# CLINICAL INVESTIGATION PLAN

A Double-blind, Randomized, Controlled Trial Comparing the Safety and Efficacy of AMDC-USR with Placebo in Female Subjects with Stress Urinary Incontinence

**Global Clinical Number 13-003**

**Sponsor:** Cook MyoSite, Incorporated
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**Summary of Changes**

| Version | Description | Date |
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| 13-003-01 | Original version | 01 May 2013 |
| 13-003-02 | Amendment | 03 June 2014 |
| 13-003-03 | Amendment | 02 November 2015 |
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# CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

**Global Sponsor Contact:**

This clinical study will be conducted in accordance with the Clinical Investigation Plan (CIP), ICH GCP, 21 CFR 312 and other applicable requirements as appropriate. The CIP will be revised, as appropriate, based on new information.

# CLINICAL INVESTIGATION PLAN SIGNATURE PAGE, CONTINUED

**Global Principal Investigator:**

I hereby confirm that I approve of this Clinical Investigation Plan and agree to comply with its terms as laid out in this document.

[redacted]

# CLINICAL INVESTIGATION PLAN SIGNATURE PAGE, CONTINUED

**Principal Clinical Investigator:**

I hereby confirm that I approve of this Clinical Investigation Plan and agree to comply with its terms as laid out in this document.

X _____ _____

Signature | Date (DD Month YYYY)

_____ _____

Printed Name | Title

_____

Clinical Site Name

# CONFIDENTIALITY STATEMENT

**This document shall be treated as a confidential document for the sole information and use of the clinical study team and the institution's Institutional Review Board (IRB).**

# Table of Contents

## 1.0 Clinical Investigation Plan Overview

This randomized, double-blind, placebo-controlled, multicenter, confirmatory study will evaluate the efficacy and safety of Cook MyoSite Incorporated Autologous Muscle Derived Cells for Urinary Sphincter Repair (AMDC-USR) compared to a placebo (vehicle) control dose in the treatment of stress urinary incontinence (SUI) in adult female patients.

Patients will be stratified for randomization according to the number of stress incontinence episodes at screening (≤ 10 stress incontinence episodes, > 10 stress incontinence episodes) and if the patients have had previous surgery for treatment of SUI. Previous surgery includes but is not limited to midurethral sling, retropubic suspension, or bladder neck sling. For each stratum, patients will be randomly assigned to one of the two treatment groups ($150 \times 10^6$ AMDC-USR or placebo control). The allocation ratio within each dose will be 2:1 (AMDC-USR: placebo control). Randomization will occur after enrollment, but prior to treatment. The study will enroll 267 patients (178 enrolled with $150 \times 10^6$ AMDC-USR and 89 enrolled with placebo control) at up to 35 clinical sites. Enrollment is expected to be completed within 4 years of initiating the study. Patients will be followed for 2 years. In addition, up to 12 roll-in patients may be treated at each investigative site, prior to enrolling patients in the main study arms. Therefore, up to 687 patients may be treated as part of this study protocol. Up to 3 initial injection procedures for each investigator may be proctored according to the study injection procedure guidelines, to ensure that investigators are familiar with the injection procedure.

Placebo-injected patients will be given the opportunity to receive the $150 \times 10^6$ cell dose following the 12-month evaluation. Patients randomized to placebo control who opt to receive AMDC-USR treatment will be followed for up to 2 years following their initial placebo injection.

The primary efficacy measure will be evaluated at 12 months post-treatment (initial) and will be based on the reduction in stress incontinence episodes, as recorded in a diary. The safety measures will be the incidence of study product-related serious adverse events (SAEs) and the incidence of study product-related, injection procedure-related, and biopsy procedure-related adverse events.

Analysis will also include evaluation of efficacy as measured by patient quality of life as reported by multiple surveys. Additionally, treatment durability at 2 years will be determined for patients randomized to AMDC-USR treatment.

Female patients at least 18 years of age with primary symptoms of SUI as confirmed by patient medical history and clinical symptoms, including a focused incontinence evaluation, will be eligible for participation. All eligible patients consenting to study participation will have skeletal muscle tissue harvested via needle biopsy during an initial outpatient procedure. The harvested muscle tissue will be [redacted] transported to Cook MyoSite, Incorporated for processing in their cell processing facility in Pittsburgh, Pennsylvania, USA. The muscle derived cells will be isolated and expanded in culture over several weeks to the final dose of 150 x $10^6$ cells for the AMDC-USR-treated patients.

After reaching the desired concentration, the isolated and expanded AMDC-USR will be frozen and shipped back to the investigating physician. [redacted] The resulting suspension will be injected into the patient's urethral sphincter in a brief outpatient procedure. Patients will be assessed for improvement in urinary incontinence symptoms at 1 month, 3 months, 6 months, 12 months, and 2 years following treatment. Adverse events will be assessed and reported at each visit and during follow-up telephone calls. The study overview is depicted in Figure 1.1.

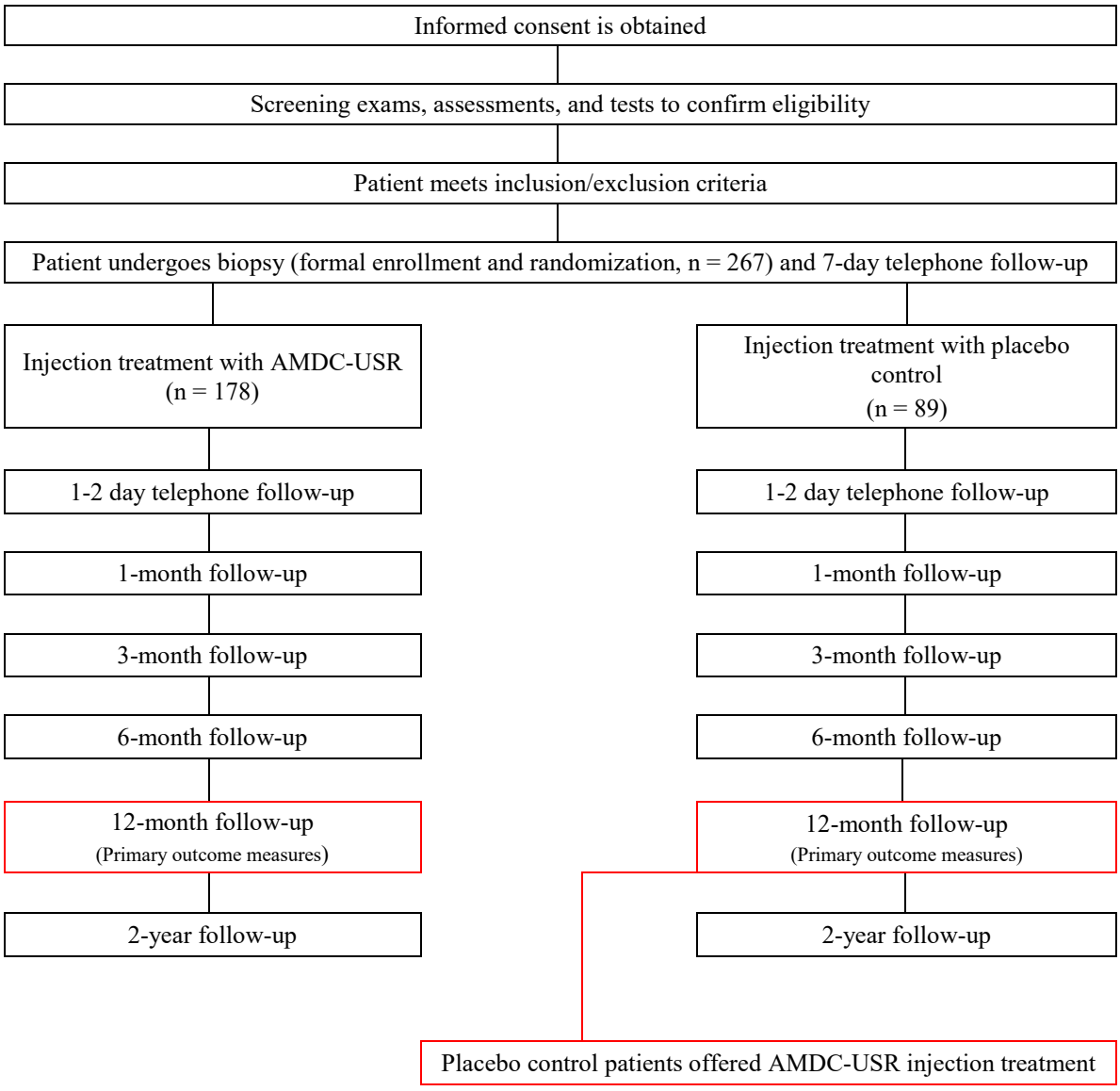


Figure 1.1. Study flow diagram

## 2.0 Objectives of the Clinical Study

### 2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy and safety of the Cook MyoSite Incorporated Autologous Muscle Derived Cells for Urinary Sphincter Repair (AMDC-USR) in the treatment of SUI in female patients at 12 months post-treatment. The primary efficacy measure will be the frequency of stress incontinence episodes, while safety will be determined by the frequency and severity of adverse events related to

study procedures and study product.

### 2.2 Secondary Objectives

The secondary objectives of the study are to evaluate additional measures of efficacy and safety of AMDC-USR in the treatment of SUI in female patients at 12 months and 2 years.

## 3.0 Product Description and Intended Use

### 3.1 General Product Description

Please reference the manufacturer's Instructions for Use (IFU) or the Investigator's Brochure (IB) for a description of the product and dose to be used in the clinical study.

[redacted] For the purpose of this study, the product will be referred to as AMDC-USR.

Cook MyoSite, Incorporated will perform cell processing and preparation of cell suspensions for study use in their cell processing facility in Pittsburgh, Pennsylvania (USA). [redacted] Cell processing will follow current Good Manufacturing Practice (cGMP) methodologies to prevent contamination and to preserve tissue function and integrity. These practices will include defined procedures for tissue and cell handling, processing, and identification.

Each AMDC-USR study agent vial supplied to the clinical site will contain cryogenically preserved autologous muscle derived cells, [redacted]

[redacted]

[redacted]

### 3.1.1 Dose Justification

The dose of 150 x $10^6$ cells was chosen based on the results of previous studies [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Based on the statistical modeling described above and no safety concerns for the doses

assessed in the previous studies, the dose of 150 x $10^6$ AMDC-USR was chosen for the study.

## 3.2 Indication for Use

The AMDC-USR treatment is intended for treatment of SUI in female patients. It is indicated for use to reduce symptoms of SUI in women who experience an average of at least one leak episode per day.

## 3.3 Product Identification and Tracking

Each product is manufactured individually and labeled with a unique product code containing enrollment number, patient initials, and six assigned digits for identification and traceability. To maintain blinding, this unique product code will not indicate the dose of AMDC-USR or whether the product is a placebo control. All cell preparations and placebo controls will be transported in identical vials with the same volume of transport medium and reconstituted to the same final volume prior to injection to maintain study blinding. Additional procedures have also been established to ensure blinding.

Products under investigation will be tracked by the clinical site throughout the course of the study through the use of a product log, which includes information such as lot numbers, quantity, and disposition of products. Additionally, information such as the quantity and lot number(s) of products used in patients will be recorded on Case Report Forms (CRFs).

## 3.4 Instructions for Use

The study Procedure Guidelines, which will be provided to physicians and appropriate study staff at the time of training, must be followed for step-by-step instructions for performing the following:

- Obtaining the muscle biopsy
- Packaging and shipping the muscle biopsy
- Storing and handling requirements
- Resuspending the final product (AMDC-USR or placebo control)
- Performing the injection procedure

Muscle Biopsy

The biopsy procedure will involve minor surgery to collect [redacted] Prior to the biopsy, patients who are currently taking any form of anticoagulant medication must stop using the medication as per standard of care for outpatient surgery procedures. Antianxiety medication, analgesia, or minimal sedation may be provided according to each site's standard of care. Muscle biopsies are obtained approximately halfway from the patella to the hip, from the middle region of the vastus lateralis, and slightly beyond the fascia using a percutaneous needle biopsy technique.

[redacted]

Using aseptic technique, the biopsy tissue will be transferred to the Biopsy Medium Vial. The Biopsy Medium Vial will be closed and packaged for shipment to the Manufacturer.

Dilution and Preparation for Injection

[redacted] The entire vial contents are used for injection.

Transurethral Cell Injection

The study product (AMDC-USR or vehicle placebo) is injected into the urethral sphincter using a transurethral approach under local anesthesia (or in accordance with site standard of care regarding anesthesia). [redacted] The injections should be made into the muscle

of the urethral sphincter. Materials contacting the urethral tissue will include the patient's own AMDC-USR, the cryogenic medium in which the cells are suspended and shipped, and the physiologic saline used to dilute the mixture for injection. Prior to the injection, patients who are currently taking any form of anticoagulant medication must stop using the medication as per standard of care for outpatient surgery procedures. Antianxiety medication, analgesia, or minimal sedation may be provided according to each site's standard of care or physician's discretion.

After the injection is completed, cystoscopy is used to ensure the injection did not cause any excessive bleeding and/or excessive trauma. A post-void ultrasound/bladder scan is performed to determine post-void residual (PVR) urine volume.

## 4.0 Summary of Preliminary Studies

Please refer to the Investigator's Brochure for a summary of non-clinical testing and a summary of previous clinical experiences with this product or similar products.

## 5.0 Risk Analysis and Risk Assessment

### 5.1 Risks and Foreseeable Adverse Events and Adverse Product Effects

Please refer to the Investigator's Brochure for a list of specific risks of study procedures and study products.

### 5.2 Methods to Minimize Risks

This product will be administered only by trained healthcare professionals who are experienced with cystoscopy, urethral injection, and use of urethral bulking agents. Patients will be selected according to the indication and in accordance with inclusion/exclusion criteria outlined in this document. Adherence to and training on the research Clinical Investigation Plan (CIP) are necessary to reduce material- and procedure-related risk. Routine catheterization and venipuncture will be performed by qualified personnel.

The product design, non-clinical testing, clinical study design, and guidelines are intended to minimize the risks associated with the use of this product. The risks of the study have been minimized and the potential benefits outweigh the risks.

## 6.0 Design of the Clinical Study

### 6.1 Type/Design of Study

This randomized, double-blind, placebo-controlled, multicenter, confirmatory study will evaluate the efficacy and safety of Cook MyoSite Incorporated AMDC-USR compared to a placebo control dose for the treatment of SUI in adult female patients.

The study will enroll 267 patients (178 enrolled with 150 x $10^6$ AMDC-USR and 89 enrolled with placebo control) at up to 35 clinical sites. Enrollment is expected to be completed within 4 years of initiating the study. Patients will be followed for 2 years.

The sponsor may evaluate up to 12 initial patients (roll-in patients) at each investigative site. Up to 3 initial injection procedures for each investigator may be proctored according to the study injection procedure guidelines, to ensure that investigators are familiar with the injection procedure. The roll-in patients will be followed according to the protocol-specified schedule but the data from these patients will not be used for primary efficacy analysis. Data from roll-in patients will be included in the safety analyses. Screening stress incontinence episodes from the roll-in patients will be collected and examined by an independent CRO (separate from the primary CRO being used for this study). Since the collection of stress incontinence episode data contributes to the primary efficacy endpoint, it is important to provide an early assessment of the

homogeneity of these data.

## 6.2 Inclusion and Exclusion Criteria

Patient eligibility for enrollment shall be based on known information at the time of the screening. Information obtained at a later date may contradict previous information, but this will not be considered a violation of the CIP.

Inclusion Criteria

A patient is deemed suitable for inclusion in the study if the patient meets the following criteria:

1. Adult female (≥ 18 years of age) with primary and moderate-to-severe symptoms of SUI (1 ≤ daily stress incontinence episodes per diary ≤ 15), as confirmed by patient medical history and clinical symptoms, including a focused incontinence evaluation and have a history of inefficient, insufficient, or refused pelvic floor muscle training (PFMT).
2. Must complain of involuntary leakage on effort or exertion or on sneezing or coughing and must produce a leak during the bladder "cough" stress test.
3. Must have bladder capacity of ≥200 mL and a PVR value of ≤ 150 mL after repeated testing (i.e., the patient has been asked to revoid to ensure complete emptying of the bladder and the PVR urine volume is ≤ 150 mL).
4. Must have low hypermobility of the urethra with Valsalva Q-tip ≤30º.
5. Must be willing and able to comply with the study procedures, be mentally competent and able to understand all study requirements, must agree to read and sign the informed consent form prior to any study-related procedures.[1]
6. Must be able to void spontaneously.
7. Must have a negative urine test (dipstick) at time of treatment.
8. Must be willing to use acceptable methods of contraception (birth control pills, barriers, or abstinence) if of childbearing potential.

[1] Patients must demonstrate proficiency and willingness to complete 3-day diaries. Patients who enter data for less than 80% of the time intervals for their screening 3-day diary must be excluded from the study.

Exclusion Criteria

Patients are excluded from enrollment in the study if any of the following are true:

Patient History-based Criteria

1. Simultaneously participating in another investigational drug or device study or has completed the follow-up phase for the primary endpoint of any previous study less than 30 days prior to the first evaluation in this study.
2. Has been treated with an investigational device, drug, or procedure for urinary incontinence within the last 6 months.
3. Has had surgical intervention in the pelvic area (e.g. surgery for SUI, mesh removal, prolapse surgery) within the last 6 months prior to the first evaluation in the study.
4. Has ever been treated with a cell therapy for SUI.
5. An average of fewer than 1 stress incontinent episodes per day, or fewer than 3 discrete episodes of stress incontinence during the screening 3-day diary (not continuously leaking, rather leakage of urine that is associated with activities such as lifting, coughing, sneezing, or exercise with periods free of leakage between episodes). An incontinent episode is a leakage of urine that would wet a pad, diaper, or other containment garment, or article of clothing.
6. An average of greater than 15 stress incontinent episodes per day, or greater than 45 discrete episodes of stress incontinence during the screening 3-day diary (not continuously leaking, rather leakage of urine that is associated with activities such as lifting, coughing, sneezing, or exercise with periods free of leakage between episodes).
7. Symptoms of only urge incontinence as confirmed by basic evaluation of etiology from a patient medical history, including a focused incontinence history.
8. Symptoms of mixed urinary incontinence where urge incontinence is the predominant factor.
9. Stress urinary incontinence symptoms for less than 6 months prior to signing the informed consent.
10. No previously attempted conservative treatment prior to signing the informed consent. (Examples of conservative treatment include behavior modifications, bladder exercises, biofeedback.)

11. Has experienced significant worsening or improvement in SUI symptoms within the last 1 month prior to signing the informed consent (i.e., symptoms have not been stable).
12. Routinely has more than 2 episodes of awakening to void during normal sleeping hours.
13. Urinary incontinence of neurogenic etiology.
14. Indwelling urinary catheter or requires intermittent catheterization for bladder emptying.
15. Systemic neuromuscular disorder (e.g., muscular dystrophy, multiple sclerosis, fibromyalgia).
16. Uncorrected congenital abnormality leading to urinary incontinence.
17. Morbidly obese (BMI $\geq$ 35).
18. Uncontrolled diabetes.
19. Adult nocturnal enuresis.
20. Severe constipation (history of impaction).
21. Compromised immune system due to disease state, chronic corticosteroid use, or other immunosuppressive therapy.
22. History of radiation treatment to the urethra or adjacent (or nearby) structures.
23. Medical condition or disorder that may limit life expectancy or that may cause CIP deviations (e.g., unable to perform self-evaluations and/or accurately report medical history, urinary symptoms, and/or data).
24. History of bleeding diathesis, uncorrectable coagulopathy, or would refuse a blood transfusion.
25. Has known allergy or hypersensitivity to bovine proteins or allergens, gentamicin sulfate, or ampicillin that medically warrants exclusion as determined by the physician.
26. History of cancer in pelvic organs, ureters, or kidneys.
27. Any cancer that has undergone treatment within the past 12 months.
28. History of adult vesicoureteral reflux.

<u>Patient Physical Examination or Testing-based Criteria</u>

1. Does not have a viable mucosal lining along the urethra and bladder.
2. Pelvic organ prolapse extending to or out of the vaginal opening, including but not limited to vaginal vault prolapse, uterine prolapse, cystocele, urethrocele, rectocele, and/or enterocele.

3. Fistula involving the urethra, uterus, bladder, vagina, and/or rectum.
4. Urethral stricture, bladder neck contracture, or bladder stones.
5. Fails to produce a leak during the bladder "cough" stress test (see Appendix D for a description of the test).
6. Ambulatory 24-hour pad test, where the increased pad weight is < 3 grams (see Appendix E for a description of the test).
7. Moderate or severe urethral fibrosis at likely injection site.
8. Voiding difficulty (complains of difficulty emptying the bladder).
9. Residual urine volume > 150 mL after repeated testing (i.e., the patient has been asked to revoid to ensure complete emptying of the bladder and the PVR urine volume is still > 150 mL).
10. Urethral hypermobility as judged by a Q-tip angle > 30 degrees (see Appendix F for a description of the test).
11. Bladder capacity < 200 mL.
12. Tests positive for Hepatitis B (required tests: Hepatitis B Surface Antigen [HBsAg] and Anti-Hepatitis B Core Antibody [Anti-HBc]), Hepatitis C (required test: Hepatitis C Antibody [Anti-HCV]), HIV (required tests: HIV Type 1 and 2 Antibodies [Anti-HIV-1, 2]), and/or Syphilis.

Patient's Current Status-based Criteria

1. Cannot be, or is not willing to be, maintained on a stable dose and/or frequency of medication known to affect lower urinary tract function, including but not limited to, anticholinergics, beta 3 adrenergic receptor agonists, tricyclic antidepressants, SNRI or SSRI antidepressants, diuretics, or alpha-adrenergic blockers, for at least 2 weeks prior to screening assessments; or use of these medications is likely to change during the course of the study.
2. Cannot, or is not willing to, maintain the current treatment regimen for existing conservative therapy (e.g., pelvic floor muscle training routine, incontinence medications).
3. Requires prophylactic antibiotics for chronic urinary tract infections, cystitis, or urethritis, or has required 2 or more courses of antibiotics for lower urinary tract infections in the 2 months prior to signing the informed consent.
4. Pregnant, lactating, or plans to become pregnant during the course of the study.
5. Any condition that could lead to significant post-operative complications, including current infection.

6. Unresolved pain or complication from prior intervention for incontinence or pelvic organ prolapse.
7. Current or acute conditions involving cystitis or urethritis.
8. Refuses to provide written informed consent.
9. Not at least 18 years of age.
10. Not available for or willing to comply with the screening, baseline, and follow-up evaluations as required by the CIP.

## 6.3 Endpoints

### 6.3.1 Primary Efficacy Endpoint

The number of diary-reported stress incontinence episodes will be used as the primary efficacy measure to assess the treatment effect of AMDC-USR for SUI symptoms at 12 months. The primary efficacy endpoint is defined as the percentage of patients who have at least 50% (≥ 50%) reduction in stress incontinence episodes at 12 months using the ITT population, which is defined as non-roll-in patients who are randomized to either AMDC-USR or placebo control treatment group.

### 6.3.2 Secondary Efficacy Endpoint Measures

- Percentage of patients with at least 75% reduction in stress incontinence episodes from baseline at 12 months;
- Percentage of patients with 0 or 1 stress incontinence episodes at 12 months; and
- Improvement (reduction) in frequency of stress incontinence episodes from baseline at 12 months.

### 6.3.3 Additional Efficacy Endpoints

- Quality of life at 12 months as determined by Incontinence Quality of Life (IQOL) Assessment, Incontinence Impact Questionnaire – Short Form (IIQ – 7), Urogenital Distress Inventory – Short Form (UDI – 6), and Global Quality of Life Assessment (GQOL);
- Association of quality of life improvement with stress incontinence episode reduction at 12 months;

- Incontinence severity as determined by Sandvik Incontinence Severity Index (ISI) at 12 months; and
- Treatment durability at 2 years.

6.3.4 Safety Endpoints

- Study product-related serious adverse events;
- Biopsy procedure-related, injection procedure-related, and study product-related adverse events; and
- Post-void residual urine volume.

6.3.5 Rationale for Endpoints

The 3-day leak diary is a commonly used measurement for evaluating changes in a patient's SUI symptoms. The selected quality of life instruments are recommended by the International Continence Society for studying the impact of treatments on patients.

The safety endpoints have been chosen as part of the overall assessment of the safety of the biopsy and injection procedures as well as the safety of the product being investigated. The assessment will include descriptive evaluations of the types and frequency of adverse events observed with a comparison to the placebo control group.

6.4 Variables to be Measured to Demonstrate Achievement of Endpoints

The primary efficacy measure for evaluating the treatment effect will be the number of stress incontinence episodes as reported in patient 3-day diaries. The primary efficacy endpoint for the study is the percentage of patients with treatment success where treatment success is defined as:

- At least 50% ($\geq$ 50%) reduction from baseline in the number of stress incontinence episodes over 3 consecutive days as recorded in a diary at 12 months after treatment.

Secondary efficacy endpoints will be measured as follows:

- Percentage of patients with at least 75% reduction in stress incontinence episodes from baseline at 12 months;
- Percentage of patients with 0 or 1 stress incontinence episodes at 12 months; and
- Improvement (reduction) in frequency of stress incontinence episodes from baseline at 12 months.

Additional efficacy endpoints will be measured as follows:

- Change from baseline in disease-specific quality of life (QOL) measurements will be measured by Incontinence Quality of Life (IQOL)[2] score and subscores, Urogenital Distress Inventory – Short Form (UDI – 6),[3] and Incontinence Impact Questionnaire – Short Form (IIQ – 7)[2] at 12 months.
- Global Quality of Life Assessment (GQOL)[4] at 12 months.
- Association of quality of life improvement with stress incontinence episode reduction at 12 months.
- Change from baseline in patient perceived symptom severity measured by the Sandvik Incontinence Severity Index (ISI)[5] at 12 months.
- Treatment durability defined as the percentage of patients who have at least (≥) 50% reduction in stress incontinence episodes at 12 months and 2 years.

Safety endpoints will be measured as follows:

- Study product-related serious adverse events and study product-related, biopsy procedure-related, and injection procedure-related adverse events where adverse events are reported on eCRFs by the clinical site study staff; and

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[2] Wagner TH, Patrick DL, Bavendam TG, et al. Quality of life with urinary incontinence: development of a new measure. *Urology* 1996;47(1):67-72.
[3] Uebersax JS, Wyman JF, Shumaker SA, et al. Short forms to assess life quality and symptom distress for urinary incontinence in women: The incontinence impact questionnaire and the urogenital distress inventory. *Neurourol Urodyn* 1995;14:131-139.
[4] The global quality of life assessment is taken from the International Prostate Symptom Score (IPSS) Assessment. The IPSS Assessment includes the same seven questions as the American Urological Association (AUA) Symptom index plus an additional quality of life (QOL) question. The question referred to here as the GQOL is the QOL question from the IPSS Assessment. Ref: AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia. Chapter 1: Diagnosis and treatment recommendations. *J Urol* 170(2 Pt 1):530-547.
[5] Sandvik H, Hundskaar S, et al. Validation of a severity index in female urinary incontinence and its implementation in an epidemiological survey. *J Epidemiol Community Health* 1993;47:497-499. Sandvik H, Selm A, et al. A severity index for epidemiological surveys of female urinary incontinence comparison with 48 hours pad-weighing tests. *Neurolurol Urodyn* 2000;19:137-145.

- Ultrasound/bladder scan determination of PVR on the day of injection and at 1, 3, 6 and 12 months.

The clinical data will be collected on eCRFs, which may serve as source documents.

### 6.5 Measures to be Taken to Avoid or Minimize Bias

This study is designed as a double-blind, prospective, randomized controlled trial to minimize bias in both assigning patients to treatments and in analyzing the results. To maintain a double-blind study, it is necessary for all patients to receive a biopsy and an injection. This assures that both the patient and doctor are blinded to the study treatments, even when patients receive the placebo control. After the biopsy is completed, a computer-generated randomization scheme will be used off-site to eliminate site participation in the randomization and to maintain blinding. Additionally, only the persons directly involved in manufacturing the product will handle the AMDC-USR and correctly dispense the proper dose into a nondescript vial (all vials will appear the same and have an anonymous identifier). Thus, persons from the sponsor (Cook MyoSite) and the CRO (Cook Research Incorporated) who interact with physicians or clinical staff at the clinical site can remain blinded whenever possible. In the event of an emergency, site personnel are able to rapidly unblind a patient for her safety if deemed necessary. In such event the data coordinating center (Cook Research Incorporated) must be contacted immediately.

## 7.0 Methods

If a patient has had a hysterectomy and/or is post-menopausal (i.e., the patient does not have a uterus and/or is no longer menstruating), then the patient is not required to complete the pregnancy tests as outlined in the visit schedule. (Note: tubal ligation is not an acceptable reason for not doing the test, as it is not guaranteed to be permanent.) For visual representation of methods specific to patient visits, refer to Table 7.1. For an illustrated overview of the study, refer to Figure 1.1.

## 7.1 Initial Patient Assessment and Pre-screening

Female patients who present with SUI symptoms may be considered for participation in this study. If available, clinical site study staff should review patient symptoms against the inclusion/exclusion criteria before consenting patients.

## 7.2 Patient Consent

Patients who appear to meet the inclusion criteria and none of the exclusion criteria will be invited to participate in this study. All patients eligible for entry into the study will have the study explained to them, as well as potential risks and benefits of their participation in the study. Each patient who agrees to participate will be required to sign and date an informed consent document prior to any study-specific testing and the procedure.

## 7.3 Pre-enrollment – Screening

Screening tests may be completed in up to 3 screening visits to accommodate site-specific scheduling. It is recommended that screening tests conducted in Visit 1 be completed within the 8 weeks preceding the biopsy visit. Bloodborne pathogen testing must be completed within 30 days before the biopsy procedure. If more than one visit is required, adverse events that occur during the screening time period shall be recorded during subsequent visits.

After providing informed consent, the patient will have her medical history recorded (including a urinary incontinence-focused history), a physical examination performed (including assessment of vital signs), and a medication log completed. A clinical assessment will be performed. Urine samples will be collected to test for pregnancy, nitrites, and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, then it is recommended a urine culture be performed. The patient will undergo a bladder “cough” stress test [redacted] and a Q-tip test [redacted]. A PVR urine volume will be measured with ultrasound. If, after multiple void attempts, the residual urine volume is > 150 mL, the patient must be excluded from the study.

The patient will be given a diary in which to record liquid intake, incontinence episodes,

and normal voids for 3 consecutive days. Instructions for the diaries will be explained in detail to the patient during this visit. The patient will also be provided with sufficient pre-weighed pads with which to complete a 24-hour ambulatory pad test that corresponds with 1 day of the 3-day diary. The patient will be instructed on how to perform the 24-hour pad test [redacted]. During the study visit, a study team member will give the patient clear instructions for completing the diary and pad test. Patients will also receive written instructions for the diary to take home as reference. The patient will complete the IIQ – 7, UDI – 6, and GQOL questionnaires (collectively QOL assessment), the IQOL assessment, and the Incontinence Severity Index (ISI) assessment. Blood samples will be collected to assess for bloodborne pathogens, hematocrit, hemoglobin, WBC count, blood urea nitrogen (BUN) or urea, and creatinine. Patients will also undergo cystoscopy for evaluation of the appearance of urethral and bladder tissue. An existing cystoscopy evaluation can be used if performed within 6 months prior to the time of consent. It is recommended that screening tests be performed from the least invasive test to the most invasive.

## 7.4 Point of Enrollment

Patients are considered enrolled in the study at the time of the biopsy procedure.

## 7.5 Medications

Patients may be given medication (including for pain or anxiety) according to the institution's standard of care or at the physician's discretion. Additionally, patients should be maintained on a stable dose and/or frequency of medication known to affect lower urinary tract function, including but not limited to, anticholinergics, beta 3 adrenergic receptor agonists, tricyclic antidepressants, diuretics, or alpha-adrenergic blockers, for at least 2 weeks prior to screening assessments and throughout the study.

## 7.6 Biopsy and Randomization

After patient eligibility is confirmed, patients will return to the clinic for an outpatient procedure in which muscle tissue is obtained using a needle biopsy technique. [redacted]

[redacted] If the biopsy procedure is scheduled for more than 30 days after the most recently completed bloodborne pathogen tests, the bloodborne pathogen tests (i.e. Hepatitis B, Hepatitis C, HIV, and Syphilis) must be repeated before the biopsy procedure to confirm the patient's continued eligibility for study participation. If appropriate, the patient will also have a urine sample collected prior to the biopsy procedure for pregnancy testing, which would be repeated at any additional biopsy visits if more than one biopsy is required. If the patient has a positive pregnancy test at this visit, the biopsy will not be performed, and the patient will be excluded from the study for safety. Additionally, the medication log will be updated if necessary. Any adverse events occurring since the last visit or before, during, or after the biopsy procedure will be recorded and reported as appropriate.

Patients will be randomized to a treatment arm after AMDC-USR product is made; patients randomized to placebo arm will not receive the product.

### 7.6.1 Post-Biopsy Follow-up

Within 7 business days after the biopsy procedure, patients will be contacted by phone to determine whether any adverse events have occurred and whether any updates to the medication log are necessary.

## 7.7 Procedure – Treatment Day 0

Within 45 days preceding the scheduled injection, patients will be given a 3-day diary to complete. Patients will complete the QOL assessments, the IQOL assessment, and the ISI assessment. The questionnaires and 3-day diary data collected preceding the injection visit will be used as the baseline data.

[redacted] after the muscle biopsy, patients will return to the clinic for a brief outpatient injection procedure. Prior to injection, patients will have a urine sample collected for a pregnancy test (if necessary), nitrites, and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, a urine culture must be performed and the injection will be delayed pending completion of an appropriate culture and course of antibiotic therapy. If the patient has a positive pregnancy test at this visit, the injection

will not be performed, and the patient will be excluded from the study for safety. The product will be injected using a transurethral injection technique. Cystoscopic evaluation of the urethra will be performed after the injection to evaluate the appearance of urethral tissue. Prior to discharge, patients should demonstrate a normal void and have their PVR urine volume determined by ultrasound. If, after multiple void attempts, the residual urine volume is > 150 mL, additional evaluation for obstruction is recommended at the discretion of the investigator. The medication log will be updated if necessary. Any adverse events occurring since the last visit or before, during, or after the procedure will be recorded and reported as appropriate.

## 7.8 Follow-up

Follow-up windows are intended as recommendations only. They are not absolute and are not intended to limit data collection due to scheduling conflicts. If a patient has a positive pregnancy test at any given follow-up visit, no further study procedures will be conducted, but the patient will be followed for safety.

### 7.8.1 Post-Treatment Follow-up – Treatment Day 1-2

Within 2 business days after treatment, patients will be contacted by phone to determine if any adverse events have occurred and if the patient has any updates for the medication log.

### 7.8.2 Follow-up Visit – Treatment Month 1 (± 1 week)

Patients will have urine samples collected for a pregnancy test (if necessary), nitrites, and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, it is recommended a urine culture be performed. Blood samples will be collected to assess for hematocrit, hemoglobin, WBC count, BUN or urea, and creatinine. Patients will also undergo ultrasound for determination of PVR urine volume. If, after multiple void attempts, the PVR volume is > 150 mL, additional evaluation for obstruction is recommended at the discretion of the investigator. During the visit, patients will complete the QOL assessments, the IQOL assessment, and the ISI assessment. Patients will be given a 3-day diary to complete. The medication log will be updated if necessary. A clinical assessment shall be performed. Patients will have height and weight assessed. Any adverse events occurring since the last visit will be recorded and reported as appropriate.

### 7.8.3 Follow-up Visit – Treatment Month 3 (± 4 weeks)

Patients will have urine samples collected for a pregnancy test (if necessary), nitrites, and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, then it is recommended a urine culture be performed. Patients will also undergo ultrasound for determination of PVR urine volume. If, after multiple void attempts, the PVR volume is > 150 mL, additional evaluation for obstruction is recommended at the discretion of the investigator. During the visit, patients will complete the QOL assessments, the IQOL assessment, and the ISI assessment. Patients will be given a 3-day diary to complete. The medication log will be updated if necessary. A clinical assessment shall be performed. Patients will have height and weight assessed. Any adverse events occurring since the last visit will be recorded and reported as appropriate.

### 7.8.4 Follow-up Visit – Treatment Month 6 (± 4 weeks)

Patients will have urine samples collected for a pregnancy test (if necessary), nitrites, and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, then it is recommended a urine culture be performed. Patients will undergo ultrasound for determination of PVR urine volume. If, after multiple void attempts, the PVR volume is > 150 mL, additional evaluation for obstruction is recommended at the discretion of the investigator. During the visit patients will complete the QOL assessments, the IQOL assessment, and the ISI assessment. Patients will be given a 3-day diary to complete. The medication log will be updated if necessary. A clinical assessment will be performed. Patients will have height and weight assessed. Any adverse events occurring since the last visit will be recorded and reported as appropriate.

### 7.8.5 Follow-up Visit – Treatment Month 12 (± 4 weeks)

Patients will have urine samples collected for a pregnancy test (if necessary), nitrites, and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, then it is recommended that a urine culture be performed. Blood samples will be collected to assess for hematocrit, hemoglobin, WBC count, BUN or urea, and creatinine. Patients will undergo ultrasound for determination of PVR urine volume. If, after multiple void attempts, the PVR volume is > 150 mL, additional evaluation for obstruction is recommended at the discretion of the investigator. Patients will also undergo cystoscopy for evaluation of the appearance of urethral tissue. During the visit, patients will complete the QOL assessments, the IQOL assessment, and the ISI assessment. Patients will be

given a 3-day diary to complete. The medication log will be updated if necessary. A clinical assessment will be performed. Patients will have height and weight assessed. Any adverse events occurring since the last visit will be recorded and reported as appropriate.

### 7.8.6 Unblinded Treatment – Day 0

Following completion of product manufacturing, placebo control patients who agree to receive the unblinded treatment will return to the clinic for a brief outpatient procedure. Prior to injection, patients will have a urine sample collected for a pregnancy test (if necessary), nitrites, and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, a urine culture must be performed and the injection will be delayed pending completion of an appropriate culture and course of antibiotic therapy. Cells will be injected using a transurethral injection technique. Cystoscopic evaluation of the urethra will be performed after the injection to evaluate the appearance of urethral tissue. Prior to discharge, patients should demonstrate a normal void and will have their residual urine volume determined by ultrasound. If, after multiple void attempts, the residual urine volume is > 150 mL, additional evaluation for obstruction is recommended at the discretion of the investigator. The medication log will be updated if necessary. Any adverse events occurring since the last visit or before, during, or after the procedure will be recorded and reported as appropriate.

Patients receiving an unblinded treatment shall be contacted for post-treatment follow-up according to the schedule specified in Sections 7.8.6.1 through 7.8.6.3.

#### 7.8.6.1 Unblinded Follow-up – Treatment Day 1-2

Within 2 business days after treatment, patients will be contacted by phone to determine if any adverse events have occurred and if the patient has any updates for the medication log.

#### 7.8.6.2 Unblinded Follow-up – Treatment Month 1 (± 1 week)

Patients will be contacted by phone to determine if any adverse events have occurred and if the patient has any updates for the medication log.

#### 7.8.6.3 Unblinded Follow-up – Treatment Month 3 (± 4 weeks)

Patients will be contacted by phone to determine if any adverse events have occurred and if the patient has any updates for the medication log.

### 7.8.7 Follow-up Visit – Treatment Year 2 (± 4 weeks)

During the visit, patients will complete the ISI quality of life assessment. Patients will be given a 3-day diary to complete. A urine sample will be collected to test for pregnancy. The medication log will be updated if necessary. A clinical assessment will be performed. Patients will have height and weight assessed. Any adverse events occurring since the last visit will be recorded and reported as appropriate. Patients randomized to the placebo control group who chose to receive AMDC-USR treatment at 12 months will also undergo cystoscopy to evaluate the appearance of urethral tissue.

The schedule for assessments is summarized in Table 7.1.

Table 7.1. Assessment and data collection schedule

| | Screening | Biopsy | | Treat. | Post-treatment | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Phone | Visit 3 | Phone | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Unblind | Phone | Phone | Phone | Visit 8 |
| | Week 1 – 8[a] | Week 2 – 10 | Week 3-11 | Day 0 | Day 1- 2 | Month 1 | Month 3 | Month 6 | Month 12 | Unblind Day 0[e] | Unblind Day 1[e] | Unblind Month 1[e] | Unblind Month 3[e] | Year 2 |
| Event | Screening | Biopsy | Follow-up | Injection | Follow-up | Office Visit | Office Visit | Office Visit | Office Visit | Injection | Follow-up | Follow-up | Follow-up | Office Visit |
| Informed Consent | X | | | | | | | | | | | | | |
| Inclusion/Exclusion[b] | X | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | |
| Vital Signs | X | | | | | X[j] | X[j] | X[j] | X[j] | | | | | X[j] |
| Medication Log | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | X | | | | | | | | | | | | | |
| Clinical Assessment | X | | | | | X | X | X | X | | | | | X |
| Bladder "cough" stress test | X | | | | | | | | | | | | | |
| Q-tip test | X | | | | | | | | | | | | | |
| Diary[c] | X | | | X[h] | | X | X | X | X | | | | | X |
| Post-void Residual Volume | X | | | X | | X | X | X | X | X | | | | |
| Quality of Life Assessments (IIQ – 7, UDI – 6, and GQOL)[c] | X | | | X[h] | | X | X | X | X | | | | | |
| Incontinence Severity Index Assessment (ISI)[c] | X | | | X[h] | | X | X | X | X | | | | | X |
| Incontinence Quality of Life Assessment (IQOL)[c] | X | | | X[h] | | X | X | X | X | | | | | |
| 24-hr Ambulatory Pad Test | X | | | | | | | | | | | | | |
| Cystoscopy | X[d] | | | X | | | | | X | X | | | | X[e] |
| Muscle Biopsy | | X | | | | | | | | | | | | |
| Injection | | | | X | | | | | | X | | | | |
| Blood Samples | X | X[i] | | | | X | | | X | | | | | |
| Urinalysis | X | | | X | | X | X | X | X | X | | | | |
| Urine Culture[f] | X | | | X | | X | X | X | X | X | | | | |
| Pregnancy Testing[g] | X | X | | X | | X | X | X | X | X | | | | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Telephone Follow-up | | | X | | X | | | | | | X | X | X | |

[a] It is recommended that required tests and assessments are completed within 8 weeks from the initial visit to the biopsy visit; screening tests conducted in Visit 1 may be completed in up to 3 screening visits to accommodate site-specific scheduling if necessary
[b] An electronic case report form system tracks inclusion/exclusion screening information
[c] Diaries, QOL assessment and IQOL will be collected in an electronic format on a handheld device
[d] An existing cystoscopy evaluation can be used if performed within 6 months prior to the time of consent
[e] Only for placebo control patients who receive the AMDC-USR dose
[f] This test is only completed if the urinalysis is positive for nitrites or leukocyte esterase
[g] If the patient has had a previous hysterectomy and/or is post-menopausal, this test is not required N/A shall be indicated on the correct data form in the electronic system, with the reason(s) specified
[h] Diary, QOL assessment and IQOL will be completed by patients within 45 days of the scheduled injection
[i] If the biopsy procedure is scheduled more than 30 days after the most recent bloodborne pathogen tests were completed, the bloodborne pathogen tests (i e Hepatitis B, Hepatitis C, HIV, and Syphilis) must be repeated before the biopsy procedure to confirm the patient's continued eligibility for study participation
[j] Only height and weight will be collected

## 7.9 Duration of Study and Patient Participation

Patients are expected to participate in this study for 2 years after the initial procedure. If placebo control patients elect not to receive cells after 12 months, their participation is concluded.

## 7.10 Criteria and Procedures for Withdrawal

A patient may decide to withdraw from the study at any time either before or after undergoing study procedures without prejudice or loss of care. The patient shall notify the investigator of her desire to withdraw. The investigator will notify the sponsor. The investigator may also decide to withdraw a patient from the study at any time based on medical judgment. In all instances of withdrawal, the appropriate study visit and study termination data shall be submitted to the data coordinating center, and shall include the reason why the patient has been withdrawn from the study. Prior to formal withdrawal, patients will be asked to complete a final follow-up visit to collect data on adverse events, current medications, clinical assessment, 3-day diary and questionnaires and allow access to their medical records for 30 days after the date of withdrawal. Any data collected on the patient up to the point of withdrawal plus 30 days may be used in the study.

In the event a patient is lost to follow-up or cannot be contacted for post-treatment assessments, at least three attempts will be made to locate the patient, and these efforts will be documented. If the patient cannot be located, a lost to follow-up entry will be submitted.

## 7.11 Participation Endpoints of the Study

A patient's participation in the study will end after any of the following:

- Patient completes all scheduled clinical and imaging evaluations to 2 years;
- Patient underwent study procedures, but fails to receive treatment (such patients will be followed for 30 days after the last study procedure);
- Patient withdrawal or lost to follow-up;
- Patient receives treatment for SUI other than the study treatment (e.g., receives an injection of a bulking agent, or completes a surgery for a sling);

- Closure of the study; or
- Patient death.

## 8.0 Statistical Considerations

### 8.1 Hypothesis to be Tested

The primary hypothesis for efficacy is that patients treated with AMDC-USR will have a superior treatment efficacy success rate (π, as defined in Section 6.3.1) at 12 months, compared to the placebo control. The null ($H_0$) and alternative ($H_A$) primary efficacy hypotheses are expressed as follows:

$$H_o \ : \ \pi_{AMDC-USR} \ \leq \ \pi_{placbeo}$$
$$H_A \ : \ \pi_{AMDC-USR} \ > \ \pi_{placbeo}$$

where $\pi_{\text{AMDC-USR}}$ is the treatment success rate for the AMDC-USR group and $\pi_{\text{placebo}}$ is the treatment success rate for the placebo control group.

The following secondary efficacy endpoints will be tested using the Holm procedure to control the type I error at the significance level of 0.025 for multiple testing.

- Percentage of patients with at least 75% reduction in stress incontinence episodes from baseline at 12 months;
- Percentage of patients with 0 or 1 stress incontinence episodes at 12 months;
- Improvement (reduction) in frequency of stress incontinence episodes from baseline at 12 months;

The hypothesis testing for each of the secondary endpoints is as follows:

- Percentage of Patients with at Least 75% (≥ 75%) Reduction in Stress Incontinence Episodes from Baseline at 12 Months

The treatment success based on an endpoint that considers stress incontinence episodes is defined as a ≥ 75% reduction in the stress incontinence episodes based on the 3-day diary at 12-month follow-up. The null and alternative hypotheses for the endpoint are:

$$H_o \ : \ C_{AMDC-USR} \ \leq \ C_{placbeo}$$

$H_A : C_{AMDC-USR} > C_{placbeo}$

where $C_{AMDC-USR}$ is the percentage of patients in the AMDC-USR group with treatment success at 12 months based on the endpoint definition and $C_{placbeo}$ is the percentage of patients in the placebo control group with treatment success at 12 months based on the endpoint definition.

- Percentage of Patients with Zero (0) or One (1) Stress Incontinence Episodes Based on the 3-Day Diary Data at 12 Months

Patients who have 0 or 1 stress incontinence episodes (stress incontinence episodes = 0 or 1) based on the 3-day diary at the 12-month visit will be defined as a treatment success for this endpoint. Patients who have stress incontinence episodes (> 1) at 12 months will be denoted as a treatment failure for this endpoint.

The null and alternative hypotheses for the endpoint are:

$H_o : \tau_{AMDC-USR} \leq \tau_{placbo}$

$H_A : \tau_{AMDC-USR} > \tau_{placbo}$

where $\tau_{AMDC-USR}$ is the percentage of patients in the AMDC-USR group with treatment success at 12 months and $\tau_{placbo}$ is the percentage of patients in the placebo control group with treatment success at 12 months.

- Improvement (Reduction) in Frequency of Stress Incontinence Episodes from Baseline at 12 Months

The improvement (reduction) in the frequency of stress incontinence episodes from baseline at 12 months is defined as the change in the number of diary-reported stress incontinence episodes from baseline to 12 months. It is calculated as *(improvement in the frequency of stress incontinence episodes) = (# of diary-reported stress incontinence episodes at 12 months) – (# of diary-reported stress incontinence episodes at baseline).*

The null and alternative hypotheses for the endpoint are:

$H_o : \mu_{AMDC-USR} \geq \mu_{placbeo}$

$H_A : \mu_{AMDC-USR} < \mu_{placbeo}$

where $\mu_{AMDC-USR}$ is the change in the frequency of stress incontinence episodes for the AMDC-USR group at 12 months and $\mu_{placbeo}$ is the change in the frequency of stress incontinence episodes for the placebo control group at 12 months.

Additional efficacy endpoints and safety measures will be analyzed to evaluate the treatment effect of AMDC-USR. A separate statistical analysis plan will detail the additional endpoints of interest and the statistical analysis methods.

## 8.2 Sample Size

The study will enroll 267 patients (178 enrolled with 150 x $10^6$ AMDC-USR and 89 enrolled with placebo control) at up to 35 clinical sites to ensure that no less than 213 patients will be injected with product (AMDC-USR or placebo control). The number of patients enrolled at each site shall not exceed 15% of the total enrollment.

The sample size for the study was calculated based on the following assumptions:

- The treatment success (defined in Section 6.3.1) rate for patients who receive 150 x $10^6$ AMDC-USR will be 50% (conservatively estimated for the purposes of sample size calculations);
- The treatment success rate for the placebo control patients will be 30%;
- A 2:1 AMDC-USR to placebo control randomization will occur; and
- A one-sided z-test with type I error of 0.025, and a power of 0.8 will be used.

Based on the assumptions above, a total sample size of 213 patients will be required to assess the primary hypotheses with sufficient power, with 142 patients assigned to AMDC-USR group and 71 patients assigned to the placebo control group. Cook MyoSite intends to enroll 267 patients (178 enrolled with 150 x $10^6$ AMDC-USR and 89 enrolled with placebo control) to account for 20% early withdraw or lost to follow-up.

Sample size calculations were performed using Proc Power in SAS 9.3.

## 8.3 Futility Analysis

There is one interim look planned in this study that will evaluate futility of the primary efficacy endpoint. The look will occur when approximately 110 of the 267 non-roll-in patients have completed 12-month visits for the collection of primary efficacy data.

Looking at the primary efficacy comparison of patients receiving $150\times10^6$ AMDC-USR versus placebo control patients the sample size is calculated under the following

conditions. Assume the efficacy success rate is 50% in the patients receiving $150\times10^6$ AMDC-USR, and 30% in placebo control patients, the O'Brien-Fleming boundary under futility analysis, a one-sided z-test with a 2:1 AMDC-USR to placebo randomization, type I error of 0.05, and a power of 0.8. A sample size of 207 patients is required.

The study will be stopped early for futility if the *p*-value is $\geq 0.249$ at the interim look. Under $H_0$, the study has a 75% chance of stopping early at the look; under $H_a$, the study has a 9% chance of stopping early at the look. The independent DSMB will review these calculations in a blinded manner to determine if the study should be stopped for futility of efficacy.

## 8.4 Randomization

Patients will be stratified for randomization based on the severity of urinary incontinence at screening and whether patients have undergone prior surgery for treatment of SUI. Each of these two strata have two levels: less than or equal to 10 ($\leq 10$) stress incontinence episodes over 3 days at screening or greater than 10 ($> 10$) stress incontinence episodes over 3 days at screening; and if the patient has undergone a prior surgery, or if the patient has not received prior surgery. At each study site, patients will be stratified based on these criteria, then randomized to one of the treatments in a 2:1 ratio (AMDC-USR: placebo control).

Assignment of patients to a treatment group will also be block randomized by site. Sites will not be informed of the block size.

## 8.5 Missing Data

The total study enrollment is augmented to achieve sufficient power to test the hypotheses in the presence of missing outcome data due to lost to follow-up or withdrawn patients.

Missing data will be addressed using three primary strategies: 1) multiple imputation, 2) complete case analysis, and 3) tipping point analysis. Multiple imputation will be the primary strategy to address missing data. Specifically, the multiple imputation method will sample from the empirical distribution of complete data, by treatment group and strata used for randomization. This method will be used to predict missing endpoint or

covariate data. It may be that the primary study endpoint depends upon certain covariates; therefore, it may be possible to model study endpoints, given a series of related covariates. This model-based imputation exercise may provide approximations of the missing data that can be utilized to estimate event rates and confidence bounds.

Both complete case and tipping point analyses may also be used to explore the impact of missing data on the primary study endpoint.

The pattern of missingness will also be evaluated to assess if missing data are related to product treatment or other relevant patient or study factors. Based on this exploratory analysis, additional imputation methods will be considered, if appropriate.

Patients who undergo biopsy, but are not randomized, will be included in the assessment of biopsy-related safety. For each patient who is biopsied, but not randomized, an additional patient will be enrolled and randomized to fulfill the required sample size.

## 8.6 Site-level Poolability

At the final analysis, poolability of data from multiple sites will be verified by examining the primary endpoint among sites. Site-level poolability will be considered appropriate provided that the endpoint is similar among sites.

It is recognized that patient baseline characteristics may differ among sites, with some sites routinely treating patients with more severe disease progression. It is anticipated that the primary endpoint measure may be related to covariates that reflect this disease progression, which are in turn related to outcome. Thus, observed primary endpoint site-specific differences will be checked for confounding with other measured covariates (e.g., age). This can be accomplished using regression models (linear and logistic where appropriate) that include site and other measured covariates as independent variables.

If one or more sites is found to differ significantly from the rest, then subsequent analyses may include the discriminating covariate or a covariate to distinguish between the unusual site(s) and those sites that are considered poolable.

### 8.7 Limitations of the Study

The primary outcome measure for defining treatment efficacy success based on the reduction from baseline in average daily number of stress incontinence episodes is not able to address all potential improvements in SUI symptoms that a patient may experience. No individual subjective or objective measure of SUI improvement has been reliably established among the urologic or regulatory communities. As such, the individual measure selected may not directly correlate for all patients, potentially causing difficulty in correctly analyzing study results.

The control group for the study will be injected with a vehicle control. This mechanism of control may create some difficulty in identifying peri- or post-injection adverse events or responses as procedure- or product-related. Additionally, the placebo control arm will be carried out to 12 months, while AMDC-USR treated patients will be evaluated for up to 2 years. This may result in challenges interpreting safety data and reduces the confidence in collected efficacy data during this time window.

## 9.0 Deviations from Clinical Investigation Plan

Investigators are not allowed to deviate from this CIP without prior authorization by the sponsor except under emergency situations when necessary to preserve the rights, safety, and well-being of study patients.

Deviations (failures to follow requirements of the CIP and guidelines) and non-compliances (failures to follow applicable regulations) will be recorded together with an explanation. Deviations or non-compliances that impact the rights, welfare, or safety of patients shall be reported to the sponsor and IRB as required and as soon as possible.

If appropriate, corrective and preventive actions will be discussed by the sponsor, investigator, and/or the IRB to determine a suitable course of action.

## 10.0 Data Collection and Reporting

### 10.1 Electronic Case Report Forms (eCRF system)

Patient data will be collected and entered by trained personnel at the clinical site into electronic Case Report Forms (eCRFs) through an Electronic Data Capturing (EDC) system. This is a secure, web-based system, allowing those with permission to access data from any location at any time. Source data are to be retained for data entered into the eCRF system. Worksheets created from the eCRF are available to each site and may serve as source documentation. Site personnel are required to undergo data entry training and will have unique login names and passwords in order to enter patient data. In accordance with 21 CFR Part 11, the eCRF system creates a secure, computer-generated, time-stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic records.

Patient questionnaire and diary information will be collected as source data on an electronic, hand-held device directly from the patient. The information collected on this device is considered source documentation and is stored in an EDC system.

### 10.2 Data Reporting

Progress reports and a final report at the conclusion of the clinical study will be submitted by the investigators and sponsor to the regulatory bodies and IRB as required by local regulations.

## 11.0 Data Management and Quality Assurance

### 11.1 Data Entry and Quality Assurance

Each principal investigator or appropriately trained designee shall enter the clinical data into the EDC system on standardized eCRFs. Investigators will provide all applicable clinical data and documentation to the sponsor. Patient data and documents pertaining to the study will be kept and archived by the sponsor. Data will be reviewed for missing data, data consistency, and reasonableness of responses. Discrepancies will be resolved through a formal query process involving direct contact with investigators or research coordinators. The data coordinating center is responsible for database management, data

verification, data archiving, and data retention.

As needed to assist the sponsor in its research (e.g., during evaluation of an adverse event), data will be accessible to the sponsor, the participating investigators, the manufacturer, and companies or individuals the sponsor authorizes.

Cook Research Incorporated (previously called MED Institute, Inc.), the data coordinating center, maintains a Safe Harbor Privacy Policy that describes the privacy principles followed with respect to the transfer of personal information from member states in Europe to the United States.

### 11.2 Data Monitoring Arrangements

The conduct of the clinical study will be supervised through a process of remote and on-site monitoring. The data coordinating center will remotely monitor the study for data completeness and for adverse events. On-site monitoring will be implemented as necessary throughout the course of the study. The investigator/institution will provide direct access to source data/documents for study-related monitoring, audits, IRB review, and regulatory inspection. Written procedures for monitoring the study are maintained by the data coordinating center [redacted]

## 12.0 Safety Monitoring and Procedures for Reporting Adverse Events

### 12.1 Safety Monitoring

A Data Safety Monitoring Board (DSMB) consisting of independent physicians and statisticians who are not investigators in the study and who do not have a perceived conflict of interest with the conduct and administration of the study will be convened on a regular basis to evaluate the clinical study progress and review adverse events.

An independent Clinical Events Committee (CEC) consisting of physicians who are not investigators in the study and who do not have a perceived conflict of interest with the conduct and administration of the study will be established to adjudicate clinical events reported during the study, as needed. This adjudication will be performed to assess whether the events were due to a pre-existing or unrelated condition, or were biopsy procedure-related, injection procedure-related, and/or study product-related.

Regularly scheduled review/monitoring of all patient data will be conducted at the data coordinating center, in part, for identification of adverse events and assurance that they are correctly reported to the DSMB and CEC.

### 12.2 Adverse Event Reporting

Adverse events are to be reported to the data coordinating center using the appropriate eCRF. In cases of adverse drug reactions or SAEs, completed forms shall be submitted to the data coordinating center as soon as possible upon knowledge of the event.

The data coordinating center will review the information submitted for possible reporting to the sponsor. Adverse events will be assessed by the investigator in terms of relationship to the biopsy procedure, relationship to the injection procedure, relationship to the AMDC-USR product, severity of the event, subsequent treatment/intervention required, and resolution status.

The sponsor shall, if required according to applicable regulations, report the event to the appropriate regulatory authority in accordance with 21 CFR 312.32. The principal investigator or designee will notify their IRB of applicable events according to institutional guidelines. Investigators and clinical sites will be notified by the sponsor, as appropriate.

## 13.0 Early Termination or Suspension of the Study

Any decision to suspend enrollment or terminate the study, either completely or at one or more sites, will be made by the sponsor and, if appropriate, the local IRB. If a decision is made to terminate the study, all patients who have undergone 1 or more study procedures (i.e., biopsy or injection) will be followed for 30 days following the most recent procedure.

## 14.0 Ethical Considerations

This clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in accordance with global regulations including 21 CFR 312 and ICH GCP.

The investigator is responsible for obtaining approval of this clinical study from the relevant IRB at the associated institution. The study will not begin until a favorable opinion of the IRB has been obtained. The investigator is responsible for complying with requirements imposed by the IRB and/or regulatory authority. Furthermore, the investigator will ensure that local regulations concerning data protection are followed.

The use of a placebo control injection is necessary to evaluate the efficacy of the AMDC-USR in the treatment of SUI. To maintain double-blinding, all patients must undergo the biopsy procedure, even if they are randomized to the placebo control group. For ethical considerations, all patients will be required to sign a consent indicating their willingness to participate, that they have been fully informed of the risks and benefits of participation, and that they may receive a placebo control treatment.

## 15.0 Publication Policy

Publication policy, rights, and obligations for this study have been negotiated, detailed, and defined in the study's contractual documents with the clinical site and investigators.

## 16.0 Clinical Study Administration and Investigators

### 16.1 Approvals and Agreements

The sponsor, global principal investigator, and the principal clinical investigators for each clinical site shall agree to this document and any modifications. A justification for any modifications will be documented. Approval and agreement will be indicated by signing the signature page provided with this document.

### 16.2 Investigators

To see a complete list of the sponsor, manufacturer, monitor, and data coordinating center along with their contact information, please refer to Appendix A. A complete list of the global clinical investigator, principal clinical investigators, and coordinating clinical investigators, along with their qualifications and contact information, will be maintained by the data coordinating center. A complete list of names and addresses of each reviewing IRB will also be maintained by the data coordinating center.

16.3 Insurance

Insurance for the study will be obtained by the sponsor prior to patient enrollment.

## 17.0 Bibliography

Please refer to the Investigator's Brochure for a complete literature review and evaluation.

## APPENDIX A

Contact Information

**Sponsor**
Cook MyoSite, Incorporated
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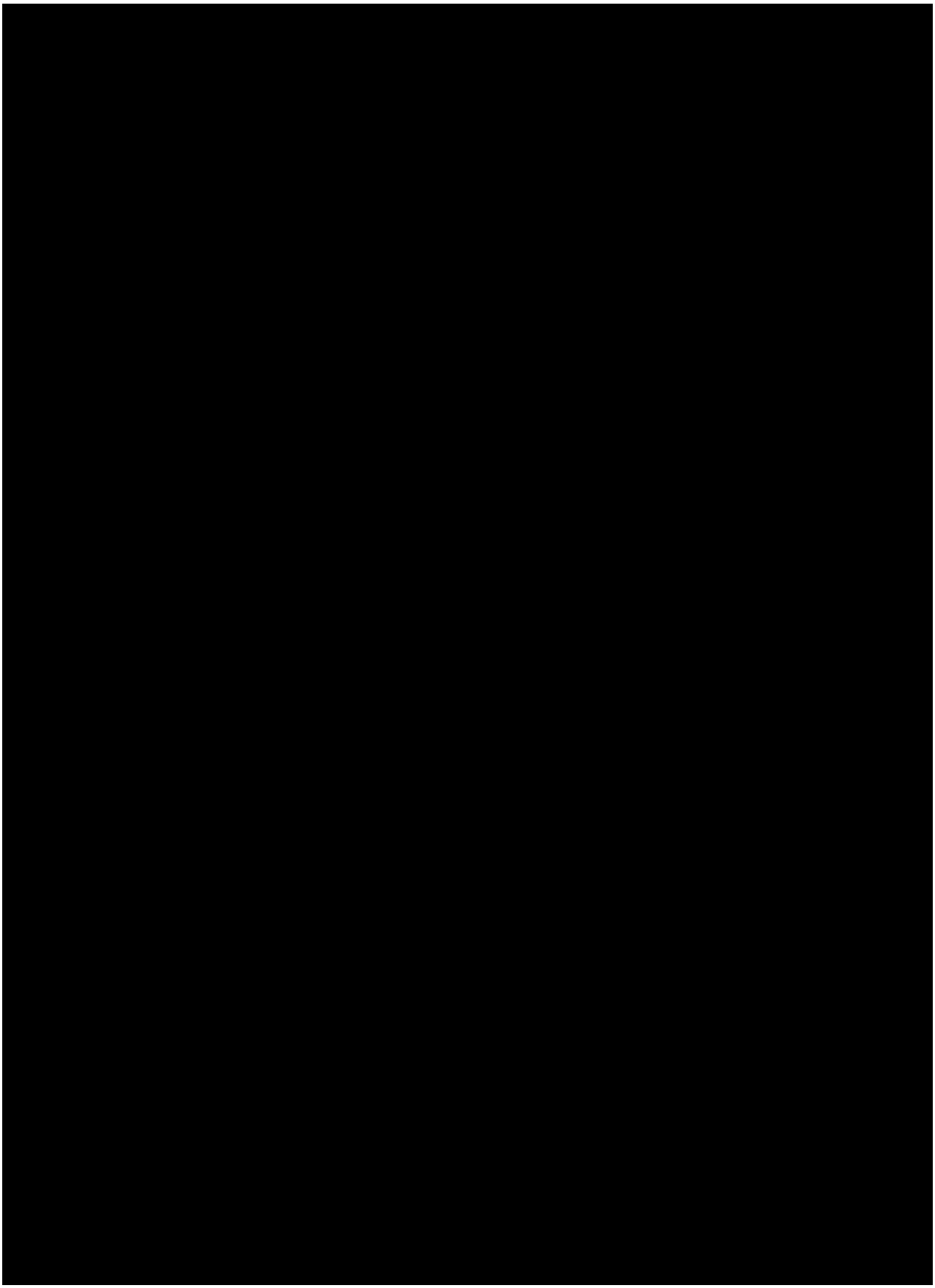
[redacted]

## APPENDIX B

Written Procedures for Monitoring Studies

[redacted]



## APPENDIX C

Definitions

Definitions for the following terms are not provided in this CIP, but can be found in the applicable regulations:

Adverse Events
Adverse Drug Reaction
Serious Adverse Events
Serious Adverse Drug Reaction
Suspected Unexpected Serious Adverse Reaction (SUSAR)

## APPENDIX D

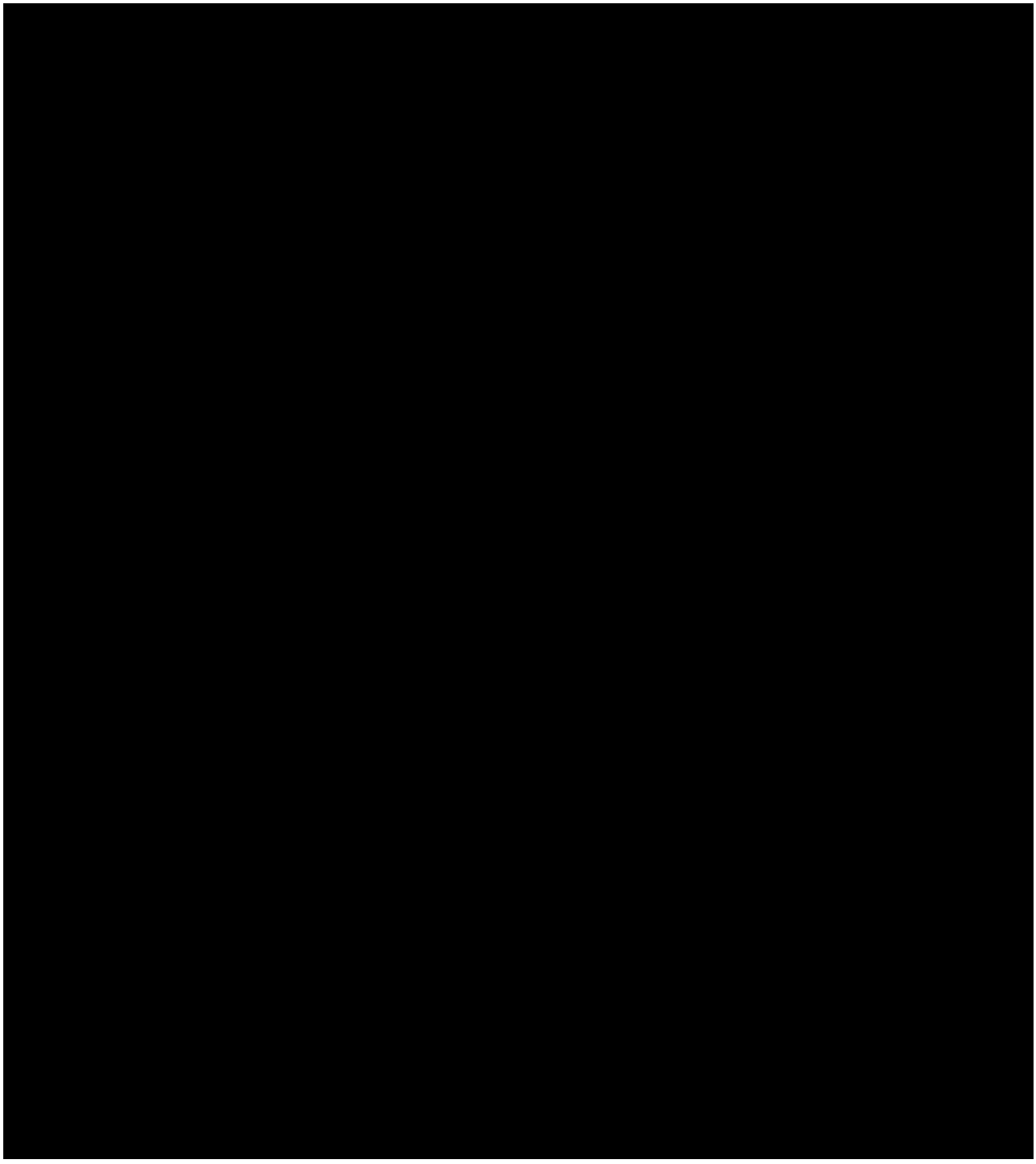
Bladder "Cough" Stress Test

As part of the exclusion criteria for the study, each patient must have a bladder stress test.

## APPENDIX E

24-hour Pad Test

All patients should have a 24-hour weighted pad test as part of the screening procedures. The 24-hour pad test must be completed during 1 day of the 3-day diary.



## APPENDIX F

Q-tip Test

[redacted]