AVANOS

Confidential

SInergy
Protocol # 105-17-0002

1 TITLE PAGE

Title:	**A Prospective, Multi-center, Randomized, Assessor Blind, Controlled Study Comparing Lateral Branch Cooled Radiofrequency Denervation to Conservative Therapy as Treatment for Sacroiliac Joint Pain in a Military and Civilian Population.**
Investigational Product:	**SInergy System**
Indication:	**Sacroiliac Joint Back Pain**
Protocol number:	**105-17-0002**
Protocol Date/Version:	**28Nov2018**
Sponsor:	**Avanos**
Medical Monitor:	**Kevin Friedman, DO** **Medical Director** **Avanos** **5405 Windward Parkway** **Alpharetta, GA 30004** **Phone: (470) 448-5405** **Email:** kevin.friedman@hyh.com
Lead Principal Investigator	**Steven Cohen, MD**

This study will be conducted per the protocol and in compliance with Good Clinical Practice (GCP) and with other applicable regulatory requirements.

Confidentiality Statement

This document is a confidential communication from Avanos. Acceptance of this document constitutes an agreement by the recipient(s) that no published information contained herein will be published or disclosed without prior written approval from AVANOS, except that this document may be disclosed to appropriate Investigational Review Boards (IRBs) or Independent Ethics Committees (IECs) under the condition that they are also required to maintain confidentiality.

Investigator Acknowledgement Signature Page

Title: A Prospective, Multi-center, Randomized, Assessor Blind, Controlled Study Comparing Lateral Branch Cooled Radiofrequency Denervation to Conservative Therapy as Treatment for Sacroiliac Joint Pain in a Military and Civilian Population

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

AVANOS

Confidential

SInergy
Protocol # 105-17-0002

Study Contact List

For questions regarding the conduct of this study, please contact:

Sponsor Contact:

William A Keck
Clinical Program Manager
Global Clinical Affairs
Avanos Medical
Phone: (470) 448-5509
Email: william.keck@hyh.com

For questions regarding safety or to report a serious adverse event, please contact:

Medical Monitor:

Kevin Friedman, DO
Medical Director
Avanos Medical
5405 Windward Parkway
Alpharetta, GA 30004
Phone: (470) 448-5405
Email: kevin.friedman@hyh.com

2 SYNOPSIS

Protocol Title	**A Prospective, Multi-center, Randomized, Assessor Blind, Controlled Study Comparing Lateral Branch Cooled Radiofrequency Denervation to Conservative Therapy as Treatment for Sacroiliac Joint Pain in a Military and Civilian Population.**
Protocol Number	105-17-0002
Study Device	The device evaluated in this protocol is the Coolief* SInergy Cooled Radiofrequency Kit (CRF) device for sacroiliac joint denervation. The CRF system is indicated for use to create radiofrequency (RF) lesions in nervous tissue. The CRF works to relieve sacroiliac joint (SIJ) pain by creating a specified precise lesion set resulting in targeted nerve ablation.
Study Design	This is a prospective, randomized, controlled, multi-center clinical study. Approximately 208 subjects will be enrolled at approximately 12-15 active duty military, veterans' care, and civilian sites. Eligible subjects will be randomized in 1:1 ratio to receive either Sacroiliac denervation using CRF (treatment group) or standard medical management ("SMM," control group).
Primary Objective	The primary objective of this protocol is to evaluate the effectiveness of CRF denervation of the sacroiliac region using CRF as a treatment for sacroiliac joint pain as compared to SMM at 3 months post randomization & treatment.
Secondary Objectives	The secondary objectives of this study are to: - To confirm the safety of CRF denervation as compared to SMM. - To characterize the economic impact of this treatment as compared to SMM.
Measures of Assessment	All endpoints will be assessed at Baseline, 1, 3, 6, 9, 12 months. Average (usual) daily pain as assessed by Numeric Rating Score (NRS – also assessed at treatment visits) - Physical functioning status evaluated using SF-36 - Functional status change evaluated using Oswestry Disability Index (ODI) - Assessment of EQ-5D-5L as a measure of health/economic status - Health care utilization questionnaire: o Physician office visits o ER visits o Hospitalization o Surgery o Other treatments (PT, Chiropractor visits, acupuncture, sacroiliac joint injections, etc.) - Analgesic usage including Opioid Following treatment, the additional endpoints will be assessed at 1, 3, 6, 9, 12 months by blinded assessors: - Patient Global Impression of Change (PGIC) - Return to work/duty - "Return-of-Pain" date

Protocol Title	**A Prospective, Multi-center, Randomized, Assessor Blind, Controlled Study Comparing Lateral Branch Cooled Radiofrequency Denervation to Conservative Therapy as Treatment for Sacroiliac Joint Pain in a Military and Civilian Population.**
Protocol Number	105-17-0002
Evaluation Schedule	Subjects who qualify for the study and are randomized to treatment group, will return for evaluation on the following schedule based off their treatment date: Screening/Baseline, Treatment, 1-Month (30 days ±7 days), 3-Month (90 days ±14 days), 6-Month (180 days ±14 days), 9-Month (270 days ±14 days), 12-Month (360 days ±14 days). Three months following randomization, subjects who were assigned physician prescribed medical management and are considered treatment failures (reporting a rating of less than 5 (Moderately better, and a slight but noticeable change) on PGIC) can elect to crossover and receive the SInergy procedure, or can opt to remain with conservative therapy for the duration of the study. Subjects who elect to crossover will be followed for 12 months post-SInergy treatment (1, 3, 6, 9 and 12 months post cross over). The study will be considered complete with regard to **all** endpoints after all enrolled subjects have completed a 12-month follow-up evaluation (starting from the time of randomization), have died, have documented premature discontinuation, or the follow-up window for final visit is closed.
Control	The control arm will utilize physician prescribed standard medical management (SMM). For this protocol, this includes, but is not limited to, medications, physical therapy, lifestyle changes, acupuncture, yoga, chiropractic and therapeutic injections into the SI ligaments or joint cavity. To standardize follow up for the control group, no acupuncture or injection will be allowed within 4 weeks prior to a study follow-up visit.
Safety Parameters	All subjects will be evaluated for AEs and serious AEs (SAEs) at each visit. Safety will be assessed for all subjects over 12 months following randomization of subjects to either the CRF or SMM treatment group. Information on pain related concomitant medications will be collected.
Inclusion Criteria	1. Age greater than or equal to 21 years. 2. Able to understand the informed consent and able to complete outcome measures 3. Sacroiliac joint pain that is refractory to standard of care treatments such as non-steroidal anti-inflammatory drugs, physical therapy, etc. 4. At least 1 positive sacroiliac joint pain provocation test (Distraction, Gaenslen's, FABER, Sacral Sulcus tenderness, thigh thrust, Compression or Sacral Thrust) 5. Back pain is predominantly below the L5 vertebrae 6. Chronic low back pain lasting for longer than three months 7. ≥50% pain relief lasting for the expected duration of anesthetic or medication from a therapeutic or diagnostic sacroiliac joint injection 8. ≥50% pain relief lasting duration of anesthetic from Lateral Branch Block (LBB) (done on different days than SIJ injection) 9. Stabilized on pain medication regimen for > 2 months as defined by a <10% change in dosage

Protocol Title	**A Prospective, Multi-center, Randomized, Assessor Blind, Controlled Study Comparing Lateral Branch Cooled Radiofrequency Denervation to Conservative Therapy as Treatment for Sacroiliac Joint Pain in a Military and Civilian Population.**
Protocol Number	105-17-0002
	10. NRS indicating a usual pain score of $\geq$ 4 over the last 7 days. (returned to pre-LBB baseline pain). 11. All other possible sources of low back pain have been ruled out as the primary pain generator, including but not limited to: suspected advanced Degenerative Joint Disease, the intervertebral discs, bone fracture, the zygapophyseal joints, the hip joint, symptomatic spondylolisthesis, tumor, and other regional soft tissue structures (this is done by physical exam, medical history, and MRI/CT/X-ray as required) 12. Willing to utilize double barrier contraceptive method if of child bearing potential 13. Willingness to provide informed consent and to comply with the requirements of this protocol for the full duration of the study 14. Physician believes CRF ablation of the Sacroiliac Joint is an appropriate treatment for the patient.
Exclusion Criteria	1. Poorly controlled severe psychiatric illness or ongoing psychological barriers to recovery, as determined by the treating physician 2. Spinal pathology that may impede recovery such as spina bifida occulta, grade II or higher spondylolisthesis at L5/S1, or scoliosis. 3. Symptomatic moderate or severe foraminal or central canal stenosis 4. Systemic infection or localized infection at anticipated introducer entry site. 5. Uncontrolled immunosuppression (e.g. Acquired Immune Deficiency Syndrome [AIDS], cancer, diabetes, etc.) 6. Chronic severe conditions such as rheumatoid/inflammatory arthritis 7. Pregnancy or recent delivery (within 3 months) 8. Active radiculopathy pain from lumbar spine 9. Active Hip Pathology 10. Major Surgery within 3 months prior to signing informed consent 11. Prior radiofrequency denervation of the lateral sacral nerves. 12. Ongoing/ unresolved Worker's compensation, injury litigation, military medical board, or disability remuneration claims 13. Allergy to injectants or medications used in procedure 14. Body mass index (BMI) > 40 kg/m^2 15. Current prescribed opioid medications equivalent to 90mg of morphine per 24 hours or greater 16. Subject currently implanted with pacemaker, stimulator, or defibrillator. 17. Participation in another clinical trial/investigation that could interfere with this trial 30 days prior to signing informed consent. 18. Subject unwillingness or unable to comply with protocol requirements
Recommended Medication Therapy	During the CRF ablation procedure subjects will not be under general anesthesia, but should be under local intravenous (IV)/sedation or monitored anesthesia care, Medications are at the Investigator's discretion.

Protocol Title	**A Prospective, Multi-center, Randomized, Assessor Blind, Controlled Study Comparing Lateral Branch Cooled Radiofrequency Denervation to Conservative Therapy as Treatment for Sacroiliac Joint Pain in a Military and Civilian Population.**
Protocol Number	105-17-0002
	Following the CRF procedure, treatment will be administered at the Investigator's discretion. It is anticipated that subjects will also be prescribed a short course of post-op analgesics per institutions' standard of care.

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	Degrees Celsius
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of Variance
AP	Anterior-Posterior
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case Report Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D-5L	Instrument for measuring health-related quality of life developed by EuroQoL
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IDET	Intradiscal Electrothermal Therapy
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat; also known as intention-to-treat
IV	Intravenous
min	Minute
MRI	Magnetic Resonance Imaging
NRS	Numeric Rating Scale
ODI	Oswestry Disability Index
PGIC	Patient Global Impression of Change
RF	Radiofrequency
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	SF-36v2® Health Survey, an instrument to measure general health
SIJ	Sacroiliac Joint
SIS	Spine Intervention Society
TAP	Thermal Annular Procedures
TEAE	Treatment Emergent Adverse Event

5 INTRODUCTION

Background

History

Mechanical low back pain is one of the top reasons for physician visits and disability in the United States, with an overall prevalence of 60 to 80%[1]. Most LBP resolves with rest and conservative therapy, but for up to 10% of patients, LBP becomes an intractable, chronic condition[2, 3]. The sacroiliac joint is the source of chronic LBP in up to 30% of these patients[4]. Though the posterior lateral branches of the dorsal rami of the sacral nerves at S1, S2, and S3 are generally considered to be the primary innervations, significant variability exists between and even within patients[5, 6].

Many pharmacological and non-pharmacological treatment options exist for the management of lower back pain emanating from the sacroiliac joint. Drug therapies include acetaminophen, non-steroidal anti-inflammatory drugs, muscle relaxants, tricyclic antidepressants, benzodiazepines, tramadol, and opioids. In most cases, the choice of medication depends on the severity and duration of a patient's pain. Non-pharmacological therapies can be classified as invasive or non-invasive. Non-invasive procedures include spinal manipulation, exercise therapy, massage, acupuncture, yoga, cognitive-behavioral therapy, and progressive relaxation. Invasive procedures include epidural injections, percutaneous adhesiolysis, lumbar epidural adhesiolysis, sacroiliac joint interventions, facet joint nerve blocks, open and minimally invasive surgeries, spinal cord stimulation, implantable intrathecal devices, and thermal annular procedures[7, 8]. Evaluation of these treatments specifically for the SIJ are limited[9, 10], and results for non-specific LBP are often extrapolated to the SIJ.

Treatment for SI joint pain are varied in their degree and duration of effectiveness. In randomized studies evaluating peri- and intra-articular corticosteroid injections in patients suspected of having SI joint pain, early results show benefit but long-term results are lacking[11, 12, 13, 14]. Studies evaluating conservative therapies are similarly marred by the lack of controlled studies and relevant pre-treatment diagnostic work-ups[15].

The use of radiofrequency for nerve ablation has been in practice since 1931 (Standard RF)[16]. This procedure uses a probe specifically placed adjacent to/on top of the nerve targeted for ablation. The heating zone for standard RF, however, is limited to the area adjacent to the probe tip, so placement must be exact[17, 18, 19]. Anatomical restraints prevent standard RF from being functional to correct this situation therefore, an alternative option is needed.

Halyard developed a modified RF electrode which is internally cooled through the circulation of water through the probe (Coolief* Cooled Radiofrequency, "CRF"). The water circulation prevents the probe tip itself from reaching high temperatures that inhibit lesion growth. The result is the creation of a larger,

more spherical lesion that extends distally from the probe tip, which is not reproducible with Standard RF. This expanded heated zone and distal projection of heat allows for greater ease of use by the physician and increases the chances of ablating a greater portion of the targeted nerve. The large size and shape of lesion also removes the issue of anatomical variation that can limit access to targeted nerves with Standard RF.

Summary of Research

The SInergy System has been investigated in a clinical setting to determine its ideal treatment parameters and to evaluate its safety and effectiveness. A study was conducted to monitor the temperature while treating subjects using the SInergy system. It was concluded that when the probe is placed at the correct distance (7 mm) from the edge of the foramen, it is highly unlikely that neurodestructive heating will occur at the level of the segmental spinal nerves.[20] The study also determined that the SInergy System provides appropriate temperatures for neuroabalation in the region lateral to the sacral foramina while temperatures in the region of the spinal nerve remain safe.

Independent anatomical work by Roberts et al 2014 confirmed significant anatomical variability of nerve course through the SI joint complex and suggested that maximizing the lesion area should be the goal of SIJ RFA and that monopolar electrodes designed to create an expanded thermal lesion distal to the tip of the electrode, such as cooled RF and multitoned expandable electrodes, may be best suited for SIJ RFA.[6]

A second independent anatomical analysis by Cox et al 2014 also revealed widespread variability of lateral branch exit points from the dorsal sacral foramen and concluded that SIJ RFA treatment approaches need to incorporate techniques which address the diverse SIJ innervation.[5]

Clinical outcome studies for cooled RF have generally shown positive results. Cohen et al.[21] demonstrated that at 1,3 and 6 months, following the procedure, 79%, 64% and 57% the patients treated with the SInergy System, respectively, experienced pain relief of 50%, or greater and significant functional improvement. For the placebo group, only 14% and 0% experienced similar pain relief, at 1 and 3 months, respectively. A case series, published by Kapural et al[22], that included 27 patients who underwent cooled RF of S1, S2, S3 lateral branches of a dorsal ramus (DR) L5, indicated significant improvements in patient's pain scores and the ability to perform everyday functions, at 3 to 4-month follow ups. At 3 to 4-month follow ups, 13 of 26 patients (50%) had at least a 50% reduction in NRS pain scores. The mean NRS scores for all of the patients decreased from 7.1$\pm$1.6 to 4.2+2.5 ($P<0.001$). Furthermore, using Global Perceived Effect (GPE) to measure improvement in pain, 18 patients (67%) rated their improvement in pain as improved or much improved, compared to 8 patients (30%) that rated their pain improvement as minimal or no improvement.

Patel and colleagues[23, 24]published interim and long-term (1 year) results of a prospective, randomized, placebo-controlled study to assess the outcomes of lateral branch neurotomy with cooled radiofrequency in patients with sacroiliac joint pain. They reported a statistically significant difference in success rates at 3 months follow-up, with 47% of patients in the cooled RFA treatment group and 12% of patients in the sham treatment group experiencing a successful outcome (P=0.015). Results were durable to 12 months, with improvements in NRS pain score, ODI score, and SF-36 physical function maintained at this visit.[24]

Additional non-Randomized, non-Controlled studies have expressed consistent and durable results as noted above. In a large retrospective study (N=126) Stelzer et al. found that 48% of patients maintained a >50% reduction in pain at 12 months and 67% stopped or decreased use of opioids. [25] Dr. Ho et al. followed 20 patients for 2 years and concluded that cooled radiofrequency denervation showed long term efficacy for up to 2 years in the treatment of sacroiliac joint pain. [26]

Rationale

A significant need exists across the medical literature for rigorous, well-defined comparative effectiveness research[27, 28]. Since two controlled RCTs evaluating cooled RF treatment of sacroiliac joint pain have been completed comparing against sham,[21, 23] a randomized controlled study comparing cooled RF denervation of the sacroiliac joint to the generally prescribed standard medical management will provide the most relevant information to help confirm the effectiveness of the treatment for SIJ pain.

Device Description and Intended Use

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.

Effective May 2018, Halyard Health changed its name to Avanos Medical.

A board-certified physician who is familiar with the anatomy of the sacroiliac joint, having experience of image-guided spine procedures should perform or supervise the procedure.

The following is a summary description of the disposable components being provided for the study (Study Device). The COOLIEF™ system components utilized in the study are the same in form and function regardless of specific product branding (COOLIEF* or SInergy*). For additional information, please refer to the Coolief* SInergy* Cooled Radiofrequency Kit “Instructions for Use” (Appendix 1).

- 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* SINERGY* Cooled Radiofrequency (RF) Probe. It includes a burette and tubing.
- HALYARD* COOLIEF* Cooled Radiofrequency Introducer or Fluid Delivery Introducer (sterile, single use): It is to be used with the HALYARD* COOLIEF* Probes only. The COOLIEF* Introducer provides a path for the COOLIEF* Probe to the nervous tissue.
- HALYARD* COOLIEF* Cooled Radiofrequency Probe (sterile, single use): It is inserted through a COOLIEF* Introducer into or near nervous tissue. Sterile water circulates internally to cool the COOLIEF* Probe while it delivers radiofrequency energy. A thermocouple in the COOLIEF* Probe measures cooled electrode temperature throughout the procedure. The active tip extends 4 mm from the introducer and delivers the energy. The “Cooled RF Set Temp” (Default Setting T = 60˚C) displayed on the COOLIEF* RF Generator refers to the cooled electrode temperature and does not reflect the immediate surrounding tissue temperature. The heat generated from the radiofrequency energy produces thermal energy with average maximum tissue temperatures greater than 80˚C.
- HALYARD* COOLIEF* SINERGY* EPSILON* Ruler (sterile, single use): it is a stainless steel, circular, ruler with a 10mm radius. It is placed on the skin over the treatment site during the procedure.
- HALYARD* COOLIEF* SINERGY* Radiofrequency QUICKCLAMP* Device (sterile, single use): It is placed on the skin over the treatment site during the procedure. It can be optionally used to support the COOLIEF* SINERGY* Introducer and Probe.

The probe is comprised of an electrically insulated shaft with a 4-mm active tip that functions as an electrode for RF energy delivery, a handle with a luer locking mechanism to connect the respective introducer, 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 EPSILON* Ruler is a stainless steel, circular, ruler with a 10mm radius to aid in placement. The QUICKCLAMP* Device is a plastic mechanism that can be used to support the probe and introducer during the procedure. The Probe, Introducer, Tube Kit, EPSILON* Ruler and QUICKCLAMP* Device 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 Coolief* Sinergy* Cooled Radiofrequency Kit Instructions for Use (IFU) documents (appendix 1) are included in each kit.

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

Primary Objective

The primary objective of this protocol is to evaluate the effectiveness of CRF denervation of the sacroiliac region using CRF as a treatment for sacroiliac joint pain as compared to standard medical management (SMM) at 3 months post randomization and treatment.

Secondary Objectives

The secondary objectives of this study are to:

- To confirm the safety of CRF denervation as compared to SMM.
- To characterize the economic impact of this treatment as compared to SMM.

6 INVESTIGATIONAL PLAN

Study Design

Study Type

This study will be a 12-month prospective, randomized, controlled, prospective, open-label, multi-center clinical study. Adult subjects over the age of 21 with diagnosed chronic intractable sacroiliac joint pain (≥ 3 months), who have been previously unresponsive to conservative therapy and who meet the selection criteria are eligible to participate in this study. Approximately 208 subjects will be enrolled at up to 15 sites in a 1:1 randomization ratio to receive either denervation using the SInergy System (CRF, treatment group) or standard medical management (SMM, control group). Follow-up will be conducted for a total of 12 months post Coolief procedure with the primary endpoint being completed at month 3.

The control arm will utilize physician prescribed standard medical management (SMM). For this protocol, this includes, but is not limited to, medications, physical therapy, lifestyle changes, acupuncture, yoga, chiropractic, and therapeutic injections.

In order to maintain the single blind for the study, each site will need to pro-actively assign Treating Investigators and Blinded Assessors for the study. Treating Investigators will need to be responsible for all screening, randomization, and initial treatment procedures. Blinded Assessors will be responsible for all follow-up visits starting with the Month 1 visit. Treating investigators can be blinded assessors for subjects they did not treat, but care will be needed to ensure the blind is maintained through the 3-month time point.

An optional crossover-to-treatment design was adopted for subjects randomized to standard medical management after their 3-month visit because it would be considered unethical to withhold treatment that

could potentially offer pain relief to those subjects undergoing standard medical management who continue to suffer from pain.

Full eligibility requirements are described in Inclusion/Exclusion criteria, but from a high level, to be eligible for the trial, at a minimum, BOTH of the following must have occurred:

- ≥50% pain relief lasting for the expected duration of anesthetic or medication from a therapeutic or diagnostic sacroiliac joint injection; AND
- ≥50% pain relief lasting for the expected duration of anesthetic from a standardized set of Lateral Branch Blocks (LBB), with total volume of no more than 2 mL of 0.5% Bupivacaine, Ropivacaine (or similar). Ideally, 2 mL should be divided equally along the lesion line (Figure 1) to mimic lesioning as described in the "Timing and Use of Study Devices" section below.

As illustrated in Figure 1, the study consists of a screening period followed by a 12-month follow-up period. It is expected that the Informed Consent Form will be presented after subjects have responded successfully to a sacroiliac joint injection, but before lateral branch blocks.

Baseline evaluation will be done after ICF, but before randomization and subjects who successfully meet the criteria for inclusion will be randomized. Randomization should occur within 45 days of ICF. A subject is considered enrolled once they have been randomized. Day 0 for control group will be considered the day of randomization. Day 0 for the treatment group will be designated as the day that Cooled RF treatment is performed.

The subjects in the treatment group should be scheduled for a CRF treatment to be administered within 30 days of randomization. If therapeutic injections are prescribed for the control group, the subjects enrolled in the control group should be scheduled for their injections (if applicable) as soon as possible post randomization (per standard of care) to adhere to study visit windows. To standardize follow up for the control group, no acupuncture or injection will be allowed within 4 weeks (30 days) prior to a study follow up visit.

After the CRF treatment (Day 0), the CRF treatment group subjects will visit the blinded assessor for follow up at 1, 3, 6, 9, and 12 months following treatment (Day 0) as described in Figure 1.

At the Month 3 visit (three months post randomization), subjects initially randomized to the conservative therapy group will be assessed to determine eligibility to receive CRF treatment.

- Subjects who were assigned physician prescribed medical management and have a rating of less than 5 (Moderately better, and a slight but noticeable change) on PGIC can elect to cross over and receive the SInergy procedure, or can opt to remain with conservative therapy for the duration of the study.

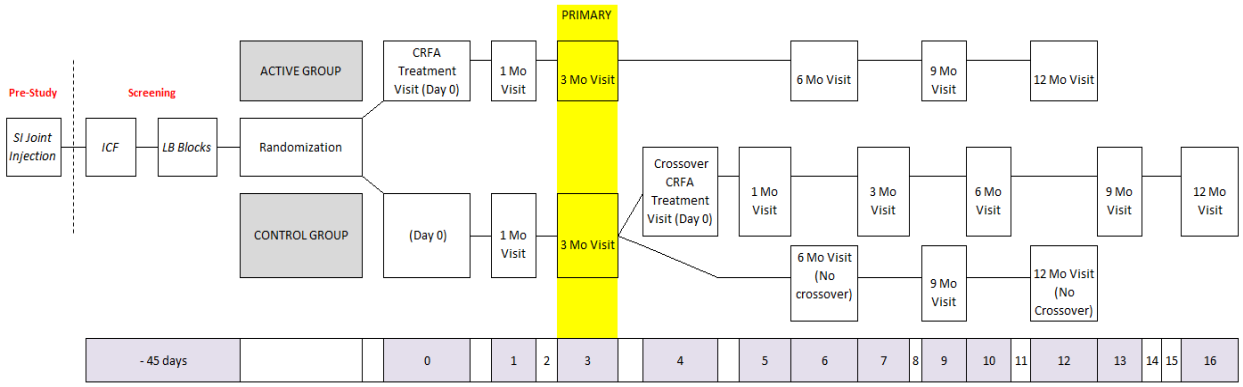
- Subjects who choose to cross over will ideally receive treatment within 30 days of their 3-month visit but they must receive treatment within 90 days of their 3-Month Visit. They will then be followed-up at 1, 3, 6, 9 and 12 months following CRF denervation (new Day 0).
- If the conservative treatment group subjects refuse or do not qualify for Cooled RF treatment at 3 months, they will subsequently be followed-up at 6, 9 and 12 months from their Day 0 (randomization date).

Regardless of randomization group, the management of pain with conservative therapy will be at the discretion of the physician.

Primary Analysis is planned after all initially treated subjects have completed their 3 Month post procedure visit as described in section 8 (Primary Analysis).

Data will also be reviewed after all treated subjects complete their 12-month visits post treatment.

Figure 1: Study Design



Selection of Study Population

The study population will consist of subjects who have experienced chronic sacroiliac joint pain that is not relieved substantially by their current non-surgical treatment regimen (pain NRS score between 4 and 9).

Subjects will meet the following inclusion and exclusion criteria:

Inclusion criteria

1. Age greater than or equal to 21 years.
2. Able to understand the informed consent and able to complete outcome measures.

3. Sacroiliac joint pain that is refractory to standard of care treatments such as non-steroidal anti-inflammatory drugs, physical therapy, etc.
4. At least 1 positive sacroiliac joint pain provocation test (Distraction, Gaenslen's, FABER, Sacral Sulcus tenderness, thigh thrust, Compression or Sacral Thrust).
5. Back pain is predominantly below the L5 vertebrae.
6. Chronic low back pain lasting for longer than three months.
7. >50% pain relief lasting for the expected duration of anesthetic or medication from a therapeutic or diagnostic sacroiliac joint injection.
8. >50% pain relief lasting duration of anesthetic from Lateral Branch Block (done on different days than SIJ injection).
9. Stabilized on pain medication regimen for > 2 months as defined by a <10% change in dosage.
10. NRS indicating an usual pain score of ≥ 4 over the last 7 days (returned to pre-LBB baseline pain).
11. All other possible sources of low back pain have been ruled out as the primary pain generator, including but not limited to: suspected advanced Degenerative Joint Disease, the intervertebral discs, bone fracture, the zygapophyseal joints, the hip joint, symptomatic spondylolisthesis, tumor, and other regional soft tissue structures (this is done by physical exam, medical history, and MRI/CT/X-ray as required).
12. Willing to utilize double barrier contraceptive method if of childbearing potential.
13. Willingness to provide informed consent and to comply with the requirements of this protocol for the full duration of the study.
14. Physician believes CRF ablation of the Sacroiliac Joint is an appropriate treatment for the patient.

Exclusion criteria

1. Poorly controlled severe psychiatric illness or ongoing psychological barriers to recovery, as determined by the treating physician.
2. Spinal pathology that may impede recovery such as spina bifida occulta, grade II or higher spondylolisthesis at L5/S1, or scoliosis.
3. Symptomatic moderate or severe foraminal or central canal stenosis.
4. Systemic infection or localized infection at anticipated introducer entry site.
5. Uncontrolled immunosuppression (e.g. Acquired Immune Deficiency Syndrome [AIDS], cancer, diabetes, etc.).
6. Chronic severe conditions such as rheumatoid/inflammatory arthritis.
7. Pregnancy or recent delivery (within 3 months).
8. Active radiculopathy pain from lumbar spine.
9. Active Hip Pathology.

10. Major Surgery within 3 months prior to signing informed consent.
11. Prior radiofrequency denervation of the lateral sacral nerves.
12. Ongoing/ unresolved Worker's compensation, injury litigation, military medical board, or disability remuneration claims.
13. Allergy to injectants or medications used in procedure.
14. Body mass index (BMI) > 40 kg/m^2
15. Current prescribed opioid medications equivalent to 90mg of morphine per 24 hours or greater.
16. Subject currently implanted with pacemaker, stimulator, or defibrillator.
17. Participation in another clinical trial/investigation that could interfere with this trial 30 days prior to signing informed consent.
18. Subject unwillingness or unable to comply with protocol requirements.

Screening Phase

Any ancillary potential sources of spinal pain should also have been eliminated including but not limited to: the intervertebral discs, bone fracture, the zygapophyseal joints, the hip joint, symptomatic spondylolisthesis, tumor and other regional soft tissue structures. It is assumed that these procedures will be completed as part of the subject's standard of care prior to the study and is a routine part of their pain management process and is not the responsibility of AVANOS.

Subjects will sign a written informed consent form prior to initiation of any study specific procedures and the process should be thoroughly documented prior to moving into the study activities. Subjects will be presented with informed consent after completion of their SIJ injection as that procedure is considered standard of care. To avoid confounding potential study results and to allow for recovery, the screening/randomization visit should be scheduled no sooner than 10 days following the SI injections, per investigator's discretion and standard of care – taking into consideration if diagnostic or therapeutic SI injection was given.

If the subject is a woman of childbearing potential she must have a negative urine pregnancy test (30 days prior to informed consent signature is acceptable with documentation confirming test occurred during an office visit) and agree to use an effective form of birth control (i.e. double barrier, surgical sterilization, oral contraceptives, intrauterine device [IUD], etc.) during the course of the study.

Randomization

It is anticipated that randomization will occur as the last item of the screening visit once it is confirmed that all inclusion and exclusion criteria have been confirmed and may occur on the same day as the Lateral Branch Blocks are completed.

For subjects randomized to the control group, the randomization visit will be the same day as their treatment visit (Day 0 Visit). The doctor will discuss the conservative therapy plan with the subject and they will be discharged to return for their Month 1 visit. If subsequent injections are to be given as part of the conservative management plan, these are not considered part of the study (costs, etc. are not the responsibility of the sponsor). If invasive treatments are necessary, these can occur on the scheduled 1 Month study visit, but no treatment should be performed within 30 days prior to any follow-up visit.

If the subject is randomized to the treatment group, they will be scheduled for sacroiliac joint denervation (should occur within 30 days of randomization).

The subject number is unique to each subject and will be sequentially assigned upon presentation of informed consent. This will serve as the subject number throughout the duration of the trial and will be captured in the electronic Case Report Form. The randomization number will be used to confirm subject was randomized correctly. A subject that has been randomized is considered enrolled.

Method of assigning subjects to treatment groups

All subjects who meet the eligibility criteria will be randomly assigned to one of two groups: (A) CRFA or (B) Standard Medical Management. 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.

Treatment Visit (Day 0)

Subjects in the Treatment group should receive the SInergy procedure as soon as possible following their Screening Visit. Ideally, the treatment visit should be scheduled within 30 days from the Randomization date. A waiver from the Sponsor will be required if scheduling requires delay. ***Pain severity will be evaluated by NRS score at this visit and subjects must still maintain a usual daily pain NRS score***

of ≥4 to receive treatment. This pain score should reflect average (usual) daily pain and function over the previous 7 days.

Subjects who are diagnosed with Bilateral Sacroiliac Joint pain must receive the SInergy treatment on both sides of their Sacroiliac Joint and both treatments must occur on the same day. If treatment is not performed on both sides on the same day it will be considered an incomplete treatment and the subject will not be eligible to remain in the study past the 1 Month visit which is completed for safety.

Day 0 for treatment group subjects (unilateral or bilateral) will be considered the day of the completed treatment. Follow-up visits should be scheduled accordingly.

For subjects randomized to the control group, the Treatment Visit (Day 0) will be the same day as their Randomization Visit. Duplicate forms completed at Screening Visit do not need to be repeated for these subjects for their Treatment Visit when the visit dates are the same.

During Coolief* procedure, the specific medications used are at the discretion of the Investigator; however, the subject should be alert and communicating with the Investigator during the procedure. Concomitant medication information used during the procedure should be recorded in the source documentation.

The treatment procedure is described in detail below and in the Instructions for Use for the Coolief* / SInergy* Cooled Radiofrequency Kit and in Appendix 2 – COOLIEF* SINERGY* Cooled RF Training Presentation. Both can also be found in the Study Regulatory Binder.

For the post-procedure treatment, the Sponsor recommends the use of bacitracin and adhesive bandages at the procedure site. Subjects may be prescribed a short course (3 days) of post-operative analgesics at the Investigator's discretion.

No additional invasive procedures should be performed during this visit.

Post-Treatment Phase

Subjects will be scheduled at the following intervals from their Day 0 Visit: 1 month (±7 days), 3 months (±14 days), 6 months (±14 days), 9 Months (±14 days) and 12 months (±14 days).

At each visit, regardless of randomization group, additional treatment and conservative management of pain therapy must be documented but is allowed and at the discretion of the physician. Subjects randomized to the treatment group, and those that choose to crossover to the treatment group, cannot receive additional

invasive procedures on this area, including SI injections. If they receive an additional invasive procedure, they will be removed from the study.

At each Follow-up Visit, blinded assessors will be utilized and assessments of pain and disability will be obtained utilizing the NRS and Oswestry Disability Index. Quality of Life will be assessed using the SF-36, EQ-5D-5L and PGIC. Concomitant medications, healthcare utilization (including physical therapy), physical examinations and AEs will also be assessed at each visit.

At the 3 Month visit, subjects initially randomized into the conservative therapy group will be evaluated to see if they qualify to receive denervation with the SInergy procedure (crossover treatment).

If eligible (less than 5 (Moderately better, and a slight but noticeable change) on PGIC), subjects should decide whether they choose to receive crossover treatment within 30 days of their 3-month Visit. Ideally crossover treatment will occur within 30 days of their 3-month Visit, but it **must** be performed within 90 days (3 months) of their 3 Month visit.

Once the subject has completed the crossover treatment, their follow-up visits should be scheduled at 1 month (±7 days), 3 months (±14 days), 6 months (±14 days), 9 Months (±14 days) and 12 months (±14 days) from Crossover treatment date (new Day 0).

Subjects initially randomized to the treatment arm and those control arm subjects who do not elect or do not qualify to crossover will continue through the trial and receive their follow-up visits based off their timing of Day 0.

Criteria for Study Discontinuation

Subjects in either treatment group may elect to terminate the study at any time for any reason. For any subject who discontinues the study prematurely, the Investigator should attempt to complete a Discontinuation Visit.

Subjects should be removed from the study if:

- They choose to undertake another invasive procedure of the SIJ (such as SI-Bone fusion, SI injection, etc.);
- They have other lumbar spinal surgical procedures including, but not limited to, RF, IDET, spinal fusion, and discectomy; OR

- If there is a change in medical condition prior to the Treatment Visit that impacts the study eligibility criteria, subjects may be required to terminate the study prior to start of the procedure.

Should the subject choose an alternative invasive procedure, attempts should be made to have the subject complete the Discontinuation Visit prior to receipt of that treatment. The specific reason and procedure planned should be noted in the subject's source and electronic Case Report Form.

Additionally, in the case of a technical malfunction of the equipment during the procedure, a subject should be followed for 30 days for safety or until consensus is obtained between the Sponsor and Investigator regarding any potential side effects of the event and the subject's status. If a technical issue occurs prior to the procedure, the subject can be rescheduled for treatment. The Sponsor should be made aware of any issues prior to rescheduling the subject and a waiver may need to be obtained prior to the procedure if the rescheduled date is outside the allowable visit window.

Procedures for Handling Incorrectly Enrolled Subjects:

Incorrect enrollment (receipt of incorrect treatment) is considered a major protocol violation and efforts should be taken to prevent this from occurring. However, if a subject receives the alternative treatment incorrectly, the follow up schedule should follow the protocol description for the treatment received. In example:

- If a subject is randomized to Active Treatment but receives SMM prior to the Coolief procedure, the subject should continue in the trial as a SMM subject (including being eligible for crossover).
- If a subject is randomized to SMM, but receives Coolief procedure instead, the subject should continue to be followed through the course of the trial as a Coolief subject.

If incorrect enrollment occurs at a site, no additional enrollments should occur prior to re-training.

Subjects are not permitted to receive the CRF procedure more than one time during this study. In the event a subject inadvertently gets re-treated (erroneously scheduled for crossover), the subject should be followed for safety for 30 days and then be dropped from the trial. This event will also be noted as a major protocol deviation.

Subjects can be re-screened as long as permission is obtained from the Sponsor prior to re-screening.

Additional subjects may be enrolled to account for attrition.

Timing and Use of Study Devices

Procedure

Cooled radiofrequency (CRF) denervation of the sacroiliac region using the SInergy System will be performed according to the technique and other technical details described in Appendix 2 – COOLIEF* SINERGY* Cooled RF Training Presentation.

The CRF procedure is generally performed under local anesthesia at the introducer tract, with the option of conscious sedation. During the procedure, subjects should be able to communicate with the physician conducting the procedure. If the subject develops pain radiating to the lower extremities or symptoms which are concordant with heating at the segmental nerve root or cauda equina, the heating protocol should be stopped immediately. The location of probes should be revisited in lateral and AP views. Probes can be repositioned and heating initiated again. If the radiating pain continues, the procedure should be permanently discontinued and subjects should be followed for safety as noted above. Information related to any event that occurs during the procedure should be recorded in the subject's source documentation and should be reported to the Sponsor immediately.

For safe and effective tissue heating and safe anatomical access abide by the following guidelines:

- For L5 dorsal ramus neurotomy the electrode should be directed at the dorsal surface of the notch between the sacral ala and the superior articular process of the sacrum. On a lateral fluoroscopic view, the introducer should be no further ventral than the anterior-posterior midline of the superior articular process (SAP). Placement more superior/ventral to the target point brings the electrode closer to the segmental nerve root, and increases the risk of inadvertent heating of this structure.

- For S1 – S3 lateral branch neurotomy, the electrode should be placed such that the active tip is at least 7 mm from the edge of nearest posterior sacral foramina. This electrode placement will ensure that there is no heating at the sacral canal. Electrode depth should be confirmed with lateral fluoroscopy prior to lesion creation. This will verify that the electrode is located superficial to the sacral surface, and confirm that it has not slipped into the nearest posterior foramen.

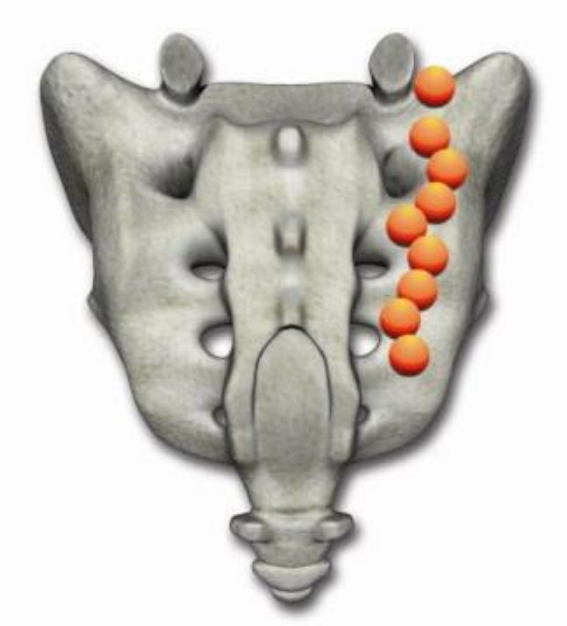
- For all targets, the introducer should be directed towards the target site until the tip is in contact with bone. When the stylet is removed and the electrode is inserted, there will be a 2-mm gap between the active tip and bony endpoint. This will achieve the appropriate electrode depth for treatment. Ensure that the probe is seated firmly in the introducer before proceeding.

- The stylet should always be replaced in the introducer prior to repositioning. The electrode is not designed to create new pathways through the dense connective tissue along the surface of the sacrum.

- Ensure that the electrode does not make physical contact with the "finder" needle during RF delivery.

Specific placement technique instructions can be found in Appendix 2 – COOLIEF* SINERGY* Cooled RF Training Presentation.

Figure 1: Lesion coverage around the sacral foramina at the S1-S3 and at the sacral ala of L5/S1



Medications/treatments permitted

Immediately before the treatment the following medications are permitted:

- Prophylactic antibiotics

During the treatment the following medications are permitted:

- Conscious sedation
- Local anesthetic at lesion sites.

Immediately after the procedure, the following medications are permitted:

- Analgesics (no more than 3 days)
- Muscle relaxants
- Antibiotics

Treatment can be terminated if:

- at the time of treatment, the subject's condition has changed considerably and they no longer meet the selection criteria,
- the subject decides they no longer want to participate,
- the subject experiences unresolvable pain radiating to legs and/or suggestive of heating at the segmental nerve root or cauda equina,
- continuing with the treatment is not possible due to unforeseen technical reasons, or
- any additional criteria at the discretion of the treating physician, such as non-compliance or unrelated injury.

When a subject is withdrawn, the treatment will be terminated and further steps will be taken to ensure the well-being of the subject at the discretion of the investigator. Depending on the point of termination this may include bandaging, antibiotic administration, or provision of analgesics. If a subject is withdrawn during the procedure, subjects should be followed for 30 days for safety. The withdrawal will be documented on a discontinuation visit electronic case report form.

Following completion of the procedure, the subject should be transferred to the recovery area and monitored per Investigator discretion (estimated to be 45 minutes), then discharged home with instructions, including a prescription for analgesics and/or muscle relaxants.

Blinding

The study is an assessor blinded trial and deliberate action will be needed to ensure the blind remains. This begins with randomization procedures and carries through the follow-up visits. It is suggested that all follow-up visit documentation not contain the visit number, but instead utilize visit dates to track progress.

Prior and concomitant therapy

No medications are prohibited prior to or during the course of the clinical trial beyond the limits identified in the Inclusion/Exclusion Criteria. Subjects are not required to alter existing medication regimens to participate in or to continue participation in this clinical trial. Regardless of randomization assignment, during the study non-invasive treatments are allowed and may be prescribed at the discretion of the Investigator.

Regardless of treatment group, prohibited invasive treatments for back pain during the study are outlined in the inclusion and exclusion criteria, including, but not limited to, RF, IDET, spinal fusion, and discectomy.

If a subject voluntarily withdraws from the study to have an invasive procedure, the information should be recorded in the subjects' source.

All information related to therapies should be captured as appropriate.

Treatment compliance

Healthcare utilization (including physical therapy or other) and concomitant medications will be recorded and captured at each follow-up visit during the course of the study; however, compliance in regard to these items will not be managed specifically during the trial.

Methods of Assessment

Effectiveness Measurements

The effectiveness outcomes in this study are derived from questionnaires administered to subjects, and study sites should be aware of potential sources of bias in these test measures. All tests should be completed by each subject in private at each visit.

Numeric Rating Scale

The NRS is a 11-point tool to measure pain by making use of a discrete scale, with the left side representing no pain (0) and the right side representing the worst pain (10). The NRS scoring method will be utilized to obtain information related to usual daily pain, worst pain, best pain and current pain in an attempt to differentiate between usual daily back pain and 'spikes' in pain. Subjects will be asked to choose a discrete value (0 to 10) representing their perception of their pain for each parameter at each visit reflecting pain and function over the previous week (usual, worst, best) or at the time of the visit (current).

The NRS related specifically to the subject's usual daily back pain is relevant for inclusion, exclusion (progression through Screening) and receipt of treatment for those randomized to Treatment group and will be evaluated as the primary effectiveness measure.

The NRS will be administered at all visits, including prior to initiation of treatment.

NRS can be potentially repeated several times prior to the Treatment visit if there is a delay between the Screening and Randomization periods. Progression to the next phase requires usual daily pain NRS to meet Inclusion Criteria. If multiple visits occur on the same day, only one NRS needs to be completed for the day.

SF-36

This questionnaire is designed to measure eight domains of health-related quality of life. The information obtained from the eight health domain scales is then aggregated to provide summary measures of the respondent's physical and mental health. The SF-36 health questionnaire will be administered at Screening visit and all follow-up visits.

Oswestry Disability Index (ODI)

This instrument is a back pain-specific disability index and quantifies how a subject's back pain affects their daily life. The ODI will be administered at Screening visit and all follow-up visits.

Patient Global Impression of Change

This instrument is a self-assessment tool that is used to measure a subject's global impression of the change in pain (improvement or lack of improvement) with treatment. The PGIC will be administered at all follow-up visits beginning at Month 1.

EQ-5D-5L

This instrument is a standardized measurement of health outcome that provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The EQ-5D-5L is a self-completed health survey that will be administered at Screening visit and all follow-up visits.

Safety Measurements

Adverse Events

The study coordinator will interview subjects for any AEs at each visit. Adverse events will be classified and reported as described in Section 7.

Other Measurements

Medication Use and Healthcare Utilization

At each study visit, the Investigator will assess the subject's overall health status and may modify the conservative treatment regimen, according to study protocol guidelines in Section 6 and based on clinical judgment. The Investigator will record back pain related medication use and utilization of any healthcare services (including physical therapy, acupuncture, chiropractic interventions, hospital/emergency room

visits, etc.). This information will be combined with other assessments in an effort to define differences between treatment groups and to quantify post treatment impact on healthcare utilization.

Physical Exam

The Investigator will also perform a Physical Exam at Screening visit and a blinded assessor will perform a Physical Exam all follow-up visits. Height and weight will be collected to calculate BMI.

Pregnancy Exam

A urine pregnancy exam will be performed for females of childbearing potential at Screening visit (if greater than 30 days since last in-office pregnancy exam), Treatment visit (prior to treatment), and Month 12 follow-up visit.

Appropriateness of Measurements

The pain questionnaires, healthcare utilization, and concomitant medication tracking will allow changes post-treatment to overall status (emotional, physical, economics, etc.) to be identified in order to quantify the overall effect of the procedure and allow comparison between groups, as well as on an individual subject basis for responder analysis.

Primary Effectiveness Endpoint

The primary effectiveness parameter is the observed change in usual daily pain as assessed by NRS score from the Baseline Visit (treatment visit for treatment group and randomization visit for control subjects) to Month 3 visit for the treatment group compared to the control group.

Secondary Effectiveness Endpoints

The control and treatment groups will be compared using the following secondary effectiveness measures:

- Proportion of subjects with an equal or greater than 2-point or 30% decrease in usual daily NRS pain score from baseline (prior to treatment for treatment group and randomization visit for control subjects) to Month 3 visit AND a rating of at least 5 on PGIC referenced to baseline at the Month 3 visit.
- Change in Physical Functioning domain SF-36 score from baseline to Month 3 visit.
- Change in ODI from baseline to Month 3 visit Oswestry Disability Index 2.0.
- PGIC (Patient Global Impression of Change) referenced to baseline at Month 3 visit.
- Change in EQ-5D-5L from baseline to Month 3 visit.

Additional Effectiveness Endpoints

The control and treatment groups will be compared using the following additional effectiveness measures at follow-up visits or change from baseline, as appropriate:

- Health care utilization questionnaire will be used to evaluate the use or need for other health care and treatments (PT, Chiropractor visits, acupuncture, sacroiliac joint injections, etc.).
- Change in back pain-related medication usage from baseline (including change in opioid use).
- Time from treatment to return to work/duty.
- Time from treatment to “Return-of-Pain” date.

All of the above effectiveness parameters will also be analyzed to compare the treatment and control groups at 6, 9 and 12 months post-randomization.

Safety Measures

AEs will be assessed at each visit. Safety events will be center-reported and monitored through normal procedures that govern clinical trials. All AEs will be followed until resolution or stabilization.

7 STUDY PROCEDURES

Center Readiness

Prior to center activation, all local regulatory requirements need to be fulfilled. Each study site must have written documentation of center/Investigator readiness, including but not limited to:

- IRB approval of the current version of the Clinical Protocol and Subject Informed Consent form.
- Signed/dated Investigator and Co-Investigator Curriculum Vitae (if applicable).
- Signed/dated Financial Disclosure.
- Signed/dated Clinical Trial Agreements.
- Signed/dated documentation of training (Investigator’s Meeting and/or Site Initiation Visit).

AVANOS will inform the clinical Investigator, in writing, when all requirements have been fulfilled for center activation.

Training

Protocol Training

Protocol training will include training items including, but not limited to: data entry, study procedures, data collection, source document requirements, safety and device accountability training. Training will be

conducted through Investigator meetings and/or Site Initiation Visits and documentation will be maintained appropriately. Ongoing training will be provided as needed during the study.

Device Training

Based on the intricacies involved in performing this procedure, it is recommended (but not required) that the first several CRFA procedures at each site should be proctored by an Avanos clinical specialist to ensure procedural consistency between sites.

Subject Informed Consent

Prior to undergoing any study procedure, 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 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).

The ICF will be provided to the subject in a language that he/she is able to read and understand.

If the subject is initially randomized to the control group and decides to crossover, the subject will be required to sign the most current approved version of the ICF to be reminded of the risks, benefits, etc. of the procedure.

The signed and dated subject ICF(s) must be maintained and be available for monitoring.

Schedule of Assessments

Assessments should occur as outlined in Table 1. The specific study plan for each enrolled subject will be variable and there are several possible visit schedules depending on randomization group and patient choices. For scheduling purposes, within this protocol, 1 Month = 30 days. Subjects who are eligible for study entry based on the Screening Phase assessments will be randomized.

Treatment Group:

For subjects randomized to the treatment group, a Treatment Visit (Day 0) will be scheduled as soon as possible, but ideally, within 30 days of randomization, during which they will receive the CRF procedure.

Follow-up Visits for all subjects should be scheduled based on their Day 0 Visit and should occur at the following time points from Day 0: 1 month±7 days, 3 months±14 days, 6 months±14 days, 9 months±14 days and 12 months±14 days.

Control Group:

Day 0 for this group is initially set as the day of Randomization. Subjects who are randomized to the control group who choose not to cross over will have the same follow-up visit schedule as CRF treated subjects. From Day 0: 1 month±7 days, 3 months±14 days, 6 months±14 days, 9 months±14 days and 12 months±14 days.

Subjects who are initially randomized to the control group and chose to cross over will have the following visit schedule from Day 0: 1 month±7 days and 3 months±14 days. They will then have a Coolief* treatment visit (new Day 0) and will return at 1 month±7 days, 3 months±14 days, 6 months±14 days, 9 months±14 days and 12 months±14 days. These visits will subsequently be scheduled based on the date of CRFA treatment (new Day 0).

CRFA treatment visits can be scheduled on the same day as the screening visit (or Month 3 visit for crossover subjects), but the visit assessments for the prior visit should be completed first.

Unscheduled Visits are designed to capture AEs or safety events for subject visits that occur between scheduled visits.

The study will be considered complete with regard to all endpoints after all enrolled subjects have completed a 12-month follow-up evaluation (based on randomization date), have died, have documented premature discontinuation, or the follow-up window for the final follow up is closed.

AVANOS

Confidential

Protocol # 105-17-0002

SInergy

Table 1: Schedule of Assessments

Study Month		Screening/Rand.	Treatment	Month 1	Month 3	Crossover Treatment	Crossover Month 1	Crossover Month 3	Month 6	Month 9	Month 12
Study Day		**Complete within 45 days of ICF**	**Within 30 days of Randomization**	**Day 30 (±7 days)**	**Day 90 (±14 days)**	**Within 30 days of Month 3 Visit (DAY 0)**	**Day 30 (±7 days from Day 0)**	**Day 90 (±14 days from Day 0)**	**Day 180 (± 14 days)**	**Day 270 (± 14 days)**	**Day 360 (±14 days)**
Informed Consent		X				X					
Relevant Medical History		X									
Physical Exam		X		X	X		X	X	X	X	X
Lateral Branch Block		X									
Urine Pregnancy Exam		X	X† (prior to treatment)			X† (prior to treatment)					X
Numeric Rating Scale (NRS)	Primary	X	X (prior to treatment)	X	X	X	X	X	X	X	X
Short Form-36 health survey (SF-36)	Secondary	X		X	X		X	X	X	X	X
Oswestry Disability Index (ODI)	Secondary	X		X	X		X	X	X	X	X
EQ-5D	Secondary	X		X	X		X	X	X	X	X
Healthcare Utilization	Secondary	X	X	X	X	X	X	X	X	X	X
Patient Global Impression of Change (PGIC)	Secondary			X	X		X	X	X	X	X
Inclusion/Exclusion		X	X			X					
Randomization		X									
Study Treatment			X			X					
Adverse Events		X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X

X† To be repeated if greater than 30 days since previous exam

Procedures by Visit

Screening (Days -45 to -0) and Randomization

The following procedures will be performed during the Screening Visit.

- Informed consent
- Relevant Medical History
- Physical Exam
- Urine Pregnancy Exam (if of child bearing potential)
- NRS assessment of pain severity to confirm that the subject meets the inclusion criterion for pain severity (usual daily pain) and entry into the trial
- SF-36
- ODI
- EQ-5D-5L
- Healthcare utilization estimate
- Assessment of concomitant medications
- Verify Lateral Branch Block procedure was performed and confirm responder status
- Assessment of adverse events
- Inclusion/Exclusion criteria
- Randomization

There is no minimum screening period required. If the subject meets the inclusion and exclusion criteria on the day they are screened, they can proceed directly to the randomization.

Subjects' current clinical treatment plan should not be modified at the Randomization Visit and should only be modified after the Treatment Visit. Medications and other non-invasive pain therapies may be prescribed or adjusted at any subsequent visits.

Treatment Visit (Day 0)

For subjects randomized to the treatment group, the treatment visit (Day 0) should be scheduled within 30 days of the Randomization Visit. A waiver from the Sponsor will be required if scheduling requires more than a 30-day delay.

The following procedures should be performed at this visit:

- Urine Pregnancy Exam (if of child bearing potential and if >30 days since most recent exam)
- NRS assessment of pain to confirm that the subject still meets the inclusion criterion for pain severity (usual daily pain) and entry into the trial

- Healthcare utilization (since Screening Visit)
- CRF Treatment with the Coolief* Cooled Radiofrequency Kit.
- Assessment of concomitant medications
- Assessment of adverse events

Post procedure, subjects should follow the Investigator's standard of care until discharge. Subjects should then be scheduled for their Month1 visit.

For subjects randomized into the control group, no specific treatment is offered, therefore, Treatment Visit (Day 0) will be the same day as Randomization.

Month 1 Visit

Month 1 visit should be scheduled 1 month (30±7 days) following Treatment Visit (Day-0) for all subjects. The following assessments should be performed:

- Physical Exam
- NRS assessment of pain severity
- PGIC
- SF-36
- ODI
- EQ-5D-5L
- Assessment of AEs
- Assessment of Concomitant Medications
- Health care utilization (including physical therapy, chiropractic care, acupuncture, etc.)

Month 3 Visit

Month 3 visit should be scheduled 3 months±14 days following Treatment Visit (Day-0 Visit) for all subjects. The following assessments should be performed:

- Physical Exam
- NRS assessment of pain severity
- PGIC
- SF-36
- ODI
- EQ-5D-5L
- Assessment of AEs
- Assessment of concomitant medications
- Health care utilization (including physical therapy, chiropractic care, acupuncture, etc.)

Additionally, during this visit, subjects who were initially randomized to the control group will be given the option to cross over and receive the CRF procedure or to remain in the control group. The subject should decide within 30 days of their Month 3 visit whether they want to receive crossover treatment. To be eligible for crossover treatment, subjects must:

- Have completed the prior protocol scheduled visits (Treatment Visit, Month 1, and Month 3 Visits).
- Remain medically appropriate as defined by the inclusion and exclusion criteria and the Investigator.
- A rating of less than 5 (Moderately better, and a slight but noticeable change) on PGIC
- Sign the current informed consent form for the study to provide consent and be reminded of risks of the procedure.

Subjects who elect to receive the crossover treatment after this visit should be scheduled for a Treatment Visit, and will return to the Post Treatment Visit schedule based off the date of their Treatment.

Crossover Treatment Visit (<u>Crossover subjects ONLY</u>)

Ideally, the Crossover Treatment will occur within 1 month±7 days of the Month 3 Visit, but it must be received prior to their Month 6 Visit (6 months from Day 0 Visit). If the crossover visit occurs on the same day as Month 3 visit, there is no need to perform duplicate tasks. However, Month 3 assessments (including NRS) need to be completed prior to receiving crossover treatment.

The following assessments should be performed:

- Urine Pregnancy Exam (if of child bearing potential)
- NRS assessment of pain severity
- Assessment of AEs
- Assessment of Concomitant Medications
- Healthcare utilization (including physical therapy, chiropractic care, acupuncture, etc.)
- CRF Treatment with the Coolief* Cooled Radiofrequency Kit.

Month 1 Crossover Visit (Crossover subjects ONLY)

Month 1 Crossover Visit should be scheduled 1 month (30 days±7 days) following the Crossover Treatment Visit. The following assessments should be performed:

- Physical Exam
- NRS assessment of pain severity
- PGIC
- SF-36

- ODI
- EQ-5D-5L
- Assessment of AEs
- Assessment of Concomitant Medications
- Health care utilization (including physical therapy, chiropractic care, acupuncture, etc.)

Month 3 (Crossover) Visit (Crossover subjects ONLY)

Month 3 crossover visit should be scheduled 3 months (90 days±14 days) following the Crossover Treatment Visit. The following assessments should be performed:

- Physical Exam
- NRS assessment of pain severity
- PGIC
- SF-36
- ODI
- EQ-5D-5L
- Assessment of AEs
- Assessment of Concomitant Medications
- Health care utilization (including physical therapy, chiropractic care, acupuncture, etc.)

Month 6 Visit

Month 6 Visit should be scheduled 6 months±14 days following Treatment Visit (Day-0) for all non-crossover subjects and 6 months±14 days following Treatment Visit (Crossover Day 0) for crossover subjects. The following assessments should be performed:

- Physical Exam
- NRS assessment of pain severity
- PGIC
- SF-36
- ODI
- EQ-5D-5L
- Assessment of AEs
- Assessment of concomitant medications
- Health care utilization (including physical therapy, chiropractic care, acupuncture, etc.)

Month 9 Visit

Month 9 visit should be scheduled 9 months ±14 days following Treatment Visit (Day 0 Visit) for non-crossover subjects and 9 months±14 days following Treatment Visit (Crossover Day 0) for crossover subjects.

The following assessments should be performed:

- Physical Exam
- NRS assessment of pain severity
- PGIC
- SF-36
- ODI
- EQ-5D-5L
- Assessment of AEs
- Assessment of concomitant medications
- Health care utilization (including physical therapy, chiropractic care, acupuncture, etc.)

Month 12 Visit

This is the final study visit. Month 12 visit should be scheduled 12 months±14 days following Treatment Visit (Day 0) for non-crossover subjects and 12 months±14 days following Treatment Visit (Crossover Day 0) for crossover subjects.

The following assessments should be performed:

- Physical Exam
- Urine Pregnancy Exam (if of child bearing potential)
- NRS assessment of pain severity
- PGIC
- SF-36
- ODI
- EQ-5D-5L
- Assessment of AEs
- Assessment of concomitant medications
- Health care utilization (including physical therapy, chiropractic care, acupuncture, etc.)

Unscheduled Visit

An unscheduled visit is designed to capture a subject visit between protocol scheduled visits to capture AEs.

Discontinuation Visit

A Discontinuation Visit is designed to capture information from a subject who withdraws from the study prior to completion of the trial. Efforts should be made to have subjects return to complete this visit in the event of a decision to withdraw from the study.

- Physical Exam
- Pregnancy Exam
- NRS assessment of pain severity
- PGIC
- SF-36
- ODI
- EQ-5D-5L
- Assessment of AEs
- Assessment of concomitant medications
- Health care utilization (including physical therapy, chiropractic care, acupuncture, etc.)
- Reason for Discontinuation

In some instances, some or all of this information may not be available, but efforts should be made to obtain as much information as possible.

Discontinuation criteria

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

- Subject withdraws consent.
- Subject receives an additional procedure in their Sacroiliac Joint.
- Investigator withdraws the subject for any reason following discussion with the sponsor.
- Investigator withdraws the subject immediately for emergent safety issues and reverts to institutional standards-of-care.

Data Quality Assurance

Prior to enrollment of any subject in the trial, the Sponsor will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on eCRF pages for this study must be consistent with the subjects' source documentation (i.e., medical records). This study is compliant with 21 CFR 11.

Adverse Events

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 looking for items that meet the reporting criteria.

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.

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

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.

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.

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.

AVANOS

Confidential

SInergy
Protocol # 105-17-0002

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

Kevin Friedman, DO

Medical Monitor

Telephone Number: 470) 448-5405

Email: kevin.friedman@hyh.com

Report serious adverse events and any supporting documentation to the Sponsor within 24 hours of becoming aware of the event. The primary mode of reporting will be through the eCRF database; however, fax can also be used.

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.

CLINICAL SAFETY MONITORING

Avanos'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, 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 determination will be used for analysis purposes.

Given the 'Exempt' status of this study, Avanos 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".

RISKS

Potential risks and benefits

Avanos 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,
- Nerve damage
- Increased pain,
- Visceral injury,
- Failure of technique,
- Paralysis, and
- Death

The known potential benefit of treatment of sacroiliac joint pain with CRF is reduced pain and improved quality of life.

Risk Mitigation: Every precaution is taken to avoid inadvertent heating of proximal spinal nerves. These include accurate fluoroscopic analysis of the probe positions and conscious, alert communication with the subject throughout the procedure to monitor sensations of lower extremity pain at which point the procedure will be terminated.

Related to fluoroscopy:

The fluoroscopy machine will be used during the study treatment and it emits x-rays.

Risks related to fluoroscopy: As fluoroscopy is an X-ray procedure, it has the same risks as other X-ray procedures, which is exposure to radiation. The amount of radiation that you will be exposed to during

this study will vary depending upon several factors, e.g. length of time it takes to place probes, number of images taken, type of machine, etc. The two major risks involved are:

- Radiation induced injuries to the skin and underlying tissues (burns) and
- The small possibility of developing a radiation induced cancer sometime later in life.

Study Investigators are encouraged to minimize the amount of radiation study subjects are exposed to during these procedures.

Risks related to conservative therapy may include, but are not limited to:

- In the event that new physical therapy, activities, injections, or medications are begun during or as a result of this trial, it is expected that secondary pain generators may be activated as functional recognition changes.
- Medication side effects are listed on the labels of the medications prescribed and these risks should be discussed with your study doctor.
- Procedural (i.e., Steroid injections, etc.) side effects should be discussed as part of normal standard of care.
- Alternative procedures (such as chiropractic and acupuncture) have their own risks associated with those procedures and prior to pursuing those treatments, risks should be discussed with the doctor.

Obligations of Investigator

The Investigator is obligated by regulations to report to AVANOS any adverse events/medical events and toxicities regardless of its severity or potential association with the device or treatment procedures.

Non-serious adverse events that are expected according to previous experiences with the investigational device (as described in the protocol, Investigator's Brochure, informed consent materials, or any approved product labeling) can be collected in a routine manner using case report forms. Non-serious events must be reported to AVANOS.

Serious adverse events (SAEs) and UADEs must be reported to AVANOS upon their occurrence or the site's knowledge of the events with written notification no later than 24 hours from their occurrence or the investigational sites knowledge of the events.

When submitting adverse event information to AVANOS, the Investigator may not delegate to someone other than a listed sub-investigator the responsibility for reviewing the accuracy of the contents of an adverse event report.

Review and reporting

Upon receipt of AEs at AVANOS, the AVANOS medical monitor will review the AE for completeness and when necessary will request clarification and/or additional information from the Investigator.

The AVANOS medical monitor is responsible for reviewing the Investigator's assessment and classification of each event. If the medical monitor disagrees with the Investigator's classification of the event, the rationale will be provided to the Investigator. If the Investigator agrees with AVANOS, the subject's AE eCRF will be updated accordingly. If the Investigator does not agree with the AVANOS classification, both determinations will be documented within the study report. However, the AVANOS determination will be used for analysis purposes.

The AVANOS medical monitor and Regulatory Department is also responsible for determining the reporting of AEs to the FDA.

Notifying Regulatory Authorities

AVANOS will immediately investigate each reported UADE to assess if expedited reporting will be required. AVANOS will notify the appropriate regulatory authorities (foreign and domestic), within the required timeline. If this event is considered to pose an unreasonable risk to subjects, termination of the investigation or the parts of the investigation that pose that risk will occur within 5 days of making that determination and not later than 10 working days from the date of notification of the event.

8 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 Month 3 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.

Determination of Sample Size

A superiority approach on reduction in pain, from baseline, at 3 months was used to estimate the sample size for this study. The lower bound of a 1-sided 95% CI will be calculated for the reduction in pain difference between treatments (CRF-SMM). If the lower bound is greater than 0, then "superiority" is achieved for the CRF treatment relative to SMM treatment. Under certain assumptions, as indicated in the table below, a minimum necessary sample size was determined to be 168 subjects.

CRF		SMM		Sample Size 5% level of significance (1-sided) 90% Statistical Power
Usual NRS reduction from baseline at 3 months	Standard deviation of NRS reduction from baseline at 3 months	Usual NRS reduction from baseline at 3 months	Standard deviation of NRS reduction from baseline at 3 months	
3.6	2.2	2.6	2.2	168

Assuming an attrition rate of 20%, 208 enrolled subjects will yield 168 completers. The total number of enrolled subjects will be managed based on this metric.

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 Screening Visit through the final 12-month visit, including all subjects who cross over from the SMM group to the CRF group.

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.

Dataset Definitions

Safety Set

All randomized subjects who receive CRF or SMM treatment will be included in the safety analyses. The safety set will also be used to provide a supplementary analysis of primary effectiveness endpoint that includes an imputation for missing data.

Complete Case-Analysis Set

All randomized subjects who receive CRF or SMM treatment and have evaluable data for the primary endpoint will be included in the Complete Case analysis set.

Per-Protocol Analysis Set

All randomized subjects who are compliant with the study protocol (i.e., who do not experience any major protocol deviations) and who receive CRF or SMM treatment and have evaluable data for the primary endpoint will be included in the Per-Protocol set.

The primary effectiveness endpoint analysis will be based on the Complete Case - analysis set, although a secondary analysis will also be performed based upon the Per-Protocol and Safety Sets (if there are differences), to assess the sensitivity of the analysis to the choice of analysis population. The analysis of primary effectiveness endpoint based on the Safety Set will include imputation for missing data. The analyses of all other endpoints will be based upon the Safety Set, where available data for the endpoint of interest is present, unless otherwise stated in the SAP. All safety analyses will be based upon the Safety Set.

Effectiveness Endpoints

Primary Effectiveness Endpoint

The primary effectiveness parameter is defined as the reduction in Numeric Rating Scale (NRS) from baseline at the Month 3 visit for the treatment group compared to the control group.

Secondary Effectiveness Endpoints

Secondary Effectiveness Endpoint 1: The proportion of subjects with at least 2 points decrease or 30% drop in usual daily pain related NRS score AND a rating of at least 5 on PGIC, referenced to baseline, at the Month 3 visit.

Secondary Effectiveness Endpoint 2: The mean change in SF-36 Physical Functioning subscale from baseline at the Month 3 visit.

Secondary Effectiveness Endpoint 3: The mean change in Oswestry Disability Index (ODI) form baseline at the Month 3 visit.

Secondary Effectiveness Endpoint 4: The mean change in EQ-5D-5L index score from baseline at the Month 3 visit.

Secondary Effectiveness Endpoint 5: The mean PGIC score, referenced to baseline, at the Month 3 visit.

Additional Endpoints

The following endpoints will be assessed at the Month 3 visit:

- The mean change in pain related medication from baseline
- The mean change in various healthcare utilization measures from baseline
- Time to return of pain
- Time to return to work/duty
- Primary and all secondary effectiveness measures at the Month 6, 9 and 12 visits

General Considerations

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

Demographic and Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, and concomitant medication will be summarized by means of descriptive statistics (number, mean, SD, median, minimum, and maximum) or frequency tables.

Effectiveness Analyses

Analyses of Primary Effectiveness Endpoint

The reduction in Numeric Rating Scale (NRS) from baseline at the Month 3 visit will be calculated and compared between the two treatment groups:

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

Where:
$\mu 1$: mean reduction in NRS pain score from baseline to the Month 3 visit for CRF group
$\mu 2$: mean reduction in NRS pain score from baseline to the Month 3 visit for SSM (control) group

The primary effectiveness analysis will be the mean reduction in NRS score from baseline to the 3 month visit for the comparison of the CRF with the SMM. For this analysis, the test will be one-sided superiority test at the 5.0% level of significance.

If the model assumptions for the t-test are not met, transformation of the changes in NRS score or non-parametric approach may be implemented.

Analyses of Secondary Effectiveness Endpoints

If the null hypothesis is rejected for the primary endpoint, i.e., CRF is concluded to be superior to SMM, the secondary effectiveness endpoints will be compared between treatment groups as detailed below. Plans for addressing familywise experimental error rate will be detailed in the stand-alone SAP.

Responder Analysis

The proportion of subjects with at least 2-point decrease or 30% drop in usual daily pain related NRS score AND a rating of at least 5 on PGIC referenced to baseline at the 3-month visit will be calculated and compared between the two treatment groups:

H_o: $\pi_1 = \pi_2$
H_a: $\pi_1 \neq \pi_2$

Where:
π1: proportion of at least 2-point decrease or 30% drop in usual daily pain related NRS score AND a rating of at least 5 on PGIC referenced to baseline at the Month 3 visit in the CRFA group
π2: proportion of subjects at least 2-point decrease or 30% drop in usual daily pain related NRS score AND a rating of at least 5 on PGIC referenced to baseline at the Month 3 visit in the SMM group.

SF-36

The mean change in SF-36 physical functioning subscale from baseline to the Month 3 visit will be calculated and compared between the two treatment groups:

Ho: μ1 = μ2
Ha: μ1 ≠ μ2

Where:
μ1 : mean change in SF-36 physical functioning sub-scale from baseline to the Month 3 visit for CRF group

μ2 : mean change in SF-36 physical functioning sub-scale from baseline to the Month 3 visit for SMM group

Analysis of variance (ANOVA) with treatment as fixed effect and center as block effect on changes in the SF-36 physical functioning sub-scale from baseline to the Month 3 visit will be performed for the comparison of the CRF with the SMM.

Oswestry Disability Index

The mean change in ODI score from baseline to the Month 3 visit will be calculated and compared between the two treatment groups:

Ho: μ1 = μ2
Ha: μ1 ≠ μ2

Where:
μ1 : mean change in ODI score from baseline to the Month 3 visit for CRF group
μ2 : mean change in ODI score from baseline to the Month 3 visit for SMM group

Analysis of variance (ANOVA) with treatment as fixed effect and center as block effect on changes in the ODI score from baseline to the Month 3 visit will be performed for the comparison of the CRF with the SMM.

EQ-5D-5L

The mean change in EQ-5D-5L score from baseline to the Month 3 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:
μ1 : mean change in EQ-5D-5L score from baseline to the Month 3 visit for CRF group
μ2 : mean change in EQ-5D-5L score from baseline to the Month 3 visit for SMM group

Analysis of variance (ANOVA) with treatment as fixed effect and center as block effect on changes in the EQ-5D-5L score from baseline to the Month 3 visit will be performed for the comparison of the CRF with the SMM.

Patient Global Impression of Change

The mean PGIC score, referenced to baseline, at the Month 3 visit will be calculated and compared between the two treatment groups:

Ho: $\mu 1 = \mu 2$
Ha: $\mu 1 \neq \mu 2$

Where:
$\mu 1$: mean of PGIC score, referenced to baseline, at the Month 3 visit for CRF group
$\mu 2$: mean of PGIC score, referenced to baseline, at the Month 3 visit for SMM group

Analysis of variance (ANOVA) with treatment as fixed effect and center as block effect on the PGIC score, referenced to baseline, at the Month 3 visit will be performed for the comparison of the CRF with the SMM.

Additional Endpoint Analysis

Analysis of additional endpoints, including change in back pain medication and healthcare utilization from baseline to the Month 3 visit, will be detailed in the stand-alone SAP. Issues of particular interest are opioid use in MEQ (Morphine Equivalent) units, physical therapy, concomitant medication usage, number of days of hospitalization, number of emergency room visits and number of subject's who are able return to work, time to return to work, and time to return of pain, etc.

Primary and secondary effectiveness parameters, measured at 6, 9 and 12 months visits, as well as change in back pain medication and healthcare utilization, will be summarized by means of descriptive statistics (number, mean, SD, median, minimum, and maximum) or frequency tables. Additional analyses may be undertaken as outlined in the SAP.

Safety Analysis

Adverse events occurring throughout the subject's participation in the study will be tabulated by body system, seriousness, severity, and Investigator reported relationship to the randomized treatment. Complete list of adverse events will also be provided by subject. Any noteworthy changes in physical examinations from Screening Phase to the Follow-Up Visit will be summarized.

Missing Data

Sensitivity analysis, including, but not necessarily limited to, last observation carried forward (LOCF) to impute missing data, will be performed for the purposes of further understanding the robustness of the results for the primary endpoint. Details will be described in the SAP.

9 ETHICAL, ADMINISTRATIVE, AND REGULATORY OBLIGATIONS

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.

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.

Access to Source Data

On-site or remote monitors will continue to make site visits to review protocol compliance and ensure that the study is being conducted according to pertinent regulatory requirements. Monitors will also assess study supply accountability; verify eCRF entries against source worksheets/documentation. The review of worksheets/documentation will be performed in a manner to ensure that subject confidentiality is maintained.

Checking of the eCRF entries for completeness and accuracy by cross-checking with source worksheets/documents, will be required to monitor the progress of the study. Moreover, regulatory authorities, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group or designated representative may wish to carry out such worksheet/documentation data checks and/or on-site audit inspections. Direct access to source worksheet/documentation will be required for these inspections and

audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor of the necessary support at all times.

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.

Data Processing

All data will be entered by the respective sites into an EDC system. The Data Management Plan to be developed during the initiation phase of the study will include specifications for consistency and plausibility checks and obvious data errors. Queries/corrections will be managed within the EDC system. The EDC system will require the Investigator's electronic signature prior to database lock.

Storage of data

Clinical notes of a routine nature will be maintained as part of the medical record. All clinical information related to the study will be stored under the supervision of outcome assessors in a locked cabinet. These research charts will remain separate from routine clinic charts. They will remain in the locked office of the outcome assessor. They will be available only to the investigator and support staff who are serving as outcome assessors. There will be no unauthorized access.

Each subject will be assigned a subject ID number. Their baseline, treatment and outcomes information will then be prospectively entered in the database in reference to this subject ID number. Only the staff involved in the study will have access to this separate database which will be password protected.

Identifying data will not be used in publications and all information separate from the facility record will be in secure storage with access restricted to the investigator. Documents available to the sponsor (data collection forms) should not contain patient identifying information per HiPAA requirements.

Archiving Study Records

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 before archiving / destroying any study records.

Minimizing study bias

The following measures have been incorporated into the study protocol to minimize potential study bias:

- All centers will be required to follow the same version of the AVANOS study protocol.
- All scheduled follow-up visits are required to take place within pre-specified follow-up windows.
- No discounts or financial incentives will be offered to study sites relating to the purchase of hardware or re-usable equipment as a result of participation in this clinical trial.
- If hardware components are provided by AVANOS for the trial, the sites are not permitted to use these items to perform procedures outside of the protocol.
- Administration of testing instruments to subjects should occur in a private area so that subject responses are not influenced by others. If a proctor is required, scores should be read word for word, no changing or paraphrasing by the reader.
- Independent monitoring
- Independent stats
- Blinded assessors
- Independent Data management.

.

Monitoring and Auditing

Avanos 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.

Monitoring visits will occur based on enrollment rate and volume, duration of the study, study compliance, and any suspected inconsistency in data that requires investigation. Remote monitoring is allowable in certain cases and must be approved by Avanos. Remote monitoring will be conducted under the same regulations as onsite monitoring. At a minimum, there will be approximately 3-4 onsite or remote monitoring visits each year at any site that has enrolled subject(s).

Avanos, 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.

Regulatory Requirements/Justification

This clinical trial will be conducted in the U.S. The study is not for registration purposes or for label expansion and therefore it is considered a post-marketing study. However, the study will be conducted in a manner consistent with the principles of Good Clinical Practices and ICH guidelines. The study will be registered on ClinicalTrials.gov.

Records and Reports

Sponsor

The Sponsor AVANOS will maintain the following records:

- All correspondence which pertains to the investigation with another Sponsor, monitor, IRB, FDA, including required reports
- Investigational product accountability reports including record of receipt, use, or disposition of the device(s) that relate to type, quantity, serial numbers of devices, and date of receipt, names of persons who received, used, or disposed of each device and why and how many devices have been returned to AVANOS or otherwise disposed
- Signed and dated Clinical Trial Agreements, Delegated Task List, and Investigator curriculum vitae
- Financial Disclosure
- All signed and dated Case Report Forms (CRFs) submitted by Investigator, templates of Subject Informed Consents, and other information provided to the subjects
- Copies of all IRB approval letters and relevant IRB correspondence

- Names and evidence of the institutions in which the clinical investigation will be conducted
- Correspondence with authorities as required by national legislation
- Forms for reporting any AEs and adverse device effects
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical investigation
- The Clinical Study Protocol, Investigator Brochure/Report of Prior Investigations Summary, and study related reports
- Study training records for site personnel and AVANOS personnel involved in the study
- Any other records that FDA and local regulatory agencies require to be maintained

Sponsor Records

AVANOS is responsible for maintaining the following records:

- Clinical Investigational Protocol
- All correspondence relating to the investigation.
- System shipment and disposition records
- Signed Investigator Agreements, curriculum vitae, and medical license
- Documentation of Ethics Committee approval
- Adverse events and complaints
- Case report forms
- Complaints

Sponsor Reports

AVANOS is responsible for preparing all of the following reports:

- Medical Device Reports
  AVANOS is responsible for notifying the relevant regulatory agencies of certain incidents/near incidents as follows:

  1) Within 10 days after AVANOS becomes aware of an incident, if the incident has led to the death or a serious deterioration in the state of health of a subject, user, or other person.
  2) Within 30 days after the AVANOS. becomes aware of an incident, if the incident has **not** led to the death or a serious deterioration in the state of health of a subject, user or other person, but could do so were it to recur.

- Withdrawal of Ethics Committee Approval

The Investigator will be notified within five (5) working days in the event of withdrawal of any Ethics Committee Approval.

Investigator

Investigator Records

The Investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records, budget and Clinical Trial Agreement(s), should be kept in the Investigator Site File (i.e., the study binder provided to the Investigator) or Subject Study Binder. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated or the date that the records are no longer required for purposes of supporting post-market regulatory requirements.

- IRB approval documentation – including all versions of protocols, informed consents, etc.
- Clinical Protocol (all approved versions and amendments)
- Investigator Brochure(s)
- Signed and dated Case Report Forms
- Subject's case history records, including:
  - Signed and dated Subject Informed Consent form and privacy authorization
  - Observations of AEs/adverse device effects
  - Medical history
  - Surgery procedure and follow-up data
- Device Disposition Logs/Accountability will be maintained during the course of the trial for all provided devices, hardware, and/or re-usable items:
  - Received dates, quantities and serial numbers (where appropriate) of investigational/disposable devices, loaned hardware or re-usable items.
  - Tracking of investigational materials (model and serial numbers of devices where appropriate) to study subjects
  - Returned-to-Sponsor dates and reasons, quantities, model and serial numbers of devices (where appropriate), hardware or re-usable material and
- Documentation of the dates and rationale for any deviation from the protocol
- Signed and dated Clinical Trial Agreement(s), Amendment(s), and confidentiality agreement(s)
- Completed Statement of Investigator or FDA Form1572 as applicable
- Investigators current curriculum vitae current by address and position
- Completed Site Delegation Log and Delegated Task List

- All correspondence between the IRB, Sponsor, monitor, FDA, and/or the Investigator that pertains to the investigation, including required reports
- Written information that the Investigator or other study staff, when member of the IRB, did not participate in the approval process
- Site personnel training documentation
- Any other records that FDA and local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis

Investigator Records

Investigators shall maintain the following records:

- Correspondence with FDA, the sponsor, Ethics Committee, and other investigators relating to this investigation.
- Record of receipt of AVANOS equipment, and necessary accountability records.
- Subject records, including informed consent, copies of case report forms, and supporting documents (e.g. fluoroscopic x-rays, etc.).
- Study protocol with data and reasons for deviations that may affect the scientific quality of the study.
- All records pertaining to the correction of raw data and subsequently those made to the database.

Investigator Reports

The Investigator shall prepare and submit the following reports. These reports are subject to FDA inspection and the retention requirements previously described.

- Medical Device Reports

The investigator shall notify AVANOS within 72 hours of the following system related incidents: An incident that has led to the death or a serious deterioration in the health of a subject, user or other person or, where it is reasonable to believe that such an incident, were it to recur, could lead to the death or a serious deterioration of the state of health of a subject, user or other person.

- Withdrawal of Ethics Committee Approval

The Investigator shall notify AVANOS. within five (5) working days of withdrawal of Ethics Committee approval.

- Use of the product without Informed Consent or for indications other than those outlined above.

If AVANOS equipment is used without obtaining and documenting Informed Consent, the Investigator shall report such use to AVANOS within five (5) working days, with an explanation of the circumstances of such use.

- Deviations from Investigational Plan

If deviation from the protocol is necessary to protect the life or physical well-being of a subject in an emergency, the Investigator shall notify AVANOS within five (5) working days. For all other changes in, or deviations from the clinical protocol, prior written approval from AVANOS. and the Ethics Committee is required.

- Monthly Progress Report

The Investigator shall submit a Progress Report to AVANOS on a monthly basis.

- Final Report

This report shall be submitted to AVANOS within three (3) months after termination or completion of the investigation.

The Investigator is responsible for the preparation (review and signature) and submission to AVANOS of all CRFs, AEs, deaths, and any deviations from the investigation plan. If any action is taken by an IRB with respect to the investigation, the information must be forwarded to AVANOS. Reports are subject to inspection and to the retention requirements as described above for Investigator records.

Subject Costs

The Lateral Branch Blocks completed post ICF, Coolief* SInergy treatment(s) and follow-up assessments outlined in Table 1 are provided to the subject at no cost as part of the study. Standard Medical Management activities will be the responsibility of the subjects. Following the SInergy or conservative treatment, a prescription for analgesics and/or muscle relaxants may be provided. The subject will be responsible for the cost of these and any subsequent medications or standard of care activities used in relation to their condition.

The subject is financially responsible for any test or treatments for their condition that are sought outside of the study protocol regardless of randomization group or as undertaken as part of the control group. These non-study related costs may include, but are not limited to, x-rays, CT/bone scans, MRIs, chiropractic care, physical therapy, acupuncture, massage, medications, and cortisone injections.

Declaration of Helsinki

The study will be conducted according to the guidelines established in the Declaration of Helsinki. Subjects will be free to withdraw from the study at any stage without prejudice to their subsequent

treatment. The investigator must be in compliance with the principles enunciated in the Declaration of Helsinki during the conduct of this clinical trial.

Ethics Committee and Competent Authority Approval

Enrollment will begin once the study receives approval is from the respective ethics committee and competent authorities at each site.

Preliminary Publication Plan

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

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

- The agreement of Avanos 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 must be cited in all publications where appropriate.

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.

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 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.

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.

10 REFERENCES

[1] Hooten WM, Cohen SP. Evaluation and treatment of low back pain: a clinically focused review for primary care specialists. Mayo Clin Proc. 2015;90(12):1699-1718.
[2] Chou R, Atlas SJ, Stanos SP, Rosenquist RW. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. Spine (Phila Pa 1976). 2009;34(10):1078-1093.
[3] Ackerman SJ, Polly DW Jr, Knight T, Holt T, Cummings J Jr. Nonoperative care to manage sacroiliac joint disruption and degenerative sacroiliitis: high costs and medical resource utilization in the United States Medicare population. J Neurosurg Spine. 2014;20(4):354-363.
[4] Rashbaum RF, Ohnmeiss DD, Lindley EM, Kitchel SH, Patel VV. Sacroiliac joint pain and its treatment. Clin Spine Surg. 2016;29(2):42-48.
[5] Cox RC, Fortin JD. The anatomy of the lateral branches of the sacral dorsal rami: implications for radiofrequency ablation. Pain Physician. 2014 Sep-Oct;17(5):459-64.
[6] Roberts SL1, Burnham RS, Ravichandiran K, Agur AM, Loh EY. Cadaveric study of sacroiliac joint innervation: implications for diagnostic blocks and radiofrequency ablation. Reg Anesth Pain Med. 2014 Nov-Dec;39(6):456-64.
[7] Chou R, Qaseem A, Snow V, Casey D, Cross JT, Jr., Shekelle P, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007 Oct 2;147(7):478-91.
[8] Manchikanti L, Boswell MV, Datta S, Fellows B, Abdi S, Singh V, et al. Comprehensive review of therapeutic interventions in managing chronic spinal pain. Pain Physician. 2009 Jul-Aug;12(4):E123-98.
[9] Flynn T, Fritz J, Whitman J, Wainner R, Magel J, Rendeiro D, Butler B, Garber M, Allison S. A clinical prediction rule for classifying patients with low back pain who demonstrate short-term improvement with spinal manipulation. Spine (Phila Pa 1976). 2002 Dec 15;27(24):2835-43.
[10] Tullberg T1, Blomberg S, Branth B, Johnsson R. Manipulation does not alter the position of the sacroiliac joint. A roentgen stereophotogrammetric analysis. Spine (Phila Pa 1976). 1998 May 15;23(10):1124-8; discussion 1129.
[11] Luukkainen RK, Wennerstrand PV, Kautiainen HH, Sanila MT, Asikainen EL. Efficacy of periarticular corticosteroid treatment of the sacroiliac joint in non-spondylarthropathic patients with chronic low back pain in the region of the sacroiliac joint. Clin Exp Rheumatol 2002; 20:52-54.
[12] Lee JH, Lee SH, Song SH. Clinical effectiveness of botulinum toxin A compared to a mixture of steroid and local anesthetics as a treatment for sacroiliac joint pain. Pain Med 2010; 11:692-700.
[13] Luukkainen R, Nissila M, Asikainen E, Sanila M, Lehtinen K, Alanaatu A, Kautianen H. Periarticular corticosteroid treatment of the sacroiliac joint in patients with seronegative spondyloarthropathy. Clin Exp Rheumatol 1999; 17:88-90.
[14] Murakami E, Tanaka Y, Aizawa T, Ishizuka M, Kokubun S. Effect of periarticular and intraarticular lidocaine injections for sacroiliac joint pain: Prospective comparative study. J Orthop Sci 2007; 12:274-280.
[15] Laux CJ1, Osterhoff G1, Werner CM1 [Sacroiliac joint pain - diagnostic algorithm and therapeutic approaches]. Praxis (Bern 1994). 2015 Jan 2;104(1):33-9.
[16] Krischner M. Zur elektrochirugie. Arch Klin Chir 1931;147:761.
[17] Helm S, Hayek SM, Benyamin RM, Manchikanti L. Systematic review of the effectiveness of thermal annular procedures in treating discogenic low back pain. Pain Physician. 2009 Jan-Feb;12(1):207-32.
[18] Finch PM, Price LM, Drummond PD. Radiofrequency heating of painful annular disruptions: one-year outcomes. Journal Of Spinal Disorders & Techniques. 2005;18(1):6-13.
[19] Gabriel C, Gabriel S, Corthout E. The dielectric properties of biological tissues: I. Literature survey. Phys Med Biol. 1996 Nov;41(11):2231-49.
[20] International Spine Intervention Society. Practice Guidelines for Spinal Diagnostic and Treatment Procedures. Bogduk N, editor. San Francisco, CA: International Spine Intervention Society; 2014.
[21] Cohen SP, Hurley RW, Buckenmaier CC 3rd, Kurihara C, Morlando B, Dragovich A. Randomized placebo-controlled study evaluating lateral branch radiofrequency denervation for sacroiliac joint pain. Anesthesiology. 2008;109(2):279-288.

[22] Kapural L, Nageeb F, Kapural M, Cata JP, Narouze S, Mekhail N. Cooled radiofrequency system for the treatment of chronic pain from sacroiliitis: the first case-series. Pain Pract. 2008;8(5):348-354.
[23] Patel N, Gross A, Brown L, Gekht G. A randomized, placebo-controlled study to assess the efficacy of lateral branch neurotomy for chronic sacroiliac joint pain. Pain Med. 2012;13(3):383-398.
[24] Patel N. Twelve-month follow-up of a randomized trial assessing cooled radiofrequency denervation as a treatment for sacroiliac region pain. Pain Pract. 2016;16(2):154-167.
[25] Stelzer W, Aiglesberger M, Stelzer D, Stelzer V. Use of Cooled Radiofrequency Lateral Branch Neurotomy for the Treatment of Sacroiliac Joint-Mediated Low Back Pain: A Large Case Series. Pain Med. 2013 Jan;14(1):29-35.
[26] Ho K, Hadi MA, Pasutharnchat K, Tan K. Cooled Radiofrequency denervation for treatment of sacroiliac joint pain: two-year results from 20 cases. Journal of Pain Research 2013:6 505-511.
[27] Dept. of Health and Human Services Federal Coordinating Council on Comparative-Effectiveness Research. Report to the President and the Congress. Presented on June 30, 2009. Available at: http://www.tuftsctsi.org/~/media/Files/CTSI/Library%20Files/FCC%20for%20CER%20Rpt%20to%20Pres%20and%20Congress_063009.ashx. Last accessed 23 June 2016.
[28] Brouwers MC, Thabane L, Moher D, Straus SE. Comparative effectiveness research paradigm: Implications for systematic reviews and clinical practice guidelines. J Clin Oncol 2012; 30: 4202-7.