A MULTI-CENTER, PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED CONTROLLED STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF THE IOVERA° DEVICE FOR THE TEMPORARY RELIEF OF PAIN ASSOCIATED WITH KNEE OSTEOARTHRITIS

PROTOCOL NUMBER:	MYO-0946 REV 04
VERSION:	3/11/2015
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Revision History

Revision	Description	DCO#	Release Date
01	• Initial Release.	2195	4/1/2012
02	• Grammar and punctuation corrections • Increase number of days Subject may participate • Increase the expected total study duration • Added language for treatment to be performed by Physician Assistant or Nurse Practitioner • Updated Table 1 Study Eligibility Criteria including Inclusion Criteria 3, 4, 5, 6, 7, 8, 9 and Exclusion Criteria 4, 5, 13, 19, 20 and 21 • Update section 9.4 Risks to describe expected side effects • Update section 10 Study Procedures to add optional Baseline Visit, Day 150 Visit and Day 180 Visit • Update visit specific activities for each study visit • Add acetaminophen dispensing and accountability • Update Table 3 Schedule of Assessments • Add lidocaine diagnostic block to Study Exit section 10.9 • Update the order of assessment in section 10.11 • Add Patient Global Impression of Change section 10.12.4 • Add 36-Item Short Form Health Survey (SF-36) section 10.12.5 • Remove Subject Diary • Update Study Endpoints section 11 • Update Adverse Event section 12 to harmonize with ISO14155:2011	2397	8/19/2014
03	• Grammar and punctuation corrections • Add diagnostic block inclusion criteria (inclusion #7) • Add knee pain map and required locations of pain • Clarify time of study enrollment • Clarify new medical diagnoses or	2431	9/17/2014

	events prior to study treatment is documented as change in medical history • At treatment visit lidocaine is used for cutaneous anesthesia and nerve anesthesia • Add Day 1 visit		
04	• Grammar and punctuation corrections • Add updated Sponsor representative • Add new medical monitor • Clarify study design in synopsis • Clarify primary endpoint in synopsis • Add secondary endpoints to synopsis • Add Safety Endpoint • Add inclusion and exclusion criteria to synopsis • Corrected wording of Inclusion Criteria #2. • Add known liver dysfunction as an exclusion • Add washout for adjuvant therapy of 72 hours prior to baseline • Change medication washout to 5 times the half life of the medication • Added to Section 9.1 to describe sham Smart Tip • Revise Figure 2 • Added "Loss of Motor Function outside the treatment area" to Section 9.4 Complications • Revised "expected side effects" to "complications" where appropriate to be in harmony with User Guide • Clarified Primary effectiveness endpoint in Section 10.1 • Added rationale to support 2:1 randomization in section 10.5 • Added "without epinephrine" in section 10.5 • Add language to section 10.6.3 regarding the timing of the single active iovera° treatment after study exit • Revised Schedule of events to include acetaminophen accountability at Day 1/Visit 4 • Revise Schedule of Events to include	2593	3/5/2015

	dispensing of acetaminophen at Treatment/Visit 3 • Revise Section 10.7 to prohibit any Sec. 12.3adjunctive treatment during study • Revision to Section 11, Statistical Methodolgy and Analyses • Corrected language in Sections 12.1.2 • Corrected language in Section 12.2 •		
04	• Admin fix to typos in page 7 and 15	2598	3/11/2015

Investigator Study Acknowledgement

Read and initial below.

____ I understand this protocol contains information that is confidential and proprietary to myoscience, Inc.

____ Any additional information added to this protocol is also confidential and proprietary to myoscience, Inc. and must be treated in the same manner as the contents of this protocol.

____ I have read the entire protocol.

____ I understand what the protocol asks me to do as an Investigator.

____ I will conduct this study following this protocol and will make a reasonable effort to complete the study in the time noted.

____ I will provide this protocol to study staff under my direct supervision. My study staff will keep the protocol and associated documents confidential.

____ I will discuss this information with the study staff to ensure they are fully informed about the study and the test articles.

____ I will not start enrolling in this study until it is approved by a governing Institutional Review Board.

____ I understand the study may be terminated or enrollment suspended at any time by myoscience, Inc., with or without cause, or by me if it becomes necessary to protect the interests of the study Subjects.

_____

Name of Investigator

_____ _____

Investigator Signature Date

Protocol Synopsis

Title	A Multi-Center, Prospective, Double-blind, Randomized, Controlled Study to Evaluate the Effectiveness and Safety of the iovera° Device for the Temporary Relief of Pain Associated with Knee Osteoarthritis
Study Device	iovera° (myoscience Inc., Redwood City, CA)
Study Objective	To evaluate the effectiveness and safety of the iovera° device for the temporary relief of pain associated with knee osteoarthritis
Study Design	Multi-center, prospective, randomized, sham-controlled double-blind
Treatment Groups	iovera° treatment vs. sham treatment with iovera° device
Duration of Participation	Up to 210 days
Study Population	Male or female, ages 35 to 75 with chronic knee pain related to grade II or III knee osteoarthritis as rated on the Kellgren-Lawrence grading scale
Total Number of Subjects	Minimum of 80 and maximum of 180 Subjects will be enrolled. Final sample size will be determined by interim analysis as specified in the statistical plan.
Number of Sites	Up to 35 sites may participate
Study Procedures	iovera° treatment with functioning Smart Tip or iovera° treatment with sham Smart Tip
Data Collection Tools	• WOMAC Questionnaire • Visual Analog Scale (VAS) Pain Assessment • Patient Global Impression of Change (PGIC) • 36-Item Short Form Health Survey (SF-36) • Subject Experience Questions
Primary Endpoint	The absolute change from baseline (after 30 days) in number of points on WOMAC A (pain) subscale. The primary endpoint hypothesis of the study is that the change in score after 30 days under iovera° is superior to that of control.
Secondary Endpoints	• Comparison of the rate of responders under iovera versus sham. A subject is defined as a responder if there is at least a 30% reduction in their WOMAC pain score at Day 30 compared to baseline. Mean and 95% confidence intervals

	for the rate of responders under iovera° versus sham will be reported. • Comparison of change in WOMAC stiffness at Day 30, • Comparison of change in WOMAC function at Day 30 and • Comparison of change in VAS at Day 30
Safety Endpoint	Incidence of device-related adverse events
Inclusion/Exclusion	**Inclusion Criteria** 1. 35 – 75 years of age 2. American College of Rheumatology (ACR) criteria for osteoarthritis of the knee. This includes radiographic evidence of osteophytes and at least one of the following: age > 50 years old, morning stiffness < 30 minute duration or crepitus on motion. 3. Grade II or III osteoarthritis of the knee as determined by Kellgren-Lawrence classification grading scale on anteroposterior (AP) x-ray within previous 6 months. 4. Subjects are ambulatory without assistive devices. 5. Knee pain of ≥ 40 mm on Visual Analog Scale (VAS) when performing one of two movements that elicit the worst pain: standing from a seated position or walking up/down stairs. 6. Subject reports knee pain in the anterior and/or inferior aspect of the knee as documented on the knee pain map in the appropriate areas. 7. A diagnostic lidocaine (without epinephrine) block of the infrapatellar branch of the saphenous nerve results in a 50% reduction in the VAS pain assessment score when performing the activity that elicits the worst pain: standing from a seated position or walking up/down stairs. **8.** Subject is able to tolerate a washout of prescription and over-the-counter pain medication used for pain relief for a duration of 5X the half-life of the medication prior to the Baseline visit. **9.** Subject is able to tolerate a washout of adjunctive therapies for knee pain for 72 hours prior to the Baseline visit. 10. Western Ontario and McMaster Osteoarthritis Index (WOMAC) NRS3.1 Pain subscore ≥ 20 at Baseline/Visit

	2. 11. Subject is able to tolerate discontinuation of all pain medication and/or adjunctive therapy for knee pain throughout the duration of the study. Acetaminophen may be used as rescue medication with a maximum dose of 4g per day. 12. Subject is able to tolerate discontinuation of rescue medication, acetaminophen, for 24 hours prior to all follow-up visits. 13. Prescription and over-the-counter pain medications must be maintained on a stable schedule for at least two weeks prior to screening. 14. Subject is willing and able to give written informed consent. 15. Subject is willing and able to comply with study instructions and commit to all follow-up visits for the duration of the study. 16. Subject is in good general health and free of any systemic disease state or physical condition that might impair evaluation or which in the Investigator's opinion, exposes the Subject to an unacceptable risk by study participation. **Exclusion Criteria** 1. History of a partial or full knee replacement of the knee to be treated. 2. Planned partial or full knee replacement within the next 12 months in knee to be treated. 3. Previous myoscience Focused Cold Therapy (FCT)™ treatment. 4. Viscosupplementation within the previous 6 months in knee to be treated. 5. Subject reports the majority of knee pain outside of the anterior/inferior aspect of the knee. 6. Intra-articular steroid injection in the knee to be treated within previous 3 months. 7. Gross deformity of the knee including varus or valgus. 8. Started physical therapy of the knee to be treated within 3 months of screening. 9. Received acupuncture for knee pain within 3 months prior to screening. 10. Body Mass Index ≥ 35. 11. Prior surgery in the treatment area that may alter the

	anatomy of the infrapatellar branch of the saphenous nerve or result in scar tissue in the treatment area. 12. Open and/or infected wound in the treatment area. 13. Disease of the spine, hip, contralateral knee or other lower extremity joint of sufficient degree affecting the assessment of the treated knee. 14. Acetaminophen intolerance or allergy. 15. Allergy to lidocaine. 16. History of cryoglobulinemia 17. History of paroxysmal cold hemoglobinuria. 18. History of cold urticaria. 19. History of Raynaud's disease. 20. History of pes anserinus bursitis in the knee to be treated. 21. Use of extended-release or long-acting opioids within previous 3 months. 22. Use of immediate-release opioids for more than 3 days per week within previous month. 23. Subject is pregnant or planning to become pregnant while enrolled in the study. 24. Current enrollment in any investigational drug or device study or participation within 30 days prior to screening. 25. Any additional diagnosis that in the opinion of the Investigator directly contributes to knee pain. 26. Any concomitant inflammatory disease or other condition that affects the joints (e.g. rheumatoid arthritis, metabolic bone disease, gout, active infection, etc.) 27. Any clotting disorder and/or use of an anticoagulant (e.g., aspirin, warfarin, clopidogrel, etc.) within seven (7) days prior to administration of the device. 28. Any local skin condition at the treatment site that in the Investigator's opinion would adversely affect treatment or outcomes. 29. Any chronic medical condition that in the Investigator's opinion would prevent adequate participation. 30. Any chronic medication use (prescription, over-the-counter, etc.) that in the Investigator's opinion would affect study participation or Subject safety. 31. For any reason, in the opinion of the Investigator, the Subject may not be a suitable candidate for study participation (i.e., history of noncompliance, drug dependency, any related knee injury due to a worker's compensation claim, etc.). 32. Known liver dysfunction.

Table of Contents

Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Device Effect
CFR	Code of Federal Regulations
CNS	Central Nervous System
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FCT™	Focused Cold Therapy™
ESE	Expected Side Effect
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IRB	Institutional Review Board
ISN	Infrapatellar branch of the Saphenous nerve
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSR	Non-Significant Risk
OTC	Over-the-Counter
PT	Preferred Terms
PGIC	Patient Global Impression of Change
QA	Quality Assurance
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOC	System Organ Classes
TENS	Transcutaneous Electrical Nerve Stimulation
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Osteoarthritis Index

1. BACKGROUND

According to the Arthritis Foundation, 27 million Americans are affected by osteoarthritis with the knee joint being one of the joints often affected. A treatment plan can include a combination of treatments. This plan may consist of medications, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), rest, physical therapy, occupational therapy, corticosteroid injections and viscosupplementation. Surgical strategies are reserved for more severe cases with joint damage and/or marked joint function limitations.[1] With the associated side effects of medications, corticosteroid injections and viscosupplementation, a nonsurgical, minimally invasive, approach to osteoarthritis pain management is desirable.

myoscience, Inc. (Redwood City, CA) has developed a device – iovera° – for a novel, minimally invasive procedure using focused cold therapy (FCT™) to target sensory nerve tissue and provide temporary pain relief through cryoanalgesia. The myoscience iovera° device uses well-established principles of cryobiology to temporarily deactivate sensory nerves that contribute to pain. Prior studies of the myoscience device, Cryo-Touch III (a.k.a. PCP 1.0) have provided evidence of effectiveness and safety for applications in this indication.

In a proof of concept study sponsored by myoscience, Inc., the Cryo-Touch III device was used to temporarily stop conduction along the Infrapatellar branch of the Saphenous Nerve (ISN) and shown to temporarily relieve pain in patients with osteoarthritis of the knee. At 7 days post-treatment, 91% of Subjects reported ≥ 1 point improvement on the visual analog scale (VAS) for pain. This study also looked at joint pain, function and stiffness using the Western Ontario and McMaster Osteoarthritis Index (WOMAC); at 7 days post-treatment, 77% of Subjects had a clinically important improvement of ≥ 2 points per question on average. Fifty-six days following treatment, 70% of Subjects reported a positive effect from treatment. There were no device-related serious adverse events reported in this proof of concept study. Ten adverse events were reported by 9 of the 33 Subjects. Four of these events, leg numbness (2), nausea during procedure (1) and tingling and foot pain (1), were reported to be definitely related or possibly related to the study device. All of these events were deemed mild or moderate and were transient in nature.

The goal of the study described herein is to compare the degree and duration of iovera° treatment as compared to sham treatment in reducing pain associated with knee osteoarthritis by targeting the infrapatellar branch of the saphenous nerve.

2. REGULATORY STATUS

The iovera° device is 510(k)-cleared (K133453) for producing lesions in peripheral nervous tissue by application of cold to selected sites for blocking pain. Cleared indications include general tissue destruction during surgical procedures and cryotreatment of nerves to block pain.

Additionally, myoscience and an independent review board have determined that the iovera° device is a non-significant risk device under 21 CFR §812.2(b) as described for use within this protocol. Therefore, an approved Investigational Device Exemption (IDE) from FDA is not required to legally perform the study described herein in the US.

[1] Arthritis Foundation: Osteoarthritis Fact Sheet, found at http://www.arthritis.org/files/images/newsroom/media-kits/Osteoarthritis_fact_sheet.pdf, accessed March 17, 2014

3. STUDY OBJECTIVE

The primary objective of this study is to evaluate the effectiveness and safety of the iovera° device for the temporary reduction of pain associated with knee osteoarthritis.

4. STUDY DESIGN

This is a multi-center, prospective, randomized, double-blind, sham-treatment controlled trial.

5. BLINDING

This is a double-blind study. The treating Investigator and Subject are blinded to study treatment. Investigators and Subjects will be unblinded as medical need arises. Every effort should be made to maintain Subject and Investigator blinding throughout the study.

6. DURATION

Each Subject participates for up to 210 days. Enrollment is expected to take up to 12 months. Total study duration is expected to be up to 18 months.

7. INVESTIGATOR QUALIFICATIONS

To participate in this study, an Investigator must have an active medical license. The Investigator must undergo training on the study device prior to enrolling Subjects in the study. Licensed qualified and trained Physician Assistants and Nurse Practitioners may perform iovera° treatments under the direction of the Investigator.

8. STUDY POPULATION

8.1 Target Patient Population

The target patient population is adult men and women ages 35 to 75 in the United States with pain associated with grade II or III knee osteoarthritis as rated on the Kellgren-Lawrence grading scale.

8.2 Subject Eligibility

To be included in the study, Subjects must meet all of the inclusion criteria and none of the exclusion criteria list in **Table 1**.

Table 1. Study Eligibility Criteria.

Inclusion Criteria

1. 35 – 75 years of age
2. American College of Rheumatology (ACR) criteria for osteoarthritis of the knee. This includes radiographic evidence of osteophytes and at least one of the following: age > 50 years old, morning stiffness < 30 minute duration or crepitus on motion.
3. Grade II or III osteoarthritis of the knee as determined by Kellgren-Lawrence classification grading scale on anteroposterior (AP) x-ray within previous 6 months.
4. Subjects are ambulatory without assistive devices.
5. Knee pain of ≥ 40 mm on Visual Analog Scale (VAS) when performing one of two movements that elicit the worst pain: standing from a seated position or walking up/down stairs.
6. Subject reports knee pain in the anterior and/or inferior aspect of the knee as documented on the knee pain map in the appropriate areas.
7. A diagnostic lidocaine (without epinephrine) block of the infrapatellar branch of the saphenous nerve results in a 50% reduction in the VAS pain assessment score when performing the activity

that elicits the worst pain: standing from a seated position or walking up/down stairs.

8. Subject is able to tolerate a washout of prescription and over-the-counter pain medication used for pain relief for a duration of 5X the half-life of the medication prior to the Baseline visit.
9. Subject is able to tolerate a washout of adjunctive therapies for knee pain for 72 hours prior to the Baseline visit.
10. Western Ontario and McMaster Osteoarthritis Index (WOMAC) NRS3.1 Pain subscore ≥ 20 at Baseline/Visit 2.
11. Subject is able to tolerate discontinuation of all pain medication or adjunctive therapy for knee pain throughout the duration of the study. Acetaminophen may be used as rescue medication with a maximum dose of 4g per day.
12. Subject is able to tolerate discontinuation of rescue medication, acetaminophen, for 24 hours prior to all follow-up visits.
13. Prescription and over-the-counter pain medications must be maintained on a stable schedule for at least two weeks prior to screening.
14. Subject is willing and able to give written informed consent.
15. Subject is willing and able to comply with study instructions and commit to all follow-up visits for the duration of the study.
16. Subject is in good general health and free of any systemic disease state or physical condition that might impair evaluation or which in the Investigator's opinion, exposes the Subject to an unacceptable risk by study participation.

Exclusion Criteria

1. History of a partial or full knee replacement of the knee to be treated.
2. Planned partial or full knee replacement within the next 12 months in knee to be treated.
3. Previous myoscience Focused Cold Therapy™ treatment.
4. Viscosupplementation within the previous 6 months in knee to be treated.
5. Subject reports the majority of knee pain outside of the anterior/inferior aspect of the knee.
6. Intra-articular steroid injection in the knee to be treated within previous 3 months.
7. Gross deformity of the knee including varus or valgus.
8. Started physical therapy of the knee to be treated within 3 months of screening.
9. Received acupuncture for knee pain within 3 months prior to screening.
10. Body Mass Index ≥ 35.
11. Prior surgery in the treatment area that may alter the anatomy of the infrapatellar branch of the saphenous nerve or result in scar tissue in the treatment area.
12. Open and/or infected wound in the treatment area.
13. Disease of the spine, hip, contralateral knee or other lower extremity joint of sufficient degree affecting the assessment of the treated knee.
14. Acetaminophen intolerance or allergy.
15. Allergy to lidocaine.
16. History of cryoglobulinemia
17. History of paroxysmal cold hemoglobinuria.
18. History of cold urticaria.
19. History of Raynaud's disease.
20. History of pes anserinus bursitis in the knee to be treated.
21. Use of extended-release or long-acting opioids within previous 3 months.
22. Use of immediate-release opioids for more than 3 days per week within previous month.
23. Subject is pregnant or planning to become pregnant while enrolled in the study.
24. Current enrollment in any investigational drug or device study or participation within 30 days prior to screening.
25. Any additional diagnosis that in the opinion of the Investigator directly contributes to knee pain.
26. Any concomitant inflammatory disease or other condition that affects the joints (e.g. rheumatoid arthritis, metabolic bone disease, gout, active infection, etc.)
27. Any clotting disorder and/or use of an anticoagulant (e.g., aspirin, warfarin, clopidogrel, etc.) within seven (7) days prior to administration of the device.

28. Any local skin condition at the treatment site that in the Investigator's opinion would adversely affect treatment or outcomes.
29. Any chronic medical condition that in the Investigator's opinion would prevent adequate participation.
30. Any chronic medication use (prescription, over-the-counter, etc.) that in the Investigator's opinion would affect study participation or Subject safety.
31. For any reason, in the opinion of the Investigator, the Subject may not be a suitable candidate for study participation (i.e., history of noncompliance, drug dependency, any related knee injury due to a worker's compensation claim, etc.).
32. Known liver dysfunction.

9. STUDY DEVICE AND TREATMENT PROCEDURE

The study device and sham treatment are described briefly below.

9.1 Description

The myoscience iovera° device is a next generation device designed to temporarily reduce pain. The device consists of a reusable, portable Handpiece, along with single-patient use Smart Tips (aka cryoprobes) and disposable nitrous oxide (N_2O) cartridges. The Smart Tip contains embedded software that manages procedure parameters and provides physician feedback throughout all states of device preparation, treatment and post-treatment via communication with the Handpiece. The Handpiece is battery powered and is stored and recharged via the Charging Dock.

The iovera° device produces the desired effect through initiation of a cooling cycle. Each cooling cycle is initiated by insertion of the Smart Tip into the selected procedure site and activation of the cryogen flow. A freezing zone forms around the end of the Smart tip affecting the adjacent tissue.

The cryogen is provided in a nitrous oxide cylinder attached to a custom filter, known as the Cartridge. To remove contaminants that may be present in the cylinder, a custom filter is added to the cylinder to filter the liquid nitrous oxide before it enters the Handpiece. This ensures optimal performance of the device.

A specially designed Smart Tip is included. The Smart Tip needles are made of stainless steel and have a closed-tip, fully enclosing the cryogen. As the cryogen gas travels through the length of the needle, an ice ball develops around the needle causing the surrounding tissue to be frozen. Operation instructions and further details on the device are provided in the ***User Guide***.

Device training will be provided to the Investigator and study staff prior to the initiation of study enrollment.

Sham Smart Tip

The appearance of the Smart Tips used for the sham treatment is identical to the tips used for an active treatment. The sham Smart Tip does not allow a freezing zone to form therefore it does not provide a therapeutic treatment. The subject does not sense or feel the subcutaneous cooling of an active Smart Tip so they are unable to discern if a sham or active Smart Tip is in use during a treatment.

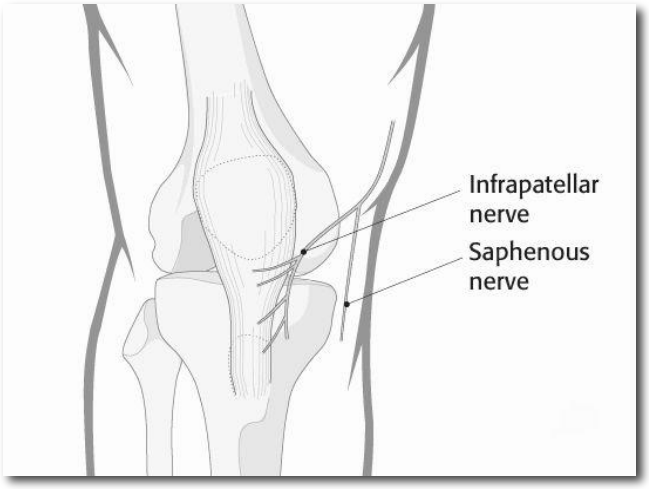
During treatment, Sham Smart Tips used with the iovera° will employ the same lights and activation features as an active Smart Tip so their operation is identical to the operator. In addition, the User Guide supports the sham Smart Tip.

9.2 Instructions for Use and Administration

Use of the iovera° device is described briefly herein. For details see the ***User Guide*** as provided by myoscience, Inc.

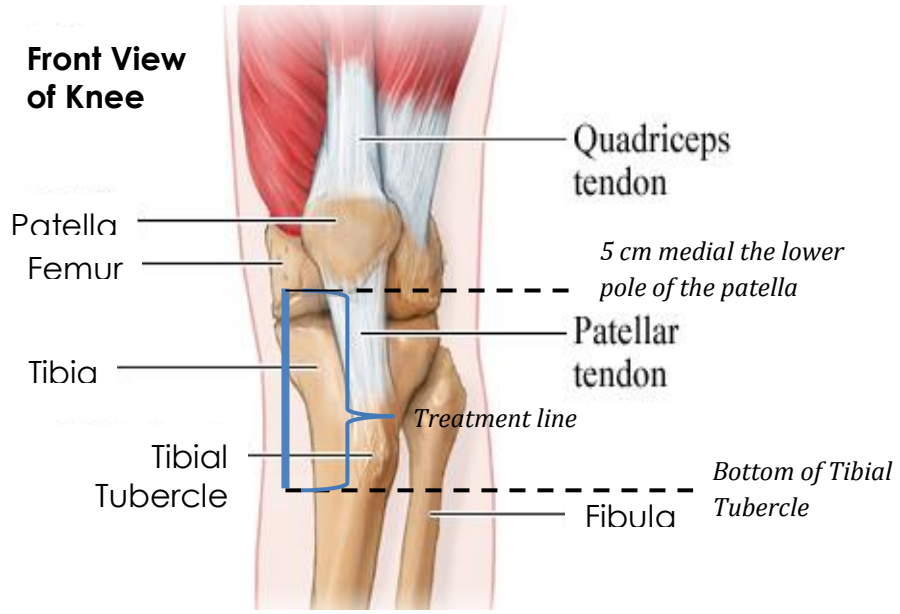
The iovera° device is used on awake Subjects who are prepared with local anesthesia only. The treatment target is the infrapatellar branch of the saphenous nerve shown in **Figure 1**. Training for the treatment procedure will be provided to the Investigator and study staff prior to the initiation of study enrollment.

Figure 1. Infrapatellar branch of the Saphenous Nerve



Treatment will be performed unilaterally and will be guided by visualization and palpation of anatomical landmarks. Landmarks and treatment line will be marked on the skin as shown in **Figure 2**.

Figure 2. Treatment Line



Note that the study Sponsor will provide the following supplies:

- iovera° devices, Smart Tips and cryogen cartridges
- Surgical pen or other marking tool
- Measuring tape
- Rulers

The investigational site will provide the following:

- Injectable lidocaine used for local anesthesia
- Syringes for administration of local anesthesia
- Needles for administration of local anesthesia
- Gauze
- Alcohol wipes

9.3 Contraindications

Use of iovera° is contraindicated in the following situations:

- Cryoglobulinemia
- Paroxysmal cold hemoglobinuria
- Cold urticaria
- Raynaud's disease
- Open and/or infected wounds at or near the treatment site

Note: physician discretion should be exercised when patient presents with existing neuromuscular disease compromising the regeneration of peripheral nerves that may be involved in the treatment.

9.4 Risks

The iovera° device involves percutaneous access to subcutaneous tissue using a needle and use of dermal anesthesia. Passage of a needle into the skin, cooling of subcutaneous soft tissue and delivery of local anesthesia are known to be associated with the following risks or expected side effects (ESE):

- Bruising (ecchymosis)
- Swelling (edema)
- Inflammation and/or redness (erythema)
- Pain and/or tenderness
- Altered sensation (localized dysesthesia)

Proper use of the device as described in the User Guide can help reduce or prevent the following complications:

- Injury to the skin related to application of cold or heat
- Hyper- or hypo-pigmentation at the treatment site
- Skin dimpling at the treatment site
- Loss of motor function outside the treatment area

Expected side effects and complications will be assessed at each follow-up visit and will be documented independently of adverse events with the exception of loss of motor function outside the treatment area. Loss of motor function outside the treatment area will be documented as an adverse event. In general, these findings have been mild to

moderate and transient in nature and usually resolve over time. Prior studies have shown a very low rate of device-related skin injury.

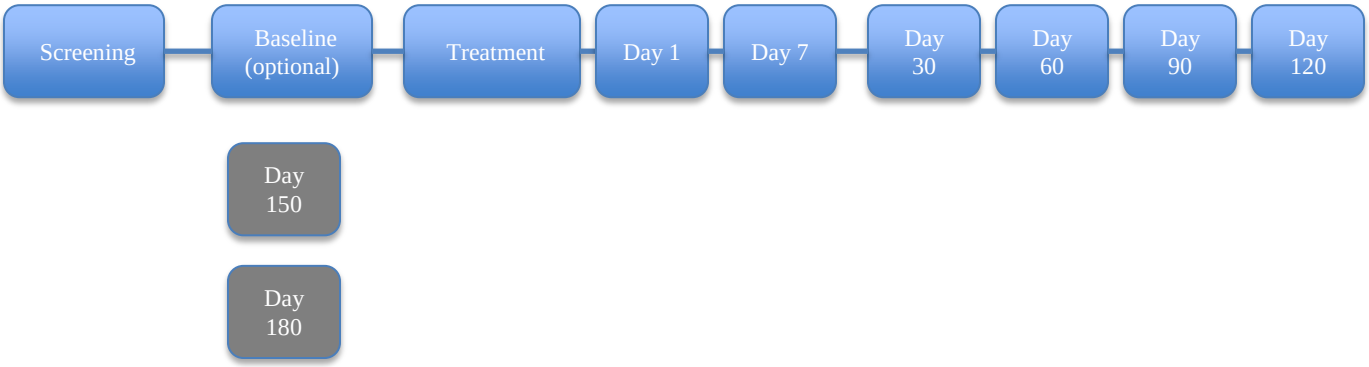
If an expected side effect or complication occurs outside 3cm radius elliptical region around the linear grouping of needle insertions, it is classified as an adverse event. If an expected side effect or complication persists ≥ 30 days, it is classified as an adverse event. Loss of motor function outside the treatment area is documented as an adverse event regardless of the duration.

10. STUDY PROCEDURES

10.1 Overview

An Overview of the study visits is shown in **Figure 3**. Eligible Subjects are randomized to iovera° treatment or to sham treatment with the iovera° device. The primary effectiveness endpoint is the comparison of change in WOMAC A Pain subscale from Baseline to Day 30.

Figure 3. Overview of Study Visits



10.2 Recruitment

Potential study participants will be recruited from clinics of participating Investigators, as well as local advertising. Any study-related advertisements will be approved by the governing IRB prior to use.

10.3 Screening /Visit 1 (0 to -30 days)

The screening and baseline visit procedures will be completed at the same visit if the Subject has discontinued all prescription and over-the-counter pain medications as well as herbal supplements and all other treatments for knee osteoarthritis for a duration of 5X the half-life of the medication and has discontinued adjunctive therapies for knee pain for 72 hours. The screening and baseline procedures will be completed at separate visits if the Subject has been taking pain medications, herbal supplements and/or other adjunctive therapies for knee osteoarthritis.

A patient who signs the informed consent document will be considered a study Subject. A Subject who withdraws from the study prior to randomization will not count toward the study's sample size. Potential participants will be screened for eligibility against **Table 1**.

Once the informed consent form is signed, the Subject is assigned a study number. The Subject number is comprised of the 2 digit site number followed by a consecutively assigned 3-digit Subject number that starts with 001. For example, the first screened Subject for site 05 will be assigned study number 05-001. The Subject number is the identification number used on eCRFs and other study documents throughout the study. In the event a Subject withdraws from the study, their Subject number cannot be reassigned to any other Subject.

The Investigator, or designee, will document the Subject's medical history, demographic information, complete an assessment of the intended treatment area and concomitant medications/concurrent procedures.

The Subject will complete a WOMAC questionnaire as well as a VAS pain assessment. The VAS pain assessment will be completed based on 2 activities; these activities include standing from a seated position and walking up/down stairs. Throughout the duration of the study, each subsequent VAS pain assessment will be based on performing the same activity which elicited the most pain during the Screening VAS pain assessment. If the screening and baseline procedures are completed at the same visit, only 1 VAS pain assessment and 1 WOMAC questionnaire will be completed. The Subject will also complete the SF-36 Questionnaire and vital signs will be taken.

To be eligible for participation, standing anteroposterior (AP) and lateral x-rays taken within the last 6 months must show grade II or grade III osteoarthritis of the knee intended for treatment. If either an AP or lateral x-ray of the knee to be treated is not available from within the previous 6 months, then the missing x-ray(s) will be taken and must show grade II or grade III osteoarthritis of the knee intended for treatment. Subjects who are pregnant are excluded from the study and will not have x-rays taken.

If the Subject remains eligible at the end of the screening visit, the Subject will be scheduled for a baseline visit. Prior to the baseline visit, the Subject must discontinue all prescription and over-the-counter pain medications as well as herbal supplements for a duration of 5X the half-life of the medication and all other adjunctive therapies for knee osteoarthritis for a minimum of 72 hours.

10.4 Baseline/Visit 2 (0 to -14 days)

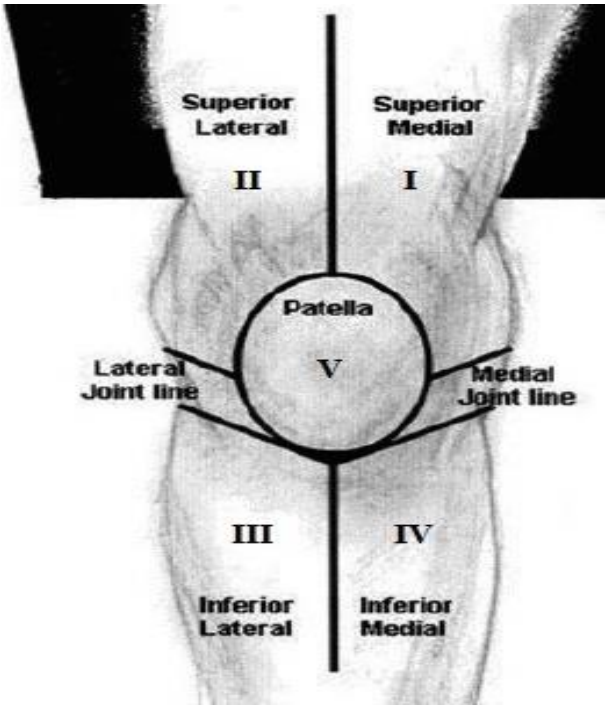
Subjects will complete a WOMAC questionnaire, VAS pain assessment and SF-36. The VAS pain assessment will be completed based on the previously indicated activity and must be $\geq$ 40mm. If the screening and baseline procedures are completed at the same visit, only one VAS pain assessment and 1 WOMAC questionnaire will be completed. Eligibility will be confirmed.

Pain will be documented on the knee pain map shown below in **Figure 4**. Subjects will indicate the area(s) of his/her knee pain that are present when performing the previously

indicated activity. The Investigator, or designee, will document the area(s). To be eligible for treatment with the study device:

- knee pain must be located in the inferior medial portion of the knee, including the medial joint line, shown in area IV in Figure 4;
- pain must not be located in the superior medial (area I) or superior lateral (area II); and
- if knee pain includes the inferior lateral area of the knee (area III), including the lateral joint line, or the patella (area V), then the majority of the pain must arise from area IV.

Figure 4. Knee Pain Map



The Investigator, or designee, will review the Subject's medical history, demographic information, concomitant medications/concurrent procedures and complete an assessment of the intended treatment area. Any new diagnosis or medical occurrence that was not present at the screening visit will be documented in the Subject's medical history.

The Investigator, or designee, will perform a diagnostic lidocaine block of the infrapatellar branch of the saphenous nerve. Following the diagnostic block and within 10 minutes, the Subject will be asked to perform the same activity that elicited the worst knee pain prior to the nerve block. The Subject will then complete a VAS pain

assessment when performing this activity. The post-diagnostic lidocaine block VAS pain assessment must show at least 50% reduction for inclusion into the study.

Once a Subject has completed the screening and baseline visits and meets all inclusion and none of the exclusion criteria, the Subject will be scheduled for the Treatment Visit. The treatment visit can be completed on the same day as screening and/or baseline visit if a washout period of 5X the half-life of prescription pain medication, over-the-counter pain medication and herbal supplements has been completed. A washout period of 72 hours must be completed for other adjunctive therapies for knee osteoarthritis.

10.5 Treatment/Visit 3 (Day 0)

Subjects will complete a VAS pain assessment based on the previously chosen activity done at Visit 1. Medical history will be reviewed as well as concomitant medications and procedures. Any change in any medical condition prior to the initiation of the study treatment will be documented as a change in medical history. Any new diagnosis or medical occurrence that was not present prior to the study treatment, will be documented in the Subject's medical history. Completion of a washout period of prescription and over-the-counter pain medication for a duration of 5X the half-life of the medication as well as a 72 hour washout period of other adjunctive therapies for knee pain. Vital signs will be taken. Eligibility will also be confirmed.

Subjects will be randomized in a 2:1 manner to either:

- **iovera° Treatment**: Subject undergoes treatment with the study device using a functioning Smart Tip.
- **Sham Treatment**: Subject undergoes treatment with the study device using a sham Smart Tip.

The 2:1 randomization maximizes the number of participants that may be treated with the active, functioning Smart Tip as those subjects who are randomized to the sham treatment are required to be free from medication or other treatment for pain for the duration of the study (other than up to 4g per day of acetaminophen).

Randomization assignments will be stratified by study center with randomly chosen block sizes of 6 or 9. Small but randomly determined block sizes preserve treatment assignment balance within study center while maintaining assignment unpredictability. The Investigator or designee will record the randomization assignment in the source documentation and eCRF. Any Investigator who is discovered to tamper with randomization will be immediately terminated from the study.

The iovera° device will be prepared by the trained Investigator (or Sponsor designee) according to the ***User Guide***. If at any time the device does not perform as expected the Investigator (or designee) will follow procedures as outlined in the ***User Guide***.

Prior to the initiation of the iovera° treatment, the Investigator, or designee, will mark the treatment line on the knee to be treated as shown in Figure 2 located in section 9.2. After marking the treatment line, skin along the treatment line will be cleansed with alcohol. Lidocaine without epinephrine will be injected along the treatment line superficially in order to achieve complete cutaneous anesthesia and deep to block conduction of the

infrapatellar branch of the saphenous nerve in the same manner as the diagnostic block performed as part of screening.

Once complete cutaneous anesthesia of the treatment line and the nerve is achieved, the Investigator, or designee, will complete the iovera° treatment along the treatment line. Regardless of the length of treatment line (down to tibial tubercle), adjacent insertions are placed along the treatment line until the entire line has been treated so all Subjects receive the same treatment. Treatment is not to be modified or influenced by any Subject response to reduction in knee pain. Representatives of myoscience, Inc. may be present during the treatment. Photos of the treatment area may be taken.

Upon completion of treatment, the treatment area will be cleansed and the skin will be left undressed. The Investigator or designee will assess the treatment area.

The Subject will be instructed to report any adverse events or expected side effects to the Investigator between and at the follow-up visits. Photographs of the treatment area may be obtained post-treatment.

Acetaminophen will be dispensed to the Subject. Acetaminophen is to be used as a rescue medication to a maximum of 4g per day. The Subject will be instructed to use only the acetaminophen provided by the Investigator.

10.6 Study Follow-Up

Study-related follow-up visits occur at Day 1, 7, 30, 60, 90, and 120 with optional visits at Day 150 and 180. The study's schedule of assessments is shown in **Table 3**.

10.6.1 Visit 4/Day 1 (+1 day), Visit 5/ Day 7(± 3 days), Visit 6/ Day 30(±7 days), Visit 7/Day 60(±7 days), and Visit 8/Day 90(±7 days)

Subjects will be evaluated and data collected per the schedule of events. Any changes in concomitant medications/concurrent procedures will be documented. Any expected side effects, adverse events, adverse device effects and/or SAE/UADE/USADE will be assessed and documented. Photographs may be taken of the treatment area.

The Subject will complete a WOMAC questionnaire, a VAS pain assessment based on the previously chosen activity, , Patient Global Impression of Change (PGIC), SF-36 and will answer Subject experience questions.

Previously dispensed acetaminophen bottles will be returned at each study visit. A pill count will be completed by the study coordinator, or designee. At the Day 1/Visit 4 Visit, acetaminphen dispensed at the treatment visit will be re-dispensed to the subject. A new supply of acetaminophen will be dispensed at each subsequent follow-up visit until the Subjects exits the study.

10.6.2 Visit 9/Day 120 (±7 days)

Subjects will be evaluated and data collected per the schedule of events. Any changes in concomitant medications/concurrent procedures will be documented. Any expected side effects, adverse events, adverse device effects and/or

SAE/UADE/USADE will be assessed and documented. Photographs may be taken of the treatment area.

The Subject will complete a WOMAC questionnaire, a VAS pain assessment based on the previously chosen activity, PGIC, SF-36 and will answer Subject experience questions.

Acetaminophen bottles will be returned. A pill count will be completed by the study coordinator, or designee.

If the Subject continues to have an effect from treatment at Day 120, acetaminophen will be dispensed and the Subject will return for a Day 150 visit. Effect will be determined by the WOMAC Pain subscore. If the WOMAC Pain subscore is less than the WOMAC Pain subscore at baseline (completed at the Baseline visit), the Subject continues to have a treatment effect.

If the WOMAC Pain subscore at Visit 9 is greater than or equal to the WOMAC Pain subscore at baseline, the Subject will be exited from the study at the completion of this visit unless the Subject has any ongoing device-related or procedure-related adverse events as described in section 10.8.

Once a Subject has completed the study and is exited from the study, the Subject may be eligible for a single active iovera° treatment of the infrapatellar branch of the saphenous nerve. This single active iovera° treatment will be completed at the discretion of the Investigator once all subjects enrolled and treated at the site have completed required study follow-up visits This treatment is completed at no cost to the Subject or Investigator and is completed outside the parameters of this clinical study.

10.6.3 Visit 10/Day 150 (±7 days)

Subjects will be evaluated and data collected per the schedule of events. Any changes in concomitant medications/concurrent procedures will be documented. Any expected side effects, adverse events, adverse device effects, and/or SAE/UADE/USADE will be assessed and documented. Photographs may be taken of the treatment area.

The Subject will complete a WOMAC questionnaire, a VAS pain assessment based on the previously chosen activity, PGIC, SF-36 and will answer Subject experience questions.

Acetaminophen bottles will be returned. A pill count will be completed by the study coordinator, or designee.

If the Subject continues to have an effect from treatment at Day 150, acetaminophen will be dispensed and the Subject will return for a Day 180 visit. Effect will be determined by the WOMAC Pain subscore. If the WOMAC Pain subscore is less than the WOMAC Pain subscore at baseline (completed at the Baseline visit), the Subject continues to have a treatment effect.

If the WOMAC Pain subscore at this visit is greater than or equal to the WOMAC Pain subscore at baseline, the Subject will be exited from the study at the completion of this visit unless the Subject has any ongoing device-related or procedure-related adverse events as described in section 10.8.

Once a Subject has completed the study and is exited from the study, the Subject may be eligible for a single active iovera° treatment of the infrapatellar branch of the saphenous nerve. This single active iovera° treatment will be completed at the discretion of the Investigator once all subjects enrolled and treated at the site have completed required study follow-up visits This treatment is completed at no cost to the Subject or Investigator and is completed outside the parameters of this clinical study.

10.6.4 Visit 11/Day 180 (±7 days)

Subjects will be evaluated and data collected per the schedule of events. Any changes in concomitant medications/concurrent procedures will be documented. Any expected side effects, adverse events, and/or SAE/UADE/USADE will be assessed and documented. Photographs may be taken of the treatment area.

The Subject will complete a WOMAC questionnaire; a VAS pain assessment based on the previously chosen activity, PGIC, SF-36 and will answer Subject experience questions.

Acetaminophen bottles will be returned. A pill count will be completed by the study coordinator, or designee.

At the completion of this visit, the Subject will be exited from the study unless the Subject has any ongoing device-related or procedure-related adverse events as described in section 10.8.

Once a Subject has completed the study and is considered exited from the study, the Subject may be eligible for a single active iovera° treatment of the infrapatellar branch of the saphenous nerve at the discretion of the Investigator once all treated at the site have completed required study follow-up.. This treatment is completed at no cost to the Subject or Investigator and is completed outside the parameters of this clinical study.

In the event that a Subject does not attend a scheduled visit, every effort will be made to reschedule and those efforts will be documented. In the event a Subject is lost to follow-up, a study exit eCRF will be completed.

If a Subject decides to withdraw participation early, the Subject will be asked to complete a final study visit and exit the study. The Investigator or Sponsor may at any time during the study remove a Subject if there is any potential safety issue or extreme non-compliance. In all cases every attempt will be made to complete a final study visit.

Table 3. Schedule of Assessments.

Assessment	Visit 1/Screening (Day 0 to -30)	Visit 2/Baseline (Day 0 to -14)	Visit 3/Treatment (Day 0)	Visit 4/Day 1	Visit 5/Day 7	Visit 6/Day 30	Visit 7/Day 60	Visit 8/Day 90	Visit 9/Day 120	Visit 10/Day 150*	Visit 11/Day 180*
Informed Consent	X										
Eligibility	X	X	X								
Medical history	X	X	X								
Medication Assessment	X	X	X	X	X	X	X	X	X	X	X
Prior/Concurrent Therapy	X	X	X	X	X	X	X	X	X	X	X
Randomization			X								
Study Treatment			X								
Photographs (if applicable)			X	X	X	X	X	X	X	X	X
Vital signs	X		X								
WOMAC Questionnaire	X	X		X	X	X	X	X	X	X	X
VAS Pain Assessment	X	X	X	X	X	X	X	X	X	X	X
PGIC				X	X	X	X	X	X	X	X
SF-36	X	X		X	X	X	X	X	X	X	X
Subject Experience Questions				X	X	X	X	X	X	X	X
Acetaminophen accountability				X	X	X	X	X	X	X	X
Dispense acetaminophen			X	X	X	X	X	X	X	X	
AE/SAE Assessment			X	X	X	X	X	X	X	X	X
Diagnostic Lidocaine Block		X									
ISN Lidocaine Block			**X**								

*These visits are performed only if there is a continued effect reported at the previous visit as determined by WOMAC Pain subscale.

Follow-up visits generally consist of the following:

- The Investigator, or designee, assesses the occurrence of health status changes and adverse events since last study visit;
- The Investigator, or designee, determines whether any changes in daily medications have occurred;
- The Investigator, or designee, examines Subject focusing on the occurrence of expected side effects and complications;
- The Subject completes WOMAC questionnaire, a VAS pain assessment based on the previously chosen activity, PGIC, SF-36 and answers Subject experience questions.
- The study coordinator, or designee, collects acetaminophen, performs accountability and dispenses new acetaminophen supply.

10.7 Post Treatment Prohibited Medications or Therapies

In this study, during the entire treatment and follow-up period, subjects will not:

- Undergo any adjunctive treatment for knee osteoarthritis including steroid injections, viscosupplementation, or knee replacement.
- Take prohibited medications including prescription and over-the-counter pain medications other than acetaminophen.

Investigator or designee will record use of these prohibited medications/treatments as a protocol deviation in the study source and eCRF. The subject will continue to be followed in the study until Day 120.

10.8 Photographs

Photographs may be taken of the treatment area at the treatment visit and at the follow-up visits. Photographs will be labeled appropriately, stored electronically (e.g., JPEG, PNG or other relevant format) and sent to the Sponsor according to Sponsor instructions.

10.9 Study Exit

When the final study visit is complete, the Subject's participation in the study is complete and the Investigator, or designee, will complete the study exit eCRF.

If a Subject is experiencing an unresolved device or procedure related adverse events at the final study visit, the Subject will be followed by the Investigator until resolution occurs.

10.10 Subject Discontinuation

A Subject may be withdrawn from the study prior to completion for any of the following reasons:

- Voluntary withdrawal of consent
- Adverse event preventing study participation
- Investigator believes risk of further subject participation outweighs benefit
- Medical need for prohibited medications or treatment
- Persistent non-compliance or lost to follow-up (A Subject is considered lost to follow-up after the site makes 3 attempts to contact the via email or phone call and a certified letter is sent to the Subject.)

The Investigator/Coordinator will complete a study exit form in the eCRF for any subject who prematurely discontinues from the study. If discontinuation was the result of an AE, the AE will also be recorded in the eCRF.

10.11 Study Termination

The Sponsor may terminate the study as a whole or at individual study sites under the following circumstances:

- Suspicion of risk to subjects, including occurrence of high rate of known AEs or unexpectedly high rate of unexpected AEs
- Poor site compliance with the study protocol
- Inadequate site enrollment
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Persistent non-compliance with IRB or regulatory requirements
- Persistent failure to comply with obligations arising from the clinical trial agreement
- Other business reasons (e.g., insolvencies or business entity liquidation)

The Sponsor will document reasons for study suspension and notify relevant site Investigators and governing IRBs. If suspension occurred because of a safety issue, all Investigators will be notified. When terminating the study, the Sponsor and Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10.12 Study-Related Assessments

10.12.1 Western Ontario and McMaster Osteoarthritis Index (WOMAC)

The WOMAC is a tri-dimensional, disease-specific, patient-reported outcome measure. It consists of 24 questions with 5 questions regarding pain, 2 questions regarding stiffness and 17 questions regarding function. A copy of the WOMAC is located in Attachment 1.

Completion of the WOMAC questionnaire will take approximately 15 minutes to complete. After competion by the Subject, the study coordinator or designee will enter into the eCRF.

10.12.2 Visual Analog Scale (VAS)

VAS pain assessment is a measure of pain intensity. The scale is made up of a 10 cm (100mm) horizontal line. The far left of the horizontal line is labeled "no Pain" while the far right of the horizontal line is labeled "worst imaginable pain."

The Subject places an X on the line representing the intensity of his/her pain. A copy of the VAS is located in Attachment 2.

The VAS will be completed by the Subject and will take approximately 5 minutes to complete. The study coordinator or designee will measure the distance to determine the score and enter into the eCRF.

10.12.3 Patient Global Impression of Change (PGIC)

The PGIC contains 1 question assessing the Subject's overall impression of change since being treated in the study. The question is answered on a 7 point scale.

The PGIC question will take less than 5 minutes to complete. After completion by the Subject, the study coordinator, or designee, will enter into the eCRF. The PGIC question is located in Attachment 3.

10.12.4 36-Item Short Form Health Survey (SF-36)

The SF-36 contains 36 questions assessing the Subject's health-related quality of life. A copy of the SF-36 is located in Attachment 4.

The SF-36 will take approximately 15 minutes to complete. After completion by the Subject, the study coordinator, or designee, will enter into the eCRF

10.12.5 Subject Experience Questions

Subject experience questions will be verbally administered by the study coordinator or designee. Questions will be asked at each follow-up visit and will take approximately 10 minutes to complete. The Subject experience questions are located in Attachment 5.

11. STATISTICAL METHODOLOGY AND ANALYSES

11.1 General Statistical Consideration

The statistical software package SAS® Version 9.2 or higher (SAS Institute, Cary, NC, USA) will be used to perform all analyses and to summarize data.

For continuous variables, descriptive statistics will include the number of patients reflected in the calculation (n), mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized using frequency counts and percentages.

The Statistical Analysis Plan will be finalized prior to the interim and final database locks for analyses. The final primary effectiveness analysis will be performed at the conclusion of study.

11.2 Analysis Population

The primary effectiveness analysis of the study objectives will be conducted on the Per-Protocol Evaluable population, defined below. Additional, supportive analyses may be conducted on the Treated Population. All safety analyses will be performed on the Treated Population.

Treated Population

The treated population will consist of all patients who are randomized and undergo the assigned treatment.

Per-Protocol Evaluable Population
The analysis population includes patients who are randomized, undergo the assigned treatment, and have complete follow-up data after 30 days.

11.3 Hypothesis and Methods of Analysis

The primary hypothesis of interest is to show that the absolute change from baseline (after 30 days) in number of points on WOMAC A (pain) subscale with iovera° is superior to that of sham.

11.3.1 Primary Effectiveness Analyses

The primary endpoint is the absolute change from baseline (after 30 days) in number of points on WOMAC A (pain) subscale. The WOMAC completed at Visit 2 is considered the baseline WOMAC score.

Trial success is demonstrated under the primary hypothesis if the one-sided p-value corresponding to the study t-test that the mean change in score under iovera is greater than that of sham is less than or equal to .025. A detailed description of the primary endpoint analysis is located in Attachment 6.

11.3.2 Secondary Effectiveness Analyses

- The responder rate at Day 30, which is defined as at least a 30% reduction in the WOMAC pain score at Day 30 compared to baseline.
- The responder rate at Day 1/Visit 4, which is defined as at least a 30% reduction in the WOMAC pain score at Day 1/Visit 4 compared to baseline
- Time to return to baseline WOMAC pain score after 30% reduction achieved
- Change in WOMAC stiffness at Day 30,
- Change in WOMAC function at Day 30, and
- Change in VAS at Day 30

The number and percent of subjects achieving 30% reduction in WOMAC pain score will be reported by treatment group with 95% confidence intervals and compared for iovera° versus sham. Mean change from baseline in WOMAC stiffness, WOMAC function, and VAS at Day 30 will be reported by treatment group with 95% confidence intervals and compared for iovera° versus sham.

Additional secondary effectiveness endpoints will be assessed to further characterize pain relief and functional performance. These include:

- Subject Experience
- SF-36 Scales and Summary Measures
- Patient Global Impression of Change

For each secondary effectiveness endpoint, the result, as well as the Change from Baseline value, will be summarized at each visit the endpoint is collected. Two sets of hypotheses tests will be performed: the paired t-test will be used to evaluate if the Change from Baseline result is statistically different from no change, while the two-independent sample t-test will be used to statistically evaluate the difference between the two treatment groups for both the original result and for the Change from Baseline result. Confidence intervals will be provided to assist in the interpretation of the results.

11.3.3 Safety Analyses

Summary tables of adverse events occurring after the initiation of study treatment, or a reported increase in severity of a pre-existing condition after the calendar date/ time of the study treatment will be produced. Similar analyses will be done for device-related AEs, SAEs, and device-related SAEs.

Safety analyses will be performed on the Treated Population defined in Section 11.2. Adverse events will be mapped to system organ classes and preferred terms using the MedDRA dictionary. Adverse events will be summarized by system organ class and preferred term. Individual patient data listing will present both verbatim and MedDRA terms. The number and percent of subjects that experienced expected side effects, maximum severity and maximum impact of the expected side effects within subjects will be presented by time period (prior to Day 7 follow up visit, between Day 7 and Day 30 follow up visit, and post Day 30 follow up visit).

11.3.4 Exploratory Analysis

Additional statistical analysis such as performing the primary effectiveness analysis on selected patient population that is exploratory in nature may be performed.

11.4 Missing Data

A sensitivity analysis will be performed on the Treated Population accounting for missing data for the primary endpoint. This analysis will be a tipping point analysis where the Sponsor assumes the same change in baseline for all missing subjects for all subjects within the sham group and separately for all subjects within the treatment group. The Sponsor will build the grid assuming missing values ranging from the first to third observed quartiles in both the control and treatment groups. The p-value of the primary endpoint analysis will then be reported under the grid of all possible combinations of values under the sham and treatment groups. The observed standard deviations will be used in the t-test so assuming similar values for the missing data does not arbitrarily decrease the standard deviation and make the t-test more powerful.

The Sponsor will report the smallest difference in assumed values for each different control rate that leads to a statistically significant test.

11.5 Study Power and Sample Size

The study's minimum sample size is 80 subjects and maximum sample size is 180 subjects. The final sample size will be determined by an adaptive design that allows for

multiple interim looks at the data in order to enable an early stop for success or futility based upon the primary efficacy endpoint.

When 80 patients are enrolled and every 20 patients enrolled thereafter, the Sponsor will make decisions to possibly stop for success, stop for futility or continue enrollment up until we have 180 total patients enrolled. These decisions will be made based on the predictive probability of success of the trial under the currently enrolled patients and under the patients that we are yet to enroll. More details of this design are described in the attached adaptive design report (Attachment 6).

Computer simulations of the above design are provided by Berry Consultants, Inc., to determine the plan's performance characteristics, located in Attachment 6. As described in the attached, the adaptive sample size design provides comparable power to a fixed design (with a total sample size of 180 patients) while limiting the number of patients to approximately 102-148 patients on average. This provides a savings of approximately 32-78 patients over a fixed design. The adaptive design also preserves an overall Type 1 error at 2.5%.

11.6 Interim Analysis

Multiple interim looks at the data in order to enable early submission based upon the primary efficacy endpoint are planned. The first interim analysis of the primary endpoint will be performed after the first 80 subjects have completed Day 30; additional interim analysis, if needed, will be performed after the next 20 subjects complete Day 30 until a maximum of 180 subjects is reached. The detailed description is provided in Attachment 6. At each interim analysis, one of the following three decisions will be made: 1) stop for success, 2) stop for futility otherwise 3) proceed to next interim.

11.7 Poolability

Data are assumed to be poolable across investigation sites due to: 1) use of the same study protocol, 2) equivalent training of all sites in the study protocol and use of the investigational device, 3) use of the same CRF at each site, and 4) stratification of randomization by site. Poolability across sites will be assessed for the primary endpoint only. If sites are demonstrably not poolable, a Bayesian hierarchical model will be used for the primary endpoint analysis.

12. ADVERSE EVENTS

The study Investigator and Coordinator will evaluate, characterize and record in the eCRF all adverse events (AEs) occurring in all subjects from the time of study treatment to study exit (or premature withdrawal). Prior to study treatment, changes will be documented in the Subject's medical history. Device or procedure related AEs will be followed until resolution. AEs may be reported spontaneously by the subject or detected by the Investigator or coordinator. AEs should be evaluated for diagnoses not just symptoms (i.e., "angina", not "chest pain").

Adverse events will be mapped to system organ classes and preferred terms using the MedDRA dictionaary. Adverse events will be summarized by system organ class and preferred terms. Individual patient data listings will present both verbatim and MedDRA terms

Adverse events[2] (AEs) will be assessed continuously from initiation of study treatment through study exit. Per ISO14155:2011, an AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, users or other persons, whether or not related to the investigational medical device. An AE can arise from any use of the device (e.g., off-label use, use in combination with any drug) and from any route of administration including an overdose.

Timely and complete reporting of all AEs assists the Sponsor in identifying any untoward medical occurrence, thereby allowing:

1) protection of the safety of study subjects;
2) a greater understanding of the overall safety profile of the device;
3) recognition of device-related toxicity or ill effects;
4) appropriate modification of study protocols;
5) improvements in study design or procedures; and
6) [2]adherence to worldwide regulatory requirements.

12.1.1 Adverse Device Effect (ADE)

Per ISO14155, an adverse device effect is an adverse event related to the use of an investigational medical device. Adverse events related to the use of iovera° include events resulting from insufficient or inadequate instructions for use, deployment, operation or any malfunction of the device. User error or intentional misuse of the device is also defined as an ADE.

ADEs may be either spontaneously reported or elicited during questioning and examination of a subject. All ADEs must be completely recorded within the subject's source documentation.

12.1.2 Serious Adverse Event (SAE)/ Serious Adverse Device Effect (SADE)/Anticipated Serious Adverse Device Effect (ASADE)/ Unanticipated Serious Adverse Device Effect (USADE)

Per ISO14155, an international clinical trial standard, an SAE is an AE that:

1. Led to a death,
2. Led to a serious deterioration in the health of the subject that
    a. Resulted in a life-threatening illness or injury,
    b. Resulted in a permanent impairment of a body structure or a body function,
    c. Required in-patient hospitalization or prolongation of existing hospitalization,
    d. Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect

An event that is serious must be recorded on the AE worksheet and requires expeditious handling to comply with regulatory requirements.

[2] Definition from ISO14155:2011

Events NOT considered to be serious adverse events are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen, and

- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of "serious" given above and not resulting in hospital admission.

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of an SAE per the ISO definition. No device-related SAEs have been reported in prior forehead wrinkle studies of the iovera° devices to date.

An SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report is defined by ISO as an unanticipated serious adverse device effect (USADE). Accordingly, an SADE which by its nature, incidence, or severity has been previously been identified in the current version of the risk analysis report is considered an anticipated serious adverse device effect (ASADE).

Any adverse events classified as "serious" by the Investigator or the Sponsor require expeditious handling and reporting to the Sponsor. All SAEs, whether or not the event was related to the study device or anticipated, must be immediately (within 24 hours of becoming aware of the SAE) reported to the sponsor by telephone or confirmed facsimile transmission:

Tracey Henry,and/or Study Manager
myoscience, Inc.
650-474-2600 (office)
650-474-2900 (fax)

12.2 AE Severity and Relatedness

Each AE occurring in the study will be characterized by the study Investigator as to severity (Table 4) and relatedness (Table 5).

Table 4. AE Severity Grading System.

Severity Grade	AE Description
Mild	AE is transient and easily tolerated by the subject, even if it causes discomfort
Moderate	AE causes the discomfort and interrupts usual activities
Severe	AE causes considerable interference with usual activities and may be incapacitating or life-threatening

Table 5. AE Relatedness Grading System.*

Grade	Relationship of AE to study device or study procedure	Description
5	Definite	An event that follows a reasonable temporal sequence from administration

		of the study device; that follows a known or expected response pattern to the study device; and that is confirmed by improvement on stopping.
4	Probable	An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.
3	Possible	An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; but may have been caused by concurrent/underlying illness, drugs, procedure, or other causes.
2	Unlikely	An event that does not follow a reasonable temporal sequence from administration of the study device; that does not follow a known or expected response pattern to the study device, or most likely was caused by concurrent/underlying illness, drugs, procedure, or other causes, because of their known effects.
1	Not related	An event almost certainly caused by concurrent/underlying illness, drugs, procedure, or other causes.

*Note that an AE occurring before treatment with the study device will be categorized as unrelated to the study device.

An **unanticipated adverse device effect** (UADE) is any SAE that is caused 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 (including a supplementary plan or application).

12.3 Adverse Event Reporting

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. All AEs must be completely recorded within the Subject's source documentation. All AEs will be evaluated by the Investigator for relationship to the iovera° device and to the treatment.

Investigators must report all SAEs to the study Sponsor and governing IRB within 24 hours or according to local IRB guidances. Investigators should call the study manager immediately upon the occurrence of an SAE. The Investigator should be able and willing to provide further information on the specific event when requested by the study Sponsor. If the Investigator learns of an SAE that occurs within 1 month after the subject completes the study, he/she should notify the Sponsor. Investigators must also report all AEs and SAEs to the governing IRB as determined by that IRB.

Prompt AE evaluation:

- protects the safety of study subjects;
- aids in understanding the overall safety profile of the device;
- prompts, if necessary, modification to the study protocol
- allows improvements in study design or procedures; and
- adheres with standard good clinical practices.

13. DEVICE TRACKING

The Sponsor will send the investigational devices to study sites. The Investigator must house study devices in a secure location. The Investigator must carefully and completely track receipt,

use and disposition of all investigational devices. The Sponsor will track sending and receiving of devices. The Sponsor will monitor site device accountability periodically.

If a Sponsor representative or designee is present at the time of use, he/she may directly take possession of used device(s). All devices will be returned to the Sponsor after the study is complete.

14. DEVICE DEFICIENCIES AND MALFUNCTIONS

Throughout the study, the Investigator and study staff will report and document all device deficiencies and malfunctions related to the identity, quality, durability, reliability, safety or performance of the device. This includes reporting of device deficiencies/malfunctions that did not lead to an AE but could have if: 1) suitable action had not been taken, 2) intervention had not been made, or 3) circumstances had been less fortunate. If possible, the Investigator should return devices suspected of deficiency or malfunction to the Sponsor for analysis.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Compliance with Good Clinical Research Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice (GCP) guidelines and with other applicable regulations. The Investigator and all study staff will conduct the study in compliance with this protocol. Voluntary informed consent will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their assigned responsibilities.

15.2 Institutional Review Board (IRB) and Informed Consent

Before study initiation, the Investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The Investigator should also provide the IRB with a copy of the product labeling, information to be provided to subjects and any updates. The Investigator will submit documentation of the IRB approval to the Sponsor. Copies of all correspondence with the IRB regarding this study must be sent to the Sponsor.

The IRB-approved consent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The Investigator/designee will explain the study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The Investigator must provide the subject with a copy of the consent form in a language the subject understands. The Investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

Withdrawal of IRB approval of the Investigator's part in the investigation must be reported to the Sponsor within 5 working days.

15.3 Protocol Compliance

The Investigator will comply to the extent possible with the IRB-approved protocol. All deviations from the protocol must be documented. The Investigator will notify the Sponsor immediately if a deviation from the protocol was required to protect patient safety.

15.4 Protocol Revisions

Revisions to the study protocol can be made only by the study Sponsor. A revised protocol can be put into place only after governing IRB approval. All administrative letters must be submitted to the IRB for their information.

New or altered consent forms required by the IRB due to a protocol change must be signed by all subjects currently enrolled in the study and must be used for any subsequent subject enrollment.

15.5 Study Monitoring

Representatives of the Sponsor will visit all study sites intermittently to review study records and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the Investigator and study staff and to verify that the Investigator, study staff and facilities remain acceptable for the conduct of the study.

Representatives of government regulatory authorities may also evaluate the study records, source documents, Investigator, study staff and facilities.

The Investigator should immediately notify the Sponsor of any audits of this study by any regulatory agency, and must promptly provide copies of any audit reports.

15.6 Safety Reporting

The Sponsor is responsible for performing ongoing safety evaluation in this study protocol. Sponsor activities regarding safety include:

- classification of all AEs,
- review of all AEs reported in the study,
- confirm site's classification of AEs in terms of severity and relatedness to the study device,
- review of severity and relatedness with the study Investigator, especially when there is disagreement between the Investigator and the Sponsor,
- review of device deficiencies and malfunctions, including determination and documentation of whether deficiencies/malfunctions could have led to an SAE,
- ensuring the reporting of all SAEs and device deficiencies/malfunctions that could have led to an SAE to the IRB and, if required, regulatory authorities in a timely fashion,
- informing all site Investigators in writing of all SAEs at all sites in a timely fashion and
- updating the risk analysis and assessment of corrective or preventive actions potentially required as a result of new information obtained in the investigation

The Sponsor will evaluate all serious adverse events against US reporting requirements (Medical Device Reporting, 21 CFR 812) and Medical Device Directive (vigilance incident reporting) as per its standard operating procedures. The Sponsor will investigate each SAE to determine whether the event represents an unanticipated serious adverse device effect (USADE, see Section 13.2). The Sponsor will report any event to regulatory authorities, Investigators and reviewing IRBs/ECs as necessary. If an investigation shows that a USADE presents an unreasonable risk to subjects, the Sponsor will terminate all investigations or parts of investigations presenting that risk as soon as possible. The Sponsor will only resume a terminated investigation after corrective actions have taken place, site Investigators are informed and IRBs/ECs have been notified and given approval to resume the study.

15.7 Electronic Case Report Forms/Electronic Data Capture

The study will use an electronic data capture (EDC) system to implement electronic case report forms (eCRF). The system will allow compliance with 21 CFR 11 Electronic Signatures. All CRFs are housed in the EDC system. The Investigator and Coordinator will be trained in use of the eCRF prior to study initiation. Retraining in use of EDC can occur at any time. The EDC system will be validated prior to use.

An eCRF is required and should be completed for each randomized Subject. The Investigator has ultimate responsibility for the collection and reporting of all data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The eCRFs must be signed by the Investigator to attest that the data contained therein are true.

The site will be provided with eCRF Completion Guidelines which will assist in data entry and data issues/questions. All persons allowed to enter or change eCRF data must appear on the Delegation of Responsibilities Log.

The Sponsor will remotely monitor eCRFs to identify possible data errors. The system will have query mechanism whereby the site Coordinator can respond to Sponsor queries. All data discrepancies will be resolved prior to database lock.

15.8 Quality Assurance Audits

Sponsor representatives or designees may conduct site quality assurance (QA) audits during the study. The Investigator must agree to provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authorities, the Investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The Investigator must notify myoscience, Inc. in the event of a FDA site audit.

15.9 Confidentiality

The Investigator is responsible for ensuring the confidentiality of subjects throughout the trial. A unique identification code will be assigned to each S participating in this trial. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity.

15.10 Records Retention

The Investigator must maintain all study records (including device disposition, informed consents, source documents, correspondence, regulatory documents, contracts etc.) for at least 2 years after study completion. At the Investigator's discretion, all records may be sent to the Sponsor for permanent storage.

The Investigator must contact the Sponsor or designee prior to destroying any records associated with this study. If the Investigator withdraws from the study, all study-associated records must be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to the Sponsor or designee.

15.11 Publication and Reporting of Study Results

The study will be registered with clinicaltrials.gov before the first patient is treated. Study results will be documented in a study report that will be signed by myoscience representatives and by the Principal Investigator of the entire Study. Individual site Principal Investigators will not be required to sign this report.

The results of this myoscience sponsored study will be published in accordance with standard editorial and ethical practices. Results from multi-center studies must be published or presented at congresses only in their entirety with data pooled from all centers. Individual Investigators may not publish data from individual centers, unless granted specific written permission by myoscience to do so.

The list of authors of any formal publication or presentation of study results may include, as appropriate, representatives of myoscience.