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18 APRIL 2023

Evaluating **E**ffectiveness of **S**ensory and **S**ubsensory Stimulation Amplitudes with **e**Coin® Tibial **N**erve Stimulation in Urgency Urinary In**C**ontinence **E**pisodes and Quality of Life (**ESSENCE**)

Device Name: eCoin® (Electroceutical Coin)

Sponsor & Manufacturer: Valencia Technologies Corporation
28464 Westinghouse Place
Valencia, CA 91355 United States

Protocol Number: 111-6133

CONFIDENTIAL

Document Number 111-6133 Rev 1

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Investigator's Responsibility

The post approval study will be carried out in accordance with Good Clinical Practice (GCP) as required by the United States (US) Code of Federal Regulations applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56).

Prior to enrolling patients in the study, the Principal Investigator must obtain written approval from his/her Institutional Review Board (IRB). This approval must be in the Principal Investigator's name and a copy sent to Valencia Technologies, among other essential documents, along with the IRB approved Informed Consent and the signed Clinical Trial Agreement.

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to all site personnel involved in this study. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study.

_____ Date:_____
Principal Investigator's Signature

Principal Investigator's Printed Name

Site Name: _____ Site #:_____

_____ Date:_____
Sponsor's Signature

1 Introduction

1-1 Name, Address and Signature of Sponsor

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Protocol Summary

Title	Evaluating **E**ffectiveness of **S**ensory and **S**ubsensory Stimulation Amplitudes with **e**Coin® Tibial **N**erve Stimulation in Urgency Urinary In**C**ontinence **E**pisodes and Quality of Life (ESSENCE)
Product	The eCoin Peripheral Neurostimulator was approved under PMA P200036
Indications for Use	As approved under PMA P200036, the eCoin device is intended to be used to treat urgency urinary incontinence in patients intolerant to or having an inadequate response to other more conservative treatments or who have undergone a successful trial of percutaneous tibial nerve stimulation. The device will be used in accordance with the indications in the approved labeling in this study.
Objectives	To explore the effectiveness of the eCoin System programmed at two different amplitude settings (sensory, subsensory) for the treatment of urgency urinary incontinence (UUI) by assessing the improvement in urinary incontinence episodes on a 3-day voiding diary.

	To assess the improvement in the patient reported quality of life utilizing the Health Related Quality of Life (HRQL) section of the Overactive Bladder Symptom Quality of Life Questionnaire (OABq) and patient satisfaction surveys at two different programming methodologies.
	This will provide valuable knowledge regarding the relationship between functional outcomes and stimulation amplitudes.
Design	This study is a prospective, multi-center, double-blinded randomized controlled clinical trial. It is designed to observe the effectiveness and QOL of two different programming methods for the FDA-approved eCoin device. Enrolled subjects who meet all eligibility criteria and are implanted with the device will be randomized into one of two groups assigned to a parallel assignment intervention model. The two groups are: an arm where subjects are programmed at sensory level and an arm where subjects are programmed at a subsensory level. Investigators will be physicians that are approved by Valencia Technologies procedural training department to perform the eCoin implantation procedure ("Approved Site"). Approved Sites will have facilities that have the appropriate infrastructure, equipment, and trained personnel to support the eCoin implantation procedure and all subsequent study visits. Participating sites will submit de-identified Subject data via case report forms (CRFs) managed by the Company.
Number of Subjects & Study Duration	This study will aim to enroll approximately 40 subjects with a maximum of 50 subjects with a 1:1 randomization. An equal number of subjects will be assigned to each arm of the study. Each subject will participate in the study for up to 7 months (up to 3 months between screening and device activation plus up to 4 months of follow-up).
Key Inclusion Criteria	The target population will be adults above 18 years old with daily UUI with a predominantly urgency component. All subjects must be intolerant of, or show an inadequate response to, at least one second or third-line therapy, i.e., drug or peripheral nerve percutaneous neurostimulation, prior to enrollment. Subjects should be appropriate for eCoin therapy based on the US-FDA approved IFU requirements.
Key Exclusion Criteria	Key exclusion criteria include neurogenic bladder dysfunction, abnormal post-void residual, recent anti-stress incontinence operation, bladder pain

syndrome, peripheral neuropathy, lower leg varicosities, venous insufficiency with skin changes or pitting edema near the ankle, or peripheral arterial disease. OAB medications should be washed out at least two weeks prior to baseline while prior percutaneous tibial nerve stimulation (PTNS) and onabotulinumtoxinA patients should have washout periods of one and nine months respectively.

Primary Endpoints

The primary endpoint is to explore the effect of two different eCoin amplitude settings on the reduction of UUI episodes per day on a 3-day voiding diary after 3 months of eCoin tibial nerve stimulation.

Secondary Endpoints

The secondary endpoints are:

1. Change from baseline in the patient reported quality of life as assessed by the Health Related Quality of Life (HRQL) portion of the Overactive Bladder questionnaire (OABq) survey after 2, 3, and 4 months of therapy.
2. Reduction from baseline in the number of urgency urinary incontinence episodes per day on a 3-day voiding diary (72 hours) after 2 and 4 months of eCoin tibial nerve stimulation.
3. Improvement from baseline of patient satisfaction with UUI symptoms as gathered from patient satisfaction surveys after 2, 3 and 4 months of therapy.

Follow-up

The study flow consists of

Enrollment/Baseline: Subjects who meet eligibility criteria will first review and complete the Informed Consent Form. Then, demographic, medical history, and medication information is collected, a physical examination is completed, a PVR is done, vital signs are collected, and eligibility criteria are reviewed. Subjects should begin a 2 week wash-off of OAB medications, or 4 week wash-off of PTNS if applicable. Subjects will return for their baseline visit with a completed voiding diary and fill their baseline surveys. A final eligibility determination is made following review of the voiding diary.
Implant Visit: Implantation procedure is completed, vital signs are collected, subject is assessed for AEs and concomitant medications, and pre/post pictures are taken.
Healing Check: Check-in on healing, vital signs are collected, subject is assessed for AEs and concomitant medications, pictures are taken.
Activation: Randomization occurs and subject is activated according to their treatment arm. Vital signs are collected, subject is assessed for AEs and concomitant medications, and pictures are taken.
2 Month: The subject should complete a voiding diary in the 7 days preceding this visit. At the visit the subject will fill the OABq survey and patient satisfaction survey and be assessed for AEs and concomitant medications.
3 Month: The subject should complete a voiding diary in the 7 days preceding this visit. At the visit the subject will fill the OABq survey

	and patient satisfaction survey and be assessed for AEs and concomitant medications. Then, the subject will be unblinded and reprogramming will be done if desired. 4 month: The subject should complete a voiding diary in the 7 days preceding this visit. At the visit the subject will fill the OABq survey and end of study survey and be assessed for AEs and concomitant medications.
Safety	Safety will be assessed by collection of adverse events related to the device and/or procedure, all serious adverse events, and device malfunctions.

1-2 Background

Overactive bladder (OAB) is a clinical diagnosis characterized by the presence of bothersome urinary symptoms including urgency, frequency, nocturia, and urgency incontinence. Urinary incontinence is a prevalent condition that markedly impacts quality of life affecting both men and women [1]. In population-based studies, the prevalence of OAB ranges from 7% to 27% in men, and 9% to 43% in women [2-9]. Urgency urinary incontinence (UUI), which affects approximately one-third of patients with OAB, is associated with substantial negative effects on quality of life (QOL) [7]. The unpredictable loss of urine and associated odor or related symptoms leads to well documented burden on quality of life.

Neuromodulation, including sacral nerve stimulation (SNM), percutaneous tibial nerve stimulation (PTNS) and implantable tibial nerve stimulation (INS) are all FDA approved treatments for urgency urinary incontinence. The conventional approach to the stimulation paradigm has been in favor of setting amplitudes that evoke sensory or potentially concurrent motor response to achieve ideal results. To optimize treatment effectiveness, increase longevity of the neurostimulator, and better understand the mechanism of the therapy, studies have been conducted comparing programming protocols of the electrical stimulation at different sensory levels. Brain mapping during stimulation with sacral neuromodulation at subsensory, sensory and above sensory stimulation settings indicated that each setting activated or suppressed different regions of the brain, with the subsensory stimulation suppressing PAG [10]. PAG activates with bladder fullness and is associated with urgency and triggering the continence reflex; possibly explaining why SNM can increase bladder capacity. Another study comparing voiding outcomes in patients treated with SNM with stimulation was set to a sensory level versus those treated at a subsensory level saw a reduction in urgency urinary incontinence in both sensory and subsensory groups [11].

This study will focus on urgency urinary incontinence and the effect of both sensory and subsensory stimulation programming on the reduction of UUI episodes with the FDA-approved eCoin Implantable Nerve Stimulator (INS) device.

1-3 eCoin Peripheral Neurostimulator System

The labelling for the device provides a full description of the eCoin Peripheral Neurostimulator System. Both trial arms will be implanted with the eCoin Peripheral Neuromodulation System.

eCoin is the first fully implantable tibial neurostimulator to be approved by FDA for treatment of urgency urinary incontinence. The eCoin device is a leadless, coin-sized neurostimulator composed of radially symmetric material lining the rim and bottom center. It emits a dome-shaped electrical field to deliver low-

duty cycle stimulation to the tibial nerve. The device is to be implanted under local anesthetic in the lower leg, and once activated delivers automatic 30-minute treatment sessions without the need for patient management. This study will explore through a standard randomized controlled trial two different amplitude settings that achieve a reduction in UUI episodes, with the goal of gathering information to optimize device programming..

1-3-1 Manufacturer name, address, and contact information

Name of device manufacturer: Valencia Technologies Corporation

Address: 28464 Westinghouse Place, Valencia, CA 91355

Contact Person: Arthur Rascon, Chief Executive Officer

Telephone Number: (661) 775-1414

Fax Number: (661) 775-1411

1-4 Indication for Use

The eCoin Peripheral Neurostimulator is intended to be used to treat urgency urinary incontinence in patients intolerant to or having an inadequate response to other more conservative treatments or who have undergone a successful trial of percutaneous tibial nerve stimulation. These indications are approved under P200036.

1-4-1 Contraindications

The eCoin Peripheral Neurostimulator is contraindicated for the following patients:

- Poor Surgical Candidates: The eCoin should not be implanted in patients who are poor surgical candidates. Poor surgical candidates include those who have:
  - Open wounds or sores on the lower leg or foot
  - Had prior surgery in the implant area
  - Had previous, unhealed trauma in the implant area
  - Pitting edema (≥2+) in the lower leg
  - Venous disease/insufficiency in the lower leg
  - Arterial disease/insufficiency in the lower leg
  - Vasculitis or dermatologic conditions in the lower leg
  - Infections near the implantation site in the lower leg
- Patient can not properly operate the Patient Controller Magnets and paper tape for use in the event of unintended or unwanted stimulation.

1-5 Prior Studies of the Valencia eCoin System

Three clinical studies have been conducted that document the safety and efficacy of eCoin in the treatment of UUI (179 unique patients implanted).

The eCoin system was tested in a prospective, multicenter feasibility study on 46 subjects in the United States and New Zealand, in a second study that invited 23 feasibility subjects to receive a replacement device, and in a prospective multicenter pivotal study on 133 subjects in the United States.

The overall findings from the 3 separate studies assessing eCoin's efficacy in UUI treatment have proven safety and effectiveness. In the feasibility trial, the responder rate at 12 months was 65%; in the follow-on study, the responder rate at 6 months was 82%; and the responder rate in the pivotal trial after 48 weeks was 68%. In each study, other diary assessments show improvement as well, with analyses demonstrating consistent improvement in urinary voids, urgency episodes and nocturia across all timepoints, as well as clinically meaningful improvements in patient reported outcomes.

The eCoin device and associated procedure caused minimal adverse events, especially events resulting in changes of amplitude, or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. As usual for neuromodulation, infection, stimulation discomfort, and migration are the key related adverse events—all occurring at low-normal rates. The device is implanted in a 20-minute office or outpatient procedure under local anesthetic. The eCoin had a low rate of related adverse events. Combined with showing a positive benefit in patients with UUI, the benefits of the eCoin outweigh the risks of the device and procedure.

Results from the pivotal trial were leveraged in the original premarket approval application (PMA) P200036. The eCoin device was approved by the FDA on March 1, 2022. There are two on-going clinical trials that continue to access the safety and efficacy of the eCoin device.

2 Investigational Plan

2-1 Purpose

This investigation is designed as a double-blinded, randomized controlled study assessing the effect of programming at and below sensory level with the Valencia Technologies eCoin system.

The objective of this study is to evaluate the effect of these two programming methodologies (setting amplitudes at sensory vs. subsensory levels) on urgency urinary incontinence symptoms, quality of life, and patient satisfaction.

Observation of these measures will provide valuable knowledge regarding the relationship between functional outcomes and stimulation amplitudes.

Valencia Technologies Corporation, the Sponsor, manufactures the study device, eCoin (electroceutical coin).

Approximately 40 subjects who give informed consent will be enrolled to participate in the study. Only subjects meeting all eligibility criteria will be enrolled. Up to 10 sites will participate in the study.

Each person will participate in the study for up to 7 months (up to 3 months between screening and device activation plus up to 4 months of follow-up).

2-2 Summary

This randomized, double-blind, prospective, multicenter trial will evaluate the effectiveness of eCoin tibial nerve stimulation (INS) at sensory and sub-sensory amplitudes in subjects with urgency urinary incontinence (UUI). The study will evaluate changes from baseline in UUI episodes as measured by voiding diaries and patient-reported quality of life outcomes through up to 4 months of eCoin therapy. The primary and secondary outcomes will be measured at 2, 3, and 4 months of eCoin therapy post-activation.

2-3 Protocol

2-3-1 Study Design

This trial is a double blind, randomized controlled, prospective, multicenter study of the effectiveness of eCoin tibial nerve stimulation programmed to different sensory levels in subjects having UUI.

Subjects will be screened. The study will enroll approximately 40 subjects and up to 50 subjects who meet all inclusion and exclusion criteria at up to 10 centers in the United States. All enrolled subjects will be scheduled to receive the therapy (eCoin for UUI) and randomized in an allocation ratio of 1:1. Depending on their randomization group, subjects will be activated to either a sensory or sub-sensory amplitude level.

After enrollment and implantation, all subjects will be randomized into one of two groups. The eCoin neurostimulation device will be implanted subcutaneously in the right or left leg of subjects with UUI. After approximately a 4 week implant healing period, all subjects will have a programming visit where the device is activated (turned ON). The subjects will either be activated to the amplitude where they first feel the stimulation (i.e. sensory), or activated to the amplitude 25% below their first sensory level (i.e. subsensory). After 2, 3, and 4 months the primary and secondary outcomes will be measured.

Subjects, principal investigators and their research staff will be blinded to the subjects' treatment assignment until the primary endpoint is reached at the 3 month visit post-activation.

2-3-2 Study Objectives

2-3-2-1 Primary and Secondary Objectives

To explore the effectiveness of the eCoin System programmed at two different amplitude settings (sensory, subsensory) for the treatment of urgency urinary incontinence (UUI) by assessing the improvement in urinary incontinence episodes on a 3-day voiding diary.

To assess the improvement in the patient reported quality of life utilizing the Health Related Quality of Life (HRQL) section of the Overactive Bladder Symptom Quality of Life Questionnaire (OABq) and patient satisfaction surveys at two different programming methodologies.

2-3-2-1-1 Primary Endpoint

The primary endpoint is to explore the effect of two different eCoin amplitude settings on the reduction of UUI episodes per day on a 3-day voiding diary after 3 months of eCoin tibial nerve stimulation

2-3-2-1-2 Secondary Endpoints

1. Change from baseline in the patient reported quality of life as assessed by the Health Related Quality of Life (HRQL) portion of the Overactive Bladder questionnaire (OABq) survey after 2, 3, and 4 months of therapy.
2. Reduction from baseline in the number of urgency urinary incontinence episodes per day on a 3-day voiding diary (72 hours) after 2 and 4 months of eCoin tibial nerve stimulation.
3. Improvement from baseline of patient satisfaction with UUI symptoms as gathered from patient satisfaction surveys after 2, 3 and 4 months of therapy.

2-3-3 Subject Selection

2-3-3-1 Patient Population

The sample size target is 40 subjects having UUI, with up to 50 subjects being enrolled. For enrollment, eligible subjects who give informed consent will be entered into a baseline evaluation period to confirm study eligibility. Baseline assessment will include complete medical history, physical examination, and completion of a 3-day voiding diary to quantify voiding behavior, symptoms, and incontinence. Only subjects who meet all the inclusion and none of the exclusion criteria, and have provided informed consent, will be enrolled.

All eligible enrolled subjects will be scheduled to be implanted with the eCoin system after baseline assessment. The physician will select the side of implantation with the subject's input.

Subjects will be randomized at activation. Approximately 4 weeks post implantation, subjects will return for the activation visit at which time they will be randomized and the device will be activated based upon their randomization group. The Valencia Technologies Field Clinical Engineers will implement the activation protocol, setting the amplitude of stimulation.

2-3-3-2 Selection Criteria

Participants will be screened in accordance with the following inclusion and exclusion criteria.

2-3-3-2-1 Inclusion Criteria

1. Women and men above 18 years old or older at time of consent
2. Individual with diagnosis of overactive bladder with urgency urinary incontinence.
3. Individual has at least one urgency urinary incontinence episode on each of three days as determined on a 3-day voiding diary.
4. Individual understood the nature of the procedure and study requirements and provided written informed consent.
5. Individual is willing to comply with specified protocol requirements and follow-up evaluations.
6. Individual is intolerant of or has an inadequate response to any of anticholinergics, β3-adrenoceptor agonists, onabotulinumtoxinA, or who have undergone percutaneous tibial nerve stimulation (PTNS).
7. Individual is determined to be a suitable surgical candidate by physician.

2-3-3-2-2 Exclusion Criteria

1. Individual is not appropriate for eCoin therapy based upon the US FDA-approved IFU requirements.
2. Individual has predominantly stress urinary incontinence (greater than 1/3 of leaks on baseline diary are stress).
3. Individual has clinically significant bladder outlet obstruction.
4. Individual has an active urinary tract infection at time of enrollment or has had four or more symptomatic UTI's in the last 12 months.
5. Individual has microscopic hematuria that has not been evaluated.
6. Individual has significant lower urinary tract pain or has been diagnosed with interstitial cystitis or bladder pain syndrome that is actively being managed.
7. Individual has post void residual greater than 200 cc.
8. Individual has an active diagnosis of bladder, urethral, or prostate cancer.
9. Individual has had a prior anti-stress incontinence surgery within the last year.
10. Individual is pregnant, breast feeding, is less than 12 months post-partum or intends to become pregnant during the study.
11. Individual has uncontrolled diabetes mellitus (Hemoglobin A1C>7).
12. Individual has an implantable neurostimulator, pacemaker, or implantable cardiac defibrillator (ICD).
13. Individual has been treated with onabotulinumtoxinA in the previous 9 months prior to enrollment.
14. Individual has been treated with percutaneous tibial nerve stimulation (PTNS) within the previous 4 weeks prior to baseline.
15. Individual has been treated with pharmacological treatment of overactive bladder (anticholinergic and β3-adrenoceptor agonists) within the previous 2 weeks prior to baseline.
16. Individual has a clotting or bleeding disorder or is unable to hold anticoagulant therapy for the implant procedure at the discretion of the investigator.
17. Individual is neutropenic or immune-compromised.
18. Individual has lower extremity pathology such as:
    a. Previous surgery and/or significant scarring at the planned implant location

b. Ongoing dermatologic condition at the implant site, including but not limited to dermatitis and autoimmune disorders
c. Clinically significant peripheral neuropathy in the lower extremities
d. Pitting edema at the implant location (≥ 2+ is excluded)
e. Inadequate skin integrity or any evidence of an infection or inflammation in either lower leg
f. Moderate to severe varicose veins
g. Open wounds or recent trauma
h. Arterial and/or vasculitis disease in the lower extremities
i. Chronic venous insufficiency with a history of skin change (hyperpigmentation, lipodermatosclerosis, ulceration) in the ankle region

19. Individual has neurogenic bladder dysfunction.
20. Individual is aware that he or she will need an MRI scan other than a head/neck/shoulder MRI during the study period.
21. Any condition that, in the investigator's opinion, would preclude participation in the study (e.g., comorbidity that places subject at increased risk for surgical intervention, medical condition that may increase the risk associated with study participation or may interfere with interpretation of study results, inability to adhere to the visit schedule, such as morbid obesity, clotting or bleeding disorder)

2-3-4 Ethical Considerations

This study involves no critical ethical issue involving actual or possible patient harm. Subjects who meet the inclusion and exclusion criteria to participate in the study are invited to participate in this study.

- All subjects will receive tibial nerve stimulation with the eCoin device in accordance with the device labelling.
- Some subjects may not receive clinical benefit from eCoin therapy in either arm; however, the expectation is that subjects will continue with the trial, at least until the primary endpoint, regardless of response. Some individuals who initially do not receive clinical benefit may benefit from late response and cumulative effects of treatment.
- At unblinding, subjects will be offered reprogramming if desired.
- Subjects are intended to be without pharmacological medications for overactive bladder. If the addition of medications is medically necessary as described herein, such information will be collected and reported.

2-4 Study Procedures

All subjects will be followed for up to 4 months post-activation. A 3-day voiding diary will be collected that reports the number and type of incontinence episodes. Subjects will be administered questionnaires including the OABq and patient satisfaction surveys at 2, 3, and 4 months post-activation.

The follow-up study visits are described in relationship to the initial activation visit occurring about 4 weeks after implantation of the study device. See Visit Overview 2-4-2 for exact timing of such visits. For any enrolled subject who is not activated, the same schedule will be followed as if the subject were activated.

Subjects should avoid concomitant therapies, including OAB medications, onabotulinumtoxinA, PTNS or TENS therapies, until the primary endpoint at 3 months. If taken, these therapies will be recorded and noted in the results. Subjects who are taking pharmacologic medication at screening should be washed off OAB medications for a period of 2 weeks prior to filling out the baseline diary.

All subjects will exit from the study after the last study visit at 4 months post activation. Patients may retain their device and remain under the care of their implanting physician.

COVID-19 Considerations

The COVID-19 pandemic may prevent subjects from coming into the clinical site for follow up visits. As an alternative, subjects may complete remote visits, in which all study activities can be performed. Patients will electronically transmit their diary and OABq/satisfaction survey responses to the site personnel, through either pictures, scans, or fax, and review all other items over the phone. If subjects or site personnel send diaries through the mail, tracked delivery services should be used. Changes in study visit schedules, remote visits, missed visits, or patient discontinuations due to COVID-19 will be documented and will be included in the final study visit report.

2-4-1 Recruitment Plans

Investigators will identify patients under their direct care and contact patients who appear to qualify from medical records. Investigators will also seek referrals from other urology, urogynecology, gynecology and primary care practices. Patients with a medical history of urgency urinary incontinence and who appear to meet the inclusion and exclusion criteria will be presented with the opportunity to participate in the study.

Such discussions may be informal or formal, may occur after a patient is scheduled for implantation of the eCoin System, or may occur alongside a discussion between the physician and patient about the patient's treatment options.

Patients who remain interested will be brought into the research clinic for further screening and informed consent.

The study device will be provided free of cost by Valencia Technologies.

2-4-2 Visit Overview

The enrollment process consists of screening (including obtaining written consent) and completing the baseline evaluation. After confirming eligibility, the eCoin system will be implanted, the subject will be randomized and the amplitude will be set depending on their randomization group. A revision procedure would not reset the initial activation date.

After all assessments for the 3 month visit have occurred (questionnaires, etc), the patient and physician will be unblinded by the Field Clinical Engineer (FCE) attending the visit. The FCE will then offer the subject reprogramming and provide the subject with information on the expected battery life and depletion date. This information allows for adequate time to prepare for and schedule eCoin device explant or replacement.

For the visit involving a 3-day diary, the diary should be completed over 3 consecutive days during the 7 days prior to the indicated visit

- Visit 1: Screening Procedures (informed consent, demographic and medical history and concomitant medication/therapy information, physical examination, and vital signs are collected, subjects begin 2 week wash-off of OAB medications or 4 week wash-off of PTNS if applicable, eligibility determination)

- Visit 2: Baseline Assessments (3-day voiding diary, OABq, patient satisfaction survey, concomitant therapy review, final eligibility determination) (Time: Between 3 and 32 days from Visit 1)

- Visit 3: Implant Procedure (vital signs collected, adverse event assessment, concomitant therapy review, pictures taken) (Time: Between 0 and 20 days from Visit 2)

- Visit 4: Incision Healing Check (vital signs collected, adverse event assessment, pictures taken, concomitant therapy review) (Time: Between 9 and 19 days from Visit 3)

- Visit 5: Initial Activation and Randomization at Sensory or Subsensory (vitals signs collected, adverse event assessment, pictures taken, concomitant therapy review) (Field Clinical Engineer present)) (Time: Between 23 and 43 days from Visit 3)

- Visit 6 (2 months post-activation): Follow-up assessments (3-day voiding diary, OABq, patient satisfaction survey, adverse event assessments, concomitant medication therapy review) (Time: Between 7 and 9 weeks from Visit 5)

- Visit 7 (3 months post-activation): Follow-up assessments (3-day voiding diary, OABq, patient satisfaction survey, adverse event assessments, concomitant medication therapy review, unblinding and reprogramming as requested (Field Clinical Engineer present)) (Time: Between 12 and 14 weeks from Visit 5)

- Visit 8 (4 months post-activation): Follow-up assessments (3-day voiding diary, OABq, end of study survey, adverse event assessments, concomitant medication therapy review) (Time: Between 16 and 18 weeks from Visit 5)

	Screening	Baseline	Implantation	Incision Healing Check	Activation (Follow up Clock Starts)	2 Month	3 Month: Primary Endpoint	4 Month
Demographics, screening exam, physical exam, & medical history	X							
Eligibility Determination	X	X						
Informed Consent	X							
3-day Voiding Diary Reminder Call		X				X	X	X
3-day Voiding Diary		X				X	X	X
OABq Assessment		X				X	X	X
Patient Satisfaction Survey		X				X	X	
End of Study Survey								X
Implant Procedure			X					
Incision Assessment				X				
Pictures Taken			X	X	X			
Vitals Taken	X		X	X	X			
Programming					X		X	
Randomization					X			
Completion of Primary Endpoint/Unblinding							X	
Completion of Study								X
Subject Assessment for AEs		X	X	X	X	X	X	X
Concomitant Medication Therapy Review	X	X	X	X	X	X	X	X

2-4-3 Screening for Eligibility Procedures

Interested adults may be prescreened for inclusion in the study. Subjects' medical records will be reviewed for inclusion/exclusion criteria.

Subjects who initially qualify will be scheduled for a screening visit to assess general health and overactive bladder condition. After patients provide their informed consent, subjects will be questioned for inclusion/exclusion criteria in addition to medical record review. Medical history will be taken, physical exam will be performed, post void residual will be completed, and general health to participate in the study will be further evaluated by the Investigator at the screening visit.

2-4-4 Prior and Concomitant Therapy

The intent of the study is to enroll subjects who are refractory to other modes of therapy, including behavioral therapy, pelvic floor exercises, and pharmacologic therapy.

Subjects who are taking pharmacologic agents for overactive bladder or other agents that may influence urination at enrollment will be expected to discontinue those medications at least 2 weeks prior to baseline, in order to obtain a true baseline. The use of agents for overactive bladder will be reported at each follow-up visit. A complete list of prescription drugs, over-the-counter drugs, or dietary supplements should be taken at screening to ensure stability of medications that can affect urination.

2-4-5 Informed Consent Procedures

The study as described in the Informed Consent Form will be presented to the individual for consideration at the screening visit. The individual will be given adequate time to have their questions answered and to carefully consider participation. If, after understanding the purpose, potential risks, potential benefits, and requirements of the study, as well as his or her rights as a research participant, the individual agrees to participate as evidenced by providing written informed consent, the subject will be further assessed at a baseline visit. The subject should be allowed to take informed consent documents home for further consideration, if needed, and scheduled with an additional visit to complete the screening visit. The signed Informed Consent Form shall be included in the patient's medical record file and noted in the screening CRF. The subject should receive a signed copy of the ICF.

2-4-6 Baseline Visit Assessments

At the conclusion of the Screening Visit, eligible subjects who have provided written informed consent will be asked to return for baseline assessments.

Baseline assessments will include:

1) Return of the 3-day voiding diary;
2) OABq questionnaire;
3) Patient Satisfaction Survey

Study staff will schedule subject's implantation procedure to follow baseline assessments. All subjects who continue to meet the inclusion and exclusion criteria through the baseline assessments will be enrolled in the study.

2-4-7 Implantation of Subcutaneous Neurostimulation System

An implant procedure is to be completed 0-20 days from the baseline visit. The eCoin system will be implanted in accordance with the procedures outlined in the approved labelling for the device. The implant procedure is conducted under local anesthesia for subcutaneous placement. An incision site healing check will be performed approximately 2 weeks post implant. Subjects will be provided approximately 4 weeks for healing prior to activation of the system.

Prior to discharge from the procedure, the research staff shall review study requirements with the subject to help ensure compliance with the follow-up schedule. Telephone numbers will be obtained from the participant at the time of informed consent to ensure the clinic is able to contact the subject and primary physician as needed. Patients will be instructed on post-procedural wound care and limitation of certain physical activities. Antibiotics and pain medication may be prescribed at the discretion of the investigator.

2-4-8 Randomization and Blinding

Randomization assignments will be generated by a software program using randomization with a 1:1 allocation to sensory or subsensory activation. After production of the allocation sequence, the sequence will be locked, password protected and placed in an online file storage system by the staff who produced it. The Field Clinical Engineer is the only study personnel who can view the randomization sequence prior to unblinding.

Both the principal investigator and patient will be blinded to the patient's treatment assignment until completion of the primary endpoint visit at 3 months post-activation. The FCE will be unblinded to the participant's treatment assignment, allowing them to activate the patient to their treatment level.

Randomization will occur on the day of the activation and after all baseline data have been collected, eligibility has been confirmed and the device has been implanted. On the day of the activation, the FCE will check the allocation sequence.

Until the primary endpoint is reached, subjects will be required to remain in their randomized treatment arm and not undergo reprogramming. If the subject reports that the stimulation in their current treatment arm is uncomfortable and requests reprogramming, a protocol deviation will be required, and the patient may not be considered in the primary analysis population.

Before the primary endpoint at 3 months post activation, unblinding of participants will only occur when medically necessary. In the event of a device- or procedure- related SAE or device malfunction, the sponsor may authorize unblinding of the physician and the participant in order to adequately assess the event.

2-4-9 eCoin Activation

All subjects will return for a device activation visit approximately four weeks after implantation. At this point, the follow-up visit clock will start to run (that is, the follow-up visits will be characterized in relationship to the date of the activation visit).

The subject will be provided with a 3-day voiding diary to complete in the 7 days prior to the next visits (occurring 2 and 3 months post-activation). At least 3 days prior to the next visit, a member of the study staff will telephone subjects to remind them that they should begin the 3-day diary.

2-4-10 Establishment of the Amplitude Setting in each Treatment Arm

Amplitude level ranges in practice from 0.5 to 15 mA. Sensory threshold is defined as the lowest amplitude where the subject first perceives sensation of the stimulation in the foot, heel, toes or eCoin device site while in a prone, seated and standing position.

Subjects will be informed that they may periodically feel a tingling or notice a muscle twitch. In particular, subjects may feel a motor response (flexing of the big toe and/or fanning of the other toes) and sensory response (a radiating sensation may be felt at the sole of the foot and in the toes). Typical descriptions of tibial nerve stimulation sensation include feeling a 'buzzing', 'tingling' and 'vibrating' sensation.

2-4-10-1 Sensory Treatment Arm Activation Protocol

The subject's sensory threshold is determined by turning the device on to 0.5 mA and increasing the amplitude by one level until the subject reports sensation. If the subject does not feel sensation at any amplitude, they will be set at 8 mA, this will be considered a deviation to the protocol.

2-4-10-2 Subsensory Treatment Arm Activation Protocol

The subject's sensory threshold is determined by turning the device on to 0.5 mA and increasing the amplitude by one level until the subject first reports sensation. Once the first sensory threshold is determined, the set amplitude will be lowered to approximately 75% of the sensory threshold, accounting for rounding. Patients who do not have sensory at the highest amplitude will be set at 11mA. See the below table for sensory threshold and level set correlations:

Sensory Threshold	Level Set
0.5 mA	Protocol Deviation, set 0.5 mA
1 mA	0.5 mA
2 mA	1 mA
3 mA	2 mA
4 mA	3 mA
5 mA	4 mA
6 mA	5 mA
7 mA	5 mA
8 mA	6 mA
9 mA	7 mA
10 mA	8 mA
11 mA	8 mA
12 mA	9 mA
13 mA	10 mA
14 mA	11 mA
15 mA	11 mA
No sensation	11 mA

2-4-11 Post Activation Follow-up Procedure

Subjects will be followed up in visits at 2, 3 and 4 months post-activation, with the primary analysis at 3 months.

1) Overactive bladder medications should be avoided, especially prior to the primary endpoint at 3 months. Any medications taken throughout the study should be noted as soon as they are added to the subject's treatment.

2) At least 3 days prior to each appointment, subjects will be responsible to complete a 3-day voiding diary to be brought with them to each appointment.
3) All other visits are also described in the Visit Overview Section 2-4-2.

If a subject is explanted for any reason they may choose to remain in the study (e.g. continue to attend visits) if they wish.

2-4-12 Plans to Minimize Loss to Follow-Up

Plans to minimize loss to follow-up include:

- Trial design and management that limits the patients' burden and inconvenience during the collection phase including: minimal number of visits and assessments, short study timeline, user friendly diary collection methods, and allowing a relatively large time window for each follow-up
- Training of the site staff to emphasize the importance of the informed consent process as a mechanism for ensuring that participants understand the commitment they are making, including their intent to complete the trial regardless of the treatment they are receiving. Training of investigators and research staff should also emphasize how to work with participants to minimize the extent of missing data.
- Regular and thorough monitoring of the trial data, identification of poorly performing sites in order to implement some form of remediation, including additional training, site visits, or even site closure.

2-4-13 Subject Compliance Monitoring

eCoin Therapy: Neurostimulation therapy is provided automatically by the implant system and has no compliance requirements.

Data: Compliance with voiding diaries is established through review by the clinical study coordinator at each center.

Appointment Compliance: Clinics' designated study coordinators will ensure subjects are compliant with study appointments within the scheduling parameters outlined in the Visit Overview described in Section 2-4-2.

2-5 Safety and Adverse Events

2-5-1 Definitions of Adverse Events

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

System and Procedure Related Adverse Event: Any adverse event related to the device or placement procedure. This can include risks associated with the procedure, implant site or stimulation such as infection, or related adverse events that occur in relation to implant placement, tibial nerve stimulation or device failure. The Sponsor maintains a list of expected adverse events and is responsible for determining anticipatedness.

Serious Adverse Event (SAE): A serious adverse event is any adverse event that results in death during the study period; is life-threatening; requires hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; results in a congenital anomaly or birth defect; requires medical or surgical intervention to preclude permanent impairment of a body function or to prevent permanent damage to a body structure, where the device is suspected to cause such intervention; other important medical events not captured by the other categories where the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes.

Unanticipated Adverse Device Effect (UADE): Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death 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), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the subject.

2-5-2 Classification of Events

2-5-2-1 Relationship to Device or Procedure

Related to study device: event has a reasonable possibility of a causal relationship to the device or tibial nerve stimulation and no other etiology explains the event.

Related to procedure: event has a reasonable possibility of a causal relationship to the procedure (device placement, removal, replacement) and no other etiology explains the event.

AEs will be considered device or procedure related if they are classified as possibly, probably, or certainly related.

Assessment of certainty:

Certain: definitive evidence to suggest causal relationship, cannot be explained by other factors

Probable: evidence to suggest a causal relationship, the influence of other factors is unlikely

Possible: some evidence to suggest a causal relationship, but other factors may have contributed to the event

Unlikely: little evidence to suggest a causal relationship (e.g. the event did not occur within a reasonable time frame after therapy administration or procedure) or another reasonable explanation for the event

Not related: No evidence of any causal relationship with the trial intervention

2-5-2-2 Recording of Adverse Events

All AEs and categories of AEs (SAE's, UADE's, and AE's) will be captured and recorded in the case report forms (CRFs) which are used at each visit. Subjects will be requested to report adverse urologic events that are inconsistent with their normal medical condition that occur in between visits to the study coordinator or medical staff who will record on AE forms. Sites will be expected to follow related adverse events until resolution. All reported adverse events will need to be evaluated and assigned review to be coordinated by the Company:

1) Relatedness or causality to the study device

2) Action taken

The Sponsor is responsible for determining if an adverse is a UADE.

At each contact with the subject, the Investigator will obtain information on AEs by specific questioning and examination. In the CRF for visits, if an event is reported, the AE checkbox will be selected. This selection will trigger a separate form to be filled out that records the following information:

1. Subject Number
2. Adverse Event (AE)
3. Date of AE onset
4. Date of AE cessation
5. Relationship to eCoin device
6. Relationship to eCoin procedure
7. Was the patient hospitalized? If yes, provide dates.
8. Will the patient continue with treatment, and will any be missed?
9. Did the patient add or change any other associated medication and what were the changes/additions?
10. Was any other action taken?

When an AE has been recorded, the PI or sub-PI for the study must sign and approve the assessment on the Sponsor-provided CRF. The Study monitor will keep track of all reported AEs.

2-5-2-3 Device and Procedure Causality Assessment

The investigator or physician sub-investigator must indicate whether they believe the AE is unrelated, or related to the device, and make an assessment of certainty.

2-5-2-4 Reporting Procedures

Serious Adverse Events (SAEs) or suspected Unanticipated Adverse Device Effects (UADEs) must be reported to the sponsor within 48 hours of learning of the event. For suspected UADEs, the Sponsor will promptly provide an expectedness determination. Non-serious unexpected device related AEs must be reported via CRF to the sponsor within 7 days of subject reporting. The Investigator must promptly inform the Ethics Board or IRB of SAEs or determined UADEs per local reporting requirements.

These events will be reported by the Sponsor as appropriate to the regulatory authorities according to relevant jurisdictional medical device regulations. The Investigator will receive notification of these events across all study centers from the Sponsor.

As the eCoin device is a PMA-approved and commercially available device in the US, Medical Device Reporting requirements (21 CFR 803) are applicable to adverse incidents reported through this Study.

2-5-2-5 Adverse Event Reporting Period

All adverse events will be recorded from the time of signature of Informed Consent until a subject is exited from the trial. If the patient presents to the Investigator after the study period and a device-related AE is

suspected, the AE should be reported to the Sponsor via commercial complaint reporting. Complaints should be sent to complaint@ecoin.us

2-5-2-6 Medical Monitoring

This study will not use a Data Monitoring Committee. A Medical Advisor will review all adverse events and device deficiencies for consistent reporting.

2-5-3 Subject Withdrawal & Termination

This section describes reasons for withdrawal of subjects and termination of the study. A Statistical Analysis Plan (SAP) will describe in detail the methods for handling data from subjects who withdraw, or are withdrawn, early from the study.

2-5-3-1 Early Withdrawal of Subjects

Subjects may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any reason. Any subject considered withdrawn will be exited from the study.

2-5-3-2 Terminating Subject Participation

A subject's continued participation in the study must be terminated if in the Investigator's opinion, continued participation would be detrimental to the subject's well-being. If the subject is unwilling or unable to attend all remaining follow-up visits, or if subject is lost to follow-up, the subject's continued participation must be terminated.

2-5-3-3 Withdrawal/Termination Procedures

If premature withdrawal occurs for any reason, the Investigator must make every effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the CRF for reporting to the Sponsor.

Subjects enrolled in the study will not be replaced if they withdraw or are terminated from the study after randomization.

2-5-3-4 Early Study Termination

The study can be terminated at any time for any reason by Valencia Technologies. Should this be necessary, the subjects should be seen as soon as possible and treated as described in the early withdrawal section for a prematurely withdrawn subject. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests. The Investigator will be responsible for informing the IRB of the early termination of the trial.

2-5-3-5 Data Collection and Follow-up for Withdrawn Subjects

Subjects who are not implanted with the eCoin study device will not be followed after termination or withdrawal from the study.

2-6 Data Analysis Plan

2-6-1 Data Collection

All study data will be recorded onto Case Report Forms (CRFs) provided by the sponsor. All CRFs will be completed using de-identified data. Valencia will enter the recorded data into a database.

Case Report Forms (CRFs): Data will be entered in the CRFs at the Study site. Trained study personnel will be responsible for entering data on the observations, tests, and assessments specified in the protocol onto the CRFs and according to the CRF instructions and sending the CRFs to the designated sponsor representative in a timely fashion.

CRFs for the study include:

1) Screening
2) Baseline
3) Implantation
4) Implant Healing Check
5) Programming
6) Follow-up (2, 3, and 4 months post-activation)
7) Adverse Event
8) Device Malfunction
9) Protocol Deviation
10) Explantation
11) Explantation Healing Check
12) Unplanned Visit
13) Concomitant Medications
14) Study Exit

Data verification will be performed using manual data review. Any data discrepancies will be referred back to the investigator or site staff. The database will be locked after it has been declared clean.

2-6-2 Interim Monitoring

All clinical sites will be monitored periodically by Valencia Technologies or its designated representatives. Telephone contacts and monitoring visits will be made throughout the course of the study.

During site visits, the monitor will review participant records and general study procedures. The monitor will also discuss any problems with the Investigator. Monitors will audit data collected on CRFs and verify data against source documentation in accordance with the Clinical Monitoring Plan. Monitors will confirm that written Informed Consent was properly obtained prior to enrollment of each participant. Any evident pattern of non-compliance will be addressed with the Investigator. If appropriate corrective actions are not

subsequently undertaken, Valencia reserves the right to suspend enrollment at the site and/or withdraw the site from the study.

At the close of the study at a research site, the clinical monitor conducts a final visit to collect all outstanding study data documents, ensure that the Investigator's files are accurate and complete, review record retention requirements with the Investigator, make a final accounting of all study supplies shipped to the Investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study.

2-6-3 COVID-19 Considerations

If the COVID-19 pandemic persists, monitors may not be able to travel to the investigational site to complete onsite monitoring of data. As an alternative, monitors will complete remote monitoring visits.

2-6-4 Analysis Plan Summary

This double-blind, randomized, controlled, prospective, multicenter study is designed to assess the effectiveness of the eCoin Peripheral Neurostimulator system at sensory and subsensory levels for the treatment of urgency urinary incontinence. The study will enroll about 40 subjects, with up to 50 subjects, from up to 10 different centers.

The remainder of this section briefly describes the analyses planned for this study. A full Statistical Analysis Plan (SAP) will be prepared. The SAP will include more technical and detailed descriptions of the statistical analyses. If there are minor differences between the analyses described in this section and the analyses in the SAP, the analyses in the SAP will prevail. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol.

2-6-4-1 Effectiveness

This randomized, double blinded study will evaluate eCoin's effectiveness reducing episodes of urgency urinary incontinence with programming at sensory and subsensory levels. The reduction in the number of urgency urinary incontinence episodes will be reported at 2 months, 3 months (primary endpoint), and 4 months post-activation.

2-6-4-2 Analysis Sets

The primary analysis will be performed in the Per-Protocol (PP) population, defined as subjects who undergo an implantation procedure, are OAB drug free, and who have data available at the primary endpoint, excluding all major protocol deviations and any significant departures from the amplitude programming protocol (no sensory at any level for sensory arm, and sensory at lowest setting for subsensory arm, reprogramming that is a significant departure from the assigned treatment stimulation, or device not activated).

In addition to the primary analysis, an analysis will be performed of the Intent-to-Treat (ITT) population defined as all subjects who undergo a procedure for implantation of eCoin and who have

data available at the primary endpoint.

Safety data will be reported on all enrolled subjects who undergo a procedure for implantation of the study device. Safety data will be reported for all device related adverse events, procedure related adverse events, and serious adverse events.

The SAP may define additional analysis sets of subjects.

2-6-4-3 Planned Analyses

2-6-4-3-1 Primary Endpoint

1. The primary endpoint is the reduction from baseline in the number of urgency urinary incontinence episodes per day on a 3-day voiding diary (72 hours) after 3 months of eCoin tibial nerve stimulation.

2-6-4-3-2 Secondary Endpoint(s)

1. The secondary endpoint is change from baseline in the patient reported quality of life in each arm as assessed by the Health Related Quality of Life (HRQL) portion of the Overactive Bladder questionnaire (OABq) survey after 2, 3 and 4 months of therapy.
2. The secondary endpoint is achieving at least a reduction from baseline in the number of urgency urinary incontinence episodes per day on a 3-day voiding diary (72 hours) after 2 and 4 months of eCoin tibial nerve stimulation.
3. Improvement of patient satisfaction with UUI symptoms as gathered from patient satisfaction surveys after 2, 3 and 4 months of therapy.

2-6-5 Sample Size Consideration

This study will explore the effect of two different amplitude settings (sensory and subsensory amplitude) on reduction of UUI episodes per day as compared to baseline. Change of average UUI per day at 3-months follow-up will be summarized with descriptive statistics for each study arm.

As detailed below, the minimum sample size required for this study is 32 subjects (16 per arm). The planned enrollment of 40 subjects implanted and up to 50 meets this minimum.

From the pivotal study, a total of n=133 patients were implanted with eCoin. Looking at the subset of patients programmed at or below sensory level, after 8 weeks of therapy there was a mean reduction in UUI episodes of 2.3 with a standard deviation of 1.4, After 12 weeks of therapy, there was a mean reduction in UUI episodes of 2.7 with a standard deviation of 1.8 per day (n=22).

Based on a confidence interval using a t-distribution, a two-sided type-I error rate of 0.05, and using a standard deviation of 2, precision was calculated for a range of sample sizes using the equation below from the PASS One Mean Module with Tolerance Probability. Margin of error, also known as precision, is the distance between the mean and edge of an interval.

$$D = \frac{t_{1-\alpha/2,n-1} * \hat{\sigma}}{\sqrt{n}}$$

Sample Size	Precision
13	1.21
14	1.15
15	1.11
16	1.07
17	1.03
18	0.99
19	0.96
20	0.94

*Standard deviation=2

We plan to use the per protocol population as our primary analysis population. This is due to the concern that the Intent to Treat (ITT) population will be diluted due to deviations from the assigned therapy. To adjust for noncompliance/nonadherence, we must estimate the proportion from the subsensory group who will have a sensory level that is cannot be reduced by 25% (i.e. their sensory threshold is the minimum setting of 0.5 mA). Based on the Pivotal trial, 3.85% (n=130) had a sensory threshold of 0.5 mA. Since this scenario only affects the subsensory arm, we estimate this this proportion to be 0.02. Additionally, in the subsensory threshold group, we must adjust for patients who have no sensory threshold, (i.e. they do not feel sensation at any amplitude level and therefore are unable to identify the sensory setting). Based on the Pivotal trial, 6.15 % (n=130) had a sensory threshold of "not identified." Since this scenario only affects the sensory arm, we estimate this scenario to be 0.03. Lastly, we plan for a 10% dropout rate.

Considering the scenarios described above, a sample size of n=16 will have a precision 1.07. For this analysis, we are considering a low assumed treatment effect as a mean reduction of 1.3. This is the 3rd quartile of mean reduction from the pivotal trial at 2 months, meaning 75% of the data lies below -1.3. The mean reduction from 8 weeks is being used for this analysis because in the pivotal study, patients had the option to reprogram at 8 weeks, therefore the 12 week results are confounded by reprogramming. Since the precision of 1.07 is below our assumed treatment effect of 1.3, the confidence interval (0.23, 2.37) does not include zero. This means if the treatment is effective, we expect to have sufficient sample size to see a result. Accounting for 15% of patients taken out of the Per Protocol population due to withdrawal or deviations from the assigned therapy group, a sample size of 13 per arm has a precision of 1.21 which is less than 1.3 UUI.

2-6-6 Calculation of Effectiveness Variables

Change in Urgency Urinary Incontinent Episodes: Urgency Urinary Incontinent episodes (UUI) are measured prospectively using 3-day voiding diaries administered at baseline, 2, 3, and 4 months post-activation of the eCoin system.

Change in Quality of Life: Quality of life is measured prospectively using the OABq and patient satisfaction questionnaires administered at baseline, 2, 3 and 4 months post-activation of the eCoin system.

2-6-7 Missing Outcome Data

Because this study is investigating an implanted device, nearly all implanted patients are expected to have data on the primary and secondary endpoints. Careful clinical planning that minimizes patient dropouts will be implemented. Missing data imputations will not be performed.

The SAP will provide further details on handling missing data for the secondary outcomes.

2-6-7-1 Concomitant Therapies

Concomitant therapies are prohibited until the primary endpoint at 3 months.

2-6-8 Safety Analysis

All device- and procedure-related adverse events and SAEs up to 4 months after activation will be summarized. Tabulations of these data will include the number of subjects exposed and the number of subjects with at least one device- or procedure-related adverse event. Tabulations of device- and procedure-related AEs and SAEs which will be provided by time point, will include the number of (S)AEs, the number of subjects who experienced the S(AE), and the percent of subjects who experienced the S(AE).

2-7 Data Handling, Record Keeping and Study Monitoring

2-7-1 Confidentiality and Security

The Investigator will ensure that the subject's confidentiality is maintained on the CRFs or other documents submitted to the Sponsor. Subjects should be identified by their initials and a subject study number only. Documents that are not for submission to the Sponsor, such as the signed informed consent forms, should be kept in strict confidence by the Investigator. In compliance with ICH GCP Guidelines, the Investigator and institution are required to permit authorized representatives of the company, of any relevant regulatory agency, and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator will inform and obtain the consent of the subject to permit named representatives to have access to his/her study- related records without violating the confidentiality of the subject. Information about study subjects will be kept confidential and managed according to the requirements of the clinical sites regulatory authority. As a part of the consent process, subjects will sign an authorization informing the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- What rights does a research subject have to revoke their authorization for use of their PHI

2-7-2 Training

Investigators for this trial must be an "Approved Site" as determined by VTC procedural training department, indicating mastery of the treatment modality. All study forms and procedures will be reviewed with medical/study staff at the participating centers. Approved Sites will have facilities that have the appropriate infrastructure, equipment, and trained personnel to support the eCoin implantation procedure and subsequent study.

2-7-3 Documentation, Case Report Forms and Source Documents

All documents will be signed off by the Sponsor and controlled such that any revisions are approved and tracked, with each document identified with a document number and revision code. Investigators will maintain the following items of documentation in the Investigator's Study File on site:

- Log of protocol changes
- Institutional Review Board (IRB)-approved protocol, with signed principal investigator (PI) signature page
- Blank Case Report Forms
- IRB-approved advertisements (if applicable)
- IRB-approved Participant Information Sheets
- IRB-approved protocol amendments
- IRB-approved Informed Consents
- IRB approval letters (e.g., protocol, protocol amendments, consent/assent documents, continuing review, advertisement or recruitment materials, physician manual, package insert)
- Original IRB application/submission
- Correspondence related to contingent approvals or stipulations
- IRB correspondence
- IRB annual renewals
- Interim/annual progress reports to the IRB
- Signed Investigator's Agreement for the PI and co-investigators
- Signed Financial Disclosure Forms for the PI and co-investigators
- Delegation of Authority Log
- Documentation of Good Clinical Practice training (for all staff members)
- Updated investigator and sub-investigator CVs (signed/dated within 2 years)
- A medical license for the PI and co-investigators, if licensed
- Clinical Monitoring Site visit log
- Clinical Monitoring Site visit letters
- Adverse event or device malfunction reports to Sponsor and IRB
- IP accountability log
- Enrollment Log

Investigators are required to prepare and maintain adequate source documentation which

includes:

- Documents relative to the subject medical history that verify eligibility criteria
- Records covering subject participation in the Study including basic identification information, results of physical examinations and diagnostic tests, Study therapy administration, concurrent medication information, and visit/consult notes.

- All key data must be recorded in the subject's source documents including the Informed Consent acquisition.

2-7-4 Device Accountability

Because the product used in the study is approved by FDA under a PMA, investigational product accountability is not applicable.

2-7-5 Monitoring Procedures, Auditing, Inspecting

A clinical research monitor will supervise conduct of the study at each site in accordance with the Clinical Monitoring Plan. The monitor will conduct remote monitoring visits at periodic intervals, in addition to maintain ongoing telephone, e-mail, and letter contact. The monitor will maintain up-to-date personal knowledge of the study through observation, review of study records and source documentation, and discussion of the study with the Investigator and study personnel. The study site will assist the monitor by providing access to all relevant study materials.
The clinical monitors will be trained on the study protocol, monitoring procedures, and standard operating procedures based on Good Clinical Practice and other applicable Federal regulations.
The investigator and his/her staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit to review the CRFs and any queries/resolutions, answer questions, and provide any missing information.

2-7-6 Protocol Deviations and Compliance

2-7-6-1 Major Protocol Deviations

A major protocol deviation is defined as one that affects the safety of the subject or the scientific validity of the results.

1) A Physician Investigator may deviate from the protocol in an emergency situation, such as when a departure from the protocol is required to protect the life or physical well-being of a participant. The Sponsor and the IRB/Ethics Committee must be notified as soon as possible, but not later than 5 days after the emergency situation occurred.
2) Any non-emergency, major deviation to the protocol must be approved by the Sponsor prior to implementation. If a major deviation occurs that is not in response to the protection of a subject, falls into the above categories or was not pre-approved by the sponsor, it must be reported to the Sponsor and IRB as non-compliance – no later than 5 days after the deviation. A PI's failure to report promptly any major deviation will be evaluated by the Sponsor. Such failure could be grounds for physician disqualification.

2-7-6-2 Minor or Administrative Protocol Deviations

A minor deviation is defined as one that does not affect the safety of the subject or the scientific validity of the results. Minor deviations from the protocol should be noted through the protocol deviation CRF and brought to the attention of the monitor at the next monitoring visit. These deviations do not need to be reported to the IRB/Ethics Committee.

Examples of a minor protocol deviation follow:

1. Deviations related to amplitude programming or use of the patient controller. For example:

a. Unable to feel sensation at any level for sensory arm,
b. Sensory threshold is at lowest setting for subsensory arm
c. Reprogramming that is a departure from the assigned treatment stimulation
d. Device not activated
e. Device turned off prior to primary endpoint

2. Follow-up visits that occurred outside the protocol required time frame because of the participant's schedule.
3. Study procedure conducted out of timeframe, e.g., 3-day diary
4. Participant failure to return patient diary
5. Copy of the ICF not given to the participant
6. Missing original signed consent, but a copy exists

Missed vitals at a follow-up visit is not considered a protocol deviation.

2-7-6-3 Analyzing Deviations

At each monitoring visit, the deviations will be reviewed along with any additional deviations that might be discovered during the monitoring visit. If any minor deviation is deemed to have an impact on the trial outcomes, the issue must be brought to the attention of the Sponsor.

2-7-7 Modification of the Protocol

All amendments to the protocol must be documented in writing, reviewed and approved by the sponsor, and submitted to the IRB for approval/positive vote prior to initiation. If the protocol amendment substantially alters the Study design or potential risk to the subject, new written informed consent must be obtained from each subject for continued participation in the Study.

2-8 Methods, Facilities, and Control Information

2-8-1 Organization and Participating Center

2-8-1-1 Principal Investigators

All U.S. based Principal Investigators participating in the study will have signed an Investigator Agreement.

2-8-2 Funding Source and Conflicts of Interest

The study is funded by Valencia Technologies. Participating centers will be paid according to clinical trial agreements. Participating physicians will have disclosed their financial relationship in the Conflict of Interest statement incorporated within the signed Investigator Agreement.

2-8-3 Institutional Review Board / Ethics Committees

Institutional Review Board / Ethics Committees will approve the protocol for each respective center pursuant to center requirements or under an independent review board.

2-8-4 Roles and Responsibilities

2-8-4-1 Sponsor

The Sponsor is committed to:

1) Protecting the rights, health, safety and welfare of study Subjects by:

a) Submitting the protocol and informed consent to IRB/Ethics Committee and awaiting approval before starting the study
b) Submitting proposed amendments to the protocol and informed consent to IRB/Ethics Committee and Regulatory Authority (where applicable and await approval, unless the change reduces the risk to subjects)
c) Assuring IRB/Ethics Committee and Regulatory Approval (where applicable) is obtained
d) Verifying the Subject informed consent process.

2) Informing the clinical investigator of any new information that may affect the health, safety or welfare of the Subjects, or which may influence their decision to continue participating in the Study.
3) Periodically reviewing the data to ensure that the investigator is in compliance with the protocol and the investigator's agreement.
4) Providing the investigator with the study protocol and access to the Study CRFs.
5) Selection and approval of investigators to participate in this Study.
6) Obtaining agreement, CV and Medical License of each Investigator.
7) Maintaining a system of study documentation associated with the Study and corresponding sites and investigators.
8) Providing training on key elements of the protocol, including Subject inclusion/exclusion criteria, and what constitutes follow up.
9) Review CRF's to ensure completeness and accuracy of study data. Sites will be asked to resolve discrepancies via correction to the CRF.
10) Acting as a resource for questions after training for the duration of the Study.
11) Controlling shipment of devices and study supplies.
12) Selecting and training monitors
13) Conducting overall administration of study.
14) Investigating unanticipated, device-related adverse events.
15) Documenting protocol deviations and violations.
16) Reviewing adverse events and safety related events and escalating as appropriate.

2-8-4-2 Investigator

The investigator will affirm by his/her signature on the Investigator's Agreement that he/she will fulfill his/her responsibilities relative to the Study. The investigator will be responsible for:

1) Ensuring that all Subjects entering the Study conform to the Subject inclusion criteria and that no exclusion criteria apply.
2) Obtaining IRB approval from the respective institution to perform the procedure, prior to enrolling any Subjects in the Study. The informed consent document to be used will also be submitted by the investigator to the IRB for approval prior to initiation of the investigator's participation in the Study. The investigator is also responsible for providing any other additional documentation relevant to the Study as required by the IRB for their complete review. Written assurance of IRB approval of the Study plan and the informed consent document must be provided to the Sponsor prior to initiation of the Study at the site.
3) Informing a patient of any known risks and potential benefits associated with use of the device, and obtaining written Informed Consent from each Subject prior to enrollment and verifying that the correct and approved IRB version is used. The signed ICF will be maintained in the Subject's medical record, and a copy of the signed ICF will become an integral part of each case report file retained by the investigator. A copy of the signed ICF shall be given to the Subject who signed the ICF.

4) The investigator will review, correct as needed, and sign off on the accuracy and completeness of the data entered on the CRFs. Original laboratory reports, procedure notes, etc. are to be retained by the investigator, and the resulting data shall be entered onto the appropriate CRFs.
5) Permitting monitor to inspect facilities and records.
6) Permitting regulatory inspections of facilities and records, if necessary.
7) Submitting annual progress reports, final reports, and adverse event reports to the IRB/Ethics Committee and to the Sponsor.
8) Returning unused study articles, recording their receipt, disposition, and return.
9) Refraining from promoting study or study articles in any manner that is not authorized by the Sponsor.
10) Conducting study in accordance with the protocol.
11) Tracking Sponsor-provided inventory and assignments.
12) Maintaining medical histories of subjects.

2-8-4-3 IRB/Ethics Committee

The following are the responsibilities of the IRB:

1) Review and approve, modify, or disapprove the study protocol and informed consent form.

2) Receive continuing and final reports on study progress.

2-8-5 Subject Compensation

Subjects will be provided a small stipend for travel and accommodation expenses associated with the study treatment and follow-up requirements. In addition, they will receive the device free of cost.

2-8-6 Physician Compensation

Participating sites will be compensated a reasonable amount, calculated to cover the costs of physician and staff time to enter data and administer the Study.

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7) Stewart WF, Van Rooyen JB, Cundiff GW et al: Prevalence and burden of overactive bladder in the United States. World J Uro 2003; 20: 327.
8) Herschorn S, Gajewski J, Schulz J, et al: A population-based study of urinary symptoms and incontinence: The Canadian Urinary Bladder Survery. BJU Int 2008; 101; 52.
9) Milsom I, Abrams P, Cardozo L et al: How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Intl 2001; 87: 760.
10) Gill BC, Pizarro-Berdichevsky J, Bhattacharyya PK, et al. Real-time changes in brain activity during sacral neuromodulation for overactive bladder. *Journal of Urology*. 2017;198(6):1379-1385. doi:10.1016/j.juro.2017.06.074
11) Elterman D, Ehlert M, De Ridder D, et al. A prospective, Multicenter, international study to explore the effect of three different amplitude settings in female subjects with urinary urge incontinence receiving interstim therapy. *Neurourology and Urodynamics*. 2021;40(3):920-928. doi:10.1002/nau.24648

3 Attachments

3-1 72 Hour Voiding Diary

3-2 OABq HRQL only

3-3 Patient Satisfaction Survey

3-4 End of Study Survey

3-5 Manuals and Labels

Commercial product labeling as approved under the PMA will be used for this study.

3-6 Sponsor Level Informed Consent Template