Valencia Technologies Corporation

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

Statistical Analysis Plan
Version 3.0
August 28, 2019

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Protocol G170301 Statistical Analysis Plan

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Synopsis

Protocol title	A multicenter, single-arm study designed to evaluate the safety and effectiveness of eCoin™ tibial nerve stimulation in subjects with urgency urinary incontinence (UUI)
Treatment assignment	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™.
Study design	After screening and baseline assessments, the eCoin™ neuromodulation device will be implanted subcutaneously in the right or left leg of subjects. After a 4 week implant healing period, all subjects will have a programming visit where the device will be activated (turned on). Subjects will be followed for 48 weeks post-device activation (equivalent to 52 weeks post-implantation). All subjects will be explanted after the final study visit at 48 weeks post-activation.
Analysis population	The primary analysis population for the effectiveness and safety analyses will be the intent-to-treat (ITT) population: all enrolled subjects who undergo a procedure for implantation of eCoin™.
Primary efficacy outcome	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
Key secondary efficacy outcome	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
Primary safety outcome	Device-related adverse events from implantation to 52 weeks after implantation of eCoin™
Key secondary safety outcome	Device-related adverse events from implantation to 28 weeks after implantation of eCoin™
Statistical method for primary efficacy analysis	The primary efficacy analysis will be based on the ITT population. The proportion of responders, defined as subjects achieving at least a 50% reduction from baseline in the number of urgency urinary incontinence episodes, along with its 2-sided 95% exact Clopper-Pearson confidence interval will be summarized after 48 weeks of therapy. The performance goal for this study is to show that at least 40% of subjects are responders after 48 weeks of therapy.

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Abbreviations

AE	adverse event
CRF	case report form
FCS	fully conditional specification
HRQoL	Health-Related Quality of Life
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
OAB	overactive bladder
OABq	Overactive Bladder Symptom Quality of Life Questionnaire
PGI-I	Patient Global Impression of Improvement Questionnaire
PP	per-protocol
PT	preferred term
PVR	post void residual
SAE	serious adverse event
SAP	statistical analysis plan
SCI	Statistics Collaborative, Inc.
SOC	system organ class
TEAE	treatment-emergent adverse event
TENS	transcutaneous electrical nerve stimulation
UUI	urgency urinary incontinence

1. Introduction

This statistical analysis plan (SAP), which is based on Version 3.6 of the study protocol dated August 27, 2019, defines the methods and analyses that Valencia Technologies Corporation (henceforth, Valencia) plans to use to analyze the data from Protocol G170301. If the protocol is subsequently amended, this SAP may be amended as well. If there are minor differences between the analyses described in the protocol and the analyses in the SAP, the analyses in the SAP will prevail.

2. Investigational plan

2.1. Study design

Valencia's protocol G170301 is a multicenter, single-arm study designed to evaluate the safety and effectiveness of eCoin™ tibial nerve stimulation in subjects with urgency urinary incontinence (UUI). Up to 135 subjects, with a target of 120 subjects, who meet all inclusion and exclusion criteria and have provided informed consent will be enrolled to participate. All subjects will be scheduled to receive the investigational therapy (eCoin™ for UUI).

The eCoin™ neuromodulation device will be implanted subcutaneously in the right or left leg of subjects. After a 4 week implant healing period, all subjects will have a programming visit during which the device will be activated (turned on). Subjects will be followed for 48 weeks post-device activation (equivalent to 52 weeks post-implantation). All subjects will be explanted after the final study visit at 48 weeks post-activation.

2.2. Long-term follow-up study

All subjects will be allowed to consent to extended follow-up. These subjects will not be explanted at 48 weeks post-activation, and will have the option to be followed for an additional 1 to 2 years. These subjects will be explanted shortly after their 96 week post-activation visit or their 144 week post-activation visit.

2.3. Overactive bladder (OAB) medications

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

2.4. Transcutaneous electrical nerve stimulation (TENS) protocol

A secondary motivation for this trial is to ascertain whether there is a relationship between responders to transcutaneous electrical nerve stimulation (TENS) and responders to eCoin™ therapy. Subjects will receive a TENS unit at baseline with instructions to perform TENS of the tibial nerve twice daily for seven days. 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 implantation with eCoin™. Response or lack of response to the TENS protocol does not affect subject eligibility.

2.5. Eligibility criteria

See the protocol for eligibility criteria.

After enrollment for this study began, Valencia discovered that one center had implanted the eCoin™ neuromodulation device in several subjects who had not met the eligibility criteria. Valencia will implement further on-site training in an effort to prevent any additional subjects from being consented and enrolled in the study without meeting all eligibility criteria. Any subjects enrolled who do not meet all eligibility criteria where the eligibility violations are mendable and found prior to device activation (e.g. missing a test at screening or not being washed off of pharmacological treatment of overactive bladder for at least two weeks prior to baseline) will be re-baselined. Subjects enrolled who do not meet eligibility criteria will still be included in the safety and efficacy analyses.

3. Study objectives and outcome measures

The G170301 study is designed to evaluate the safety and efficacy of eCoin™ tibial nerve stimulation in subjects with UUI. See Table 1 for the study objectives and outcome measures. The primary outcomes will be measured after 48 weeks of eCoin™ therapy (equivalent to 52 weeks post-implantation). The secondary outcomes will be measured at 24 weeks of eCoin™ therapy (equivalent to 28 weeks post-implantation). The primary and secondary efficacy outcome measures will be based on data collected from 3-day voiding diaries. The diaries should be completed over three consecutive days during the seven days prior to each visit. Accordingly, the primary efficacy outcome measured at the post-activation week 48 visit will be based on voiding diary data collected within 7 days prior to the week 48 visit.

Table 1. Study objectives and outcome measures

Primary effectiveness Objective: to assess the effectiveness of eCoin™ on the proportion of responders, that is, subjects achieving at least a 50% improvement in the number of UUI episodes per 24 hours on a 3-day voiding diary after 48 weeks of therapy Assessment of outcome: proportion of responders after 48 weeks of therapy
Key secondary effectiveness Objective: to assess the effectiveness of eCoin™ on the proportion of responders, that is, subjects achieving at least a 50% improvement in the number of UUI episodes per 24 hours on a 3-day voiding diary after 24 weeks of therapy Assessment of outcome: proportion of responders after 24 weeks of therapy
Primary safety Objective: to assess safety 52 weeks after implantation of eCoin™ Outcome: device-related adverse events from implantation to 52 weeks after implantation of eCoin™
Key secondary safety Objective: to assess safety 28 weeks after implantation of eCoin™ Outcome: device-related adverse events from implantation to 28 weeks after implantation of eCoin™
Secondary The following secondary objectives and outcomes will be based on data after both 24 and 48 weeks from activation: Objective: to evaluate the effectiveness of eCoin™ with respect to the following outcome measures: • Proportion of subjects achieving 75% improvement in the number of UUI episodes per 24 hours on a 3-day voiding diary • Proportion of subjects achieving 100% improvement in the number of UUI episodes per 24 hours on a 3-day voiding diary • Change from baseline in the number of UUI episodes per 24 hours on a 3-day voiding diary • Change 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 • Change from baseline in the number of urgency episodes per 24 hours on a 3-day voiding diary • Change 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 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

4. Study schedule

Study visits will be conducted as presented in Exhibit 1. Study day is presented in reference to the device initial activation ("Day 1"). The enrollment process consists of screening (including obtaining written consent), completing the baseline evaluation, implanting the eCoin™ system, and establishing the participant's amplitude setting. Subjects will return two weeks after implantation for an incision healing check (Visit 4). The eCoin™ device will be activated four weeks after implantation (Visit 5). Follow-up assessments will occur at 4 (Visit 6), 8 (Visit 7), 12 (Visit 8), 24 (Visit 9), 36 (Visit 10), and 48 (Visit 11) weeks post-activation. Re-programming visits will occur at 8 (Visit 7b), 24 (Visit 9b), and 36 (Visit 10b) weeks post-activation. The device explant visit (Visit 12) will occur between 0 and 15 days from Visit 11 and a final incision healing check (Visit 13) will occur 2 weeks post-explantation.

Exhibit 1. Schedule of visits

Procedure	Screen-ing (Visit 1)	Base -line (Visit 2)	Implant procedure (Visit 3)	Incision healing check (Visit 4)	Initial activation (Visit 5)	Visit 6	Visit 7	Visit 7b	Visit 8	Visit 9	Visit 9b	Visit 10	Visit 10b	Primary endpoint (Visit 11)	Explant visit (Visit 12)	Incision healing check (Visit 13)
	Day -106 to -33	Day -78 to -30	Day –43 to -23	Day -34 to -4	Day 1	Day 23 to 33	Day 51 to 61	Day 51 to 68	Day 79 to 89	Day 163 to 173	Day 163 to 180	Day 247 to 257	Day 247 to 264	Day 331 to 341	Day 331 to 356	Day 340 to 375
Informed consent	X															
Urinalysis	X															
Post void residual (PVR)	X															
Demographics, screening exam, physical exam, and medical history	X															
Vital signs[a]	X	X	X	X		X	X		X	X		X		X		X
Eligibility determination	X	X														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3-day voiding diary[b]		X	X			X	X		X	X		X		X		
OABq assessment		X	X			X	X		X	X		X		X		
TENS instructions		X														
Patient reported satisfaction assessment[c]			X			X	X		X	X		X		X		
Patient global impression of improvement[c]			X			X	X		X	X		X		X		
Return of TENS unit			X													
Implant or explant procedure			X												X	
Incision assessment				X												X
Activation / re-programming					X			X			X		X			
Completion of study																X

a. Weight, height, body mass index, temperature, pulse rate, respiratory rate, and blood pressure will be assessed at the screening visit. Only pulse rate, temperature, and blood pressure will be collected at subsequent visits. In addition, respiratory rate will be collected at visit 4 and visit 13.
b. 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.
c. Visit 3 (Implant procedure) will assess satisfaction and impression of improvement relative to the TENS therapy. All other visits will be relative to the eCoin™ neuromodulation device.

5. Analysis populations

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.

5.1. Intent-to-Treat (ITT)

The intent-to-treat (ITT) population will consist of all enrolled subjects who undergo a procedure for implantation of eCoin™. This is the primary analysis population for the safety and effectiveness analyses.

5.2. Modified Intent-to-Treat (mITT)

The modified intent-to-treat (mITT) population will consist of all eligible subjects in the ITT population.

5.3. OAB drug-free

The OAB drug-free population will include all subjects in the mITT population who took no medication for OAB during the study period.

5.4. Per-protocol (PP)

The per-protocol population will include all subjects in the OAB drug-free population with no major protocol violation. See Section 8.2 for a description of major protocol deviations.

5.5. Responders

The responders population will include all subjects who respond to treatment, defined as those who achieve at least a 50% reduction in the number of UUI episodes from baseline to 48 weeks post-activation.

5.6. TENS cohort analysis

The TENs cohort analysis will consist of the ITT population except those who do not respond to the TENS protocol. Response to the TENS protocol 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.

5.7. Long-term completers

The long-term completers population will consist of 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.

6. Sample size consideration

The study protocol specifies enrollment of up to 135 subjects, with a target of 120 subjects. The study is designed to estimate the proportion of responders. A responder is a subject who achieves a clinically meaningful level of improvement, defined as having at least a 50% improvement in the number of UUI episodes per 24 hours on a 3-day voiding diary after 48 weeks of therapy.

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_0 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 ≤ 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 a 1-sided 2.5% significance level. Calculations were performed using PASS 2019, v19.0.2.

For illustration purposes, the table below shows 95% confidence intervals for various observed proportions of responders, assuming a sample size of 120. An observed proportion of responders of at least 0.50 will give a lower bound of the 2-sided 95% exact Clopper-Pearson confidence interval slightly above 0.40.

Table 2. Confidence intervals by observed proportion of responders

	Observed proportion of responders					
Sample size=120	0.5	0.55	0.6	0.7	0.8	0.9
	(0.41, 0.59)	(0.46, 0.64)	(0.51, 0.69)	(0.61, 0.78)	(0.72, 0.87)	(0.83, 0.95)

The published literature on sacral neuromodulation supports the clinical significance of a 40% responder rate. The justification for the performance goal of 40% comes from published literature for the approved third-line device for UUI—a fully-implanted neuromodulation device called "Interstim".

The observed modified ITT responder rates in the well-cited ROSETTA study were 51% in patients who had at least 4 months of completed diaries and 52% in patients who had at least 6 months of completed diaries. The estimated lower bounds of the 95% confidence intervals are 43% and 41%, respectively [1]. Importantly, these results are not ITT. In the review of the Insite study, the Sponsor derived an ITT responder rate of 59% from the available as-treated analysis. This deduced ITT rate leads to a lower bound of the 95% confidence interval of 44% [2]. Both of these published data were measured at 6 months whereas the primary efficacy endpoint in this study is at 48 weeks. If either published study was extended to 12 months, the number of subjects responding would likely be even smaller, resulting in a lower bound at or below 40%.

7. Statistical analysis: general conventions and considerations

Descriptive and inferential statistics will be used to summarize results of Protocol G170301. Standard descriptive statistics, such as number of subjects, mean, standard deviation, quartiles, minimum, and maximum, will be calculated for continuous variables. For discrete variables, descriptive analyses will display numbers of subjects and related percentages.

All tabular presentations will display one column of results showing the single treatment regimen of this study. Medical history and adverse event summaries will display coded results using the appropriate coding dictionaries. Any partial dates in the medication and adverse event data will be imputed. See Section 13.1 for details. All presentations and statistical analyses will be generated using SAS® Version 9.4 or higher or other validated software.

7.1. Study days

For the purpose of the analysis, study day will be calculated relative to device implantation or initial activation, depending on the analysis:

- Study day relative to implantation = date of visit/test – implantation date + 1.
- Study day relative to activation = date of visit/test – activation date + 1.

If the date of visit/test occurs before the date of interest, then study day = date of visit/test – implantation/activation date. Day 0 will not exist.

7.2. Baseline

Baseline efficacy measures will be defined as the last measure taken up to and including the baseline visit (Visit 2). Baseline safety measures will be defined as the last measure taken prior to device implantation.

7.3. Changes to planned analyses

Changes to the analyses described in this plan will be fully documented in a revised version of the plan written prior to locking the study database and conducting the primary outcome

analysis. Changes made after locking the study database will be described in the clinical study report and characterized as "exploratory".

8. Study population summaries

8.1. Subject disposition

The number and percentage of subjects who fall into each of the following categories will be presented:

- Total enrolled
- Total enrolled subjects who undergo a procedure for implantation of eCoin™ (the ITT population)
- Total implanted with eCoin™
- Subjects in the ITT population meeting all eligibility criteria (the mITT population)
- Implanted subjects with the device activated
- OAB drug-free population
- Per-protocol population
- Responders population
- TENS cohort analysis population
- Early termination from the study
- Long-term completers
- Completed study

For subjects who withdraw from study early, the number and percentage withdrawing by reason will also be presented. The eCoin™ device must be recommended to be explanted if an early termination occurs.

A by-subject listing of early terminations will also be presented, including study day and the reason for early termination.

8.2. Eligibility and protocol deviations

Inclusion and exclusion criteria not met at screening (screen failures) will be presented for all screened but not enrolled subjects. Eligibility criteria not met for enrolled subjects will also be presented.

Protocol deviations are collected throughout the study and will be summarized. A major protocol deviation is defined as one that affects the safety of the subject or the scientific validity of the results. A minor deviation is defined as one that does not affect the safety of the subject or the scientific validity of the results.

The following are examples of minor protocol deviations:

- Use of OAB medications
- Follow-up visits that occurred outside the protocol required time frame because of the participant's schedule
- Study procedure conducted out of timeframe
- Participant failure to initial every page of the consent form
- Participant failure to return the patient diary
- Copy of the informed consent form not given to the participant
- Missing original signed consent, but a copy exists
- Patient not given implant card

8.3. Demographics and baseline characteristics

Demographic and baseline characteristics will be summarized by age, gender, ethnicity, race, current smoker, and any abnormal findings from a complete physical exam.

Age in years will be calculated as the integer portion of the following:

$$[(\text{Date of enrollment} - \text{Date of birth}) + 1] / 365.25$$

Percentages will be calculated relative to the number of subjects enrolled.

OAB history will be presented. It will include duration of OAB and success of prior treatments (PTNS therapy, TENS therapy, OAB medications, and Botox). Success will be categorized as "yes", "no", or "short-term/partial response."

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class (SOC) and preferred term (PT).

Prior medications, defined as medications started prior to device implantation, will be presented by their drug generic names, as reported on the prior medication case report form (CRF). The number and percentage of subjects who took at least one drug within each generic type will be presented. Prior medications will be presented separately for OAB and non-OAB medications.

8.4. Treatment exposure

Duration of device implantation and device activation, in weeks, will be summarized for all enrolled subjects.

8.5. Concomitant therapy

A concomitant therapy is defined as therapy (other than eCoin™) started on or after implantation. A therapy taken prior to implantation is not considered a concomitant therapy. If a subject stops taking or changes the dosage of a medication recorded in the medical history at screening, or begins taking a new medication, then this medication will be included as a concomitant medication. Information on concomitant medications will be summarized by generic name as reported on the concomitant medication CRF.

The number and percentage of subjects who took at least one drug within each generic type will be presented. Concomitant medications will be presented separately for OAB and non-OAB medications.

9. Follow-up assessments

9.1. 3-day voiding diary assessments

Throughout the study, subjects will complete 3-day voiding diaries to quantify voiding behavior, symptoms, and incontinence. The diary should be completed over three consecutive days during the seven days prior to each visit involving a 3-day diary. The site should telephone subjects to remind them of the diary requirement at least three days prior to each visit. The voiding diaries will collect the following information per 24 hours over 3 days:

- total number of daytime voids (6:01 a.m. – 9:59 p.m.)
- total number of night voids (10:00 p.m. – 6:00 a.m.)
- total number of voids
- total amount voided
- total number of toilet urgent episodes
- total number of leaks
- total amount leaked
- total number of urge leaks

The voiding diary CRF will report the total over the three days for each measure, which will then be averaged. All efforts will be made to ensure that all diaries are completed over the full three day period. Any incomplete diaries will be reported and averaged over the total days in which they were completed.

9.2. Patient surveys

Three separate patient surveys will be administered several times over the course of the study.

9.2.1. Overactive Bladder Symptom Quality of Life Questionnaire (OABq)

The OABq is a 33-item questionnaire that measures quality of life. It contains a "symptom bother" subscale and a Health-Related Quality of Life (HRQoL) subscale. Each question is scored using a six-point scale, with higher scores indicating more severe symptoms or poorer

quality of life. The scores are summed separately for the 2 subscales and transformed into 2 composite scores ranging from 0 to 100.

9.2.2. Patient reported satisfaction assessment

The patient reported satisfaction assessment will rate each subject's level of satisfaction with the eCoin™ neuromodulation system on a scale of one to five, where one is "Not at all satisfied" and five is "Completely satisfied." The satisfaction assessment will ask the following three questions:

- "How satisfied is the subject with the eCoin device itself?"
- "How satisfied is the subject with the programming of the device?"
- "How satisfied is the subject with the stimulation of the device?"

9.2.3. Patient Global Impression of Improvement (PGI-I) questionnaire

The PGI-I questionnaire will assess patient-reported overactive bladder condition on a scale of one to seven. The questionnaire inquires "Compared to how the subject's urinary leakage was before treatment, subject now reports that he or she feels", with responses ranging from one ("Very much better") to seven ("Very much worse").

10. Efficacy analyses

10.1. Primary efficacy analysis

This open label, single-arm study will evaluate the effectiveness of eCoin™ in reducing episodes of UUI. The primary efficacy outcome is achieving at least a 50% reduction from baseline in the number of UUI episodes per 24 hours on a 3-day voiding diary after 48 weeks of eCoin™ tibial nerve stimulation. The proportion of subjects achieving at least a 50% reduction along with its 2-sided 95% exact Clopper-Pearson confidence interval will be summarized for subjects in the ITT population.

Because this study is investigating an implanted device, nearly all implanted subjects are expected to have data on the primary endpoint. Careful clinical planning that minimizes

subject dropouts will be implemented. Any missing data for the primary outcome will be handled as follows:

- Any subject explanted, except for those explanted for an 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 UUI 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. See Section 13.2 for further details and example SAS code.
- 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. See Section 13.2 for further details and example SAS code.
- Any subject who undergoes a procedure for implantation of eCoin™, whether or not the device is activated, will be treated as if they were activated.

10.2. Key secondary efficacy analysis

The key secondary effectiveness outcome is achieving at least a 50% reduction from baseline in the number of UUI 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 for subjects in the ITT population.

Any missing data for the key secondary efficacy outcome will be handled the same as missing data for the primary outcome.

10.3. Secondary efficacy analyses

The secondary efficacy outcomes will be based on data after both 24 and 48 weeks from device activation. The analyses will be done for the ITT population, unless otherwise specified.

The proportion of subjects achieving a 75% improvement from baseline in the number of UUI episodes per 24 hours on a 3-day voiding diary will be summarized along with its 2-sided 95% exact Clopper-Pearson confidence interval. The proportion of subjects achieving dryness (100% improvement from baseline in UUI episodes) will be summarized along with its 2-sided 95% exact Clopper-Pearson confidence interval. Any missing data for either analysis will be handled the same as missing data for the primary outcome.

The change from baseline will be summarized with descriptive statistics (n, mean, median, standard deviation, 25^{th} quartile, 75^{th} quartile, minimum, and maximum) for the following measures per 24 hours on a 3-day voiding diary. Boxplots with observed values and change from baseline may also be presented. Missing data will not be imputed for these analyses.

- Number of urgency urinary incontinence episodes
- Number of urinary voids (for subjects in the ITT population whose baseline value is more than 10 voids per day)
- Number of urgency episodes
- Number of nocturia episodes

The change from baseline in OABq score will be summarized with descriptive statistics. Boxplots with observed values and change from baseline may also be presented. OABq scores will be presented by subscale composite score (symptom bother and Health-Related Quality of Life). Missing data will not be imputed for these analyses.

Observed scores for the patient reported satisfaction assessment and PGI-I questionnaire will be summarized with descriptive statistics. Boxplots with observed values may also be

presented. Missing data will not be imputed for these analyses. The scores for the three-question patient reported satisfaction assessment will be presented by question.

10.4. 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.

10.4.1. Exploratory subgroup analyses

The proportion of subjects who respond to treatment (achieve at least a 50% reduction from baseline in the number of UUI episodes per 24 hours on a 3-day voiding diary after 48 weeks of eCoin™ tibial nerve stimulation) will be summarized for various subgroup populations based on baseline characteristics, demographics, and effectiveness endpoints. For each subgroup, a forest plot will show the proportion of responders along with its 95% confidence interval. A logistic regression may also be used to describe the relationship between response to treatment and different subgroup populations.

10.4.2. 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. Any subjects who have taken OAB medications will be included in the primary effectiveness outcome variable analysis. 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.

11. Safety summaries

11.1. Adverse events

Adverse events (AEs) will be continuously monitored throughout the study. Investigators will classify each AE according to its relationship to study device (certainly, probably, possibly, unlikely, not related, or unclassified), intensity (mild, moderate, or severe), and seriousness. AEs will be coded using version 20.0 or later of the MedDRA dictionary and summarized by system organ class (SOC) and preferred term (PT). AEs will be summarized by subject, not event. All summaries will include the number of subjects who undergo a procedure for implantation of eCoin™ and the number of subjects with at least one event.

All AE presentations will summarize treatment-emergent adverse events (TEAEs), defined as AEs with onset on or after the device implantation procedure. AEs with completely missing onset date will be assumed treatment-emergent events. The ITT population will be used for all AE analyses.

The following presentations of treatment-emergent adverse events will be generated:

- All adverse events
- All adverse events related to study device (i.e., AEs classified as certainly, probably, and possibly related)
- All adverse events related to study device up to 52 weeks after implantation (the primary safety outcome)
- All adverse events related to study device up to 28 weeks after implantation (the secondary safety outcome)
- All adverse events related to study procedure
- Serious adverse events, and
- Adverse events leading to study discontinuation.

All AEs will be presented in a listing with SOC, PT, onset and resolution dates, study day relative to implantation, study day relative to device activation, seriousness, relationship to study device, relationship to study procedure, actions taken with study device, and outcome.

11.2. Assessment of the incision

All subjects will have an incision healing check visit two weeks after both implantation and explantation. Any adverse symptoms (site pain, site warmth, site swelling, fever, etc.) will be summarized by visit and severity (mild, moderate, or severe).

11.3. Vital signs

Vital signs (weight, height, body mass index, temperature, pulse rate, respiratory rate, and blood pressure) are collected according to the schedule in Exhibit 1. All available vital signs data will be presented in a by-subject listing.

12. References

1. Amundsen CL, Richter HE, Menefee SA, et al. (2016). OnabotulinumtoxinA vs sacral neuromodulation on refractory urgency urinary incontinence in women: a randomized clinical trial. *JAMA* 316(13):1366–1374.

2. Siegel S, Noblett K, Mangel J, et al. (2015). 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): 224-230.

13. Appendix

13.1. Partial dates

Partial dates in the medication and adverse events data will be imputed. Completely missing dates will not be imputed. Partial start dates will be imputed as follows:

- Dates with only missing day will be imputed to the first of the month. However, if the month and year of the partial date are the same as the month and year of the device implantation date, the partial start date will be imputed to the device implantation date.
- Dates with missing day and month will be imputed to January 1st of the given year. However, if the year of the partial date is the same as the year of the device implantation date, the partial start date will be imputed to the device implantation date.

Partial end dates will be imputed as follows:

- Dates with only missing day will be imputed to the end of the month.
- Dates with missing day and month will be imputed to December 31st of the given year.

13.2. Missing data for primary efficacy outcome

The primary efficacy analysis is based on the proportion of responders at 48 weeks post-activation. Subjects for whom 48 week post-activation data are unavailable but the device is known not to have been explanted or subjects who have been explanted for an MRI will have the primary endpoint data imputed. The missing data for the primary effectiveness outcome variable will be assumed missing at random and will be handled with multiple imputation.

The multiple imputation procedure will use fully conditional specification (FCS) and create 100 imputed datasets. The type of model used for FCS will depend on the variable with missing outcome data. Continuous variables will use regression with predictive mean matching; ordinal and nominal classification variables will use response logistic regression. All variables will be assessed for collinearity before inclusion in the multiple imputation model. Table 3 lists the variables with descriptions that will be used in the model.

The imputation will follow the sample SAS version 9.4 code provided in Exhibit 2. The SAS code may be modified slightly as needed according to software updates and compatibility with actual data. For example, the order of the variables in the VAR statement of the PROC MI procedure will be adjusted to approach monotone missingness. The variables are imputed sequentially in the order specified in the VAR statement with FCS.

The 100 complete datasets created by multiple imputation will be analyzed separately by imputation. The SAS PROC MIANALYZE procedure will be used to combine results from the 100 analyses.

Table 3. Variables in the multiple imputation model

Type	Variable	Description
Binary	SEX	Sex
Continuous	AGE	Age
Continuous	BMI	BMI at baseline
Binary	TENSR	Response to the TENS protocol
Continuous	BASE_OABQ	Baseline OABq total score
Continuous	OABQ4	Week 4 OABq total score
Continuous	OABQ8	Week 8 OABq total score
Continuous	OABQ12	Week 12 OABq total score
Continuous	OABQ24	Week 24 OABq total score
Continuous	OABQ36	Week 36 OABq total score
Continuous	OABQ48	Week 48 OABq total score
Ordinal	PGI4	Week 4 PGI-I questionnaire score
Ordinal	PGI8	Week 8 PGI-I questionnaire score
Ordinal	PGI12	Week 12 PGI-I questionnaire score
Ordinal	PGI24	Week 24 PGI-I questionnaire score
Ordinal	PGI36	Week 36 PGI-I questionnaire score
Ordinal	PGI48	Week 48 PGI-I questionnaire score
Continuous	BASE_VOID	Baseline urinary voids averaged per 24 hours on a 3-day voiding diary
Continuous	VOID4	Week 4 urinary voids averaged per 24 hours on a 3-day voiding diary
Continuous	VOID8	Week 8 urinary voids averaged per 24 hours on a 3-day voiding diary
Continuous	VOID12	Week 12 urinary voids averaged per 24 hours on a 3-day voiding diary
Continuous	VOID24	Week 24 urinary voids averaged per 24 hours on a 3-day voiding diary
Continuous	VOID36	Week 36 urinary voids averaged per 24 hours on a 3-day voiding diary
Continuous	VOID48	Week 48 urinary voids averaged per 24 hours on a 3-day voiding diary
Continuous	BASE_UUI	Baseline UUI episodes averaged per 24 hours on a 3-day voiding diary
Continuous	UUI4	Week 4 UUI episodes averaged per 24 hours on a 3-day voiding diary
Continuous	UUI8	Week 8 UUI episodes averaged per 24 hours on a 3-day voiding diary
Continuous	UU12	Week 12 UUI episodes averaged per 24 hours on a 3-day voiding diary
Continuous	UUI24	Week 24 UUI episodes averaged per 24 hours on a 3-day voiding diary
Continuous	UUI36	Week 36 UUI episodes averaged per 24 hours on a 3-day voiding diary
Continuous	UUI48	Week 48 UUI episodes averaged per 24 hours on a 3-day voiding diary

Exhibit 2. Sample SAS code for multiple imputation for primary analysis

```
**** Impute missing values to create 100 imputed datasets;
proc mi data=OBSERVE nimpute=100 seed=938279 out=OBSERVE2;
   class SEX TENSR PGI4 PGI8 PGI12 PGI24 PGI36 PGI48;
   var SEX TENSR PGI4 PGI8 PGI12 PGI24 PGI36 PGI48 BMI AGE BASE_UUI UUI4 UUI8 UUI12
       UUI24 UUI36 UUI48 BASE_VOID VOID4 VOID8 VOID12 VOID24 VOID36 VOID48 BASE_OABQ
       OABQ4 OABQ8 OABQ12 OABQ24 OABQ36 OABQ48;
   fcs regpmm (BASE_UUI UUI4 UUI8 UUI12 UUI24 UUI36 UUI48 BASE_VOID VOID4 VOID8
               VOID12 VOID24 VOID36 VOID48 BASE_OABQ OABQ4 OABQ8 OABQ12 OABQ24 OABQ36
               OABQ48 / details) ;
   fcs logistic (SEX TENSR PGI4 PGI8 PGI12 PGI24 PGI36 PGI48 / link=logit
                 likelihood=augment);
run;
```