Original Application for an Investigational Device Exemption

25 August 2020

PIVOTAL STUDY OF SUBCUTANEOUS TIBIAL NERVE STIMULATION WITH eCoin® FOR URGENCY URINARY INCONTINENCE

Device Name: eCoin® (Electroceutical Coin)

IDE Number: G170301

Sponsor & Manufacturer: Valencia Technologies Corporation
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CONFIDENTIAL

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1 Introduction

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1-2 *Overview*

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 (HRQOL) (7). The unpredictable loss of urine and associated odor or related symptoms leads to well documented burden on quality of life. This study will focus on urgency urinary incontinence.

While physical therapy and surgery are relatively effective treatments for stress urinary incontinence, disorders of the detrusor muscle and/or neural regulation of the lower urinary tract system remain quite challenging to treat well. A number of treatments, including first line behavioral therapies and second line medications (anti-muscarinics or oral β_3-adrenoceptor agonists), are available; however, many patients remain in poor control. For those not well treated by behavioral therapy or medications, or intolerant of medications, percutaneous tibial nerve stimulation (PTNS) as well as sacral nerve stimulation (SNS) are approved for marketing by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom and by the Food and Drug Administration in the United States. For PTNS, given the need for maintenance therapy over the long-term (10), the expense of such maintenance visits and waning efficacy of the therapy when conducted in the home (11), the use of a tiny fully-implantable device

is likely to have advantages in implementation. Such advantages may include automated compliance, lower cost over device life compared with long-term visit costs, and improved efficacy through accurate device placement compared with percutaneous administration at home.

1. Burgio KL, Locher JL, Goode PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. Jama 1998;280:1995-2000.
2. Choo MS, Ku JH, Lee JB et al: Cross-cultural differences for adapting overactive bladder symptoms: results of an epidemiologic survey in Korea. World J Uro 2007; **25**: 505.
3. Corcos J and Schick E: Prevalence of overactive bladder and incontinence in Canada. Can J Urol 2004; **11**: 2278.
4. Coyne KS, Sexton CC, Vats V et al: National community prevalence of overactive bladder in the United States stratified by sex and age. Urology 2011; **77**: 1081.
5. Tikkinen, KA, Auvinen A, Tiitinen A. et al: Reproductive factors associated with nocturia and urinary urgency inin women: A population-based study in Finland. Am J Obstet Gynecol 2008: **199**: 153 e1.
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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. Yoong, Wai, et al. "Neuromodulative treatment with percutaneous tibial nerve stimulation for intractable detrusor instability: outcomes following a shortened 6-week protocol." *BJU international* 106.11 (2010): 1673-1676.
11. van der Pal F, van Balken MR, Heesakkers JP, et al: Percutaneous tibial nerve stimulation in the treatment of refractory overactive bladder syndrome: is maintenance treatment necessary? BJU Int 2006, 97(3):547–550.

2 Report of Prior Investigations

2-1 *Prior Publications of Animal Studies*

The underlying science in support of tibial nerve stimulation for treatment of overactive bladder including urgency urinary incontinence has been well described in published scientific literature. For example, in 1966, McPherson demonstrated in a cat model that stimulation of the cut ends of dorsal spinal roots or various peripheral nerves including the posterior tibial nerve can effectively inhibit bladder contractions (12). The hypothesis for this effect was an action of neural circuitry in the forebrain, as intercollicular decerebration or thoracic spinal cord transection abolished the effect (13). In 1980, Sato et al. verified that electrical stimulation of afferent nerves to hind limb muscles, but not cutaneous afferents, inhibited reflex bladder activity in the anesthetized cat (14). Three years later, McGuire and Morrissey used electrical stimulation of the hindquarter nerves to treat detrusor instability in spinal injured nonhuman primates before moving on to demonstrate a similar effect in the clinical setting in 16 patients (15). Case studies on percutaneous tibial nerve stimulation (PTNS) for overactive bladder were then conducted followed by several randomized, controlled trials.

The tibial nerve is a mixed nerve comprised of sensory and motor nerve fibers. It is by action of central afferent fibers that neuromodulation of the tibial nerve works to restore normal control of an imbalanced voiding reflex. The large diameter somatic afferent fibers of the tibial nerve cause inhibition of bladder activity by way of central inhibition of the micturition reflex pathway in the spinal cord or the brain. This action is confirmed by studies in anaesthetized female cats (14). Neuromodulation of the tibial nerve is presumed to improve or restore normal control of an imbalanced voiding reflex by action of the central afferents (12, 17). Thus, the therapy aims to cause detrusor inhibition by acute electrical stimulation of afferent tibial nerve fibers. Interestingly, the same spinal roots (L4-S3) appear to be targeted by both sacral nerve stimulation and tibial nerve stimulation. It appears that stimulation of the sacral roots, sacral nerve, pudendal nerve and tibial nerve all affect central components of the neural circuits controlling the bladder, yet we can deduce some distinctions in the action. Tai et al. showed that short duration stimulation of the tibial nerve causes a persistent post-stimulation inhibition and increase of bladder capacity (18) that is replicated by many tibial nerve clinical studies, yet the effects of sacral nerve stimulation are shown to go away once stimulation is stopped (19).

As the bladder is controlled by sympathetic, parasympathetic, and somatic nervous systems that are regulated by the pontine micturition center (PMC), tibial nerve stimulation is likely to act on the PMC, either via the pelvic nerve or pudendal nerve or both. The pelvic nerve (S2-S4) controls bladder contraction (micturition) while the hypogastric (T10-L2) and pudendal (L4-S3) nerves control continence; stimulation of the large somatic afferent fibers of the tibial nerve, with spinal roots from L4-S3, is postulated to finds its effect on the bladder via either the pelvic or the pudendal nerve.

12. McPherson A. The effects of somatic stimuli on the bladder in the cat. J Physiol. 1966;185(1):185–96.
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17. Vandoninck, Vera, et al. "Posterior tibial nerve stimulation in the treatment of urge incontinence." *Neurourology and urodynamics* 22.1 (2003): 17-23.
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19. Herbison GP, Arnold EP. Sacral neuromodulation with implanted devices for urinary storage and voiding dysfunction in adults. Cochrane Database Syst Rev. 2009; Suppl 2:CD004202. doi:10.1002/14651858.CD004202.pub2
20. Oerlemans, Dennis JAJ, and Philip EV Van Kerrebroeck. "Sacral nerve stimulation for neuromodulation of the lower urinary tract." *Continence*. Springer London, 2009. 217-226.

2-2 *Human Studies*

2-2-1 Prior Publications of Tibial Nerve Stimulation for Overactive Bladder

McGuire et al. (21) first described inhibition of detrusor activity by peripheral neuromodulation of the posterior tibial nerve. More recent authors, such as Govier et al. (22), van Balken et al. (23) and Vandoninck et al. (24), have confirmed a 60–80% positive response rate after 12 weekly treatments with percutaneous tibial nerve stimulation. A meta-analysis by Gaziev et al. (25) showed level 1 evidence is available and supportive of the safety and effectiveness of tibial nerve stimulation for overactive bladder. Data available on the safety of percutaneous tibial nerve stimulation show no major concerns for safety. For example, in the 24 month follow-up study to the SUmiT trial, the authors found no reported treatment related adverse events in the 50 subjects through 24 months (26). Four subjects reported five adverse events with unknown causes (UTI, pulling feeling on feet, bladder pressure, pinched nerve and slow stream).

21. McGuire, E. J., et al. "Treatment of motor and sensory detrusor instability by electrical stimulation." *The Journal of urology* 129.1 (1983): 78-79.
22. Govier, Fred E., et al. "Percutaneous afferent neuromodulation for the refractory overactive bladder: results of a multicenter study." *The Journal of urology* 165.4 (2001): 1193-1198.
23. van Balken, Michael R., et al. "Posterior tibial nerve stimulation as neuromodulative treatment of lower urinary tract dysfunction." *The Journal of urology* 166.3 (2001): 914-918.
24. Vandoninck, Vera, et al. "Posterior tibial nerve stimulation in the treatment of urge incontinence." *Neurourology and urodynamics* 22.1 (2003): 17-23.
25. Gaziev, Gabriele, et al. "Percutaneous tibial nerve stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: a systematic review." *BMC urology* 13.1 (2013): 1.

26. Peters, Kenneth M., et al. "Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial." *The Journal of urology* 183.4 (2010): 1438-1443.
27. Finazzi-Agrò, Enrico, et al. "Percutaneous tibial nerve stimulation effects on detrusor overactivity incontinence are not due to a placebo effect: a randomized, double-blind, placebo controlled trial." *The Journal of urology*184.5 (2010): 2001-2006.
28. Amarenco, G., et al. "Urodynamic effect of acute transcutaneous posterior tibial nerve stimulation in overactive bladder." *The Journal of urology* 169.6 (2003): 2210-2215.
29. Peters, Kenneth M., et al. "Sustained therapeutic effects of percutaneous tibial nerve stimulation: 24-month results of the STEP study." *Neurourology and urodynamics* 32.1 (2013): 24-29.

2-2-2 Prior Studies of the Valencia Technologies eCoin™ System

The eCoin™ system is being tested in an ongoing prospective, multicenter study on 46 subjects in the United States and New Zealand. A review of the available data on both safety and effectiveness of eCoin™ when implanted next to the tibial nerve for treatment of urgency urinary incontinence (UUI) is set forth in subsections 2-2-2-1 and 2-2-2-2.

The Valencia Technologies eCoin™ system was tested in a prospective, multicenter study to confirm the effectiveness and safety of median nerve stimulation using bilateral eCoin™ devices in resistant or drug-intolerant hypertensive human subjects. A review of the data on safety of eCoin when implanted in the periphery subcutaneously is given in subsection 2-2-2-3.

2-2-2-1 Effectiveness of eCoin™ Tibial Nerve Stimulation for UUI

The feasibility study of eCoin™ tibial nerve stimulation enrolled and implanted 46 subjects. Two subjects (08-07 and 07-06) did not complete an adequate baseline diary or follow-up diaries. Age may have been a factor in the inadequate diary completion: both subjects were 78 years old. A third subject (07-17) was explanted prior to receiving treatment (device activation). The following analysis excludes data from those three subjects.

As of the time of this writing, all 43 subjects have reached three months of follow-up—the primary endpoint and the time point for all data presented herein. With an average baseline of 5.25 ± 2.93 urge leaks per day, the average change at 3 months is -3.30± 2.99 (N=43) urge leaks per day. The average percentage change in urge leaks in comparison to baseline is -61%.

Ten of the 43 subjects (23%) showed no urge leaks (i.e., a 100% improvement); 19 (44%) showed at least a 75% improvement in urge leaks, and 30 (70%) showed at least a 50% improvement.

Patient reported outcomes also showed improvement. Specifically, 72% of subjects (31 of 43) report improvement of at least 10 points in their quality of life as measured by the Incontinence Quality of Life Questionnaire (iQoL). Similarly, the average score on the Patient Global Impression of Improvement (PGI-I) scale, which was measured on a scale of 1 to 7 from very much worse to very much better, was 5.44.

In conclusion, the objective diary data and patient reported data show promise for eCoin™ as a treatment of UUI.

2-2-2-2 Safety of eCoin™ Tibial Nerve Stimulation for UUI

The feasibility study of eCoin™ tibial nerve stimulation implanted 46 subjects; the last implantation procedure was performed on October 1, 2017. At the time of this writing, all subjects have had the device implanted for at least six months, where one month is the critical period for the incident of expected related adverse events in a leadless neurostimulator. All subjects have also reached the primary endpoint of 3 months. Per protocol, subjects attend an incision check visit two weeks after implantation. They then attend a visit one month after implantation at which the wound is reviewed again and programming is done. The safety data presented herein reflect all reported and known safety data to date.

Thirteen (13) related adverse events (AEs) and three serious adverse events (SAEs) (one related [SAE#1] and two unrelated [SAE #2 and [SAE#3]) have occurred. For purposes of this section, “related” includes “possibly related” as well as “related”. See table of related adverse events in Attachment 04-32. All the AEs have now been resolved. Subject 01-10’s adverse event of mild swelling and Subject 03-05’s incidence of mild to moderate swelling and ankle pain that were previously reported as ongoing are now resolved.

The related serious adverse event (SAE #1; Subject 07-17) involved severe cellulitis of the subject’s calf secondary to the ankle wrap. See Attachment 04-32 for the SAE report including the hospital report. The subject was admitted to the hospital with infection and given IV antibiotics. The infection was resolved with antibiotics. Nonetheless, the subject desired to have the device explanted, which was done November 1, 2017.

The second serious adverse event (SAE #2) was a limp on the leg where the device was implanted. The subject, a patient who did not respond to the therapy and who had peripheral edema at screening, desired to have the device removed. The device was successfully removed on December 7, 2017. The patient returned for an incision healing check on December 21, 2017. The SAE is now resolved with no sequelae. Both the center and the DSMB later categorized the SAE #2 as unrelated. Subject also had bursitis of the hip, which was inflamed, responded to injections, and later returned once effect of injections had worn off.

The third SAE (SAE#3 of 3) was an unrelated incident of pneumonia that resolved.

Finally, there were two slightly misplaced devices (up to one centimeter) at one New Zealand center noticed by the DSMB during review of photographs taken at the subjects’ healing check visits. An investigation was opened to determine how the misplacements occurred and to decide whether the center should continue implantations. The DSMB determined that the center had not used a measurement tool optimally. In response, the surgical trainer retrained the appropriate PI on this tool, updated and clarified the surgical manual, and communicated with all PIs on the correct use of the measurement tool. The DSMB was satisfied that actions taken would prevent further misplacements and allowed continued implantations at the affected center. The Sponsor believes that

proctoring of all first implants, as done in the United States where no misplacements occurred, provides assurance that all devices will be optimally placed.

In summary, the safety data suggest that the primary concern is mild to moderate wound healing, which resolved in all cases.

2-2-2-3 Safety of eCoin™ Median Nerve Stimulation for Hypertension

The global multicenter feasibility study on hypertension is complete and thus the safety data are available for review and presented herein. Among the 48 subjects with 96 implanted eCoin™ devices, two related Serious Adverse Events (SAEs) (called out as "SAE #1" and "SAE #2" in this Section) occurred.

Nine subjects have experienced inflammation tenderness or redness at the incision site or hand. Four subjects have been treated for an infection at the implant site. One of these infections occurred six months post implant and led to the explant of the device (SAE #1). Three of the four infections occurred at one clinical center which was subsequently shut down at the recommendation of the DSMB. One additional explant of a device occurred at this same center due to an unconfirmed infection (SAE #2). All remaining Adverse Events were judged to be unrelated to the device or therapy.

Attachment 4-12 presents the case report forms for the four reported infections. In addition, a fifth case report form is included for what the DSMB regarded as an infection leading to explant that was not appropriately handled by the center in Ottawa, Canada (Site 12).

The five subjects who had adverse events of infection or were explanted can be summarized as follows: 12-005 reported moderate bilateral device infection resolved with antibiotics; 04-008 reported severe left arm infection treated initially with antibiotics, but ultimately resulting in explantation of device from the left arm; 14-006 self-reported a mild small infection for a few days that resolved on its own; 12-007 reported mild right forearm infection that resolved with antibiotics; and 12-004 reported middle finger cellulitis initially treated with antibiotics, but ultimately resulting in explantation of the device from the right arm. The corresponding adverse event logs, organized according to patient number, are enclosed.

The DSMB investigation into the higher than average infection rate at Site 12 found that the Site was not timely in its filing of adverse event reports; and pointed out that the AE on 12-004 stated that the patient's swollen middle finger was observed on the day of implantation. After discussions with site 12 the DSMB was unconvinced that Site 12 had put in place an effective plan for confronting its high infection rate. The DSMB recommended suspension of implantation at Site 12 (see attached letter from DSMB – Attachment 4-13). After discussions with the Principal Investigator at Site 12, the Company decided to suspend indefinitely any further implantations at Site 12.

2-2-2-4 Conclusions

Adverse events related to the eCoin™ therapy are associated primarily with inflammation or infection at the implant site. In the completed hypertension feasibility study on 48 subjects with bilateral implants, two subjects had related SAEs (one infection and one unconfirmed infection), both of which were resolved by explant of the device.

In the ongoing OAB feasibility study on 46 subjects, all subjects have been followed at least six months post-operatively and the safety results appear slightly better than the

aforementioned hypertension study. One subject had a related SAE (severe cellulitis of the calf secondary to ankle wrap provided for post-operative care), and two subjects had unrelated SAEs (one pneumonia and one limp associated with underlying bursitis of the hip and peripheral edema present at screening). The other adverse events were associated primarily with wound healing, all of which were resolved.

2-3 *Executive Summary of Non-Clinical Studies*

Preclinical testing of the eCoin™ subcutaneous neuromodulation system has been performed to assure conformance to the design specifications.

The eCoin™ subcutaneous neuromodulation system was developed under an ISO 14971:2012 compliant risk management process to identify potential harms and to eliminate risk or reduce risks to an acceptable level.

2-3-1 Bench Testing - eCoin™ Device

The eCoin™ device is designed to be compliant with all applicable clauses of ISO 14708-1:2014 Implants for surgery – Active implantable medical devices – Part 1: General requirements for safety, marking and for information to be provided by the manufacturer and ISO 14708-3:2008 Active implantable medical devices -- Part 3: Implantable neurostimulators.

2-3-1-1 Stimulus Output (207-1093 2.2.1-2.2.5, 2.3.1; 207-1082 2.1-2.5, 2.8)

The stimulation output pulse amplitude, current regulation (at loads of 300, 600, 1000, 1500, and 2500 Ohms), pulse width and pulse rate of the eCoin™ device were verified at room temperature, 20 °C, and 45 °C and over battery voltages of 2.7 V, 3 V and 3.2 V.

Folder: “VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports”

File: “004_207-1093 SNS Design Verification Test Report.” Refer to Sections 2.2.1-2.2.5 and 2.3.1.

File: “003_207-1082 SNS PCBA Verification Test Report.” Refer to Sections 2.1-2.5 and 2.8.

2-3-1-2 Internal Moisture (207-1093 2.3.2, 2.3.3)

Residual gas analysis was performed to verify the internal moisture of the hermetically sealed eCoin™ device is no more than 1.5%. This test was repeated on eCoin™ devices after 24 hour water immersion at 80 °C water and a pressure of 2 atm.

Folder: “VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports”

File: “004_207-1093 SNS Design Verification Test Report.” Refer to Sections 2.3.2 and 2.3.3.

2-3-1-3 Temperature Exposure (207-1093 2.3.4, 202-1254)

The eCoin™ device in a sterile pack passed final functional test after one hour of temperature exposure at -10 °C and 55 °C per ISO 14708-3 clause 26.2. In addition as part of the packaging validation, eCoin™ devices passed functional test after exposure to climatic conditioning per ASTM D4332-13.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.4.

Folder: "VOL_020_IDE Attachment 4-18 Sterile Packaging Validation Report"

File: "001_4.18 202-1254 SNS Device Packaging Validation Report"

2-3-1-4 Pressure Exposure (207-1093 2.3.5)

The eCoin™ device passed final functional test after one hour of pressure exposure at 70 kPa and 150 kPa per ISO 14708-1:2014 clause 25.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.5.

2-3-1-5 Random Vibration (207-1093 2.3.7)

The eCoin™ device passed final functional test after random vibration at 5 Hz to 500 Hz for 30 minutes in each of three mutually perpendicular axes per ISO 14708-1:2014 clause 23.2.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to section 2.3.7.

2-3-1-6 Mechanical Shock (207-1093 2.3.8)

The eCoin™ device passed final functional test after mechanical shock per ISO 14708-1:2014 clause 23.7 (1 ms duration 500 g half-sine).

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.8.

2-3-1-7 Mechanical Squeeze Test (207-1093 2.3.9)

The eCoin™ device passed final functional test following a ten minute exposure to a force of 45 N applied to the top center of the device over an area of 0.5 cm squared.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.9.

2-3-1-8 Battery UL Testing (EA1821)

The eCoin™ device battery passed testing per UL 1642 5th edition including short circuit (room temperature and 55 °C), abnormal charging, crush, impact, shock, vibration, heating, temperature cycling, low pressure and projectile.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "013_EA1821_RPT_Valencia CR1612_UL1642."

2-3-1-9 Battery External Short Test (207-1093 2.3.12)

The eCoin™ device battery under an external short circuit fault condition was verified to generate less than a 2 °C temperature rise at the device surface when implanted subcutaneously (ISO 14708-3:2008 clause 17.1).

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.12.

2-3-1-10 Electrocautery Immunity Test (207-1093 2.3.13)

The eCoin™ device passed final functional test following a 10 second exposure to a conducted 500 kHz sine wave delivering 10 V peak to peak between the anode and cathode approximating the signal from monopolar electrocautery applied no closer than 25 cm from the eCoin™ device.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.13.

2-3-1-11 Corrosion Test (207-1093 2.4.1)

No corrosion of the eCoin™ case, feed through anode or cathode in phosphate buffered physiological saline at 37 °C was observed after continuous stimulation at maximum amplitude until battery depletion.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.4.1.

2-3-1-12 Battery Service Life and Elective Replacement (207-1082 2.6, 2.7; 201-1016, 201-1111)

The eCoin™ battery discharge current and accelerated battery discharge capacity at 37 °C were used to verify a 2 year service life at nominal amplitude after a 12 month shelf life and a 1 year elective replacement at the maximum amplitude after a 12 month shelf life.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File 1: "003_207-1082 SNS PCBA Verification Test Report." Refer to Sections 2.6 and 2.7.

File 2: "022_ER 201-1016 Rev 1 - CR1612 Battery"

File 3: "023_ER 201-1111 Rev 1 – CR1612 Battery Discharge Capacity RIR 419-356"

2-3-1-13 Accelerated Life Test (207-1082 2.9)

The eCoin™ electronics assembly (PCBA) passed final functional test following a highly accelerated life test (HALT) at 125 °C for 1000 hours while under power with a supply voltage of 3.2 volts.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "003_207-1082 SNS PCBA Verification Test Report." Refer to Section 2.9.

2-3-1-14 Temperature Cycling Test (207-1082 2.10)

The eCoin™ electronics assembly (PCBA) passed final functional test following temperature cycling test per MIL-STD-883H Method 1010, Condition B (10 cycles, -55 +0/-10 degrees Centigrade to 125 +15/-0 degrees Centigrade, 10 minute dwell time minimum).

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "003_207-1082 SNS PCBA Verification Test Report." Refer to Section 2.10.

2-3-1-15 Laser Seam Weld Validation (202-1436)

The eCoin™ device laser seam weld process was validated (IQ, OQ, PQ) to demonstrate that it produces a reliable hermetic seam weld. Acceptance criteria included visual inspection, fine leak, gross leak and cross section for weld penetration.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "001_202-1436 PVR SNS Device Seam Weld Top Cover and Feed thru Case."

2-3-2 Bench Testing External Controller

The External Controller is designed to be compliant with all applicable clauses of AAMI / ANSI ES60601-1:2005/(R) 2012 and A1:2012, c1:2009/(R) 2012 and a2:2010/(r) 2012 (consolidated text) Medical Electrical Equipment – Part 1: General requirements for basic safety and essential performance, IEC 60601-1-2:2014 Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic disturbances - Requirements and tests.

2-3-2-1 External Controller Output (207-1541 4.2.1- 4.2.8)

The External Controller was verified to meet all output command and command data transmission and timing requirements.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "005_207-1541 SNS External Controller Verification Test Report." Refer to Sections 4.2.1 – 4.2.8.

2-3-2-2 External Controller Battery Discharge and Charge Time (207-1541 4.2.9, 4.2.10)

The External Controller was verified to provide at least 7 days of standby operation and 15 minutes of transmit operation on a single battery charge. The External Controller charging with fully discharged battery was verified to complete within 6 hours.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "005_207-1541 SNS External Controller Verification Test Report." Refer to Sections 4.2.9 and 4.2.10.

2-3-2-3 External Controller Battery Safety Testing (RSZBHST 160325326, VTC-002A (IEC 60950-1 4.3.8), 207-1541 4.2.11 – 4.2.13, 4.2.15)

The External Controller rechargeable Li-polymer battery has undergone safety testing and passed per IEC62133:2012. In addition, the battery protection circuitry for over-charging, over-discharge, and over-heating were verified to operate as specified. Battery short-circuit protection was verified to operate as specified and also passed testing per IEC 60950-1 4.3.8.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File 1: "014_005_RSZBHST 160325326."

File 2: "021_External Controller Safety Testing VTC_002A IEC 60601-1 3rd ed Ec01 Remote."

File 3: "005_207-1541 SNS External Controller Verification Test Report." Refer to Sections 4.2.11 – 4.2.13 and 4.2.15.

2-3-2-4 External Controller Over-heat Shutdown (207-1541 4.3.2, 4.3.3)

The External Controller has been verified to shut-down transmission if the temperature of the device exceeds 48 °C.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "005_207-1541 SNS External Controller Verification Test Report." Refer to Sections 4.3.2 and 4.3.3.

2-3-2-5 External Controller IEC 60601-1 (VTC-002A)

The External Controller has passed applicable clauses of IEC 60601-1: 2005 + CORR. 1 (2006) + CORR. 2 (2007) + AM1 (2012) or IEC 60601-1: 2012. This includes clauses 5.7 Humidity, 8.7 Leakage Current, 8.8.3 Dielectric Strength, 8.8.4.1 Enclosure Ball Pressure Test, 11.1.1 Excessive Temperatures, 11.6.1 Cleaning, Sterilization Disinfection and 15.3 Mechanical Strength (Push, Drop and Mould Stress Relief).

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "021_External Controller Safety Testing VTC_002A IEC 60601-1 3rd ed Ec01 Remote"

File Attachments: "017_External Controller Safety Testing VTC-002A Attachment A Photographs;" "018_External Controller Safety Testing VTC-002A Attachment B Schematics;" "019_External Controller Safety Testing VTC-002A Attachment C Calibration;" and "020_External Controller Safety Testing VTC-002A Attachment D Specifications."

2-3-3 MR Compatibility

The eCoin™ Subcutaneous Neuromodulation System has been evaluated for safety and compatibility in the MRI environment and is considered MRI Conditional. Patients with the eCoin™ implant can safely undergo Magnetic Resonance Imaging (MRI) for head, neck, or shoulder so long as the device remains outside of the machine and in magnetic fields of less than or equal to 152 ± 10 Gauss/cm. Additional details can be found in the eCoin MR Labeling.

2-3-4 Electrical Safety and Electromagnetic Compatibility

2-3-4-1 Electromagnetic Non-Ionizing Radiation Immunity (SD72116479-0516, 207-1093 2.3.6)

The eCoin™ device passed final functional test after and remained immune during exposure to electromagnetic non-Ionizing radiation per ISO 14708-3 Clause 27.

Folder: "VOL_018_IDE 4-16 Design Verification and Validation Reports"

File 1: "016_SD72116479-0516-0516 CISPR 11 Class B ESD and ISO14708-3 Test Report." Refer to Section 4.

File 2: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.6.

2-3-4-2 Current Leakage (207-1093 2.3.10)

The direct current leakage between the anode and cathode of the eCoin™ was verified to be less than less than 0.75 microamperes / square millimeter of electrode surface per ISO 14708-3 clause 16.2. Notes: For a direct current leakage less than 1 microampere, the 4.0 ±0.2mm diameter cathode current density is less than 0.08 microamperes per mm-squared. The cathode is worst case since it has a smaller surface area than the anode.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.10.

2-3-4-3 Insulation Leakage (207-1093 2.3.11)

After preconditioning by total immersion into 9 g/l saline at 37 °C for at least 10 days, the eCoin™ insulation at maximum stimulation amplitude was verified to be greater than 3.3 kOhm based on no more than a 10% reduction in amplitude when the load is reduced from 600 Ohms to 300 Ohms (measured greater than 30 kOhm).

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.11.

2-3-4-4 Electrostatic Discharge (SD72116479-0516)

The eCoin™ device passed final functional test and demonstrated safe operation after exposure to electrostatic discharge per IEC 61000-4-2 up to ± 8 kV direct contact and up to ± 15 kV air discharge.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "016_SD72116479-0516 CISPR 11 Class B ESD and ISO14708-3 Test Report." Refer to Section 3.1.

2-3-5 Electrical Safety and EMC External Controller

2-3-5-1 Electromagnetic Emissions and Non-Ionizing Radiation Immunity (SD72110544-1015)

The External Controller has undergone testing and passed EMC emissions and immunity per IEC 60601-1-2:2014. This includes radiated and conducted emissions per CISPR 11 Class B, harmonic current emissions per EN61000-3-2 Class A and voltage fluctuations and flicker per EN 61000-3-3. Immunity testing includes electrostatic discharge per IEC 61000-4-2, amplitude modulated RF EM fields per IEC 61000-4-3, proximity RF fields from wireless communication equipment per IEC 61000-4-3, electrical fast transients per IEC 61000-4-4, surge per IEC 61000-4-5, RF common mode per IEC 61000-4-6, power magnetic field of 30 A/m at 50Hz and 60 Hz per IEC 61000-4-8 and voltage dip and interruptions per IEC 61000-4-11.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "015_SD72110544-1015 External Controller EMC Test Report." Refer to Section 3.

2-3-6 Software eCoin™ Device (209-1035, 209-1061, 303-1122)

The level of safety concern for the eCoin™ device firmware is Moderate since a failure or latent design flaw could directly result in a minor injury to the patient by leading to uncomfortable levels of stimulation and/or the need for premature device explant.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports**"**

File 1: "006_209-1035 SNS Firmware Verification Test Report"

File 2: "007_209-1061 Firmware Unit Test Report" (plus 008_209-1061 Appendix A & 009_209-1061 Appendix B)

File 3: "024_209-3264 Rev 1 - SNS Firmware Verification Test Report OAB"

Folder: "VOL_028_IDE Attachment 4-26 303-1122 Software Design Specification SNS**"**

File: "001_4.26 303-1122 Software Design Specification SNS."

2-3-7 Software External Controller (207-1541, 303-1122)

The level of safety concern for the External Controller firmware is Minor since its function is limited such that a failure or design flaw is unlikely to cause any injury to the patient or operator. Verification and validation testing has been completed with all software design requirements met.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports**"**

File: "005_207-1541 SNS External Controller Verification Test Report."

Folder: "VOL_028_IDE Attachment 4-26 303-1122 Software Design Specification SNS**"**

File: "001_4.26 303-1122 Software Design Specification SNS."

2-3-8 Biocompatibility

2-3-8-1 Cytotoxicity ISO 10993-5 (PBL 14E0355G-M01G)

Based on the qualitative evaluation of cells exposed to eCoin™ test article extract, the eCoin™ test article was not considered to have a cytotoxic effect (no reactivity).

Folder: "VOL_029 IDE Attachment 4-27 Biocompatibility Reports**"**

File: "001_Cytotoxicity Pacific BioLabs Study No. 14E0355G-M01G."

2-3-8-2 Sensitization ISO 10993-10 (PBL 14H0049G-X01G)

Under the conditions of the study, the eCoin™ test article did not elicit sensitization reactions.

Folder: "VOL_029_IDE Attachment 4-27 Biocompatibility Reports**"**

File: "002_Report Sensitization Pacific BioLabs Study No 14H0049G-X01G."

2-3-8-3 Irritation ISO 10993-10 (PBL 14H0048G-X01G)

Based on erythema and edema scores, no irritation was noted with the eCoin™ test article when compared to control. Under the conditions of the study, the eCoin™ test article met the requirements for the Intracutaneous (Intradermal) Reactivity Test.

Folder: "VOL_029_IDE Attachment 4-27 Biocompatibility Reports**"**

File: "003_Irritation Pacific BioLabs Study No 14H0048G-X01G."

2-3-8-4 Acute Systemic Toxicity ISO 10993-11 (PBL 14H0051G-X01G)

None of the animals treated with eCoin™ test article extract exhibited a greater biological activity when compared to those treated with the control. Under the conditions of the study, the eCoin™ test article met the requirements of ISO 10993-11.

Folder: "VOL_029_IDE Attachment 4-27 Biocompatibility Reports**"**

File: "004_Acute Systemic Toxicity Pacific BioLabs Study No 14H0051G-X01G."

2-3-8-5 Sub-Chronic Systemic Toxicity 90 Day ISO 10993-6 (PBL 16C0069G-X01G)

The results suggest that the device, when implanted subcutaneously, was well-tolerated in male and female Sprague Dawley rats over a period of 94 days. There was no evidence of test article effect on body weights and body weight changes. Changes in several hematology and clinical chemistry parameters that reached statistical significance were not considered test article related because they appeared to be sporadic and values were within the normal range typical for this animal species. There were no statistically significant differences in coagulation factors.
There were no microscopic observations in the systemic tissues or organs of male and female rats that were considered to be related to the subcutaneous implantation of the test article. There were two notable lesions that were identified macroscopically in two female rats from the test group; a lump present near the implant site (Animal #13) and right eye opacity (Animal # 12). The lesion near the implant site observed in one female animal was identified as M-adenocarcinoma of mammary gland and was considered incidental. The ocular changes observed in Animal #12 were considered to be of a traumatic etiology. The local, subcutaneous tissue response to both the control article and test article was comparable for male and female rats as characterized primarily by fibrosis, neovascularization, and cellular infiltrates.

Folder: "VOL_029 IDE Attachment 4-27 Biocompatibility Reports**"**

File: "005_Sub-chronic Toxicity Pacific BioLabs Study No. 16C0069G-X01G."

2-3-8-6 Genotoxicity ISO 10993-3 (PBL 14E0349G-X01G, 16E0213G-X01G)

Based on the criteria and conditions the Bacterial Mutagenicity Test (Ames Assay) used, the eCoin™ test article was considered non-mutagenic. In a ISO 10993-3:2014 compliant mouse lymphoma assay, the mutant frequencies and cloning efficiencies of preparations treated with the eCoin™ test article were within limits defined for a negative response. Accordingly, the eCoin™ is considered to be non-mutagenic and non-clastogenic in the mouse lymphoma assay test system.

Folder: "VOL_029 IDE Attachment 4-27 Biocompatibility Reports**"**

File 1: "006_Genotoxicity AMES PBL No 14E0349G-X01G."

File 2: "007_Genotoxicity Mouse Lymphoma 16E0213G-X01G."

2-3-8-7 Implantation 90 Day ISO 10993-6 (PBL 14E0356G-X01G)

Under the conditions of the study, the eCoin™ test article was considered a non-irritant to the tissue as compared to the negative control article.

Folder: "VOL_029 IDE Attachment 4-27 Biocompatibility Reports**"**

File: "008_Implantation Pacific BioLabs Study No. 14E0356G-X01G."

2-3-8-8 Pyrogen - Material Mediated ISO 10993-11 (PBL 16C0182G-X01G)

The test was performed according to ISO 10993-11 and USP <151> guidelines. All animals appeared healthy during the test and none of the tested rabbits exhibited individual increase in temperature greater or equal to 0.5°C when compared to the control temperature. Based on criteria for this test, the test article meets USP <151> requirements for the absence of pyrogens.

Folder: "VOL_029_IDE Attachment 4-27 Biocompatibility Reports**"**

File: "009_Material-Mediated Pyrogenicity 16C0182G-X01G."

2-3-8-9 Ethylene Oxide Sterilization Residuals ISO 10993-7 (Nelson 749416)

The ethylene oxide residual for the eCoin™ device was less than 0.012 mg (1.2 micrograms per centimeter squared of device surface area). The ethylene chlorohydrin residual for the eCoin™ device was less than 0.038 mg (3.8 micrograms per centimeter squared of device surface area). Both of these are within the ISO 10993-7 limit for permanent implants and the tolerable contact limit.

Folder: "VOL_029_IDE Attachment 4-27 Biocompatibility Reports**"**

File: "010_EO Residuals 749416 8XL."

2-3-9 Particulate (Nelson Lab Number 884283-01)

The eCoin™ device particulate counts meet requirements per ISO 14708-1:2014 clause 14.2.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports**"**

File: "010_884283-S01 Particulate Test."

2-3-10 Sterility (2002-1206)

The eCoin™ device ethylene oxide sterilization process was validated per ISO 11135 using half cycle batch release approach with the over kill method (ISO 11135-1:2007(E) Annex B).

Folder: "VOL_019_IDE Attachment 4-17 Ethylene Oxide Sterilization Validation Reports**"**

File: "001_Ethylene Oxide Sterilization Validation Reports"

2-3-11 Packaging (202-1254; Westpak 225-15-0053A)

Validation of the eCoin™ device packaging demonstrated that the integrity of the final package is maintained under the severities of distribution, storage and handling. After 3x (worst case) sterilization, baseline samples were tested for seal strength per ASTM F88M:2009 and seal integrity per ASTM F1886-09. Remaining samples underwent climatic conditioning followed by shipping and handling testing per ASTM D4169-14. Zero-aged samples were then tested for seal strength per ASTM F88M:2009 and seal integrity per ASTM F1886-09. Remaining samples underwent accelerated and real time shelf-life aging (see 2-3-12).

Folder: "VOL_020_IDE Attachment 4-18 Sterile Packaging Validation Report**"**

File 1: "001_202-1254 SNS Device Packaging Validation Report."

File 2: "003_Appendix B Test Lab Report No 225-15-0053A"

2-3-12 Shelf Life (202-1254; Westpak 225-15-0053B, 225-15-0053C)

Accelerated and real time aging of the eCoin™ device and its packaging demonstrated that the integrity of the final package and device functionality is maintained over the 1 year device shelf-life. Accelerated aging equivalent to a 13 month shelf life was completed per ASTM F1980-07. Real-time aging for 13 months was completed at ambient conditions (approximately 25 °C and 50% relative humidity). After aging, packaging samples were then tested for seal strength per ASTM F88M:2009 and seal integrity per ASTM F1886-09 and the eCoin™ device underwent final functional testing.

Folder: "VOL_020_IDE Attachment 4-18 Sterile Packaging Validation Report**"**

File 1: "001_202-1254 SNS Device Packaging Validation Report"

File 2: "004_Appendix C Test Lab Report No 225-15-0053B."

File 3: "005_Appendix C Test Lab Report No 225-15-0053C 13 Month Real Time Aging of the SNS."

3 Investigational Plan

3-1 *Purpose*

This investigation is designed as a pivotal study of the safety and effectiveness of the Valencia Technologies eCoin™ system in the treatment of urgency urinary incontinence. This study is designed to develop sufficient safety and effectiveness data to be incorporated in a Pre-Market Approval Application.

Valencia Technologies Corporation, the Sponsor, manufactures the study device, eCoin™ (electroceutical coin). eCoin™ is an investigational device to be utilized in the treatment of patients with urgency urinary incontinence (UUI).

Up to 135 subjects, with a target of 120 subjects will be consented and enrolled to participate in the study. Only subjects meeting all inclusion and exclusion criteria will be enrolled.

Each person will participate in the study for up to 63 weeks (up to 15 weeks between screening and device activation plus 48 weeks of follow-up).

The primary aims are to evaluate the safety and effectiveness of eCoin™ for the treatment of UUI.

3-2 *Summary*

This prospective, multicenter, single-arm trial will evaluate the safety and effectiveness of eCoin™ tibial nerve stimulation in subjects with urgency urinary incontinence (UUI) as defined by the American Urological Association (30). The study will evaluate changes from baseline in OAB symptoms as measured by voiding diaries and patient-reported outcomes through 48 weeks of eCoin™ therapy (which is the same as 52 weeks from study device implantation). The primary outcome will be measured at 48 weeks of eCoin™ therapy; the key secondary outcomes will be measured at 24 weeks of eCoin™ therapy. Safety will be summarized by data on reportable adverse events and device deficiencies.

The eCoin™ neuromodulation device will be implanted subcutaneously in the right or left leg of subjects with UUI. After a 4 week implant healing period, all subjects will have a programming visit where the device is activated (turned ON). After 48 weeks (occurring about 52 weeks post-implant), the primary effectiveness and primary safety endpoints will be assessed.

30. American Urological Association, OVERACTIVE BLADDER DIAGNOSIS AND TREATMENT OF OVERACTIVE BLADDER IN ADULTS AUASUFU Guideline (2012); Amended (2014).

3-3 *Protocol*

3-3-1 Study Design

This trial is a prospective, multicenter, single-arm study of the safety and effectiveness of eCoin™ tibial nerve stimulation in subjects having UUI.

Subjects will be screened. Up to 135 subjects, with a target of 120 subjects, who meet all inclusion and exclusion criteria will be enrolled to participate. All subjects will be scheduled to receive the investigational therapy (eCoin™ for UUI).

This document may refer to eCoin™ as "eCoin™," "eCoin™ therapy", the "eCoin™ system," or the "study device." All such terms refers to the active study device called eCoin™ by the manufacturer.

3-3-2 Subject Selection

3-3-2-1 Patient Population

The primary sample size target is 120 subjects having UUI. For enrollment, eligible subjects will be consented and 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 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 investigator will select the side of implantation. Approximately 4 weeks post implantation, subjects will return for a programming visit at which time the device will be activated. A programming technician will implement the activation procedure, setting amplitude of stimulation according to the upper level of a subject's comfort.

3-3-2-2 Selection Criteria

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

3-3-2-2-1 *Inclusion Criteria*

1. Women and men between 18 and 80 years old.
2. Diagnosis of overactive bladder with urgency urinary incontinence or mixed urge and stress incontinence with a predominant urgency component (self-reported), for at least 6 months.
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 gives written informed consent.
5. Individual is mentally competent and able to understand all study requirements.
6. Individual is willing and able to complete a 3-day voiding diary and quality of life questionnaire.

7. Individual is without pharmacological treatment of overactive bladder (antimuscarinics and β3-adrenoceptor agonists) for 2 weeks prior to baseline or longer if the investigator judges that the therapeutic effect is still present.
8. Individual is intolerant of or has an inadequate response to any of anticholinergics, β3-adrenoceptor agonists, onabotulinumtoxinA, or percutaneous tibial nerve stimulation.

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3-3-2-2-2 *Exclusion Criteria*

1. Individual has predominantly stress urinary incontinence with more than 1/3 stress urinary incontinent episodes when compared to total urinary incontinent episodes.
2. Individual has clinically significant bladder outlet obstruction. (Suspected bladder outlet obstruction will be initially assessed by uroflow study with those having a maximum flow rate < 15mL/s requiring additional evaluation.)
3. Individual has clinically significant pelvic organ prolapse beyond the hymenal ring.
4. Individual has had a prior anti-stress incontinence operation within the last year.
5. Individual has known polyuria.
6. Individual has significant lower urinary tract pain or has been diagnosed with interstitial cystitis or bladder pain syndrome.
7. Individual has abnormal post void residual (i.e., greater than 200 cc initially and on repeat testing after double voiding).
8. Individual has clinically significant urethral stricture disease or bladder neck contracture. (Suspected disease or contracture will be initially assessed by uroflow study with those having a maximum flow rate < 15mL/s requiring additional evaluation.)
9. Individual has an active urinary tract infection at time of enrollment.
10. Individual has recurrent urinary tract infections defined as 4 or more UTI's in the last 12 months.
11. Individual has peripheral arterial disease.
12. Individual has chronic venous insufficiency with a history of skin change (hyperpigmentation, lipodermatosclerosis, ulceration) in the ankle region.
13. Individual has morbid obesity and in the opinion of the investigator is not a good candidate for the study.
14. Individual has had diagnosis of bladder, urethral, or prostate cancer.
15. Individual has neurogenic bladder dysfunction.
16. Individual is taking an alpha-blocker for benign prostatic hyperplasia.
17. Individual is pregnant or intends to become pregnant during the study.
18. Individual is breast feeding or is less than 9-months post-partum.
19. Individual is participating or intends to participate in another interventional clinical study during this study.
20. Individual has the presence of urinary fistula, bladder stone, or interstitial cystitis.

21. Individual has uncontrolled diabetes mellitus (Hemoglobin A1C>7) or diabetes with significant peripheral complications. (Uncontrolled diabetes will be ruled out by blood test excluding those with Hemoglobin A1C>7).
22. Individual has an implantable neurostimulator, pacemaker, or implantable cardiac defibrillator (ICD).
23. Individual has been previously treated with sacral nerve stimulation.
24. Individual has been treated with onabotulinumtoxinA in the previous 9 months prior to enrollment.
25. Individual has been treated with percutaneous tibial nerve stimulation (PTNS) within the previous 4 weeks prior to enrollment or more time if the principal investigator judges that the therapeutic effect is present.
26. Individual is currently using transcutaneous electrical nerve stimulation (TENS) in the pelvic region, back, or legs.
27. Individual is aware that he or she will need an MRI scan during the study period.
28. Individual has a clotting or bleeding disorder and in the opinion of the investigator is not a good candidate for the study (antiplatelet and anticoagulant therapy may be continued or held at the discretion of the investigator).
29. Individual has a clinically significant peripheral neuropathy.
30. Individual has nerve damage that could impact either the tibial nerve or pelvic floor function.
31. Individual is neutropenic or immune-compromised.
32. Individual has had previous surgery and/or significant scarring at the implant location.
33. Individual has pitting edema at implant location ($\geq$ 2+ is excluded).
34. Individual has ongoing dermatologic condition at the implant site, including but not limited to dermatitis and autoimmune disorders.
35. Individual has inadequate skin integrity or any evidence of an infection or inflammation in either lower leg.
36. Individual has a history of infection in the involved lower leg.
37. Individual has varicose veins and is symptomatic.
38. Individual has varicose veins in the involved lower leg or both lower legs.
39. Individual has bladder stones or neoplasia. (Suspected bladder stones or neoplasia will be ruled out with a urine dipstick showing no more than trace blood.)
40. In the opinion of the investigator, Individual is not a good candidate for participation in the study.

3-3-3 Ethical Considerations

This study involves no critical ethical issue. Subjects who are refractory to second or third line therapy have the potential to gain a new treatment modality through participation in the study and to assess the impact of this treatment modality on their incontinence with minimal risk.

- All subjects will receive tibial nerve stimulation with the eCoin™ device for 48 weeks offering them an opportunity to try an investigational therapy that might provide benefit.

- While other device modalities are more invasive (i.e., sacral neuromodulation or botulinum toxin of the bladder) and drug therapy is fraught with poor compliance, as an investigational device, the study will only include patients who have an inadequate response to second or third line therapies.
- Some subjects may not receive clinical benefit from eCoin™ therapy, but are to continue with follow-up until study completion even if they ask for eCoin™ to be explanted. Some individuals who initially do not receive clinical benefit may benefit from late response and cumulative effects of treatment.
- 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.

3-4 *Study Procedures*

All subjects will be followed for 48 weeks post-activation (which is the same as 52 weeks post-implantation). A 3-day voiding diary will be collected that reports the number and type of incontinence episodes, number of micturitions; and administering questionnaires including the OABq, and PGI-I at 4, 8, 12, 24, 36, and 48 weeks post-activation.

The follow-up study visits are described in relationship to the initial activation visit occurring 4 weeks after implantation of the study device. Thus, 52 weeks post-implantation occurs at the 48 weeks post-activation visit, and 28 weeks post-implantation occurs at the 24 weeks post-activation visit. See Visit Overview 3-4-2 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.

All subjects are expected to remain free of pharmacological medications for overactive bladder, unless medically necessary, until the primary endpoint is measured at 48 weeks post-activation. Subjects who are taking pharmacologic medication at screening should be washed off OAB medications for a period of 2 weeks prior to the baseline visit.

All subjects will either be explanted after the study visit at 48 weeks post-activation, or, if they consent to extended follow up, they will be explanted shortly after their 96 week post-activation visit or their 144 week post-activation visit.

COVID-19 Considerations

Due to the COVID-19 pandemic, subjects may not be able or would be at risk coming in to the investigational site for remaining follow up visits. As an alternative, subjects may complete remote visits, in which all study activities can be performed with the exception of taking vitals. The patient will electronically transmit their diary and OABq responses to the investigational site personnel, through either pictures, scans, or fax, and review all other items over the phone. 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.

3-4-1 Recruitment Plans

Investigators will identify patients who are currently 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. A member of the site's clinical research team shall assess whether the individual seems suitable for the study. The patient should have a medical history of overactive bladder

with urgency urinary incontinence. Patients with urgency urinary incontinence who appear to meet the inclusion/exclusion criteria from medical records will be contacted by the Investigator or designated study staff and presented with the opportunity to participate in the study, including:

- reason for being identified (OAB with urgency urinary incontinence)
- description of therapy
- potential benefits
- potential risks
- compensation (see 3-11-6)

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

3-4-2 Visit Overview

The ordered enrollment process consists of screening (including obtaining written consent), completing the baseline evaluation, implanting the eCoin™ system, and establishing the participant's amplitude setting. This Section includes a table of the visit schedule and contents thereof. The timing of visits 1 through 4, 12 and 13, is described in relationship to the visit named, while the timing of visits 6 through 11 is described in relationship to the initial activation visit (Visit 5). A revision procedure would not reset the initial activation date.

For visits involving a 3-day diary, the diary should be completed over 3 consecutive days during the 7 days prior to each indicated visit. The site should give patients a telephone call to remind them of the diary requirement at least 3 days prior to each follow-up visit.

- Visit 1: Screening Procedures (informed consent, urinalysis, PVR, history and physical examination, subjects begin 2 week wash-off of OAB medications if applicable, concomitant medication therapy review, eligibility determination)
- Visit 2: Baseline Assessments (3-day voiding diary, OABq, subject receive TENS instructions, final eligibility determination) (Time: Between 3 and 28 days from Visit 1)
- Visit 3: Implant Procedure (Return of 3-day voiding diary completed alongside TENS, adverse event assessment, concomitant therapy review, patient surveys including OABq, patient satisfaction, and patient global impression of improvement, return of the TENS unit, pre and post-op pictures) (Time: Between 7 and 35 days from Visit 2)
- Visit 4: Incision Healing Check (week 2) (Time: Between 9 and 19 days from Visit 3) including pictures
- Visit 5: Initial Activation (week 4) (Time: Between 23 and 43 days from Visit 3) including pictures
- Visit 6 (4 weeks post-activation): Follow-up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including OABq, patient satisfaction, and patient global impression of improvement) (Time: Between 23 and 33 days from Visit 5)
- Visit 7 (8 weeks post-activation): Follow-up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including OABq, patient satisfaction, and patient global impression of improvement) (Time: Between 51 and 61 days from Visit 5)
- Visit 7b (8 weeks post-activation): Second programming to make any adjustments (Time: Between 51 and 68 days from Visit 5; Visit 7b may occur on the same day as Visit 7 or about one week following Visit 7)
- Visit 8 (12 weeks post-activation): Follow-up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including OABq, patient satisfaction, and patient global impression of improvement) (Time: Between 79 and 89 days from Visit 5)

- Visit 9 (24 weeks post-activation): Follow-up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including OABq, patient satisfaction, and patient global impression of improvement) (Time: Between 163 and 173 days from Visit 5)
- Visit 9b (24 weeks post-activation, described elsewhere as 28 weeks post-implantation): Third programming to make any adjustments (Time: Between 163 and 180 days from Visit 5; Visit 9b can occur on the same day as Visit 9 or about one week following Visit 9)
- Visit 10 (36 weeks post-activation): Follow-up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including OABq, patient satisfaction, and patient global impression of improvement) (Time: Between 247 and 257 days from Visit 5)
- Visit 10b (36 weeks post-activation): Fourth programming to make any adjustments (Time: Between 247 and 264 days from Visit 5; Visit 10b can occur on the same day as Visit 10 or about one week following Visit 10)
- Visit 11 (48 weeks post-activation, described elsewhere as 52 weeks post-implantation): Follow-up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including OABq, patient satisfaction including final study questionnaire, and patient global impression of improvement) May be done remotely if necessary with consideration to COVID-19. (Time: Between 331 and 341 days from Visit 5)
- Visit 12 (For subjects who consent to extended follow up and have their device in place at 2 years) (96 weeks post-activation): Follow-up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including OABq, patient satisfaction, and patient global impression of improvement) (Time: Between 662 and 682 days from Visit 5)
- Visit 13 (For subjects who consent to extended follow up and have their device in place at 3 years) (144 weeks post-activation, described elsewhere as 52 weeks post-implantation): Follow-up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including OABq, patient satisfaction, and patient global impression of improvement) (Time: Between 998 and 1,018 days from Visit 5)
- Visit 14: Explant Visit (Time for those not consenting to follow up through 3 years: Between 0 days and 15 days from Visit 11) (Time for those consenting to follow up through 3 years: Between 0 days and 15 days from Visit 12 or from Visit 13) including pre and post-op pictures
- Visit 15: Incision Healing check (2 weeks post-explantation): visit to assess wound healing including pictures. (Time: Between 9 and 19 days from Visit 14).

	Screening	Baseline	Implantation	Incision Healing Check	Activation (Follow up Clock Starts)	4, 12 Week Visits	48 Weeks Follow-Up: Primary Endpoint	8, 24, 36 Week Visits	Explant Visit	Incision Healing Check
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	X		
3-day Voiding Diary		X	X			X	X	X		
Return of TENS unit and diary			X							
Post Void Residual (PVR)	X									
Urinalysis	X									
Pictures Taken of Incision Site			X	X	X				X	X
OABq Assessment		X	X			X	X	X		
Patient Reported Satisfaction Assessment			X			X	X	X		
Patient Global Impression of Improvement			X			X	X	X		
Implant or Explant Procedure			X						X	
Incision Assessment				X						X
Activation / Re-programming					X			X		
Completion of Primary Endpoints							X			
Completion of Study										X
Subject Assessment for AEs		X	X	X	X	X	X	X	X	X

Figure 3-1: Summary of Study Process

3-4-3 Screening for Eligibility Procedures

Interested adults who are known or present at the research site with UUI may be initially screened 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. Subjects will be questioned for inclusion/exclusion criteria in addition to medical record review. A history will be taken, physical exam will be performed, and general health to participate in the study will be further evaluated by the Investigator at the screening visit. After patients provide their informed consent, and urinalysis will be utilized to rule out UTI. A blood sample will be taken of those subjects with a history of diabetes to confirm the condition is controlled.

3-4-4 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. Subjects will be expected to remain agent-free until the primary endpoint. 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.

3-4-5 Informed Consent Procedures

The study as described in the Informed Consent Form (see Attachment 4-5) 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.

3-4-6 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) TENS (transcutaneous electrical nerve stimulation) protocol instructions provided to subjects.

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

3-4-7 TENS Protocol

One secondary purpose of this trial is to ascertain whether there is a relationship between responders to TENS and responders to eCoin therapy. Therefore, at baseline, subjects will be sent home with a TENS unit and instructions to perform TENS of the tibial nerve twice daily for seven days. The electrical paradigm will be preset to match the electrical paradigm of eCoin (pulse width of 0.2 ms and frequency of 20 Hz), but the subject will set the amplitude of stimulation to the upper level of comfort. Subjects should perform one thirty minute session in the morning and one in the evening for 7 days (total of 14 sessions). Subjects will be asked to complete a voiding diary in the last three days of the TENS protocol. This TENS protocol will occur after the baseline visit but before the implantation visit. Subject eligibility is not affected by response or lack of response to the TENS protocol.

Study staff will schedule subject's implantation procedure to follow collection of three-day diary completed during the last three days of the TENS protocol.

3-4-8 Implantation of Subcutaneous Neuromodulation System

An implant procedure is to be completed following, but no later than, 28 days from the baseline visit. The eCoin™ system will be implanted in accordance with the procedures outlined in the Surgical Implant Manual set forth in Attachment 4-2 for Manuals and Labels. The implant procedure is conducted as an outpatient procedure under local anesthesia for subcutaneous placement. An incision site healing check will be performed 2 weeks post implant. Subjects will be provided a minimum of 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 will be prescribed at the discretion of the investigator.

3-4-9 eCoin™ Activation

All subjects will return for a device activation visit 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 4, 8, 12, 24, 36, and 48 weeks 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.

3-4-10 Establishment of the Amplitude Setting

The programming technician will follow programming procedures, setting the amplitude according to the subject's upper level of comfort. Subjects will be informed that they may periodically feel a tingling or notice a muscle twitch; but if they do, it would be transient

and they should not feel anything most of the time, if at all. 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).

3-4-11 Post Activation Follow-up Procedure

Subjects will be followed up in visits at 4, 8, 12, 24, 36, and 48 weeks post-activation, with the primary analysis at 48 weeks.

1) Overactive bladder medications should not be given at any time during the 48 week study (unless medication is medically necessary according to the "Escape Treatment" guidelines below).
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) Assessments at visits 4, 8, 12, 24, 36, and 48 weeks post-activation contain the same procedures. They are described in the Visit Overview Section 3-4-2. The 8, 24, and 36 week visits will include a scheduled reprogramming to check in on how the patient is doing with the device settings.
4) All other visits are also described in the Visit Overview Section 3-4-2.

At the follow-up visit 48 weeks post-activation, the primary effectiveness endpoint will have been reached.

3-4-12 Escape Procedure

Unless judged medically necessary, medications for overactive bladder are not allowed until the primary effectiveness endpoint is reached at 48 weeks post activation. Agents added or withdrawn are at the discretion of the Investigator and managing physician. Any such adjustment is to be noted on the CRFs. Patients are also asked at each follow-up visit whether they have taken any medication for overactive bladder. Any answer of "yes" will be reported on the visit CRF and a corresponding concomitant medication CRF.

3-5 *Study Objectives*

3-5-1 Primary and Key Secondary Objectives

3-5-1-1 Primary Effectiveness Objective

To assess the effectiveness of eCoin™ on the proportion of subjects achieving at least a 50% improvement in the number of urgency urinary incontinence episodes per 24 hours on a 3 day voiding diary after 48 weeks of therapy.

3-5-1-2 Key Secondary Effectiveness Objective

To assess the effectiveness of eCoin™ on the proportion of subjects achieving at least a 50% improvement in the number of urgency urinary incontinence episodes per 24 hours on a 3 day voiding diary after 24 weeks of therapy.

3-5-1-3 Primary Safety Objective

To assess safety 52 weeks after implantation of eCoin™.

3-5-1-4 Key Secondary Safety Objective

To assess safety 28 weeks after implantation of eCoin™.

3-5-2 Secondary Objectives

The following objectives refer to measures taken after 24 and 48 weeks of therapy.

To assess the proportion of subjects achieving 75% improvement in the number of urgency urinary incontinence episodes per 24 hours on a 3 day voiding diary.

To assess the proportion of subjects achieving 100% improvement in urgency urinary incontinence episodes ("Dryness") per 24 hours on a 3 day voiding diary.

To assess the reduction in the number of urgency urinary incontinence episodes per 24 hours on a 3 day voiding diary.

To assess the reduction in the number of urinary voids per 24 hours on a 3 day voiding diary in those subjects whose baseline shows more than 10 voids per day.

To assess the reduction in the number of urgency episodes per 24 hours on a 3 day voiding diary.

To assess the reduction in the number of nocturia episodes per 24 hours on a 3 day voiding diary.

To assess the improvement in the patient reported quality of life utilizing the Overactive Bladder Symptom Quality of Life Questionnaire (OABq).

To assess the improvement in patient reported overactive bladder condition utilizing the Patient Global Impression of Improvement (PGI-I) questionnaire.

To assess the patient reported satisfaction with eCoin™ therapy utilizing the custom patient satisfaction rating survey.

3-6 *Rationale for the Selection of Outcome Measures and Study Design*

eCoin™ therapy is expected to have a positive effect on a number of symptoms of overactive bladder, including number of urinary urgency incontinent episodes, voiding volume, frequency, and nocturia. The primary outcome is the therapeutic effect of eCoin on UUI.

Urinary incontinence is associated with substantial routine care costs and a clinically significant decrement in health-related quality of life that is similar to the impact of other chronic medical conditions like osteoarthritis, chronic obstructive pulmonary disease, and stroke (31). Thus, the primary outcome focuses on an objective and significant symptom of overactive bladder: the number of incontinence episodes in a 3-day period in all subjects. Of the secondary outcomes, quality of life is an important measure of the

overactive bladder condition because overactive bladder is a symptom-based diagnosis. The degree of bother caused by symptoms directly affects care seeking, treatment intensity, and satisfaction with treatment; however, patient reported questionnaires on the quality of life of incontinence patients have not been well standardized in the past. Selection of the two questionnaires is based on evidence that each, the OABq and the PGI-I, is a valid and reproducible self-administered measure for assessing quality of life in patients with urinary incontinence (32, 33).

The Sponsor's feasibility study for which the study device, eCoin™, was implanted in 46 subjects showed a benign safety profile. In particular, no infection at the implant site occurred that required explant. At the time of this writing, all subjects have been followed for at least six months since implantation of the study device. Given that the primary safety concern is infection and that all serious infections are expected to occur by one month after implantation, the adverse event information compiled thus far is promising. Three serious adverse events (SAEs) have occurred: one unrelated pneumonia incident, one unrelated limp due to underlying bursitis of the hip present at screening, and one related cellulitis of the calf secondary to the ankle support suggested as post-operative care. See Attachment 04-32 for additional information on safety. Furthermore, given the expected therapeutic similarity of percutaneous nerve stimulation of the tibial nerve to eCoin™ stimulation of the tibial nerve, the therapy is not expected to cause adverse events. Nonetheless, safety will be reported through adverse event reporting for the study duration.

While an important benefit to the eCoin™ system is that delivery of therapy does not require the patient to operate a percutaneous device and locate the tibial nerve on a regular basis, it is also important to understand how well patients tolerate the device. In order to assess patient acceptance, a patient satisfaction grade will be documented for each subject at all follow-up visits.

31. Schultz SE, Kopec JA. Impact of chronic conditions. Health Rep. 2003;14:41–53.
32. Wagner, T. H., et al. "Quality of life of persons with urinary incontinence: development of a new measure." *Urology* 47.1 (1996): 67-71.
33. Hajebrahimi, Sakineh, et al. "Validity and reliability of the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form and its correlation with urodynamic findings." *Urology journal* 9.4 (2012): 685.

3-7 *Risk Analysis*

3-7-1 Overview

The eCoin™ system risk assessment (Attachment 4-14) has been completed per FDA-recognized Consensus Standard 5-40: ISO 14971. The risk analysis method identifies each potential hazard that could result in patient harm, with action taken to reduce risk when the estimated risk for any potential hazard exceeds an acceptable level. The risk analysis for the eCoin™ system and the controller was performed early in the design process and has been updated throughout the process. The identified, anticipated risks have been mitigated so that all potential hazards are reduced to an acceptable severity and occurrence.

To verify mitigation of risk, the eCoin™ system has undergone testing for safety, essential performance, design verification and marking per applicable parts of IEC

60601-1:2005+A1:2012(E) and ISO 14708-1:20000(E) as well as biocompatibility testing to be compliant with all applicable ISO 10993 standards.

The table in attachment 4-15 summarized the potential risks to human health and traces them to specific FMEA assignments and risk mitigation measures.

3-7-1-1 Clinical Safety Data as Validation of Risks

The eCoin™ system has been used in a successful first-in-human feasibility trial from 2013 through 2016 for the treatment of drug-resistant hypertension in adults and in a human feasibility trial for the treatment of overactive bladder (OAB) in adults. The system parameters for the hypertension study were 2 pulses per second at a pulse width of 0.5 ms with amplitudes ranging from 0.5 mA to 25 mA. No adverse event related to stimulation therapy occurred during the two year hypertension study. Section 2-2-2-2 is a summary of the safety results. In this proposed study and in the ongoing OAB study, the eCoin™ system parameters will be 20 pulses per second at a pulse width of 0.2 ms with amplitudes ranging from 0.5 mA to 15 mA. In the OAB study, one adverse event related to stimulation occurred for which the subject experienced moderate pain during the intermittent stimulation (i.e., 30 minutes every other day). This was the first subject programmed with the device in the U.S. and it was learned that the subject required more time for healing in order to provide better sensory feedback and to set the device to the upper level of comfort. The adverse event was resolved with a reprogramming. The proposed system parameters match those utilized by many percutaneous tibial nerve stimulation studies for which no stimulation-related adverse event has been reported (3, 13, 17) and the same parameters used by FDA-cleared devices (K132561) that also stimulate the tibial nerve for treatment of overactive bladder. According to the American Urological Association's guideline on the diagnosis and treatment of overactive bladder (34), percutaneous tibial nerve stimulation carried minor adverse events in reviewed studies. The most frequently reported events were painful sensation during stimulation that did not interfere with treatment and minor bleeding at the insertion site. In the panel's view, benefits outweigh risks and burdens for the use of percutaneous tibial nerve stimulation in the thoughtfully-selected and counseled patient who is highly motivated to make the office visits required for repeated percutaneous administration of tibial nerve stimulation.

34. Gormley A, Lightner D, Burgio K, Chai T, Clemens JQ, Culkin D, Das A, Foster HE, Scarpero HM, Tessier C, Vasavada SP, Diagnosis and Treatment of Overactive Bladder (Non-neurogenic) in Adults: AUA/SUFU Guideline. American Urological Association Education and Research https://www.auanet.org/education/guidelines/overactive-bladder.cfm

3-7-2 Description of Patient Population

The eCoin™ system is indicated for the treatment of patients having UUI. For inclusion, subjects must meet all inclusion criteria and none of the exclusion criteria. For more information about inclusion criteria, see Inclusion Criteria 3-3-2-2-1.

Patients with overactive bladder, including those with the symptom of urgency urinary incontinence, have a clinically and statistically significant lower quality of life, lower depression status, and poorer quality of sleep than other people (35). Overactive bladder causes additional health problems including increased risk of falls and fractures (presumably from nocturia in the elderly), urinary tract and skin infections, sleep disturbances and depression (36). Most studies investigating the cost of overactive bladder focus on the economic burden of overactive bladder, showing a total cost to the

US healthcare system of $26.3B a year (37). Patients with refractory urgency urinary incontinence are those who are not achieving adequate control of incontinence symptoms through available modes of therapy. Such modes include behavioral therapy, pelvic floor exercises, and pharmacological therapy. Refractory patients may be eligible for inclusion in this study.

35. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P,Herzog AR, Corey R, Hunt TL and Wein AJ, Prevalence and burden of overactive bladder in the United States (NOBLE Study), World J Urol (2003) 20: 327–336.
36. Brown JS, McGhan WF, and Chokroverty S, Comorbidities Associated With Overactive Bladder, The American Journal of Managed Care, Vol. 6, No. 11, SUP (2000), S574-S579.
37. Wagner TH, Hu TW. Economic costs of urinary incontinence in 1995. Urology 1998;51:355-361.

3-7-3 Justification for Investigation

3-7-3-1 Potential Benefits of Treatment

According to the American Urological Association (AUA) and its guideline for diagnosis and treatment of overactive bladder, an AUA Panel interpreted the available percutaneous tibial nerve stimulation data to indicate that percutaneous tibial nerve stimulation can benefit a carefully selected group of patients characterized by moderately severe baseline incontinence and frequency and willingness to comply with regular return visits for administration of the percutaneous therapy. The Grade C evidence supports a potential benefit of tibial nerve stimulation in overactive bladder patients of improvements to incontinence episodes, voiding volume, quality of life, frequency, and nocturia. Furthermore, in a study by Finazzi-Agro et al., patients matching some features of the population for the proposed study—females with detrusor overactivity incontinence—showed statistically and clinically significant improvements in mean incontinence episodes per 3 days, mean voids per day, mean voided volume, and mean QoL score (17). Thus, potential benefits of tibial nerve stimulation by eCoin™ include improvements to the number of incontinence episodes, voiding volume, frequency, and quality of life.

This current study is primarily concerned with UUI.

3-7-4 Additional Safety Profile Information

3-7-4-1 Description of Procedure

eCoin™ is placed into a subcutaneous pocket in the lower leg. The anatomical structures involved in the implantation procedure are skin, subcutaneous tissue, and fascia. The eCoin™ sits above the fascia so the deeper structures are not affected. No significant nerves or vessels, other than subcutaneous veins which are of minimal significance, are present in the subcutaneous pocket. eCoin™ is placed about 3 mm above its target nerve (tibial nerve).

Similar to other inert prosthetic devices, a fibrous capsule is expected to form around the eCoin™ system. This capsule stabilizes the implant at its desired location and compartmentalizes it from the surrounding tissues (skin, subcutaneous fat, and fascia).

3-7-4-2 Therapeutic or Stimulation Risks

Although stimulation could briefly exceed a comfortable level during the activation procedure, no serious complication from tibial nerve stimulation is known or anticipated. Stimulation pulses are charge balanced at a charge density level known to be safe for neuromodulation with platinum electrodes (≤ 100 $\mu C/cm^2$). If stimulation intensity above the subject's comfort level is reached during programming in the clinic, the subject may feel discomfort or pain until the stimulation level is turned down. The subject may experience a muscle twitch related to stimulation of the tibial nerve. Discomfort or muscle twitch is managed through optimal setting of stimulation amplitude to subject comfort levels. Adjustments to stimulation levels are made only in the clinic where the patient response can be monitored and adjustments made as needed.

The energy discharge of the eCoin™ battery is such that no harm will arise from heating due to a battery short. Direct shorting of the 75mAh battery delivers less than 200 mW or 20 mW/cm^2 of heat from the device surface to tissue. This ensures a safe level of tissue heating (less than 2 degrees Centigrade) in a worst case direct short failure condition.

3-7-4-3 Risks of eCoin™ Implantation

The most probable risks associated with eCoin™ implantation include the following: ecchymosis, erythema, and incisional pain at the implant site; intermittent paresthesias of the toes, foot, or lower leg; and other wound healing complications. Other risks that are categorized as uncommon or rare are reported below:

UNCOMMON
- Hematoma at the incision site
- Implant site infection that leads to device explant
- Persistent implant site pain
- Severe pain during or shortly after the procedure
- Persistent wound healing complications lasting beyond 8 weeks post implant
- Persistent stimulation discomfort

RARE
- Wound dehiscence
- Allergic reactions to local anesthesia
- Inflammation of nearby tendons
- Localized neuritis
- Surgical injury to adjacent nerves, vessels or tendons
- Allergic reaction to implanted materials
- Implant device failure leading to explant
- Implant device extrusion
- Implant device migration requiring explant or revision
- Implant device inversion

Device-related risks of the eCoin™ system can be deduced from the 50 year field of neuromodulation. The primary risks of importance are infection and lead-related problems (e.g., leadwire break or migration). For the leadless eCoin™ system, lead-related problems are not relevant. Reasonable estimation of the rate of infection can be based upon other neuromodulation devices, the sponsor's feasibility study testing eCoin™ for hypertension, and the sponsor's feasibility study testing eCoin™ for OAB. Infection can be mitigated through surgical training, adequate manufacturing controls, and adequate after-care instructions. Infection can be resolved through antibiotics generally and, in a worst case scenario, explantation of eCoin™.

If needed, explantation of the eCoin™ device can be performed easily through simple opening of the capsule and removal of the device. If the capsule itself has a significant problem such as deep infection or dense scar tissue causing significant discomfort, then the capsule might require surgical excision, a procedure known as capsulectomy.

In the ongoing clinical study of eCoin™ for OAB conducted under an IDE, no patient required explant due to infection. One cellulitis of the calf secondary to the ankle wrap occurred where the patient chose to have the device explanted prior to activation of the device. The aforementioned safety data are current as of the date of this writing at which time all patients have been followed at least six months from implantation. See Attachment 04-28 for a table on reported related adverse events. In the OUS clinical study of eCoin™ for hypertension, the proportion of infection requiring explant, on a per patient basis was approximately 4.2%. See Subsection 2-2-2-1 and 2-2-2-2 for details on the adverse events that occurred during both studies.

The eCoin™ utilizes established biocompatible materials and manufacturing processes that are typical of implantable neurostimulators (titanium hermetic enclosure, silicone elastomer insulation coating (MED-4870) and with platinum stimulating electrodes).

3-7-5 Standards Conformance Demonstrating Safety

The eCoin™ system has been developed under design control in accordance with QSR 21 820.30 and ISO 13485.

3-7-5-1 Risk Management

Risk management conforms to ISO 14971:2012(E). A Risk Assessment has been completed for the SNS system based on Use, Design and Process FMEAs (See Risk Assessment Report 110-1493 in attachment 4-14).

3-7-5-2 Development Process and Design Verification Testing

Safety, Essential Performance, Design Verification and Marking have been completed per applicable parts of IEC 60601-1:2005+A1:2012(E) in compliance with active implantable medical devices ISO 14708-1:2000(E) and software life cycles per IEC 62304:2006. Attachment 4-16 is a summary of design verification testing results.

3-7-5-3 Biological Evaluation

The eCoin™ system is an active implantable device for long term patient contact duration (>30 days). The eCoin™ system has been subject to biocompatibility testing in accordance with the ISO 10993 series of standards. Biocompatibility compendiums were obtained from the suppliers of all materials to confirm that the supplier is also compliant with ISO 10993 requirements. The testing summarized in Table 3-2 was performed on sterile devices representing the final product using Good Laboratory Practices. Test Article Preparation was performed in accordance with ISO 10993-12. Based on the results of the in vitro testing, the eCoin™ Subcutaneous Neuromodulation System is safe and effective as an implant for the intended use.

Standard	Title	Result
ISO 10993-3:2003	Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.	
	ISO Bacterial Mutagenicity Test – Ames Assay	Pass
	Mouse Lymphoma Assay	Pass
ISO 10993-5:2009	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity.	
	Cytotoxicity – Elution Test- MEM Extract	Pass
ISO 10993-6:2007	Subcutaneous Implantation Test – 90 days	Pass
	Systemic Toxicity Study of "SNS Biocompatibility Test Device" in Sprague Dawley Rats following Subcutaneous Implantation for 90 Days	Pass
ISO 10993-7:2008 /AC:2009	Biological evaluation of medical devices -- Part 7: Ethylene oxide sterilization residuals.	Pass
ISO 10993-10:2010	Biological evaluation of medical devices - Part 10: Tests for irritation and delayed-type hypersensitivity.	
	Intracutaneous (Intradermal) Reactivity Test in New Zealand White Rabbits	Pass
	Maximization Test for Delayed-Type Hypersensitivity in Hartley Guinea Pigs	Pass
ISO 10993-11:2006	Biological evaluation of medical devices - Part 11: Tests for systemic toxicity	
	Acute Systemic Toxicity Test in CD-1 Mice	Pass
	Pyrogen Test in New Zealand White Rabbits	Pass

Table 3-2: ISO 10993 Biocompatibility Testing

3-7-5-4 Sterilization and Sterile Packaging

The ethylene oxide sterilization process for the eCoin™ device has been developed, validated and is controlled per ISO 11135:2007 (see attachment 4-17). The sterile package sealing process and shelf life were developed and validated per ISO 11607 (see attachment 4-18).

3-8 *Description of the Device*

Valencia Technologies eCoin™ therapy for urgency urinary incontinence provides electrical stimulation to the tibial nerve from a small self-contained implant placed in the subcutaneous space over the tibial nerve in the lower leg. Subjects receive the implant unilaterally in a simple procedure under local anesthetic.

To stimulate the tibial nerve with the eCoin™ implant, the same parameters as previously demonstrated in animal, in human studies, and in the eCoin™ for OAB feasibility trial are applied. The stimulation rate is 20 pulses per second (pps) at a pulse width of 0.2 ms. The stimulation pulse amplitude is adjusted to the highest comfortable level for the subject with an external controller. After activation, the implant automatically

provides 30 minute stimulation sessions according to a fixed treatment interval schedule. In between sessions, the amplitude can be adjusted or automatic therapy can be turned off. The device contains a battery that will typically operate for 2 to 4 years before the device requires replacement.

3-8-1 Components

1) eCoin™ Implant – The implant is a coin-sized leadless battery powered device 23 mm in diameter and 3.2 mm thick. The electronics and battery are hermetically enclosed in a titanium case. The materials in direct contact with tissue are the platinum electrodes, and the silicone elastomer jacket (NuSil MED 4870) that covers the titanium housing. Each implant receives a unique traceable serial number including labeling to place in recipient medical records.

2) External Controller – The external controller programs the device via a magnetic field using a custom access code secured wireless protocol.

3-8-2 Stimulation Settings/Parameters

Amplitude Range: 0.5 up to 15 mA (programmable)

Rate: 20 pulses per second (fixed)

Pulse Width: 0.2 ms (fixed)

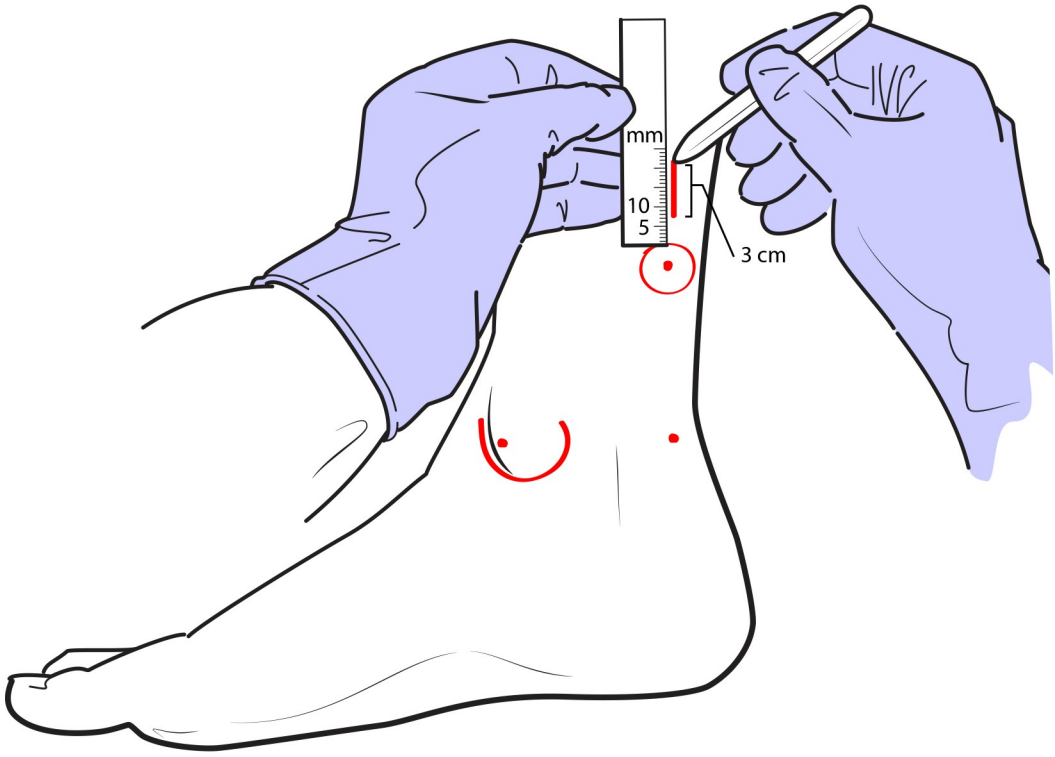
Treatment Duration: 30 Minutes (fixed)

Treatment Interval:3 days for the first 18 weeks (42 sessions) and every 4 days thereafter (fixed)

3-8-3 Implant Procedure

Subcutaneous implantation of the eCoin™ is done under local anesthesia. The most prominent point of the medial malleolus will be palpated and marked. With the foot positioned at a 90-degree angle, a second marking is made 3 cm posterior to the medial malleolus marking. The implantation target location is found 3 cm cephalad to this second point along a line parallel to the posterior margin of the calcaneal tendon. Continuing on this line, the incision is made 8 mm cephalad to the target implantation site. The incision is made to the depth of the fascia with a width slightly smaller than that of the eCoin™. Then, the eCoin™ is slid on top of the fascia until it reaches the

implantation site. The incision is then closed and dressed. See Attachment 4-2 for a complete surgical implant manual.



3-8-4 Activation of eCoin™ System

After a 4 week period of implant healing, the eCoin™ devices are activated with the stimulation amplitude set to the subject's upper most comfortable level. Once activated, the eCoin™ applies a 30 minute session of neuromodulation therapy at the programmed amplitude every 3 days for a 18 week period and then every 4 days thereafter. All subjects are activated and the schedule of therapeutic sessions is automated as discussed.

3-8-5 Subject Compliance Monitoring

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

Drug Therapy: Subjects will be asked whether they are taking an overactive bladder medication through the primary endpoint to confirm that subjects are free of overactive bladder medication.

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 3-4-2.

3-8-6 Safety and Adverse Events

3-8-6-1 Medical Monitoring

The study will be approved by a study-wide independent ethical committee or institutional review board. The participating Investigators will monitor the subjects medically.

3-8-6-2 Definitions of Adverse Events

Adverse Event (AE): Any untoward medical occurrence in a study participant whether or not there may be a causal relationship with this treatment / intervention. This can include (but is not limited to) worsening of subject's overactive bladder condition and/or occurrence of serious sudden events.

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 unexpected 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 expectedness.

3-8-6-3 Classification of Events

3-8-6-3-1 *Relationship*

YES- related: The event has a reasonable possibility of a causal relationship to the administration of tibial nerve stimulation (procedure, device, or stimulation) and no other etiology explains the event.

NO- not related: The event is independent of tibial nerve stimulation (procedure, device, or stimulation) and/or the event appears to be explained by another etiology.

3-8-6-3-2 *Severity*

Mild: Transient or mild discomfort (<48 hours); no medical intervention/therapy required and does not interfere with the subject's daily activities.

Moderate: Some limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.

Severe: Marked limitation in activity; interrupts participant's usual daily activity and may require medical intervention/therapy; hospitalization possible.

Serious: 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.

3-8-6-3-3 *Expectedness*

Expected: Any adverse reaction whose nature and intensity are consistent with that described under risk assessment.

Unexpected: Any adverse reaction not included under risk assessment.

3-8-6-4 Recording of Adverse Events

Expected device-related AEs will be recorded on case report forms as shown in Attachment 4-9, which are used at each visit. Unexpected or unrelated AEs or any requiring medical attention will be reported on CRFs and further recorded on AE forms. 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. All adverse events will need to be evaluated and assigned by a medical reviewer on or designated by the Data and Safety Monitoring Board (DSMB) with regards to:

1) Relatedness or causality to the study device
2) Severity
3) Expectedness
4) Action taken

The Sponsor is responsible for determining if an adverse event is unexpected. If expectedness is assessed by a medical reviewer as unexpected, the Sponsor will be notified and will evaluate and assign a final determination that may or may not result in a requirement to report expeditiously to regulators, IRBs, or both.

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. Severity
6. Expectedness
7. Causality
8. Was the patient hospitalized? If yes, provide dates.
9. Will the patient continue with treatment, and will any be missed?
10. Did the patient add or change any other associated medication and what were the changes/additions?
11. 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 form. The Study monitor will keep track of all reported AEs. A sample of the AE report form is in Attachment 4-9.

3-8-6-5 Reporting Procedures

For Serious Adverse Events (SAEs) or suspected Unanticipated Adverse Device Effects (UADEs), the Study Coordinator, the PI, and the Sponsor will be alerted. The timeline for medical review and assessment is 24 hours for SAEs and 7 days from subject reporting of non-serious unexpected device related AEs. For suspected UADEs, the Sponsor will promptly provide an expectedness determination. The Investigator must

promptly inform the Ethics Board or IRB of SAEs or determined UADEs per local reporting requirements.

The SAE form provided by the Sponsor should be completed and signed by the Investigator or physician sub-investigator and faxed or emailed to the Sponsor per the instructions on the form. The entire SAE form needs to be completed, if possible, to make available in a timely manner complete relevant information thus limiting requests for additional information. Each SAE reported on an SAE form must also be reported in the adverse event section of the CRF.

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.

3-8-6-6 Adverse Event Reporting Period

Adverse event information will be collected throughout the entire study between Informed Consent and final follow-up. 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 using the post-study AE form provided by the Sponsor. Post-study adverse events should be reported to the Sponsor after the study period if they are:

1) AEs that are device-related resulting in a revision surgery or explant (explant for reasons other than for normal end of life – e.g. battery depletion) for which the patient presents to the PI.
2) AEs that occur during or related to an explant procedure performed at the normal device end of life.

3-8-7 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.

3-8-7-1 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. The devices must be recommended to be explanted if the subject is withdrawn.

3-8-7-2 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. If the subject is explanted for any reason, subject participation must be terminated.

The subject's eCoin™ system must be recommended to be explanted if the subject's participation is terminated.

3-8-7-3 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 Case Report Form for reporting to the Sponsor.

Subjects enrolled in the study will not be replaced if they withdraw or are terminated from the study after device activation. Provisions for device explantation will be arranged.

3-8-7-4 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. If required, provisions for the explant of the eCoin™ system will be arranged.

3-8-7-5 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.

3-8-8 COVID-19 Related Delayed Explantation

Subjects who do not or did not consent to extended follow up may have an explant well beyond the final study visit window because of COVID-19 considerations. However, the database may be locked through the 48 week final study visit following complete monitoring. Subjects who do not or did not consent to extended follow up will not undergo study procedures beyond those originally consented but will continue to be followed for adverse events and complaints until explantation is performed and healing is observed. This will be done under the extension portion of this protocol.

3-8-9 Data and Safety Monitoring Board

A Data and Safety Monitoring Board of at least three members will review data including a quarterly report of Adverse Events. This DSMB will meet by telephone monthly until all subjects reach one month post-implantation and at least quarterly until all subjects reach 52 weeks post-implantation to review aggregate and individual subject data related to safety, data integrity, and overall conduct of the trial. The DSMB will be responsible for reviewing adverse events. The DSMB will provide recommendations to continue or terminate the trial depending upon this review. A DSMB charter is set forth in a DSMB Charter document (see 4-10).

3-9 *Data Analysis Plan*

3-9-1 Data Collection

All study data will be recorded onto Case Report Forms (CRFs) provided by Valencia Technologies. All CRFs will be completed using de-identified data. The CRFs will also serve as the source documents for the study. Valencia will enter the recorded data from CRFs into an Electronic Data Capture (EDC) system supported by Company eSOCDAT. eSOCDAT's system maintains the integrity of patient privacy using a secure server and patient information is still de-identified, using patient numbers only.

CRF completion may be delegated to other study personnel, but the Investigator remains responsible for the accuracy and integrity of all data entered on CRFs. CRFs will be completed and sent to the designated representative for Valencia Technologies as directed, in an expedited fashion. All CRFs will be completed by study personnel only. Valencia or its designee will work with participating sites to secure data clarification and to obtain additional relevant medical documentation on participants enrolled into this trial.

CRFs for the study include:

1) Screening
2) Baseline
3) Implantation (Part 1 and Part 2)
4) Implant Healing Check
5) eCoin™ Programming
6) Follow-up (4, 8, 12, 24, 36, and 48 weeks post-activation)
7) Adverse Event
8) Study Termination
9) Protocol Deviation
10) Explantation
11) Explantation Healing Check
12) Unplanned Visit

3-9-2 Interim Monitoring

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

During site visits, the monitor will review participant records, device accountability and storage, 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 in Attachment 4.22. 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 will make a final on-site 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.

COVID-19 Considerations

Due to the COVID-19 pandemic, monitors may not be able to travel to the investigational site to complete onsite monitoring of data. As an alternative, monitors are to complete remote monitoring visits. This involves scanning source and CRFs by site personnel to the monitor and verifying all documentation in accordance with the Clinical Monitoring Plan in Attachment 4.22. Due to personnel lay offs or temporary site closures, some data may not be able to be accessed, or monitoring may be delayed. Any deviations from the monitoring plan will be documented in the corresponding monitoring reports.

3-9-3 Analysis Plan Summary

This prospective, multicenter, single-arm study is designed to assess the safety and effectiveness of the eCoin™ tibial nerve neuromodulation system for the treatment of urgency urinary incontinence. Up to 135 subjects, with a target of 120 subjects, from approximately 20 different centers will be enrolled.

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 elaboration 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.

3-9-3-1 Rationale for Design Choice

3-9-3-1-1 *Safety*

The feasibility trial of eCoin™ treating OAB with UUI in the US and New Zealand was conducted at 7 centers with 46 subjects implanted. The results described in Section 2-2-2-2 show a minimally invasive procedure under local anesthesia and minor wound healing problems.

Under this protocol, eCoin™ will be tested to confirm that eCoin™ has a similar benign safety profile at more centers (20) with more (135) implanted subjects.

3-9-3-1-2 *Effectiveness*

Pivotal Study of Subcutaneous Tibial Nerve Stimulation with eCoin® for Urgency Urinary Incontinence.

This open label, single-arm study will evaluate eCoin™'s effectiveness in reducing episodes of urgency urinary incontinence. The proportion of subjects achieving at least a 50% reduction from baseline in the number of urgency urinary incontinence episodes will be reported.

Valencia considered a controlled trial against an approved drug or placebo. Such a trial would be very difficult to blind. Recruitment to a trial comparing eCoin™ to Interstim would be difficult because many people are unwilling to use Interstim.

3-9-3-2 Analysis Sets

Effectiveness analyses will be generated for all analysis populations described below. Safety data will be reported on all enrolled subjects who undergo a procedure for implantation of the study device

1) Intent-to-Treat (ITT): All enrolled subjects who undergo a procedure for implantation of eCoin™. This is the primary analysis population for the safety and effectiveness analyses.
2) Modified Intent-to-Treat (mITT). All subjects in the ITT population meeting all eligibility criteria.
3) OAB drug-free. All subjects in the mITT population who took no medication for OAB during the study period.
4) Per-protocol (PP): The subset of OAB drug-free subjects excluding all subjects with any other major protocol violation. The SAP will define major protocol deviations.
5) Responders: Subjects who respond to treatment, defined as those who achieve at least a 50% reduction in the number of urgency urinary incontinence episodes from baseline to 48 weeks post-activation.
6) TENS Cohort Analysis (TNS): The subset of ITT subjects less any patients who do not respond to the TENS protocol where response is defined as a 30% reduction in urgency urinary incontinence episodes or a 30% reduction in urgency episodes from baseline after 7 days of TENS.
7) Long-term Completers: All mITT subjects who attend a particular visit. This is the primary analysis population for the effectiveness and safety analyses performed at 2 and 3 years post-activation for subjects who consent to extended follow-up.

The SAP may define additional analysis sets of subjects.

3-9-3-3 Planned analyses

3-9-3-3-1 *Primary Effectiveness Outcome*

The primary effectiveness outcome is achieving at least a 50% reduction from baseline in the number of urgency urinary incontinence episodes per 24 hours on a 3 day voiding diary after 48 weeks of eCoin™ tibial nerve stimulation.

The proportion of responders along with its 2-sided 95% exact Clopper-Pearson confidence interval will be summarized after 48 weeks of therapy.

3-9-3-3-2 *Key Secondary Effectiveness Outcome*

The key secondary effectiveness outcome is achieving at least a 50% reduction from baseline in the number of urgency urinary incontinence episodes per 24 hours on a 3 day voiding diary after 24 weeks of eCoin™ tibial nerve stimulation.

The proportion of subjects with at least 50% reduction from baseline along with its 2-sided 95% exact Clopper-Pearson confidence interval will be summarized after 24 weeks of therapy.

3-9-3-3-3 *Primary Safety Outcome*

The primary safety outcome is device-related adverse events from implantation to 52 weeks after implantation of eCoin™.

All device-related adverse events up to 52 weeks after implantation of eCoin™ will be summarized by preferred term. Tabulations of these data will include the number of subjects exposed and the number of subjects with at least one device-related adverse event.

3-9-3-3-4 *Key Secondary Safety Outcome*

The key secondary safety outcome is device-related adverse events 28 weeks after implantation of eCoin™.

All device-related adverse events up to 28 weeks after implantation of eCoin™ will be summarized by preferred term. Tabulations of these data will include the number of subjects exposed and the number of subjects with at least one device-related adverse event.

3-9-3-3-5 *Secondary Outcomes*

The secondary outcomes listed in this section are based on data after 24 and 48 weeks from activation (28 and 52 weeks after implantation). These outcomes, which are for descriptive purposes, will not be formally analyzed statistically. The SAP will describe in detail analyses of the secondary outcomes.

- Achieving 75% improvement in the number of urgency urinary incontinence episodes per 24 hours on a 3 day voiding diary.
- Achieving 100% improvement in urgency urinary incontinence episodes (“Dryness”) per 24 hours on a 3 day voiding diary.
- Reduction from baseline in the number of urgency urinary incontinence episodes per 24 hours on a 3 day voiding diary.
- Reduction from baseline in the number of urinary voids per 24 hours on a 3 day voiding diary in those subjects whose baseline shows more than 10 voids per day.
- Reduction from baseline in the number of urgency episodes per 24 hours on a 3 day voiding diary.

- Reduction from baseline in the number of nocturia episodes per 24 hours on a 3 day voiding diary.

- Change from baseline in patient-reported quality of life utilizing the Overactive Bladder Symptom Quality of Life Questionnaire (OABq).

- Change from baseline in patient-reported overactive bladder condition utilizing the Patient Global Impression of Improvement (PGI-I) questionnaire.

- Patient-reported satisfaction with eCoin™ therapy utilizing the custom patient satisfaction rating survey.

3-9-3-4 Exploratory Subgroup Analyses

Subjects who respond to treatment (i.e., who achieve at least a 50% reduction from baseline to 48 weeks post-activation in the number of urgency urinary incontinence episodes per 24 hours on a 3 day voiding diary) will be compared to non-responders in terms of baseline characteristics, demographics, and effectiveness endpoints.

3-9-4 Sample Size Consideration

The study is designed to estimate the proportion of subjects achieving a clinically meaningful level of improvement, defined as subjects with at least a 50% reduction from baseline in the number of urgency urinary incontinence episodes after 48 weeks of therapy. Up to 135 subjects will be enrolled, with a target enrollment of 120 subjects. The performance goal for this study is to show at least a 40% response rate after 48 weeks of therapy. The primary efficacy analysis will be performed by testing the null hypothesis H_o that the percentage responding is less than or equal to 40% against the alternative hypothesis H_1 that the percentage is greater than 40%. The test will be performed at an overall 1-sided 2.5% level of significance.

H_0: the true percentage responding $\leq$ 40%
H_1: the true percentage responding > 40%

The study will be considered successful if the lower bound of the 2-sided 95% exact Clopper-Pearson confidence interval for the percentage responding is greater than 40%.

The study is designed to detect an improvement in the percentage responding compared with a historical percentage of 40%. The study will enroll a target of 120 subjects to ensure collection of sufficient efficacy and safety data. The study will have 80% power to detect a 13% increase in the percentage responding from 40% to 53%, 90% power to detect a 15% increase from 40% to 55%, and 95% power to detect a 17% increase from 40% to 57%, at 1-sided 2.5% significance level. Calculations used PASS 2019, v19.0.2.

The justification for the performance goal of 40% comes from published literature for the approved and thought to be clinically significant third-line device for UUI—a fully-implanted neuromodulation device called “Interstim”. Note that given this study’s sample size, to observe 50% of patients improve by at least 50% in their urgency urinary incontinence symptoms as measured at the 12 month point, the lower bound

of a 95% confidence interval is 40%. The published literature on sacral neuromodulation supports the clinical significance of a 40% responder rate. From the observed modified ITT responder rate in the well-cited ROSETTA study (38), it can be deduced that there is a lower bound of 41% for those with diaries for all 6 months, and 43% for those with at least 4 months of diaries. Importantly, these results are not ITT. In the review of the Insite study (39), the Sponsor derived an ITT responder rate of 59% from the available as-treated analyses. From this ITT deduction, the lower bound of the 95% confidence interval is 44%. Both of these published data were measured at 6 months whereas the endpoint in the study contemplated by this IDE is 12 months. If either study was extended to 12 months, the number of subjects reporting would likely be even smaller, resulting in a lower bound at or below 40%.

38. Amundsen CL, Richter HE, Menefee SA, et al. “OnabotulinumtoxinA vs Sacral Neuromodulation on Refractory Urgency Urinary Incontinence in Women: A Randomized Clinical Trial.” *JAMA.* (2016); 316(13):1366–1374.
39. Siegel, Steven, et al. "Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder." *Neurourology and Urodynamics* 34.3 (2015): 224-230.

3-9-5 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, 4, 8, 12, 24, 36, and 48 weeks post-activation of the eCoin™ system.

Change in Frequency: Frequency of urination is measured prospectively using 3-day voiding diaries administered at baseline, 4, 8, 12, 24, 36, and 48 weeks post-activation of the eCoin™ system.

Change in Quality of Life: Quality of life is measured prospectively using the OABq questionnaires administered at baseline, 4, 8, 12, 24, 36, and 48 weeks post-activation of the eCoin™ system.

Patient Global Impression of Improvement: The level of patient satisfaction with the eCoin™ neuromodulation system will be rated by the subject on a descriptive scale of very much worse, much worse, worse, about the same, better, much better, and very much better.

Patient Reported Satisfaction: The level of patient satisfaction with the eCoin™ neuromodulation system will be rated by the subject on a scale of 1 to 5 where 1 is Not at All Satisfied, 2 is Slightly Satisfied, 3 is Somewhat Satisfied, 4 is Very Satisfied and 5 is Completely Satisfied.

3-9-6 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.

For the primary effectiveness outcome variable, missing data will be handled as follows:

- Any subject explanted, except for those explanted for MRI, prior to 48 weeks post-activation will be imputed as a non-responder (meaning the subject will be imputed as having not achieved at least a 50% reduction from baseline in the number of urgency urinary incontinence episodes).

- Subjects who are explanted for an MRI will have data post-MRI imputed. These imputed data for the primary effectiveness outcome variable will be assumed missing at random and will be handled with multiple imputation.

- Any subject for whom 48 week post-activation data are unavailable and the study investigator does not know whether the device has been explanted will be assumed to be a non-responder.

- Subjects for whom 48 week post-activation data are unavailable but the device is known not to have been explanted will have their missing data imputed. The missing data for the primary effectiveness outcome variable will be assumed missing at random and will be handled with multiple imputation.

- Any subject who undergoes the procedure for implantation of eCoin™ whether or not the device is actually activated, will be treated as if they were activated.

- An addendum to the SAP addresses missing data related to COVID-19 impact.

Multiple imputation will be performed under fully conditional specification (FCS) with 100 imputed datasets. The model will include the following variables: sex, age, body mass index (BMI), response to the TENS protocol, OABq total score at baseline and all follow-up visits, Patient Global Impression of Improvement questionnaire score at all post-baseline visits, average urinary voids per 24 hours on a 3-day voiding diary at baseline and all follow-up visits, and average UUI episodes per 24 hours on a 3-day voiding diary at baseline and all subsequent visits. The SAP will contain further details and SAS code concerning the modelling for multiple imputation.

The SAP will provide further details on handling missing data for the secondary outcomes. For the analysis of safety variables, only partial dates may be imputed; otherwise, missing data will be treated simply as missing. Conventions for imputing partial dates will be described in the SAP.

3-9-7 Sensitivity and additional analyses

The primary and secondary efficacy analyses will be repeated for all analysis populations (mITT, OAB drug-free, Per-protocol, Responders, and TENS cohort analysis). These analyses will also be repeated for the mITT analysis population excluding any subjects enrolled but not meeting all eligibility criteria who were subsequently re-baselined to correct any eligibility violations.

Additional sensitivity analyses may be conducted to evaluate different methods of handling missing data, such as tipping point, best-case, and worst-case scenario analyses. Additional sensitivity analyses are described in the SAP addressing COVID-19 impact.

3-9-7-1 Additional OAB medications

Medications for OAB are not allowed until the primary effectiveness endpoint is reached at 48 weeks post-activation, unless judged medically necessary. For the primary effectiveness outcome variable, the primary analysis will include all subjects who have taken OAB medications. OAB medication use will be reported alongside the primary analysis. The timing of OAB medications will be displayed, including duration of treatment, start and end dates, and dosage.

The following additional sensitivity analyses may be performed.

- For the primary effectiveness outcome variable at week 48, data for subjects who have taken OAB medications while on study will be considered missing and imputed assuming they had not taken any OAB medication.
- For weeks 4, 8, 12, 24, 36, and 48, 2 different sets of analyses will be performed.
    - *While on OAB medication.* Subjects will be imputed as non-responders while they are taking OAB medication.
    - *Any OAB medication.* A very conservative set of analyses will consider a subject a non-responder at every visit after she starts OAB medication.

For example, no matter what subjects write on their diaries, the “while on OAB medication” analyses will consider subjects as non-responders from week 12 through week 36 if they take OAB medication at week 12 and stop that medication at week 36. The “any OAB medication” analyses will consider such subjects non-responders from week 12 through week 48.

3-9-8 Safety Analysis

All AEs will be coded using the preferred terms described in Subsection 3-7-4 Additional Safety Profile Information. All AEs will be summarized by preferred term. Tabulations of general AEs, which will be provided by time point, will include the number of subjects exposed, the number of subjects with at least one AE, and the number of subjects with at least one AE by preferred term. These tabulations will be repeated for all AEs recorded as having a causal relationship to the eCoin™ system. Tabulations of local AEs will be provided at 24 and 48 weeks after activation (28 and 52 weeks after implantation), and will include the number of subjects exposed, the number of subjects with at least one AE, and the number of subjects with at least one AE by preferred term. Separate tables will be provided, if relevant, for SAEs or events leading to withdrawal from study.

3-10 *Data Handling, Record Keeping and Study Monitoring*

3-10-1 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

3-10-2 Training

All study forms and procedures will be reviewed with medical/study staff at the participating centers. Investigators or their surgical designees will also be medically trained and certified by the Sponsor to perform the implant procedure. Training will include any combination of cadaver training, video, or supervised procedures. To perform the procedure, the Investigator or designated medical doctor will need to be experienced in urology or uro-gynecology, and be certified by the Sponsor.

3-10-3 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:**

- Protocol and any amendments
- Consent forms (sample, and subject signed and dated)
- IRB/ERC approval for the protocol and consent form
- Agreement letter sent to Sponsor
- Case Report Forms
- Adverse event or Problem reports to Sponsor and IRB
- Inventory control log
- Enrollment Log
- Records of deviations, violations, and amendments
- Implant Registration Cards, where required by local regulations

Case Report Forms: All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not completed or the question was not asked, select "N/D". If the item is not applicable to the individual case, select "N/A". If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. Case Report Forms will be kept in the Study File.

Source Documents: medical records, voiding diaries, QoL questionnaires, etc. will be maintained at the study clinic.

3-10-4 Device Accountability

Each device has a unique serial number assigned. The device box will have 2 adhesive labels with the serial number of the device. At the time of implantation, one sticker will be placed on the Implantation CRF and the other sticker will be placed on the patient implantation card (see 4-7). The Sponsor is responsible for managing the device accountability log across the study. Each site will have a device tracker to be reconciled at the conclusion of the study.

3-10-5 Monitoring Procedures, Auditing, and Inspecting

A clinical research monitor will supervise conduct of the study at each site in accordance with the Clinical Monitoring Plan provided in Attachment 4-22. The monitor will visit the Investigator and the study facility 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 qualified members of the Clinical Research Department of Valencia Technologies who have been trained on the study protocol, monitoring procedures, and standard operating procedures based on Good Clinical Practice and other applicable Federal regulations.

The monitor's responsibilities are:

- Conduct Site Initiation visit (after IRB approval/before first subject enrollment).
- Conduct periodic monitoring visits.
- Compare case report forms to source documents.
- Review Investigator's files for accuracy, currency, and completeness.
- Ensure that informed consents are obtained.
- Ensure that IRB review is current.
- Ensure protocol compliance; document deviations.
- Prepare reports of visits.
- Ensure adverse events are reported.
- Conduct closeout visit (after all case report forms are received in house).

3-10-6 Protocol Deviations and Compliance

3-10-6-1 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 and the IRB/Ethics Committee prior to implementation. If a major deviation occurs that is not in response to the protection of a subject, the event is considered non-compliance if it occurs without prior approval. Non-compliance must be reported to the IRB/Ethics Committee promptly – no later than 5 days after the deviation. A PI's failure to report promptly any major deviation for which the PI did not obtain prior approval is itself an incident of non-compliance and will be evaluated by the Sponsor. Such failure could be grounds for physician disqualification.

Use of a medication for OAB is not considered a major protocol deviation.

3-10-6-2 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 on the protocol deviation log at the site and brought to the attention of the monitor at the next CRA visit. These deviations do not need to be reported to the IRB/Ethics Committee. Examples of a minor protocol deviation follow:

1) Follow-up visits that occurred outside the protocol required time frame because of the participant's schedule.
2) Study procedure conducted out of timeframe, e.g., 3-day diary
3) Participant failure to initial every page of the consent form
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
7) Patient not given implant card
8) Use of a medication for OAB

3-10-6-3 Analyzing Deviations

At each monitoring visit, the deviations log 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.

3-10-6-4 Statement of Clinical Compliance

The study will be conducted in accordance with the design and specific provisions of this IRB/Ethics Committee approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. The Investigator will assure that no deviation from, or change to, the protocol will take place without prior agreement from

the Sponsor and documented approval from the IRB/Ethics Committee, except where necessary to eliminate an immediate hazard to the trial participants. The Investigator will promptly report to the IRB/Ethics Committee and the Sponsor any changes in research activity and all unanticipated problems involving risk to human subjects, or others.

3-11 *Methods, Facilities, and Control Information*

3-11-1 Device Manufacturer

3-11-1-1 Manufacturer name, address and contact information

Name of device manufacturer: Valencia Technologies Corporation
Address: 28464 Westinghouse Place, Valencia, CA 91355
Contact Person: Stacy Chambliss, Chief of Administration
Telephone Number: (661) 775-1414
Fax Number: (661) 775-1411

3-11-1-2 Manufacturer compliance with Subpart C, Design Controls (section 820.30), the Quality System Regulations (21 CFR Part 820)

The eCoin™ Subcutaneous Neuromodulation System is manufactured by Valencia Technologies Corporation under design controls per QSR 21 820.30 and ISO 13485.

3-11-1-3 Device Design and Manufacturing Information

3-11-1-3-1 Device Design

Engineering drawings of the eCoin™ Subcutaneous Neuromodulation System described in section 3-8 are in attachment 4-19. Materials used outside of the hermetic package in the eCoin™ device are in attachment 4-20.

Design inputs for the eCoin™ Subcutaneous Neuromodulation System include the requirements for functional performance and safety including applicable regulatory and legal requirements as well as the outputs of risk management. The design outputs for the eCoin™ Subcutaneous Neuromodulation System are captured in functional specification requirements. These design outputs are verified in the testing summarized in Attachment 4-16 using test articles that are representative of the final product. The clinical use of the eCoin™ device has been validated in a successful first in human feasibility trial from 2013 through 2016 for the treatment of drug resistant hypertension in adults per the protocol in Attachment 4-11. Subsequent to this trial and more relevant to the protocol described herein, the clinical use of eCoin™ in the treatment of OAB with urge urinary incontinence has been validated in a feasibility trial and the protocol is attached as Attachment 4-33.

Design Reviews are conducted with representatives of functions concerned with the design and development stage being reviewed. Other specialist personnel are included as needed. Design changes arising from these reviews are verified and validated before approval and release.

3-11-1-4 Manufacturing Controls

Assembly procedures with test procedures are in place to ensure the eCoin™ device is produced in accordance with the design and performance specifications (attachment 4-

23). Each device is tracked individually by serial number with traceability to components and all production steps maintained in a device history record.

3-11-1-5 Processing, Packaging, Storage

The procedures for sterile packaging, sterilization and storage are in Attachment 4-24.
Study Sites and Investigators

3-11-2 Organization and Participating Center

3-11-2-1 Principal Investigators

All U.S. based Principal Investigators participating in the study will have signed an Investigator Agreement, a template of which is enclosed as Attachment 4-21 in compliance with § 812.43. New U.S. based Principal Investigators will be required to sign the Investigator Agreement before being added to the study. Attachment 4-25 is the list of 20 investigators and centers.

Sponsor

Valencia Technologies Corporation
Stacy Chambliss, Tel: +1 (661)775-1414 ext. 1002
28464 Westinghouse Place
Valencia CA, 91355
United States

3-11-3 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 have disclosed their financial relationship in the Conflict of Interest statement incorporated within the signed Investigator Agreement,

3-11-4 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.

3-11-5 Roles and Responsibilities

3-11-5-1 Investigator

The Investigator has the following responsibilities:

1) Assure IRB/Ethics Committee approval of protocol and informed consent is obtained.
2) Follow the study protocol.
3) Permit monitor to inspect facilities and records.
4) Permit regulatory inspections of facilities and records, if necessary.
5) Inform a patient of any known risks and potential benefits associated with use of the device, and obtain the patient's written consent for its use.
6) Enroll subjects, execute study, and transcribe data from source documents to Case Report Forms.
7) Submit annual progress reports, final reports, and adverse event reports to the IRB/Ethics Committee and to the Sponsor.
8) Return unused study articles, record their receipt, disposition, and return.
9) Refrain from promoting study or study articles in any manner that is not authorized by the Sponsor.
10) Conduct study in accordance with the protocol.
11) Track Sponsor-provided inventory and assignments.
12) Maintain medical histories of subjects.
13) Retain records for 10 years or as required by law following completion of the study.

3-11-5-2 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.

3-11-5-3 Sponsor

The Sponsor has the following responsibilities:

1) Submit protocol and informed consent to IRB/Ethics Committee and FDA and await approval before starting the study.
2) Submit 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).
3) Assure IRB/Ethics Committee and Regulatory Approval (where applicable) is obtained.
4) Select and train monitors.
5) Select and train Investigators and study personnel.
6) Obtain agreement letter and c.v. of each Investigator.
7) Control shipment of devices and surgical tools.
8) Conduct overall administration of study.
9) Investigate unanticipated, device-related adverse events.
10) Document protocol deviations and violations.
11) Report and respond to the DSMB.

3-11-5-4 DSMB

1) The responsibilities of the DSMB are outlined in the DSMB Charter (see Attachment 4-10).

3-11-6 Subject Compensation

Subjects will not be paid for participation in this study. However, they will be provided a small stipend for travel and accommodation expenses associated with the study treatment and follow-up requirements.

3-12 *Study Timetable*

Study initiation is planned for July 2018. Study enrollment of up to 135 subjects is expected to be completed by March 2019. All subjects are expected to complete the study by April 2020. Monitoring is expected to be completed by June 2020.

4 Attachments

4-1 *3-day Voiding Diary*

4-2 *Manuals, and Labels*

4-3 *Investigator's Brochure*

4-4 *Patient Trial Brochure and Advertisement*

4-5 *Informed Consent Document*

4-6 *Patient Global Impression of Improvement*

4-7 *Patient Implantation Card*

4-8 *Case Report Forms*

4-9 *Adverse Event Form*

4-10 *DSMB Charter*

4-11 *OUS Study for Hypertension Protocol*

4-12 *OUS Study for Hypertension CRFs for Infections*

4-13 *OUS Study for Hypertension DSMB Letter Recommending Suspension of Implantation at Site 12*

4-14 *SNS Risk Assessment (110-1493)*

4-15 *Summary of Risks and Mitigations*

4-16 *Design Verification and Validation Reports*

4-17 *Ethylene Oxide Sterilization Validation Reports*

4-18 *Sterile Packaging Validation Report*

4-19 *Engineering Drawings*

4-20 *eCoin™ Device Materials*

4-21 *Template Investigator Agreement*

4-22 *Clinical Monitoring Plan*

4-23 *Assembly Procedure eCoin™ Device*

4-24 *Assembly Procedure Sterilization and Packaging Clinical Monitoring Plan*

4-25 *List of Investigators, CVs, and Centers*

4-26 *303-1122 Software Design Specification SNS*

4-27 *Biocompatibility Reports*

4-28 *Bacterial Endotoxins Test Method*

4-29 *Bioburden Levels and Raw Data*

4-30 *Battery Receiving Inspection Instructions*

4-31 *References*

4-32 *eCoin™ for OAB Feasibility: Safety*

4-32-1 Adverse Event Table

4-32-2 Subject 01-10 One Month Follow-up Implant Site Picture

4-32-3 Subject 07-17 AE report

4-33 *eCoin™ for OAB Feasibility Study Protocol*