for each adverse event (AE) or Adverse Device Effect (ADE):

- Date of the AE or ADE.
- Date Principal Investigator (or authorized designee) became aware of AE or ADE
- Description of AE or ADE, relevant diagnostic findings
- Treatment
- Resolution
- Assessment of:

1. severity of the event
    a. Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    b. Moderate: minimal, local or noninvasive intervention indicated; limiting
    c. Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling
        i. Life-threatening: urgent intervention indicated, disabling
        ii. Fatal: death related to AE
2. relationship of the event to the investigational device (related, unlikely related, possible related, probable related or causal relationship)
3. relationship of the event to the index procedure (related, unlikely related, possible related, probable related or causal relationship)
4. causality

a. disease under study
b. lack of performance of the investigational device or comparator/worsening of treated condition
c. medical history
d. concomitant or previous medication
e. other (specify)

The principal investigator will supply the sponsor and/or designee, with any additional information related to the safety reporting of a particular event upon request.

The sponsor is responsible for the classification of all adverse events and ongoing safety evaluation of the clinical investigation and shall:

1. Review the investigator's assessment of all adverse events and determine and document in writing their seriousness, severity and relationship to the investigational device; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties.
2. Review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties.
3. Ensure the reporting to the Ethics Committee (EC) by the principal investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or by the EC.
4. Review and report all reportable events (including device deficiencies) according to national regulations in acceptable timely conditions and shall monitor for increased incidence and severity.
5. Ensure that the EC or other applicable regulatory authorities are informed of significant new information about the clinical investigation, and
6. In case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether corrective or preventive action is required.

9. STATISTICAL CONSIDERATIONS

9.1 Sample Size

The primary analysis will be the mean change in index hip pain on walking from baseline to 6 months as measured by the Numerical Rating Scale.

The hypothesis to be tested is:

H_0: $\mu_{DMON} = 0$ versus H_A: $\mu_{DMON} > 0$.

In this hypothesis, μ_{DMON} is the mean change in pain on walking from baseline at 6 Months in CINGAL treated patients.

The data will be analyzed via a one sample t-test.

It is assumed that a mean change in pain from baseline of 2 points represents a clinically significant improvement with a standard deviation of 2 - 2.5 points, for 80% power and alpha of 5%

then a total of 15 subjects are required. To ensure sufficient subjects are available at the 6 month follow up, it is proposed to enroll and treat at least 25 subjects which should be more than adequate to demonstrate that treatment of the study population with CINGAL would reduce joint pain at 6 months.

Single sites should not enroll and treat more than 50% of the total enrollment.

9.2 Statistical Methods

Tabulation of summary statistics, graphical presentations, and statistical analyses will be performed. 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. All testing and confidence intervals will use a significance level of 5%.

9.2.1 Demographic and Baseline Characteristics

All demographic and baseline characteristics will be tabulated. Medical history findings, physical examinations and concomitant medications will be tabulated.

9.2.2 Adverse Events

Subjects with AEs will be summarized with frequencies and percentages by system organ class and preferred term, severity, and relationship to investigational product/procedure. In summaries of AEs by severity and relationship to investigational product/procedure, subjects reporting multiple episodes will be counted once under the worst severity and the strongest relationship, respectively. Serious Adverse Events will also be presented by relationship to investigational product/procedure.

Adverse events occurring prior to the index treatment will not be recorded in this trial.

9.2.3 Subject Populations

The Safety Population will be defined as all subjects who undergo Study Treatment, and the safety analysis will be performed on this population.

The primary analysis on the primary endpoint will be performed on the Intent to Treat (ITT) population, defined as all patients who were treated in the study. 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 6 Months, this is all subjects who complete the 6 Month assessment and who do not have a major deviation from the protocol. For all other assessments, this is defined as the subjects who complete those assessments according to the protocol.

10. DATA MANAGEMENT CONSIDERATIONS

10.1 Data Collection

The CRFs will be completed based on source documents. Once CRFs have been completed by the site, the data management group will begin the data cleaning process.

10.2 Data Management

Once the CRFs are ready for review, the data management group will complete manual validation checks 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.

10.3 Data Retention

All correspondence related to this clinical study should be archived in appropriate study files. Patient records including consent forms, source documents, CRFs, device records including regulatory authority (CA and IRB/EC) and Sponsor correspondence pertaining to the study must be kept on file. All original subject and device inventory records relating to the study shall be retained for not less than two years following notification by Anika Therapeutics, Inc. that the applicable regulatory authority approved an application for the marketing of the study device or that all investigations using the study device have been discontinued. Thereafter, records will not be destroyed without giving Anika Therapeutics, Inc. prior written notice.

11. CLINICAL SUPPLIES

11.1 Packaging and Labeling

The Sponsor will provide the investigational sites with the investigational product.

Cingal syringes will be labeled with investigational use only labels specific to this clinical trial.

The contents of the syringe are sterile if the syringe is intact. Each Cingal syringe is provided packaged in a sealed container within a carton and should not be used if the container has been opened or damaged.

The syringe, container and carton will have the required labeling information and caution statements.

The investigational sites are responsible for providing the paracetamol rescue medication to subjects.

11.2 Storage Requirements

The storage requirements for Cingal are to be maintained in a secure controlled environment at room temperature below 77° F / 25° C. DO NOT FREEZE. Refrigerated Cingal should be allowed to reach room temperature (approximately 20 to 45 minutes) prior to use.

11.3 Instructions for Use

Instructions for Use will be provided with the Investigational Product.

11.4 Device Accountability

It is important to account for the disposition of all Investigational Product (IP) received by a clinical

site. Required information includes the date received, date injected, lot number, expiry date and the Subject who received the device.

The site will use a form to document device accountability which will be reviewed by the study monitor during routine monitoring visits. Each time an investigational product is dispensed, the following information should be recorded: Subject ID, date used, Lot Number and the initials of the person completing the device accountability log. At the termination of the study, Anika Therapeutics, Inc. will instruct sites on the disposition of unused investigational product.

12. DATA QUALITY ASSURANCE

Anika Therapeutics, Inc. performs quality assurance checks on all clinical trials that it Sponsors. Before enrollment of a subject in this study, a monitor (from Anika or designee) and the site staff will review the protocol, the CRFs and instructions for completing them, the procedure for obtaining informed consent, the procedure for reporting AEs and all other relevant study procedures and forms.

13. REGULATORY OBLIGATIONS

The Principal Investigator agrees that the clinical study will be conducted according to the relevant national guidelines which may include: International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), EN ISO 14155:2011, Council Directive 93/42/EEC and Commission Directive 2005/28/EC.

The Principal Investigator agrees that the clinical study will be conducted according to ethical principles that have their origins in the World Medical Association Declaration of Helsinki, and local ethical and legal requirements.

13.1 Clinical Trial Information

Before the beginning of this expanded indication study, the Investigator will be given the Investigator's Brochure. If the Investigator's Brochure is revised during the study, the Investigator will receive a copy of the revised version. The Investigator's Brochure is a confidential communication from Anika Therapeutics, Inc.

Acceptance to participate in this study constitutes an agreement by the recipient investigator 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 standard operating procedures (SOPs) of the IRB/EC and other applicable oversight committees with the agreement that these committees are required to keep the information confidential. Institutional Review Board (IRB)/Ethics Committee (EC) Approval

The protocol and the ICF must have the approval of a properly constituted IRB/EC responsible for approving clinical trials at the site. Prior to activation of the site for enrollment, written IRB/EC approval of the protocol and ICF and a signed contract between the site and Sponsor will be obtained.

13.2 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 Anika Therapeutics, Inc. and the Investigator and documented with written protocol amendments. The Investigator is not to conduct any protocol modifications without prior written permission from Anika Therapeutics Inc. Each Investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria.

13.3 Amendments to the Protocol

Changes to the study protocol after IRB/EC approval must be documented in a protocol amendment and signed by the Investigator and Sponsor. All amendments must be submitted to the CA and IRB/EC in accordance with applicable regulations. The protocol amendment may be implemented after it has been approved by the appropriate regulatory agencies, unless immediate implementation of the change is necessary for subject safety.

13.4 Protocol Deviations

Deviations from the protocol include, but are not limited to missed assessments, out of window assessments, etc. All protocol deviations will be documented and explained. All subjects with protocol deviations will continue to be followed for improvement and safety. Analysis of study data will be done on both the ITT and PP populations.

13.5 Informed Consent

Written informed consent for each subject participating in the trial will be obtained in accordance with GCP and the relevant national and local regulatory authority requirements. An ICF template will be provided to each Investigator. If changes are made to the template, the Investigator must send a copy of the ICF to Anika Therapeutics Inc. or designee for review to assure compliance with the ICH requirements prior to submitting to the IRB/EC. The IRB/EC approved consent form will be provided to the subject and will be signed prior to any study procedures being performed. 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. Subjects will be made aware of any new information that becomes available during the course of the study.

13.6 Adverse Event Reporting

The Investigator agrees to document and report all AEs to Anika Therapeutics, Inc. or its designee. The Investigator is further responsible for ensuring that any study staff promptly brings AEs to the attention of the Investigator. The Investigator is also responsible for informing the participating IRB/EC and other regulatory authorities (as applicable) of any reportable events and adhering to local IRB/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 experienced.

13.7 Permission to Review Subject's Source Records

The Investigator agrees that Anika Therapeutics, Inc., its employees or agents, and the respective Competent Authorities and Ethics Committees will have the right, both during and after this trial, to audit and review pertinent medical records related to the clinical study. Subject study data will not be identified by name, and confidentiality of information in medical records will be preserved.

13.8 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.

13.9 Study Monitoring

A study monitor from Anika Therapeutics, Inc. or designee will maintain contact with the Investigator and may visit the Clinical Trial Site for the purpose of overseeing the progress of the study, and ensuring it is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and applicable regulatory requirements.

13.10 Confidentiality

All information that is provided to the Investigator regarding Cingal is regarded as confidential. Subjects will be told that data will be handled in compliance with European Union Data Protection Directive or relevant national laws on the protection of personal data. Subjects will be informed that Anika Therapeutics, Inc. or designee will have access to their medical records. Subject's participation in the study will be treated as confidential and subjects 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 regulatory authorities.

13.11 Early Study Discontinuation

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

Conditions that may warrant termination 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 device.
- 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 IRB/EC promptly and provide the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution.

13.12 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 CRF. Examples of reasons for premature withdrawal of a subject from the study include:

- 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 or IRB/EC
- Other (reason to be documented in the CRF)

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

13.13 Use and Publication of Study Results

All unpublished documentation (including the protocol and CRF) 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 regulatory authorities 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 executed study contract.

13.14 Pre-Study Documentation

The Investigator must provide the following documents prior to the enrollment of any subjects as appropriate to local country regulation:

- Signed and dated protocol signature page by the Principal Investigator (Investigator) and all Sub-Investigators.
- Signed and dated protocol amendment(s) signature page by the Investigator and all Sub-Investigators, when applicable.
- Current curriculum vitae (CV) for the Investigator and all Sub-Investigators

- 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 as required.
- 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.

13.15 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 Cingal and the requirements for clinical, efficacy and safety follow-up.
- The Investigator should be familiar with and trained on the appropriate use of Cingal as described in the protocol and in the current Instructions for Use.
- The Investigator is responsible to ensure that the Cingal is administered only by trained personnel in accordance with the protocol and instructions for use.
- The Investigator should disclose any potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of the results.
- The Investigator should be trained on and comply with GCP regulations and the applicable regulatory requirements.
- The Investigator should demonstrate that the proposed Clinical Trial Site has the following:
    - One or more qualified Investigators;
    - Qualified site staff;
    - Adequate facilities for the foreseen duration of the clinical study;

  - Required number of eligible subjects needed within the agreed recruitment period.

- The Investigator must create and maintain source documentation throughout the clinical study and make it available as requested during monitoring visits and audits.
- The Investigator should permit monitoring and auditing by the Sponsor or Sponsor's designee and inspection by the appropriate regulatory 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. Instructions for Use, 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 must be aware of the AE and adverse reaction reporting process, including reactions related to application of the CINGAL.
- 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 CINGAL, knowledge of the requirements for storage, handling, administration, and destruction or disposal of the CINGAL including any hazard to those handling the product and close contacts and the risk to the environment.
- The Investigator must ensure that the particular requirements for the application of the Cingal, such as standardization of injection procedures if possible and training of the healthcare professionals involved, are communicated to the site staff including the physicians or other specialists involved.
- The Investigator shall ensure maintenance and calibration of the equipment relevant for the assessment of the clinical study is appropriately performed and documented, when applicable.
- The Investigator must be knowledgeable with the method of obtaining informed consent.

- The Investigator shall ensure and document appropriate training if any authorized designee is appointed to conduct the informed consent process.
- The Investigator must inform the trial subject of the particular issues that arise for the Cingal. In particular, both the ICF and any other written information to be provided to the subjects should include an explanation of the following:
    - Provisions for subject data protection and confidentiality;
    - The arrangements for follow-up before and after the end of the trial, including after subjects withdraw from the study and including the information to be provided to the subject for use in the event of problems arising after the end of the trial;
    - The length of follow-up;
    - The definition of the end of the trial and its relationship to the follow-up after the end of the trial;
    - The need to keep an accurate subject diary;
- 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:
    - 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,
    - Some means of showing the subjects participation in the clinical study, together with identification and compliance information for the concomitant treatment measures (If appropriate).

13.16 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 EN 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 establish the particular requirements for the application of the Cingal, and train the Investigator in the requirements for storage, handling, administration, and destruction or disposal of the Cingal including hazards to those handling the product and close contacts and the risk to the environment.
- Anika Therapeutics, Inc. will designate or appoint one or more monitors, or otherwise assume the responsibilities of the monitor(s) and ensure documentation of training, experience and scientific or clinical knowledge for all the relevant parties involved in order to adequately conduct the clinical study. This includes training on the following:
    - Use of the Cingal
    - 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
- Sponsor's written procedures; EN 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 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. or designee 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 Cingal trial.
- 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, where required.
- 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 Cingal, through the Instructions for Use 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 Cingal trial and share this with the Investigators;
- Anika Therapeutics, Inc. or designee 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.

14. GENERAL INFORMATION

Study Contact Information

Name	Address/Phone Number	Responsibility
Study Sponsor	Anika Therapeutics Inc. 32 Wiggins Avenue Bedford, MA 01730 USA Tel: (781) 457-9000 Fax: (781) 305-9720	Sponsor
Manufacturer	Anika Therapeutics Inc. 32 Wiggins Avenue Bedford, MA 01730 USA Tel: (781) 457-9000 Fax: (781) 305-9720	Manufacturer
EU Representative	Anika Therapeutics, S.R.L Corso Stati Uniti, 4/U 35127 Padova (PD) Italy	Authorized Representative
Sponsor Contact Adrian Orr	Anika Therapeutics Inc. 32 Wiggins Avenue Bedford, MA 01730 USA Tel: (781) 457-9000 Fax: (781) 305-9720 Email: aorr@anikatherapeutics.com	Director, Clinical Affairs
CRO	MD-Clinicals Route de Denges 28C 1027 Lonay Switzerland	Conduct of clinical trial
Medical Monitor	MD-Clinicals Route de Denges 28C 1027 Lonay Switzerland	Medical Monitoring

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

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27 Cingal 13-02: An Open -Label, Follow-On study to Cingal 13-01 to Evaluate the Safety of Repeat Injection of Cross-Linked Sodium Hyaluronate Combined with Triamcinolone Hexacetonide (Cingal) to Provide Symptomatic Relief of Osteoarthritis of the Knee 2013.
28 Cingal 16-02 Study Data: " A 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 2019
29 Cingal 17-02 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

16. Summary of Revision History

Edition	Section	Change
01		Initial Release
02	11.2 11.3 14	Addition of text to for refrigerated Cingal to be brought to room temperature prior to use. Instructions for Use to be provided in the Investigator's Brochure. Addition of roles and responsibilities including the authorized representative.
03	7.4 11.3	Clarification that Intra-articular injection of the index hip joint may be conducted under fluoroscopic or ultrasound guidance as required by standard of care treatment. Revised Instruction for Use to be provided with the Investigational Product.

Appendix 1: Patient Global Assessment

To be assessed by the Subject as the first questionnaire.
The pain the subject felt in INDEX HIP caused by osteoarthritis during the last 24 hours.
Have the Subject record their response with an "X":

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

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

0	1	2	3	4	5	6	7	8	9	10
No Pain	Mild			Moderate			Severe			Worst Pain

Appendix 2: Numerical Pain Scale NRS for Joint Pain on Walking

INSTRUCTIONS

1. Place an "X" in the box below that indicates the amount of pain the subject feels in joint on walking on a flat surface in the last 24 hours.
2. Complete for the following joints:

INDEX

HIP

0	1	2	3	4	5	6	7	8	9	10
No Pain	Mild			Moderate			Severe			Worst Pain

KNEE

0	1	2	3	4	5	6	7	8	9	10
No Pain	Mild			Moderate			Severe			Worst Pain

ANKLE

0	1	2	3	4	5	6	7	8	9	10
No Pain	Mild			Moderate			Severe			Worst Pain

CONTRALATERAL

HIP

0	1	2	3	4	5	6	7	8	9	10
No Pain	Mild			Moderate			Severe			Worst Pain

KNEE

0	1	2	3	4	5	6	7	8	9	10
No Pain	Mild			Moderate			Severe			Worst Pain

ANKLE

0	1	2	3	4	5	6	7	8	9	10
No Pain	Mild			Moderate			Severe			Worst Pain

Appendix 3 Index of Severity for Osteoarthritis of the Hip by Lequesne et al.

Overview:

Lequesne et al developed an index of severity for osteoarthritis for the hip (ISH). This can be used to assess the effectiveness of therapeutic interventions.

Sections for index:

(1) pain or discomfort

(2) maximum distance walked

(3) activities of daily living

I Pain or Discomfort

Parameter	Finding	Points
pain or discomfort during nocturnal bedrest	none	0
	only on movement or in certain positions	1
	without movement	2
duration of morning stiffness or pain after getting up	none	0
	< 15 minutes	1
	>= 15 minutes	2
remaining standing for 30 minutes increases pain	no	0
	yes	1
pain on walking	none	0
	only after walking some distance	1
	early after starting	2
pain or discomfort in sitting position for 2 hours	no	0
	yes	1

II. Maximum Distance Walked

Parameter	Finding	Points
maximum distance walked	unlimited	0
	> 1 kilometer but limited	1
	about 1 kilometer (about 15 minutes)	2
	about 500 - 900 meters (about 8-15 minutes)	3
	from 300 - 500 meters	4
	from 100 - 300 meters	5
	< 100 meters	6
walking aids required	none	0
	1 walking stick or crutch	1
	2 walking sticks or crutches	2

III. Activities of Daily Living

Parameter	Finding	Points
Can you put on socks by bending forward?	easily	0
	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0
Can you pick up an object from the floor?	easily	0
	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0
Can you go up and down a standard flight of stairs?	easily	0
	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0
Can you get into and out of a car?	easily	0

	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0

index of severity =

= SUM(points for all parameters)

Interpretation:

- minimum points for each section: 0
- maximum points for each section: 8
- minimum index score: 0
- maximum index score: 24

Index Score	Handicap
0	none
1 - 4	mild
5 - 7	moderate
8 - 10	severe
11 - 13	very severe
>= 14	extremely severe

Modifications to Index

The index was modified in 1991 (Table 2) by the addition of a question for sexual activity in sexually active women being evaluated for hip prosthesis. This was graded as for the activities of daily living. This results in a maximum index score of 26.

The index was modified in 1997 with some minor changes to morning stiffnes and termed the "algofunctional index".

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