Official Title: **A POST-MARKET, PROSPECTIVE, RANDOMIZED, CONTROLLED STUDY TO EVALUATE THE IOVERA° DEVICE**

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A POST-MARKET, PROSPECTIVE, RANDOMIZED, CONTROLLED STUDY TO EVALUATE THE IOVERA° DEVICE IN TREATING PAIN ASSOCIATED WITH TOTAL KNEE ARTHROPLASTY

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Revision	Description	DCO#	Release Date
01	• Initial Release	3269	10/02/2017

Investigator Protocol Signature Page (REV 01)
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 Post-Market, Prospective, Randomized, Controlled Study to Evaluate the iovera° Device in Treating Pain Associated with Total Knee Arthroplasty
Study Device	iovera° (Myoscience Inc., Fremont, CA)
Study Objective	To evaluate the outcomes of patients undergoing iovera° treatment of the ISN and AFCN prior to total knee arthroplasty to provide temporary postoperative pain relief
Study Design	Single site, prospective, randomized
Treatment Groups	Pre-operative iovera° treatment vs. standard of care treatment
Duration of Participation	Up to 16 weeks (12 weeks post-op)
Study Population	Male or female, ages 22 to 79 scheduled to undergo a total knee replacement as a result of osteoarthritis
Total Number of Subjects	Up to 120 subjects (randomized 1:1)
Number of Sites	1
Study Procedures	iovera° treatment introducing temporary nerve conduction block of the ISN and AFCN
Data Collection Tools	• KOOS JR. • NRS for Pain
Primary Endpoint	Cumulative Opioid Consumption at 6 weeks post-TKA Surgery
Secondary Endpoints	• Changes from Baseline in KOOS JR. Scores through 6 weeks post-TKA • Changes from Baseline through 6 weeks post-TKA in NRS for Pain • Changes from Baseline through 6 weeks post-TKA in Timed Get Up and Go (TUG) test
[redacted]	[redacted]
Safety Assessment	• Adverse Event/Safety

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Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AFCN	Anterior Femoral Cutaneous Nerve
AO	Anticipated Observation
ASDE	Anticipated Serious Device Effect
CFR	Code of Federal Regulations
CNS	Central Nervous System
CRF	Case Report Form
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
KOOS JR.	Knee Injury and Osteoarthritis Outcomes Score
MedDRA	Medical Dictionary for Regulatory Activities
NRS Pain	Numeric Rating Scale for Pain
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSR	Non-Significant Risk
OTC	Over-the-Counter
QA	Quality Assurance
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOC	System Organ Classes
TKA	Total Knee Arthroplasty
UG	User Guide
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

1. BACKGROUND

Total Knee Arthroplasty (TKA) is a highly effective procedure to relieve symptoms in patients with severe arthritis. Improvements in pain, physical function, and enhanced quality of life in patients who have undergone TKA are well established in the literature[1,2]. However, post-operative pain associated with TKA is severe. Effective pain control following TKA allows for earlier ambulation and initiation of physical therapy, which speeds recovery, reduces hospital length of stay, and decreases the risk of postoperative complications[3]. The VHA/DoD and the American Society of Anesthesiologists have both issued guidelines suggesting that wherever possible, practitioners should use multimodal pain management[4]. Clinical management of post-op TKA pain should include both pharmacologic and non-pharmacologic modalities and minimize preventable postoperative complications[5]. As demand for primary TKAs is projected to grow to 3.48 million procedures per year by 2030 in the United States alone[6], the need for effective and economic multi-modal pain management has never been greater.

Managing pain via multi-modal strategies, including peripheral nerve blocks, in the inpatient postoperative phase has been shown to decrease opioid consumption[7], decrease opioid related side effects, decrease hospital stay, and increase time to ambulation[8,9,10]. Nursing, hospital, and pharmacy utilization in managing PCA, continuous regional nerve blocks, and administration of oral opioid dosing are associated with higher costs of care and introduce sources for staff error[11,12]. Furthermore, the idea of multi-modal pain management extends beyond the in-patient phase of treatment. Decreasing prescription opioid use during outpatient rehabilitation decreases NSAID and opioid related side effects, especially important among the aging population[13,14].

The iovera° device introduces a new mode of pain management delivery in TKA. The iovera° system uses liquid nitrous oxide contained within the device and closed-end needles to create a precise zone of cold at the target nerve sites. This Focused Cold Therapy™ delivery platform causes a temporary peripheral nerve block based on a process called Wallerian degeneration (2nd degree axonotmesis) without disrupting connective nerve tissue. With nerve conduction blocked, pain is relieved in sensory nerves (nerves that pass impulses from receptors toward or to the central nervous system). Degeneration of the nerve axons is followed by a predictable restoration of nerve function involving axon regeneration from the point of treatment to the distal end of the nerve at a rate of 1.0–1.5 mm a day[15,16]. Early clinical study results have demonstrated that the duration of effect of iovera°, when applied to the infrapatellar branch of the saphenous nerve for knee pain, is two to three months; longer than that of other clinically adopted modalities (PCA opioids, single shot regional nerve blocks, continuous regional nerve blocks, extended-release peri-operative local opioids, oral and IV NSAIDs, acetaminophen, and oral opioids). Early clinical data further suggests that iovera°, when applied to the infrapatellar branch of the saphenous nerve (ISN) and anterior femoral cutaneous nerve (AFCN) prior to TKA, reduces the amount of opioids requested by subjects to maintain similar levels of pain relief[17].

This study is designed to investigate whether iovera° treatment prior to TKA decreases cumulative patient opioid use over the course of 6 weeks following TKA while maintaining similar levels of pain relief. The study will also investigate whether there is a relationship between patients treated with iovera° and patient reported pain and function as measured by KOOS JR., NRS for Pain, [redacted]

2. REGULATORY STATUS

The iovera° device is 510(k)-cleared (K133453 and K161835) and is used to destroy tissue during surgical procedures by applying freezing cold. It can also be used to produce lesions in peripheral nervous tissue by the application of cold to the selected site for the blocking of pain. It is also indicated for the relief of pain and symptoms associated with osteoarthritis of the knee for up to 90 days. The iovera° system is not indicated for treatment of central nervous system tissue

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.

3. STUDY OBJECTIVE

To evaluate the outcomes of patients undergoing iovera° treatment of the ISN and AFCN prior to total knee arthroplasty to provide temporary postoperative pain relief.

4. STUDY DESIGN

This is a single-site, prospective, randomized trial.

5. DURATION

Each Subject participates for up to 16 weeks. Enrollment is expected to take up to 5 months. Total study duration is expected to be up to 8 months.

6. INVESTIGATOR QUALIFICATIONS

To participate in this study, an Investigator must have an active medical license and board certification in Orthopedic Surgery, Anesthesia, Pain Management, or Physical Medicine and Rehabilitation. The Investigator or designee must undergo training conducted by Myoscience, Inc., on the study device prior to enrolling Subjects in the study.

7. STUDY POPULATION

7.1 Target Patient Population

The target patient population is adult men and women ages 22 to 79 in the United States scheduled to undergo primary unilateral TKA under spinal anesthesia for primary diagnosis of osteoarthritis.

7.2 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. 22 to 79 years of age
2. Scheduled to undergo primary unilateral TKA under spinal anesthesia for primary diagnosis of osteoarthritis
3. Subject is a class I-III on the American Society of Anesthesiology (ASA) Physical Classification System
4. Anticipation of discharge to home after inpatient acute post-op phase based on age, co-morbidities, home environment, and social support are in favor of discharge to home in the opinion of the Investigator.
5. Subject is willing and able to give written informed consent.
6. Subject is fluent in verbal and written English.
7. Subject is willing and able to comply with study instructions and commit to all follow-up visits for the duration of the study.
8. 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. Chronic opioid use (defined as daily or almost daily use of opioids for >3 months).
2. Concurrent painful physical condition, surgery, or musculoskeletal disease that requires analgesic treatment during study follow-up that is not strictly related to the target knee being treated with iovera°, which have the potential to confound the postoperative assessments (e.g., significant pain from other joints, chronic neuropathic pain, concurrent or planned contralateral TKA, concurrent foot, neck, spine, hip, or other musculoskeletal disease, arthritis, or planned surgery, etc.).
3. Greater than 15° malalignment (varus or valgus) on pre-operative radiograph.
4. Previous Myoscience treatment.
5. Previous Partial or Total Knee Arthroplasty. Partial or Total Knee Arthroplasty of the contralateral knee is permitted if surgery was completed at least nine (9) months prior to Screening.
6. Body Mass Index ≥ 40
7. Prior surgery in the treatment areas that may alter the anatomy of the infrapatellar branch of the saphenous nerve (ISN) or the anterior femoral cutaneous nerve (AFCN) or result in scar tissue in the treatment area.
8. Any clotting disorder and/or use of an anticoagulant (e.g. warfarin, clopidogrel, etc.) within seven (7) days prior to administration of the device. Low dose aspirin (81mg or less daily) for cardiac prophylaxis allowed.
9. Any local skin condition at the treatment sites that in the Investigator's opinion would adversely affect treatment or outcomes.
10. Open and/or infected wound in the treatment areas.
11. Allergy to lidocaine.
12. History of cryoglobulinemia
13. History of paroxysmal cold hemoglobinuria.
14. History of cold urticaria.
15. History of Raynaud's disease.
16. History of opioid or alcohol abuse.
17. Subject is pregnant or planning to become pregnant while enrolled in the study.

18. Current enrollment in any investigational drug or device study or participation within 30 days prior to screening.
19. Currently being treated for related knee injury under worker's compensation claim or equivalent (i.e. legal case).
20. Any chronic medical condition that in the Investigator's opinion would prevent adequate participation.
21. Any chronic medication use (prescription, over-the-counter, etc.) that in the Investigator's opinion would affect study participation or Subject safety.
22. 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, etc.).

8. STUDY DEVICE AND TREATMENT PROCEDURE

The study device is described briefly below.

8.1 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 sterile 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 fully inserting the Smart Tip into the selected procedure site and activating 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.

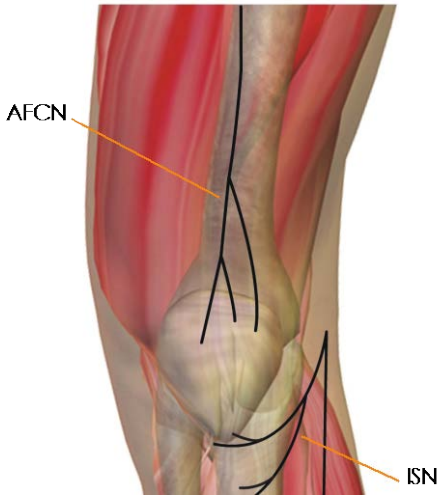
8.2 Instructions for Use and Administration

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 targets are the infrapatellar branch of the saphenous nerve (ISN) and the

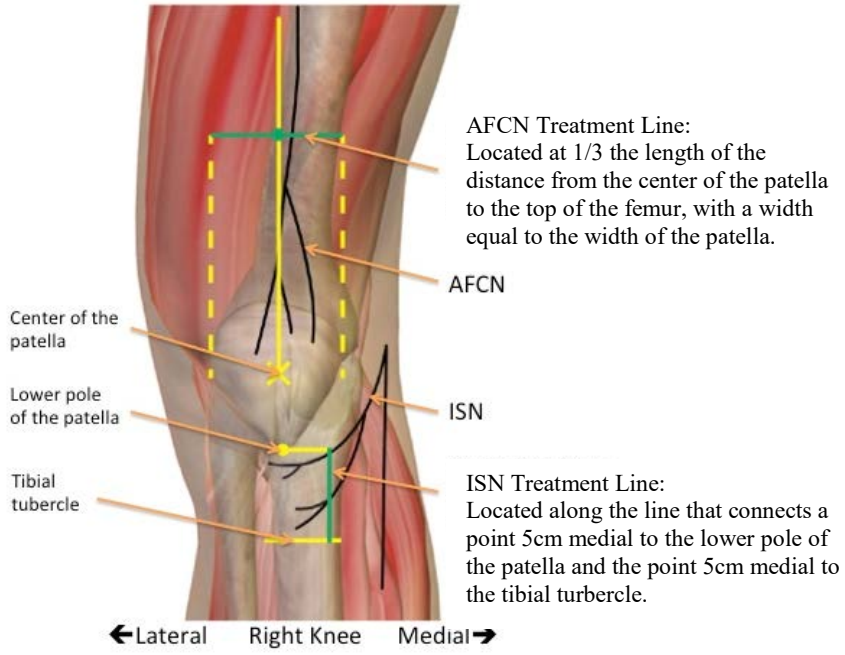
anterior femoral cutaneous nerve (AFCN) shown in Figure 1. Training for the treatment procedure will be provided to the Investigator and study staff prior to the initiation of study enrollment.

Figure 1. Infrapatellar branch of the Saphenous Nerve and Anterior Femoral Cutaneous 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 Lines (not to scale)



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
- Goniometers (2)

- Stop Watch
- Marking Ruler

The investigational site will provide the following:

- Injectable lidocaine (no epinephrine) used for local anesthesia
- Syringes for administration of local anesthesia
- Needles for administration of local anesthesia
- Gauze
- Alcohol wipes
- Wound dressing(s)

8.3 Contraindications

Use of iovera° is contraindicated in the following situations:

- Cryoglobulinemia
- Paroxysmal cold hemoglobinuria
- Cold urticaria
- Raynaud's disease
- Open and/or infected wounds in the target treatment area

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.

8.4 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:

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

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

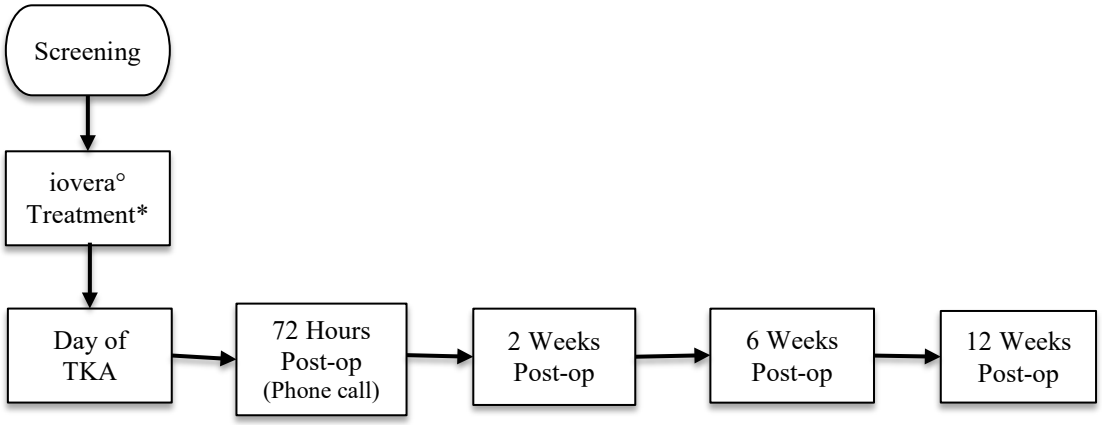
- Injury to the skin related to application of cold or heat
- Hyper- or hypo-pigmentation at the treatment site
- Skin dimpling at the treatment site
- Loss of motor function outside the target area

9. STUDY PROCEDURES

9.1 Overview

An Overview of the study visits is shown in **Figure 3**. Eligible Subjects are randomized to iovera° treatment or to the standard of care group. The standard of care group treatment consists of all of the standard pre-, peri- and post-operative protocols except that the iovera treatment is not provided. The primary endpoint is cumulative opioid consumption at 6 Weeks Post-TKA.

Figure 3. Overview of Study Visits



*Screening and Treatment can occur on the same day.

9.2 Recruitment

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

9.3 Screening /Visit 1 (-30 to -1 days)

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 01 will be assigned study number 01-001. The Subject number is the identification number used on CRFs 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, obtain vital signs and complete an assessment of the intended treatment areas and concomitant medications/concurrent procedures. Subjects will be asked to bring all prescription opioid bottles to all study follow-up visits. A pill count will be completed by the study coordinator, or designee.

Once a Subject has been determined to meet all inclusion and none of the exclusion criteria, the Subject will complete the following:

Assessments:

- NRS for Pain when standing from a seated position in target knee
- KOOS JR. (English version 1.0)
- [redacted]

Physical Performance Measures in the following order:

- [redacted]
- Timed Get Up and Go Test

Subjects may be complete Screening / Visit 1 and iovera° Treatment / Visit 2 on the same day.

9.4 Randomization

After meeting all of the inclusion and none of the exclusion criteria and prior to study treatment, Subjects will be randomized in a 1:1 manner to either:

- **iovera° Treatment**: Subject undergoes treatment with the study device using study supplied Smart Tip.
- **Standard of Care Treatment**: Subject does not undergo iovera° Treatment

The Investigator or designee will record the randomization assignment in the source documentation and CRF. Any Investigator who is discovered to tamper with randomization will be immediately terminated from the study.

9.5 iovera° Treatment/Visit 2 (5 Days +- 2 days prior to TKA)

Medical history will be reviewed as well as concomitant medications and procedures. Blood pressure and heart rate will be assessed. The Investigator, or designee, will reconfirm all eligibility criteria are met.

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 lines on the knee to be treated as shown in Figure 2 located in section 8.2.

Then the skin along the treatment lines will be cleansed with alcohol. Lidocaine, no epinephrine, will be injected along the treatment lines superficially in order to achieve cutaneous anesthesia and to the bottom of the subcutaneous layer, atop the fascia, to temporarily block conduction of the infrapatellar branch of the saphenous nerve and the anterior femoral cutaneous nerve.

Once localized anesthesia of the treatment lines and the nerves is achieved, the Investigator, or designee, will complete the iovera° treatment along the treatment lines. Regardless of the length of treatment lines (width of patella or from lower pole of the patella down to tibial tubercle), adjacent insertions are placed along the treatment lines 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 changes 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 areas will be cleansed and the skin will be left undressed. The Investigator or designee will assess the treatment areas for adverse events. A dressing may then be applied.

The Subject will be instructed to report any adverse events to the Investigator between and at the follow-up visits.

9.6 Visit 3 / Total Knee Arthroplasty (Day 0)

The Investigator or Designee will confirm their ability to safely perform TKA within the following protocol requirements. All surgical and in-patient data, safety information including adverse event assessments, will be collected retrospectively from hospitalization records:

- Pre-operative History & Physical Exam, including assessment of the target knee, must be documented in the medical record and included as study data.
- Surgery and Implant - Medial parapatellar surgical approach; cruciate-retaining or posterior-stabilized TKA; all surfaces replaced.
- Pre-emptive analgesia – medications administered prior to TKA, orally, intravenously, or otherwise, for the purpose of pain management before, during, or after surgery, are to be recorded in the medical record and included as study data.
- Procedural anesthesia – during Arthroplasty this will be limited to spinal anesthesia, the formulation, or "cocktail," of medications used are to be recorded in the medical record and included as study data.
- Local Infiltration Analgesia – The control group (standard of care) may utilize local infiltration analgesia (including periarticular and posterior capsule infiltration). The use of periarticular local infiltration analgesia (eg. Exparel) is not permitted to be used as part of this protocol in the treatment (iovera) group. However, for the treatment group, local infiltration analgesia may be used in the posterior capsule as the iovera treatment does not affect this region of the knee. The medications used in both groups are to be recorded in the medical record and included as study data.
- Regional nerve block for post-operative analgesia – single shot Adductor Canal Block required, the formulation, or "cocktail," of medications used are to be recorded in the medical record and included as study data.
- Post-operative analgesia will be prescribed as detailed below. All opioid or other pain medications used are to be recorded in the medical record and included as study data.
    - Oxycodone, 5mg, q4h/PRN, N=40
    - Tramadol, 50mg q6, N=40
    - Tylenol, 100mg, TID, N=40
    - Neurontin, 100mg, TID, N=40
    - Meloxicam, 15mg, OD, N=15
- Post-operative discharge criteria: Ability to tolerate fluids, ambulate with physical therapist for first ambulation, Void >200cc, Pain under control.
- Other data to be collected retrospectively from hospitalization medical records may include: [redacted] pain scores collected during physical therapy and adverse events, including Opioid-related adverse events.

Outpatient analgesia – The subject will be required to bring all of their unused prescription narcotic medications dispensed during study participation to all study follow-up visits for pill count. A pill count/ accountability will be completed by the study coordinator, or designee. Any other over-the-counter analgesic medications or other pain relief therapies

used (per patient report) will also be recorded by the study coordinator, or designee, at each follow-up visit.

9.7 Study Follow Up

Study-related follow-up visits occur at the investigational site at, 72 Hours (Visit 4) Post-TKA as well as Week 2 (Visit 5), Week 6 (Visit 6), and Week 12 (Visit 7) Post-TKA. The study's schedule of assessments is shown in Table 2.

Follow Up Visit 4 (72 hours ± 24 hours post op) - Phone Call

Visit 4 (72 Hours Post-TKA) will occur via a phone follow-up. No physical performance measures will be collected at these visits. Subjects will self-report the amount of opioids used. Subjects will report the NRS Pain Scores, answer the KOOS Jr. questions and report any AEs if present.

Follow Up Visit 5 (2 Weeks; ±3 Days Post Op), and Visit 6 / 6 Weeks Post-op (6 weeks; ±5 Days Post-Op)

Subjects will be evaluated and data collected per the schedule of events. Any changes in concomitant medications/concurrent procedures will be documented. Any anticipated observations, 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 KOOS JR. questionnaire and NRS for Pain when standing from a seated position for all follow-up visits. The Subject will also complete a [redacted] will answer Satisfaction questions at Visit 6.

The subject will complete the Physical Performance Measures for Visit 5, 6 and 7 in the following order under supervision of the investigator or designee:

- [redacted]
- Time Get-Up and Go

[redacted]

Subjects will be asked to bring all prescription opioid bottles to all study follow-up visits. A pill count will be completed by the study coordinator, or designee, and opioid medication will be returned to subjects.

Follow Up Visit 7 (12 Weeks; ±7 days Post-Op)

Subjects will be evaluated and data collected per the schedule of events. Any changes in concomitant medications/concurrent procedures will be documented. Any anticipated

observations, 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 KOOS Jr. questionnaire, NRS for Pain when standing from a seated position. The Subject will also complete a [redacted] will answer Satisfaction questions.

The subject will complete the Physical Performance Measures in the following order under supervision of the investigator or designee:

- [redacted]
- Get up and Go Test

The total number of outpatient Physical Therapy visits conducted between each study visit will also be obtained. Additional Data collected from Physical Therapy Visits will include:

- [redacted]
- Pain while seated
- [redacted]

[redacted]

Subjects will be asked to bring all prescription opioid bottles to all study follow-up visits. A pill count will be completed by the study coordinator, or designee, and opioid medication will be redispensed to subjects.

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

Table 2. Schedule of Assessments

Assessment	Visit 1 / Screening	Visit 2 / iovera° Treatment	Visit 3 / DAY OF TKA (Day 0)	Visit 4 / 72 Hours Post-op	Visit 5 / 2 Weeks Post-op	Visit 6 / 6 Weeks Post-op	Visit 7 / 12 Weeks Post-op
Informed Consent	X						
Eligibility	X	X					
Medical history	X	X					
Concomitant medication assessment	X	X	X	X	X	X	X
Prior/Concurrent Therapy	X	X		X	X	X	X
Randomization*	X						
Study Treatment		X					
Physical Exam	X						
Vital signs	X	X					
Knee Circumference	X						
KOOS JR. Questionnaire	X			X	X	X	X
NRS for Pain	X			X	X	X	X
[redacted]							
Subject Satisfaction Questions						X	X
Physical Performance Measures	X				X	X	X
Pain Medication Accountability				X	X	X	X
AE/SAE Assessment		X	X	X	X	X	X

* Randomization occurs after the subject has met eligibility criteria

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 performs drug accountability (pill counts) of post-operative outpatient opioid medication and re-dispenses unused opioid medications to subjects after use. The Investigator or designee records other over-the-counter concurrent pain medication use and pain relief therapies used per subject report;
- The Subject completes a KOOS JR. questionnaire, [redacted] Satisfaction questions (Visit 6 and 7 only), and reports NRS for Pain when standing from a seated position;
- The Investigator or designee performs Physical Performance Measures ([redacted] Get Up and Go Test).

9.8 Photographs

Photographs are optional; and may be requested by sponsor in the event a local skin reaction occurs at the treatment site. Photographs will be labeled appropriately, stored electronically (e.g., JPEG, PNG or other relevant format) and sent to the Sponsor according to Sponsor instructions.

9.9 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 CRF.

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

9.10 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 continued 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 Subject 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 CRF 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 CRF.

9.11 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.

9.12 Study-Related Assessments

9.12.1 Knee Injury and Osteoarthritis Outcomes Score (KOOS JR.)

The KOOS JR. score consists of 7 questions from 3 subscales: Stiffness (1 question), Pain (4 questions), and Function in daily living (2 questions). Standardized answer options are given (5 Likert boxes) and each question is assigned a score from None (0) to Extreme (4). A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated. A copy of the KOOS JR. is located in Attachment 1.Completion of the KOOS JR. questionnaire will take approximately 5 minutes to complete. After completion by the Subject, the study coordinator or designee will enter into the CRF.

9.12.2 Numeric Rating Scale for Pain (NRS for Pain)

The Numeric Rating Scale for Pain (NRS for Pain) is a measure of pain intensity. The investigator or designee conducts the 11-point scale verbally with the research subject in reference to the target knee. The investigator or designee will ask the following questions,

- "On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain IN THE PAST 7 DAYS when standing from a seated position?"
- "On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain RIGHT NOW when standing from a seated position?"

The Subject responds verbally and the study coordinator or designee will record the response.

The NRS for Pain will be completed by the Subject and will take approximately 2 minutes to complete. The study coordinator or designee will enter the data into the CRF.

9.12.3 Subject Satisfaction Questions

Subject satisfaction questions will be verbally administered by the study coordinator or designee at Visit 6 and Visit 7. Questions will take approximately 3 minutes to complete. The Subject satisfaction questions are located in Attachment 2.

[redacted]

[redacted]

[redacted]

10. STATISTICAL METHODS

10.1 Introduction

This is a prospective, randomized, single-site, post-market trial to evaluate the iovera° device in treating pain associated with total knee arthroplasty (TKA). The study is designed to investigate whether iovera° treatment prior to TKA decreases cumulative patient opioid use over the course of 6 weeks following TKA while maintaining similar levels of pain and functioning as measured by reductions from the Baseline visit in the KOOS JR. score.

The study will also investigate whether there is a treatment effect of iovera° on the following measures of effectiveness: NRS for Pain, Timed Get Up and Go Test, [redacted]

One study site within the United States will screen a sufficient number of subjects to ensure that 120 subjects (randomized 1:1 to obtain approximately 60 iovera° subjects and 60 Standard of Care subjects) will be randomized.

10.2 General

Categorical data will be summarized using frequency tables, presenting subject counts and percentages. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum).

The SAS system will be used to perform all statistical analyses.

Exact binomial confidence intervals will be generated for proportions. Confidence intervals based on the t-distribution will be generated for means and differences of means. Fixed sequential testing will be performed to control the overall Type I error rate.

Except where noted otherwise, within-subject change-from-baseline (pre-treatment baseline) values for a variable are calculated as:

Change-from-Baseline = Follow-Up value – Pre-Treatment value,

such that a positive value indicates an increase from the pre-treatment value to the follow-up value, whereas a negative value indicates a decrease.

10.3 Analysis Populations

10.3.1 Screening Population

All subjects who are screened for the study will be included in the Screening Population. For this population, only an accounting of the numbers of subjects screened in the study, plus the reasons given for subjects not being enrolled in the study, will be summarized.

10.3.2 ITT (Intent to Treat) Population

All subjects who are randomized will be included in the ITT Population. Subjects will be analyzed according to the treatment group to which they were randomized. The primary analyses of effectiveness will be conducted based on the ITT Population.

10.3.3 Per-Protocol Population

The Per-Protocol Population is defined as the group of subjects who are randomized, who receive the treatment to which they were randomly assigned, and who complete their 6-week visit without any major protocol deviations. Subjects will be analyzed according to the treatment group to which they were randomized. Secondary analyses of effectiveness will be conducted based on the Per-Protocol Population.

10.3.4 Safety Population

All subjects who receive study treatment will be included in the Safety Population. Subjects will be analyzed according to the treatment they actually receive, regardless of their randomized treatment. All safety analyses will be based on the Safety Population.

10.4 Study Endpoints

10.4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the cumulative consumption of opioids from the time of hospital discharge to 6 weeks post-TKA Surgery. Opioid consumption will be converted to morphine equivalents, and subject consumption will be verified by pill count at follow-up visits. The cumulative morphine equivalent will be divided by the number of days to provide the Total Daily Morphine Equivalent (TME) for the subject.

The difference in the mean TME between the two treatment groups will be calculated as Standard of Care TME mean – Active TME mean, such that a positive difference indicates that the Standard of Care Treatment group had a larger mean TME than the Active Treatment group, while a negative difference indicates the opposite. A positive difference between the two treatment groups reflects a positive outcome for the study.

Let $\mu_{1,Active}$ and $\mu_{1,SOC}$ denote the true mean TMEs for the active and standard of care treatments, respectively. Then the null and alternative hypotheses for the primary effectiveness endpoint are as follows:

H_0: $\mu_{1,Active} \geq \mu_{1,SOC}$

H_1: $\mu_{1,Active} < \mu_{1,SOC}$

A one-sided, two-independent sample, Satterthwaite t-test will be used to test the null hypothesis. The Primary Effectiveness Study Objective will be met if this t-test is statistically significant using a one-sided $\alpha = 0.025$ level of statistical significance.

This endpoint will be summarized by treatment group using descriptive statistics. The difference in mean TMEs between the two treatment groups and a 95% confidence interval based on the t-distribution for the true difference in the mean TMEs between the two treatments will also be provided.

The database will be "soft-locked" after all 6 week data has been collected (all data monitored with the exception of data points collected beyond 6 weeks). An interim analysis of the primary endpoints will be performed on the soft-locked data for internal Myoscience purposes. The full dataset will be locked upon completion of all visit and adverse event follow-ups and this data will be reported in the clinical study report.

10.4.2 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints are as follows:

1. AUC/time (see definition of AUC/time below) based on Changes from Baseline in KOOS JR. Scores through 6 weeks post-TKA
2. AUC/time based on Changes from Baseline through 6 weeks post-TKA in NRS for Pain
3. AUC/time based on Changes from Baseline through 6 weeks post-TKA in Timed Get Up and Go (TUG) test

Change in KOOS JR. scores from the Baseline visit to each post-baseline visit will be calculated for each subject as:

Change in KOOS JR. score =
Post-Baseline Visit KOOS JR. score – Baseline Visit KOOS JR. score,

such that a positive value indicates an increase in the KOOS JR. score, while a negative value indicates a decrease. The first and key secondary effectiveness endpoint, AUC/time based on Changes from Baseline in KOOS JR. scores through 6 weeks post-TKA, is the area under the curve (AUC) of Change in KOOS JR. scores from the Baseline visit through the 6-week visit divided by the number of days from TKA until the 6-week visit. AUC will be calculated using the trapezoidal rule and the changes in the KOOS JR. score at the following time points: Baseline (change=0), 72 hours, 2 weeks, and 6 weeks post-TKA.

The difference in mean AUC/time between the two treatment groups will be calculated as the mean Active AUC/time – the mean Standard of Care AUC/time, such that a positive difference indicates that the Active Treatment group had a larger mean AUC/time based on Change in KOOS JR. score than the Standard of Care Treatment group, while a negative value indicates the opposite. Because a positive Change in the KOOS JR. score is indicative of pain relief, a positive difference between treatment groups reflects a positive outcome for this endpoint.

Let $\mu_{2,Active}$ and $\mu_{2,SOC}$ denote the true mean AUC/time based on the Change from Baseline in KOOS JR. score from the Baseline visit through the six-week visit for the active and standard of care treatments, respectively. Then the null and alternative hypotheses for the test for non-inferiority for this endpoint are as follows:

H_0: $\mu_{2,SOC} - \mu_{2,Active} \geq \delta$

H_1: $\mu_{2,SOC} - \mu_{2,Active} < \delta$,

where the non-inferiority margin δ=14.

The null hypothesis will be tested using a two-independent sample t-test. One of the secondary objectives of the study is to show that, over the 6-week post-TKA period, the Active Treatment group has similar levels of pain and functioning as compared to the Standard of Care Treatment group. This objective will be met if the t-test for non-inferiority is statistically significant using a one-sided $\alpha = 0.025$ level of statistical significance.

The fixed sequential testing procedure will be used for the comparison of the two treatments with respect to the first (and key) secondary effectiveness endpoint. Therefore, for this endpoint, the analysis comparing the two treatments will be formally conducted only if the analysis for the primary effectiveness endpoint yields a statistically significant result. For informational purposes, however, the results of the analysis (i.e., p-value) will be presented regardless of the results for the primary effectiveness endpoint.

Each secondary effectiveness endpoint will be summarized by treatment using descriptive statistics. For each treatment, the null hypothesis that the true mean AUC/time equals zero will be tested using a paired t-test. Ninety-five percent confidence intervals based on the t-distribution for the true mean AUC/time for each treatment and for the true difference in these means between treatments will be provided. In addition, for each secondary effectiveness endpoint, the initial result (e.g., KOOS JR. score at 6-weeks post-TKA), as well as the Change from Baseline value, will be summarized at each visit at which data for the endpoint are collected using descriptive statistics.

The database will be "soft-locked" after all 6 week data has been collected (all data monitored with the exception of data points collected beyond 6 weeks). An interim analysis of the secondary endpoints will be performed on the soft-locked data for internal Myoscience purposes. The full dataset will be locked upon completion of all visit and adverse event follow-ups and this data will be reported in the clinical study report.

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10.4.4 Safety

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) are adverse events with onset after study treatment begins and that are not present at baseline or, if present at baseline, have worsened in severity. For AEs with missing start dates, the AE will be considered treatment-emergent unless there is additional information indicating that the AE started prior to study treatment. Only treatment emergent AEs will be summarized.

The number and percentage of subjects with at least one TEAE, at least one device-related TEAE, at least one serious TEAE, at least one serious adverse device effect, at least one unanticipated serious adverse device effect, at least one anticipated serious adverse device effect, and at least one TEAE leading to study withdrawal will be presented by treatment group. AEs that are definitely, probably, or possibly related to the device, or for which the relationship to the device is missing, will be considered device-related. TEAEs will be summarized at the subject level by MedDRA system organ class (SOC) and preferred term using frequencies and percentages. TEAEs will also be tabulated at the event level by severity and by relationship to the device for each treatment group.

10.5 Handling of Dropouts or Missing Data

Missing data for the primary effectiveness endpoint and the first secondary effectiveness endpoint will be imputed using multiple imputation methods. First, the relatively uncommon, non-monotone missing data will be imputed using the MCMC option of SAS® PROC MI. For example, for the primary effectiveness endpoint, the imputation model will include a term for treatment and the pill counts at visits 4, 5, and 6. Second, the monotone missing values will be imputed using the chained equation method by SAS® PROC MI option MONOTONE REG. For each subject within each imputed dataset, the value of the endpoint will then be determined. The imputed data sets will each be analyzed as specified in Sections 10.4.1 and 10.4.2, and the results will be summarized using PROC MIANALYZE.

10.6 Analysis Windows

All analyses will be based on nominal visits.

10.7 Sensitivity Analyses

Sensitivity analyses may be considered and will be described in the final Statistical Analysis Plan for the study. Nevertheless, the primary results will be used when evaluating overall Study Success.

10.8 Sample Size Determination

The required sample size was determined based on providing at least 80% power for the primary effectiveness endpoint using a one-sided, two-independent sample, Satterthwaite t-test to test for non-inferiority of iovera treatment to Standard of Care treatment, with a significance level of 0.025, assuming a 1:1 allocation to treatment, a true treatment effect ($\mu_{1,Active}$ - $\mu_{1,SOC}$) of -12.0 mg, and true standard deviations of 16.9 mg and 26.0 mg, for the iovera and Standard of Care treatments, respectively. Based on these specifications, the required sample size is 57 subjects per treatment group, for a total of 114 subjects. To account for a small number of the subjects withdrawing early or not having data available for the analysis of the primary effectiveness endpoint, the required sample size was increased to 120 randomized subjects (approximately 60 Active Treatment subjects and 60 Standard of Care Treatment subjects).

11. ADVERSE EVENTS

The study Investigator and Coordinator will evaluate, characterize and record in the CRF all adverse events (AEs) occurring in all subjects from the initiation of study treatment to study exit (or premature withdrawal). 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”).

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.

In addition to verbatim terms, the Sponsor will categorize all AEs using MedDRA preferred terms and system organ classes (SOC). Analysis will report both verbatim and MedDRA terms.

Adverse events[1] (AEs) will be assessed continuously from the 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.

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 ill effects;
4) appropriate modification of study protocols;
5) improvements in study design or procedures; and
6) adherence to worldwide regulatory requirements.

11.1 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 and reported to the Sponsor within 48 hours of Investigator becoming aware of the ADE.

11.2 Serious Adverse Event (SAE)/ Serious Adverse Device Effect (SADE)/Anticipated Serious 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.

[1] Definition from ISO14155:2011

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.

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.

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, email, or confirmed facsimile transmission:

Kent Jones, and/or Study Manager
Myoscience, Inc.
[redacted](office)
[redacted](fax)
kjones@Myoscience.com

11.3 AE Severity and Relatedness

Each AE occurring in the study will be characterized by the study Investigator as to severity (Table 3) and relatedness (Table 4).

Table 3. 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 4. AE Relatedness Grading System.*

Grade	Relationship of AE to study device or 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 change in medical condition occurring between Screening and the initiation of Study Treatment will be reported as a change in Medical History.

12. 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.

13. 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.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 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.

14.2 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.

14.3 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.

14.4 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.

14.5 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.

14.6 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 and/or study procedure,
- 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 AE or SAE,
- ensuring the reporting of all SAEs and device deficiencies/malfunctions that could have led to an AE or 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 12.1.2). 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.

14.7 Case Report Forms

Case Report Forms (CRFs) will be provided in order to collect required data points. Data will be routinely monitored and collected by the sponsor, or designee, to identify inconsistent or missing data and to ensure compliance with the study protocol.

An CRF 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 CRFs 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 CRFs must be signed by the Investigator to attest that the data contained therein are true. Investigators will be responsible for the accurate and timely completion of CRFs during the trial.

14.8 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.

14.9 Confidentiality

The Investigator is responsible for ensuring the confidentiality of subjects throughout the trial. A unique identification code will be assigned to each Subject 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.

14.10 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.

14.11 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.

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