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REVISION HISTORY

REV	DESCRIPTION OF CHANGE	**DCO**
A	Initial Release.	14878
B	• Added Fecal Incontinence references throughout document to include FI cohort for expansion of patient pool for long-term data collection • Replaced date range of implants occurring between March 2022 to 2023 or prior to March 1, 2023 to any patient ≥ 1-year post-implant is considered • Added clarification to Inclusion 4 – baseline diary must be pre-PNE • Added requirement for completion of bowel diary to support the FI cohort • Added protocol deviation reporting section for clarification	15626
C	• Removed inclusion criteria #5 • Changed minimum of 7-day pre-PNE bowel diary for FI to minimum of 5-day	15741

CLINICAL STUDY PROTOCOL
Protocol 105-0118, Revision C

15 May 2024

F15 FOLLOW-UP STUDY
Study to collect long-term clinical data for the recharge free Axonics SNM System (INS Model 4101)

SPONSOR:

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2. ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Record
FI	Fecal Incontinence
GCP	Good Clinical Practice
ICF	Informed Consent Form
IFU	Instructions for Use
INS	Implantable Neurostimulator
IRB	Institutional Review Board
ISO	International Standard Organization
OAB	Overactive Bladder
PHI	Protected Health Information
PI	Principal Investigator
PNE	Peripheral Nerve Evaluation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SNM	Sacral Neuromodulation
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect
UF	Urinary Frequency
UR	Urinary Retention
UUI	Urinary Urgency Incontinence

3. STUDY SYNOPSIS

Title of the Study	F15 Follow-up Study: Study to collect long-term clinical data for the recharge free Axonics F15 SNM System (INS Model 4101)
Indications for Use	**Axonics Sacral Neuromodulation (SNM) System for Urinary Control** Axonics SNM Therapy for urinary control is indicated for the treatment of urinary retention and the symptoms of overactive bladder, including urinary urgency incontinence and significant symptoms of urgency-frequency alone or in combination, in patients who have failed or could not tolerate more conservative treatments. This therapy is not intended for patients with mechanical obstruction such as benign prostatic hypertrophy, cancer, or urethral stricture. **Axonics SNM Therapy for Bowel Control** Axonics SNM Therapy for bowel control is indicated for the treatment of chronic fecal incontinence in patients who have failed or are not candidates for more conservative treatments.
Study Devices	Axonics F15 SNM System (INS Model 4101)
Study Sponsor	Axonics, Inc. 26 Technology Drive Irvine, CA 92618 USA
Objectives	To obtain long-term clinical data for the recharge free Axonics F15 SNM System (also referred to as INS Model 4101).
Study Design	Multicenter, prospective study comparing bladder or bowel diaries at baseline to minimum of 1 year follow up and up to 2 years. Participants will be identified through a retrospective chart review of all patients implanted with the Axonics F15 SNM who are ≥ 1-year post-implant and who have baseline bladder or bowel diaries.
Study Sites	Participants will be consented and enrolled at up to 20 centers. Sites are selected based on implant history of the Axonics F15 SNM System and completion of patient bladder or bowel diaries at baseline.
Subject Population	Adults aged 18 or older, previously diagnosed with urinary urge incontinence (UUI) with or without urinary frequency (UF) and/or chronic fecal incontinence (FI), who received the Axonics F15 SNM System device and who have baseline bladder or bowel diaries.
Study Timelines	Expected study start: Q1 - 2024 Expected enrollment duration: 6 months Expected study end: Q4 - 2024

Inclusion Criteria	**1.** 18 years or older **2.** Provides written informed consent **3.** Primary indication of UUI (with or without UF) or chronic FI who failed or could not tolerate more conservative treatments and implanted with the Axonics F15 SNM System and who have reached 1-year or greater, post-implant **4.** Completion of a baseline pre-PNE 3-day bladder diary for UUI or a minimum of 5-day pre-PNE bowel diary for FI
Exclusion Criteria	**1.** Any significant medical condition that is likely to interfere with trial procedures, device operation, or likely to confound evaluation of trial endpoints (i.e., exclusion of neurological conditions such as multiple sclerosis) **2.** Any psychiatric or personality disorder that is likely to interfere with trial procedures at the discretion of the participating physician; this may include poor understanding or compliance with trial requirements **3.** A female who is breastfeeding **4.** A female with a positive urine pregnancy test **5.** Intradetrusor chemodenervation with OnabotulinumtoxinA (Botox) injections within 6 months prior to study follow-up visit **6.** Prior history of pelvic or rectal cancer **7.** Prior history of pelvic radiation
Primary Outcome	Comparison from baseline to follow-up for the following: • ≥ 50% reduction in UUI episodes per day on a 3-day bladder diary OR • ≥ 50% reduction in FI episodes on a minimum of 5-day bowel diary
Secondary Outcomes	• Complete urinary or fecal continence • Device parameters (programming settings, impedance values) • Procedure and/or device-related adverse events • Serious adverse events (SAEs) • Patient satisfaction

4. STUDY DESCRIPTION

4.1 OBJECTIVE

To obtain long term clinical data for the recharge free Axonics F15 SNM System (INS Model 4101).

4.2 RATIONALE AND PURPOSE

The Axonics® SNM System (Axonics System) for urinary control is FDA-approved and indicated for the treatment of OAB, including UUI and 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 in patients who have failed or are not candidates for more conservative treatments.

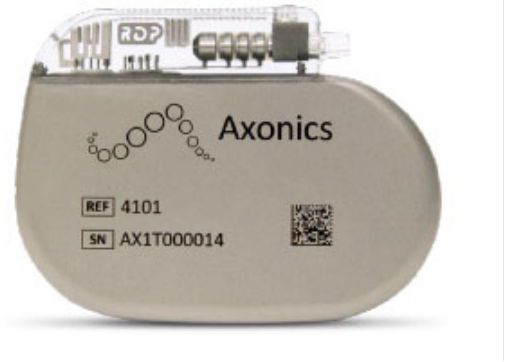
The purpose of this study is to obtain long-term data of the Axonics F15 SNM System. Participants with baseline bladder or bowel diaries will be prospectively evaluated for specified outcome measures at a minimum of 1-year follow-up. For participants who are eligible for longer-term follow-up, 2-year data may be collected.

4.3 STUDY DEVICE

The Axonics F15 SNM System is an implantable device comprised of implantable and non-implantable components.

- Implantable Neurostimulator (INS) (model 4101), as illustrated in **Figure 1**. The model 4101 INS is a non-rechargeable device which provides electrical pulses to stimulate the sacral nerve. The INS is connected to the Axonics Tined Lead, which conducts stimulation pulses from the INS to a sacral nerve, typically the 3rd and occasionally the 4th sacral nerve root.

FIGURE 1. Neurostimulator (INS)



- Tined Lead (Model 1201 and 2201) connects to the INS (which creates a series of electrical pulses) to stimulate the S3 and S4 sacral nerves (**Figure 2**). The Tined lead has four (4) cylindrical electrodes that are equal in length and spaced equidistantly along the distal end of the lead. The distal end of the lead has tines to anchor the lead in the sacrum and surrounding connective tissue. There are also markers to indicate the lead depth during implantation and the level of tine deployment. The proximal end of the lead has a marker to facilitate complete insertion of the lead into the INS header.

FIGURE 2. Tined Lead

4.4 STUDY DESIGN

Multicenter, prospective study comparing bladder or bowel diaries at baseline to minimum of 1 year follow up and up to 2 years if participant is eligible (i.e., participants implanted between March-July 2022). Participants will be identified through a retrospective chart review of all patients at the selected sites who were implanted with the Axonics F15 SNM and who have baseline bladder or bowel diaries

Device parameters and safety data will be collected, and a patient satisfaction questionnaire will be administered at the follow-up visit.

4.4.1 STUDY POPULATION

Participants with primary diagnosis of UUI (with or without UF) and/or chronic FI who were implanted with an Axonics F15 SNM and who have a baseline bladder or bowel diary, will be included. Participants must meet the eligibility requirements specified in this protocol.

4.4.2 SITE SELECTION AND ENROLLMENT

Sites will be selected based on implant history of the Axonics F15 SNM System (INS Model 4101).

Up to 80 participants with primary indication for UUI and/or chronic FI will be enrolled. When the required number of participants have been enrolled, the sites will be notified to discontinue enrollment.

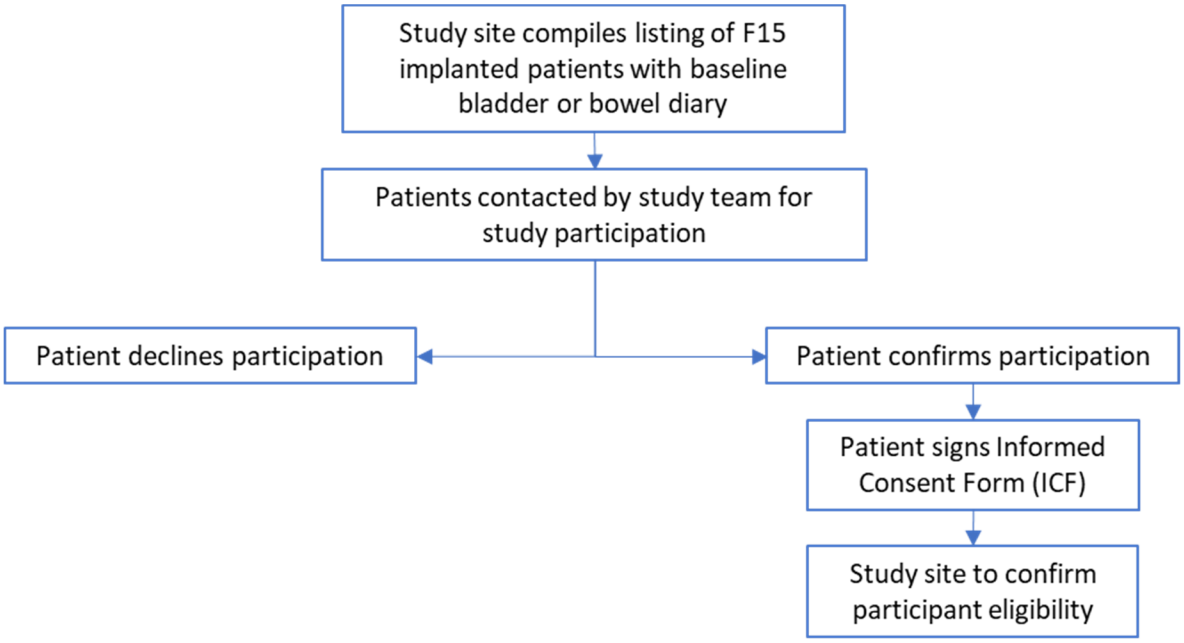
5. STUDY PROCEDURES

5.1 PATIENT SCREENING AND ENROLLMENT

A screening log of all participants will be maintained by the enrolling study sites. This will include information on any patients who do not meet the inclusion/exclusion criteria specified in §5.2 and §5.3.

See **Figure 3** for the screening process.

Figure 1 – Screening Process Flow



5.2 INCLUSION CRITERIA

A patient who meets all of the following criteria may be considered as a potential study participant:

1. 18 years or older
2. Provides written informed consent
3. Primary indication of UUI (with or without UF) or chronic FI who failed or could not tolerate more conservative treatments and implanted with the Axonics F15 SNM System and who have reached 1-year or greater, post-implant
4. Completion of a baseline pre-PNE 3-day bladder diary for UUI or a minimum of 5-day pre-PNE bowel diary for FI

5.3 EXCLUSION CRITERIA

A participant who meets any of the following criteria shall be excluded:

1. Any significant medical condition that is likely to interfere with trial procedures, device operation, or likely to confound evaluation of trial endpoints (i.e., exclusion of neurological conditions such as multiple sclerosis)
2. Any psychiatric or personality disorder that is likely to interfere with trial procedures at the discretion of the participating physician; this may include poor understanding or compliance with trial requirements
3. A female who is breastfeeding
4. A female with a positive urine pregnancy test
5. Intradetrusor chemodenervation with OnabotulinumtoxinA (Botox) injections within 6 months prior to study follow-up visit
6. Prior history of pelvic or rectal cancer
7. Prior history of pelvic radiation

5.4 PARTICIPANT INFORMED CONSENT

Written consent, documented on the ICF in accordance with Good Clinical Practice standards and study center regulations, will be obtained from each patient.

Participants must be informed that their medical records may be reviewed by the Sponsor and its authorized designee. Participants will be informed that they are free to withdraw participation in this clinical study at any time without loss of benefits to which they are otherwise entitled, and without prejudice to future care.

The original signed informed consent for each participant must be retained by the clinical site. A copy of the signed informed consent form must be provided to the participant.

If the participant does not comply with requirements as stated in the informed consent, the Principal Investigator (PI) has the authority to withdraw the participant from the study.

5.5 FOLLOW-UP REQUIREMENTS

Participants who have completed a 3-day baseline bladder diary for UUI or a minimum of 5-day bowel diary for FI and who have reached 1-year or greater, post-implant will be followed. Participants will consent to the retrospective baseline data collection and will complete follow-up requirements as stated in **Table 1**, below. At follow-up, they will be asked to complete a 3-day bladder diary for UUI or a 5-day bowel diary for FI and a patient satisfaction questionnaire. Adverse events will be reviewed and recorded on the adverse event source document worksheet.

TABLE 1 – SCHEDULE OF ASSESSMENTS

ASSESSMENT	Baseline	Follow-Up
Clinical evaluation/Adverse events	X	X
UUI 3-day bladder diary OR FI 5-day bowel diary*	X	X
Patient satisfaction questionnaire		X
Device parameters	X	X

*Per primary indication

6. STUDY EVALUATIONS

6.1 PRIMARY STUDY OUTCOME

Comparison from baseline to follow-up through review of baseline bladder or bowel diary data compared to the patient's follow-up bladder or bowel diary data for the following:

- A ≥ 50% reduction in UUI episodes
- A ≥ 50% reduction in FI episodes

6.2 SECONDARY STUDY OUTCOMES

- Complete urinary or fecal continence
- Device parameters (programming settings, impedances)
- Procedure and/or device-related adverse events
- Serious adverse events (SAEs)
- Patient satisfaction

7. DATA MANAGEMENT

7.1 DATA CAPTURE

The study will utilize an Electronic Data Capture (EDC) system for data collection. Participants will be anonymized and given a specific study identification number in the EDC system. Only delegated and trained personnel will be able to enter data in the electronic Case Report Form (eCRF). All eCRF pages will be reviewed and signed by the investigator at each study site at the time of the final database lock. Applicable source document worksheets will need to be signed by the Principal Investigator or Sub-Investigator(s) if the task has been assigned and identified on the Delegation of Authority (DOA) log. Queries should be resolved in a timely manner; generally, within 60 days of the date of issuance.

7.2 DATA COLLECTION

Review of medical history and baseline bladder or bowel diaries will be performed by an Axonics designee. Data will be entered by the site study staff delegated to data entry as identified on the DOA. Data collection for the follow-up visit(s) will be completed by the delegated study staff.

Retrospective chart review will be conducted for all patients implanted with the F15 SNM device at each of the selected sites. This will include EMR confirmation of therapy status (i.e. explant or recent visit with confirmation of therapy), intra and post-operative complications, hospital readmissions and re-operations/revisions or explants.

8. ADVERSE EVENTS

An adverse event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, whether related to the study device and whether anticipated or unanticipated.

Investigators at each site will be responsible for reporting all adverse events, per protocol and per their IRB and institutional requirements.

Serious Adverse Events (SAEs) and device-related AEs that occur during the study will be assessed and adequately reported to comply with applicable regulations and vigilance requirements (ISO 14155:2020, Clinical investigation of medical devices for human subjects - Good Clinical Practice).

8.1 ADVERSE EVENT DEFINITIONS

8.1.1 SERIOUS ADVERSE EVENT (SAE)

The event is serious and should be reported when the outcome is/led to:

- Death
- Serious deterioration in the health of the participant, users, or other persons as defined by one or more of the following:
  - a life-threatening illness or injury
  - a permanent impairment of a body structure or a body function including chronic disease
  - in-patient hospitalization or prolonged hospitalization
  - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function
  - fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

8.1.2 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

Unanticipated serious adverse device effect (USADE) which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Investigators shall submit to Axonics and to the reviewing IRB a report of any USADE as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. Investigators must submit to Axonics the documentation of the report made to the IRB.

9. RESPONSIBILITIES

9.1 SPONSOR RESPONSIBILITIES

Axonics is responsible as the Sponsor to ensure:

- Proper regulatory IRB approvals are obtained
- Proper site and Investigator selection
- Investigator has signed applicable agreements
- Sites are adequately trained to the requirements as stated in this protocol
- Delegations are documented and approved by the Principal Investigator prior to execution of study tasks
- Management and monitoring of the study with special attention to verification of all clinical requirements, adherence to protocol, good clinical practices and compliance with applicable institutional regulations

9.2 INVESTIGATOR RESPONSIBILITES

The investigator(s) will conduct this study in accordance to this study protocol, Good Clinical Practice (GCP) and all applicable government and institutional regulations. The Principal Investigator (PI) is responsible for obtaining proper regulatory approvals and for adhering to reporting requirements, such as adverse events, to the applicable regulatory agencies. Where Sub-Investigators are delegated certain responsibilities, the Principal Investigator remains responsible for the proper conduct of the clinical study.

Axonics must be informed of new study staff before training and delegation of responsibilities to ensure qualification has been assessed. If a satellite site is used, the Investigator or designee must inform the Sponsor and ensure the additional site(s) is governed by the primary site's IRB.

Written IRB approval of the protocol and ICF must be provided to the Sponsor prior to the enrollment of any participant. The investigator is responsible for ensuring that informed consent is obtained prior to any study-specific tests or treatments. Since the initial chart review is retrospective of the patients

implanted at the selected site, no prospectively collected consents are necessary for reviewing participant eligibility. Patient data will be protected by current HIPAA standards. In addition, participants contacted by the Therapy Support Services (TSS) Team have signed a consent form to participate in the Patient Care Management (PCM) program (Attachment I).

To ensure compliance with the applicable guidelines, the Sponsor, an independent body, or the applicable regulatory agency may audit the study. By participating in this study protocol, all Investigators and their institutions acknowledge the potential for Sponsor, IRB and/or regulatory inspections related to the study. They also agree to provide authorized individuals with access to source data and documentation as well as the right to copy records, provided such activities do not violate participant consent and participant data confidentiality.

If a non-compliance is noted throughout the duration of the study, Axonics will formally communicate with the Principal Investigator in an attempt to maintain compliance. All communication attempts should be documented and maintained in the study Trial Master File (TMF). Continued non-compliance by any Investigator may result in notification to the site IRB and/or removal of the Investigator from the study.

10. PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the investigator or research personnel/research coordinator did not conduct the trial according to the protocol.

For reporting purposes, deviations are classified as major or minor.

- **Major deviations** – will be reported to Axonics Clinical Affairs within 48 hours but no later than 3 business days of awareness of the major deviation. The deviation needs to be documented on the appropriate source worksheet and eCRF provided; and to the IRB/EC per their guidelines.
    - Any deviations impacting participant safety and welfare
    - Any deviation from participant inclusion and exclusion criteria
    - Any deviation from participant informed consent procedures
- **Minor deviations** – will be reported to Axonics Clinical Affairs in writing on the appropriate source worksheet or eCRF provided.
    - Deviation from a protocol requirement such as incomplete procedures

11. CONFIDENTIALITY AND PARTICIPANT RIGHTS

11.1 PARTICIPANT DATA CONFIDENTIALITY

Throughout the study, participant confidentiality shall be observed at all times by all parties involved, including in reports and publications. All data will be secured and stored according to the requirements.

The participating sites shall ensure that data (e.g. source records, worksheets etc.) forwarded to Axonics does not contain any Protected Health Information (PHI) (such as name, birth date, etc.). Documents containing PHI should be redacted and participant IDs should be used to identify all participant-specific documentation.

Only authorized personnel identified in the ICF will have access to study-specific data. Participant data may be made available to Regulatory Agencies, Health or other Governmental Authorities, but under strict confidentiality.

11.2 PARTICIPANT RIGHTS

The participant has the right to withdraw from the study at any time and without reason.
Upon early withdrawal from the study, all available and necessary participant data should be entered in the appropriate CRFs. The reason(s) for withdrawal should be documented if possible.

12. TRIAL REQUIREMENTS AND RESPONSIBILITIES

The regulations listed in Table 2 must be observed to comply with Axonics' policies for conduct of clinical trials and they represent good clinical practice. It is the responsibility of the investigator(s) and the research staff at the clinical site to comply with the requirements set forth in the below regulations.

TABLE 2: REGULATIONS AND GUIDELINES

- Institutional Review Board (IRB), 21 CFR Part 56
- Protection of Human Participants, 21 CFR Part 50
- Financial Disclosure, 21 CFR part 54
- ISO 14155, Clinical investigation of medical devices for human subjects – Good Clinical Practice

13. MONITORING

Monitoring will be conducted per the Axonics standard operating procedures, to assure the integrity and quality of the study data and to assure overall compliance to the study protocol and applicable regulations.

All data entered in the database will be monitored by an Axonics designee.

14. STUDY COMPLETION

A final clinical report will be compiled once data collection is complete. Such reports include all information required and outlined in this protocol. The final report may be provided to regulatory agencies and/or institutional review boards as per applicable laws. The final clinical report will be filed in the study TMF.

15. PUBLICATION

Axonics, as the Sponsor of this Clinical study, has a proprietary interest in the outcome of this study. Authorship and manuscript composition will reflect cooperation between multiple Investigators and with Axonics. Authorship will be established prior to writing of the manuscript by Axonics. All information collected will be considered confidential and remains the sole property of Axonics, Inc.

The Investigator agrees to use this information only for the purposes of this study and will not use this information for other purposes without Axonics' written permission. The Investigator understands that the information developed from this study will be used by Axonics and may be disclosed to regulatory agencies, as required. To permit the information derived from the Clinical study, the Investigator is obliged to provide Axonics (or authorized representative) all data obtained from this study.

Protocol Signature Page (PSP)

The signature below confirms the review of this protocol and provides necessary assurances that the Principal Investigator has read the protocol, understands it, and will comply according to all stipulations of it, and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for Good Clinical Practices, 21 CFR Part 56 Institutional Review Board (IRB), 21 CFR Part 50 Protection of Human Participants, 21 CFR part 54 Financial Disclosure, ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice) and ICH E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), or the applicable local, state and federal regulations.

_____

Principal Investigator Printed Name

_____ _____

Principal Investigator Signature Date