Clinical Study Protocol

Protocol Title:	A Prospective, Multi-center, Randomized, Clinical Trial Evaluating the Safety and Effectiveness of Using COOLIEF™ Cooled Radiofrequency Probe to Create Lesions of the Genicular Nerves and Comparing a Single Injection of Hyaluronic Acid in the Management of Knee Pain.
Protocol #:	105-17-0001
Study Short Name:	Genicular Nerve Lesion Study
Test Article(s):	Treatment Group: COOLIEF™ Cooled Radiofrequency Probe (CRFA) Control Group: Synvisc-One (HA)
Regulatory Classification:	Class II Medical Device: Probe (cleared under K053082) used in conjunction with radiofrequency generator (cleared under K072478). Specific clearance for use for osteoarthritis (OA) knee pain under K163461
Study Phase:	Pivotal
Indications:	Pain Management; Osteoarthritis of the knee; RF Ablation
Sponsor:	Avanos Medical 5405 Windward Parkway Alpharetta, GA 30004
Study Director:	David Curd, MS 5405 Windward Parkway Alpharetta, GA 30004
Medical Monitor:	Dr. Hilton Kaplan, MBBCh FCSSA PhD 5405 Windward Parkway, Alpharetta, GA 30004
Lead Principal Investigator	Antonia F. Chen, MD/MBA
Current Protocol Version:	Version 4.0 (dated 28Mar2019)
Previous Protocol Versions:	Version 3.0 (dated 8Feb2018) Version 2.0 (dated 06Dec2017) Version 1.0 (dated 20Sep2017)

The study will be conducted in compliance with this protocol and the following applicable regulations & Good Clinical Practices (GCPs):

21CFR 11
21 CFR 50
21 CFR 54
21 CFR 56
21 CFR 812.2 (b)

1 GENERAL INFORMATION

This study is being performed to assess the relative effectiveness of the COOLIEF™ Pain Management System (formerly owned by Halyard Health, and now owned by Avanos Medical; Alpharetta GA) to manage moderate to severe knee pain in patients with osteoarthritis (OA) of the knee when compared to a single Viscosupplementation injection. The product under study is currently marketed in the United States and has been cleared via 510(k) by the FDA under application K053082 and K163461 in combination with the Halyard Radiofrequency (RF) Generator (PMG-115-TD/PMG-230-TD, or PMG-BASIC/PMG-ADVANCED K072478) for use in creating radiofrequency lesions in nervous tissue. It is also indicated for creating radiofrequency lesions of the genicular nerves for the management of moderate to severe knee pain of more than 6 months with conservative therapy, including medication, in patients with radiographically-confirmed osteoarthritis (grade 2-4) and a positive response (≥ 50% reduction in pain) to a diagnostic genicular nerve block.

A Long-Term Extension will capture data allowing the assessment of the long term clinical outcomes (such as current level of pain, function, and progression of disease) for patients who received COOLIEF* as their initial treatment. Subjects who received COOLIEF* as their initial treatment will be asked to return for 2 additional visits representing 18 and 24 months post initial treatment.

Investigator Acknowledgement Signature Page

Title: A Prospective, Multi-center, Randomized, Clinical Trial Evaluating the Safety and Effectiveness of Using COOLIEF™ Cooled Radiofrequency Probe to Create Lesions of the Genicular Nerves and Comparing a Single Injection of Hyaluronic Acid in the Management of Knee Pain

I have read the attached protocol and agree that it contains all the necessary details for performing the study. I agree to conduct the study according to the protocol.

I will provide copies of the protocol and of the pre-clinical information on the Study Device (e.g., Investigator Brochure or Report of Prior Investigations) that was furnished to me by the Sponsor to all members of the study team responsible to me. I will discuss this material with them to assure that they are fully informed regarding the Study Device and the conduct of the study.

Once the protocol has been approved by the IRB/IEC, I will not modify this protocol without obtaining the prior approval of the Sponsor and of the IRB/IEC. I will submit all protocol modifications and/or any informed consent modifications to the Sponsor and the IRB /IEC, and approval will be obtained before any modifications are implemented. I will also submit all Serious Adverse Events and Protocol Violations to the IRB/IEC per their requirements.

_____

Investigator Printed Name

_____

Signature Date

2 SYNOPSIS

Protocol Title:	105-17-0001: A Prospective, Multi-center, Randomized, Clinical Trial Evaluating the Safety and Effectiveness of Using COOLIEF™ Cooled Radiofrequency Probe to Create Lesions of the Genicular Nerves and Comparing a Single Injection of Hyaluronic Acid) in the Management of Knee Pain.
Test Article(s):	Treatment Group: COOLIEF™ Cooled Radiofrequency Probe (CRFA) Control Group: Synvisc-One (HA)
Planned Number of Sites:	Up to 15 centers will be included in this study
Planned Number of Subjects:	Approximately 168
Study Design:	Prospective, Multicenter, Randomized, Comparison, Human, Interventional
Study Duration:	The primary study concludes at 12 months post randomized treatment, however; an extension study will be offered to those who received COOLIEF* as their originally randomized treatment to allow data collection through 24 months. **Treatment Group:** Up to 24 months following index procedure **Control Group:** Up to 13 months, depending upon receipt of Crossover procedure.
Effectiveness Endpoints:	• Numeric Rating Scale (NRS, Usual Level of Pain) • Western Ontario & McMaster University Osteoarthritis Index (WOMAC) • EQ-5D-5L Health-Related Quality of Life Questionnaire • Global Perceived Effect Scale
Objectives:	• To compare the effectiveness of CRFA to HA in the management of moderate to severe knee pain in patients with radiologically-confirmed osteoarthritis to treatment with Viscosupplementation injection. • To confirm the safety of CRFA for creating radiofrequency lesions of the genicular nerves for management of moderate to severe knee pain in patients with radiologically-confirmed osteoarthritis. • To capture the long term clinical outcomes (such as current level of pain, function, and progression of disease through 24 months) for patients who received CRFA as their initial treatment.
Selection Criteria:	**Inclusion Criteria** 1. Age ≥ 21 years 2. Able to understand the informed consent form and provide written informed consent and able to complete outcome measures 3. Chronic knee pain for longer than 6 months that interferes with functional activities (for example, ambulation, prolonged standing, etc.) 4. Continued pain in the target knee despite at least 3 months of conservative treatments, including activity modification, home exercise, protective weight bearing, and/or analgesics (for example, acetaminophen or non-steroidal anti-inflammatory drugs [NSAIDs])

	5. Positive response (defined as a decrease in numeric pain scores of at least 50%) to a single genicular nerve block of the index knee 6. Pain on NRS ≥ 6 on an 11-point scale for the index knee 7. Radiologic confirmation of arthritis (x-ray/MRI/CT) of OA grade of 2 (mild), 3 (moderate) or 4 (severe) noted within 6 months for the index knee 8. An intra-articular hyaluronic acid injection is indicated as an appropriate treatment option 9. WOMAC Knee Score group at baseline of Score of ≥ 2 (0 to 4 scale) on WOMAC question 1 (Pain) and a mean score of ≥ 1.5 on all five questions of the WOMAC pain subscale. 10. Analgesics including membrane stabilizers such as Neurontin/gabapentin and antidepressants for pain such as Cymbalta duloxetine must be clinically stable (defined as stable dosage for ≥ 6 weeks prior to the screening visit) and shall not change during the course of the study without approval of the investigator 11. Agree to see one physician (study physician) for knee pain during the study period 12. Willing to utilize double barrier contraceptive method if of child bearing potential 13. Willing to delay any surgical intervention for the index knee for the period of the study follow up 14. Willingness to provide informed consent and to comply with the requirements of this protocol for the full duration of the study **Exclusion Criteria** 1. Evidence of inflammatory arthritis (for example, rheumatoid arthritis) or other systemic inflammatory condition (for example, gout, fibromyalgia) that could cause knee pain 2. Evidence of neuropathic pain affecting the index knee 3. Previous or pending lower limb amputation 4. Intra-articular steroid injection into the index knee within 90 days from randomization 5. Hyaluronic acid injection, platelet rich plasma (PRP), stem cell, or arthroscopic debridement/lavage injection into the index knee within 180 days from randomization 6. Prior radiofrequency ablation of the genicular nerves of the index knee 7. Prior partial, resurfacing, or total knee arthroplasty of the index knee (residual hardware) 8. Clinically significant ligamentous laxity of the index knee 9. Clinically significant valgus/varus deformities or evidence of pathology (other than osteoarthritis of knee) that materially affects gait or function of the knee or is the underlying cause of the knee pain and/or functional limitations 10. Body mass index (BMI) > 40 kg/m^2 11. Extremely thin patients and those with minimal subcutaneous tissue thickness that would not accommodate a radiofrequency lesion of up to 14 mm in diameter to limit the risk of skin burns 12. Pending or active compensation claim, litigation, or disability remuneration (secondary gain) 13. Pregnant, nursing or intent of becoming pregnant during the study period 14. Chronic pain associated with significant psychosocial dysfunction

	15. Beck's Depression Index score of > 22 (indicates clinically depressed state) 16. Allergies to any of the medications to be used during the procedures, including known hypersensitivity (allergy) to hyaluronate preparations or allergies to avian or avian-derived products (including eggs, feathers, or poultry) 17. Active joint infection or systemic or localized infection at needle entry sites (subject may be considered for inclusion once infection is resolved) 18. History of uncontrolled coagulopathy, ongoing coagulation treatment that cannot be safely interrupted for procedure, or unexplained or uncontrollable bleeding that is uncorrectable 19. Identifiable anatomical variability that would materially alter the procedure as described in the protocol 20. Within the preceding 2 years, subject has suffered from active narcotic addiction, substance, or alcohol abuse 21. Current prescribed opioid medications greater than 60 morphine equivalent daily opioid dose 22. Uncontrolled immunosuppression (e.g. AIDS, cancer, diabetes, etc.) 23. Subject currently implanted with pacemaker, stimulator or defibrillator. 24. Participating in another clinical trial/investigation within 30 days prior to signing informed consent 25. Subject unwilling or unable to comply with follow up schedule or protocol requirements
Safety Parameters / Endpoints:	Safety Endpoint: Proportion of subjects experiencing adverse events through final follow up.

Table of Contents

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
SAE	Serious Adverse Event
CRF	Case Report Form
CRFA	COOLIEF™ Radiofrequency Ablation
CFR	US Code of Federal Regulations
Cm	Centimeter
CTA	Clinical Trial Agreement
HA	Synvisc-One (Hylan G-F 20)
IRB	Institutional Review Board
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
PI	Principal Investigator
PDMP	Prescription Drug Monitoring Program
QOL	Quality of Life
RF	Radiofrequency
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect

4 INTRODUCTION

4.1 BACKGROUND / STUDY POPULATION

With the population aging in the United States and around the world, chronic knee pain from conditions such as osteoarthritis (OA) is becoming a more prominent problem on the medical landscape. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line treatment for OA for the purpose of reducing pain and inflammation and allowing for the maintenance of activities. Physical therapy or other exercise-based modalities are also considered to be standards of care in the earliest stages of OA to maintain patient mobility to the extent possible.

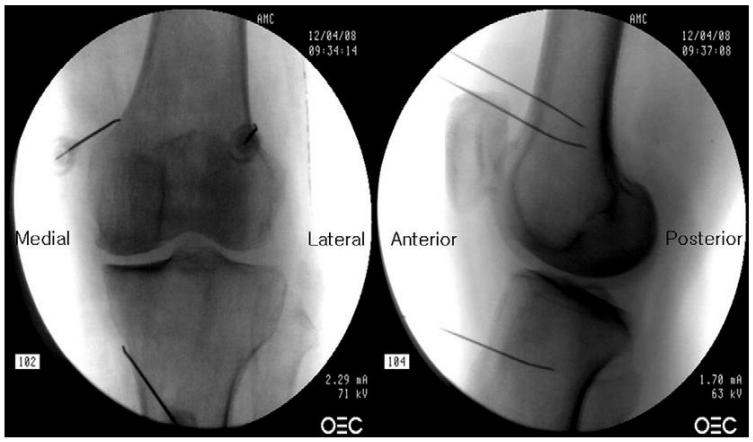
While total joint replacement is a well-established terminal treatment for late stage OA of major joints, such as the hip and knee, not all patients are well-suited for this procedure due to issues of age, health, or other factors. In addition, total knee replacement, while generally considered effective, has been associated in at least one study with ongoing moderate to significant pain in up to 53% of patients, with patients in that study noting a median average pain score of 3 of 10 and worst pain score of 5 of 10.[1]

Currently, there are a limited number of treatment options available for patients who are not candidates for total joint replacement and/or for whom drugs are either ineffective or are interfering with their overall quality of life and general health. Corticosteroid injection provides significant short term improvement as far as pain relief [2], but multiple treatments are required and the steroid and analgesic medication may actually exacerbate cartilage destruction if used over an extended period of time.[3] Viscosupplementation (the injection of protein-based gel/fluids into the joint space to improve synovial fluid viscosity) has shown some moderate effectiveness in some studies,[4] [5] but its clinical utility for knee OA has recently been called into question by the American Academy of Orthopaedic Surgeons (AAOS).[6]

COOLIEF™ (CRFA) is a well-established method for delivering lesions into nervous tissue to accomplish neurotomy procedures. Multiple references exist in the literature noting the clinical outcomes of patients treated with CRFA cooled radiofrequency for pain managing denervation in other anatomic locations, including the sacroiliac joint[7,8,9,10] and the lumbar spinal disc.[11,12,13] Recent human studies have started to demonstrate the effects of CRFA when specifically used for genicular neurotomy procedures in patients with chronic knee pain resulting from conditions such as OA[14].

Sensory innervation of the knee joint is accomplished by the articular branches of several nerves, including the femoral, tibial, saphenous, obturator, and common peroneal nerves. As a group, these nerves have been termed “genicular nerves.”[15,16] Radiofrequency-generated lesions of the genicular nerves (i.e., genicular neurotomy) using standard, non-cooled radiofrequency ablation has been defined

in the literature. Choi and colleagues[17] published a prospective, randomized, double-blind controlled trial of genicular neurotomy in a series of 38 elderly OA patients with severe knee pain who had failed conservative therapy but responded to a diagnostic block. In this study, the superomedial and inferomedial branches of the saphenous nerve and the superolateral branch of the femoral nerve were targeted for treatment. The probe placement is demonstrated in the figure below taken from Choi*, et al*. They showed statistically significant improvements in pain, Oxford Knee Score, and global perceived effect when compared to placebo at up to 3 months post treatment. Ikeuchi and colleagues[18] also published a prospective randomized study comparing RF neurotomy to diagnostic block alone. In their study, at 12 weeks post treatment, 44% of the RF group rated "good or excellent" compared to only 12% of the block group. The probe placement and lesioning pattern in the Ikeuchi, *et al* study differed from the method of Choi, *et al*.



A recent sponsored study was completed which compared CRFA to intraarticular steroid injections (IAS) for painful OA of the knee and demonstrated statistically significant improvements in pain, function, and global perceived effect of CRFA at 6[14] and 12 months[19]. A subset of those patients were followed through 24 months and it was identified that CRFA has the potential to provide sustained effect through this time period. This potential was previously suggested by Ho 2015 where patients reported 24 months of relief following CRFA when used to ablate the lateral branches that innervate the sacroiliac joint[20] . The nerve targets were identical to those utilized in the Choi research.

In 2014, Franco[21] *et al* completed a cadaveric dissection study which confirmed the locations of the genicular nerves identified by Choi *et al* and identified an additional nerve target – the middle branch from the vastus intermedius, which will be incorporated as part of the lesioning for this protocol.

This protocol outlines a prospective, single arm, multicenter study examining pain relief as well as other important clinical efficacy indicators of using CRFA to create lesions of the genicular nerves. The probe placement method and lesioning pattern will include the 3 targets utilized in the Choi *et al* and Davis *et al* with targeting of the superomedial and inferomedial branches of the saphenous nerve and the superolateral branch of the femoral nerve, and will include the additional nerve target identified by Franco et al - middle branch from the vastus intermedius.

4.2 PRODUCT DESCRIPTIONS AND INTENDED USE

The following is a summary description of the Study Device. For additional information, please refer to the COOLIEF* "Instructions for Use" (Appendix 1). The COOLIEF™ system components utilized in the study are the same in form and function regardless of specific product branding (COOLIEF*, SInergy*, or Halyard Health). The COOLIEF™ system is comprised of three primary components (collectively known as 'disposables') and is used in conjunction with the Pain Management generator, pump unit, connector cables (collectively known as 'Hardware') and dispersive electrodes (also known as 'grounding pads'):

- Cooled Radiofrequency Sterile Tube Kit (sterile, single use, non-body contact): It is used for closed-loop circulation of sterile water through a Cooled Radiofrequency Probe. It includes a burette and tubing.
- Cooled Radiofrequency Introducer (sterile, single use): It is to be used with the Probes only. The Cooled Radiofrequency Introducer provides a path for the Probe to the targeted nervous tissue.
- Cooled Radiofrequency Probe (sterile, single use): It is inserted through an Introducer into or near nervous tissue. The active tip extends 4mm from the introducer and delivers energy. Sterile water circulates internally to cool the Probe while it delivers radiofrequency energy. A thermocouple in the Probe measures the cooled electrode temperature throughout the procedure.

The product is comprised of an electrically insulated shaft with an active tip that functions as an electrode for RF energy delivery, a handle, tubes with luer locks and a cable with a 7-pin connector. The Introducer includes an insulated stainless steel cannula and a stylet. The Tube Kit is comprised of a burette and flexible tubing fitted with luer locks for connection to the Probe. The Probe, Introducer, and Tube Kit are ethylene oxide sterilized and supplied sterile. These components can be packaged together in a kit or as separate components. The devices should be stored in a cool, dry environment. The Instructions For Use (IFU) documents (Appendix 1) are included in each kit.

Avanos Medical maintains a list of all model numbers and sizes for the system components.

The control product/device, Synvisc-One® (hylan G-F 20) (HA), is an elastoviscous high molecular weight fluid containing hylan A and hylan B polymers produced from chicken combs. Hylans are derivatives of hyaluronan (sodium hyaluronate). Hylan G-F 20 is unique in that the hyaluronan is chemically crosslinked. Hyaluronan is a long-chain polymer containing repeating disaccharide units of Na-glucuronate-N-acetylglucosamine.

Synvisc-One is a single injection regimen therapy indicated for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, e.g., acetaminophen.

The Synvisc-One® (hylan G-F 20) Instructions For Use is attached as Appendix 2.

4.3 EXEMPT STUDIES DETERMINATION

As both products being utilized in this study are commercially available and are being used according to their labeled indications, the sponsor has determined that this study meets the criteria for the *'Exempt Studies' as* specified in 21 CFR 812.2 (c)(2) and confirmed in the Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors - Frequently Asked Questions About Medical Devices (January 2006)**,** which states that "studies of an already cleared medical device in which the device is used or investigated in accordance with the indications in the cleared labeling are exempt from Part 812."

4.4 SUMMARY OF PRIOR INVESTIGATIONS

As mentioned above, a recent investigation has been performed in this population using the COOLIEF* device for performing genicular neurotomy procedures for managing patients with chronic knee pain due to conditions such as osteoarthritis [14]. This prospective randomized study compared CRFA against intraarticular steroid injections (IAS) and the two treatment groups were homogenous for demographic, pain and functional parameters at baseline. Mean Numeric Rating Scale (NRS) at baseline was 7.3 ± 1.2 (Mean ± SD) for the CRFA group and 7.2 ± 1.0 for the IAS group. One hundred and twenty-six (126) patients remained in the study and were evaluated at 6-months post treatment (n = 58 CRFA and n = 68 IAS). In the CRFA group, 74.1% of patients had ≥ 50% reduction in NRS pain score compared to 16.2% in the IAS group at 6 month follow up ($p < 0.0001$, primary endpoint). At 6 months, the resting mean NRS was 2.5 ± 2.3 for the CRFA group and 5.9 ± 2.2 for the IAS group ($p < 0.0001$), representing a 4.9 point drop in NRS for the CRFA group. The mean Oxford Knee Score (measure of function) improved from 16.7 ± 4.4 at baseline to 35.7 ± 8.8 in the CRFA group at 6 months, compared to 22.4 ± 8.5 in the IAS group ($p < 0.0001$). At 6 months, 91.4% of subjects in the CRFA group reported improvement in Global Perceived Effect (GPE) compared to 23.9% in the IAS group ($p < 0.0001$). No serious adverse events

related to either procedure were noted, and overall adverse event profiles were similar. The primary results noted above are described in Davis *et al* 2017 [14].

These results were sustained at the 12 month time point in that 65.4% of subjects reported ≥ 50% reduction in NRS pain score in the CRFA group. In addition, the CRFA patient group's Oxford Knee Score indicated continued functional improvement at 12 months with a mean score of 34.3 ± 11.1. 75% of subjects reported being 'Improved' on their GPE 12 months after treatment.[19]

A subset of these subjects were followed through 24 months. Eighteen (18) subjects returned at 24 months post CRFA procedure and their average NRS score was reported as 3.6 ± 2.7 for these subjects. Eleven (11) of the 18 reported pain levels that were ≥ 50% reduced from their baseline values. Functional improvements were maintained as well.[22]

Multiple prior investigations using the CRFA device for delivering radiofrequency lesions into nervous tissue have been conducted and published, as described in section 4.1 above.

Information related to clinical experience with the control product (HA) can be found in the Synvisc-One Instructions for Use document (Appendix 2).

4.5 RATIONALE FOR STUDY

This prospective, multi-center, randomized, comparison study is examining the effects of the COOLIEF * Cooled Radiofrequency Probe used for radiofrequency neurotomy compared to a single injection of Hyaluronic Acid (Hylan G-F 20) in subjects to manage knee pain. The study does not introduce any experimental procedures, as both products will be used in a manner that is consistent with their labeled indications. The primary rationale for conducting this study is to assist with reimbursement support for the product.

The rationale for the long-term extension is to capture data to understand the long term clinical effects of utilizing CRFA for the treatment of OA knee pain.

4.6 POTENTIAL RISKS & BENEFITS

The potential benefits of COOLIEF * when used for creating radiofrequency lesions in the genicular nerves of knee pain subjects are to provide pain relief, improve function, improve overall quality of life, and reduce the need for other modalities to control pain such as prescription opioids.

Avanos Medical follows rigorous Quality Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. The risk

analysis process for COOLIEF* is performed in accordance with industry standards for 'Risk Management for Medical Devices' and ensures that the level of risk is acceptable prior to starting the clinical study.

The potential risks to subjects in which a radiofrequency neurotomy procedure is performed, regardless of the treatment modality, may include the following, all of which are anticipated adverse events that have been identified as possible complications of procedures involving lesioning of nervous tissue:

- Infection,
- Damage to collateral nervous tissue,
- Increased pain,
- Visceral injury,
- Failure of technique,
- Superficial burns;
- Damage to collateral tissue (i.e., bruising or hematoma),
- Deafferentation dysesthesiae
- Paralysis, and
- Death

The potential risks specifically associated with the use of COOLIEF* for radiofrequency neurotomy are anticipated to be the same as those listed above, with the exception of visceral injury and paralysis, as the device will not be used in any anatomic location in this study other than the index knee.

As described in Appendix 2, the potential benefits of single injection of Hyaluronic Acid (Hylan G-F 20) include short to medium term pain relief, assistance with therapeutic exercise, and some restoration of function.

Hylan injection involves inserting a needle directly into the space inside your knee. This procedure carries certain risks, including:

- Arthralgia
- Arthritis
- Arthropathy
- Gait disturbance
- Injection site pain
- Joint effusion
- Joint stiffness
- Joint swelling
- Joint warmth

There are other Hylan products on the market which have reported the following risks:

- Rash
- Hives
- Itching
- Fever
- Nausea
- Headache
- Dizziness
- Chills
- Muscle cramps
- Paresthesia
- Peripheral edema
- Malaise
- Respiratory difficulties
- Flushing
- Facial swelling

5 STUDY OBJECTIVES

This study is designed to:

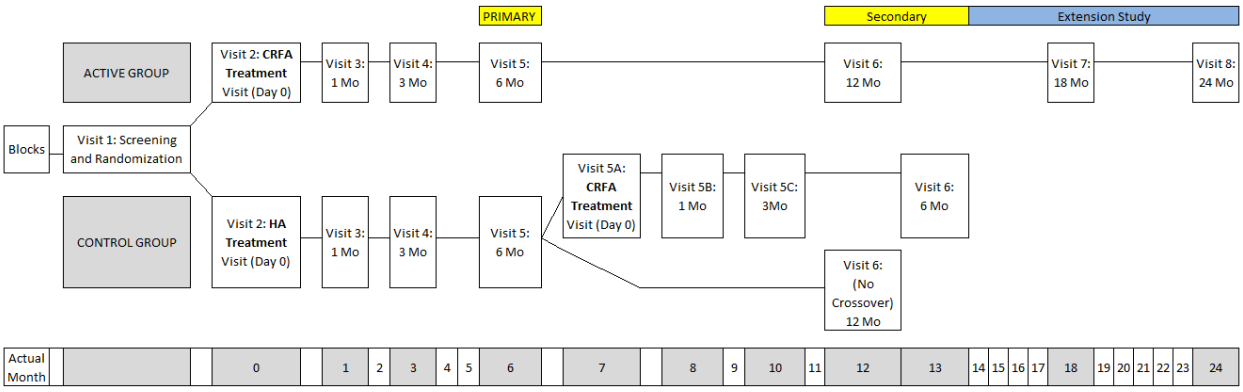
- Determine the effectiveness (primarily measured by pain relief) of COOLIEF * when used to create radiofrequency lesions of the genicular nerves compared to pain relief following a single injection of Hyaluronic Acid (Hylan G-F 20); and
- Confirm the safety of COOLIEF * when used to perform radiofrequency lesions of the genicular nerves in subjects to manage knee pain compared to safety of single injection of Hyaluronic Acid (Hylan G-F 20).
- To describe the long term clinical effects (such as current level of pain, function, and progression of disease through 24 months) for patients who initially randomized to and received CRFA for treatment of their OA knee pain.

6 INVESTIGATIONAL PLAN

6.1 STUDY DESIGN

This is a prospective, randomized, multicenter comparison study examining the outcomes of subjects with OA and knee pain undergoing a procedure to create a radiofrequency lesion of the genicular nerves with the CRFA system compared to subjects receiving HA. A total of approximately 168 subjects will be enrolled into this study, with subjects undergoing either CRFA or HA injection in a 1:1 randomization scheme. Follow up will be conducted for a total of 12-months post randomized procedure with the

primary endpoint being completed at month 6. Subjects randomized to the comparison (HA) group will have the option to cross over to the neurotomy group after completing the 6-month endpoint assessment. They would then be followed for an additional 6 months. Pain, overall outcome, quality of life, pain medication use, and adverse events will be compared between the two treatment groups in order to determine success. Unless they have received an additional procedure on their index knee, subjects who were randomized to and received CRFA as their initial treatment will have the option to add 2 additional visits at 6-month intervals, representing 18 and 24 months post initial treatment.



CRFA = Genicular Neurotomy using Cooled Radiofrequency Ablation
HA = Hyaluronic Acid Injection (Synvisc-One 6 mL injection)

6.2 ENDPOINTS

6.2.1 Primary Endpoints

Primary Effectiveness Endpoint:

The proportion of subjects whose knee pain is reduced by ⩾ 50% based on the NRS scale at 6 Months.

Primary Safety Endpoint:

The proportion of subjects experiencing adverse events through final follow up.

6.2.2 Secondary Endpoints

Secondary Effectiveness Endpoints:

- The proportion of subjects whose knee pain is reduced from baseline by ⩾ 50% based on the NRS at 12 months.
- The change in WOMAC score from baseline to the 6 month visit and 12 month visit.

6.2.3 Tertiary Endpoints

- Tertiary effectiveness endpoint 1: The change in measured EQ-5D-5L scale from baseline at the 6-month visit and 12-month visit.
- Tertiary effectiveness endpoint 2: The measured Global Perceived Effect scale at the 6-month visit and 12-month visit.

6.2.4 Exploratory Analyses

Other variables of interest, which include, but are not limited to, WOMAC subscales (pain, stiffness, physical function), change in pain medication usage from baseline as measured by subject self-reported average daily dosage, healthcare utilization, and change in weight from baseline, will be summarized at various visit intervals.

In addition, the endpoints listed above will also be summarized at 18 and 24 months post treatment.

6.3 MEASURES TO MINIMIZE/AVOID BIAS

All subjects presenting to the study centers who report knee pain will be evaluated for eligibility for study participation. Routine evaluations of all site screening logs will be conducted to assure that no subjects are excluded based on investigator bias. Further, the primary endpoint measurements in this study are primarily subject generated and are not based on the opinion of the investigator, thus minimizing the potential for bias related to the outcome of the procedure.

Independent monitoring, Data Management and Statistics will also be utilized to ensure accuracy of the data collected.

6.4 DURATION OF SUBJECT PARTICIPATION

The screening period could take up to 60 days to complete for all subjects. Subjects will participate in the study for approximately 13 months from time of randomization treatment visit + 12-month follow up, except for subjects who participate in the optional crossover group or the long-term extension. Crossover subjects will be on study for approximately 15 months from randomization (initial treatment + 6-month follow-up followed by crossover treatment with an additional 6-month follow up period).

Those who initially received CRFA at Visit 2 will be given the option to return for 2 additional visits, representing 18 and 24 months post initial procedure. If they agree, their entire study participation will be approximately 25 months.

Enrollment is anticipated to take approximately 8-10 months.

6.5 STUDY-STOPPING CRITERIA

The study may be terminated if the sponsor determines that there is a clinical or other reason to do so. In such cases, subjects already enrolled will be followed according to the protocol and further recruitment will be stopped. Potential reasons for early termination may include (but are not limited to):

- Withdrawal of IRB/ethics committee approval
- Administrative reasons

6.6 TEST ARTICLE STORAGE, ADMINISTRATION, & ACCOUNTABILITY

6.6.1 Instructions for Use

Study products should be maintained according to the manufacturers recommendations as indicated in their respective Instructions For Use (IFU) documents. The IFU for the COOLIEF* product is included within each kit. A copy is attached as Appendix 1.

The Synvisc-One IFU document is attached as Appendix 2

6.6.2 Product Labeling, Packaging, and Storage

As part of this protocol, the sponsor will provide the disposable products needed to manage the Treatment Arm procedure (CRFA) and the sites will be responsible for maintaining according to manufacturer's guidelines as outlined in the IFU. The COOLIEF* Kit contains 1 Probe, 3 Introducers, and 1 Tube Kit. In addition to the kits, a Dispersive Electrode (single use) and an additional Introducer for each subject will be supplied to each site. The COOLIEF* Kit and additional introducer are provided sterile, having been sterilized by ethylene oxide. The devices should be stored in a cool, dry environment, with limited access to the environment. The Lot numbers and expiration dates of provided supplies will be captured for each subject as the kits are utilized. Provided supplies should be maintained in a secure location and should be utilized only for eligible study subjects.

The sites will be responsible for securing the post market supplies for the Control Arm (HA) as per their standard procedures. Storage should follow instructions provided for the product. The Lot numbers and expiration dates of control supplies will be captured for each subject as the kits are utilized.
Study products may only be used on enrolled study subjects for the procedures as described in this protocol.

6.6.3 Treatment Assignment

At visit 1, all subjects who meet the eligibility criteria will be randomly assigned to one of two groups: (A) CRFA or (B) HA injection. Randomly generated treatment assignments (1:1 randomization) have been prepared by the study statistician using a computerized randomization program, and will be loaded into the electronic data management system being utilized in the study. Upon confirmation that a subject is eligible for randomization, sites will log into the system to randomize the subject. Specific instructions will be provided. The monitor will confirm that the randomization process is being appropriately followed and documentation is being maintained as appropriate. Any deviation from the randomization process must be immediately reported to the sponsor and IRB as appropriate and documented appropriately.

6.6.4 Procedural Description

For the diagnostic block, a local anesthetic (preferably Marcaine 0.5% or similar) will be injected at each target site (with an ideal volume of 0.60 - 0.75 mL at each site). Subjects will be noted as positive responders if the participant experiences a decrease in numeric pain scores of at least 50% at least 15 minutes after the injection. All subjects with a positive response will be eligible for the study.

Subjects randomized to CRFA will be placed in a supine position on a fluoroscopy table with a pillow under the popliteal fossa to alleviate discomfort. The true AP fluoroscopic view of the tibiofemoral joint will be obtained to show the tibiofemoral joint space with equal width interspaces on both sides. An appropriately sized cooled radiofrequency needle will be placed overlying the affected knee joint and using fluoroscopic guidance, the needle will be advanced to a bony endpoint on the superiolateral portion of the femoral condyle of the affected knee. A second needle will be advanced to a bony endpoint on the superiomedial portion of the femoral condyle. A third needle will be advanced to the bony endpoint at the inferiomedial portion of the tibial condyle. The final needle will be placed at the midline of the femur about 2 cm cephalad of the upper patellar border. Lateral x-ray views should be taken to confirm appropriate location at 50% depth of the femur and tibia prior to lesioning. Care should be taken to avoid inserting the RF probe into the inferolateral area of the knee to avoid the common peroneal nerve and potential foot drop. If pooling of blood or fluid is seen in the stylet, aspirate and reposition as necessary.

AP and lateral x-ray views should be taken during the procedure which show all the needles in final positioning for maintenance in the source documentation. Motor stimulation must be tested at 2.0 volts with no leg movement. Sensory stimulation should be conducted at < 0.5 volts in all four locations with concordant pain reproduction. A mixture consisting of lidocaine (1% or 2% preferred) should then be slowly injected. Then, radiofrequency ablation of each of the four targeted geniculate nerves will be conducted at 60°C for 2 minutes and 30 seconds at each of the 4 anatomic locations. At the conclusion of the procedure, the needles will be removed, the insertion sites will be treated with appropriate closure, and the subject will be allowed to properly recover prior to discharge home. Instillation of post-operative analgesic pain medication is permissible per institutional standard of care.

Additionally, selected sites will also collect information during the procedure from the generators utilizing a sponsor provided laptop computer loaded with the TeraTerm Software package. This open sourced software collects blinded information from the generator during the procedure. The laptops should be attached to the generator prior to the initiation of the procedure. The reports will be saved utilizing the subject number assigned to the study as an identifier, and the data will be sent to the sponsor for analysis. Specific training will be provided for participating sites and details will be described in a TeraTerm Plan.

Synvisc-One is administered as a single intra-articular and subjects randomized to the HA group will receive the dose per the Instructions For Use for the product. The preferred approach is the suprapatellar, pending anatomic limitations. Strict aseptic administration technique must be followed and the procedure should be performed per the instructions for use for the product.

- Optional: If necessary, using an 18- to 20-gauge needle, remove synovial fluid or effusion before injecting Synvisc-One.
- Do not use the same syringe for removing synovial fluid and for injecting Synvisc-One; however, the same 18- to 20-gauge needle should be used.
- Twist the tip cap before pulling it off, as this will minimize product leakage.
- To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub.

Precaution: Do not over tighten or apply excessive leverage when attaching the needle or removing the needle guard, as this may break the syringe tip.

- Inject the full 6 mL in one knee only.

If concurrent minor procedures, such as arthrocentesis, are performed on the index knee prior to administration of either treatment, volume information should be captured in the subject's source documentation.

Subjects will be encouraged to refrain from strenuous activity for 48 hours following both procedures.

6.6.5 Test Article/Supply Accountability

The investigator must ensure that accurate records of receipt of study devices, dispensing information, and the prompt return or destruction of unused supplies are maintained at all times. A device accountability log will be supplied to the site for the purposes of recording study device dispensation and will be monitored by periodically sponsor personnel. All provided supplies and unused test articles must be returned or destroyed per the sponsor at the end of the study after final accountability has been conducted by sponsor personnel.

7 SUBJECT SELECTION

Subjects will include male and non-pregnant females $\geqslant$ 21 years of age who present with chronic knee pain resulting from osteoarthritis and meet all inclusion and exclusion criteria.

7.1 INCLUSION CRITERIA

1. Age ≥ 21 years
2. Able to understand the informed consent form and provide written informed consent and able to complete outcome measures
3. Chronic knee pain for longer than 6 months that interferes with functional activities (for example, ambulation, prolonged standing, etc.)
4. Continued pain in the target knee despite at least 3 months of conservative treatments, including activity modification, home exercise, protective weight bearing, and/or analgesics (for example, acetaminophen or non-steroidal anti-inflammatory drugs [NSAIDs])
5. Positive response (defined as a decrease in numeric pain scores of at least 50%) to a single genicular nerve block of the index knee
6. Pain on NRS ≥ 6 on an 11-point scale for the index knee
7. Radiologic confirmation of arthritis (x-ray/MRI/CT) of OA grade of 2 (mild), 3 (moderate) or 4 (severe) noted within 6 months for the index knee
8. An intra-articular hyaluronic acid injection is indicated as an appropriate treatment option
9. WOMAC Knee Score group at baseline of Score of ⩾ 2 (0 to 4 scale) on WOMAC question 1 (Pain) and a mean score of ⩾ 1.5 on all five questions of the WOMAC pain subscale.
10. Analgesics including membrane stabilizers such as Neurontin/gabapentin and antidepressants for pain such as Cymbalta/duloxetine must be clinically stable (defined as stable dosage for ≥ 6 weeks prior to the screening visit) and shall not change during the course of the study without approval of the investigator
11. Agree to see one physician (study physician) for knee pain during the study period
12. Willing to utilize double barrier contraceptive method if of child bearing potential.
13. Willing to delay any surgical intervention for the index knee for the period of the study follow up
14. Willingness to provide informed consent and to comply with the requirements of this protocol for the full duration of the study

7.2 EXCLUSION CRITERIA

1. Evidence of inflammatory arthritis (for example, rheumatoid arthritis) or other systemic inflammatory condition (for example, gout, fibromyalgia) that could cause knee pain
2. Evidence of neuropathic pain affecting the index knee
3. Previous or pending lower limb amputation
4. Intra-articular steroid injection into the index knee within 90 days from randomization

5. Hyaluronic acid injection, platelet rich plasma (PRP), stem cell, or arthroscopic debridement/lavage injection into the index knee within 180 days from randomization
6. Prior radiofrequency ablation of the genicular nerves of the index knee
7. Prior partial, resurfacing, or total knee arthroplasty of the index knee (residual hardware)
8. Clinically significant ligamentous laxity of the index knee
9. Clinically significant valgus/varus deformities or evidence of pathology (other than osteoarthritis of knee) that materially affects gait or function of the knee or is the underlying cause of the knee pain and/or functional limitations
10. Body mass index (BMI) > 40 kg/m^2
11. Extremely thin patients and those with minimal subcutaneous tissue thickness that would not accommodate a radiofrequency lesion of up to 14 mm in diameter to limit the risk of skin burns
12. Pending or active compensation claim, litigation or disability remuneration (secondary gain)
13. Pregnant, nursing or intent on becoming pregnant during the study period
14. Chronic pain associated with significant psychosocial dysfunction
15. Beck's Depression Index score of > 22 (indicates clinically depressed state)
16. Allergies to any of the medications to be used during the procedures, including known hypersensitivity (allergy) to hyaluronate preparations or allergies to avian or avian-derived products (including eggs, feathers, or poultry)
17. Active joint infection or systemic or localized infection at needle entry sites (subject may be considered for inclusion once infection is resolved)
18. History of uncontrolled coagulopathy, ongoing coagulation treatment that cannot be safely interrupted for procedure, or unexplained or uncontrollable bleeding that is uncorrectable.
19. Identifiable anatomical variability that would materially alter the procedure as described in the protocol
20. Within the preceding 2 years, subject has suffered from active narcotic addiction, substance, or alcohol abuse
21. Current prescribed opioid medications greater than 60 morphine equivalent daily opioid dose
22. Uncontrolled immunosuppression (e.g. AIDS, cancer, diabetes, etc.)
23. Subject currently implanted with pacemaker, stimulator or defibrillator.
24. Participating in another clinical trial/investigation within 30 days prior to signing informed consent
25. Subject unwilling or unable to comply with follow up schedule or protocol requirements

8 STUDY PROCEDURES

8.1 CENTER READINESS

Prior to initiating study procedures, all applicable regulatory requirements must be fulfilled. Each study site must have written documentation of readiness including but not limited to:

A. Investigational Review Board (IRB) approval of the current version of the Clinical Investigation Plan (Protocol) and Informed Consent Form (ICF)
B. Signed/dated Curriculum Vitae and current medical licensure for Investigator and Sub-Investigator(s)
C. Signed/dated Financial Disclosure Forms for Investigator and Sub-Investigator(s)
D. Signed/dated Clinical Trial Agreement / Statement of Investigator

8.2 INFORMED CONSENT PROCEDURES

Prior to undergoing any study procedure or baseline testing, each subject must indicate their consent by signing and dating the current IRB-approved Informed Consent Form. Consent forms must be approved by both Avanos Medical and the IRB prior to implementation and must be provided to the subject in their primary language complying with the requirements of 21 CFR 50.

The principal investigator or qualified delegate will administer informed consent procedures by providing to and reviewing with the potential subject the IRB approved informed consent form (ICF) in accordance with 21 CFR 50. The subject must be allowed adequate time to review the consent document and ask any questions. The subject must indicate their consent by personally signing (or making their legal mark) and dating the consent form. The investigator or qualified delegate must countersign the consent form. The subject must receive a copy of the signed/dated consent form for their records. Information detailing the Informed Consent process must be clearly documented in each subject's medical / study record (source document).

Subjects in the treatment group who remain in the study through the 12-month time period will be offered the option to continue participation through 24 months. Subjects will need to sign an additional informed consent in order to participate in the extension. Subjects who have received an additional procedure on their index knee will not qualify for the extension study.

8.3 ELECTRONIC CASE REPORT FORMS

All study data will be entered into an Electronic Case Report Form (eCRF). The investigator is responsible for ensuring the accuracy of all data entered on the eCRF. Each eCRF entry must be supported by source documentation in the subject's medical records.

8.4 MEASURES AND METHODS OF ASSESSMENT

The following assessments will be utilized throughout the study in accordance with the assessment schedules described in sections 9 and 10.

8.4.1 Demographic information

Age, gender, race, BMI, osteoarthritis diagnosis and treatment history, comorbidities, and concomitant medications will be collected for demographic analysis.

8.4.2 Index Knee

The "index" knee is defined as the knee that is being studied and to which the eligibility criteria are applied. This is the knee that will be treated with either CRFA or HA injection. Subjects may have moderate osteoarthritis in the contralateral limb and still be included in the clinical trial; however, only one knee may meet eligibility and be entered into the study.

8.4.3 Radiographic Evaluation

All subjects are required to have radiographic confirmation of arthritis (x-ray/MRI/CT) of OA grade of 2 (mild), 3 (moderate) or 4 (severe) noted within 6 months prior to study enrollment. OA grade will be based on the classification system of Kellgren-Lawrence[23] diagnosed by standard x-rays. Radiographic evaluations will also be assessed at each subject's Visit 6 (12 Month Visit) and at 24 months as appropriate.

8.4.4 Subject Reported Clinical Symptoms of Chronic Knee Pain

All subjects are required to complete a Numeric Rating Scale[24] (NRS) for pain at multiple points during the clinical study. Subjects will be asked to rate their usual pain, worst pain, least pain, and current pain in each knee at each time point. ***An NRS of ⩾ 6 (usual daily pain) for their index knee is required for entrance in the study.*** An accurate assessment of NRS is critical at all points in the study, especially at the 6-month visit, as this will be used as the primary endpoint of the study.

8.4.5 Combined Investigator/Subject Reported Outcomes

The WOMAC is a disease-specific validated outcomes instrument that is routinely used to evaluate the overall condition of subjects with osteoarthritis of the knee[25]. This instrument assesses pain, stiffness and physical function subscales and requires inputs from both the subject and the investigator.

For study inclusion, WOMAC Knee Score group at baseline of Score of 2 or 3 (0 to 4 scale) on WOMAC question A1 (pain while walking on flat surface) and a mean score of 1.5 to 3.5 on all five questions of the WOMAC subscale A (pain) are required.

8.4.6 Intraoperative Radiographic Assessment

An antero-posterior (AP) and lateral fluoroscopic views of the treated knee will be obtained intraoperatively to confirm placement of the RF probes. The images must be captured on archive media and maintained as described in section 6.6.4.

8.4.7 Post-Treatment Care

Unless there is an adverse event requiring further medical intervention, subjects will be discharged home from the treatment facility on the day of the procedure with strict instructions for a caregiver or other individual to drive them home. Subjects will be encouraged to refrain from strenuous activity for 48 hours following both procedures. It is anticipated that subjects will feel some pain and discomfort at the site of the procedure for up to 1-2 weeks following the procedure. Subjects will be instructed to use common conservative therapy such as ice packs at the procedure site and may be prescribed analgesic medication to decrease their discomfort, if needed. Subjects will be instructed to return to ambulation based upon their own pain tolerance and using any modalities such as a cane that was employed prior to the RF procedure.

8.4.8 Subject-Reported Quality of Life Outcome Measures

The EQ-5D-5L scale [26], a validated instrument for subject quality of life and overall health status, will be obtained at all visits. The EQ-5D-5L allows assessments of impact on healthcare systems to be undertaken.

The Global Perceived Effect (GPE) scale[27], a validated instrument for subject quality of life outcomes, will be used for this study. The GPE has been validated to measure health transitions in subjects with musculoskeletal disorders such as osteoarthritis. The GPE will be obtained at all follow up visits.

9 SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

										Extension Study	
	V1	V2	V3	V4	V5	V5A [2]	V5B [2]	V5C [2]	V6	V7	V8
	Screen/ Rand.	Index Procedure / Treatment (DAY = 0)	1 Month	3 Months	6 Months	Cross-Over Tx (DAY = 0)	1 Months Post Cross-Over	3 Months Post Cross-Over	12 Months (Tx Group) or 6 Months (Crossover)	18 Months (Tx Group)	24 Months (Tx Group)
	Complete Within 60 Days of ICF	Within 30 Days of Randomization	30 +/- 7 Days	90 +/- 14 Days	180 +/- 14 Days from Treatment	Within +30 Days from V5	30 +/- 7 Days from V5A	90 +/- 14 Days from V5A	360 +/- 14 Days or 180 +/- 14 Days from V2/5A	540 +/- 14 Days from V2	720+/- 14 Days from V2
Informed Consent	X					X				X	
Inclusion/Exclusion	X	X[1]				X[1]					
Pregnancy Test (if applicable)	X	X				X					
Relevant Medical History	X										
Radiographic Exam	X[3]								X		X
Physical Exam	X[3]				X				X	X	X
Knee Exam	X				X				X	X	X
Diagnostic Block Procedure	X										
Beck's Depression Index	X										
Numeric Rating Scale	X		X	X	X	X	X	X	X	X	X
WOMAC	X		X	X	X	X	X	X	X	X	X
EQ-5d	X		X	X	X	X	X	X	X	X	X
Healthcare Utlization	X	X	X	X	X	X	X	X	X	X	X
Global Perceived Effect Score			X	X	X	X	X	X	X	X	X
Randomization	X										
Coolief (CRFA) Applications		X				X[2]					
Viscosupplementation (HA) Knee Injection		X									
Adverse Event Assessment[4]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X
Patient Stipend (if applicable)	X	X	X	X	X	X	X	X	X	X	X

[1] Verify continued eligibility
[2] Crossover Subjects only. Visits 5B, 5C and 6 based off Visit 5A date for crossover subjects.
[3] Includes BMI and vitals during exam at all visits.
[4] Includes Concurrent Knee Procedures
[5] Acceptable within 6 months of ICF

10 PROCEDURES BY VISIT

10.1 VISIT 1- Screening / Randomization

Perform the following assessments:

(1) Subject Selection / Informed Consent.

(2) Follow institutional standard protocol for confirming pregnancy status prior to treatment.

(3) Obtain demographic information and medical history.

(4) Assess subject radiographs for eligibility.

(5) Perform Physical Exam (including BMI and vital signs).

(6) Knee exam

(7) Obtain baseline Beck's Depression Index (subject completed questionnaire).

(8) Perform Numeric Rating Scale assessment for pain (subject completed questionnaire).
(9) Obtain a baseline WOMAC Score (subject completed questionnaire).
(10) Obtain a baseline EQ-5D-5L Score (subject completed questionnaire).
(11) Obtain Healthcare Utilization Form
(12) Assess concomitant medications.
(13) Verify that diagnostic block procedure was performed and confirm responder status.
(14) Verify subject eligibility and randomize subject.
(15) Perform adverse event assessment (if screening visit occurs over more than one day)
(16) Assess concomitant medications.
(17) Schedule Treatment visit

The screening procedures/visit can occur on more than one day, but must be concluded (patient should be randomized) within 60 days of signing informed consent.

10.2 Visit 2 – Index Treatment (Day 0)

It is permissible that Visit 2 can occur on the same day as Visit 1/Randomization date, but it should occur within 30 days from the date of randomization.

Perform the following assessments:

(1) Verify that subject continues to meet all eligibility criteria.
(2) Follow institutional standard protocol for confirming pregnancy status prior to treatment (if applicable and >30 days since previous one)
(3) Obtain Healthcare Utilization Form
(4) Perform CRFA or HA injection procedure per section 6.6.4.
(5) Perform adverse event assessment.
(6) Assess for changes to concomitant medications.
(7) Provide subject with perioperative care and at-home care instructions
(8) Schedule next clinic visit

It is recommended (but not required) that the first several CRFA procedures at each site should be proctored by a Avanos Medical clinical specialist to ensure procedural consistency between sites.

10.3 VISIT 3-6 – FOLLOW-UP ASSESSMENTS

Visit 3/1 Month Visit should occur at post-operative day 30 ± 7 days. Visit 4/3 Month Visit should occur at post-operative day 90 ± 14 days. Visit 5/6 Month Visit should occur at post-operative day 180 ± 14 days. Visit 6 should occur at post-operative day 360 ± 14 days.

Perform the following assessments:

(1) Subjects will return at months 1, 3, 6 and 12 after the procedure within the allowable follow-up intervals described above.
(2) Obtain a Numeric Rating Scale for pain (subject completed questionnaire).
(3) Obtain WOMAC Score (subject completed questionnaire).
(4) Obtain an EQ-5D-5L Assessment (subject completed questionnaire).
(5) Obtain a Global Perceived Effect Score (subject completed questionnaire).
(6) Obtain Healthcare Utilization Form
(7) Perform Physical Exam including BMI and vital signs (Visits 5 and 6 only).
(8) Perform Knee Exam (Visits 5 and 6 only).
(9) Perform adverse event assessment.
(10) Assess concomitant medications.
(11) Schedule next clinic visit.
(12) Collect and assess Radiographs (Visit 6 only).

10.4 VISIT 7-8 – LONG TERM FOLLOW-UP ASSESSMENTS

These visits are only available to those subjects who originally received CRFA at Visit 2 and who signed the informed consent to continue participation in the study. Visit 7/18 Month Visit should occur at post-operative day 540 ± 14 days and Visit 8/24 Month Visit should occur at post-operative day 720 ± 14 days.

Perform the following assessments:

(1) Obtain Informed consent (only at Visit 7).
(2) Obtain a Numeric Rating Scale for pain (subject completed questionnaire).
(3) Obtain WOMAC Score (subject completed questionnaire).
(4) Obtain an EQ-5D-5L Assessment (subject completed questionnaire).
(5) Obtain a Global Perceived Effect Score (subject completed questionnaire).
(6) Obtain Healthcare Utilization Form.
(7) Perform Physical Exam including BMI and vital signs.
(8) Perform Knee Exam.
(9) Perform adverse event assessment.
(10) Assess concomitant medications.
(11) Schedule next clinic visit (only at Visit 7).
(12) Collect and assess Radiographs (only at Visit 8).

10.5 DISCONTINUATION / EARLY TERMINATION (ET)

Subjects may withdraw from the study at any time for any reason. Early terminations can occur under the following circumstances:

1. Subject withdraws consent.
2. Subject receives an additional procedure on their index knee.
3. Investigator withdraws the subject for any reason following discussion with the sponsor.
4. Investigator withdraws the subject immediately for emergent safety issues and reverts to institutional standards-of-care.

If it becomes necessary to exit the subject from the study early, the following exit procedures should be conducted if at all possible:

(1) Obtain a Numeric Rating Scale for pain (subject completed questionnaire).
(2) Obtain WOMAC Score (subject completed questionnaire).
(3) Obtain an EQ-5D-5L Assessment (subject completed questionnaire).
(4) Obtain a Global Perceived Effect Score (subject completed questionnaire).
(5) Obtain Healthcare Utilization Form
(6) Collect and assess Radiographs
(7) Perform Physical Exam including BMI and vital signs
(8) Perform Knee Exam
(9) Perform adverse event assessment.
(10) Assess concomitant medications.

The study may be terminated by the sponsor at any time for any reason. If a subject is withdrawn or the study is terminated, investigators will revert to institutional standards-of-care.

10.6 Crossover visit (visit 5a)

Only subjects initially randomized to the control group (HA injection) who remain in **significant** pain at Visit 5 are eligible to receive crossover. Significant pain is defined as pain substantial enough to warrant receipt of a minimally invasive procedure (i.e., CRFA) per the investigators and subject assessment. Subjects do **not** need to formally requalify for the study to receive crossover per the inclusion/exclusion criteria; however, ***confirmation and documentation is needed that subjects remain a medically appropriate candidate*** for the CRFA procedure in order to be eligible.

Prior to receiving the Crossover procedure, the subject should be reminded of the risks of the CRFA procedure as described in section 4.6 and should sign the Crossover section of the informed consent document as noted in Section 8.2.

If the subject is still receiving relief from the HA injection at the time of this visit and/or is not medically appropriate for the CRFA procedure or elects not to Crossover, the subject should not receive crossover treatment and should continue to complete Visit 6.

It is anticipated that the Crossover procedure will occur on a different day than the 6 Month visit (Visit 5); however, it is allowable to perform the procedure on the same day if the Visit 5 items are completed first. Otherwise, the crossover treatment should occur within 30 days of Visit 5. If Visit 5A occurs on the same day as Visit 5, overlapping assessments noted below that were completed as part of Visit 5 do not need to be re-done (i.e., NRS, WOMAC, Healthcare Utilization, etc.).

If a subject choses crossover, the timing of their follow up visits (5B, 5C and 6) will now be based off their Visit 5A treatment date. Visit 5B/1 Month Visit should occur at post-operative day 30 ± 7 days. Visit 5C/3 Month Visit should occur at post-operative day 90 ± 14 days and the 6 Month Visit/Visit 6 should occur at post-operative day 180 ± 14 days.

At the Crossover Visit, the following assessments must be performed.

(1) Verify Crossover consent was obtained
(2) Verify and document that the subject remains medically appropriate for the procedure.
(3) Obtain a Numeric Rating Scale for pain (subject completed questionnaire).
(4) Obtain WOMAC Score (subject completed questionnaire).
(5) Obtain an EQ-5D-5L Assessment (subject completed questionnaire).
(6) Obtain a Global Perceived Effect Score (subject completed questionnaire).
(7) Obtain Healthcare Utilization Form
(8) If applicable, follow site standard procedures for confirming pregnancy status prior to treatment.
(9) Perform CRFA procedure per section 6.6.4.
(10) Perform adverse event assessment.
(11) Assess concomitant medications.
(12) Provide subject with perioperative care and at home care instructions.
(13) Schedule next clinic visits (1, 3, and 6 months as noted above).

11 ADVERSE EVENT REPORTING

11.1 ADVERSE EVENTS (AE) ASSESSMENT

Subjects should be instructed to contact the Investigator (or designee) immediately if an AE occurs. At each visit, the investigator (or authorized designee) should further query the subject to determine if any

new adverse events have occurred. Adverse Events will be assessed from the time the subject signs consent until study exit. All adverse events must be reported according to the following procedure.

Sites will be instructed to follow their normal /routine processes for adverse event reporting of post market products to the FDA per 803.20 – Individual Adverse Event Reports, however; related events that result in death, serious injury or malfunction that could cause death or serious injury will be specifically monitored for. As an additional measure of control, the sponsor will periodically review reported events as described in section 11.6 looking for items that meet the reporting criteria.

11.1.1 Definitions and Classification

Adverse Event (AE):

Any untoward medical occurrence that occurs in a subject or clinical investigation subject using a study device including any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of the study device, whether or not considered related to the device.

Treatment Emergent Adverse Event (TEAE):

An AE that begins or worsens in severity after the subject has used at least one study device

Non-Treatment Emergent Adverse Event:

An AE that begins or worsens in severity between the time that the consent form is signed and the first use of the study device

Serious Adverse Event (SAE):

A Serious Adverse Event is defined as any untoward medical occurrence that falls into one of the following categories:

A. Results in death
B. Is life threatening, meaning that the subject is at risk of death at the time of the event; this does not mean that the event hypothetically might have caused death if it were more severe.
C. Requires inpatient hospitalization or prolongation of existing hospitalization
D. Results in persistent or significant disability or incapacity
E. Is a congenital anomaly or birth defect in a subject's fetus or baby
F. Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but that may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

Unanticipated Adverse Device Effect (UADE):

Any serious adverse effect on health or safety or any life-threatening problem or death cause by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

11.2 SEVERITY OF ADVERSE EVENTS

The Investigator (or authorized delegate) will assess the severity of each AE based on the following definitions:

Severity	Definition
Mild	An AE in which the subject is aware of signs or symptoms, but which does not interfere with the subject's usual activities of daily living, or is transient and resolves without treatment or sequelae
Moderate	A sign or symptom which interferes with the subject's usual activities of daily living or requires treatment
Severe	An AE that results in incapacity with inability to do work or do usual activities of daily living. Severe AEs require treatment or medical intervention to resolve

11.3 RELATIONSHIP OF ADVERSE EVENTS

For each AE, the Investigator (or qualified delegate) will assess the causality/relationship to the investigational device according to the following criteria:

Relatedness	Definition
Unrelated	A clearly evident relationship to other etiologies, such as concomitant medications or conditions or subject's known clinical state
Unlikely	Based upon available information regarding subject history or disease process, relationship of adverse event to test article(s) is unlikely
Possible	The association of the AE with the test article is unknown; other etiologies are also possible

Probable	A reasonable temporal sequence of the AE with test article administration exists and based upon the medical professional's clinical experience, the association of the AE with the test article seems likely
Definite	A causal relationship exists between the test article and the AE, and other conditions (e.g., concomitant illness, progression or expression of the disease state, reaction to concomitant medications) do not appear to explain the AE

For AE's, the most likely cause (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated on the eCRF with details of the concomitant disease or medication or other cause.

11.4 REPORTING ADVERSE EVENTS

A. All AEs must be recorded in the subject's medical record and the appropriate eCRF. The description of the AE will identify the date of onset, date of remission, severity, causal relationship to the study product, action taken along with the results of any diagnostic procedures or laboratory tests, all treatments that were required and the outcome of the event.

B. The Investigator will follow all study device related AEs until there is a return to baseline or until a clinically satisfactory resolution is achieved.

11.5 REPORTING SERIOUS ADVERSE EVENTS

The Investigator must report any SAE to the Sponsor within 24 hours of becoming aware of the event. All deaths, whether or not considered study-related, must be reported immediately to the Sponsor with a copy of the autopsy report and death certificate provided when and if available.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

Dr. Hilton Kaplan, MBBCh FCSSA PhD

Medical Monitor

Telephone Number: 646-499-0132

Email: Hilton.Kaplan@avanos.com

Fax/Scan the Serious Adverse Event form and supporting documentation to ***(678) 669-2791*** within 24 hours of becoming aware of a Serious Adverse Event.

The Investigator and the Sponsor will review each SAE report to evaluate the seriousness and the causal relationship of the event to study device. In addition, the Sponsor will determine if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan. Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

All SAEs will be captured from signing of informed consent throughout the study. The Investigator must notify the IRB in writing of all SAEs in accordance with IRB requirements.

11.6 CLINICAL SAFETY MONITORING

Avanos Medical's Medical Director will conduct periodic safety monitoring and oversight throughout the course of the study by reviewing all Serious Adverse Event reports, conducting Adverse Event listing reviews, and monitoring post-market surveillance reports.

Upon receipt of any Serious Adverse Event (SAE) report at Avanos Medical, the medical monitor will review the SAE report for completeness and when necessary, will request clarification and/or additional information from the investigator. The designated medical monitor is responsible for reviewing the investigator's assessment and classification of each event. If the designated medical monitor disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the designated medical monitor, the subject's Adverse Event Report Form will be updated accordingly. If the investigator does not agree with the designated medical monitor classification, both determinations will be documented within the study report. However, the Avanos Medical determination will be used for analysis purposes.

Given the 'Exempt' status of this study, Avanos Medical has determined that a Data Monitoring Committee (or DSMB) is not required based on the FDA guidance document, "Establishment and Operation of Clinical Trial Data Monitoring Committees".

12 STATISTICAL METHODS AND DATA ANALYSIS

Prior to initiation of the analysis, a stand-alone Statistical Analysis Plan (SAP) will be prepared, which will provide detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final integrated study report.

The primary analysis is planned when the last enrolled subject completes the 6-month follow-up visit. The subjects will continue to be followed through 12 months, and a final analysis is planned at the conclusion of the study after the last subject completes the 12-month follow-up visit.

An additional analysis will be conducted once the last subject completes the extension study to analyze data collected at 18 and 24 months.

12.1 DETERMINATION OF SAMPLE SIZE

A non-inferiority approach on response rate was used to estimate the sample size for this study, with "response" defined as ⩾ 50% reduction in pain on the NRS scale from baseline. The upper bound of a 2-sided 95% CI will be calculated for the rate difference between treatments (Standard minus Test). If the upper bound is less than (δ), then "non-inferiority" is achieved for the test treatment relative to standard treatment, as described in the table below:

Success Rate of CRFA (based on 50% Pain Score Reduction in VAS)	Success Rate of Standard (Based on 30% Pain Score Reduction in VAS)	Non-Inferiority Margin (δ)	Sample Size 5% Level of Significance (2-sided) 90% Statistical Power
62%*	40%**	5%	134
* - [14] Davis, et al, RAPM 2017, In Press /FDA clearance K163461 ** - [5] Chevalier, X et al. "Single, intra-articular treatment with 6 ml Hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomized, multi-center, double-blind, placebo controlled trial" *Ann Rheum Dis* 2010 69: 113-119.			

Assuming an attrition rate of 20%, 168 subjects enrolled into the study will yield 134 completers.

12.1.1 Disposition of Subjects

The number and percentage of subjects entering the study will be presented. Reasons for any screen failures and/or early terminations will be summarized. A flow chart will present the aggregate disposition of subjects from Visit 1 (Screening Visit) through the final 24-month visit, including all subjects who cross over from the viscosupplementation injection group to the CRFA denervation group.

12.1.2 Protocol Deviations

Deviations from the protocol, including violations of inclusion/exclusion criteria, will be assessed as "minor" or "major" by the sponsor prior to database lock and analysis. Major deviations from the protocol will lead to the exclusion of a subject from the Per-Protocol Set.

Certain clinical situations may require waivers for the safety of the subjects enrolled, integrity of the data or scheduling conflicts. Any waiver request will be reviewed on an independent basis and must be documented in writing prior to the event occurrence. Clinical decisions will be made by the medical monitor.

12.2 DATASET DEFINITIONS

12.2.1 Safety Set

All randomized subjects who receive CRFA or HA injection treatment will be included in the safety analyses.

12.2.2 Full-Analysis Set

All randomized subjects will be analyzed following the principle of intention-to-treat (ITT) provided they received CRFA or HA injection treatment and had at least one effectiveness observation.

12.2.3 Per-Protocol Set

All randomized subjects who are compliant with the study protocol (i.e., who do not experience any major protocol deviations) and who receive CRFA or HA injection treatment and have at least one effectiveness observation will be included in the Per-protocol Set.

The primary effectiveness endpoint analysis will be based on the Full Analysis Set, although a secondary analysis will also be performed based upon the Per-Protocol Set (if there are differences), to assess the sensitivity of the analysis to the choice of analysis population. The analyses of all other endpoints will be based upon the Full Analysis Set only unless otherwise stated in the SAP. All safety analyses will be based upon the Safety Set.

Crossover subjects that continue to meet all Inclusion/Exclusion criteria will be included in the Per-protocol Set, and may be combined with CRFA randomized subjects for purposes of overall assessment of the CRFA procedure.

12.3 EFFECTIVENESS PARAMETER

12.3.1 Primary Effectiveness Parameter

The primary effectiveness parameter is defined as the proportion of subjects whose knee pain is reduced from baseline by $\geqslant$ 50% based on the Numeric Rating Scale (NRS) at the 6-month visit.

12.3.2 Secondary Effectiveness Parameters

Secondary Effectiveness Endpoint 1: The proportion of subjects whose knee pain is reduced from baseline by $\geqslant$ 50% based on the Numeric Rating Scale (NRS) at the 12-month visit.

Secondary Effectiveness Endpoint 2: The change in the WOMAC Score from baseline to the 6 month visit and 12-month visit.

12.3.3 Tertiary Effectiveness Parameter

Tertiary effectiveness endpoint 1: The change in measured EQ-5D-5L scale from baseline at the 6-month visit and 12-month visit.

Tertiary effectiveness endpoint 2: The measured Global Perceived Effect scale at the 6-month visit and 12-month visit.

12.3.4 Exploratory Analysis

Other variables of interest, which include, but are not limited to, WOMAC subscale analysis (pain, stiffness, physical function), change in pain medication usage from baseline as measured by subject self-reported average daily dosage, healthcare utilization, and change in weight from baseline, will be summarized at various visit intervals as discussed below in section 12.5.

In addition, the endpoints listed above will also be summarized at 18 and 24 months post treatment.

12.4 GENERAL CONSIDERATIONS

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated in the statistical analysis plan (SAP). Continuous data will be summarized by randomized device assignment and other subset (center, age, etc.) groupings using descriptive statistics (number, mean, median, standard deviation [SD], minimum, and maximum). Categorical data will be summarized by randomized device assignment and other subset groupings using frequency tables (frequencies, percentages, confidence intervals). The natural log transformation will be applied to variables which are highly skewed. If the model assumptions for the ANOVA are not met, transformation of the data or non-parametric analysis may be implemented.

12.5 DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND CONCOMITANT MEDICATIONS

Demographic data, medical history, and concomitant medications will be summarized by means of descriptive statistics.

12.6 EFFECTIVENESS ANALYSES

12.6.1 Primary Effectiveness Analysis

The primary efficacy parameter is the response rate which is defined as the proportion of subjects whose knee pain is reduced from baseline by $\geqslant$ 50% based on the NRS scale at 6 months after treatment. Each subject's response to the treatment will be treated as an independent binomial event:

H_o: $\pi_C - \pi_T \geqslant 0.05$

H_a: $\pi_C - \pi_T < 0.05$

Where:

Π_T: proportion of subjects with $\geqslant$ 50% decrease from baseline in NRS pain score from baseline at the 6 months post randomization in the CRFA group

Π_C: proportion of subjects with $\geqslant$ than 50% decrease from baseline in NRS score from Screening at the 6 months post randomization in the HA injection group

The non-inferiority margin is set at 5% for the primary efficacy parameter expressed as proportion. The difference of proportions between treatment groups will be calculated and a two sided 95% confidence interval will be constructed using Wald asymptotic confidence limits approach or exact binomial limits approach. If the upper bound is less than 0.05, then 'Non-inferiority' is established for the CRFA group relative to the HA injection group. If, in addition, the upper bound of the confidence interval is below zero, the CRFA group can be determined to be 'Superior' to the HA injection group.

Treatment by study center interaction may be examined graphically across study center to determine the association between treatment and response rate is in the same direction or using logistic regression with response rate at 6 months as the response variable, and the study center, treatment group, study center by treatment group interaction as predictor variables in the model.

12.6.2 Secondary Effectiveness Analysis

If the null hypothesis is rejected for the primary endpoint, i.e., CRFA is concluded to be either non-inferior or superior to the HA injection, the secondary endpoints will be compared between treatment groups as detailed below.

12.6.2.1 Knee Pain Reduction

The proportion of subjects whose knee pain is reduced from baseline by ⩾ 50% based on the Numeric Rating Scale (NRS) at the 12 month will be calculated and compared between the two treatment groups and within each group as described in section 12.7.1 for the primary endpoint. The method for controlling the secondary endpoint familywise error rate will be detailed in the SAP.

12.6.2.2 WOMAC

The change in the WOMAC Score from baseline to the 6 month and 12 month visits will be calculated and compared between the two treatment groups:

H_o: $\mu_1 = \mu_2$
H_a: $\mu_1 \neq \mu_2$

Where:
μ_1: mean of WOMAC Score change between the Baseline and the Follow-Up at 6 months and 12 months for the CRFA group
μ_2: mean of WOMAC Score change between the Baseline and the Follow-Up at 6 months and 12 months for the HA injection group

Analysis of variance (ANOVA) with treatment as fixed effect and study center as block effect on changes in the WOMAC between the Baseline and the Follow-Up at 6 months and 12 months separately will be performed for the comparison of the CRFA with the HA injection groups.

Treatment by study center interaction may be examined using analysis of variance (ANOVA) with treatment, study center and treatment by study center interaction effects on changes in the WOMAC between the baseline and the Follow-Up at 6 months and 12 months in the model.

12.6.3 Tertiary Effectiveness Analysis

The change in the EQ-5D-5L Score from baseline to the 6 month and 12 month visits will be calculated and compared between the two treatment groups:

H_o: $\mu_1 = \mu_2$
H_a: $\mu_1 \neq \mu_2$

Where:

μ_1: mean of EQ-5D-5L Score change between the Baseline and the Follow-Up at 6 months and 12 months for the CRFA group
μ_2: mean of EQ-5D-5L Score change between the Baseline and the Follow-Up at 6 months and 12 months for the HA injection group

Analysis of variance (ANOVA) with treatment as fixed effect and study center as block effect on changes in the EQ-5D-5L Score between the Baseline and the Follow-Up at 6 months and 12 months separately will be performed for the comparison of the CRFA with the HA injection groups.

Treatment by study center interaction may be examined using analysis of variance (ANOVA) with treatment, study center and treatment by study center interaction effects on changes in the EQ-5D-5L Score between the baseline and the Follow-Up at 6 months and 12 months in the model.

The GPE scale at the 6 month and 12 month visit will be calculated and compared between the two treatment groups:

H_o: $\mu_1 = \mu_2$
H_a: $\mu_1 \neq \mu_2$

Where:
μ_1: mean of GPE score at 6 months and 12 month for CRFA group
μ_2: mean of GPE score at 6 months and 12 month for the HA injection group

Analysis of variance (ANOVA) with treatment as fixed effect and center as block effect on the GPE score at 6 months and 12 months separately will be performed for the comparison of the CRFA with the HA injection groups.

Treatment by study center interaction may be examined using analysis of variance (ANOVA) with treatment, study center and treatment by study center interaction on the GPE score at the Follow-Up at 6 months and 12 months in the model.

12.7 SAFETY ANALYSES

12.7.1 Safety Parameter

All adverse events that occur during the study will be recorded per the protocol definitions. An overall adverse event rate will be summarized for both treatment groups.

12.7.2 Method of Analysis

Adverse events occurring during the study will be tabulated by body system, severity, and Investigator reported relationship to the study device. Any deaths or serious device associated AEs will be summarized. From enrollment to follow up visit at 6 months, adverse events will be stratified by subjects randomization assignment. After follow up visit at 6 months to follow up visit at 12 months (end of study), adverse events will be stratified among subject status between CRFA, HA and Crossover.

12.8 HANDLING OF MISSING DATA

For the primary outcomes using the full analysis set, last observation carried forward (LOCF) procedures may be used to impute missing data. A sensitivity analysis will be performed to evaluate the effect of assumption of imputation. For the secondary outcomes and safety analysis, missing data will not be imputed.

13 ETHICAL, ADMINISTRATIVE, AND REGULATORY OBLIGATIONS

13.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The study protocol, ICF document(s), subject recruitment materials, and any amendments must be submitted to and approved by the IRB/IEC prior to enrolling subjects. The IRB must be operating in compliance with 21CFR Part 56.

13.2 HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA)

In accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996, the Investigator must obtain authorization from the subject to use and/or disclose protected health information (PHI). HIPAA authorization may be obtained as part of the ICF or in a separate document. HIPAA authorization must include:

A. Identification of the parties that can use and disclose the PHI
B. Identification of the parties to whom the PHI may be disclosed
C. A meaningful description of the PHI
D. A description of each purpose for the use and disclosure
E. Information about the subject's rights related to the authorization
F. Information about the expiration of the authorization
G. Instructions on how to revoke the authorization
H. A statement about what may happen if the authorization is not signed
I. A warning that once information has been released, it may be released again without further authorization

14 DATA AND QUALITY MANAGEMENT

All data obtained during this study will be entered into a 21 CFR 11 compliant Electronic Data Capture (EDC) system. All eCRF data must be supported by source documentation in the subject's medical/research record.

The sponsor will designate a qualified Monitor (CRA) to verify that study data are supported by adequate source documentation and are complete, accurate, and verifiable. Instances of inconsistent, missing or illogical data will be communicated to the Investigator or study coordinator and queried for resolution.

Site personnel will enter all data into the EDC system. The specific procedures for using the EDC system, including, but not limited to, entering and editing eCRF data and reviewing and resolving queries will be provided to investigative sites during training sessions and a training manual.
A Data Management Plan prepared by the sponsor will document the specifications for consistency and plausibility checks. Queries/corrections will be managed within the EDC system via the 'query process.' Prior to database lock, the Principal Investigator must electronically sign each eCRF.

15 RECORDS RETENTION AND ARCHIVAL

Study records must be maintained for a period of 2 years after the later of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Prior approval by the study sponsor is required before destroying or moving any study records off site.

After database lock, a CD or other electronic media containing a copy of the eCRF data will be provided to the investigator and must be maintained in the Trial Master File.

All source worksheets/documents, records, and reports must be retained by the study site in accordance with 21 CFR 812.140. All primary data or copies thereof (e.g., laboratory records, source documents, data sheets, correspondence, photographs, and computer records), which are a result of the original study observations, and are necessary for the reconstruction and evaluation of any study report, must be retained at the study site until otherwise notified by the Sponsor. Please contact Avanos Medical before archiving / destroying any study records.

16 MONITORING AND AUDITING

Avanos Medical will assign a qualified Monitor (CRA) to each site. The Monitor will visit the site at regular intervals throughout the study and at study completion to assess:

A. Compliance with applicable regulations and Good Clinical Practices

B. Adherence to the study protocol
C. Adequacy and accuracy of record keeping and source documentation
D. Acceptability of storage of clinical trial materials and accountability of test articles
E. Accuracy of eCRF data

Medical records for all subjects participating in the trial, eCRFs and study related documents (IRB approval, Instructions for use, correspondence pertaining to the trial, etc.) must be made available to monitor at each visit and upon request. The sponsor will create a Monitoring plan that outlines the anticipated schedule, processes, and expectations.

Avanos Medical, the IRB or regulatory authorities may also audit the study center to evaluate the conduct of the study. The clinical Investigator(s)/institutions(s) shall allow trial related monitoring, audits, IRB review and regulatory inspections by providing direct access to source worksheets/documents.

17 STUDY / SITE TERMINATION

Avanos Medical reserves the right to terminate the study or a study site at any time. Acceptable reasons for termination may include but are not limited to:

- Non-compliance with the Investigational Plan, Protocol, Regulatory Obligations, etc.
- Administrative Reasons

18 PUBLICATION PLAN

Avanos Medical will devise a plan for communications and publications regarding the study (primary, secondary, and extension objectives, sub analysis) and sub studies.

18.1 GENERALITIES

The publication policy described below applies for all publications related to this study.

- The agreement of Avanos Medical is mandatory before any submission made before the publication of any paper.
- Sub-investigators participating in the study may be listed on the paper at the discretion of the Steering Committee.
- Co-authors' order in the Authorship list will be submitted to each journal per journal-specific requirements; journal guidelines on the number of allowable authors will be followed.
- Avanos Medical must be cited in all publications where appropriate.

18.2 STEERING COMMITTEE

A Steering Committee will be established and will be responsible for assisting and guiding publication(s) of study results. The steering committee should consist of one or more clinicians qualified by experience.

The chair of the steering committee is the study Principal Investigator. If the study Principal Investigator leaves that role during the study, the steering committee will decide upon a replacement. A minimum of one Avanos Medical employee will facilitate the steering committee interaction. Members may be added or removed from the steering committee at any time as needs change or previously agreed to timelines get missed.

18.3 AUTHORSHIP CRITERIA

Authors for all publications should be qualified by experience and have participated in the clinical trial as an enrolling investigator or be a consultant responsible for key elements of the study process (e.g. protocol design, results interpretation, clinical strategy, etc.).

Lead Principal Investigator will be listed as the lead author, the Steering Committee will be represented, then authorship order will be determined by enrollment ranking pending journal allowances. Enrollment is defined as the number of patients who successfully reached the primary objective taking into account major data quality issues. A Working Group will be created which may allow for inclusion of participating investigators or referring sub-investigators who provided significant scientific contribution leading to the successful conduct of the trial.

18.4 PRIMARY PRESENTATIONS

Study presentations occurring at a public conference or meeting. Author affiliation with the associated society will be taken into account as part of the decision-making process for choosing presenters.

- **Primary speaker:** Principal investigator of the study shall have first right of refusal.
- **Secondary speaker or back-up speaker:** if more than one speaker is necessary or the principal investigator of the study is not available, the principal investigator of the highest enrolling center will be given the next priority, and so on. If neither of the first two options are available or interested, a steering committee member will be chosen.

Speakers for subsequent presentations can be any of the authors noted and should be confirmed by the steering committee.

19 REFERENCES

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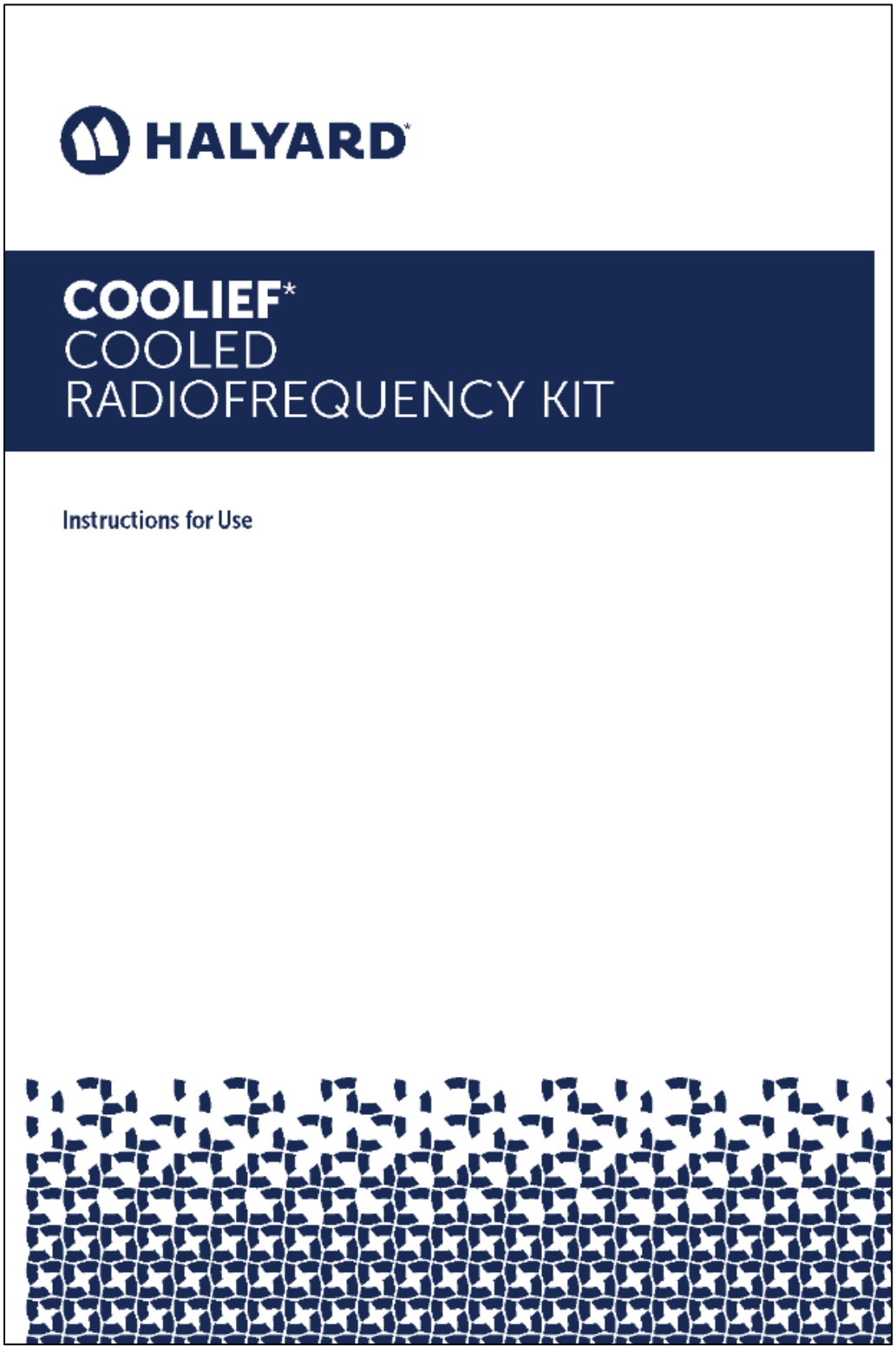
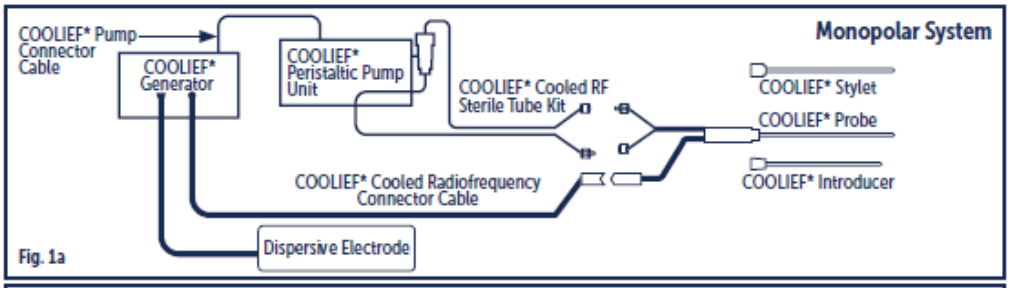
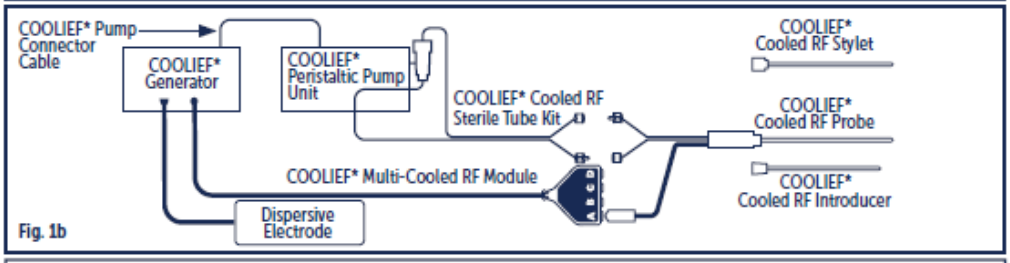
APPENDIX 1 – COOLIEF* INSTRUCTIONS FOR USE


HALYARD
COOLIEF*
COOLED
RADIOFREQUENCY KIT
Instructions for Use


Monopolar System
COOLIEF* Pump Connector Cable
COOLIEF* Generator
COOLIEF* Peristaltic Pump Unit
COOLIEF* Cooled RF Sterile Tube Kit
COOLIEF* Stylet
COOLIEF* Probe
COOLIEF* Introducer
COOLIEF* Cooled Radiofrequency Connector Cable
Dispersive Electrode
Fig. 1a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COOLIEF* Cooled RF Stylet
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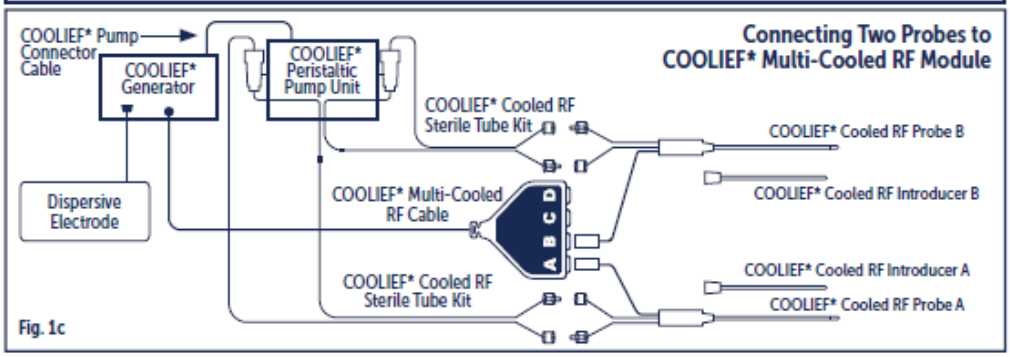
COOLIEF* Multi-Cooled RF Module
A B C D
Dispersive Electrode
Fig. 1b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COOLIEF* Generator
COOLIEF* Peristaltic Pump Unit
COOLIEF* Cooled RF Sterile Tube Kit
COOLIEF* Cooled RF Probe B
COOLIEF* Cooled RF Introducer B
Dispersive Electrode
COOLIEF* Multi-Cooled RF Cable
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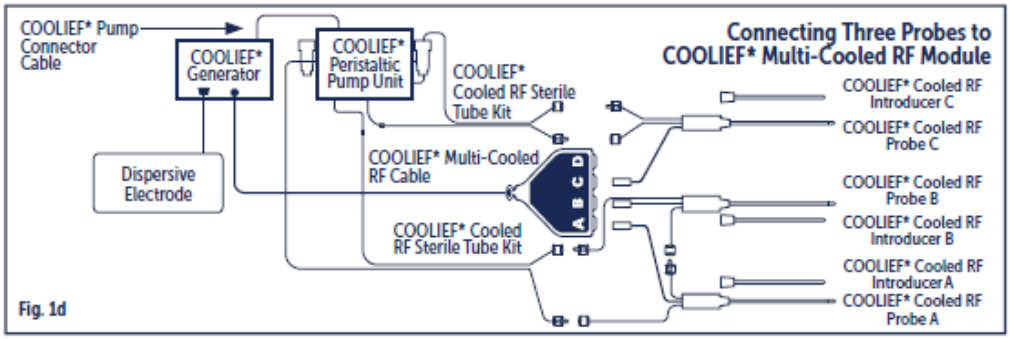
COOLIEF* Cooled RF Probe A
Fig. 1c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COOLIEF* Generator
COOLIEF* Peristaltic Pump Unit
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COOLIEF* Cooled RF Introducer C
COOLIEF* Cooled RF Probe C
Dispersive Electrode
COOLIEF* Multi-Cooled RF Cable
A B C D
COOLIEF* Cooled RF Probe B
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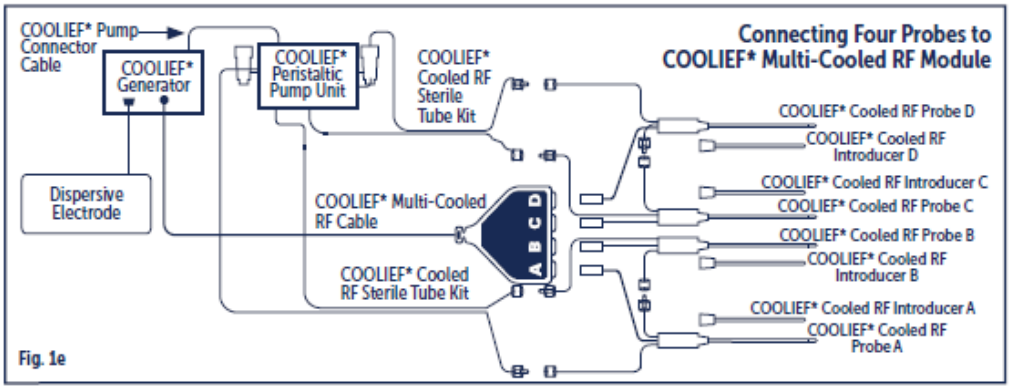
Fig. 1d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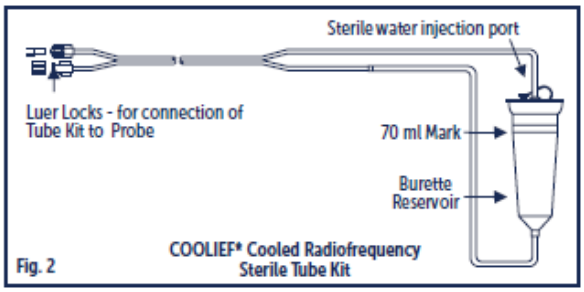
COOLIEF* Cooled RF Sterile Tube Kit
COOLIEF* Cooled RF Probe D
COOLIEF* Cooled RF Introducer D
COOLIEF* Cooled RF Introducer C
COOLIEF* Cooled RF Probe C
Dispersive Electrode
COOLIEF* Multi-Cooled RF Cable
A B C D
COOLIEF* Cooled RF Probe B
COOLIEF* Cooled RF Introducer B
COOLIEF* Cooled RF Sterile Tube Kit
COOLIEF* Cooled RF Introducer A
COOLIEF* Cooled RF Probe A
Fig. 1e


Sterile water injection port
Luer Locks - for connection of Tube Kit to Probe
70 ml Mark
Burette Reservoir
Fig. 2
COOLIEF® Cooled Radiofrequency Sterile Tube Kit

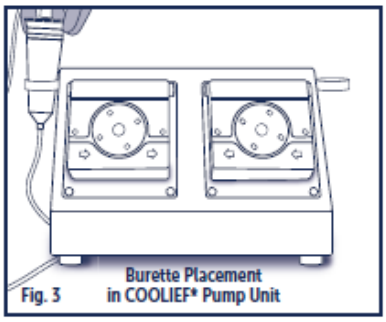
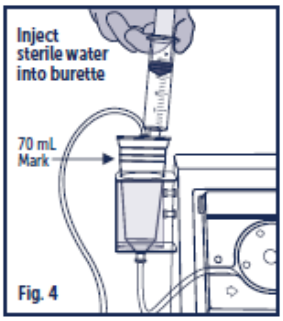
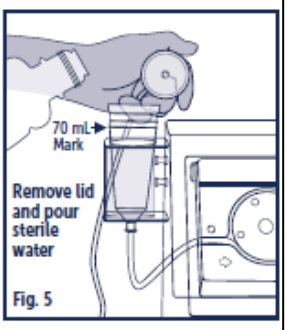
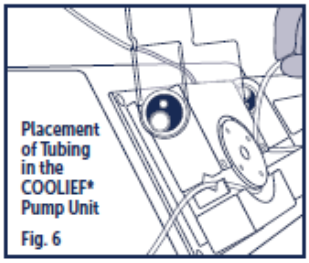


Fig. 3
Burette Placement in COOLIEF® Pump Unit


Inject sterile water into burette
70 mL Mark
Fig. 4


70 mL Mark
Remove lid and pour sterile water
Fig. 5


Placement of Tubing in the COOLIEF® Pump Unit
Fig. 6

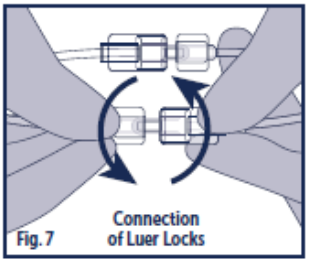


Fig. 7
Connection of Luer Locks

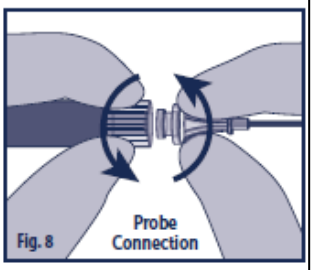


Fig. 8
Probe Connection


Single Use Only
STERILE EO
Rx Only
Do not use if package is damaged
Non-Pyrogenic
Follow instructions for use
Keep away from sunlight
Dispose of properly

HALYARD* COOLIEF* Cooled Radiofrequency Kit

Rx Only: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

Device Description

HALYARD* COOLIEF* Cooled Radiofrequency Sterile Tube Kit (sterile, single use, non-body contact): It is used for closed-loop circulation of sterile water through a HALYARD* COOLIEF* Cooled Radiofrequency (RF) Probe. It includes a burette and tubing.

HALYARD* COOLIEF* Cooled Radiofrequency Introducer (sterile, single use): It is to be used with the Probes only. The Cooled Radiofrequency Introducer provides a path for the Probe to the nervous tissue.

HALYARD* COOLIEF* Cooled Radiofrequency Probe (sterile, single use): It is inserted through a Introducer into or near nervous tissue. Sterile water circulates internally to cool the Probe while it delivers radiofrequency energy. A thermocouple in the Probe measures cooled electrode temperature throughout the procedure.

Indications For Use

The HALYARD* COOLIEF* Cooled Radiofrequency Kit, in combination with the HALYARD* COOLIEF* Radiofrequency (RF) Generator (PMG-115-TD/PMG-230-TD/PMG-ADVANCED) (formerly Baylis Pain Management Generator or KIMBERLY-CLARK® Pain Management Generator) is indicated for use to create radiofrequency lesions in nervous tissue.

Contraindications

For patients with cardiac pacemakers, a variety of changes can occur during and after the treatment. In sensing mode the pacemaker may interpret the RF signal as a heartbeat and may fail to pace the heart. Contact the pacemaker company to determine if the pacemaker should be converted to a fixed-rate pacing during the radiofrequency procedure. Evaluate the patient's pacing system after the procedure.

Check the compatibility and safety of combinations of other physiological monitoring and electrical apparatus to be used on the patient in addition to the COOLIEF* RF Generator.

If the patient has a spinal cord, deep brain, or other stimulator, contact the manufacturer to determine if the stimulator needs to be in the bipolar stimulation mode or in the OFF position.

This procedure should be reconsidered in patients with any prior neurological deficit.

The use of general anesthesia is contraindicated. To allow for patient feedback and response during the procedure, it should be performed under local anesthesia.

Systemic infection or local infection in area of the procedure.

Blood coagulation disorders or anticoagulant use.

Warnings

The Kit contains single-use devices. Do not reuse, reprocess, or resterilize these medical devices. Reuse, reprocessing, or resterilization may 1) adversely affect the known biocompatibility of the device, 2) compromise the structural integrity of the device, 3) lead to the device not performing as intended, or 4) create a risk of contamination and cause the transmission of infectious diseases resulting in a patient injury, illness, or death.

The COOLIEF* Probe must be used with the correct connector cable. Attempts to use it with other connector cables can result in electrocution of the patient or operator.

Laboratory staff and patients can undergo significant x-ray exposure during radiofrequency procedures due to the continuous use of fluoroscopic imaging. This exposure can result in acute radiation injury as well as increased risk for somatic and genetic effects. Therefore, adequate measures must be taken to minimize this exposure.

Discontinue use if inaccurate, erratic or sluggish temperature readings are observed. Use of damaged equipment may cause patient injury.

Do not modify HALYARD* Equipment. Any modifications may compromise safety and efficacy of the device.

When the COOLIEF* RF Generator is activated, the conducted and radiated electrical fields may interfere with other electrical medical equipment.

The RF Generator is capable of delivering significant electrical power. Patient or operator injury can result from improper handling of the Probes, particularly when operating the device.

During power delivery, the patient should not be allowed to come in contact with grounded metal surfaces.

Do not remove or withdraw the device while energy is being delivered. There is a rare potential for localized skin burn if RF lesion site has insufficient subcutaneous tissue (<15mm) or is near a shallow metal implant.

There is a rare potential for unintended nerve or vascular damage if RF lesion is created over a nerve or vessel:

Ensure proper selection of the appropriate sized active electrode tip to achieve the desired lesion size.

Active Tip Size	Lesion Size and Shape (T=60°C)	Typical Anatomy Placement
2 mm	4 – 6 mm, Oblate Spheriod	Cervical Spine
4 mm	10 – 12 mm, Spherical	Lumbar Spine, Knee, Hip
5.5 mm	12 mm, Spherical	Thoracic Spine

Precautions

Do not attempt to use the Kit before thoroughly reading the accompanying Instructions for Use and the User's Manual for the COOLIEF* RF Generator and Dispersive Electrode (PMA-GP-BAY).

Apparent low power output or failure of the equipment to function properly at normal settings may indicate: 1) faulty application of the dispersive electrode or 2) power failure to an electrical lead. Do not increase power level before checking for obvious defects or misapplication.

To prevent the risk of ignition, make sure that flammable material is not present in the room during RF power application.

Only physicians familiar with RF lesion techniques should use the COOLIEF* Kit components.

It is the physician's responsibility to determine, assess and communicate to each individual patient all foreseeable risks of the RF lesion procedure.

The sterile packaging should be visually inspected prior to use to detect any compromise. Ensure that the packaging has not been damaged. Do not use the equipment if the packaging has been compromised.

Proper sterile techniques must be used when assembling and filling the Tube Kit. Do not place the lid down on a non-sterile surface.

HALYARD* COOLIEF* Cooled Radiofrequency Sterile Tube Kit

The COOLIEF* Tube Kit is for use with a single Probe.

Care must be taken to ensure all luer fittings are secure to prevent leaking. Do not disconnect luer fittings while the pump is running.

Arrange equipment to minimize tubing tripping hazards.

Do NOT perform cooled RF lesion procedures if water is not circulating through the Tube Kit, water is leaking or air bubbles are seen in the tubing. Immediately stop the procedure and correct circulation before restarting the procedure.

Do NOT pinch the tubing of the Tube Kit.

HALYARD* COOLIEF* Cooled Radiofrequency Introducer

Be careful while handling the COOLIEF* Introducer. The sharp tip can cause injury to the operator if handled carelessly.

Handle the Introducer safely when it is in use due to electric currents.

Do not move the Introducer without the stylet fully inserted.

Choose the properly sized Introducer.

HALYARD* COOLIEF* Cooled Radiofrequency Probe

The Tube Kit should never be disconnected from the Probe when RF delivery is in progress. The lumen of the Tube Kit should not be obstructed in any way during the procedure, as this will stop cooling of the Probe.

Disconnect the Probe by pulling the connector, not the cable.

Handle the Probe safely when it is in use due to electric currents and the hot tip.

While inserting the Probe through the Introducer watch the fluoroscope for any buckling. Do not attempt to further insert the Probe if any buckling is observed or significant resistance is felt.

Do not move the Introducer when the Probe is in it. If repositioning is needed, retract the Probe from the Introducer and then reposition the

Introducer with the stylet inserted.

The "Cooled RF Temp" displayed on the COOLIEF® RF Generator refers to the cooled electrode temperature and not the hottest tissue temperature.

Adverse Events

Potential complications associated with the use of this device include but are not limited to: infection, nerve damage, increased pain, visceral injury, failure of technique, paralysis, and death.

Product Specifications

The COOLIEF® Probe is comprised of an electrically insulated shaft with an active tip that functions as an electrode for RF energy delivery, a handle, tubes with luer locks and a cable with a 7-pin connector.

The COOLIEF® Introducer includes an insulated stainless steel cannula and a stylet.

The COOLIEF® Tube Kit is comprised of a burette and flexible tubing fitted with luer locks for connection to the Probe.

The COOLIEF® Probe, Introducer, and Tube Kit are ethylene oxide sterilized and supplied sterile. The devices should be stored in a cool, dry environment.

Note: *Please contact Halyard Health for a list of all model numbers and sizes.*

Inspection Prior To Use

The sterile packaging should be visually inspected prior to use to detect any compromise. Ensure that the packaging has not been opened or damaged. Do not use the equipment if the packaging has been compromised.

Equipment Required

Procedures should be performed in a specialized clinical setting equipped with a fluoroscopy unit. The equipment required to perform RF procedures include:

- COOLIEF® Cooled Radiofrequency Probe
- COOLIEF® Cooled Radiofrequency Introducer(s)
- COOLIEF® Cooled Radiofrequency Peristaltic Pump Unit and Cable
- COOLIEF® Cooled Radiofrequency Sterile Tube Kit
- COOLIEF® Cooled Radiofrequency Connector Cable (Monopolar System) or COOLIEF® Multi-Cooled Radiofrequency (MCRF) Module (CRX-BAY-MCRF)
- Dispersive Electrode
- COOLIEF® Radiofrequency Generator (PMG-115-TD/PMG-230-TD/ PMG-ADVANCED)

Instructions for Use

Monopolar System (Fig. 1a – 1e)

Assemble all the equipment required for the procedure. Set up the COOLIEF® Radiofrequency Generator (PMG-115-TD/PMG-230-TD/PMG-ADVANCED) and the COOLIEF® Pump Unit (pump), as directed in their Instructions for Use. Connect the COOLIEF® Cooled RF Connector Cable to the RF Generator as described in its Instructions for Use.

Open the package in the sterile field using appropriate sterile techniques. Inspect the devices visually to make sure there is no damage to them. Do NOT perform the procedure with any damaged equipment.

HALYARD® Cooled Radiofrequency Sterile Tube Kit (Fig. 2)

1. Place the burette into the burette holder on the side of the Pump Unit. The side of the burette with two or three ports indicates the top of the burette. **(Fig. 3)**
2. Fill the burette with room temperature sterile water. Use sterile handling techniques. Fill the burette to the 70 mL mark. Burette can be filled by injecting sterile water through a port in the lid, or by temporarily removing the lid and pouring sterile water in.
   Warning: BE SURE TO FILL THE BURETTE TO THE 70 mL MARK. Not filling the burette to the 70 mL mark will result in an inadequate supply of water for circulation.
   Use ONLY sterile, room temperature water.
   Ensure the lid is snapped back onto the body of the burette after filling. (Figs. 4-5)
   Inject sterile water into burette OR remove lid and pour sterile water.
3. Place the thick-walled tubing coming out of the bottom of the burette into the pumphead of the Pump Unit. Place the tubing in the channels of the L-shaped bracket to ensure that the tubing is not obstructed while closing the pumphead. Close the lid on the pumphead to clamp down on the tubing.
4. Remove the caps on the male and female luer locks. Connect the appropriate luer lock to the corresponding luer lock on the COOLIEF® Probe. Do not over tighten the connection. **(Fig. 6)**
   Caution: Connect one Tube Kit to one Probe. **(Fig. 7)**
5. At the end of the procedure, discard the Tube Kit appropriately.

HALYARD® COOLIEF® Cooled Radiofrequency Introducer

1. With the stylet in the COOLIEF® Introducer, carefully insert the Introducer into the patient using fluoroscopic guidance to place it at the desired lesion location.
2. Once the Introducer is in the proper position, carefully remove the stylet from the Introducer.
3. Repeat steps 1-2 with a second Introducer if necessary.

HALYARD® COOLIEF® Cooled Radiofrequency Probe

1. Insert the COOLIEF® Probes into the tissue through the Introducer. Never force the Probe in if significant resistance is felt.
2. Connect the Probe to the Introducer using the luer lock on the Probe Handle. **(Fig. 8)**
3. Attach the Dispersive Electrode to the COOLIEF® RF Generator and place the Dispersive Electrode Pad on the patient as directed in the Instructions for Use accompanying the package.
4. Connect the Probe to the Tube Kit.
5. Connect the 14-pin connector of the COOLIEF® Cooled RF Connector Cable into the RF Generator. Connect the Probe to the 7-pin connector on the Cooled RF Connector Cable.
6. Select the Treatment mode in the RF Generator. Set advanced settings and the parameters for RF delivery in the RF Generator as described in the User's Manual.
7. Perform the procedure as described in the RF Generator User's Manual. The procedure comprises pre-cooling, treatment and optional post-cooling stages.
   Note: *Other than reproduction of their usual referred pain or irritation due to probe introduction, monitor the patient for unexpected symptoms that may indicate, for example, spinal cord or nerve root irritation. If these indications are suspected, discontinue energy delivery.*
8. After treatment remove the Probes and the Introducer and discard as biohazards. Remove the Dispersive Electrode from the patient and discard appropriately. Disconnect the Cooled RF Connector Cable from the RF Generator. Follow standard hospital techniques to handle reusable items.

Troubleshooting

The following table is provided to assist the user in diagnosing potential problems.

PROBLEM	TROUBLESHOOTING
No temperature measurement OR Inaccurate, erratic or sluggish temperature reading	Ensure all connections are made: • COOLIEF® Probe(s) to COOLIEF® Cooled RF Connector Cable • Cooled RF Connector Cable to the COOLIEF® RF Generator • RF Generator to power outlet Check for an error message on the RF Generator Visually inspect the Probe or Cable for damage. Ensure that devices are dry and at room temperature. If problem persists, discontinue use.
Water does not flow through the COOLIEF® Probe and Tube Kit	• Stop the procedure immediately. • Check the luer lock connections to ensure the Tube Kit is connected to the Probe. • Check the Pump to ensure the lid is not open. • Check RF Generator for any error messages.
Probe Connector does not fit in Probe Plug-in	• Check that the connector's keys are lined up in the proper orientation. • Ensure that the Connectors are clean and unobstructed.
Damage to Insulation on COOLIEF® Probe or Introducer	Do not use. Discard immediately.

PROBLEM	TROUBLESHOOTING
Water is not circulating through tubing during pre-cooling, ON and post-cooling states	• Ensure the COOLIEF* Tube Kit is correctly connected to the COOLIEF* Probe. • Ensure the Tube Kit has been correctly placed in the pumphead. • Ensure the burette reservoir has been filled. • Visually inspect the Tube Kit tubing and joints for leaks and occlusions. • Ensure that the float ball in the burette is floating and not occluding the outflow of water from the burette. • Ensure the pump tubing (thick-walled tubing that is coming directly out of the bottom port of the burette) is placed in the pumphead.
Water is not dripping into the burette	Check to see if water is running down the wall of the burette.
Float is stuck on bottom port of the burette	Close the pumphead lid. Gently shake the burette to try and loosen the ball from the bottom of the burette.
The lid of the burette cannot be removed	Inject sterile water through the port of the lid, rather than removing the lid.
COOLIEF* Tube Kit breaks, is leaking or is occluded	Immediately discard the Tube Kit.

Customer Service and Product Return Information

If you have any problems with or questions about HALYARD* Equipment, contact our technical support personnel.

Halyard Health
5405 Windward Parkway
Alpharetta, GA 30004 USA
E-mail: PMPorders@hyh.com
1-844-425-9273 (1-844-HALYARD)

Notes

For further detail on the creation of RF lesions in nervous tissue utilizing the Cooled RF Probe, please contact Customer Service and request to speak with a clinical specialist.

In order to return products under limited warranty you must have a return authorization number before shipping the products back to Halyard Health.

Limited Warranty

Halyard Health warrants that these products are free from defects in original workmanship and materials. If these products prove to be defective in original workmanship or original materials, Halyard Health, in its absolute and sole discretion, will replace or repair any such product, less charges for transportation and labor costs incidental to inspection, removal or restocking of product.

This limited warranty applies only to original factory delivered products that have been used for their normal and intended uses. Halyard Health's limited warranty shall NOT apply to Halyard Health's products which have been repaired, altered or modified in any way and shall NOT apply to Halyard Health's products which have been improperly stored or improperly installed, operated or maintained contrary to Halyard Health's instructions. The warranty period for HALYARD* RF Probes and RF Generator Connector Cables is 90 days from the date of purchase, unless otherwise stated.

Disclaimer and Exclusion of Other Warranties

There are no warranties of any kind, which extend beyond the description of the warranties as previously mentioned. Halyard Health disclaims and excludes all warranties, whether express or implied, of merchantability or fitness for a particular use or purpose.

Limitation of Liability for Damages

In any claim or lawsuit for damages arising from alleged breach of warranty, breach of contract, negligence, product liability or any other legal or equitable theory, the buyer specifically agrees that Halyard Health shall not be liable for damages for loss of profits or claims of buyer's customers for any such damages. Halyard Health's sole liability for damages shall be limited to the cost to buyer of the specified goods sold by Halyard Health to buyer which give rise to the claim for liability.

The buyer's use of this product shall be deemed acceptance of the terms and conditions of these limited warranties, exclusions, disclaimers and limitations of liability for money damages.

HALYARD

COOLIEF* COOLED RADIOFREQUENCY (RF) PROBE

FOR GENICULAR PROCEDURES, THIS DOCUMENT SUPPLEMENTS THE INSTRUCTIONS FOR USE DOCUMENT INCLUDED IN THE COOLIEF* COOLED RADIOFREQUENCY KIT

Special Instructions for Use

Prior to administrating this procedure, all patients will have a positive response (≥ 50% reduction in pain) to a diagnostic genicular nerve block.

In a diagnostic genicular nerve block, the targets for the injection of local anesthetic are the superomedial and inferomedial branches of the saphenous nerve and the superolateral branch of the femoral nerve.

Genicular Neurotomy Procedure

Place patient in a supine position on a fluoroscopy table with a pillow under the popliteal fossa to alleviate discomfort.

The true AP fluoroscopic view of the tibiofemoral joint will be obtained to show the tibiofemoral joint space with equal width interspaces on both sides.

An appropriately sized cooled radiofrequency introducer will be placed overlying the affected knee joint and using fluoroscopic guidance the introducer will be advanced to a bony endpoint on the superolateral portion of the femoral condyle of the affected knee (**See Figure 1**).

A second introducer will be advanced to a bony endpoint on the superomedial portion of the femoral condyle.

A third introducer will then be placed over the inferomedial portion of the tibial condyle until a bony endpoint is met. Attempted aspiration should yield no blood.

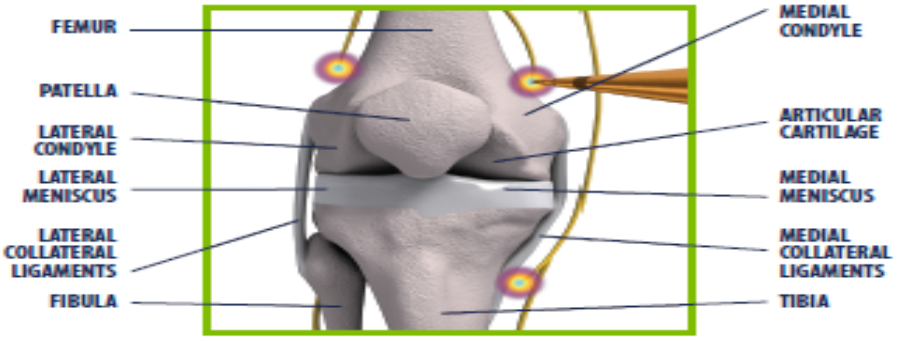


Figure 1

Highlighted areas indicate the three anatomic locations for RF probe placement for genicular neurotomy procedures.

Lateral x-ray views taken during the procedure should show all the introducers and probes at 50% depth of the femur and tibia.

Motor stimulation must be tested at 2.0 volts with no leg movement. Sensory stimulation should be conducted at <0.5 volts in all three locations with concordant pain reproduction. All images must be saved in AP and lateral views.

A mixture consisting of 1% lidocaine should then be slowly injected.

A radiofrequency ablation of each of the three targeted geniculate nerves will be conducted at a set temperature of 60° C for 2 minutes and 30 seconds at each of the 3 anatomic locations.

At the conclusion of the procedure, the introducers and probes will be removed, the insertion sites will be treated with appropriate closure, and the patient will be allowed to properly recover prior to discharge home.

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Halyard Health, Inc., 5405 Windward Parkway, Alpharetta, GA 30004 USA

2017-07-18
15-H2-065-0-00 / 70207974

APPENDIX 2 – SYNVISC-ONE INSTRUCTIONS FOR USE

SYNVISC ONE® **Rx Only**
HYLAN G-F 20
Package contents provided sterile.
Genzyme Biosurgery, a division of Genzyme Corporation
1125 Pleasant View Terrace
Ridgefield, New Jersey 07657
Telephone: 1-888-3-SYNVISC (1-888-379-6847)
www.synvisc.com

Information for Prescribers
Caution: Federal law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

DESCRIPTION
Synvisc-One® (hylan G-F 20) is an elastoviscous high molecular weight fluid containing hylan A and hylan B polymers produced from chicken combs. Hylans are derivatives of hyaluronan (sodium hyaluronate). Hylan G-F 20 is unique in that the hyaluronan is chemically crosslinked. Hyaluronan is a long-chain polymer containing repeating disaccharide units of Na-glucuronate-N-acetylglucosamine.

INDICATIONS FOR USE
Synvisc-One is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, e.g., acetaminophen.

CONTRAINDICATIONS
- Do not administer to patients with known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations.
- Do not inject Synvisc-One in the knees of patients having knee joint infections or skin diseases or infections in the area of the injection site.

WARNINGS
- Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence.
- Do not inject Synvisc-One extra-articularly or into the synovial tissues and capsule.
- Intravascular injections of Synvisc-One may cause systemic adverse events.

PRECAUTIONS
General
- The safety and efficacy of Synvisc-One in locations other than the knee and for conditions other than osteoarthritis have not been established.
- The safety and effectiveness of the use of Synvisc-One concomitantly with other intra-articular injectables have not been established.
- Use caution when injecting Synvisc-One into patients who are allergic to avian proteins, feathers or egg products.
- The safety and efficacy of Synvisc-One in severely inflamed knee joints have not been established.
- Strict aseptic administration technique must be followed.
- STERILE CONTENTS. The syringe is intended for single use. The contents of the syringe must be used immediately after its packaging is opened. Discard any unused Synvisc-One.
- Do not use Synvisc-One if package is opened or damaged. Store in original packaging (protected from light) at room temperature below 86°F (30°C). DO NOT FREEZE.
- Remove any synovial fluid or effusion before injecting Synvisc-One.
- Synvisc-One should be used with caution when there is evidence of lymphatic or venous stasis in the leg to be injected.

Information for Patients
- Provide patients with a copy of the Patient Labeling prior to use.
- Mild to moderate pain, swelling and/or effusion of the injected knee have been reported in clinical trials that were related to intra-articular injection of Synvisc-One. These events were typically transient and usually resolved on their own or with conservative treatment.
- As with any invasive joint procedure, it is recommended that the patient avoid strenuous activities (for example, high-impact sports such as soccer, tennis or jogging) or prolonged weight-bearing activities for approximately 48 hours following the intra-articular injection. The patient should consult his or her physician regarding the appropriate time to resume such activities.

Use in Specific Populations
- **Pregnancy:** The safety and effectiveness of Synvisc-One have not been established in pregnant women.
- **Nursing mothers:** It is not known if Synvisc-One is excreted in human milk. The safety and effectiveness of Synvisc-One have not been established in lactating women.
- **Pediatrics:** The safety and effectiveness of Synvisc-One have not been established in pediatric patients. Pediatric patients are defined as patients ≤ 21 years of age.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH
Reported Device-Related Adverse Events
The most commonly reported adverse events associated with Synvisc-One are the following:
- Arthralgia
- Arthritis
- Arthropathy
- Injection site pain
- Joint effusion

A complete list of the frequency and rate of adverse events identified in the clinical study are provided in the Safety section (Table 3).

Potential Adverse Events
The following adverse events are among those that may occur in association with intra-articular injections, including Synvisc-One
- Arthralgia
- Joint stiffness
- Joint effusion
- Joint swelling
- Joint warmth
- Injection site pain
- Arthritis
- Arthropathy
- Gait disturbance

A complete list of the frequency and rate of adverse events identified in the clinical study are provided in the Safety section (Table 2).

Post-marketing Experience
SYNVISC® (3-injection regimen) post-marketing experience has identified the following systemic events to occur rarely with administration: rash, hives, itching, fever, nausea, headache, dizziness, chills, muscle cramps, paresthesia, peripheral edema, malaise, respiratory difficulties, flushing and facial swelling. There have been rare reports of thrombocytopenia coincident with SYNVISC (3-injection regimen) injection.

Hypersensitivity reactions including anaphylactic reaction, anaphylactoid reaction, anaphylactic shock and angioedema have been reported.

PIVOTAL CLINICAL TRIAL
Study Design
To determine the safety and effectiveness of a single injection regimen of Synvisc-One in the reduction of the pain score in osteoarthritis of the knee, a prospective, randomized, double-blind, 2-arm (parallel group) clinical trial in 21 centers in six European countries was conducted. A total of 253 patients were randomly assigned to study treatment; 123 received 6 mL of Synvisc-One and 130 received 6 mL of Phosphate-Buffered Saline. Neither the patients nor the clinical observers knew the patients' treatment allocations. The outcome measures collected included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; Likert 3.1 A version); patient global assessment (PTGA); clinical observer global assessment (COGA); and use of rescue analgesic (see Treatment and Evaluation Schedule). The intent-to-treat (ITT) population (all patients randomized) was used for the primary analysis. The primary efficacy analysis was a comparison over 26 weeks between the two treatment groups of change from baseline in the WOMAC A (Pain) Subscale (see Patient Population and Demographics), performed by analysis of covariance (ANCOVA).

Patient Population and Demographics
Study patients had primary osteoarthritis of the knee per American College of Rheumatology criteria and were at least 40 years old. The diagnosis was confirmed via recent radiograph showing at least one osteophyte in the target knee. Study patients had continued target knee pain despite use of conservative treatment and analgesics/non-steroidal anti-inflammatory drugs (NSAIDs). Patients with severe disease (Grade IV) per Kellgren-Lawrence criteria, or who had prior arthroplasty in the target knee, were excluded. At the beginning of the study, subjects had moderate or severe target knee pain when walking on a flat surface (on a 5-point Likert scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe 4 = extreme), and an average score of 1.5 to 3.5 on the five questions of the WOMAC A (Pain) Subscale. The WOMAC A Subscale asks study subjects to rate their degree of pain when:

1. Walking on a flat surface
2. Going up and down stairs
3. Resting during the night
4. Sitting or lying
5. Standing upright

Table 1 summarizes the demographics and baseline characteristics. There were no clinically meaningful differences between treatment groups in any baseline parameter.

Treatment and Evaluation Schedule
Initial Treatment Phase
Patients were followed for 26 weeks. Study visits were scheduled for screening, baseline, and weeks 1, 4, 8, 12, 18 and 26. Injections were performed aseptically at the baseline visit after arthrocentesis to withdraw any effusion or synovial fluid present. Patients were not permitted to take long-acting NSAIDs (including cyclo-oxygenase II inhibitors), opioid analgesics or corticosteroids (by any route) during the study, but were permitted to take up to 4 g per day of acetaminophen as needed for "rescue" of injected knee pain. "Rescue" medication was not permitted within 48 hours of any study visit. Injected knee assessment, patient and clinician global assessments (PTGA & COGA), WOMAC and safety evaluations were performed at each study visit.

Repeat Treatment Phase
If patients in either blinded treatment group had at least mild pain in the injected knee at the week 26 visit (and did not experience any significant clinical concerns after the first treatment administration), they were offered an injection of (open-label) Synvisc-One. Those who chose to receive the second injection were followed for 4 weeks for safety only.

Adverse Event Summary
The frequency and type of adverse events (AEs) were similar between the group of patients that received Synvisc-One and the group that received saline control.

Initial Treatment Phase: The overall proportions of patients with Treatment-Emergent AEs regardless of device relatedness (Synvisc-One: n=70, 56.9%; Saline Control: n=79, 60.8%) and with injected knee AEs regardless of device relatedness (Synvisc-One: n=44, 35.8 %; Saline Control: n=44, 33.8 %) were comparable between the two treatment groups (See Table 2). Table 3 lists the incidences of AEs in the injected knee that were assessed by the investigator to be device-related, defined as related to either the study injection or the study treatment.

Device-related AEs involving the injected knee were mild or moderate in nature and were treated symptomatically. There were no serious AEs in the injected knee in either the Synvisc-One or the saline control group.

Repeat Treatment Phase: The repeat treatment phase evaluated the safety profile of the initial phase of patients receiving a second injection of Synvisc-One. One hundred and sixty patients were treated during this phase of the study, of which 77 patients received a second injection of Synvisc-One. Of these 77 patients, 4 (5.2%) experienced five device related AEs in the injected knee. All such events were mild to moderate and were treated symptomatically. These events were arthralgia (n=2), arthritis (n=1), injection hematoma (n=1) and injection site pain (n=1). Patients who developed injected knee AEs during the initial phase of the study, and who subsequently received repeat treatment, did not experience injected knee AEs upon repeat exposure to Synvisc-One.

Overall Injected Knee Safety Summary: The safety profile of Synvisc-One is similar to the Clinical and Post-marketing experience seen with SYNVISC (3 injection regimen) where pain, swelling and effusion were the most frequently occurring AEs in the injected knee.

Cases of acute inflammation, characterized by joint pain, swelling, effusion and sometimes joint warmth and/or stiffness, have been reported following an intra-articular injection of Synvisc-One. Analysis of synovial fluid reveals aseptic fluid with no crystals. This reaction often responds within a few days to treatment with Non Steroidal Anti Inflammatory Drugs (NSAIDs), intra-articular steroids and/or arthrocentesis.

Clinical benefit from the treatment may still be apparent after such reactions.

Adverse Events Outside of the Injected Knee

Overall 101 patients (Synvisc-One: n=47, 38.2%; Saline Control: n=54, 41.5%) experienced at least one AE outside the injected knee regardless of device relatedness. The most commonly occurring (5 % or greater in either group) AEs outside the injected knee were headache, back pain, nasopharyngitis and influenza. In the Synvisc-One group there was one AE of syncope considered device-related.

No new systemic AEs were identified during this study as compared to SYNVISC.

Primary Efficacy Endpoint:

The primary endpoint for the study, the difference between the treatment groups in change from baseline over 26 Weeks in the WOMAC A Pain Score (Table 4) was met.

Synvisc-One also demonstrated superiority to saline control in multiple pre-defined secondary outcome measures, which included PTGA over and at 26 weeks, COGA over and at 26 weeks, and pain while walking on a flat surface (WOMAC A1) over and at 26 weeks (see Figure 1 and Table 5).

The WOMAC A1 responder rate (where response was defined as a 1-or-more category improvement from baseline and the patient did not withdraw from the study) was significantly higher in the Synvisc-One group than in the saline control group. Seventy-one percent (71%) of the patients were responders at week 18 in the Synvisc-One group (versus 54% in the saline control group). At week 26, 64% of patients in the Synvisc-One group were responders, while only 50% of patients in the saline control group were responders.

DETAILED DEVICE DESCRIPTION

Synvisc-One combines the three doses of SYNVISC (hylan G-F 20) which consists of hylan A (average molecular weight 6,000,000 daltons) and hylan B hydrated gel in a buffered physiological sodium chloride solution, pH 7.2. Synvisc-One has an elasticity (storage modulus G') at 2.5 Hz of 111 ± 13 Pascals (Pa) and a viscosity (loss modulus G") of 25 ± 2 Pa (elasticity and viscosity of knee synovial fluid of 18 to 27-year-old humans measured with a comparable method at 2.5 Hz: G' = 117 ± 13 Pa; G" = 45 ± 8 Pa.)

Each 10 mL syringe of Synvisc-One combines the three 2-mL doses (16 mg each) of a complete SYNVISC treatment regimen (48 mg). Each Synvisc-One 10-mL syringe contains:

- Hylan polymers (hylan A + hylan B) 48 mg
- Sodium chloride 51 mg
- Disodium hydrogen phosphate 0.96 mg
- Sodium dihydrogen phosphate monohydrate 0.24 mg
- Water for injection q.s. to 6.0 mL

HOW SUPPLIED

Synvisc-One is supplied in a 10 mL glass syringe containing 3 doses (48 mg) of hylan G-F 20. The contents of the syringe are sterile and non-pyrogenic.

DIRECTIONS FOR USE

Precaution: Do not use Synvisc-One if the package has been opened or damaged. Store in the original packaging (protected from light) at room temperature below 86°F (30°C). DO NOT FREEZE.

Precaution: The syringe containing Synvisc-One is intended for single use. The contents of the syringe must be used immediately after the syringe has been removed from its packaging.

Precaution: Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence.

Synvisc-One is administered as a single intra-articular. Strict aseptic administration technique must be followed.

- Using an 18- to 20-gauge needle, remove synovial fluid or effusion before injecting Synvisc-One.
- Do not use the same syringe for removing synovial fluid and for injecting Synvisc-One; however the same 18- to 20-gauge needle should be used.
- Twist the tip cap before pulling it off, as this will minimize product leakage.
- To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub.

Precaution: Do not over tighten or apply excessive leverage when attaching the needle or removing the needle guard, as this may break the syringe tip.

- Inject the full 6 mL in one knee only.

MANUFACTURED AND DISTRIBUTED BY:
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SYNVISC ONE®
HYLAN G-F 20
PATIENT INFORMATION

Be sure to read the following important information carefully. This information does not take the place of your doctor's advice. If you do not understand this information or want to know more, ask your doctor.

Glossary of Terms

Hyaluronan (pronounced hy-al-u-ROE-nan): is a natural substance that is present in very high amounts in joints. It acts like a lubricant and a shock absorber in the joint and is needed for the joint to work properly.

Non-steroidal anti-inflammatory drugs: also known as "NSAIDs"; medication used to treat pain or swelling. There are many examples of NSAIDs, including (but not limited to) aspirin and ibuprofen. Some of these are over-the-counter drugs, and some can only be obtained by prescription.

Osteoarthritis (pronounced OS-te-o-arth-RI-tis): (OA) is a type of arthritis that involves the wearing down of cartilage (the protective covering on the ends of your bones) and loss of cushioning fluid in the joint

Table of Contents

What is the Synvisc-One® product?

Synvisc-One is a gel-like mixture that comes in a syringe containing 6 mL (1 ½ teaspoon) and is injected into your knee. It is made up of hylan A fluid, hylan B gel, and salt water. Hylan A and hylan B are made from a substance called hyaluronan (pronounced hy-al-u-ROE-nan), also known as sodium hyaluronate that comes from chicken combs. Hyaluronan is a natural substance found in the body and is present in very high amounts in joints. The body's own hyaluronan acts like a lubricant and a shock absorber in the joint and is needed for the joint to work properly.

How is the Synvisc-One® product used? (Indications)

The FDA-approved indication for Synvisc-One is:

Synvisc-One is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g., acetaminophen.

How is the Synvisc-One® product given?

Your doctor will inject Synvisc-One into your knee.

Are there any reasons why I should not receive a Synvisc-One® injection? (Contraindications)

Your doctor will determine if there is any reason why you are not an appropriate candidate for Synvisc-One. You should be aware that Synvisc-One:

- Should not be used in patients who have had any prior allergic reactions to SYNVISC, Synvisc-One or any hyaluronan-based products. Signs of an allergic reaction may include swelling of your face, tongue, or throat; difficulty breathing or swallowing; shortness of breath; wheezing; chest pain; a tightness in your throat; sleepiness; rash; itching; hives; flushing; and/or fever.
- Should not be used in patients with a knee joint infection, skin disease or infection around the area where the injection will be given.

What should my doctor warn me about?

The following are important treatment considerations for you to discuss with your doctor and understand in order to help avoid unsatisfactory results and complications:

- Synvisc-One is only for injection into the knee, performed by a doctor or other qualified health care professional. Synvisc-One has not been tested to show pain relief in joints other than the knee.

- Synvisc-One has not been tested to show better pain relief when combined with other injected medicines.
- Tell your doctor if you are allergic to products from birds such as feathers, eggs, and poultry.
- Tell your doctor if you have significant swelling or blood clots in the leg.
- Synvisc should be used with caution when there is evidence of lymphatic or venous stasis in the leg to be injected.
- Synvisc-One has not been tested in pregnant women, or women who are nursing. You should tell your doctor if you think you are pregnant, or if you are nursing a child.
- Synvisc-One has not been tested in children (≤ 21 years of age).

What are the risks of getting a Synvisc-One® injection?

The side effects (also called reactions) sometimes seen after any injection into the knee, including Synvisc-One, include: pain, swelling, heat, redness, and/or fluid build-up around the knee. These reactions are generally mild and do not last long. Reactions are generally treated by resting and applying ice to the injected knee. Sometimes it is necessary to give pain relievers by mouth such as acetaminophen or NSAIDs, or to give injections of steroids, or to remove fluid from the knee joint. Patients rarely undergo arthroscopy (a surgical inspection of the knee joint) or other medical procedures related to these reactions.

Other side effects seen with SYNVISC or Synvisc-One are: rashes, hives, itching, muscle pain/cramps, flushing and/or swelling of your face, fast heart beat, nausea (or feeling sick to your stomach), dizziness, fever, chills, headache, difficulty breathing, swelling in your arms and/or legs, prickly feeling of your skin, and in rare cases a low number of platelets in the blood (platelets are a type of blood cell that are needed to help your blood clot when you are cut or injured). Allergic reactions, some which can be potentially severe, were observed during the use of Synvisc-One.

Rare cases of knee joint infection have been reported after SYNVISC injections. If any of the above side effects or symptoms appear after you are given Synvisc-One, or if you have any other problems, you should call your doctor.

What are the benefits of getting a Synvisc-One® injection?

As shown in a medical study of 253 patients with osteoarthritis (OA) of the knee, where approximately half received either a single injection of Synvisc-One or an injection of the same volume of salt water (a "Saline Control" injection), the major benefits of Synvisc-One are pain relief and improvement in other symptoms related to OA of the knee.

What do I need to do after I get Synvisc-One® injection?

It is recommended you avoid strenuous activities (for example, high-impact sports such as tennis or jogging) or prolonged weight-bearing activities for approximately 48 hours following the injection. You should consult your doctor regarding the appropriate time to resume such activities.

What other treatments are available for OA?

If you have OA, there are other things you can do besides getting Synvisc-One. These include:

Non-drug treatments

- Avoiding activities that cause knee pain
- Exercise or physical therapy
- Weight loss
- Removal of excess fluid from your knee

Drug therapy

- Pain relievers such as acetaminophen and narcotics
- Drugs that reduce inflammation (signs of inflammation are swelling, pain or redness), such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs, for example ibuprofen and naproxen)
- Steroids that are injected directly into your knee.

When should I call my doctor? (Troubleshooting)

If any of the side effects or symptoms described above appear after you are given Synvisc-One, or if you have any other problems, you should call your doctor.

What did the clinical studies show?

A study was conducted in 6 countries outside the United States with 21 physicians. The patients in the study had mild to moderate knee OA, moderate to severe pain, and did not have sufficient relief of their pain and symptoms with medications taken by mouth.

A total of 253 patients in the study were assigned by chance to receive either a single injection of Synvisc-One (n=123 patients), or an injection of the same volume of salt water (a "Saline Control" injection) (n=130 patients). Neither the patients nor the doctors evaluating them knew which treatment they received. Any fluid that was present in the patient's knee was removed before the injection. The patients were seen by their doctor at standard times over 6 months. Information was collected about how much pain they were experiencing doing various types of activities, how much they were limited in their daily activities by their OA, and on their overall condition. Their doctor also provided an overall rating of their OA.

The main measure of the study was how much pain the subjects had doing five common types of activities over the 6 months duration of the study. Daily activity limitations and overall evaluations were also compared between the group of patients receiving Synvisc-One injection and the group receiving salt water injection. The study showed that patients receiving Synvisc-One had significantly less pain over 6 months, and felt significantly better than the patients who received the salt water injections. The difference in pain score reduction from baseline to 6 months between the Synvisc-One and salt water control injection was 0.15 out of a 5 point scale for the measurement of OA pain in the knee.

What adverse events were observed in the clinical study?

The following are the most common adverse events that occurred during the clinical trial of Synvisc-One:

- Pain in the knee or at the injection site
- Stiffness, swelling or warmth in or around the knee
- Changes in the way that you walk (e.g., limping)

Severe adverse events were not observed in the Synvisc-One trial. Joint infections did not occur in the injected knee in the Synvisc-One clinical trial. The most commonly occurring adverse events outside of the injected knee were headache, back pain, sore throat and the flu. One patient had a single episode of feeling faint.

How do I get more information about the Synvisc-One® product? (User Assistance)

If you have any questions or would like to find out more about Synvisc-One, you may call Genzyme Biosurgery at 1-888-3-SYNVISC (1-888-379-6847) or visit www.synvisc.com.

MANUFACTURED AND DISTRIBUTED BY:

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Table 1. Summary of Demographic and Baseline Characteristics

Parameter/Category	Synvisc-One® (N=124)*	Saline Control (N=129)*	Total (N=253)
Age, n *	124	129	253
Mean (SD)	63.6 (9.6)	62.5 (9.2)	63.0 (9.4)
Range	42, 83	43, 84	42, 84
Sex, n *	124	129	253
Female, n (%)	92 (74%)	88 (68%)	180 (71%)
Race, n *	124	129	253
Caucasian, n (%)	118 (95%)	125 (97%)	243 (96%)
Non-Caucasian, n (%)	6 (5%)	4 (3%)	10 (4%)
Body Mass Index (kg/m²), n	123	129	252
Mean (SD)	29.1 (4.8)	29.8 (5.7)	29.4 (5.4)
Range	20.7, 46.0	19.5, 52.4	19.5, 52.4
Prior Corticosteroids In Target Knee, n†	123	130	253
Yes – n (%)	40 (32%)	31 (24%)	71 (28%)

Table 1. Summary of Demographic and Baseline Characteristics (continued)

Parameter/Category	Synvisc-One® (N=124)*	Saline Control (N=129)*	Total (N=253)
Prior Arthroscopy In Target Knee, n †	123	130	253
Yes – n (%)	26 (21%)	28 (22%)	54 (21%)
Tibio-Femoral Joint Modified Kellgren-Lawrence Numerical Grading System†			
Grade II	63 (51%)	51 (39%)	114 (45%)
Grade III	60 (49%)	78 (60%)	138 (55%)
Grade IV	0	1 (1%)	1 (0%)
Total WOMAC Score (0–96); Mean (SD) *	55.1 (10.5)	54.8 (9.4)	
WOMAC A Score (0–4); Mean (SD) *	2.30 (0.43)	2.25 (0.41)	
PTGA – Mean (SD) (0–4) *	2.57 (0.67)	2.50 (0.64)	
COGA – Mean (SD) (0–4) *	2.44 (0.76)	2.49 (0.75)	

*ITT Population
†Safety Population

Table 2: Patients with Adverse Events in the Injected Knee Regardless of Relatedness

MedDRA Preferred Term	Synvisc-One® N=123 n (%)	Saline Control N=130 n (%)
Any Treatment-Emergent Adverse Event	44 (35.8%)	44 (33.8%)
Arthralgia	31 (25.2%)	28 (21.5%)
Joint stiffness	10 (8.1%)	13 (10.0%)
Joint effusion	7 (5.7%)	7 (5.4%)
Joint swelling	5 (4.1%)	7 (5.4%)
Joint warmth	2 (1.6%)	5 (3.8%)
Post-traumatic pain	0	3 (2.3%)
Injection site pain	1 (0.8%)	1 (0.8%)
Synovial cyst	0	2 (1.5%)
Arthritis	1 (0.8%)	0

Table 2: Patients with Adverse Events in the Injected Knee Regardless of Relatedness (continued)

MedDRA Preferred Term	Synvisc-One® N=123 n (%)	Saline Control N=130 n (%)
Arthropathy	1 (0.8%)	0
Gait disturbance	1 (0.8%)	0
Joint range of motion decreased	0	1 (0.8%)
Ostheoarthritis	0	1 (0.8%)

Note: Patients are counted once for each unique AE regardless of device relatedness, and may have had more than one unique AE.

Table 3: Patients with Device-Related Adverse Events in the Injected Knee

MedDRA Preferred Term	Synvisc-One® N=123 n (%)	Saline Control N=130 n (%)
Any Device-Related Adverse Event	7 (5.7%)	4 (3.1%)
Arthralgia	2 (1.6%)	3 (2.3%)
Arthritis	1 (0.8%)	0
Arthropathy	1 (0.8%)	0
Injection site pain	1 (0.8%)	1 (0.8%)
Joint effusion	2 (1.6%)	0

Note: Patients are counted once for each unique AE, and may have had more than one unique AE.

Table 4. Primary Efficacy Results: WOMAC A (Pain) Score Overall Change from Baseline over 26 Weeks – ITT Population

	Baseline Mean (SE) (0–4 Scale)	Mean Post-treatment (SE) (0–4 Scale)	Estimated Change (SE)	Estimated Difference from Saline Contol (95% CI)	p-value (ANCOVA)
Synvisc-One® (n=124)	2.30 (0.04)	1.43 (0.06)	-0.84 (0.06)	0.15 (-0.302, -0.002)	0.047
Saline Control (n=129)	2.25 (0.04)	1.59 (0.06)	-0.69 (0.06)		

WOMAC A scale using 5 point Likert scale, where 0 = no pain and 4 = extreme pain
Repeated measures Analysis of Covariance was used for the WOMAC A pain score change from the baseline.

Table 5. Clinical Meaning of Secondary Efficacy Endpoints

	Odds Ratio*		Definition	Explanation
Generalized Estimating Equation for categorical data				
WOMAC A1	*Over 26 weeks*	0.64‡	The odds (probability [Worse] / Probability [Better]) for Synvisc-One for over 26 weeks and at 26 weeks is approximately 64%, and 56%, respectively, to the odds for control.	Synvisc-One patients were 1.56 times more likely to self-report pain relief while walking on a flat surface compared to those patients treated with saline control over 26 weeks and 1.79 times more likely to self-report pain relief while walking on a flat surface compared to those patients treated with saline control at 26 weeks.
	At week 26	0.56‡		
PTGA	*Over 26 weeks*	0.69‡	The odds (probability [Worse] / Probability [Better]) for Synvisc-One for over 26 weeks and at 26 weeks is approximately 69% and 51%, respectively, to the odds for control. PTGA: Patient Global Assessment has 5 scales (Very well, Well, Fair, Poor, Very poor)	Synvisc-One patients were 1.45 times more likely to self-report improvement in overall health status compared to those patients treated with saline control over 26 weeks and 1.96 times more likely to self-report improvement in overall health status compared to those patients treated with saline control at 26 weeks.
	At week 26	0.51‡		
COGA	*Over 26 weeks*	0.71‡	The odds (probability [Worse] / Probability [Better]) for Synvisc-One for over 26 weeks and at 26 weeks is approximately 71%, and 56%, respectively, to the odds for control. COGA: Clinical Observer Global Assessment has 5 scales (Very well, Well, Fair, Poor, Very poor)	Blinded clinical observers were 1.41 times more likely to assess patients treated with Synvisc-One as showing overall improvement in disease status compared to those patients treated with saline control over 26 weeks and 1.79 times more likely to assess patients treated with Synvisc-One as showing overall improvement in disease status compared to those patients treated with saline control at 26 weeks.
	At week 26	0.56‡		
OMERACT-OARSI Responder	*Over 26 weeks*	0.66	This response analysis did not reach statistical significance between the treatment groups.	
	At week 26	0.69		

Table 5. Clinical Meaning of Secondary Efficacy Endpoints (continued)

	Odds Ratio*		Definition	Explanation
Generalized Estimating Equation for categorical data				
Estimate of Treatment Difference (Analysis of Covariance)				
WOMAC C	*Over 26 weeks*	-0.18	The study did not show a statistically significant difference in functional improvement between the treatment groups.	
	At week 26	-0.11		

Odds ratio = (Probability [Worse] / Probability [Better]) for Synvisc-One / Probability [Worse] / Probability [Better]) for Control If odds ratio <1, then in favor of Synvisc-One
*Odds ratio = Odds for Synvisc-One/Odds for control
†Statistically significant at the 5% significance level; not adjusted for multiplicity

Figure 1: Plot for Categorical Secondary Endpoints – ITT Population

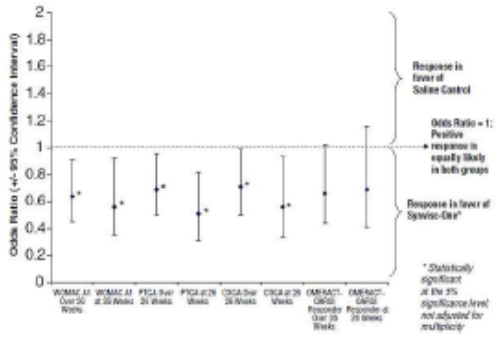
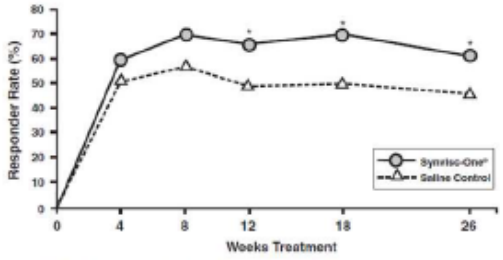


Figure 2: Patient Responder Rate on WOMAC A1 (Walking Pain) -ITT Population



Note: Analyzed using generalized estimating equation (GEE) for binary outcomes
* Statistically significant at the 5% significance level; not adjusted for multiplicity

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