Protocol Number: MON 18-03

Version 1.0

11 July 2019

Study Title: **A Prospective Study of a Single Injection Cross-linked Sodium Hyaluronate (MONOVISC) to Provide Symptomatic Relief of Osteoarthritis of Ankle Joint**

Short Title: **MONOVISC for Ankle Joint Pain Relief**

Signatures for the Sponsor that have reviewed and approved the protocol

Author Director, Clinical Affairs or designee Adrian Orr	Signature	15 JULY 2019 Date
Regulatory Affairs or designee	Signature	15JUL2019 Date

STUDY SPONSOR:

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PROTOCOL SIGNATURE PAGE

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My signature below confirms that I have read and understand the clinical protocol contained herein and agree to conduct the study according to 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
AOFAS	American Orthopedic Foot & Ankle Society
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 (MONOVISC) to Provide Symptomatic Relief of Osteoarthritis of ankle Joint
Study Objective	Obtain real world, post market data to confirm the clinical improvement and safety in patients treated with a single injection of MONOVISC for the symptomatic relief of osteoarthritis in the ankle joint.
Investigational Product	**Monovisc®:** A chemically cross-linked sodium hyaluronate supplied as a 4-mL unit dose in a 5-mL glass syringe.
Mode of Delivery	Monovisc will be injected into the intraarticular (IA) space of the index ankle using an 18-22 gauge needle.
Study Design	Prospective, multi-center, open label post market clinical follow up clinical trial.
Phase	Phase IV
Sample Size	25 subjects will be enrolled.
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 August 2019.
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 joint (Kellgren-Lawrence grade I to III) to be treated with MONOVISC injection. 4. Failed conservative treatment for joint osteoarthritis. 5. NRS pain on walking ≥4 and ≤9 in the index joint. 6. Subject must be willing to abstain from other treatments of the index joint 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 2. Infection or skin disease in the area of the injection site or index joint 3. NRS pain on walking > 3 in the contralateral joint 4. NRS pain on walking > 3 in the ipsilateral knee or hip 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 index 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 joint only) corticosteroid prior 30 days of signing the ICF are excluded. Topical corticosteroid use at any site other than the index joint is allowed. 9. Significant trauma to the index ankle within 26 weeks of screening 10. Chronic use of narcotics or cannabis. 11. Ligament instability or tear in index joint. 12. Chronic impingement in the index joint requiring surgical treatment 13. Diagnosis of fibromyalgia 14. Diagnosis of osteonecrosis in index joint 15. Subject has significant varus or valgus deformity greater than 10 degrees in either knee. 16. Subject requires consistent use of an assistive device (e.g. wheelchair, walker, etc.) Occasional use of a cane is acceptable. 17. Uncontrolled diabetes with HbA1c of >7%. 18. 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. 19. Subject is receiving or in litigation for worker's compensation. 20. 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 Baseline Exclusion Criteria 1. Subject has a decrease of ≥ 2 in the NRS pain on walking from Screening to Baseline in the index joint. 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 joint Numerical Rating Scale (NRS) pain on walking from baseline to 6 Months post injection. **Secondary Endpoints:** • Improvement in AOFAS 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 the index joint 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 MONOVISC in the ankle joint.
Sites	Up to 20 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

MONOVISC® is Anika's next generation sodium hyaluronate device for treating joint pain. It has been designed to deliver comparable benefits to those of ORTHOVISC® with a single injection.

MONOVISC has previously shown clinical improvement when studied for osteoarthritis of knees. The MONOVISC 07-02 results show MONOVISC achieved a 44% improvement from baseline in WOMAC A scores.

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. *J 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 MONOVISC for ankle osteoarthritis. Specifically, this study will provide confirmation to the effectiveness and safety of MONOVISC at relieving ankle joint pain to 6 months post-treatment.

4. BENEFITS / RISKS

4.1 Benefits

Intra-articular injections of MONOVISC 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 MONOVISC to treat ankle 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.

Adverse events associated with single intra-articular knee injections of MONOVISC can be found in the MONOVISC Instructions for Use. These events are expected to be similar for ankle injections. In the clinical trial for MONOVISC 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 index joint for MONOVISC were:

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

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

- temporary injection site pain, swelling or tenderness
- temporary stiffness of the ankle
- 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 ankle 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 ankle 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

The following contraindications are included in the package insert (AML 500-263/E):

Monovisc is composed of cross-linked sodium hyaluronate and may contain trace amounts of gram positive bacterial proteins. The following pre-existing conditions may constitute relative or absolute contraindications to the use of MONOVISC

- Known sensitivity to any of the materials contained in MONOVISC
- Pre-existing infections of the skin region of the intended injection site
- Known infection of the index joint
- Known systemic bleeding disorders

5.2 Warnings

There are no warnings specific to Monovisc (AML 500-263/E).

5.3 Precautions

The following precautions are cited in the package insert (AML 500-263/E):

- Those precautions normally considered during injection of substances into joints are recommended.
- Only medical professionals trained in accepted injection techniques for delivering agents to joint spaces should inject sodium hyaluronate for this application.
- The amount of Monovisc necessary to be injected depends on specific site and patient anatomy and needs to be defined by the medical professional performing the procedure. An excess quantity of sodium hyaluronate should not to be used and the patient should be monitored closely.
- The synovial space should not be overfilled.
- If pain increases during the injection procedure, the injection should be stopped and the needle withdrawn.
- Transient pain or swelling may occur after the intra-articular (IA) injection.
- As with any invasive joint procedure, it is recommended that patients avoid strenuous or prolonged (i.e., more than one hour) weight-bearing activities such as running or tennis within 48 hours following the intra-articular injection.
- **Pregnancy**: The safety and effectiveness of the use of MONOVISC® in pregnant women has not been tested.
- **Nursing Mothers:** It is not known if MONOVISC® is excreted in human milk. The safety and effectiveness of the use of the product in lactating women has not been tested.
- **Pediatrics**: The safety and effectiveness of the use of MONOVISC® in pediatric patients (≤ 21 years of age) has not been tested.

6. ENDPOINTS

6.1 Primary Endpoint:

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

6.2 Secondary Endpoints:

- Improvement in AOFAS index joint from baseline to 6 months post injection.
- Improvement in Patient Global Assessment (PGA) from baseline to 6 months post injection.
- OMERACT-OARSI in the index joint responder rate 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, post market clinical follow-up (PMCF) multi-center, open-label study to evaluate the residual risk of injections of MONOVISC for relief of pain in patients with a diagnosis of an osteoarthritic ankle 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 MONOVISC.

Up to 25 subjects will be enrolled at up to 20 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 joint (Kellgren- Lawrence grade I to III) to be treated with MONOVISC injection.
4. Failed conservative treatment for joint osteoarthritis.
5. NRS pain on walking ≥4 and ≤9 in the index joint.
6.
7. Subject must be willing to abstain from other treatments of the index joint for the duration of the study.
8. 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.
9. 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.
10. 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).
11. 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
2. Infection or skin disease in the area of the injection site or index joint
3. NRS pain on walking > 3 in the contralateral joint
4. NRS pain on walking> 3 in the ipsilateral knee or hip 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 index 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 joint only) corticosteroid within 30 days of signing the ICF are excluded. Topical corticosteroid use at any site other than the index joint is allowed.

9. Significant trauma to the index ankle within 26 weeks of screening
10. Chronic use of narcotics or cannabis.
11. Ligament instability or tear in index joint.
12. Chronic impingement in the index joint requiring surgical treatment
13. Diagnosis of fibromyalgia
14. Diagnosis of osteonecrosis in index joint
15. Subject has significant varus or valgus deformity greater than 10 degrees in either knee.
16. Subject requires consistent use of an assistive device (e.g. wheelchair, walker, etc.) Occasional use of a cane is acceptable.
17. Uncontrolled diabetes with a HbA1c of >7%.
18. 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.
19. Subject is receiving or in litigation for worker's compensation.
20. 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

6.6.4 Baseline Exclusion Criteria

1. Subject has a decrease of ≥ 2 in the NRS pain on walking from Screening to Baseline in the index joint.
2. 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
AOFAS index for index and contralateral ankle	X	X	X	X	X
Index and Contralateral Joints Pain (0-10 Numeric Rating Scale) for Hip, Knee and Ankle joints	X	X	X	X	X
Physical Evaluation of Index and Contralateral Joints for Hip, Knee and Ankle joints	X	X	X	X	X
Study Injection		X			
Dispense Subject Diary		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 joint – 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 index joint. Topical corticosteroids are allowed at any other site other than the index 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 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 index 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)
- AOFAS index
- Index & Contralateral Hip, Knee and Ankle Joint Pain on Walking (NRS Scale)
    - Confirm the 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 will always perform the Study Injection to the index joint as standard of care dictates.

Intra-articular injection of the ankle joint should be conducted under fluoroscopic or ultrasound guidance. Guidelines for the injection procedural steps are provided below. Modifications to this technique should be recorded in the CRFs.

- Patient is supine.
- Prep the skin at injection site with 1% betadine solution or equivalent.
- Peri- articular injection site anesthesia of lidocaine or topical refrigerant anesthetic (e.g. ethyl chloride) may be utilized.
- The ankle is dorsiflexed to a neutral position. Injection site is located in the anteromedial portal of the ankle joint as described for ankle arthroscopy
- Fluoroscopic or ultrasound guidance may be utilized if required to insert 18-22 gauge needle. Traction can be applied if required to gain access.
- Insert needle until resistance against the articular surface and then withdraw the needle 1-2 mm.
- 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.
- 2 ml of MONOVISC 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 joint 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)
- AOFAS 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. ADVERSE EVENTS

8.1 Reporting

8.1.1 Adverse Events

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 Investigatory 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 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.

8.1.2 Serious Adverse Events/Serious Adverse Device Effects

All SADE/SAEs 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 device or not.

9. STATISTICAL CONSIDERATIONS

9.1 Sample Size

The primary analysis will be the mean change in index joint pain 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 from baseline at 6 Months in MONOVISC 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 MONOVISC would reduce joint pain at 6 months.

Single sites should not enroll 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 index lesion locations and across study centers. Relevant summaries for individual lesion locations and centers, or combinations of index lesions and centers, may be presented for primary data. 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 by treatment group. 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

10.1Data 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.

10.2Data 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.

10.3Data 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

11.1Packaging and Labeling

As MONOVISC is a released product and this is a PMCF, there are no requirements to maintain clinical trial material / device accountability.

The contents of the syringe are sterile if the syringe is intact. Each MONOVISC 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.

11.2Storage Requirements

The MONOVISC syringe should be stored as detailed in the Instructions for Use.

11.3Instructions for Use

Instructions for Use (IFU) are supplied with each MONOVISC syringe.

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 post-market study, the Investigator will be given the OVT Instructions for Use. If the Instructions for Use are revised during the study, the Investigator will receive a copy of the revised version. The protocol 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 MONOVISC 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 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 andCRF) 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 MONOVISC and the requirements for clinical, efficacy and safety follow-up.
- The Investigator should be familiar with and trained on the appropriate use of MONOVISC as described in the protocol and in the current Instructions for Use.
- The Investigator is responsible to ensure that the MONOVISC 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 MONOVISC.
- 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 MONOVISC, knowledge of the requirements for storage, handling, administration, and destruction or disposal of the MONOVISC 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 MONOVISC, 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 MONOVISC. 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 MONOVISC, and train the Investigator in the requirements for storage, handling, administration, and destruction or disposal of the MONOVISC 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 MONOVISC
    - Instructions for Use
    - 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; 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 Instructions for Use 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 MONOVISC.
- 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 MONOVISC, 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 MONOVISC 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	OVT Manufacturer
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.

Appendix 1: Numerical Pain Scale NRS on Walking for Joint Pain

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	Contralateral
Hip	Hip
Knee	Knee
Ankle	Ankle

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

Appendix 2 American Orthopedic Foot and Ankle Score AOFAS

Ankle-Hindfoot Scale (100points Total)

I Pain (40 points)

None	40
Mild, occasional	30
Moderate, daily	20
Severe, almost always present	0

II Function (50 points)

Activity limitations, support requirement	
No limitations, no support	10
No limitation of daily activities, limitation of recreational activities, no support	7
Limited daily and recreational activities, cane	4
Severe limitation of daily and recreational activities, walker, crutches, wheelchair, brace	0

Maximum walking distance, blocks	
Greater than 6	5
4-6	4
1-3	2
Less than 1	0

Walking surfaces	
No difficulty on any surface	5
Some difficulty on uneven terrain, stairs, inclines, ladders	3
Severe difficulty on uneven terrain, tairs, inclines, ladders	0

Gait abnormality	
None, slight	8
Obvious	4
Marked	0

Sagittal motion (flexion plus extension)	
Normal or mild restriction (30° or more)	8
Moderate restriction (15°-29°)	4
Severe restriction (less than 150)	0

Hindfoot motion (inversion plus eversion)	
Normal or mild restriction (75%-100% normal)	6
Moderate restriction (25%-74% normal)	3
Marked restriction (less than 25% normal)	0

Ankle-hindfoot stability (anteroposterior, varus-valgus)	
Stable	8
Definitely unstable	0

III Alignment (10 points)

Good, plantigrade foot, midfoot well aligned	15
Fair, plantigrade foot, some degree of midfoot malalignment observed, no symptoms	8
Poor, nonplantigrade foot, severe malalignment , symptoms	0

Total=100

American Orthopaedic Foot and Ankle Society

From: http://www.aofas.org/i4a/pages/index.cfm?pageid=3494

Appendix 3 Patient Global Assessment

To be assessed by the Subject as the first questionnaire.
The pain the subject felt in INDEX joint 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 ankle caused by your osteoarthritis during the last 24 hours.

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

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