CLINICAL STUDY PROTOCOL

Version B: 12 November 2020

Axonics SNM Registry Study (ARTISTRY)

Protocol Number 105-0076

SPONSOR:

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1. STUDY SYNOPSIS

Study Title:	**A**xonics Sac**R**al Neuromodula**TI**on **S**ystem Regis**TRY** study (ARTISTRY)
Study Device:	Axonics Sacral Neuromodulation System (SNM) System(s).
Study Design:	Prospective, multi-center, open-label registry study
Indication for Use:	The Axonics Sacral Neuromodulation Therapy for urinary control is indicated for the treatment of urinary retention (UR) and the symptoms of overactive bladder (OAB), including urinary urge incontinence (UUI) and significant symptoms of urgency-frequency (UF) alone or in combination, in patients who have failed or could not tolerate more conservative treatments. Axonics SNM therapy for bowel control is indicated for the treatment of chronic fecal incontinence (FI) in patients who have failed or are not candidates for more conservative treatments.
Objective:	To assess the post-market clinical outcomes with use of the Axonics Sacral Neuromodulation System(s)
Participants:	Approximately 300 study participants with the Axonics implantable neurostimulator (INS), with the indications for OAB, UR and FI.
Centers:	Approximately 30 centers (U.S. and Canada)
Study Duration:	The study duration is expected to be approximately 36 months. The enrollment phase will be approximately 24 months. Participants will participate in the study for 1 year post activation.
Outcome Measures:	**For all indications/patient populations:** ▪ Patient symptom questionnaire ▪ Participant satisfaction with treatment and charging questionnaire ▪ Edmonton Frail scale for participants ≥65 years old ▪ Medication usage & Healthcare utilization ▪ Device performance metrics ▪ Device-Related Adverse Events (AEs) ▪ Serious Adverse Events (SAEs)

For OAB:

- Quality of life questionnaires (ICIQ-OABqol)

For UR:

- AUA Urinary Symptom Index Questionnaire (AUA-SI)

For FI:

- Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS)
- Fecal Incontinence Quality of Life (FIQL)

For UF:

- O' Leary Sant

For Constipation:

- Cleveland Clinic Constipation Score (CCCS)
- Patient Assessment of Constipation Symptoms (PAC-SYM)

For Sexual Dysfunction:

- Female Sexual Function Index (FSFI)
- Sexual health inventory for Men (SHIM)

For participants that had a prior InterStim System:

- Conversion questionnaire

Effectiveness outcomes:

The following effectiveness endpoints are planned in participants with the External Trial stimulator (ETS)

- Trial responder rate – i.e. percentage of Trialed participants that were considered responders and received the INS implant

The following indication-specific effectiveness endpoints are planned in participants with an ETS or with Axonics lead wire and INS (i.e. Full System implant):

- Therapy responder rate at follow-up i.e. percentage of ETS or Full System implant (FS) participants that received at least 50% reduction in symptoms as compared to baseline and received an INS
- Change in indication-specific patient symptoms from baseline to follow-up
- Participant satisfaction with therapy and charging

- For OAB-UUI and OAB-UF, change in ICIQ-OABqol score at follow-up compared to baseline
- For OAB-UF, change in O'Leary Sant score at follow-up compared to baseline
- For UR, change in AUA-SI score at follow-up compared to baseline
- For FI, change in CCF-FIS and FIQL scores at follow-up compared to baseline

Safety outcomes: Rate of Serious Adverse Events (SAEs)

Rate of device-related AEs, including their seriousness

Inclusion Criteria:

1. Patients scheduled to be trialed with the Axonics External Trial System (ETS), or patients scheduled to receive an Axonics Implantable neurostimulator (INS) or Axonics FS implant
2. Willing and capable of providing informed consent
3. Capable of participating in all testing associated with this clinical investigation

Exclusion Criteria:

For all indications:

1. Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints
2. Any psychiatric or personality disorder at the discretion of the study physician
3. History of allergic response to titanium, zirconia, polyurethane, epoxy, or silicone
4. A female who is breastfeeding
5. A female with a positive urine pregnancy test

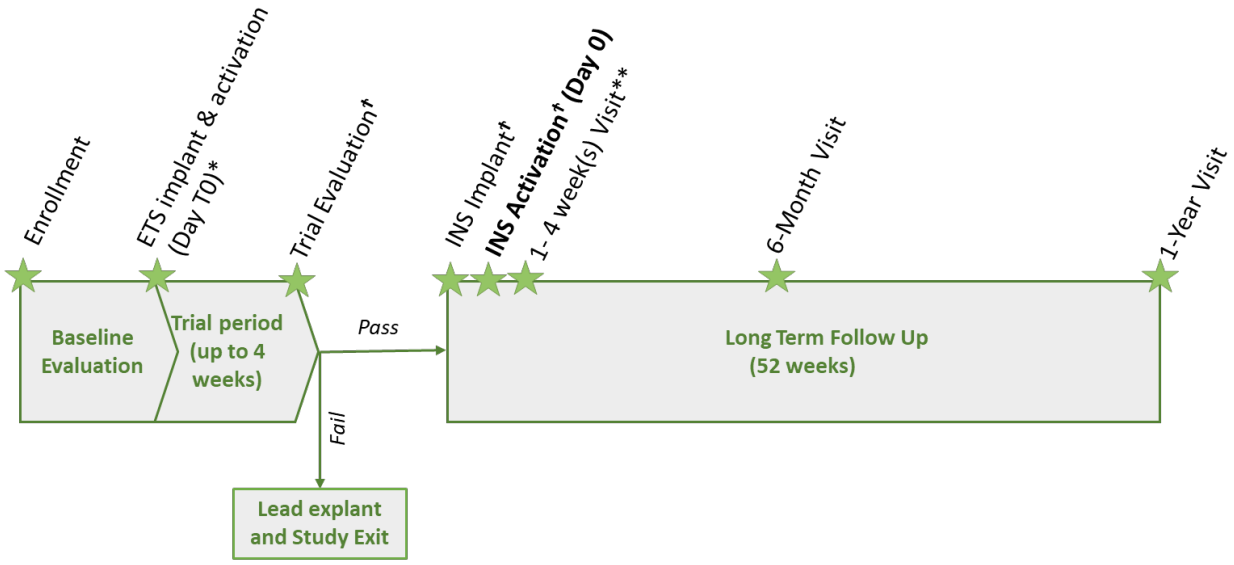
For OAB & UR:

6. Current urinary tract mechanical obstruction (e.g. benign prostatic enlargement or urethral stricture)
7. Current symptomatic urinary tract infection (UTI)

For FI only:

8. Rectomucosal prolapse or congenital anorectal malformation

Figure 1: Study schematic



*Some patients may not get an ETS system(Trial) and move directly to the INS implant.
† Trial evaluation, INS implant and INS Activation may occur on the same day.
**Visit to be completed anytime between 1-4 week(s) post- INS implant

Figure 2: Participant Flowchart

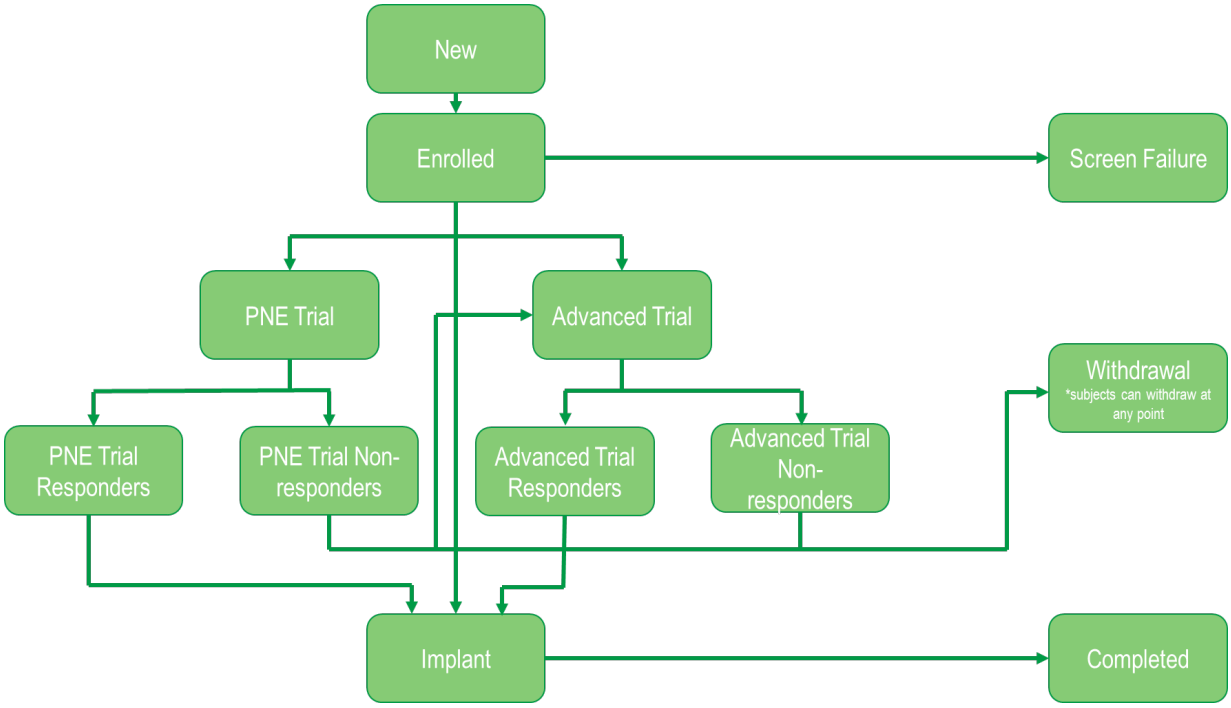


Table 1: Study Visit Schedule

Visit schedule & Assessments	Baseline	Trial surgery & Activation (Day T0)	Trial Evaluation (Day 3-14)* (Day 7-28)**	INS Implant & Activation (Day 0) ***	1-4 Week (s) Visit (Day 3-31)	6-Month Visit (Day 160-200)	1-Year Visit (Day 320 - 410)	Unscheduled Visit
Informed Consent	X							
Demographics & Medical History	X							
Inclusion/ Exclusion Criteria	X							
Edmonton Frail Scale (EFS) *(In participants ≥ 65 years old¥)*	X							
Patient Symptoms Questionnaire	X		X†		X	X	X	
International Consortium for Incontinence Questionnaire - Overactive Bladder quality of life (ICIQ-OABqol) *(In OAB participants only)*	X				X	X	X	
AUA Urinary Symptom Index (AUA-SI) (*In UR participants only)*	X				X	X	X	
O' Leary Sant *(In UF participants only)* §	X				X	X	X	
Cleveland Clinic Florida- Fecal incontinence Score (CCF-FIS)§	X				X	X	X	
Fecal Incontinence Quality of Life (FIQL)Ⱶ	X				X	X	X	
Cleveland Clinic Constipation Score (CCCS)§	X				X	X	X	
Patient Assessment of Constipation Symptoms (PAC-SYM) ⱵⱵ	X				X	X	X	
Sexual Dysfunction questionnatires §§: Female Sexual Function Index (FSFI)/ Sexual Health Inventory for Men (SHIM)	X				X	X	X	
Participant Satisfaction with Treatment and Charging questionnaire††					X	X	X	
Conversion questionnaire *(in participants that had a prior Interstim full system and subsequently received an Axonics implant)*	X				X	X		
Medication Usage & Healthcare Utilization	X		X		X	X	X	X
Adverse Event Form		X	X	X	X	X	X	X
Device Performance		X		X	X	X	X	X

*For PNE evaluations, ** For Tined lead evaluations, ***Reset to Day 0 at INS Activation ¥ At the time of consent

† A question on "time to experience efficacy with Trial" will be asked at this time-point

§ At baseline, all participants will be administered these questionnaires. At follow-up, these questionnaires will be administered in participants that meet the following criteria at baseline: O'Leary Sant will be administered only in participants with baseline score ≥6; CCF-FIS will only be administered in participants with baseline CCF-FIS score ≥6 or participants that reported as having FI on the Patient Symptoms Questionnaire; CCCS will only be administered in participants with baseline CCCS score ≥15.

Ⱶ At baseline and follow-up visits, this questionnaire will be administered only in participants with baseline CCF-FIS score ≥6 or participants that reported as having FI on the Patient Symptoms Questionnaire

ⱵⱵ At baseline and follow-up visits, this questionnaire will be administered only in participants with baseline CCCS score ≥15

†† Charging-related questions from this questionnaire will not be administered at Trial Evaluation and 1-4 Week(s) Visit

§§ Gender-specific Sexual Dysfunction questionnaires will be administered only in participants who responded being sexually active at the time of the study visit. FSFI is a female-specific questionnaire, and SHIM is a male-specific questionnaire.

1 STUDY DESCRIPTION

1.1 History/Rationale

The American Urological Association guidance document provides an extensive and systematic literature review on the use of SNM for voiding dysfunction[1]. The guidance states that given the negative effects on quality of life associated with severe incontinence and frequency, the panel judged that benefits of SNM in the appropriate patients outweigh the risks/burdens.

The Axonics® SNM System (Axonics System) is FDA-approved and indicated for the treatment for bladder and bowel symptoms including overactive bladder (OAB), non-obstructive urinary retention (UR) and fecal incontinence (FI). As of August 2020, the Axonics System has been commercially implanted in approximately 4000 patients[2]. Additionally, two sponsored clinical studies (RELAX-OAB & ARTISAN-SNM) have implanted a total of 180 patients with symptoms of Overactive Bladder (OAB), including UUI, and urgency-frequency alone or in combination with UUI. Long-term results from both of these studies show that the Axonics System is safe and effective. Specifically, at 2 years, the ARTISAN-SNM study showed 93% success rate in patients with UUI[2]. Similarly, the RELAX-OAB study showed a 90% responder rate in OAB patients at 2 years[3].

1.2 Purpose

The ARTISTRY study is a post-market, clinical study designed to assess the real world clinical outcomes with use of the Axonics Sacral Neuromodulation System(s) for the treatment of the symptoms of OAB, UR, and FI.

1.3 Safety

The following types of Adverse Events will be recorded in the ARTISTRY study:

- Serious Adverse Events (SAEs), regardless of relatedness to the device or procedure
- Device-related AEs

The definition of Serious Adverse Events is provided in Section 7.5.

Specifically, the number and participant rates of device-related AEs (including device-related SAEs) will be tabulated and reported.

1.4 Outcome Measures

The following metrics will be measured according to the study schedule in Table 1:

[1] Gormley, E. A., Lightner, D. J., Burgio, K. L., Chai, T. C., Clemens, J. Q., Culkin, D. J., Vasavada, S. P. (2014). Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. Retrieved from https://www.auanet.org/common/pdf/education/clinical-guidance/Adult-Urodynamics.pdf.

[2] Company data on file up to end of August 2020

[3] Blok B, Van Kerrebroeck P, de Wachter S, et al. Two-year safety and efficacy outcomes for the treatment of overactive bladder using a long-lived rechargeable sacral neuromodulation system. *Neurourol Urodyn*. 2020;39(4):1108-1114.

For all indications:

- Patient Symptom Questionnaire
- Participant satisfaction with treatment and charging questionnaire
- Edmonton Frail scale for participants ≥65 years old
- Medication usage & Healthcare utilization
- Device performance metrics
- Device-related Adverse Events (AEs)
- Serious Adverse Events (SAE)

For OAB:

- International Consortium for Incontinence Questionnaire- Overactive Bladder quality of life (ICIQ-OABqol)

For UF :

- O' Leary Sant score

For UR:

- AUA Urinary Symptom Index (AUA-SI)

For FI:

- Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS)
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For Constipation:

- Cleveland Clinic Constipation Score (CCCS)
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For Sexual Dysfunction:

- Female Sexual Function Index (FSFI)
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For participants that had a prior InterStim System:

- Conversion questionnaire

1.5 Study Justification

The study will be a prospective, multi-center, single-arm, post-market registry study. Participant outcomes will be compared to their baseline, with participants serving as their own control.

The study is anticipated to begin enrollment in the last quarter of 2020 and is expected to complete enrollment in approximately 24 months. The study will be conducted at approximately 30 centers in the United States and Canada. The scheduled visits are shown in the Study Schematic (Figure 1) and Study Visit Schedule (Table 1). Figure 2 shows the Participant Flowchart throughout the study. Participants will be permitted unscheduled visits as needed.