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A PROSPECTIVE NON-RANDOMIZED UNBLINDED STUDY EVALUATING THE TREATMENT OF KNEE OSTEOARTHRITIS WITH THE CRYO-TOUCH III DEVICE

MYO-0601 REV 04

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Revision History:

Revision	Description	Justification	DCO#	Release Date
01	Initial Release.	Initial Release	N/A	10/15/2012
02	Updated the Schedule of Events in Appendix B	Schedule of Events for Visit 5 did not originally reflect the requirement for completion of Subject Post-Treatment Questionnaire as required by protocol	N/A	11/27/2012
03	Increase enrollment Enrollment based on number of subjects rather than number of "treatments Remove "lidocaine with epinephrine" and replace with "Local anesthesia" Spelling and grammar edits	Allow for additional enrollment Provide clarification Allow investigators to use local anesthetic of choice to achieve complete cutaneous anesthesia Provide clarification	N/A	12/19/2012
04	Define end of study Remove secondary endpoint: Analgesic Use	Provide end date of Day 84 for any subject who has treatment effect at or beyond Day 56 Data not collected for this secondary endpoint	1740	6/25/2013

A PROSPECTIVE NON-RANDOMIZED UNBLINDED STUDY EVALUATING THE TREATMENT OF KNEE OSTEOARTHRITIS WITH THE CRYO-TOUCH III DEVICE

Protocol Number:	MYO-0601/04
Protocol Date:	6/25/2013
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Protocol Synopsis

Title	A Prospective Non-Randomized Unblinded Study Evaluating the Treatment of Knee Osteoarthritis with the Cryo-Touch III Device
Study Device	Cryo-Touch III (a.k.a. PCP 1.0)
Study Objective	A proof of concept study to evaluate the feasibility of safe and effective treatment through optimization of the Cryo-Touch III device for temporary relief of pain.
Treatment Groups	Multiple
Duration of Study	Enrollment and follow-up is expected to take approximately 4 months. A subject will participate for approximately 10 weeks.
Study Population	Healthy subjects, male or female, ages 18 and older with chronic knee pain related to a diagnosis of osteoarthritis of the knee.
Total Number of Subjects	Up to 50 subjects will be enrolled.
Number of Sites	1-2
Inclusion Criteria	Eligible subjects must meet the following criteria: 1. Male or female, 18 years of age and older. 2. Trial participants must meet American College of Rheumatology (ACR) criteria for osteoarthritis of the knee (unilateral or bilateral). 3. Any medications must be maintained on a stable schedule for at least two weeks prior to treatment. No washout period is allowed. 4. Must have an average score for pain of ≥ 4 Visual Analog Scale (VAS) over the last 30 days. 5. Subject is willing and able to give written informed consent. 6. Subject is willing and able to comply with study instructions and commit to all follow-up visits for the duration of the study. 7. 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	A subject is ineligible if one or more of the following criteria applies: 1. A partial or full knee replacement (in the treated knee). 2. Any use of systemic injections (in any area) within the last 6 months. 3. Current enrollment in an investigational drug or a device study that specifically targets pain treatment. 4. Any additional diagnosis that in the opinion of the investigator directly contributes to knee pain.

	5. Any concomitant inflammatory disease or other condition that affects the joints (e.g. rheumatoid arthritis, metabolic bones disease, gout, active infection, etc.) 6. Any clotting disorder and/or has used an anticoagulant (e.g., warfarin, clopidogrel, etc.) within seven (7) days prior to administration of the device. 7. Allergy or intolerance to local anesthetic. 8. Any local skin condition at the treatment site that in the investigator's opinion would adversely affect treatment or outcomes. 9. Any chronic medical condition that in the investigator's opinion would prevent adequate participation. 10. Any chronic medication use (prescription, over-the-counter, etc.) that in the investigator's opinion would affect study participation or subject safety. 11. 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.).
Study Visit Schedule	1. Visit 1/Screening (-30 Days to Day 0) 2. Visit 2/Treatment (Day 0) 3. Visit 3/ Maintenance (Day 7) 4. Visit 4/ Maintenance (Day 30) 5. Visit 5/Study Exit (Day 56) – Telephone Follow-Up
Primary Outcome	An improvement in the Visual Analog Scale (VAS) for pain at Day 7.
Secondary Outcomes	1. Improvement (pain, stiffness, and functionality) as determined by the Western Ontario and McMaster Osteoarthritis Index (WOMAC) Scale at Day 7. A significant difference is observed as ≥ 2-points. 2. Duration of Treatment Effect

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Declaration of Investigator

I confirm that I understand the protocol and agree to conduct the study as detailed herein. I will not make changes in the protocol without approval from the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

I agree to inform any subjects, or any persons in the study, that the investigational product(s) are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 812.150(a)(1). I have read and understand the information in the product description, including any potential risks and side effects of the product.

I agree to maintain adequate and accurate records in accordance with 21 CFR 812.140 and to make those records available for inspection in accordance with 21 CFR 812.140.

I will ensure the IRB complies with the requirements of 21 CFR Part 56 and will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB and Sponsor all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without Sponsor and IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 812.110 and 812.150. I also agree to adhere to the internationally recognized Declaration of Helsinki, International Conference on Harmonisation (ICH) guidelines, and Good Clinical Practices (GCP).

Signature: _____ Date: _____

Printed Name: _____

1. Introduction

1.1. Background

Over 100 million patients in the United States suffer from chronic pain. Chronic pain conditions are often debilitating, taking a toll on a patient's physical and mental welfare. Though a variety of pain management techniques currently exist, the most common nonsurgical options provide slow-acting and/or short-term relief. Medication, often in the form of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, comes with an array of side effects such as nausea and vomiting. Medication also presents the possibility of more serious effects such as increased risk of heart attack and stroke, and tolerance or dependency issues. Surgical strategies tend to be reserved for more severe cases and are limited by the risks and complications typically associated with surgery including bleeding, bruising, scarring, and infection. A nonsurgical, minimally invasive, long-lasting approach to chronic pain management is desirable.

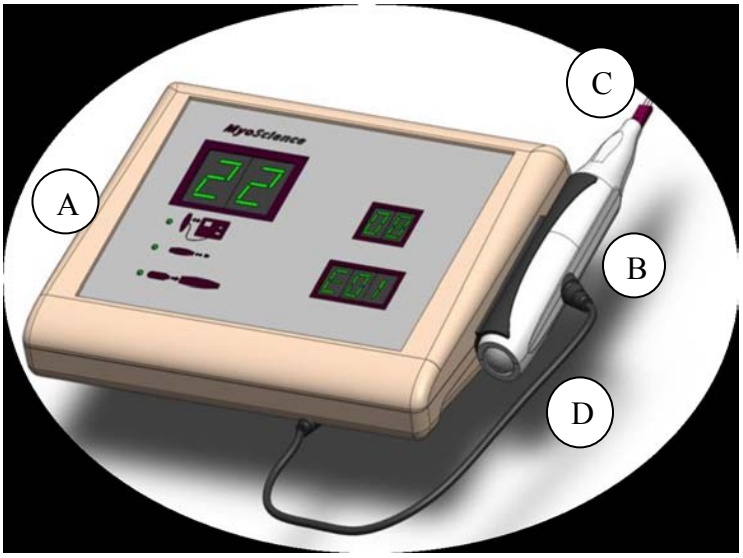
Myoscience, Inc. (Redwood City, CA) has developed a pain management device – the Cryo-Touch III – for a novel, minimally invasive procedure using focused cold therapy to target sensory nerve tissue and offer long-lasting pain relief through cryoanalgesia. The device operates on the well-established cryobiology principle that localized exposure to controlled moderately low temperature conditions can alter tissue function. The therapy treats nerves with low temperatures via a cold probe in the form of an assembly of small diameter needles, creating a highly localized treatment zone around the probe. This focused cold therapy creates a conduction block that prevents nerve signaling. Prior studies of Cryo-Touch, Cryo-Touch II, Cryo-Touch III (a.k.a. PCP 1.0) have provided preliminary evidence of effectiveness on motor nerves and have been shown to be safe with no serious device-related adverse events.

Though studies have proven efficacious in targeting motor nerves, the device's effect on sensory nerves has yet to have been investigated in the clinical setting. The goal of the study described herein is to evaluate the degree and duration of effect of the Cryo-Touch III in reducing chronic pain by targeting sensory nerves.

1.2. Device Description

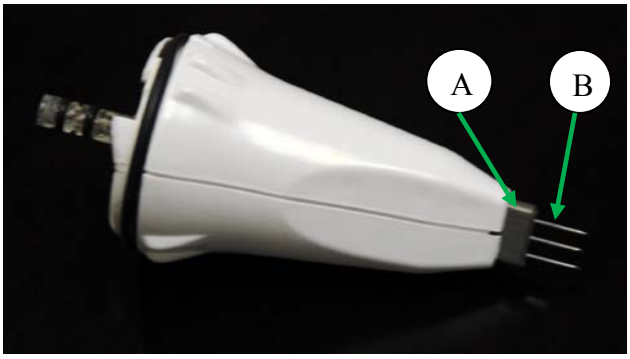
The Cryo-Touch III device (a.k.a. PCP 1.0) (Figure 1) is a minimally invasive needle-based device. The device consists of a re-usable portable Control Unit, Handpiece, single use Cryoprobes (Figure 2) and Cryogen Cartridges. The Control Unit and Handpiece are powered by the Control Unit utilizing connection to a standard power outlet and is microprocessor controlled. Its functionality is driven by an operator controlled on/off switch. The unit displays indicator lights to guide the operator. The system produces the desired effects through initiation

of a cooling cycle. Each cooling cycle is initiated by subcutaneous insertion of the Cryoprobe into the selected site and activation of the cryogen flow. A freezing zone forms around the tip of the Cryoprobe and the adjacent tissue. The Cryogen Cartridges are provided in individually sealed pouches. Each cartridge contains a nitrous oxide cylinder encased with a safety cap and filtering. The Cryoprobes are supplied in sterile packaging and are single-patient use. The Cyroprobe tips are closed, no cryogen enters the insertion site. A skin warmer provides warming at the base of the Cryoprobe tips to keep the surface above freezing temperatures.



A. Control Unit
B. Handpiece
C. Cryoprobe
D. Cryogen Cartridge

Figure 1. Picture of Cryo-Touch III device.



A. Skin Warmer
B. Cryoprobe Tips

Figure 2. Picture of the Cryoprobe.

1.3. Regulatory Status

The myoscience Cryo-Touch III device has been cleared by the U.S. FDA as a class II medical device, K120415. Approved indications include general tissue destruction during surgical procedures and cryo-treatment of nerves to block pain.

Additionally, myoscience and an independent review board has determined that the Cryo-Touch III 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.

2. Study Protocol

2.1. Design

This is a prospective non-randomized unblinded study.

2.2. Study Duration

Enrollment and follow-up is expected to take approximately 4 months.

2.3. Sample Size

Up to 50 subjects will be enrolled.

2.4. Subject Inclusionary Criteria

1. Male or female, 18 years of age and older.
2. Participants must meet American College of Rheumatology (ACR) criteria for osteoarthritis of the knee (unilateral or bilateral). Clinical criteria includes knee pain and at least three of the following 6 criteria: 50 years of age or older, stiffness lasting less than 30 minutes, crepitus, bony tenderness, bony enlargement, and/or no warmth to the touch.
3. Any medications (prescription and/or over-the counter) must be maintained on a stable schedule for ≥ 2 weeks prior to treatment. No washout period is allowed.
4. An average Visual Analog Scale (VAS) for pain ≥ 4 over the last 30 days.
5. Subject is willing and able to give written informed consent.
6. Subject is willing and able to comply with study instructions and commit to all follow-up visits for the duration of the study.

7. 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.

2.5. Subject Exlusionary Criteria

1. A partial or full knee replacement (in the treated knee).
2. Any use of systemic injections (in any area) within the last 6 months.
3. Current enrollment in an investigational drug or a device study that specifically targets pain treatment.
4. Any additional diagnosis that in the opinion of the investigator may directly contribute to knee pain.
5. Any concomitant inflammatory disease or other condition that affects the joints (e.g. rheumatoid arthritis, metabolic bones disease, gout, active infection, etc.).
6. Any clotting disorder and/or has used an anticoagulant (e.g., warfarin, clopidogrel, etc.) within seven (7) days prior to administration of the device.
7. Allergy or intolerance to local anesthetic.
8. Any local skin condition at the treatment site that in the investigator's opinion would adversely affect treatment or outcomes.
9. Any chronic medical condition that in the investigator's opinion would prevent adequate participation.
10. Any chronic medication use (prescription, over-the-counter, etc.) that in the investigator's opinion would affect study participation or subject safety.
11. 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.).

2.6. Schedule of Events

See Appendix B.

2.6.1. Visit 1/Screening (Day -30 to Day 0)

Subjects will be informed of all study activities and requirements. After the subject has had ample opportunity to ask and have questions answered an informed consent form will be signed and a copy provided to the subject.

The investigator, or designee, will document the subject's medical history, demographic information, concomitant medications/concurrent procedures, and any other required data points to determine subject eligibility.

Once the subject is determined to be eligible, the subject will be scheduled for the next visit. The Screening Visit 1 and Treatment Visit 2 may occur on the same day. Every effort will be made to reduce the time between Screening and Treatment Visits if possible.

2.6.2. Visit 2/Treatment (Day 0)

2.6.2.1. Pre-Treatment/Evaluation Preparation

No special preparation by the subject is required prior to the treatment. The investigator will reaffirm eligibility criteria and the subject's willingness to continue participation in the trial. Any changes in concomitant medications/concurrent procedures will be recorded. Any adverse events that may have occurred prior to treatment will be documented as a change in medical history.

Non-invasive ultrasound imaging of the treatment area may be captured. Nerve stimulation may be used to assess location of nerves via a percutaneous nerve stimulator or a transcutaneous nerve stimulator.

The Cryo-Touch III device will be used on awake subjects who are prepared with dermal anesthesia only. The skin in the treatment area will be cleansed with alcohol. Local anesthetic will be injected into target sites with the goal of complete cutaneous anesthesia at the target treatment areas prior to the treatment.

The target of treatment is the infrapatellar branch of the saphenous nerve. The nerve will be accessed by locating adjacent landmarks and treating in a linear fashion to capture the nerve as it travels inferiorly (see Figure 3).

Subjects with a bilateral indication will receive treatment in both knees.

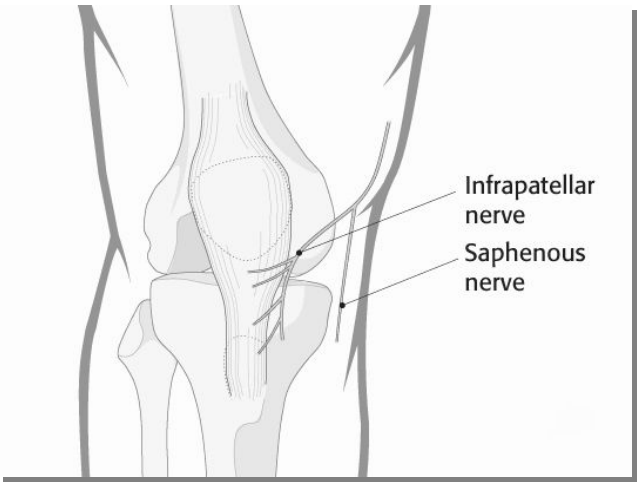


Figure 3: Nerve map of intended treatment.

2.6.2.2. Treatment

The Cryo-Touch III device will have been prepared by the trained investigator (or Sponsor designee) according to the ***Instructions for Use (IFU)*** as provided by myoscience (see supplementary material). Representatives of myoscience may be present at the treatment. Photography of the treatment area may be taken. Videography may also be captured during the treatment.

Varying treatment algorithms will be pre-determined by the sponsor and placed into cohorts as appropriate for anyalysis. This is intended to determine the most effective method of treatment and device optimization. Algorithms may include the following parameters: temperature, length of treatment, number of treatment cycles, probe tip design, and probe length.

If at any time the device does not perform as expected the investigator (or designee) we follow procedures as outlined in the IFU.

2.6.2.3. Post-Treatment

Upon completion of treatment, the treatment area will be cleansed and the skin will be left undressed. Pressure to the treatment area with gauze 5-10 minutes may be applied to minimize bleeding. The subject will be instructed in post-treatment care.

The subject will be instructed to report any adverse events or treatment side effects (e.g., excessive redness, swelling, bruising, soreness, altered sensation, etc.) to the investigator between and at follow-up visits. Non-invasive ultrasound may be used to assess the volume and location of the

soft tissue treated below the dermis. Photography and videography of the treatment area may be obtained.

The subject will be scheduled and instructed for their follow-up visits and discharged from the clinic.

2.6.3. Visit 3/ Maintenance (Day 7) & Visit 4/Maintenance (Day 30)

Subject will be evaluated and data collected per the schedule of events. Any changes in concomitant medications/concurrent procedures will be assessed. Any anticipated observations, adverse events, and/or SAE/UADE of the previous treatment site(s) will be assessed and documented. Non-invasive ultrasound imaging of the treatment area may be captured. Photography may be taken of the treatment area.

2.6.4. Visit 5/Study Exit (Day 56) – Telephone Follow-Up

Subject will be contacted via telephone and data collected since their last visit per the schedule of events. Any changes in concomitant medications/concurrent procedures will be assessed. Any anticipated observations, adverse events, and/or SAE/UADE of the previous treatment site(s) will be documented.

If the treatment effect remains at Day 56 the subject will be followed every four (4) weeks via telephone until Day 84. Any clinically significant adverse event will be followed until resolution. The subject will exit the study after Day 56 once there is no longer a treatment effect or the Day 84 follow-up is completed and no ongoing clinically significant events.

Study exit data will be collected and the subject reminded to contact the investigator if any new previously unreported event occurs as it related to the treatment.

A subject is considered to have exited (a completer) the study after completing all scheduled visits. 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 of a subject lost to follow-up a study exit will be completed.

If a subject decides to withdraw participation early, the subject will be requested 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.

3. Outcome Measures and Assessments

Outcome measures will be assessed around multiple endpoints. These measures will be: pain, function, range of motion, anticipated observations, duration of improvement, and safety. Additional assessments may also be taken but not part of analysis (i.e. subject post-treatment questionnaire). The specific assessment tools, collection method and time points are listed herein.

3.1.1. Primary Outcome Measure

Improvement of knee pain as measured on the Visual Analog Scale (VAS) for pain at Day 7 as compared to baseline (Day 0). See Appendix.

3.1.2. Secondary Outcome Measures

3.1.2.1. Improvement (pain, stiffness, and functionality) as determined by the Western Ontario and McMaster Osteoarthritis Index (WOMAC) Scale at Day 7. A significant difference is observed as ≥ 2-points. See Appendix.

3.1.2.2. Duration of Treatment Effect/No Effect [Data Collection Tool]

3.1.3. Ancillary Measures (Potential measures not part of analysis)

3.1.3.1. Subject Post-Treatment Questionnaire (See Appendix)

3.1.4. Anticipated Observations (AO) [Data Collection Tool]

During each visit, the area to be treated will be assessed by the investigator (observation and subject query) for the following anticipated observations (AO's). These AO's will be collected independent of adverse events.

- Bruising (ecchymosis)/Soreness
- Tingling/altered sensation (transient paresthesia/dysesthesia/anesthesia)
- Redness/inflammation (erythema)
- Swelling
- Itching (pruritus)
- Local pain/tenderness
- Erosion/ulceration
- Eschar/crusting
- Dimpling/depression
- Hyperpigmentation
- Hypopigmentation

3.1.5. Safety Measures [Data Collection]

Adverse events and SAEs/UADEs will be assessed at all visits. Incidence of serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) will be recorded. A serious adverse event is one that meets the ISO definition of SAE (see section 4.2.1).

3.2. Adverse Event Reporting

Adverse events (AEs) will be assessed continuously from initiation of study treatment through study exit. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a device, without any judgment about causality. 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) adherence to worldwide regulatory requirements.

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. All AEs must be completely recorded within subject's source documentation. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of participation, or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. If possible, report the outcome of any AE that caused permanent discontinuation or that was present at the end of the study particularly if the AE was considered by the investigator to be definitely, probably, or possibly related to the study device.

The investigator will instruct the subject to report any adverse events that may occur during the study. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject's overall condition since the previous visit.

3.2.1. Serious Adverse Event (SAE)/Unanticipated Adverse Device Effect (UADE)

A device-related SAE is an AE that meets the ISO definition for SAE and is rated by the investigator to be related to the study device. No device-related SAEs have been reported in prior studies of Cryo-Touch II.

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.

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.

An **unanticipated adverse device effect** (UADE) is any of the following events 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):

- Any serious adverse effect on health or safety.
- Any life-threatening problem.
- Death.
- Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Report of any UADEs shall be submitted to Sponsor within 24 hours of knowledge of the event.

UADEs and AEs that are classified as "serious" by the investigator or the Sponsor require expeditious handling and reporting to the Sponsor. All SAEs, whether related or unrelated to the study device, must be immediately (within 24 hours of becoming aware of the SAE) reported to the sponsor by telephone or confirmed facsimile transmission:

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

In addition, such information should also be provided to the site's respective IRB per their governing guidelines for SAE/UADE reporting. If only limited information is initially available, follow-up reports are required. Should the investigator become aware of an SAE (regardless of its relationship to the device) that occurs within 30 days after completion of the study, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to the Sponsor, if available.

As required, the Sponsor will notify all investigators of any UADE within 10 working days of the Sponsor's receipt of the effect.

Upon receiving such notices, the investigator must review and retain the notice and immediately submit a copy of this information to the responsible IRB according to local regulations. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of Safety Updates by the investigator to Health Authorities should be handled according to local regulations.

3.3. Statistical Analysis Plan

Not Applicable.

4. Risk/Benefit Analysis

4.1. Benefits

Subjects may experience an improvement in pain post-treatment or may experience no improvement at all.

4.2. Risks

The Cryo-Touch III device involves percutaneous access to subcutaneous tissue using a needle and use of dermal anesthesia. Passage of a needle into the skin and delivery of local anesthesia are known and may be documented as anticipated observations (AO). See list in section 3.1.4.

These reactions do not typically require medical intervention on the part of the investigator and are usually transient. Self-care with compression or oral non-narcotic analgesics usually suffices.

In the event that an AO exceeds the expected response to the treatment, either in severity or in duration by the investigator's assessment, they will be reported as AEs per Section 3.2.

Additional adverse events which have occurred but are considered to be rare include:

- Infection/Fever
- Weakness which could result in difficulty ambulating
- Limitations in range of motion of joint
- Vasovagal reaction to needle insertion
- Burns, blistering, or scarring due to heat or cold injury

5. Study Management and Quality Control

5.1. Data Collection

Incoming data will be reviewed by the Sponsor or designee to identify inconsistent or missing data and to ensure compliance with the study protocol.

Investigators will be responsible for the accurate and timely completion of all source documents, case report forms, and any other required study data (i.e., worksheets, questionnaires, etc.) during the trial.

5.2. Investigator Responsibilities

Investigators are responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol, and applicable regulatory agency regulations. This section describes these responsibilities.

5.2.1. 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. The protocol, informed consent documents, recruitment advertisements and any amendments to these items will have IRB approval prior to study initiation. Every subject prior to the initiation of any study-related procedures will give voluntary informed consent. The rights, safety and welfare 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.

5.2.2. Institutional Review Board (IRB)

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 will submit documentation of the IRB approval to the Sponsor or designee.

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/designee must provide the subject with a copy of the consent form, in a language the subject understands.

The investigator/designee 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 shall be reported to the Sponsor within 5 working days.

5.2.3. Device Accountability

The investigator is responsible for providing a secure storage location for the devices, supervising device use, as well as the disposal of the device or return of the device as instructed by the Sponsor or designee. In addition, investigators will maintain records of receipt, use or disposition of all devices. The Sponsor or designee will maintain records of all shipments and disposition of the investigational devices and will routinely inspect for device accountability at the clinical sites participating in this trial.

All used units and probes shall be stored and upon request returned to the Sponsor or designee for analysis unless otherwise directed. 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.

5.2.4. 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.

5.2.5. Record Retention

The investigator must maintain all study records (including device disposition, informed consents, case report forms/worksheets, source documents, correspondence, regulatory documents, contracts etc.) for the maximum period required by the Sponsor or the institution where the study is conducted, whichever is longer.

The investigator must contact the Sponsor prior to destroying any records associated with this study.

If the investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee.

5.3. Sponsor Responsibilities

Myoscience or designee's responsibilities in the study include:

- Completing IRB approvals and reporting.
- Ensuring device availability.
- Providing site training on all study aspects and procedures.
- Managing the data: data collection, verification, records storage, etc.
- Analyzing results and assisting with presentation(s) and/or publication(s).
- Retaining custodianship of the multi-center clinical data generated.

5.3.1. Study Monitoring

Representatives of the Sponsor or designee must be allowed to visit all study sites, 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 or designee of any audits of this study by any regulatory agency, and must promptly provide copies of any audit reports.

5.3.2. Protocol Revisions

The Sponsor or designee must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. All correspondence with the IRB regarding this study must be maintained in the site regulatory file and made available to the Sponsor or designee.

The most recent IRB approved version of the informed consent form (ICF) must be administered to all subjects upon enrollment. In some cases, due to new information or protocol amendments, an ICF may be updated. Subjects only need to be re-consented using the latest approved version if directed so by the IRB and/or Sponsor.

5.3.3. Trial Registration

The trial will be registered on a publicly accessible study database such as clinicaltrials.gov.

6. Data Ownership

Myoscience, Inc., the study Sponsor, retains ownership of all data generated in this study, and controls the use of the data for purposes of regulatory submissions to the United States and/or other governments. Investigator(s) and institution(s) (which shall include their employees, agents, and representatives) may not issue or disseminate any press release or statement, nor initiate any communication of information regarding this study (written or oral) to the communications media or third parties without the prior written consent of myoscience.

7. Publication Policy

Participating investigators and/or Institutions may publish information or data collected or produced as a result of participation in appropriate scientific conference or journals or other professional publications subject to written permission from myoscience, provided

that drafts of the material are provided to myoscience for purposes of review and comment at least sixty (60) days prior to the first submission for publication or public release. Investigators may not publish information regarding site-specific data until a multicenter study report has been published.

Appendix A: Abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
AO	Anticipated Observations
ASR	Anticipated Site Reaction
CFR	Code of Federal Regulations
US FDA	United States Food and Drug Administration
EOS	End of Study
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board/Independent Review Board
ISO	International Organization for Standardization
NSAID	Non-Steroidal Anti-Inflammatory Drug
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analog Scale

Appendix B: Schedule of Events

Study Activity	V1 Screening	V2 Treatment	V3	V4	V5 Phone Follow-up/EOS
	Day -30 to Day 0	*Day 0*	*Day 7**	*Day 30**	*Day 56**
Obtain Informed Consent	X				
Review eligibility criteria	X	X			
Physical examination	X				
Medical history	X				
Concomitant medications/procedures	X	X	X	X	X
WOMAC		X	X		
Visual Analog Scale (VAS) for pain	X	X	X	X	
Treatment		X			
AO Assessment	X		X	X	X
Subject Post-Treatment Questionnaire		X	X	X	X
Adverse events/procedures review		X	X	X	X
Duration of Treatment Effect/No Effect			X	X	X

**** A variance of +/- 3 days is allowed.***

Appendix C: Pain Visual Analog Scale

Instructions: Adults may have difficulty using a number scale and may be assisted with the use of the six facial expressions suggesting various pain intensities. Ask the subject to choose the face that best describes how they feel. The far left face indicates 'No hurt' and the far right face indicates 'Hurts worst'. Document number below the face chosen.

Faces rating scale (FRS)

Appendix D: WOMAC

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a widely used, proprietary set of standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. The WOMAC has also been used to assess back pain, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia. It can be self-administered and was developed at Western Ontario and McMaster Universities in 1982. [1]

The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). [2]. Physical functioning questions cover everyday activities such as stair use, standing up from a sitting or lying position, standing, bending, walking, getting in and out of a car, shopping, putting on or taking off socks, lying in bed, getting in or out of a bath, sitting, and heavy and light household duties. [3]

A WOMAC test takes about 12 minutes, but is also available in a short form, (although this has not been as extensively tested as the full version). Versions of the WOMAC have also been developed that can be used in telephone or online surveys. [3]

The WOMAC is among the most widely used assessments in arthritis research. For example, it appears as a search keyword in more than 1500 papers cataloged in PubMed, as of June 2012. It has been translated into more than 65 languages. [1]

The American College of Rheumatology notes that the test-retest reliability of the WOMAC varies for the pain, stiffness, and function subscales. The ACR says the pain subscale "has been variable across studies but generally meets the minimum standard." Reliability for the physical function scale "has been more consistent and stronger... but the stiffness subscale has shown low test-retest reliability."[3] When used in clinical studies, the WOMAC pain and function subscales perform comparably or better than other tests in being responsive to change from experimental interventions, but this varies for the different subscales and types of intervention.

An example of a intended WOMAC index is attached for reference.

1. ^ [a] [b] "WOMAC Osteoarthritis Index". Retrieved 6 June 2012.
2. ^ Quintana, Jose; Escobar, Arostegui, Bilbao (January 2006). "Health-Related Quality of Life and Appropriateness of Knee or Hip Joint Replacement". *Archives of Internal Medicine* **166**: 220–226.
3. ^ [a] [b] [c] American College of Rheumatology. "Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)--General Description". ACR. Retrieved 6 June 2012.

Appendix E: Subject Post-Treatment Questionnaire

Instructions: To better help the sponsor understand the dynamics of the treatment the following questions have been compiled. The investigator, or designee, will request a response from the subject at the designated time and complete the source document as appropriate. If no response or not applicable check the appropriate box.

Day 0/Visit 2/Post-Treatment

1. How nervous were you during the procedure? On a scale from 1-5, 1 being extremely nervous and 5 being completely relaxed.
2. Prior to your treatment today, how effective or helpful was the information provided beforehand (information pamphlet, informed consent, etc.)? On a scale from 1-5, 1 being not at all effective/helpful to 5 being very effective/helpful.
3. Was the treatment painful? On a scale from 1-5, 1 being not at all painful to 5 being very painful.

Visit 3/Day 7 and Visit 4/Day 30

1. If you any had anticipated observations (AO) from your treatment (i.e., bruising, swelling), how much did they/it impact your daily routine? On a scale from 1-5, 1 being the AO had a very negative impact to 5 being no impact at all.
2. Would you recommend this treatment to a friend or family member? Yes or No.
3. Would you have the treatment again if available? Yes or No.
4. Is there any pain present from the treatment? On a scale from 1-5, 1 being not at all painful to 5 being very painful.